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CHAPTER 18: INTEGUMENTARY SYSTEM

Interfollicular epidermis of the guinea pig

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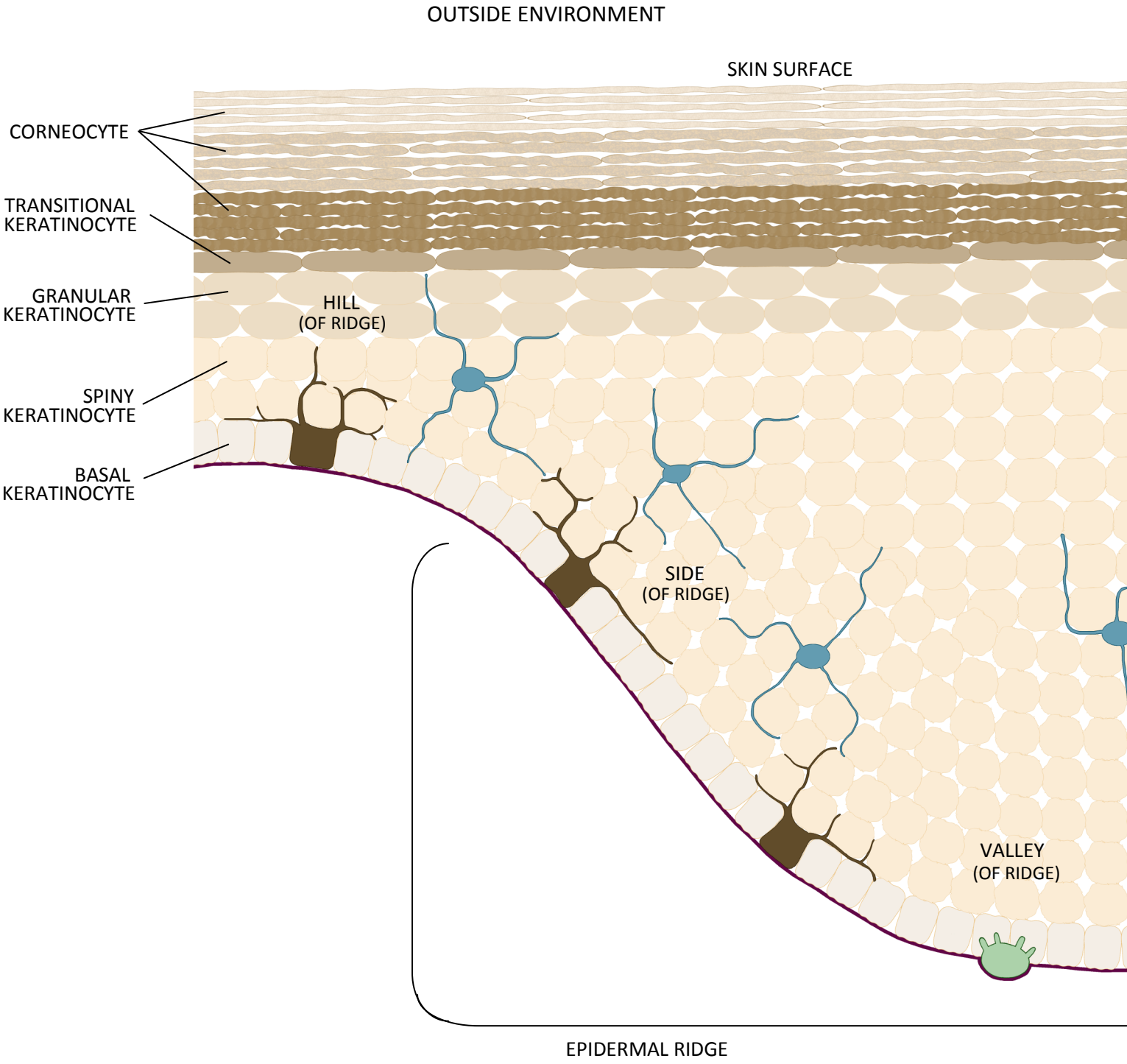
TABLE OF CONTENTS

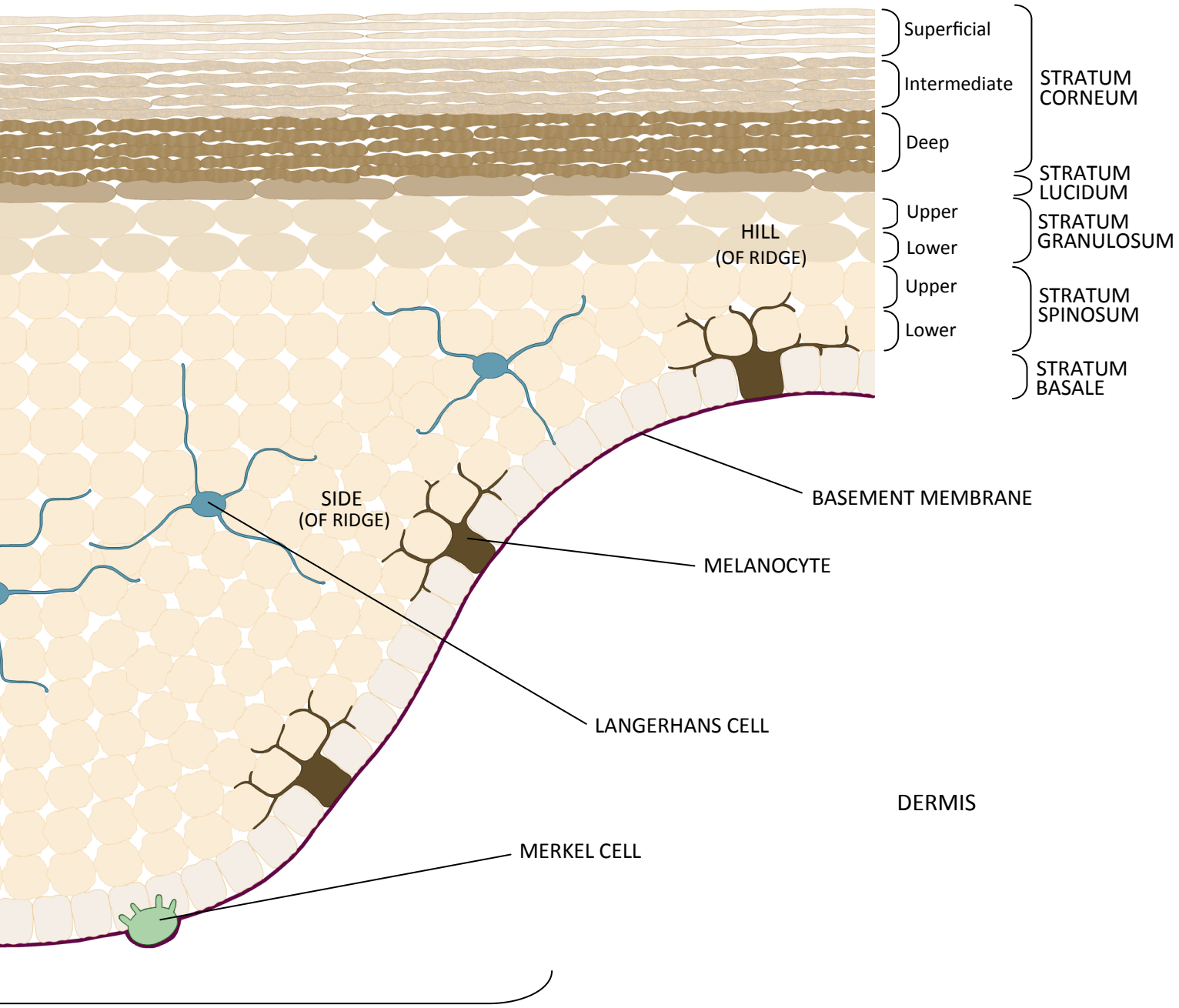
INTRODUCTION

The epidermis is the topmost layer of the skin. It is a type of epithelial tissue,[84] and ectodermic in origin.[2] It functions primarily as a barrier to the outside world, keeping the insides in and the outsides out. It achieves this through the differentiation of epidermal cells up five main layers, or strata: the *stratum basale*, the *stratum spinosum*, the *stratum granulosum*, the *stratum lucidum*, and the *stratum corneum*. These layers may be further divided, or combined,



depending on the literature's preference. This paper will take the splitter option in order to allow for the most detailed descriptions possible for the differentiation of guinea pig epidermal cells. Therefore, the *stratum spinosum* is further divided into *lower* and *upper*, the *stratum granulosum* is further divided into *lower* and *upper*, and the *stratum corneum* is further divided into *deep*, *intermediate*, and *superficial*.

The epidermis is comprised of a *basement membrane* and four main cell types: *keratinocytes*, *melanocytes*, *Langerhans cells*, and *Merkel cells*. There are also *free nerve endings*.



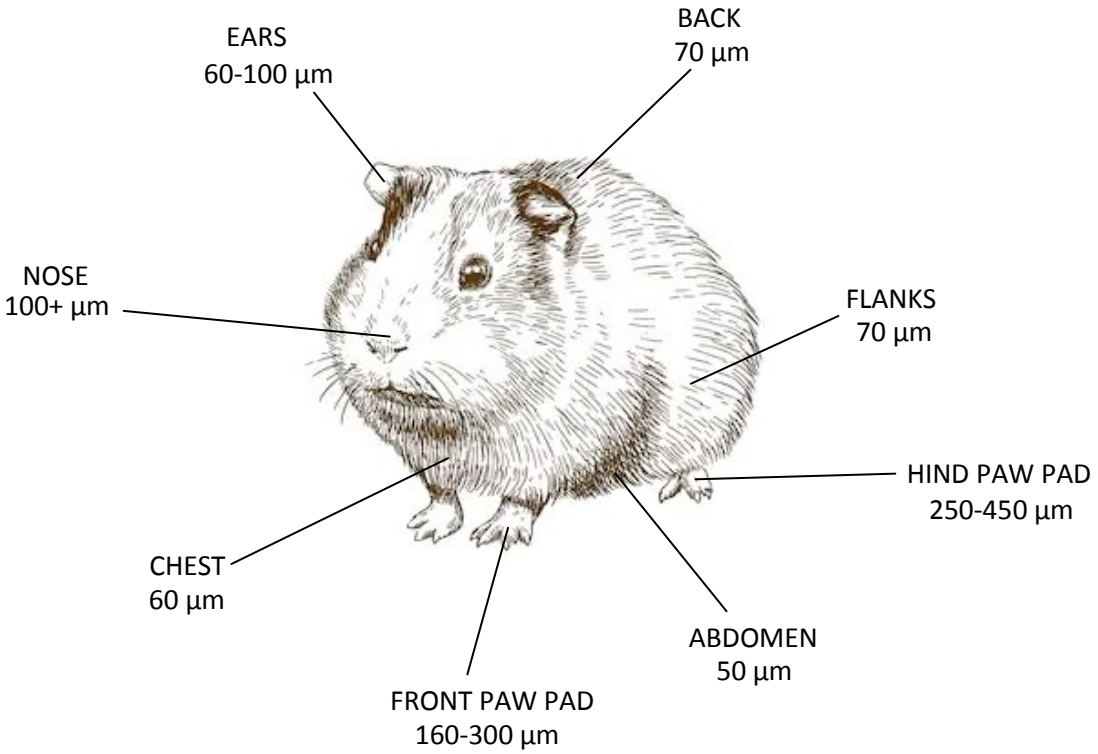
THICKNESS

The epidermis is typically quite thin in the guinea pig,[38] though the actual thickness differs depending on the area of the body. The thickness also varies within the same area due to the presence of *epidermal ridges*; the stratum spinosum on the hills are thinner than the stratum spinosum in the valleys.[51] This is particularly noticeable in the ears, which have been studied extensively in guinea pigs. At the top of the hills the stratum spinosum is only 2 rows thick,[2][27][43][242] whereas at the bottom of the valleys there may be as many as 10 rows.[2][17][27][145]

Epidermal thickness can be classified into two simplified groups: *thin skin* and *thick skin*. *Thin skin* lacks a continuous *stratum lucidum*, which instead appears either intermittently as lone cells, or not at all. *Thick skin* retains a continuous *stratum lucidum*. Thick skin is found on the foot pads, nose,[2] muzzle, nipples, and around the genital and anal orifices.[38] Thin skin is found on the ears, abdomen, and back.[2]

The hairier parts of the body tend to have a thinner epidermis than the less hairy parts of the body.[51] This is likely because the hairy skin is protected by hair, whereas the hairless skin is not and so needs a thicker epidermis to make up for it. Thickness is decided not by cell proliferation rate, as originally thought,[187] but the differentiation rate of the stratum spinosum; the keratinocytes in thicker areas spend more time in the stratum spinosum stage, increasing the width of that layer, and therefore the whole epidermis.[51]

Reported thicknesses of guinea pig epidermis vary dramatically between papers, even when studying the same area. For example, figures range from 2 µm[2] to 48 µm[151] on the abdomen. Based on the size of the keratinocytes, the number of keratinocyte rows in these areas, comparison to other species, and personal examination of microscope photographs, the larger numbers are likely more accurate. Below are estimations of the average epidermal thicknesses, based on all available information.[2][17][20][25][27][40][43][48][51][63][69][80][91][96][99][119][132][145][151][183][188][242]



WEIGHT AND RESPIRATION

The epidermis is avascular, meaning that it doesn't contain any blood vessels. The lower cells take their oxygen and other nutrients from the dermis below. As they mature, and younger cells develop and push them higher up the epidermis, they move further from the blood supply and subsequently starve.

Guinea pig skin is unusual compared to other rodents in that it has a big epidermis relative to the dermis. The ratio, by weight, of epidermis to dermis in guinea pigs is as high as 2.0 when measured in the ear.[230] This is in comparison to 0.3 in rats[230] and 1.4 in mice.[55] Due to having a relatively larger epidermis, guinea pig skin also has higher metabolic activity than other mammals.[230] Guinea pig epidermis has an average respiration rate of 5.29 µl/mg/hour. For comparison, the dermal respiration rate is 2.21 µl/mg/hour, and the epidermal respiration rates in other rodents are: 2.95 µl/mg/hour in mice and 3.69 µl/mg/hour in rats.[55]

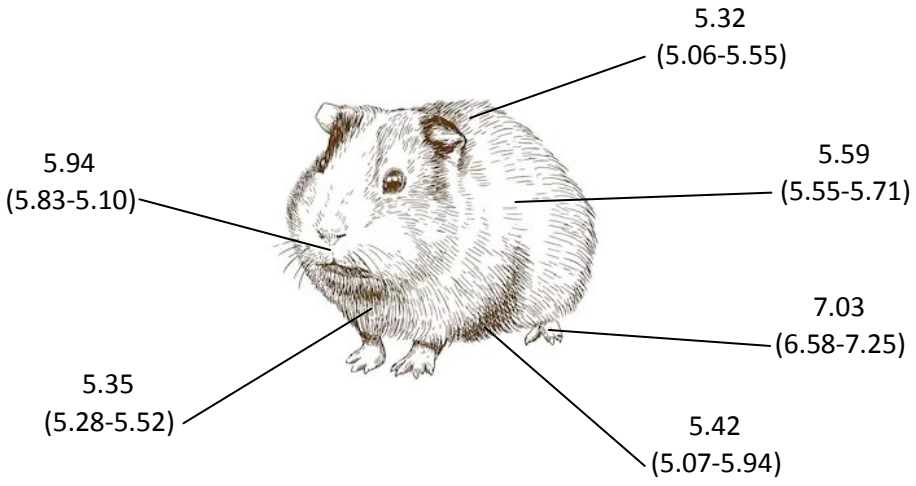
MICROFLORA

No studies have been done on the microflora of guinea pig epidermis. However, it stands to reason that they would have commensal microbes living on the skin surface and inside the follicles, as in humans and other animals. Most microbes live in the surface grooves made between the outermost cells, called squames. Sometimes these microbes will become pathogenic, either by penetrating an injury site or by overgrowth, such as that caused by humidity or metabolic or immune disease.[219]

pH

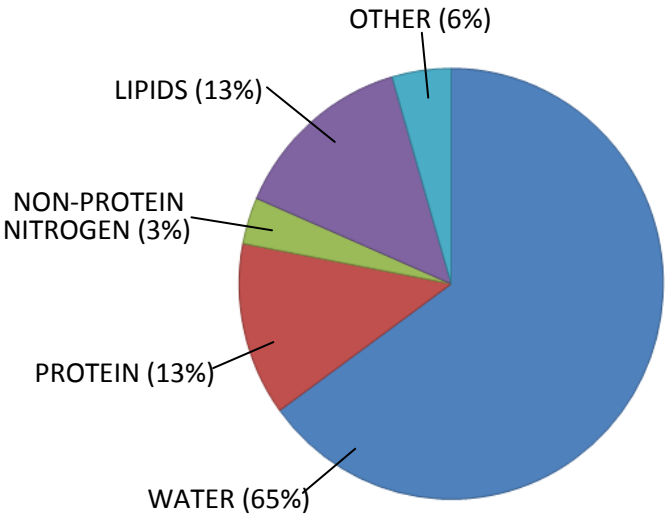
The total average pH of guinea pig epidermis is 5.5.[117] This is higher than in humans (which are pH 4.8), though lower than other species studied; ungulates, carnivorans, monkeys, rabbits, and rats all have an epidermal pH above 5.9.[117] There is no difference between sexes.[121] Different areas of the body may have a slightly different pH, as shown below.[121]

The acidity has three sources: the breakdown products of filaggrin, such as urocanic acid and pyroglutamic acid; free amino acids in the stratum corneum; and lipids, like cholesterols and free fatty acids.[117] This acidity is possibly a defence mechanism against cutaneous diseases and pathogens.[117]



WHOLE COMPOSITION

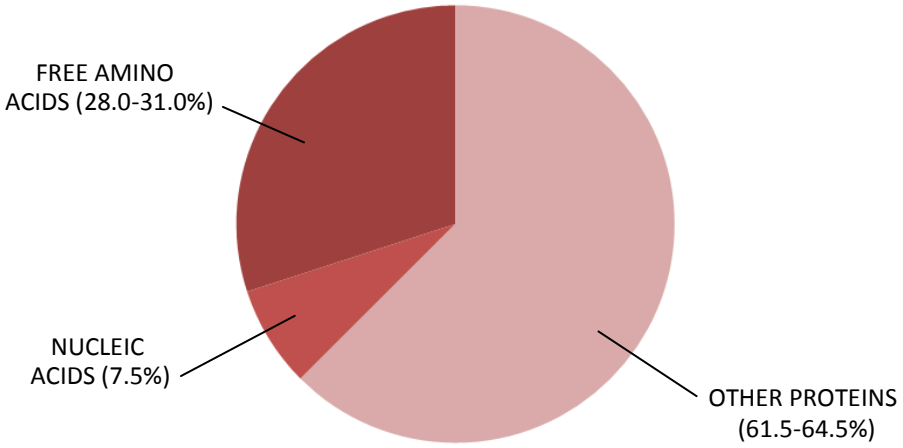
The water content of guinea pig epidermis ranges from 58% to 70%,[206] with a consistent average of 64 to 65% reported in the literature (64.0%,[211] 64.4%[206], and 65.0%[209]).



PROTEIN

Total protein accounts for 12.7% of the guinea pig epidermis by wet weight.[210] Of this, 28.0% to 31.0% is free amino acids and 7.5% is nucleic acids.

Protein nitrogen accounts for 4.2%[206][211] (range 3.7 to 4.6%)[206] of the epidermis by wet weight.



Free amino acids

Free amino acids comprise 2.9 to 4.1% of the epidermis by wet weight,[206] with an average of 3.6%.[206][209] By mole, papers have reported 298,[206] 299,[211] 305,[209] and 338[235] µmoles per gram (wet weight). This is higher than in other organs; the next highest contents after the epidermis are the kidneys (110 µmoles),[206] the spleen (80[235] to 103[206] µmoles), and the liver (64 µmoles).[206] Even the plasma has two-hundred-fold lower concentrations of most amino acids (excluding serine, glycine, citrulline, arginine, and threonine) than the epidermis.[209]

Most of the free amino acids in the epidermis are found in the intercellular space of the stratum corneum.[209] Only around 10% of the free amino acid content is found intracellularly.[209] The percentages of specific amino acids differs depending on where the analysis is taken. Serine, glycine, citrulline, arginine, and threonine are found primarily in the hair follicles, so their values will be different for hairy and glabrous skin. For example, epidermal concentrations of citrulline and threonine are higher in the chest than in the feet, and concentrations of ornithine are higher in the feet than in the chest.[209]

Guinea pigs have higher amino acid levels in their epidermis than in other studied species; humans, dogs, rats, and mice are reported at 200 µmoles, 183 µmoles, 113 µmoles, and 110 µmoles, respectively.[235]

Alanine accounts for 6.0[206][211] to 8.4%[209] of the amino acids by weight, or 8.2[206][211] to 10.9%[209] by mole. Papers report levels of 24.5[206][211] and 33.6[209] µmoles per gram of epidermis (wet weight).

Arginine accounts for 8.5[206][211] to 8.6%[209] of amino acids by weight, or 5.9%[206][209][211] by mole. Papers report a level of 17.6 µmoles per gram of epidermis (wet weight).[206][209][211]

Asparagine may be detected in trace amounts, though the values may not be trustworthy.[209]

Aspartic acid accounts for 1.5[209] to 2.0%[206][211] of amino acids by weight, or 1.2[209] to 1.8%[206][211] by mole. Papers report levels of 3.9[209] and 5.5[206][211] µmoles per gram of epidermis (wet weight).

Citrulline accounts for 13.8[209] to 15.1%[206][211] of amino acids by weight, or 9.4[209] to 10.5%[206][211] by mole. Papers report levels of 28.2[209] and 31.3[206][211] µmoles per gram of epidermis (wet weight).

Cysteine and **cystine** are confined mainly to the keratin and, to a lesser extent, the nuclei.[191][206] Because they are always bound to something, they are not detectable as free amino acids.[206][209]

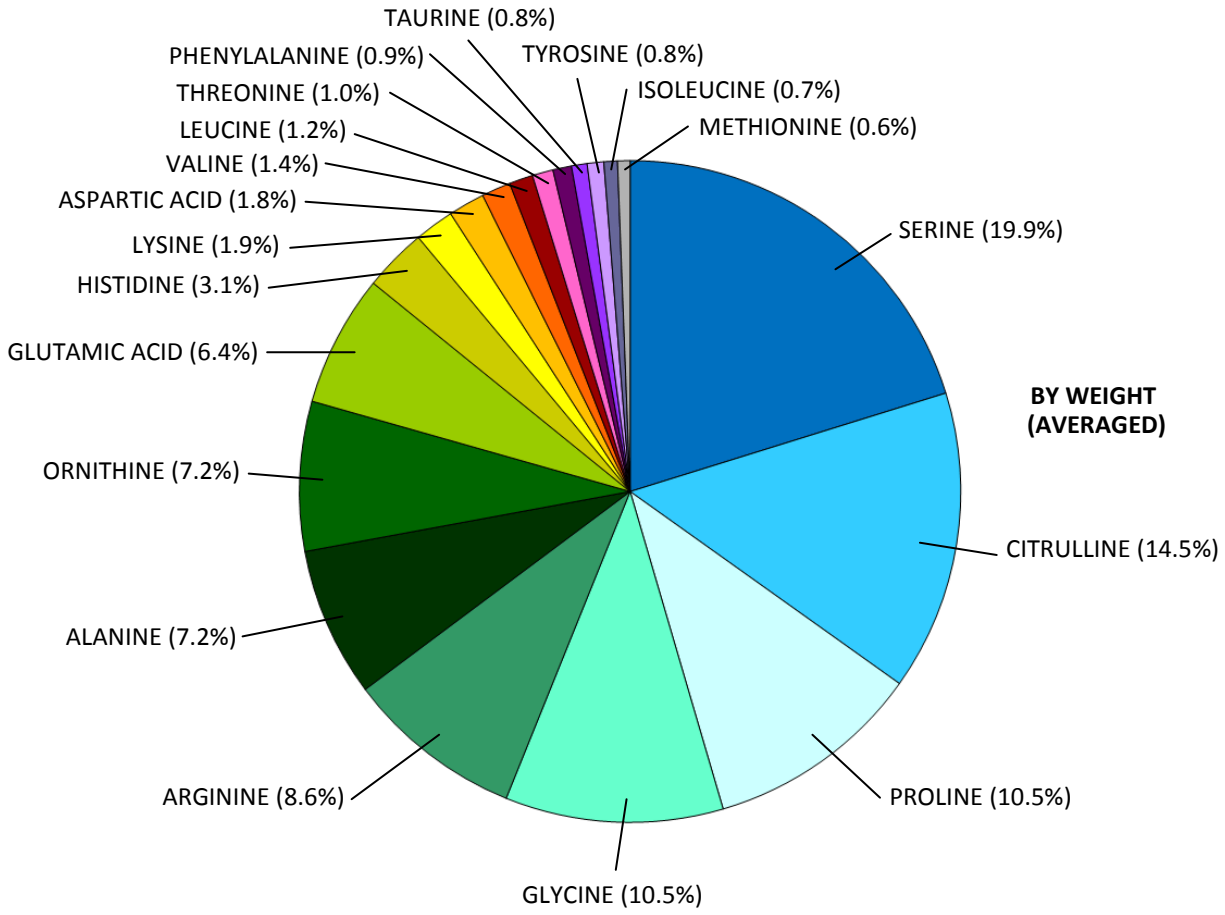
Glutamic acid accounts for 4.9[209] to 7.8%[206][211] of the amino acids by weight, or 4.0[209] to 6.5%[206][211] by mole. Papers report levels of 12.0[209] and 19.4[206][211] µmoles per gram of epidermis (wet weight).

Glutamine may be detected in trace amounts, though the values may not be trustworthy.[209]

Glycine accounts for 10.2[209] to 10.8%[206][211] of the amino acids by weight, or 15.6[209] to 17.5%[206][211] by mole. Papers report levels of 48.3[209] and 52.3[206][211] µmoles per gram of epidermis (wet weight).

Histidine accounts for 2.8[209] to 3.3%[206][211] of the amino acids by weight, or 2.2[209] to 2.6%[206][211] by mole. Papers report levels of 6.5[209] and 7.6[206][211] µmoles per gram of epidermis (wet weight).

Isoleucine accounts for 0.6[209] to 0.7%[206][211] of the amino acids by weight, or 0.5[209] to 0.6%[206][211] by mole. Papers report levels of 1.6[209] and 1.9[206][211] µmoles per gram of epidermis (wet weight).


TAURINE (0.8%)
PHENYLALANINE (0.9%)
TYROSINE (0.8%)
THREONINE (1.0%)
ISOLEUCINE (0.7%)
LEUCINE (1.2%)
METHIONINE (0.6%)
VALINE (1.4%)
ASPARTIC ACID (1.8%)
SERINE (19.9%)
LYSINE (1.9%)
HISTIDINE (3.1%)
GLUTAMIC ACID (6.4%)
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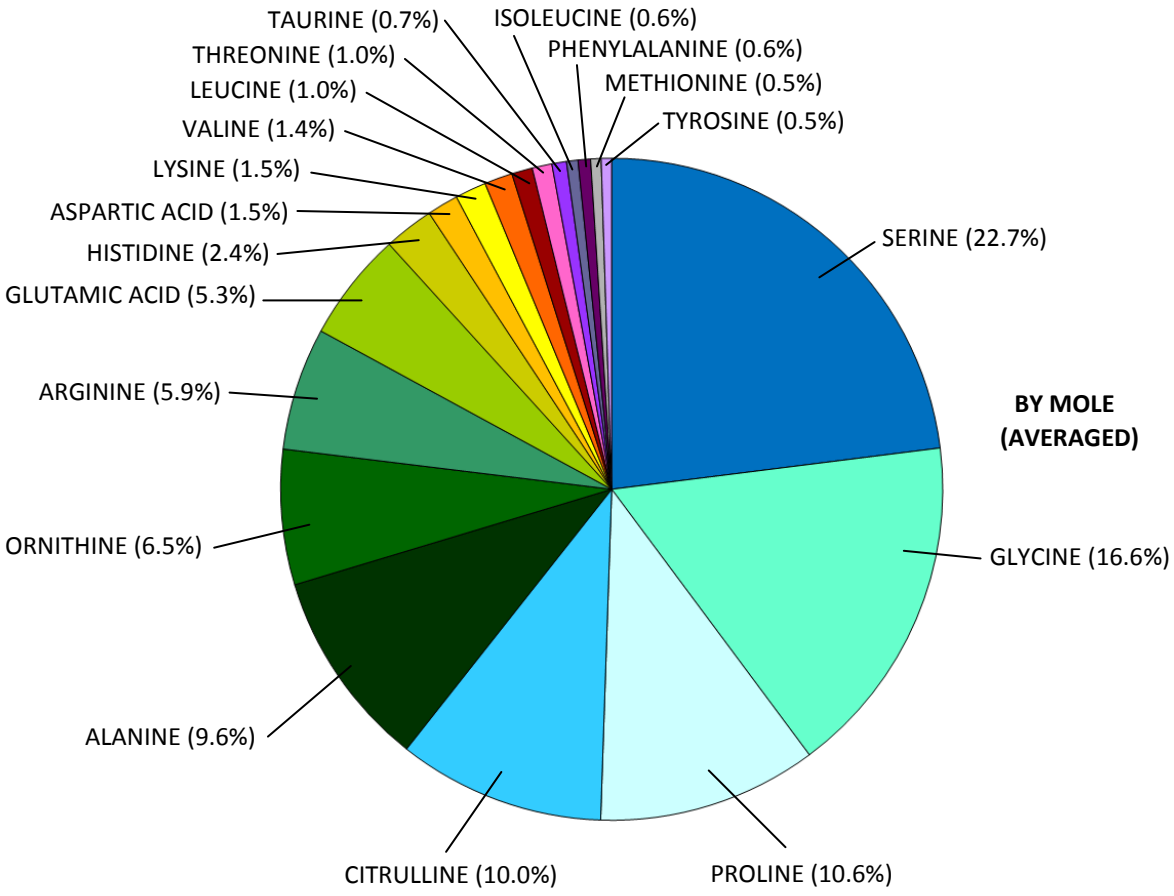
ARGININE (8.6%)
PROLINE (10.5%)
GLYCINE (10.5%)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ORNITHINE (6.5%)
GLYCINE (16.6%)
ALANINE (9.6%)
CITRULLINE (10.0%)
PROLINE (10.6%)

Leucine accounts for 1.1[206][211] to 1.2%[209] of the amino acids by weight, or 1.0%[206][209][211] by mole. Papers report levels of 3.1[206][211] and 3.3[209] µmoles per gram of epidermis (wet weight).

Lysine accounts for 1.9% of the amino acids by weight, or 1.5% by mole. A level of 4.5 µmoles per gram of epidermis (wet weight) is reported.[209]

Methionine accounts for 0.5[209] to 0.7%[206][211] of the amino acids by weight, or 0.4[209] to 0.6%[206][211] by mole. Papers report levels of 1.2[209] and 1.7[206][211] µmoles per gram of epidermis (wet weight).

Ornithine accounts for 7.2% of the amino acids by weight, or 6.5% by mole. A level of 19.5 µmoles per gram of epidermis (wet weight) is reported.[209]

Phenylalanine accounts for 0.9% of the amino acids by weight, or 0.6% by mole. A level of 1.9 µmoles per gram of epidermis (wet weight) is reported.[209]

Proline accounts for 9.7%[206][211] to 11.2%[209] of the amino acids by weight, or 10.2[206][211] to 10.9%[209] by mole. Papers report levels of 30.5[206][211] and 34.8[209] µmoles per gram of epidermis (wet weight).

Serine accounts for 17.3[206][211] to 22.5%[209] of the amino acids by weight, or 20.2[206][211] to 25.1%[209] by mole. Papers report levels of 59.8[206][211] and 76.8[209] µmoles per gram of epidermis (wet weight).

Taurine accounts for 0.6[206][211] to 0.9%[209] of the amino acids by weight, or 0.6[206][211] to 0.8%[209] by mole. Papers report levels of 1.9[206][211] and 2.6[209] µmoles per gram of epidermis (wet weight).

Threonine accounts for 0.9[209] to 1.1%[206][211] of the amino acids by weight, or 0.8[209] to 1.1%[206][211] by mole. Papers report levels of 2.7[209] and 3.3[206][211] µmoles per gram of epidermis (wet weight).

Tyrosine accounts for 0.8% of the amino acids by weight, or 0.5% by mole. A level of 3.4 and 4.5 µmoles per gram of epidermis (wet weight) is reported.[209]

Valine accounts for 1.3[206][211] to 1.5%[209] of the amino acids by weight, or 1.3[206][211] to 1.4%[209] by mole. Papers report levels of 4.0[206][211] and 4.5[209] µmoles per gram of epidermis (wet weight).

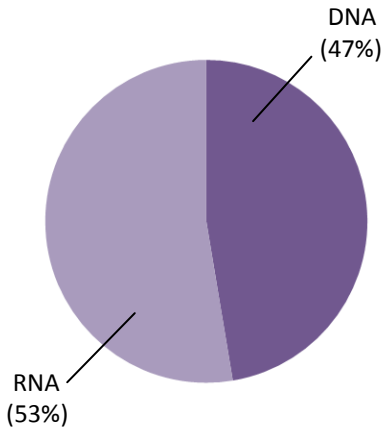
Nucleic acids

Nucleic acids comprise almost 1.0% of the epidermis by wet weight.[206][211] This is relatively low, compared to other organs like the liver or pancreas.[206]

Deoxyribonucleic acid (DNA) accounts for 0.34 to 0.67% of the epidermis by wet weight,[206] with an average of 0.44%[206][211] to 0.46%.[210]

Ribonucleic acid (RNA) accounts for 0.38% to 0.64% of the epidermis by weight weight,[206] with an average of 0.50%.[206][211]

The epidermis has a low ratio of RNA to DNA, at 1.2 or less.[206][211] This is due to the keratinocytes' short lifespans.[206] It is likely that the stratum basale has a higher RNA/DNA ratio than the other layers, though this has not been tested. [206]



Other proteins

At least fifteen nonenzymatic proteins have been described in guinea pig epidermis.

The contractile proteins **myosin** and **actin** were discovered to form an *epidermal actomyosin complex*, which likely helps push the keratinocytes up the layers of the epidermis. The myosin has three polypeptide fractions, with molecular weights of 200,000, 16,500, and 13,000. It supports ATPase activity, and utilises Ca^{2+} better than Mg^{2+}. When utilizing Ca^{2+} it has a pH range of 6.0 to 9.0, with an optimum of 6.5. The amino acid composition is similar to rabbit skeletal muscle myosin and hepatocyte myosin: 19.7% glutamic acid, 11.4% leucine, 10.9% aspartic acid, 9.2% alanine, 8.5% lysine, 5.8% glycine, 5.4% threonine, 5.3% serine, 5.2% arginine, 5.2% valine, 3.5% methionine, 2.4% isoleucine, 2.1% histidine, 1.7% tyrosine, 1.3% proline, 1.2% phenylalanine, and 0.9% cysteine. The actin has not been studied in detail.[16]

Collagen accounts for up to 1.8% of the epidermis by wet weight, and is in the form of bound hydroxyproline.[206]

Cytokeratin,[31] and neuropeptides such as **met-enkephalin**, have been described in the Merkel cells.[[31]114]226]

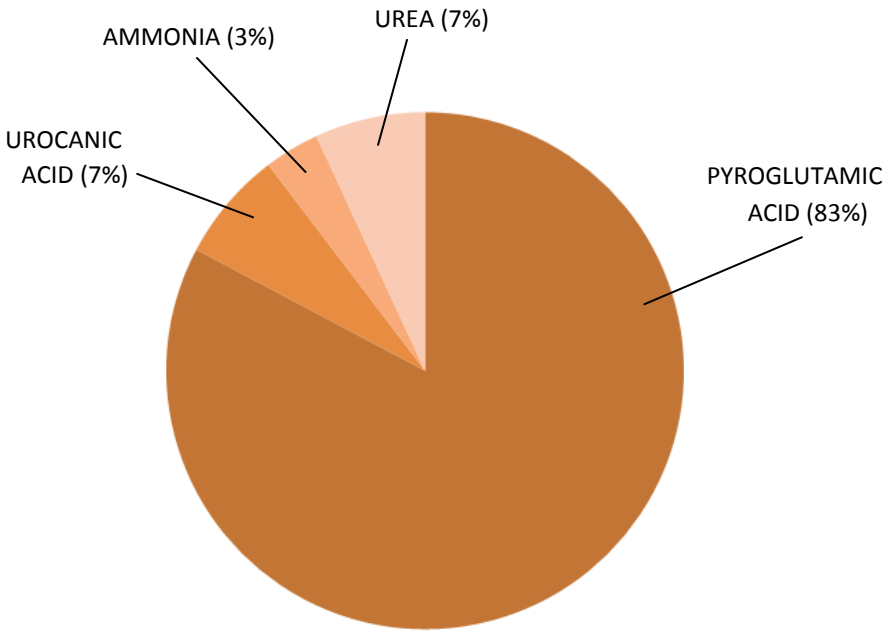
L-dihydroxyphenylalanine (L-DOPA) and **kinesin** have been described in the melanocytes.[26][80]

Stem cell factor (SCF),[84] **corneodesmosin**,[134] **keratohyalin**, cytokeratin,[97] **involucrin**,[42] **calmodulin**,[196] **profilaggrin**, and the two filaggrins **histidine-rich protein B** and **histidine-rich protein C** have been described in the keratinocytes.[163]

57 **enzymes** have been described in guinea pigs; due to the quantity, they will be discussed in their own section.

NON-PROTEIN NITROGEN

Non-protein nitrogen accounts for roughly 3.0% (range 1.8% to 4.1%) of the epidermis by wet weight. Nitrogenous products are found primarily in the intercellular space, with only 15.0% or less found intracellularly.[206] Four non-protein nitrogenous products have been described in guinea pig epidermis.



Pyroglutamic acid

Pyroglutamic acid is also known as pyrrolidone carboxylic acid (PCA).[209][235] It is the primary soluble[235] and hydrolysable[209] nitrogenous compound in the guinea pig epidermis. It is derived from the deamination of glutamine in the stratum corneum keratinocytes.[235] In guinea pigs the pyroglutamic acid takes the L form, and is typically referred to as L-pyrrolidone carboxylic acid in the literature.[235]

A level of 186 µmoles per gram of epidermis (wet weight) is reported.[235] The percentage of the epidermis by weight differs between papers, with values of 1.3%,[116] 2.4%,[235] and 3.5%[209] given. This is higher than in other organs of the body; the highest level after the epidermis is in the brain, still with only 4 µmoles.[235]

Guinea pigs have much higher pyroglutamic acid levels in their epidermis than in other studied species;[116][235] humans, dogs, rats, and mice are reported at 50 µmoles, 31 µmoles, 21 µmoles, and 19 µmoles, respectively.[235]

Urocanic acid

Urocanic acid is derived from the deamination of histidine in the stratum corneum keratinocytes.[206] It accumulates in the epidermis, creating much higher concentrations than seen in other organs.[206] It comprises 0.1% to 0.3% of the epidermis by wet weight, with an average of 0.2%.[205][206][211]

Ammonia

Ammonia comprises 0.10[209] to 0.14%[206][211] of the epidermis by wet weight. Rodents appear to have higher concentrations of ammonia in their epidermis than other mammals do.[206]

Urea

Urea comprises 0.23% of the epidermis by wet weight.[209] Rodents appear to have higher concentrations of urea in their epidermis than other mammals do; both guinea pigs and mice have much higher concentrations than is found in humans.[206]

LIPIDS

Total lipid numbers have not been described in guinea pigs, though based on figures from other animals[297] and the knowledge that guinea pigs have a particularly lipid-rich epidermis,[249] it can be estimated at between 13.0% and 15.0% of the epidermis by wet weight.

43.7% of skin lipids are found in the epidermis, compared to only 12.3% in mice and 11.4% in dogs.[249] Epidermal lipids are less affected by temperature than the dermal lipids; this is because keratinocyte lipids are more viscous and stable than fibroblast lipids.[160] However, guinea pig epidermal lipids are still less viscous than those found in human epidermis.[160]

Lipids that have been described in guinea pig epidermis include wax esters, glycerides, triglycerides[30], phospholipids, prostaglandins (particularly prostaglandin D_2), steroids (particularly cholesterol), sphingolipids (particularly cerebrosides and ceramides), and fatty acids (particularly arachidonic acid and dihomo-γ-linoleic acid). Neither the ratios nor quantities of these lipids has been studied.

Sphingolipids

Sphingolipids are the most important and plentiful lipid group in the epidermis.[223] Seven types have been found in guinea pigs.

Three types of **cerebroside** have been found. Of these, two are known to be glucocerebrosides, and two are known to be esterified, though only one has been described: glycosyl N-(O-linoleoyl-omeda-hydroxylignoceroyl) sphingosine.[223]

Four types of **ceramide** have been found.[223] Most ceramides are found in the stratum corneum, where they accumulate as part of the barrier lipids.[106] Three of the ceramides have been named: ceramide 1,[103] esterified cerebroside 1, and esterified cerebroside 2.[140]

Steroids

Δ^7-cholestene-3-β-ol comprises 15% of the steroids found in the epidermis.[45] Cholesterols account for the remainer,[42] [219] including cholesterol sulphate,[42] saturated sterol esters, monounsaturated sterol esters, and diunsaturated sterol esters.[67]

Fatty acids

The most important fatty acids described in the literature are arachidonic acid, linoleic acid, and dihomo-γ-linoleic acid. Arachidonic acid comprises 6 to 10% of the epidermal fatty acids.[128][248][249] Dihomo-γ-linoleic acid comprises less than 1% of the epidermal fatty acids.[128]

Phospholipids

Phospholipids are found primarily in keratohyalin granules[190] and bound to keratin.[188]

CARBOHYDRATES

Two carbohydrates have been described in the guinea pig epidermis: polysaccharides and glycogen. Polysaccharides have been found in[2] and below[181] the stratum basale. Glycogen has been found in the stratum spinosum keratinocytes[66] and the Merkel-neurite complexes.[127]

VITAMINS

Tocopherol (vitamin E) and ascorbic acid (vitamin C) have been described in the guinea pig epidermis. The tocopherol has an antioxidant effect in the stratum corneum,[219] and the ascorbic acid protects the tocopherol from UV radiation.[219] Ascorbic acid comprises 0.05-0.06% of the epidermis by wet weight.[131]

MINERALS

Mineral levels have not been studied for whole epidermis, but they have been studied from each layer. Calcium, chlorine, magnesium, manganese, phosphorus, potassium, sodium, and sulphur have been described.

Calcium levels increase slightly up the epidermis, though it is highest in the stratum spinosum.[227]

Chlorine levels increase very slightly up the epidermis.[227]

Magnesium levels decrease slightly up the epidermis, in line with phosphorus levels. This is because magnesium is often bound to nucleic acids and thus is lost along with them. Magnesium is important in keratinocyte adhesion.[227]

Manganese levels have not been studied in the guinea pig epidermis. It has, however, been found to have a negative impact on keratinocyte adhesion and metabolism, and on proteins such as calmodulin, adenylate cyclase, and tyrosine kinase.[227]

Phosphorus decreases up the epidermis, in line with the breakdown of filaggrin and the loss of nucleic acids from the keratinocytes.[227] Phosphorus comprises 0.02% of the epidermis by wet weight.[206]

Potassium decreases up the epidermis, in line with the sodium concentration increasing. This change occurs in time with the cell dying.[227]

Sodium increases up the epidermis. This is likely due to the cell dying and failing to pump out excess sodium.[227]

Sulphur increases up the epidermis, in line with keratin formation.[227]

ENZYMES

At least 57 enzymes have been described in the literature from guinea pig epidermis. This includes oxidoreductases, transferases, hydrolases, and lyases, but not isomerases, ligases, or translocases.

Transferases

Five transferase enzymes have been described.

One **phosphotransferase** has been described: tyrosine kinase.[196]

Four **aminoacyltransferases** have been described: γ-glutamyl cyclotransferase, and three types of transglutimase.

γ-glutamyl cyclotransferase is responsible for converting glutamic acid into pyroglutamic acid.[116] Guinea pig epidermis is rich in γ-glutamyl cyclotransferase activity,[116] with a reported production rate of 3 µmoles per hour per cm^2.[9]

Protransglutimase E, *transglutaminase K*, and *transglutaminase C* have been described. Protransglutaminase E is responsible for most of the soluble transglutaminase activity. It is the zymogen of epidermal transglutaminase E, and has a molecular weight of 77,800. Transglutaminase K has a molecular weight of 92,000. The molecular weight of transglutaminase C has not been reported.[100]

Lyases

Only one lyase has been described: adenylate cyclase.[196]

Oxidoreductases

Eight oxidoreductase enzymes have been described.

One **peroxidase** has been described: catalase.[4]

Four **dehydrogenases** are described: lactic dehydrogenase (LDH), malic dehydrogenase (MDH),[4] succinic dehydrogenase,[131] and thioredoxin reductase.[204] Thioredoxin reductase is produced in keratinocyte cell membranes for UV protection.[204]

Three **oxygen receptors** have been described: cyclooxygenase,[101][128] lipoxygenase,[101][128] and superoxide dismutase.[44] Guinea pigs lack epidermal desaturase activity.[128][247]

Cyclooxygenase converts arachidonic acid into prostaglandin D_2.[157] The production of prostaglandin D_2 is likely to have a role in immune regulation and inflammation.[157]

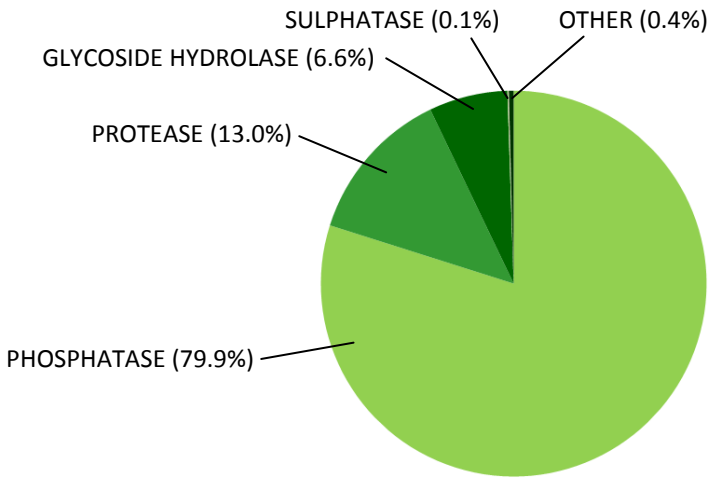
Lipoxygenase converts dihomo-γ-linoleic acid into hydroxyeicosatrienoic acid (HETE).[128] It is typically found in the endoplasmic reticulum of the keratinocytes,[247] and has a production rate of 300 nmoles/mg protein/min.[128]

Superoxide dismutase is important in aerobic cells, and cleans up the superoxide (O_2^-) free radicals left behind by oxygen metabolism. Guinea pigs have the copper-zinc form and the manganese form, but not the iron form. The copper-zinc form has a molecular weight of 16,500 and is typically found in the cytosol. The manganese form has two bands with molecular weights of 23,500 and 47,000, and is typically found in the mitochondria. They are similar to the ones in humans, but have greater mobility than those from mice or cattle. A level of 0.014 mg per gram of epidermis has been reported. The epidermis is relatively low in this enzyme compared to other organs; the liver and the heart have reported levels of 0.372 and 0.114 mg per gram, respectively.[44]

Normally in mammals, *Δ6 desaturase* converts linoleic acid into γ-linoleic acid, and *Δ5 desaturase* converts dihomo-γ-linoleic acid into arachidonic acid.[247] Because guinea pig epidermis lacks activity of both these enzymes,[128][247] however, it cannot convert linoleic acid into arachidonic acid.[166] This is reportedly ameliorated by the ability of phospholipase A_2 to convert phospholipids into arachidonic acid.[102]

Hydrolases

Forty-three hydrolase enzymes have been described.



One **ureohydrolase** has been described: arginase.[206]

One **adenosine triphosphatase (ATPase)** has been described: Na^+/K^+-ATPase. It is found in the membranes of the keratinocytes[213] and Langerhans cells.[14][85][148][222]

One **phosphodiesterase** has been described: phospholipase A_2 (PLA_2). Phospholipase A_2 converts phospholipids into arachidonic acid in the keratinocytes, after activation by Ca^{2+}. Flavonoids, especially biflavones, inhibit PLA_2 activity, subsequently reducing arachidonic acid production.[102]

Two **acid anhydrides** have been described: thiamine pyrophosphatase and inosine diphosphatase. Both are found in the Golgi cisternae, endoplasmic reticulum, and lamellar bodies of the keratinocytes.[243]

Two **ceramidases** have been described: ceramidase I and ceramidase II.

Ceramidase I has a molecular weight of 60,000 and an optimal pH of 7.0 to 9.0.[245]

Ceramidase II has a molecular weight of 148,000 and an optimal pH of 7.5 to 8.5.[245]

Two **sulphatases** have been described: two types of aryl sulphatase. These comprise 0.12% of the hydrolase activity of the epidermis.[125]

Aryl sulphatase A has an optimal pH of 4.6.[123] A production rate of 0.46 nmoles per minute per gram of epidermis is reported.[125]

Aryl sulphatase B has an optimal pH of 6.0.[123] A production rate of 1.3 nmoles per minute per gram of epidermis is reported.[125] It is found in the lysosomes and endoplasmic reticulum.[243]

Two **carboxylesterases**, also known as carboxylic ester hydrolases, have been described: carboxylic esterase[122][4][123] and cholinesterase.

Carboxylic esterase breaks down short- and medium-chain esters, but not long-chain esters. It has an optimal pH of 4.0 to 5.5.[123]

Cholinesterase has been found in Merkel cells.[234]

Seven **proteases**, also known as peptidases or proteinases, have been described: pepsin,[4] arylamidase, pyrrolidone carboxyl peptidase, aminopeptidase, and three types of cathepsin. Proteases comprise 13% of the hydrolase activity of the epidermis.[125]

Aminopeptidase has been found in Langerhans cells.[148][222][241]

Pyrrolidone carboxyl peptidase has a reported production rate of 30 nmoles per hour per cm^2 of epidermis.[9]

Arylamidase has an optimal pH of 7.8.[124] A production rate of 50 to 390 nmoles[124] (average 120[125] to 150[232] nmoles) per minute per gram of epidermis is reported.

Cathepsin B_1 has a pH range of 5.0 to 6.5, with an optimum of 6.4.[124] A production rate of 14[124] to 22[125] nmoles (average 17 nmoles)[124] per minute per gram of epidermis is reported. It has both exopeptidase and endopeptidase activity, meaning it breaks both non-terminal and terminal amino acids from peptide chains.[124]

Cathepsin C has a pH range of 5.0 to 6.0, with an optimum of 5.0.[124] A production rate of 28 to 57 nmoles[124] (average 42[125] to 43[124] nmoles) per minute per gram of epidermis is reported. It has exopeptidase activity, meaning it breaks terminal amino acids from peptide chains.[124]

Cathepsin D has a pH range of 3.0 to 4.0, with an optimum of 3.4.[124] A production rate of 0.3 to 1.7 nmoles[124] (average 0.9 nmoles)[124][125] per minute per gram of epidermis is reported. It has endopeptidase activity, meaning it breaks non-terminal amino acids from peptide chains.[124]

Seven **phosphatases** have been described: nucleotide phosphatase, glucose-6-phosphatase, alkaline pyrophosphatase, acid pyrophosphatase, alkaline phosphatase, and two types of acid phosphatase.

Nucleotide phosphatase has been found in the Langerhans cells.[241]

Glucose-6-phosphatase has been found in the membranes of the keratinocytes.[243]

Alkaline pyrophosphatase has been found in the intercellular space. It requires Mg^{2++} to activate, and probably originates from the dermis.[210]

Acid pyrophosphatase comprises 3.9% of the hydrolase activity of the epidermis.[125] It has an optimum pH of 4.8.[123] A production rate of 60 to 120 nmoles[123] (average 56 nmoles[171]) per minute per gram is reported.

Alkaline phosphatase is found in the Langerhans cells,[123] the Merkel cells,[232] and the keratinocytes in every layer except for the stratum corneum.[210] It mostly has alkaline 5' nucleotidase activity, with only weak alkaline phosphatase activity.[210]

Acid phosphatases are often bound to keratohyalin granules,[129] and comprise 76% of the hydrolase activity of the epidermis.[125] A production rate of 930[123] to 1,100[125] nmoles per minute per gram is reported. *Acid phosphatase 1 ($APase_1$)* has a specific[129] optimal pH of 3.2.[123] *Acid phosphatase 2 ($APase_2$)* has a broad optimal pH range of 4.8 to 6.0.[129]

Seven **glycoside hydrolases** have been described: α-mannosidase, β-acetylglucosaminidase, β-glucuronidase, two types of glucosidase, and two types of galactosidase. Glycoside hydrolases comprise 6.6% of the hydrolase activity of the epidermis.[125]

α-*glucosidase* has an optimal pH of 5.5.[122] A production rate of 4.1[122] to 5.3[125] nmoles (average 4.4 to 4.9 nmoles)[122] per minute per gram is reported.

β-*glucosidase* has an optimal pH of 4.6.[122] A production rate of 1.4[122] to 3.5[125] nmoles (average 2.3 to 2.9 nmoles)[122] per minute per gram is reported.

α-*galactosidase* has an optimal pH of 3.0 to 4.6.[122] A production rate of 1.8[122] to 7.8[125] nmoles (average 4.1 to 5.7 nmoles)[122] is reported.

β-*galactosidase* has an optimal pH of 3.6.[122] A production rate of 28.0[122] to 38.0[125] nmoles (average 34.0 to 37.0 nmoles)[122] per minute per gram is reported.

α-*mannosidase* has an optimal pH above 5.9.[122] A production rate of 2.7[125] to 9.0 nmoles[122] (average 4.8[122] to 7.8[171] nmoles) per minute per gram is reported.

β-*acetylglucosaminidase* has an optimal pH of 3.6.[122] A production rate of 17 to 38 nmoles[122] (average 25 nmoles)[122][125] per minute per gram is reported.

β-*glucuronidase* has an optimal pH of 2.4 to 3.6.[122] A production rate of 2.0[122] to 8.1[125] nmoles (average 3.2 to 6.0 nmoles)[122] per minute per gram is reported.

Eleven **nucleases** have been described: 2 types of deoxyribonuclease, and 9 types of ribonuclease. Nucleases are important because the nucleic acids inside the nuclei, mitochondria, and ribosomes are hydrolysed into oligonucleotides as the keratinocytes move up the layers.[118]

Deoxyribonucleases (DNAases) are found primarily in the lysosomes and in the stratum corneum, though around 45% is in the intercellular fluid. *Deoxyribonuclease I (DNAase I)* is found with high activity, and has an optimal pH of 6.5 to 7.0. *Deoxyribonuclease II (DNAse II)* is found with only trace activity, and has an optimal pH of 5.0 to 5.5. The ratio of DNAase I to DNAase II stays in the range of 1.0 to 2.4, with an average of 1.1. The DNAases in guinea pig epidermis are different to those in other rodents; for example, rats do not have any DNAase I activity, and have higher DNAase II activity. [208]

Ribonucleases (RNases) are found primarily in the intercellular fluid and in the stratum corneum.[207] All of the RNases except for RNase I have endonuclease activity, meaning they break non-terminal nucleotides from polynucleotide chains.[118]

Ribonuclease I (RNase I) has a molecular weight of 35,000 and an optimal pH of 7.0. Unlike the other RNases, it has exonuclease activity, meaning it breaks terminal nucleotides from polynucleotide chains.[118]

Ribonuclease II (RNase II) has a molecular weight of 36,500 and an optimal pH of 6.8.[118]

Ribonuclease III (RNase III) has a molecular weight of 17,500 and an optimal pH of 7.5.[118]

Ribonuclease A (RNase A) has a molecular weight of 27,000 and an optimal pH of 5.6.[118]

Ribonuclease B_1 (RNase B_1) has a molecular weight of 34,000 and an optimal pH of 7.8.[118]

Ribonuclease B_2 (RNase B_2) has a molecular weight of 35,000 and an optimal pH of 6.8.[118]

Ribonuclease B_3 (RNase B_3) has no molecular weight reported, and an optimal pH of 5.8.[118]

Ribonuclease C (RNase C) has a molecular weight of 22,000 and an optimal pH of 6.9.[118]

Ribonuclease D (RNase D) has a molecular weight of 10,000 and an optimal pH of 7.0.[118]

BASEMENT MEMBRANE

The basement membrane connects the epidermis to the dermis, and provides a bed for the stratum basale to sit on. It is 20 to 50 nm wide[181] and comprised of three main layers: the *lamina lucida*, the *lamina densa*, and the *lamina reticularis*.

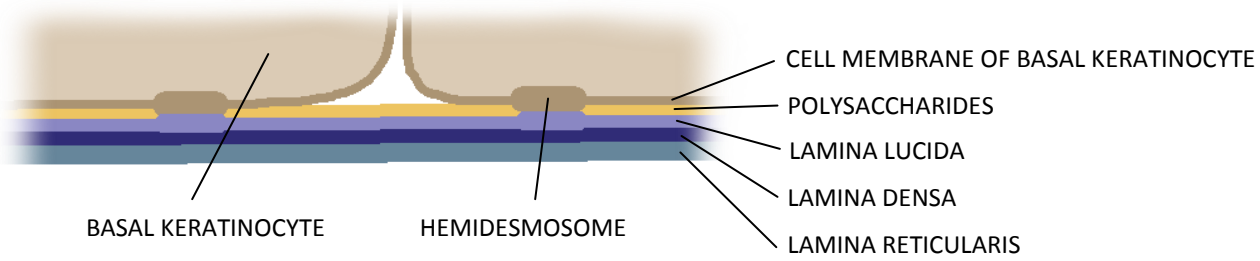
The **lamina lucida** is the uppermost layer of the basement membrane. It appears light (electron-lucent) under the microscope.[132]

The **lamina densa** is the middle layer of the basement membrane. It contains Type IV collagen, which is important in adhering the basal keratinocytes to the basement membrane.[136] It appears dark (electron-dense) under the microscope.[132]

The **lamina reticularis** is the bottommost layer of the basement membrane. It may be referred to as the subbasal lamina and classified separately to the rest of the basement membrane. It contains the attachment proteins and fibres necessary to connect the lamina to the dermis.[132]

Between the lamina lucida and the cell membrane of the basal keratinocyte, there is a 30 nm translucent region of polysaccharides.[181] Hemidesmosomes cause apposing thickenings on the basal keratinocyte membrane and the lamina lucida.[181]

The basement membrane moulds to the shape and contouring of the basal keratinocytes above it.[181] In areas with low density of hair, such as the foot pads, nose, and ears, the basement membrane is more heavily undulated. In areas with high density of hair, such as the back and abdomen, there is limited undulation.[2]



KERATINOCYTES

Keratinocytes are the most important and common cell in the epidermis[84] They are organised into layers, or strata, based on their age. Regeneration occurs at the bottom and cells move upwards as they mature, toward the surface of the epidermis, where they eventually die and slough off as dead skin. These epidermal cell layers were first described in 1785,[105] and the term 'keratinocyte' appears to have been coined in 1956.[1] Keratinocytes are divided into types based on where they are in the layers: *basal keratinocyte* for those in the stratum basale, *spiny keratinocyte* for those in the stratum spinosum, *granular keratinocyte* for those in the stratum granulosum, *transitional keratinocyte* for those in the stratum lucidum, and *corneocyte* for those in the stratum corneum.

The life cycle of the keratinocytes corresponds to their transit time through the layers, from production in the stratum basale to desquamation in the stratum corneum. This can differ between areas, depending on how thick the epidermis in that area is. In the ears, each keratinocyte will move up approximately 0.7 rows per day,[145] giving a transit time of 12 to 14 days.[51][52] In the back, each keratinocyte will move up approximately 1.5 rows per day,[145] giving a transit time of 8 days.[51] The transit time for the flank ranges from 7.3 to 9.7 days, with an average of 6.5 days.[186] The average rate for the whole body is 11 days.[214] Approximately two-thirds of the transit time is the cell moving from the stratum basale to the stratum granulosum. The remaining one-third is movement through the stratum corneum.[145]

The keratinocytes serve four important functions in the epidermis: barrier protection, sun protection, immunity, and vitamin production.

Barrier protection. Keratinocytes comprise up to 95% of the cells of the epidermis,[72] and as such are vital for its general bulk. They serve as a physical barrier between the guinea pig and its environment, ensuring that the insides stay in and the outsides stay out. The keratinocytes in the stratum corneum layer, known as corneocytes, further support this barrier role through the excretion of lipids. The lipids create a water barrier, preventing the passage of liquids or nutrients. This stops the guinea pig from desiccating in dry environments, or absorbing too much water in wet environments.

Sun protection. Corneocytes produce the enzyme thioredoxin reductase, which helps protect the deeper skin from UV radiation.[161][204]

Immunity. Aside from the immunity granted from external pathogens by the barrier protection,[49] keratinocytes can also scavenge up foreign bodies. When injected with a marker compound, keratinocytes develop phagosomes, a type of large vacuole, which then gobble up the marker. If a foreign body enters the dermis, it will be pushed up into the epidermis, where the basal or spiny keratinocytes take it into their phagosomes. As the keratinocyte moves up through the layers, the foreign body remains inside it. The keratinocyte eventually sloughs off as its natural life cycle ends, expelling the foreign item from the body.[237]

Vitamin production. Keratinocytes synthesise vitamin D in response to UVB light.[141]

STRATUM BASALE

The stratum basale is the bottommost layer of the epidermis and consists of a single row of cells.[2] It is also referred to as the *stratum germinativum*, or the *basal layer* or *germinal layer*. The keratinocytes in this layer are called *basal keratinocytes* or, in the context of the epidermis, simply *basal cells*. The average adult guinea pig has around 600 to 800 million basal keratinocytes.[88][187]

The purpose of the stratum basale is production of new keratinocytes. The cells here are able to divide because they are getting an oxygen supply from the underlying dermis. The stratum basale has high levels of DNA synthesis,[58] and around 1% of the basal keratinocytes are reproducing at any one time.[187] At some point after a new cell is produced,[50] it enters the epidermal column above the parent cell and begins its migration up through the epidermal layers.[71] On average, each epidermal column will produce one new cell a day.[52] Reproduction is up to 10-15 times faster on the sides of the epidermal ridges than in the valleys.[23]

Basal keratinocytes have an affinity for attaching to a collagen substrate,[194] which serves two purposes: it helps to keep them anchored, and it regulates reproduction.

Anchorage. Basal keratinocytes are particularly attracted to Type IV collagen, which is the type found in the basement membrane. They will readily adhere to that but not to other types of collagen. They have no interaction with fibronectin, which is the protein responsible for attaching fibroblasts to collagen.[136]

Reproduction. Attachment to a collagen substrate increases the metabolic activity of keratinocytes.[147] Being in contact with the basement membrane is necessary for keratinocytes to reproduce – once detached they stop reproducing.[194] This is what allows daughter cells to move up into the epidermal column and differentiate without reproducing, and parent cells to remain behind and continue reproducing without differentiating.[194]

Basal keratinocytes are 10.5 to 12.5 µm tall[187][215] and 6.0 to 7.0 µm wide.[187] They typically have rounded edges[147] and are elongated along the vertical axis.[2][41][182] Sometimes they will have indentations in the surface of the cell, above where the nucleus is.[120] Outside of this indentation, the cell surface is smooth.[120] Unlike in humans, guinea pigs have little to no undulating on the bottom of the cell, and no projections into the dermis.[184]

Whole composition

Protein. Along with the stratum spinosum, the stratum basale is richer in methionine and poorer in histidine than the stratum granulosum.[69] Cysteine has been found in this layer,[191] along with *stem cell factor (SCF)*, a protein which stimulates the proliferation of melanocytes and their production of melanin.[84]

Lipids. Skin lipogenesis occurs in the sebaceous glands (sebocytes) and the stratum basale and stratum spinosum (keratinocytes). These are chemically different.[230] Although not studied in guinea pigs, in mammals in general, the skin keratinocyte lipogenesis is responsible for 6% of the body's total sterol production.[166] The skin is able to select which amino acids it needs to use for the synthesis of specific lipids.[230] Free lipid droplets take up 0.01% of the cytoplasm.[3]

Carbohydrates. Basal keratinocytes test positive with periodic acid-Schiff staining (the PAS reaction), which indicates the presence of polysaccharides.[2]

Minerals comprise 1.7[113] to 2.1%[227] of the stratum basale by wet weight. The quantities of each mineral differ somewhat between papers.

Sodium comprises 0.12[113] to 0.26%[227] of the stratum basale by wet weight. Quantities of 54.11[113] and 111.43[227] µmoles per gram are reported.

Magnesium comprises 0.01[113] to 0.04%[227] of the stratum basale by wet weight. Quantities of 4.63[113] and 15.66[227] µmoles per gram are reported.

Phosphorus comprises 0.48[113] to 0.63%[227] of the stratum basale by wet weight. Quantities of 152.37[113] and 204.70 [227] µmoles per gram are reported.

Sulphur comprises 0.10[227] to 0.30%[113] of the stratum basale by wet weight. Quantities of 31.68[227] and 93.27[113] µmoles per gram are reported.

Chlorine comprises 0.18[113] to 0.26%[227] of the stratum basale by wet weight. Quantities of 51.62[113] and 73.34[227] µmoles per gram are reported.

Potassium comprises 0.61[113] to 0.83%[227] of the stratum basale by wet weight. Quantities of 155.22[113] and 212.89 [227] µmoles per gram are reported.

Calcium comprises 0.01[227] to 0.03%[113] of the stratum basale by wet weight. Quantities of 2.85[113] and 7.83[227] µmoles per gram are reported.

Cell physiology

The volume of a basal keratinocyte consists of 32% nucleus, 36% organelles, and 31% cytosol.[3] They have a dark (electron-dense) cytosol.[63]

The outside of the **cell membrane,** particularly on and near the desmosomes,[237] is coated in *glycocalyx.*[35][239] The glycocalyx of neighbouring keratinocytes fuse and form a cementing substance to bridge the intercellular gap between them.[239] Cell membrane Na^+/K^+-ATPase enzymatic activity is highest in the basal keratinocytes; it has a relative activity of 1.9, compared to 1.3 in spiny keratinocytes and 1.1 in granular keratinocytes.[213]

The **nucleus** is large,[147] taking up 32% of the volume of the cell.[3] It ranges from 7.8 to 8.6 µm long and 5.6 to 6.8 µm wide, with an average of 8.5 µm and 5.6 µm, respectively.[187] It is relatively dark in colour,[17] and is mostly euchromatic, with some heterochromatin around the periphery.[63] It has an irregular oval shape,[63][120][181][182][215] often with one or more indentations.[63][182] Two membranes make up the *nuclear envelope*.[181][182] The inner membrane is 30 nm thick, and the outer membrane is thinner, but with no specified width reported.[181][182] There is a 20 nm gap between the inner and outer membrane.[181] The *nucleolus* is found within the heterochromatin.[182] There may be up to eight nucleoli in a nucleus,[120] though just one is most common. The nucleoli can vary in size and depth.[120]

There is both rough and smooth **endoplasmic reticulum**.[147][243] They are formed by several clear vesicles of varying shapes and sizes.[181] Cisternae are only found in the cytoplasm unoccupied by tonofilaments.[243] They show enzyme activity for acid phosphatase, aryl sulphatase B, inosine diphosphatase, thiamine pyrophosphatase, and glucose-6-phosphtase.[243] The *rough endoplasmic reticulum* serves an important role in the synthesis of protein and phospholipids, and the storage and transport of proteins.[243] It is elongated in shape and the most dominant type of endoplasmic reticulum in the cytoplasm.[243] It takes up approximately 0.8% of the volume of the cell.[3] The *smooth endoplasmic reticulum* serves an important role in the synthesis of steroids, the metabolism of polysaccharides, and the transport of enzymes.[243] It is comprised of tubular or vesicular cisternae, which are particularly rich in enzymatic activity.[243] Sometimes the smooth endoplasmic reticulum will be missing.[243]

There is a developed **Golgi complex**.[181][182][243] It is located near the distal side of the nucleus.[181][243] Some cells have more than one complex, in which case they may be next to each other or on the opposite side of the nucleus.[243] They are formed by a dense accumulation of vesicles;[243] usually several large saucer-shaped vesicles surrounded by smaller smooth vesicles.[181][182] The cisternae are small[110] and stacked.[243] The Golgi complex(es) take up approximately 0.8% of the volume of the cell.[3] There are no ribosomes attached to them. The cisternae show enzymatic activity, particularly in the curved cisternae, for thiamine pyrophosphatase, inosine diphosphatase, and nucleosidetriphosphatase.[243] The membranes show mild enzymatic activity for aryl sulphatase B and glucose-6-phosphatase.[243]

There may be many **ribosomes** attached to the outside of the endoplasmic reticulum,[181] attached to the outside of vesicles,[182] and scattered about the rest of the cytoplasm.[181][182] Free ribosomes are abundant,[63] and take up as much as 16.6% of the volume of the cell.[3] They are usually found in less dense areas of the cytoplasm, away from the hubbub of the middle of the cell.[147]

There are many **mitochondria**,[63][181][182] taking up around 5.5% of the volume of the cell.[3] They are found both singly and in small clusters,[181][182] with the clusters typically situated near the longitudinal ends of the nucleus.[147] They are spherical to oval in shape.[182] Their length ranges from 0.2 to 0.8 µm, with an average of around 0.4 µm.[182] They have an inner and outer membrane.[181] The inner membrane is folded in on itself to form the cristae.[181]

There are many **tonofilaments**,[63][71][181][182] both singly and in bundles,[181][182] scattered throughout the cytoplasm.[182] Often they will congregate near or even attach to the inner membrane of the desmosomes,[147][181][182] and are found more sparsely around the nucleus.[215] They are poorly stained, and are much lighter than those in the spiny keratinocytes.[41] They take up around 11.8% of the volume of the cell.[3]

There are a few clear **lysosomes** which vary in size and shape.[182][243] They appear when they bud off from the Golgi complex to function as a carrier for enzymes.[243] These enzymes are produced by the rough endoplasmic reticulum[110] to break down proteins[237] and debris.[110] This enzymatic activity includes acid hydrolases, such as acid phosphatase,[110] aryl sulphatase B, indoxyl esterase, and thioacetic acid esterase.[243] They have a single membrane[243] which often has many ribosomes attached to the outside of it.[182] They are found mainly around the periphery,[147] and comprise up to 0.3% of the volume of the cell.[3]

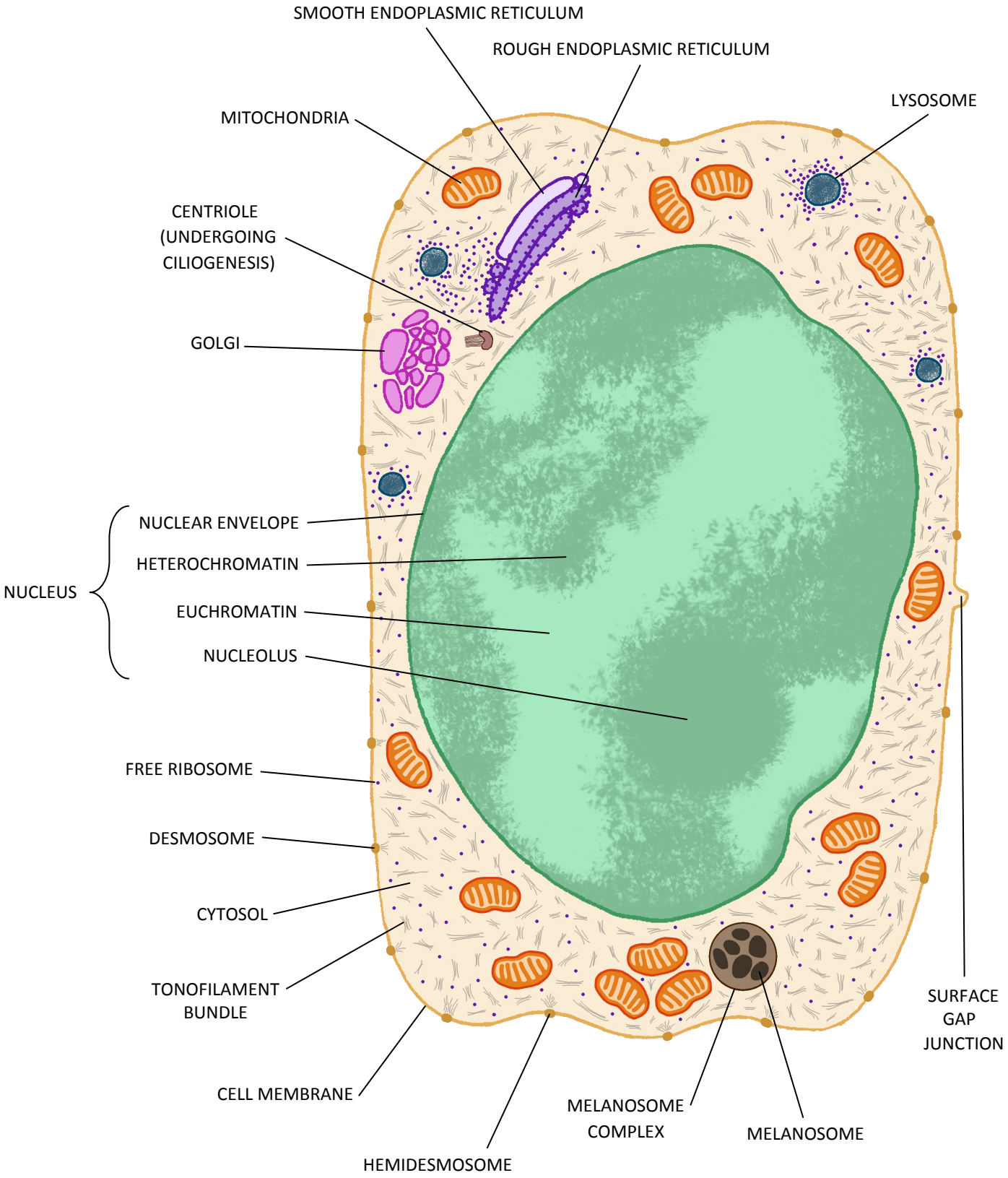
There may be other non-lysosome **vesicles**, which comprise another 0.2% of the volume of the cell.[3]

A **centriole** may be found near the Golgi complex, usually between the complex and the nucleus. There will commonly be ribosomes, endoplasmic reticulum, and/or mitochondria, but rarely tonofilaments, between the centriole and the nucleus. On rare occasions there may be two centrioles within a cell.[65] Centrioles are 210 to 230 nm in diameter and may be undergoing *ciliogenesis*. They are comprised of 27 microtubules, in nine lots of three, called *triplets*. These triplets are embedded in a darker matrix with a lighter centre. In the centre there are small protrusions known as *dense feet*.[65]

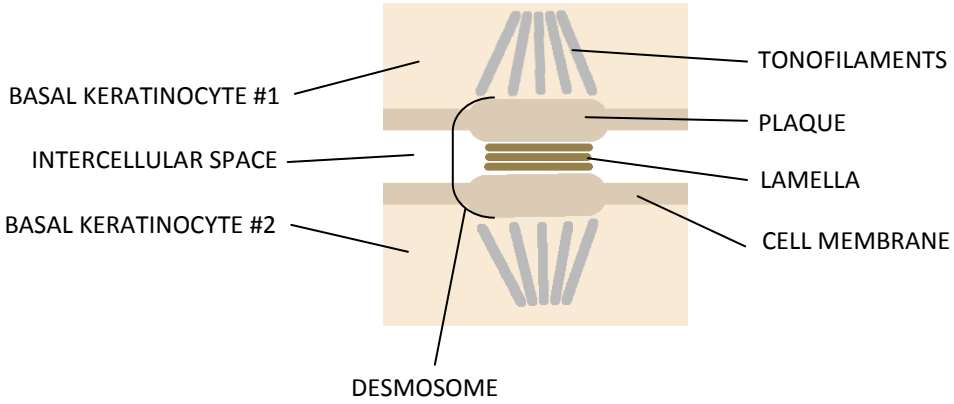
Melanosome transfer normally occurs in the stratum spinosum, though occasionally a **melanosome complex** will transfer to a basal keratinocyte. When this happens, the complex may be found anywhere in the cytoplasm and ranges from 0.25 to 1.0 µm in diameter.[181][182]

Gap junctions, also referred to as nexuses (singular nexus), may be found in small amounts. They are relatively uncommon, however, and are more likely to appear in the spiny keratinocytes.[5]

BASAL KERATINOCYTE



Periodically along the cell membrane there are round or oval thickenings, known as *plaques*.[181][182][184] Plaques are 70 to 85 nm long[181][184] and around 25 nm thick.[184] A plaque will appose the corresponding plaque of a neighbouring cell. Between the plaques is a 35 nm zone with three dark 5 nm-thick lamellae.[181][184] Together the two plaques and three lamellae are called a **desmosome**, which is responsible for attaching the two cells to each other.[71][184] Desmosomes are often accompanied by a tonofilament bundle. The filaments will fan out as they approach the plaque, probably to serve an anchoring role.[184]



Hemidesmosomes are desmosomes that attach the basal keratinocyte to the basement membrane instead of a neighbouring cell.[42][63][182] In these, the plaque of the basal keratinocyte apposes a thickening of the basement membrane. The zone between the thickenings is 30 nm thick, and contains only one 5 nm-thick lamella instead of three.[184]

β_2 adrenergic receptors have not been studied in guinea pig keratinocytes. However, they serve an important role in the keratinocyte life cycle and thus will be discussed here using knowledge from other mammals. They regulate the calcium concentration inside the cell via voltage-gated calcium channels.[175] Because increased calcium levels trigger keratin expression,[74] mineralisation, and hardening,[225] these channels are important for cornification. The receptors increase the calcium concentration inside the keratinocyte as it moves from the stratum basale to the stratum corneum.[175] The receptors are also useful for regulating keratinocyte migration during wound healing. Lower calcium levels increase proliferation of new keratinocytes, whereas higher calcium levels decrease proliferation.[175]

The stratum spinosum is divided into two sublayers: the *lower* stratum spinosum and the *upper* stratum spinosum. It is also referred to as the *spiny layer*, the *spinous layer*, the *prickle layer*, or the *suprabasal layer*.[34][35] The stratum basale and stratum spinosum may be grouped into a single layer called the *Malpighian layer*. The keratinocytes in this layer are called *spiny keratinocytes* or, in the context of the epidermis, simply *spiny cells*. They are named due to their appearance under the microscope; during preparation they lose water and appear shriveled, but because they are still attached to each other via the desmosomes, they take on a star-like[225] or spiny appearance.

The stratum spinosum is the most variable layer when it comes to thickness. In most areas of thin skin it is three rows thick, and in most areas of thick skin it is around eight rows thick.[2] However, it can be as thin as two rows in the chest and abdomen,[2][25][183] and as thick as ten rows in the ridges of the ear.[27] In thick skin, the lower stratum spinosum keratinocytes rise vertically and form columns. Upon entering the upper stratum spinosum, they start to rise diagonally and form a brick-style pattern.[43]

Lower spiny keratinocytes are 12.5 µm in diameter or less, whereas upper spiny keratinocytes are 12.5 to 15 µm.[215] They are less elongated than basal keratinocytes, and become somewhat cubic by the upper stratum spinosum.[43] Cells that had an indentation in the surface, above where the nucleus is, retain this indentation after moving into this layer.[120] The cell surface develops more undulations moving into this layer, possibly to help keep the cells lock into place with their neighbours.[181]

Whole composition

Protein. Along with the stratum basale, the stratum spinosum is richer in methionine and poorer in histidine than the stratum granulosum.[69]

Lipids. Skin lipogenesis occurs in the sebaceous glands (sebocytes) and the stratum basale and stratum spinosum (keratinocytes). These are chemically different.[230] Although not studied in guinea pigs, in mammals in general, the skin keratinocyte lipogenesis is responsible for 6% of the body's total sterol production.[166] The skin is able to select which amino acids it needs to use for the synthesis of specific lipids.[230] Free lipid droplets take up 0.01% of the cytoplasm, as in the stratum basale.[3]

Minerals comprise 1.7[113] to 2.0%[227] of the stratum spinosum by wet weight. The quantities reported for each mineral differ between papers.

Sodium comprises 0.13[113] to 0.31%[227] of the stratum spinosum by wet weight. Quantities of 54.47[113] and 133.14 [227] µmoles per gram are reported.

Magnesium comprises 0.02[113] to 0.06%[227] of the stratum spinosum by wet weight. Quantities of 6.76[113] and 23.50 [227] µmoles per gram are reported.

Phosphorus comprises 0.47[113] to 0.49%[227] of the stratum spinosum by wet weight. Quantities of 152.37[113] and 158.78[227] µmoles per gram are reported.

Sulphur comprises 0.09[227] to 0.31%[113] of the stratum spinosum by wet weight. Quantities of 27.06[227] and 95.76 [113] µmoles per gram are reported.

Chlorine comprises 0.19[113] to 0.27%[227] of the stratum spinosum by wet weight. Quantities of 52.33[113] and 75.12 [227] µmoles per gram are reported.

Potassium comprises 0.57[113] to 0.78%[227] of the stratum spinosum by wet weight. Quantities of 145.25[113] and 199.35[227] µmoles per gram are reported.

Calcium comprises 0.01[113] to 0.04%[227] of the stratum spinosum by wet weight. Quantities of 3.20[113] and 9.61[227] µmoles per gram are reported.

Cell physiology

The volume of a spiny keratinocyte consists of 12% nucleus, 49% organelles, and 39% cytosol.[3]

As in the basal keratinocytes, the outside of the **cell membrane**, particularly on and near the desmosomes,[237] is coated in *glycocalyx*.[35][239] In the lower stratum spinosum there is not much change in cell membrane Na^+/K^+-ATPase enzymatic activity from the stratum basale.[213] In the upper stratum spinosum, cholesterol from the lamellar bodies reduces the fluidity of the membrane, in turn decreasing the Na^+/K^+-ATPase activity.[213] It has a relative activity of 1.3, compared to 1.9 in basal keratinocytes and 1.1 in granular keratinocytes.[213]

The **nucleus** decreases in size, taking up 12% of the volume of the cell.[3] It ranges from 5.5 to 7.0 µm long and 4.5 to 5.0 µm wide.[63] It is mostly euchromatic, with some heterochromatin around the periphery.[63] It may retain the irregular oval shape,[2][63] or look more kidney-shaped,[215] often with one or more indentations of variable size.[63] The *nucleolus* is around 1 µm in diameter.[63]

There is both rough and smooth **endoplasmic reticulum**.[243] Cisternae are only found in the cytoplasm unoccupied by tonofilaments.[243] They show enzyme activity for acid phosphatase, aryl sulphatase B, inosine diphosphatase, thiamine pyrophosphatase, and glucose-6-phosphatase.[243] The *rough endoplasmic reticulum* is elongated in shape and the most dominant type of endoplasmic reticulum in the cytoplasm.[243] It reduces in size to approximately 0.3% of the volume of the cell.[3] It is more developed in the upper spiny keratinocytes than the lower spiny keratinocytes.[243] The *smooth endoplasmic reticulum* has tubular or vesicular cisternae, which are particularly rich in enzymatic activity.[243]

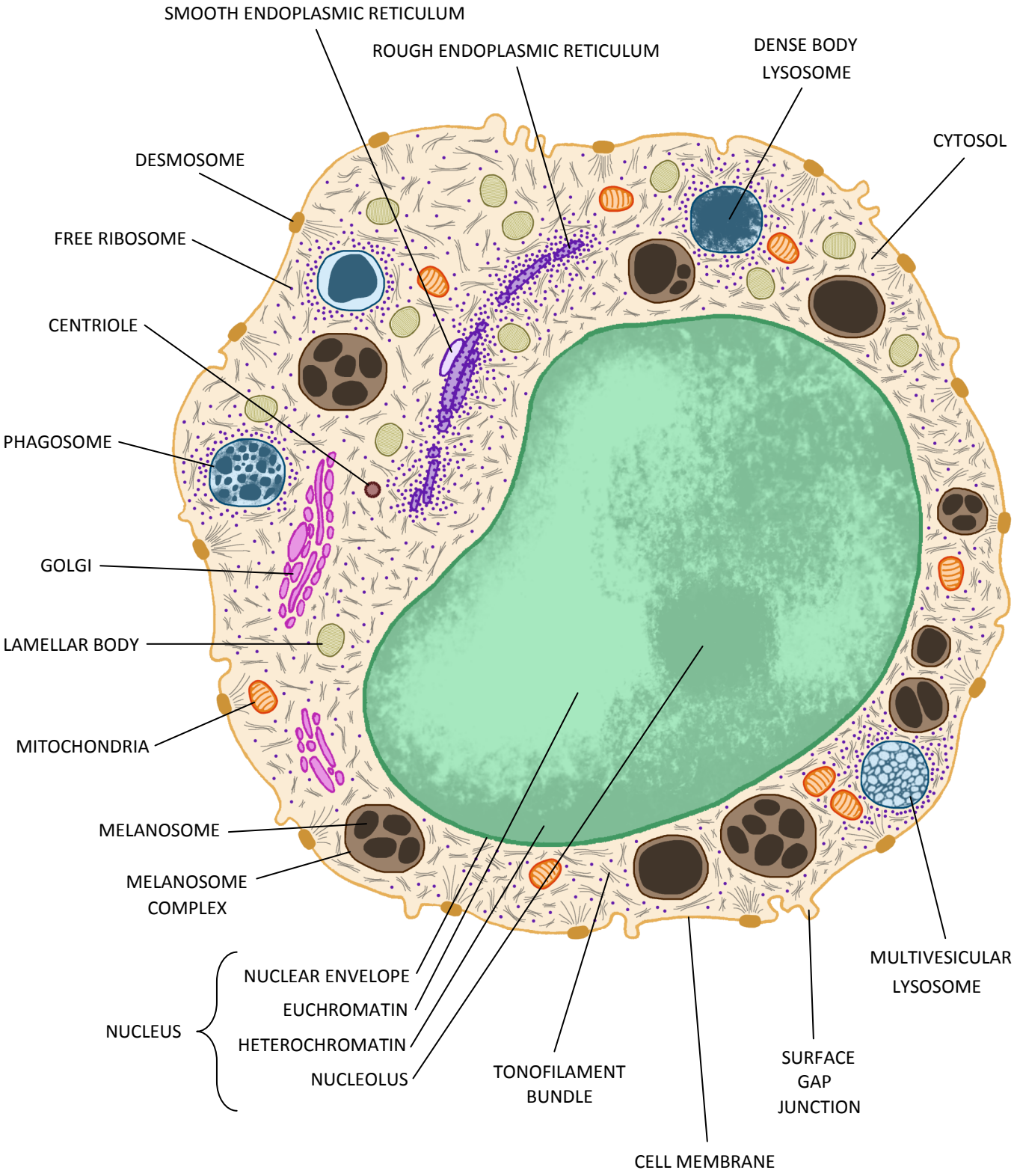
There are one or more developed **Golgi complex**(es), though the vesicles reduce in size and quantity,[243] to approximately 0.2% of the volume of the cell.[3] The cisternae are still small[110] and stacked.[243] The cisternae show the same enzymatic activity as in the stratum basale,[243] though there is less nucleoside triphosphatase,[243] and the upper spiny keratinocytes also produce acid phosphatase.[110][243] The membranes retain mild enzymatic activity for aryl sulphatase B and glucose-6-phosphatase.[243]

There are many free **ribosomes**,[181] though less than in the stratum basale. They take up approximately 9.3% of the volume of the cell.[3]

There are half as many **mitochondria**,[181] taking up around 2.2% of the volume of the cell.[3] They may be spherical to oval in shape,[181] or have a tapered appearance.[243]

The **tonofilaments** are easier to see[71] and stain much darker[41] than those from the stratum basale. More filaments are rapidly synthesized,[93][225] increasing their volume in the cell to 32.1%.[3] Single filaments cluster together into bundles,[181] with the bundles being larger than in the stratum basale[184] and forming a reticulated pattern through the cytoplasm.[40] They condense in large amounts near the desmosomes,[63] probably to support them and help them stabilise the cells against the stresses imposed on the epidermis.[181] Bundles may be as long as 1.0 to 2.0 µm.[181]

LOWER SPINY KERATINOCYTE



The **lysosomes** vary in size and shape.[243] They consist mainly of the *dense body* or *multivesicular* types.[243] Enzymatic activity is largely the same as it was in the stratum basale.[243] The number of lysosomes reduces to 0.1% of the volume of the cell.[238] They are important for phagocytosis: after injecting foreign particles into guinea pig skin, the particles end up in phagocytic lysosomes (called *phagosomes*). A phagosome may take in a single large particle, up to 0.8 µm in diameter, or multiple small particles.[110] They are also important for cellular recycling: large molecules move into the lysosome and are unable to leave.[110] The lysosome breaks the molecules down into smaller parts, which then leave and get used by the cell in other processes.[110][243] Lysosomes may interact with melanosome complexes.[110]

Non-lysosome **vesicles** reduce in number, comprising no more than 0.1% of the volume of the cell.[3]

The **centriole** may be undergoing *ciliogenesis*, though less commonly than in the stratum basale. In lower spiny keratinocytes, it's position near the Golgi complex is largely unchanged from the stratum basale. In upper spiny keratinocytes it loses it's specific positioning and may be found elsewhere in the cell. A region of 60 to 80 nm around the centriole is free of ribosomes.[65]

Lamellar bodies, also called Odland bodies,[237][243] membrane-coating granules (MCG),[39][215] or keratinosomes,[39] are produced,[3][39][71] to take up approximately 0.5% of the volume of the cell.[3] They are typically round or oval,[36][243] though may uncommonly be dumb-bell shaped.[243] They vary from 0.1 to 0.7 µm long[243] and 0.1 to 0.5 µm wide,[36] though are more typically around 0.2 µm in diameter.[36][93] They are rich in lipids, such as glycosphingolipids and cholesterols,[93] and enzymes,[93] including acid phosphatase and small amounts of iosine diphosphatase and thiamine pyrophosphatase.[243] They are found near the nucleus, Golgi complex, and smooth endoplasmic reticulum,[243] typically concentrated on the upper side of the cell.[151] The bodies contain flattened parallel lamellae,[94] with many 8 nm-thick[36][243]alternating dark (electron-dense) and light (electron-lucent) rows.[243] In the lower spiny keratinocytes, the membrane of the bodies have three layers.[243] In the upper spiny keratinocytes, one or more of these membranes may become fainter or seem to disappear.[36] The bodies become larger and more plentiful as the keratinocyte moves up the spiny rows,[243] and by the upper stratum spinosum are very noticeable in quantity.[36]

There may be trace **keratinohyalin granules**, though these don't typically occur until the stratum granulosum. If they do occur they comprise no more than 0.04% of the volume of the cell.[3]

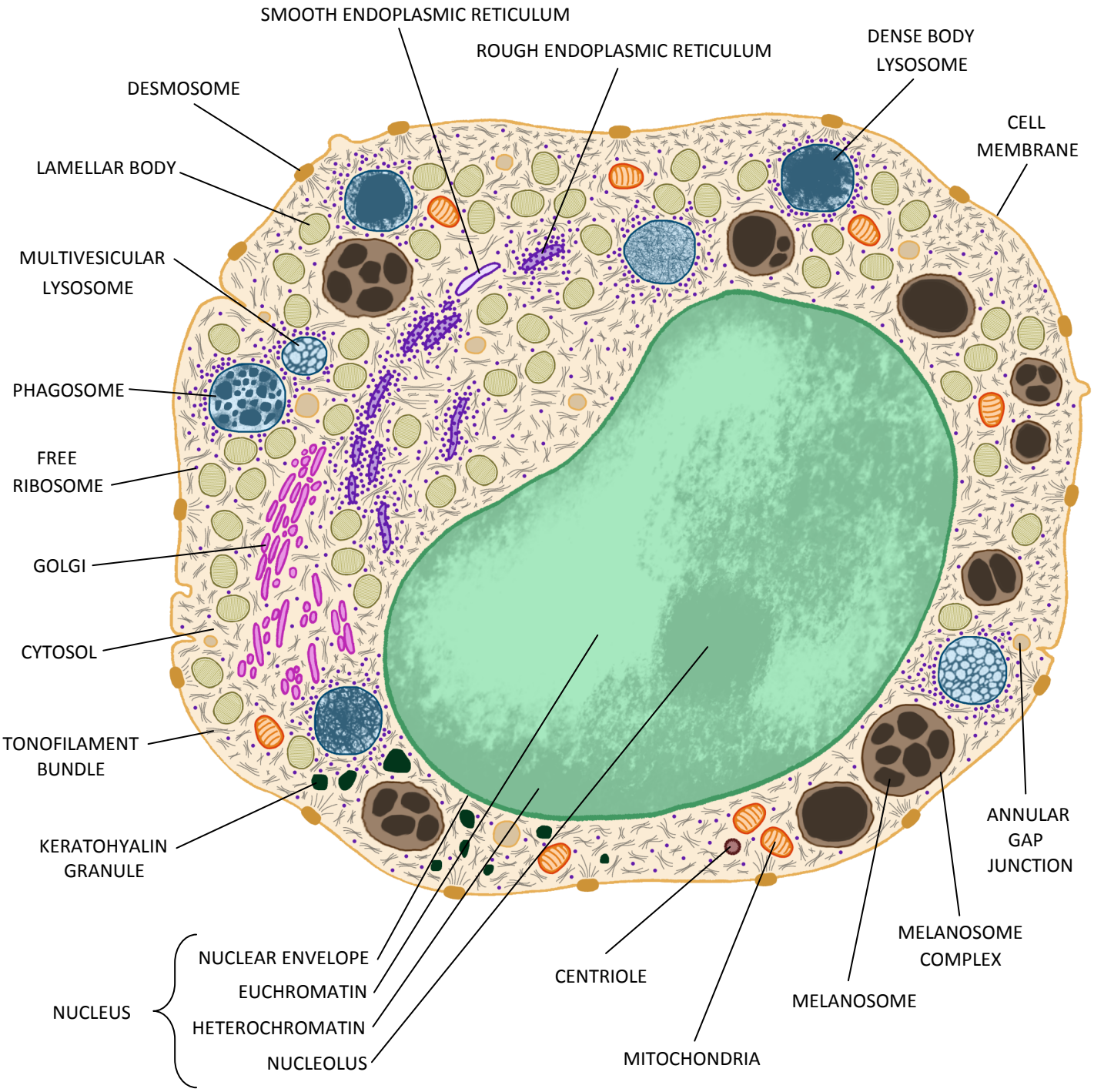
Melanosome transfer primarily occurs in the bottom row of the stratum spinosum,[236] so lower spiny keratinocytes accept many **melanosome complex**es. A keratinocyte ends up with 10 to 34 *melanosomes* (average 14 to 25) bound within the complexes.[80] Complexes tend to be concentrated near the surface of the keratinocyte.[27][185]

Gap junctions are areas where the membranes of adjacent cells come together, narrowing the intercellular space in the process to only 5 nm. They are important for electrochemical communication, allowing transfer of signaling and regulatory substances, such as ions, between the cells.[5] There are two types of gap junctions found in guinea pig keratinocytes: *annular* and *surface*.

Surface gap junctions, also called abutment nexuses, are the most prevalent type in the lower spiny keratinocytes. They form 'loops' and 'bulges' that invaginate into adjacent cells, particularly near the desmosomes. These invaginations are larger and more extensive in the epidermis than in the oral epithelia.[5]

Annular gap junctions are the most prevalent type in the upper spiny keratinocytes. They occur after an invagination pinches off and moves inwards, forming an intracytoplasmic inclusion. They are circular in shape and around 0.4 µm in diameter. They have an irregular osmiophilic membrane, with a different density inside compared to the surrounding cytosol. They often entrap organelles, particularly lamellar bodies, though will sometimes contain pieces of rough endoplasmic reticulum, ribosomes, glycogen, or rarely, a single whole mitochondrion.[5]

UPPER SPINY KERATINOCYTE



Desmosomes become easier to see[71] and provide a stronger attachment between neighbouring cells. There may be up to fifty desmosomes on a spiny keratinocyte,[181] each one extending around 0.2 µm into the cells[63][40][181][184] and covering an area of membrane 0.5 to 0.9 µm long.[184] They have no enzyme activity[243] but likely contain phospholipids.[181] The tonofilament bundles attached to the **desmosomes** are larger than those in the stratum basale.[184] In upper spiny keratinocytes, the desmosomes have clusters of 10 to 15 ferritin particles.[216]

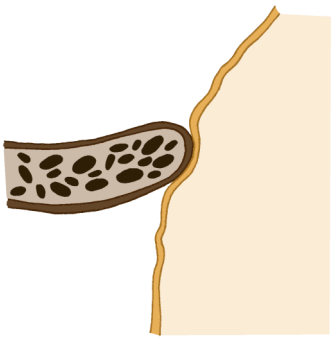
Spiny keratinocytes do not have **hemidesmosomes**.

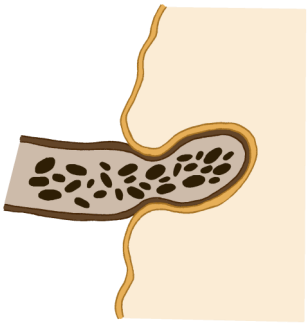
Melanosome transfer

The darkness of a guinea pig's skin pigmentation is based on the number of melanosomes that are transferred from the melanocytes to the basal[80] and spiny keratinocytes.[141] Juvenile guinea pigs have slightly less melanosome transfer than adult guinea pigs,[185] which is likely why pigmentation deepens as the animal gets older, particularly in acromelanic albinos. Certain parts of the body also have more or less melanosome transfer; for example, ear keratinocytes have more transferred melanosomes than back keratinocytes.[224] There are four primary stages of melanosome transfer.[104]

Stage 1. Dendrite introduction.

The melanocyte is sedentary in the epidermis, but its dendrites may move around and extend or retract. It is through the dendrites that it makes contact with the keratinocytes. Sometimes the dendrite will touch a keratinocyte and withdraw; sometimes the dendrite will touch a keratinocyte and donate melanosomes.[148] When donating melanosomes, the membrane of the keratinocyte where it touches the dendrite becomes 'ruffled.'[104]



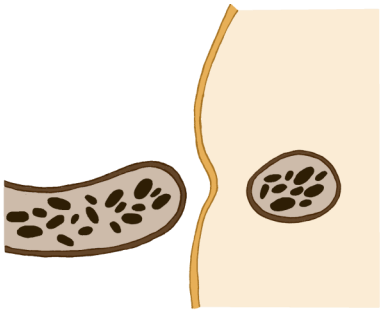


Stage 2. Apocopation.

The dendrite typically contains 20 to 100 melanosomes. The tip of it becomes embedded in the cytoplasm of the keratinocyte, and the keratinocyte slowly pinches off the end of the dendrite,[104] a process known as cytophagy.[146] The cell membrane of both cells remains intact.[104] In humans, a receptor called *protease-activated receptor 2* (PAR-2) is responsible for triggering this pinch-off; the greater the expression of the protein, the more pinch-offs that occur and melanosomes that are transferred, and the darker-skinned the individual.[141] Although this has not been studied specifically in guinea pigs, a similar protein and process is likely.

Stage 3. Dendrite withdrawal

As the keratinocyte pinches off the dendrite, a package containing the membrane and cytoplasm of the dendrite is transferred into the keratinocyte.[236] The dendrite then withdraws from the keratinocyte.[104]



This package is known as a *melanosome complex*, and is actually a type of phagosome,[238] which in turn is a type of secondary lysosome.[243] Larger melanosomes of 0.8 to 1.3 µm may have a complex all to themselves, whereas

smaller melanosomes of 0.1 to 0.5 µm will be transferred together in a complex.[236] A typical keratinocyte will end up with 10 to 34 melanosomes,[80] with at least half of those melanosomes bound within complexes that have 3 to 7 melanosomes in them.[238] While in the stratum spinosum, complexes tend to be more concentrated on the surface side of the keratinocyte,[27][185] near the nucleus.[104][155][236]

Complexes have enzymatic activity for acid phosphatase, aryl sulphatase, and rarely acid hydrolase.[243] The acid phosphatase is likely obtained from the lysosomes they fuse with.[238]

Interactions between lysosomes and melanosome complexes are frequent, and they will often fuse inside the keratinocyte to form melanosome-lysosome complexes.[236] Whether melanosome complexes interact with each other has been reported in two studies, with contradicting results. One reports that interactions between complexes are rare,[236] whereas the other reports that they often fuse together to form larger complexes.[238]

The ratio and distribution of small to large melanosomes in the keratinocyte forms the *pigment pattern*.[236] This pigment pattern contributes to the end colouration of the guinea pig's skin. For example, black guinea pigs have more single large eumelanosomes,[236][238] whereas brown guinea pigs have more small eumelanosome complexes.[236] Black-skinned guinea pigs also produce more melanosomes,[238] and have a higher number of intact eumelanosomes and melanosome complexes remaining in the stratum corneum.[236]

Stage 4. Melanin package digestion.

When the keratinocyte enters the stratum granulosum,[236][238] typically between 24 and 48 hours later, the acid phosphatase activity inside the complex increases.[91] Whether the membrane degrades and the melanosomes disperse conflicts between studies, and is quite possibly a result of different pigment patterns.

When the membrane degrades, such as in lighter-skinned guinea pigs (e.g. brown skin) the melanosomes disperse around the cytoplasm.[104] These loose melanosomes are often called *melanin granules*.

When the membrane remains intact,[236][238] such as in darker-skinned guinea pigs (e.g. black skin) the melanosomes are broken down into smaller particles, commonly referred to as *melanin dust* or *melanosome dust*.[238] This breakdown usually takes around 5 days from the time of transfer.[236] The intact complexes, full of melanin dust, remain until the stratum corneum, where they flatten along with the corneocytes.[83]

STRATUM GRANULOSUM

The stratum granulosum is divided into two sublayers: the *lower* stratum granulosum and the *upper* stratum granulosum. It is also referred to as the *granular layer*.[2] The keratinocytes in this layer are called *granular keratinocytes* or, in the context of the epidermis, simply *granular cells*. They are named due to the appearance of the keratohyalin granules, which give the cell a particularly grainy appearance under the microscope.[225]

Although there is still some metabolic activity in the cells,[71] the stratum granulosum is where the cells begin to die due to no longer receiving an oxygen supply. This begins the process of rapid keratinisation.[66]

This layer is less variable in thickness and has less rows compared to the stratum spinosum. At its thinnest points, on the back, it is only one row thick.[188] At its thickest point, on the nose, it can be up to four rows thick.[2] The stratum granulosum forms a brick-style pattern of arrangement.[66] Unlike the upper stratum spinosum, where the cells are layered straight, the angle of the cells here are more diagonal when sitting on top of each other.[43]

Granular keratinocytes are 15 µm or greater in length,[215] and flatten out more as they move up the rows.[181] They are somewhat convex-shaped, and elongated on the horizontal axis.[66] The cell surface, particularly where the cell borders the stratum corneum, becomes more undulated, with each undulation around 0.4 µm in height.[40]

Whole composition

Protein. The stratum granulosum is poorer in methionine and richer in histidine than previous layers.[69] Up to 40% of the histidine in the epidermis is found as profilaggrin in the keratinohyalin granules of this layer.[81] Corneodesmosin is found in the cytoplasm of the lower stratum granulosum, but moves outside the cell membrane in the upper stratum granulosum.[134] Bound cysteine has been found in this layer.[191]

Lipids. Free lipid droplets increase in size and/or quantity, now comprising up to 0.3% of the volume of the cell.[3]

Carbohydrates. Little to no glycogen is found.[66]

Minerals comprise 1.2% of the stratum granulosum by wet weight.[227]

Sodium comprises 0.13% of the stratum granulosum by wet weight. A quantity of 56.96 µmoles per gram is reported.[227]

Magnesium comprises 0.05% of the stratum granulosum by wet weight. A quantity of 19.58 µmoles per gram is reported.[227] It is richer in magnesium than in previous layers.[109]

Phosphorus comprises 0.21% of the stratum granulosum by wet weight. A quantity of 66.22 µmoles per gram is reported.[227]

Sulphur comprises 0.15% of the stratum granulosum by wet weight. A quantity of 47.70 µmoles per gram is reported.[227]

Chlorine comprises 0.28% of the stratum granulosum by wet weight. A quantity of 79.39 µmoles per gram is reported.[227]

Potassium comprises 0.30% of the stratum granulosum by wet weight. A quantity of 77.25 µmoles per gram is reported.[227]

Calcium comprises 0.03% of the stratum granulosum by wet weight. A quantity of 8.19 µmoles per gram is reported.[227] It is richer in calcium than in previous layers.[45][109]

Iron content is small or absent in the stratum granulosum.[109]

Cell physiology

The volume of a granular keratinocyte consists of 3% nucleus, 60% organelles, and 37% cytosol.[3] The cytoplasm is lighter than in the upper spiny keratinocytes.[40] In this layer the organelles begin to break down and be destroyed.

The **cell membrane** thickens.[54][71] As in basal and spiny keratinocytes, the outside of the membrane, particularly on and near the desmosomes, is coated in *glycocalyx*.[35][239] Cholesterol from the lamellar bodies continues to reduce the fluidity of the membrane and decrease the Na^+/K^+-ATPase activity.[213] It has a relative activity of 1.1, compared to 1.9 in basal keratinocytes and 1.3 in spiny keratinocytes.[213]

The **nucleus** decreases in size, taking up 3% of the volume of the cell.[3] It is around 6.3 µm long and 3.5 µm wide, with multiple mild indentations.[63] There is more heterochromatin,[63] and the DNA has started to degrade and disappears along with the nucleus during the transition to the stratum corneum.[71] It elongates and flattens along with the cel.[71] The outer membrane of the *nuclear envelope* is partially destroyed,[71][181] and the inner membrane has started to degrade.[181] The *nucleolus* is circular, speckled in appearance, and around 0.8 to 0.9 µm in diameter.[63]

There is both rough and smooth **endoplasmic reticulum,**[243] though they have much fewer cisternae.[181] Cisternae are only found in the cytoplasm unoccupied by tonofilaments or keratohyalin.[243] They still show enzyme activity for acid phosphatase, aryl sulphatase B, inosine diphosphatase, thiamine pyrophosphatase, and glucose-6-phosphatase.[243] The *rough endoplasmic reticulum* is elongated in shape.[243] It takes up approximately 0.4% of the volume of the cell.[3] The *smooth endoplasmic reticulum* has tubular or vesicular cisternae, which are particularly rich in enzymatic activity.[243] Smooth cisternae may increase in size or quantity, and/or branch out, although they are still less numerous than in other non-epidermal cells.[243] As the keratinocyte moves up the rows of the stratum granulosum, both smooth and rough cisternae elongate, break up, and scatter about the cytoplasm.[243] By the upper stratum granulosum they have started to diminish, along with the degradation of other organelles.[243]

The **Golgi complex**(es) flatten along with the cell, and the size and quantity of the vesicles reduce,[243] to approximately 0.1% of the volume of the cell.[3] In the lower stratum granulosum, the cisternae have enzymatic activity for acid phosphatase, specifically Na-β-glycerophosphatase.[243] Unlike the lower granular keratinocytes in follicular epidermis, the cisternae in interfollicular epidermis do not show any indoxyl esterase activity.[243] In the upper stratum granulosum there is less or no more enzymatic activity,[243] and the vesicles scatter around the cytoplasm to form multiple small Golgi areas.[243]

There are still many free **ribosomes**, which take up approximately 9.2% of the volume of the cell.[3]

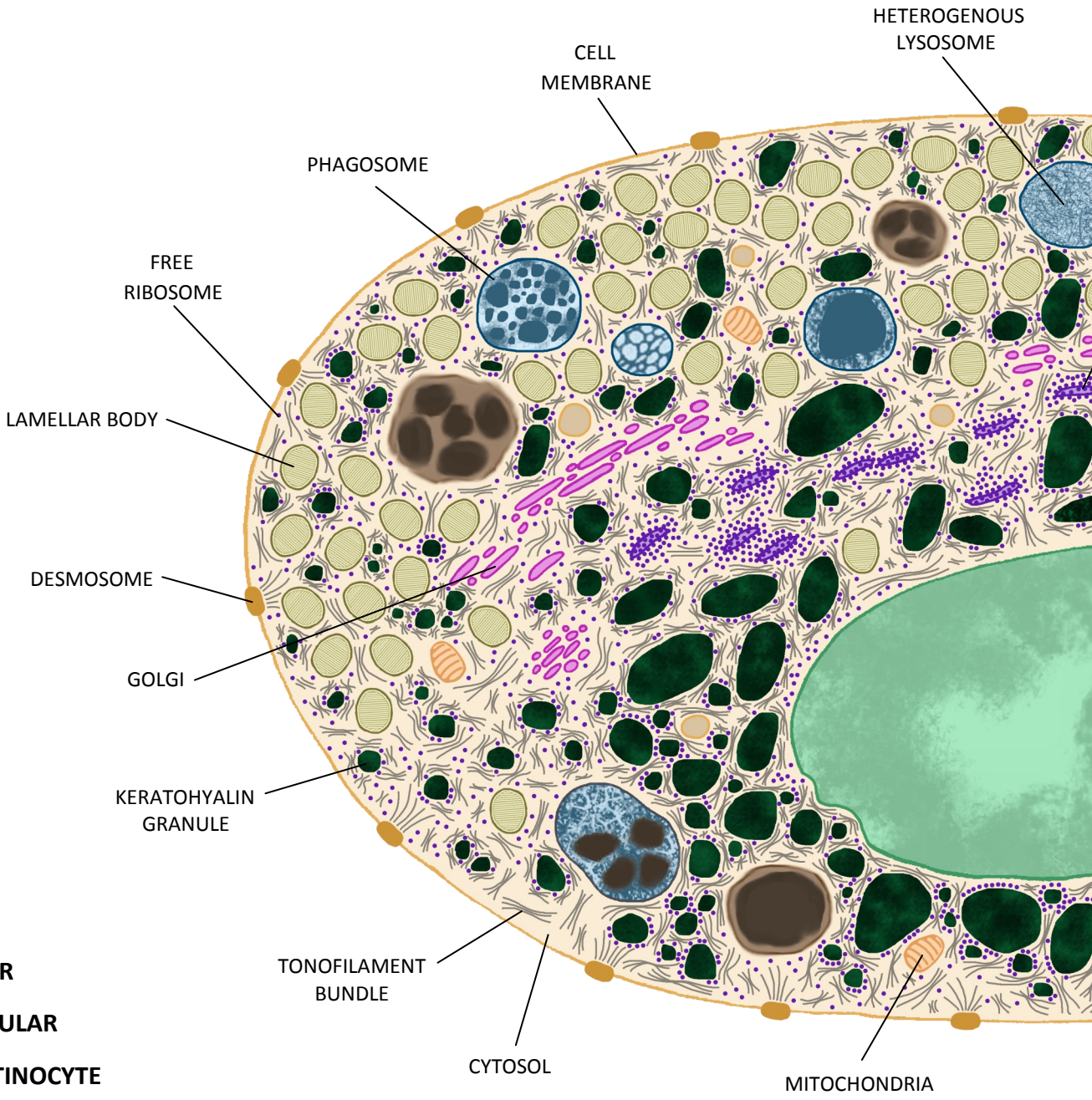
There are fewer **mitochondria**,[181] taking up around 0.7% of the volume of the cell.[3] The mitochondria that remain are starting to disintegrate.[66][181] Their outer membrane has degraded and their inner membrane is starting to.[40]

The **lysosomes** vary in size and shape,[243] typically 1 µm in diameter or less.[110] The number of lysosomes reduces to less than 0.1% of the volume of the cell.[3] They consist mainly of the *heterogeneous*/*granular* or *multivesicular* types, or may contain old pieces of organelles and debris.[243] They are important for transferring acid phosphatase, specially Na-β-glycerophosphatase, to melanosome complexes.[243] Enzymatic activity reduces in the upper stratum granulosum;[243] lysosomes with no enzymatic activity left are called *postlysosomes*.[110] *Telolysosomes* are those that have taken in undigestible material and are no longer functional.[243]

There are no longer any non-lysosome **vesicles** in the cell.[3]

The **tonofilaments** increase in quantity to encompass 40.5% of the volume of the cell.[3] An average tonofilament bundle is a bit less than 0.1 µm wide and 1.5 µm long.[184] Bundles are found less around the periphery and more toward the centre of the cell and the nucleus.[66] They may cluster around the keratohyalin granules and attach to them,[40][181] even forming bridge-like structures between two or more granules.[40] Tonofilaments are either α-keratin filaments[176] or precursors to them,[41] and are incorporated into the keratohyalin granules to form the filamentous portion of keratin.[41]

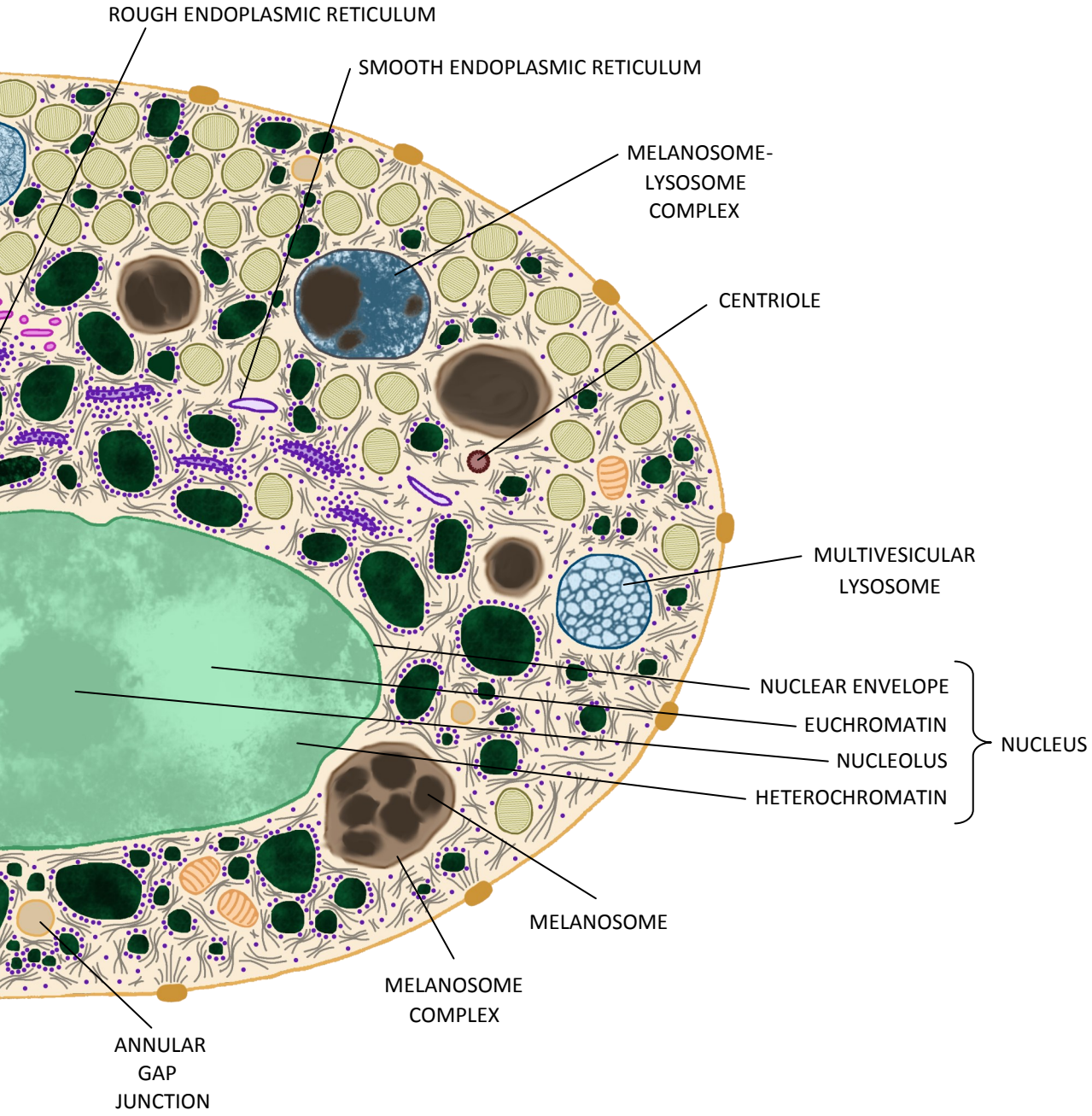
The **centriole** may be found anywhere in the cell. It is never seen undergoing *ciliogenesis*.[65]



LOWER GRANULAR KERATINOCYTE

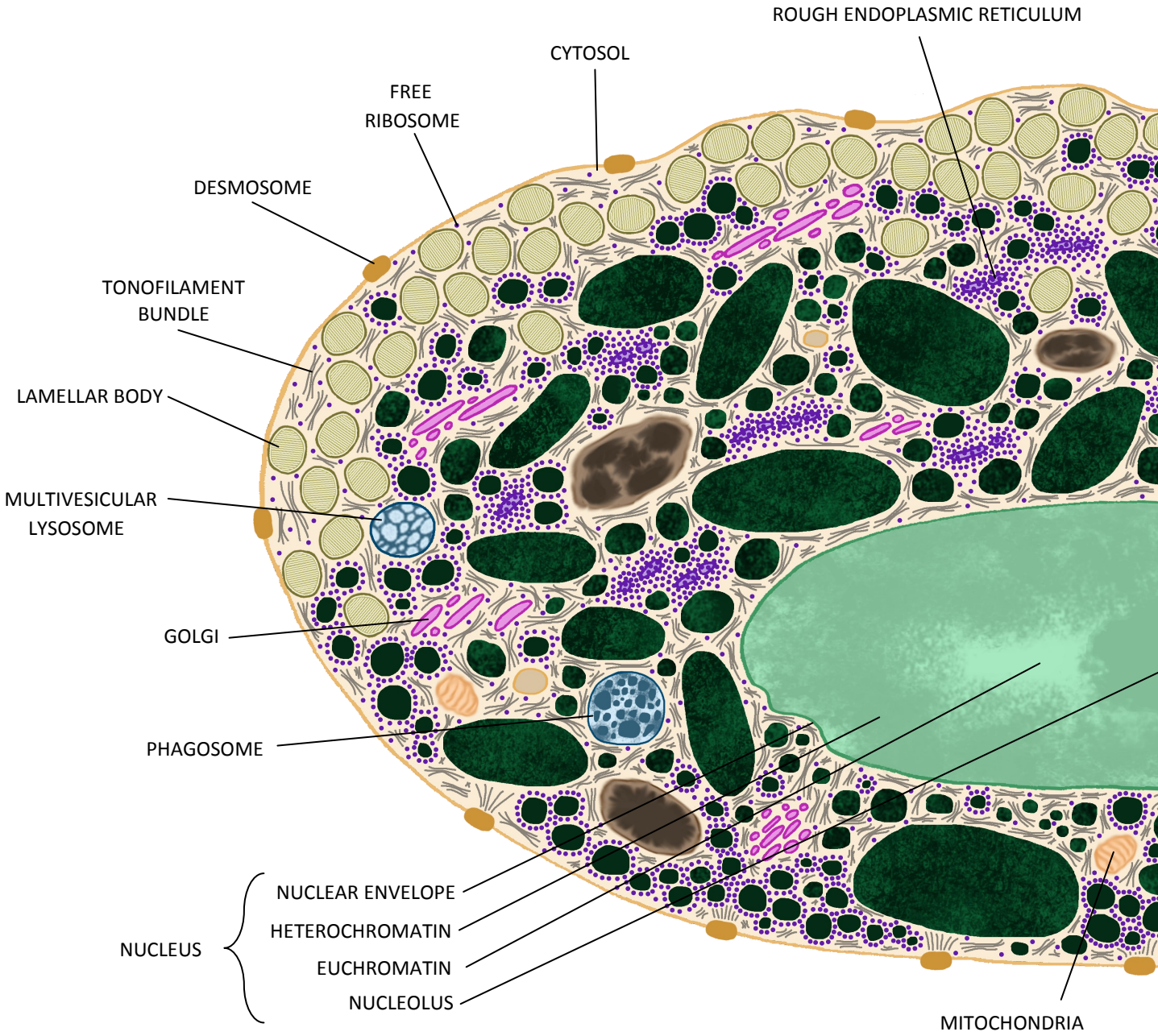
Lamellar bodies become larger and may be more plentiful[243] and visible than in the stratum spinosum.[39][243] They have more acid phosphatase activity, and sometimes will also have small amounts of iosine diphosphatase, thiamine pyrophosphatase, and/or aryl sulphatase B.[243] In the lower granular keratinocytes they are concentrated on the upper side of the cell,[25] and begin migrating toward the periphery.[243] Some may still have a faint membrane, but most don't.[36] In the upper granular keratinocytes, they attach to the cell membrane[60] and excrete their lipid lamellae into the intercellular space via exocytosis.[39][60][135][243]

The **melanosome complex**es are evenly distributed around the cell.[27][185] The melanosomes or the complex membrane begins to degrade, depending on the pigment pattern. See the section on *melanosome transfer*.



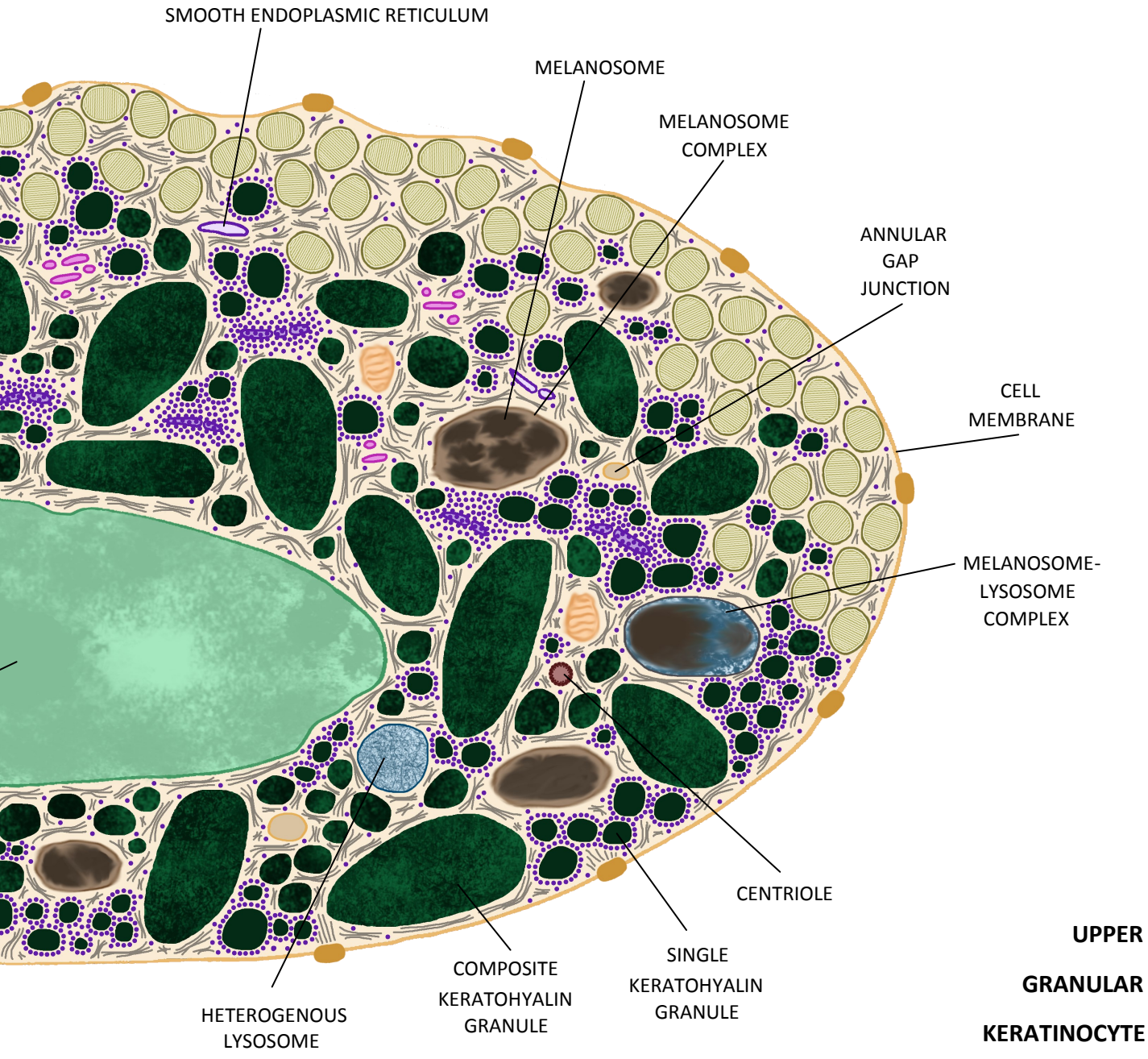
Gap junctions consist primarily of the *annular* type. Sometimes, clumps of keratohyalin may clump around a junction, though it is never found inside. They tend to accumulate deep inside the cytoplasm of the cell, and remain there as the keratinocyte matures and desquamates.[5]

Desmosomes are still intact and relatively unchanged.[184] In lower granular keratinocytes, the desmosomes have clusters of 10 to 50 ferritin particles.[216] Where the topmost desmosomes are between an upper granular keratinocyte and deep corneocyte, the laminae fuse, and the plaque of the granular cell is there, but it is not apposing any corresponding plaque on the corneocyte.[184]



Keratohyalin granules

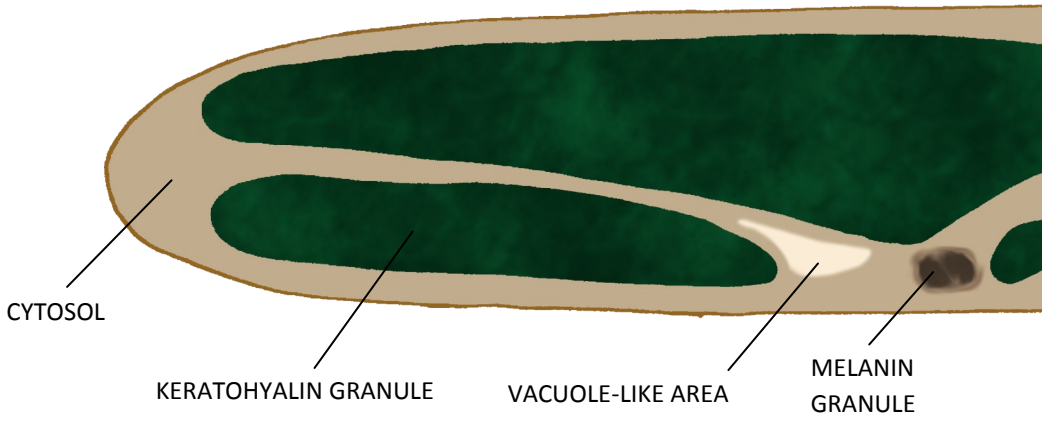
Keratohyalin granules appear in large numbers.[63][71][181] As they do not have a membrane, they are not considered organelles.[190] They vary in size,[63][190] between 0.2 µm to 1.5 µm long,[40][54][63][181] and typically get larger as they move up the rows of the stratum granulosum.[40][181] They are coacervates of polypeptides, phospholipids, salts of calcium and probably magnesium, and possibly some kind of metal.[190] In the upper granular keratinocytes there are visibly two kinds of granules.[87]



Single granules are also referred to as *dense homogenous deposits*[81] or *small granules*.[163] They are small,[40][81] round,[40] dense, and homogenous in appearance.[87] They are rich in cysteine[81][163] and sulphur.[81][87] They are typically found near the periphery of the cell and are unassociated with tonofilaments.[87] They may be surrounded by a *halo* of ribosomes.[181][182]

Composite granules are also referred to as *large granules*[163] or *larger granules*.[81] They are larger,[81][87] elongated and more irregular in shape,[40][87] and heterogenous in appearance.[87] They tend to be found around the nucleus.[40][66] They are rich in histidine[163] and phosphorus,[81][87] and poor in sulphur.[87] They have a dense interior that is rich in protein, and a periphery consisting of single granules embedded in a fibrous[87] phospholipid-rich[190] material called the *interstice*.[190] The protein found in these granules has a molecular weight of 340,000[70][163] to 350,000[81] in guinea pigs, and is called *profilaggrin*[81] or histidine-rich protein A.[182] It has a slightly acid to neutral pH.[81] The amino acid analysis, by mole, of guinea pig profilaggrin is 0.2% phenylalanine, 0.3% tyrosine, 0.4% isoleucine, 0.6% leucine, 0.6% threonine, 0.6% valine, 0.9% lysine, 3.9% alanine, 4.1% aspartate and asparagine, 5.2% histidine, 5.6% phosphate, 9.2% glycine, 11.7% proline, 12.4% serine, 14.5% arginine, and 31.0% glutamate and glutamine.[81][163] The lifespan is 6 to 48 hours,[163] but more commonly 12 to 16 hours.[81] As the upper granular keratinocyte turns into a corneocyte, the profilaggrin breaks down into smaller histidine-rich proteins called filaggrin.[81] The method of breakdown is dephosphorylation, where a phosphate group is removed from the molecule.[96] The breakdown of the profilaggrin triggers the disaggregation of the keratohyaline granules and the transition to corneocyte.[163]

The majority of papers agree that keratohyalin is the precursor to the *interfilamentous matrix* in keratin, and that it combines with tonofilaments to form the keratin in the deep stratum corneum.[40][87][163][181] Two papers argue that because keratin, but not keratohyalin, is found in the epidermis of mice tails,[189] reptiles, or amphibians,[190] it cannot be important to keratin production.[189][190] Based on the composition of the single and composite granules, the most likely scenario is that the cysteine-rich single granules become the interfilamentous keratin matrix, and the histidine-rich interior of the composite granules becomes the *natural moisturising factor* discussed later.



STRATUM LUCIDUM

The stratum lucidum is also referred to as the *translucent layer*, *clear layer*, or *transitional layer*.[40][71] When it does not form a continuous layer, the keratinocytes may be referred to as *transitional keratinocytes* or, in the context of the epidermis, simply *transitional cells* or *T-cells*.[40] The latter term should be avoided due to confusion with immune T-cells. They are named so in mammals because they have mostly died and lost their cellular components, thus appearing clearer. However, contrary to human stratum lucidum, the cytoplasm of guinea pig transitional keratinocytes is darker than in the upper stratum granulosum.[40] The stratum lucidum is typically found as a solid, continuous layer in the thick skin, such as in the foot pads and nose. However, in thin skin, such as the back, the layer may not be complete, and appears as a broken layer, or as single cells at the bottom of the stratum corneum or top of the stratum granulosum. In particularly thin skin the layer may not be present at all.[40][192]

Transitional keratinocytes are flattened, and similar in shape to the bottom row of the deep corneocytes.[40] They range between 0.5 and 1.3 µm high, though are more commonly around 0.8 µm.[40] The shrinkage is due to the water loss caused by keratinisation.[192] Very little has been studied about guinea pig transitional keratinocytes; only one paper has examined them specifically.

Cell physiology

The **cell membrane** is dark, irregular, and 15 nm wide.[40]

By this stage the **nucleus** has typically disappeared,[40] along with most other organelles.

The small corpse of a **mitochondrion** may remain.[40]

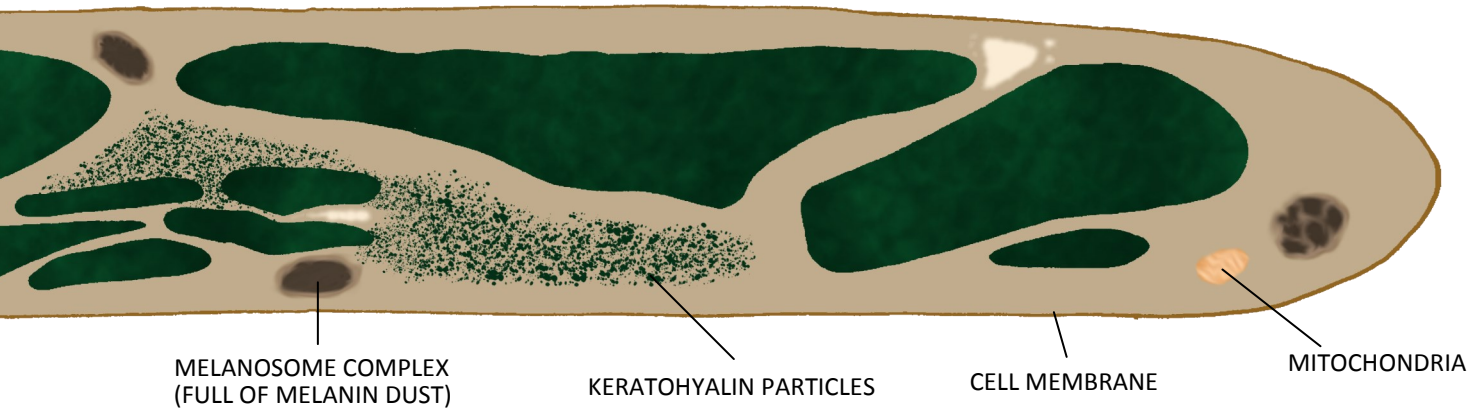
There are no visible **tonofilaments**;[40] by this stage they are probably incorporated into the granules.

Depending on the pigment pattern, **melanosome complexes** or **melanin granules** are often still visible.[40]

Vacuole-like areas of lighter cytosol may be seen around the keratohyalin granules.[40]

There are large **keratohyalin granules**, most of which have massed together in the middle. The granules contain particles which form a mattress-like appearance, with each particle being 10 to 25 nm in diameter.[65] This is likely the keratohyalin and tonofilaments turning into keratin. Smaller granules or lose particles may be seen around the larger ones.[40]

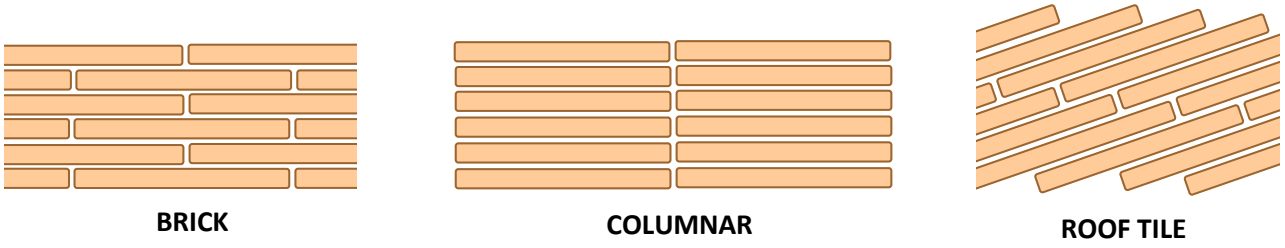
TRANSITIONAL KERATINOCYTE



STRATUM CORNEUM

The stratum corneum is also referred to as the *corny layer*, *cornified layer*, *horny layer*, *outermost layer*, *cutaneous layer*, or *corium layer*. It is divided into three sublayers: the *deep* stratum corneum, the *intermediate* stratum corneum, and the *superficial* stratum corneum. The deep stratum corneum is commonly called the basal zone or basal layer, but to avoid confusion between it and the stratum basale, it will be referred to only as the deep stratum corneum here. The superficial stratum corneum is the topmost section of the skin; the upper surface of a superficial corneocyte is in contact with the outside environment. In some literature, the intermediate and superficial stratum corneum are grouped together as the stratum disjunctum, and the deep stratum corneum is then called the stratum conjunctum.[188] The keratinocytes in this layer are called *corneocytes*[219] or, in the context of the epidermis, *corny cells* or *horny cells*. They are named so because they have finished the process of keratinisation, and thus are dead and completely keratinisied, or 'cornified'.

Guinea pig corneocyte organisation is less consistent than in other rodents.[50][115] Areas that are less than 38 µm thick typically follow a columnar alignment,[43][50] whereas those thicker than 46 µm will follow a brick-style[50] or roof tile[43] pattern. The region between 38 and 46 µm may be any of the three. This is called the *change from order to disorder*,[50] and is considered to be a result of proliferation rate; the faster the cells reproduce, the harder it is for them to remain organised.[50][115]



BRICK **COLUMNAR** **ROOF TILE**

The stratum corneum is the most important layer in the epidermis, and the end goal of epidermal cell differentiation.[93] It serves four primary roles, all of which have a barrier function: against liquid loss, liquid gain, pathogens, and light.

Liquid loss barrier. The deep stratum corneum is responsible for the main water barrier of the epidermis.[166] It prevents water loss and therefore dehydration and desiccation;[93] thanks to the barrier, the average adult guinea pig will lose only 1.8 to 3.4 grams of water per day through their skin.[88][212] It is also important in preventing the loss of minerals and electrolytes;[144] without the lipids in the stratum corneum, the hydrophilic substances in the skin are quickly leeched out on contact with water.[244]

Liquid entrance barrier. The lipids in the stratum corneum helps protect the lower layers from the absorption of environmental liquids.[149] Without the lipids, the epidermis quickly swells and weakens when contacted with water.[93] [244] This additionally prevents the entrance of unwanted minerals or electrolytes.[144]

Pathogen barrier. The lipid barrier of the stratum corneum provides a barrier against both microorganisms[144] and unwanted molecules. Most environmental molecules penetrate the stratum corneum through breaks inside the glands or hair follicles, which account for only 0.1% of the skin surface; the remaining interfollicular epidermis is protected by the stratum corneum.[212]

Photoprotection. The urocanic acid content[205] and the thickness of the stratum corneum[219] is important in protecting the lower layers of skin against UV radiation. In humans, the stratum corneum reflects around 5% of the light hitting it,[219] and absorbs an additional 50% of UVA and UVB.[212]

The stratum corneum is often described as a 'two-compartment'[93] or 'brick and mortar' system,[150] which describes the two main components: the cells and the intercellular space. The cells, or 'bricks', are rich in protein but poor in lipids, and form the structural basis. The intercellular space, or 'mortar', is rich in lipids, ions, enzymes, and free amino acids, and forms the adhesive basis.[93][150] The pH of the stratum corneum is 6.3 to 6.4.[212]

Corneocytes are very flattened and long,[181] commonly reaching 460 µm in length.[142][244] When viewed from above they appear triangular, rhomboid, or trapezoid.[244] They are often interposed; this prevents oxygen being taken up from the atmosphere to them or the lower layers,[66] and is likely because the cells are more useful dead than alive. They may be somewhat swollen due to the keratin absorbing water from the stratum lucidum and from the atmosphere.[192]

The **plasma membrane** is thick,[191] resistant,[163] and rich in cysteine.[190][191]

The **cornified cell envelope** (CE) has not been studied in guinea pigs, though it is likely to be similar to other mammals. In humans it is a membrane, 7 to 15 nm thick, which either derives from or replaces the inner leaflet of the plasma membrane.[86] The protein involucrin is produced by the keratinocyte and becomes incorporated into the cornified envelope.[42] Involucrin is rich in glutamate[42] and makes the cell more rigid and insoluble as it moves up the layers.[86]

Whole composition

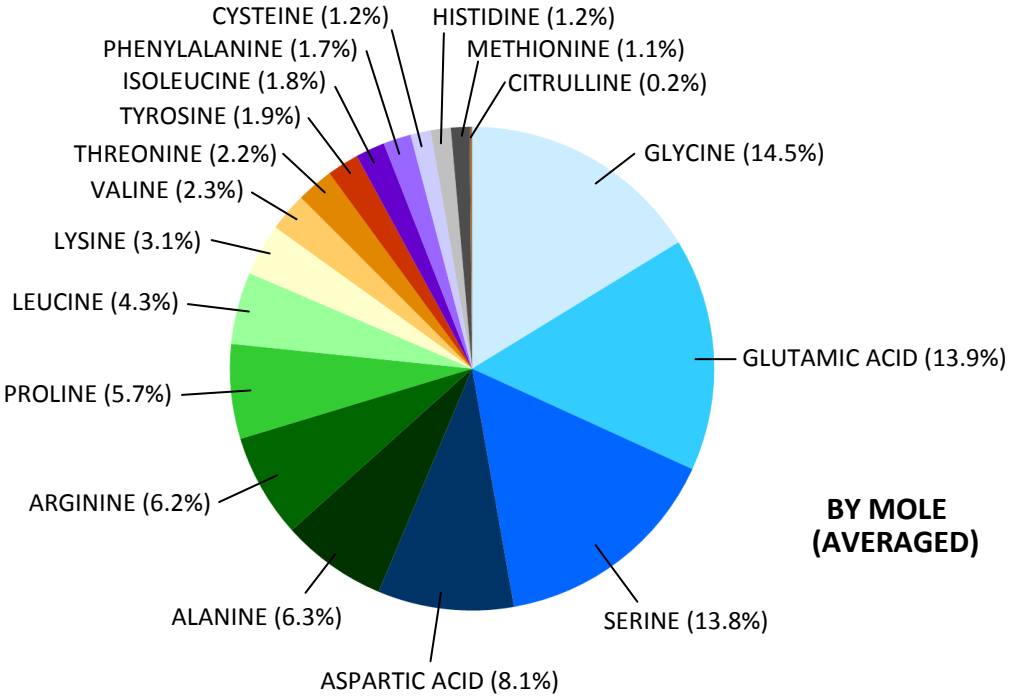
Protein.

There are no *nucleic acids* in the stratum corneum.[192]

There are large quantities of *free amino acids* in the stratum corneum. 70 to 100% of these come from the breakdown of filaggrin in the deep stratum corneum.[150][164][212]

Alanine comprises 6.3% of the amino acids of the stratum corneum, by mole.[6]

Arginine comprises 6.2% of the amino acids of the stratum corneum, by mole.[6]



Aspartic acid comprises 7.9%[164] to 8.3%[6] of the amino acids of the stratum corneum, by mole.

Citrulline is present as L-[ureido-^{14}C-]citrulline.[67] It is derived from arginine, which is deiminated in the deep stratum corneum.[81][96] This is unusual for rodents, as citrulline is not found in the corneocytes of other studied rodents (rats, mice, and hamsters).[108] It comprises 0.1 to 0.2% of the amino acids of the stratum corneum, by mole.[108]

Cystine is found in the deep corneocytes, but not the intermediate or superficial corneocytes.[191] There is no free cystine; instead it is bound loosely to phospholipids and the keratin matrix.[191]

Cysteine comprises 1.2% of the amino acids of the stratum corneum, by mole.[6]

Glutamic acid comprises 13.9% of the amino acids of the stratum corneum, by mole.[6]

Glycine comprises 10.6%[164] to 18.4%[6] of the amino acids of the stratum corneum, by mole.

Histidine comprises 1.2% of the amino acids of the stratum corneum, by mole.[6]

Isoleucine comprises 0.6%[164] to 2.9%[6] of the amino acids of the stratum corneum, by mole.

Leucine comprises 0.7%[164] to 7.9%[6] of the amino acids of the stratum corneum, by mole.

Lysine comprises 1.2%[164] to 5.0%[6] of the amino acids of the stratum corneum, by mole.

Methionine comprises 1.1% of the amino acids of the stratum corneum, by mole.[6]

Phenylalanine comprises 0.3%[164] to 3.0%[6] of the amino acids of the stratum corneum, by mole.

Proline comprises 1.5%[6] to 9.8%[164] of the amino acids of the stratum corneum, by mole.

Serine comprises 12.4%[6] to 15.1%[164] of the amino acids of the stratum corneum, by mole.

Threonine comprises 0.5%[164] to 3.9%[6] of the amino acids of the stratum corneum, by mole.

Tyrosine comprises 0.5%[164] to 3.3%[6] of the amino acids of the stratum corneum, by mole.

Valine comprises 1.1%[164] to 3.5%[6] of the amino acids of the stratum corneum, by mole.

There are at least five enzymes in the stratum corneum: γ-glutamyl cyclotransferase, pyrrolidone carboxyl peptidase, thioredoxin reductase, and two types of ceramidase.

36% of the *γ-glutamyl cyclotransferase* activity of the epidermis is found in the stratum corneum. A production rate of 1.69 µmoles per hour per cm^2 is reported.[9]

29% of the *pyrrolidone caryboxyl peptidase* activity of the epidermis is found in the stratum corneum. A production rate of 0.01 µmoles per hour per cm^2 is reported.[9]

Thioredoxin reducatase is found the plasma membrane of the corneocytes.[204] It utilises the protein thioredoxin[161] and works in combination with nicotinamide adenine dinucleotide phosphate (NADPH).[161] It competes for electrons, thus reducing the free radicals produced by UV radiation, and helping to prevent cell damage.[161][204] It is more effective against UVB than UVA.[204]

Ceramidases are enzymes that hydrolyse ceramides into sphingosines and fatty acids, and are important for regulating the ratio of those compounds.[245] There is more ceramidase activity in the guinea pig epidermis than in the brain.[245] Two ceramidases have been described in guinea pig epidermis: *ceramidase I* and *ceramidase II*. Ceramidase I has a molecular weight of 60,000 and an optimal pH range of 7.0 to 9.0. Ceramidase II has a molecular weight of 148,000 and an optimal pH range of 7.5 to 8.5.[245]

Non-protein nitrogen.

Pyroglutamic acid (PCA), also known as pyroglutamate[116] or pyrrolidone carboxylic acid,[9] is an important *natural moisturising factor*.[9] It is derived from the breakdown of glutamine in the filaggrin of deep corneocytes.[9]

Urocanic acid absorbs UV radiation.[205] It is derived from the breakdown of histidine in the filaggrin of deep corneocytes.[205]

Lipids.

Glycolipids,[150] wax esters, triglycerides,[219] sphingolipids, cholesterols, phospholipids, and free fatty acids are found in the stratum corneum. Most stratum corneum lipids are found in the intercellular space.

The most important sphingolipids are the *ceramides*,[93] which are largely responsible for the lipid barrier.[93][106][150] Nine classes of ceramides are found in guinea pig stratum corneum.[144] Of these, most are esterified with linoleic acid (18:2),[60][140] and/or a mixture of lacceroic acid (32:1), psyllic acid (33:1), and geddic acid (34:1).[140] Two acylglucosylceramides have been described: *esterified cerebroside 1* and *esterified cerebroside 2*, with the respective structures of (2S,3R,4E,23'Z)-1-O-(β-D-glucopyranosyl)-N-(32'linoleoyloxy-23'-dotriacontenoyl)-4-sphingenine and (2S,3R,4E)-1-O-(β-D-glucopyranosyl)-N-[24-(linoleoyloxy)teteracosanoyl]-4-spingenine.[140] These acylceramides are the main hydrophobic component in the intercellular lipids.[144] Another ceramide, known as *ceramide 1*, is important in organising the intercellular lipid lamella.[103]

The *cholesterols* include *cholesterol sulphate* and other *esterified cholesterols*. The cholesterol sulphate acts like a cementing substance in the intercellular space to keep the corneocytes stuck together. Hydrolysis of the cholesterol sulphate causes desquamation of the corneocytes.[60] Esterified cholesterols, often called sterol esters, are on average 31% saturated, 48% monounsaturated, and 21% diunsaturated.[67] Which cholesterol is esterified is most likely dependent on what fatty acids are available in the skin.[67]

Unlike in humans,[39] guinea pig stratum corneum is fairly poor in phospholipids.[219]

The main *free fatty acid* of the intercellular lipids is palmitic acid (16:0).[103] Other fatty acids include myristic acid (14:0), pentadecylic acid (15:0), margaric acid (17:0), and stearic acid (18:0).[67]

Carbohydrates.

None have been reported in guinea pig stratum corneum.

Minerals.

Minerals comprise 0.6% of the stratum corneum by dry weight.[227]

Calcium comprises 0.04% of the stratum corneum by dry weight. A quantity of 25.00 µmoles per gram is reported.[227]

Chlorine comprises 0.28% of the stratum corneum by dry weight. A quantity of 224.00 µmoles per gram is reported.[227]

Magnesium comprises 0.02% of the stratum corneum by dry weight. A quantity of 21.00 µmoles per gram is reported.[227]

Phosphorus comprises 0.03% of the stratum corneum by dry weight. A quantity of 24.00 µmoles per gram is reported.[227]

Potassium comprises 0.06% of the stratum corneum by dry weight. A quantity of 46.00 µmoles per gram is reported.[227]

Sodium comprises 0.03% of the stratum corneum by dry weight. A quantity of 34.00 µmoles per gram is reported.[227]

Sulphur comprises 0.16% of the stratum corneum by dry weight. A quantity of 139.00 µmoles per gram is reported.[227]

Vitamins.

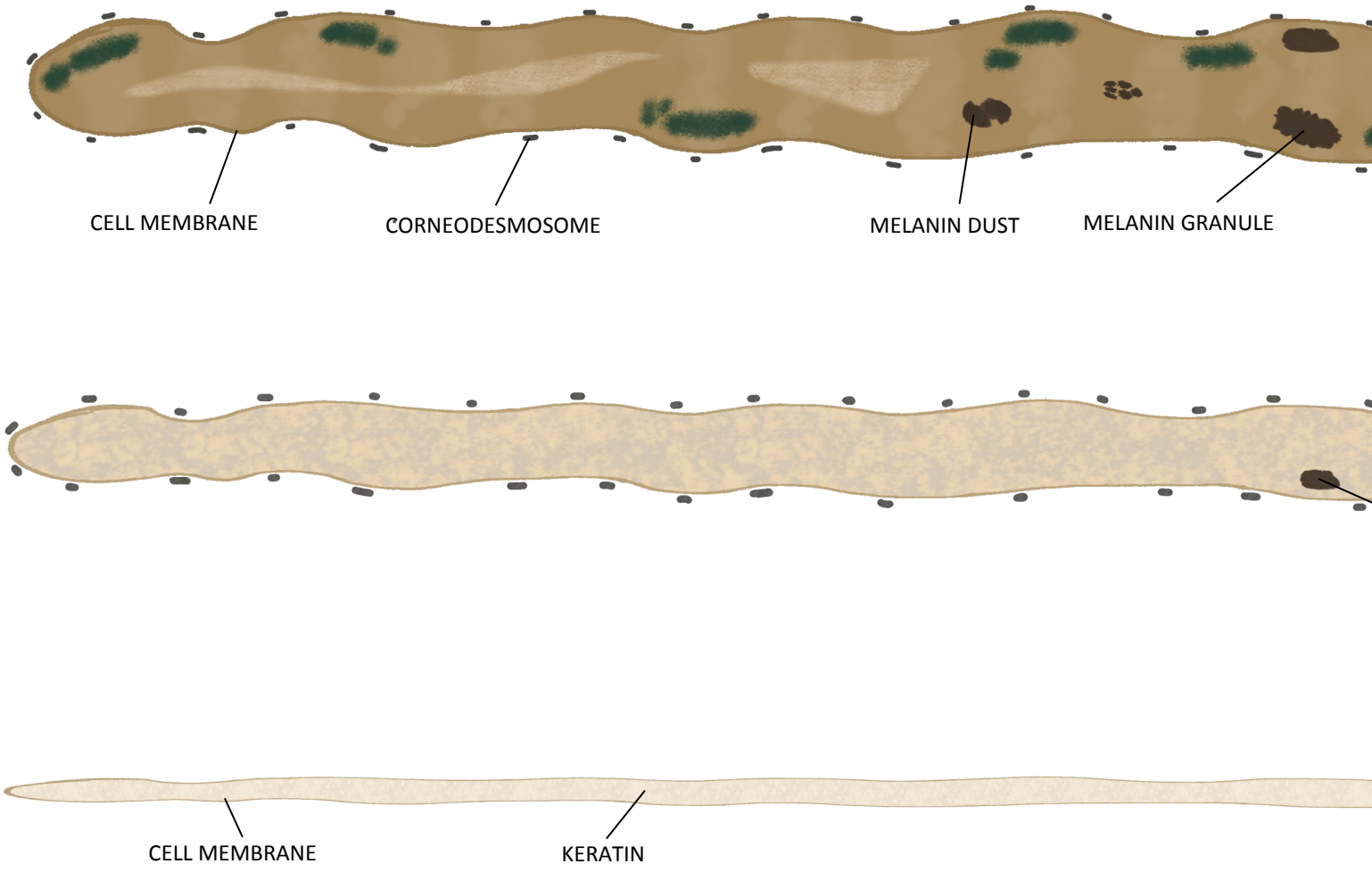
Tocopherol (vitamin E) is present in the stratum corneum and has an antioxidant effect. It protects the lipids from oxidative damage known as peroxidation, which is caused by free radicals degrading the lipids. However, UV light destroys the vitamin E content in the stratum corneum, so ascorbic acid (vitamin C) is also present to help protect the vitamin E.[219]

Deep stratum corneum

The deep stratum corneum is also referred to as the *basal stratum corneum* or the *stratum corneum conjunctum*.[188] By this stage, the organelles are mostly destroyed.[93][181][225] Deep corneocytes are very elongated and flat, typically only around 0.6 µm high.[41] They are rich in cysteine[191] and phospholipids that are bound to the keratin proteins.[188]

There is a sharp change in the **cytoplasm** between the stratum lucidum and the deep stratum corneum.[191] It is darker,[41] with light-dark striations that are perpendicular to the surface.[181]

The **plasma membrane** is thickened[190] and around 20 nm wide.[40][41] The outline of the cell may be difficult to see[188] due to the dark keratin matrix obstructing it.[184]



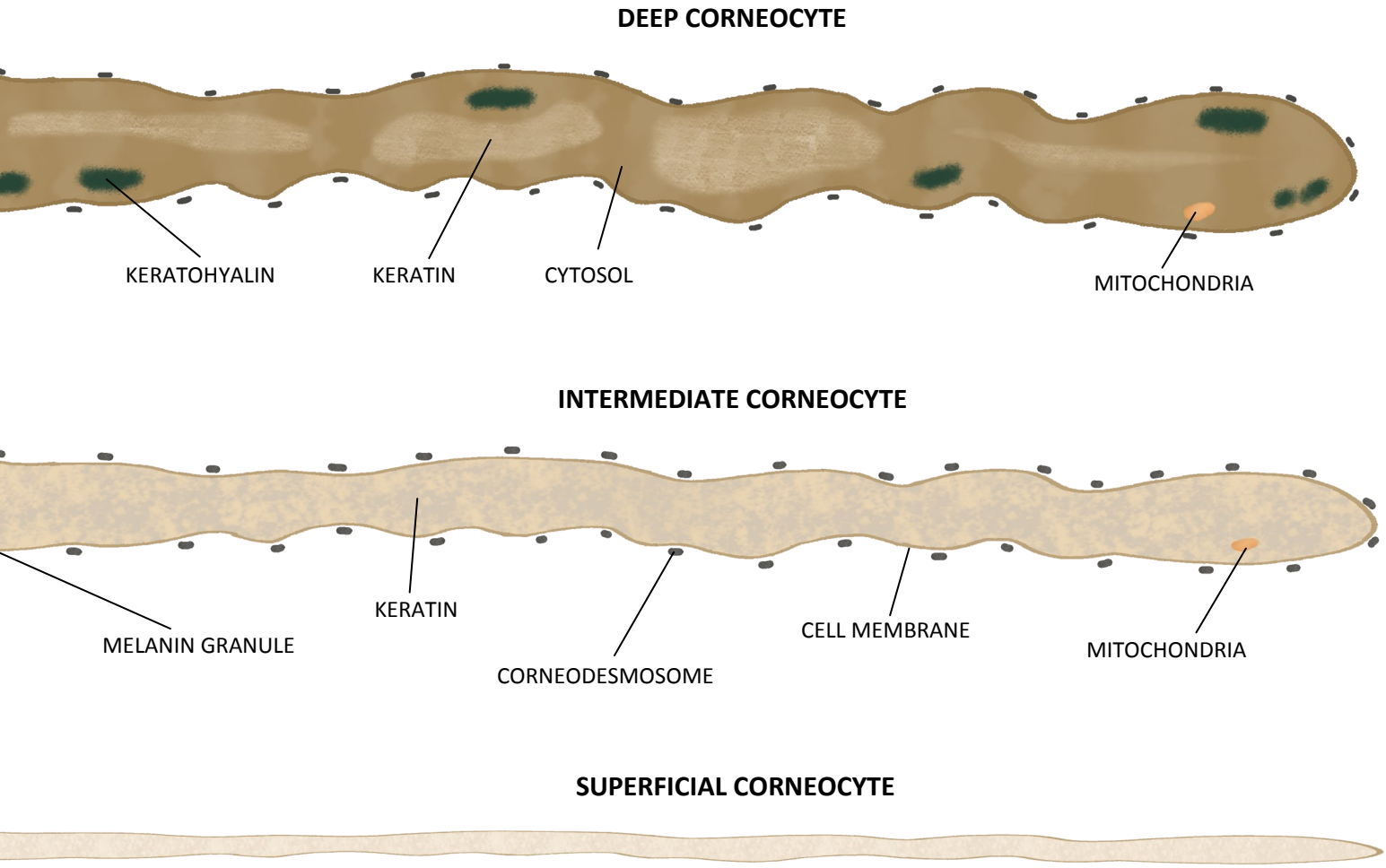
Rarely there will be shreds of **nucleus** remaining,[181] though more commonly there is no nucleus left.[71] The DNA is completely, or at least mostly, destroyed by this stage.[71]

Rarely, the featureless corpse of a leftover **mitochondria** is visible. In this case, they are around 0.3 µm long, with a jagged and degraded membrane.[41]

Melanin granules may still be intact.[17] In dark skin, **melanosome complexes** will often aggregate in the centre of the cell, where the nucleus used to be.[119]

The excreted lipid sheets from the **lamellar bodies** completely fill the intercellular space,[39] forming the *intercellular lipid lamella*.[103] They are rich in free fatty acids, particularly palmitic acid, and ceramide 1, which is important in organising the lamellar structure.[103] They are important for barrier function and corneocyte cohesion;[39][237] without these lipids, the skin is easily brushed off.[244] Alkaline substances[244] and fatty acid deficiencies[93] can strip away or deplete the lamellar lipids, leading to dandruff,[244] hyperproliferation, scaliness, and inflammation.[93] Most, if not all, of the lipids inside the deep stratum corneum are derived from these lipid lamellae.[144]

The **intercellular space** is most often around 10[41] to 30[184] nm wide, though sometimes it will be as wide as 56 nm.[41] It is filled by the lamellar lipids.[42] It is poor in phospholipids[219] and moisture.[142]



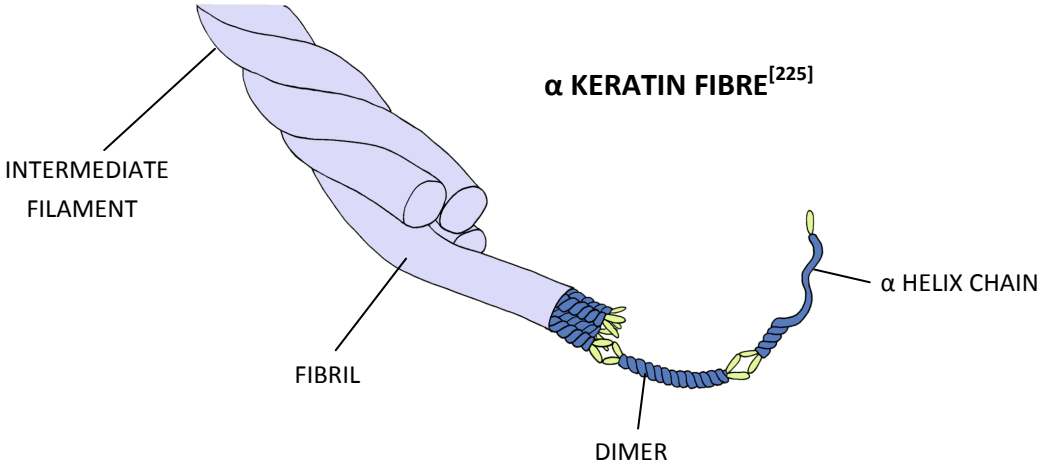
There are no more **desmosome** plaques.[184] Instead the desmosomes fuse together to form a single dense body between the cells,[184] called a *corneodesmosome* or an *intercellular body*. These bodies are homogenous in appearance and separated from the cell membranes by narrow laminae.[184] They are 30 to 60 nm thick,[41][184] and may be up to 400 nm long,[184] though are more commonly around 150 nm.[41] Cornedesmosomes contain a protein called *corneodesmosin*, which in guinea pigs has a molecular weight of 52,000 and an alkaline pH.[134] Degradation of the corneodesmosomes via proteolysis is important in desquamation of the corneocytes.[134][219]

As the upper granular keratinocyte turns into a deep corneocyte, the phospholipids that hold the keratohyalin together in the **keratohyalin granules** break down, and the contents dissipate,[189][190] giving any leftover granules a light and patchy appearance.[190] At the same time, the profilaggrin breaks down into smaller histidine-rich proteins called *filaggrin*.[81]

Filaggrin is named so because it acts on the filaments:[42][81] it helps bring together the tonofilaments to form the keratin pattern.[42][81][93][176] The amino acid analysis, by mole, of guinea pig filaggrin is: 28.6% glutamate and glutamine, 13.8% serine, 12.9% arginine, 11.5% glycine, 10.8% proline, 5.5% histidine, 4.5% alanine, 3.8% aspartate and asparagine, 2.2% citrulline, 1.3% lysine, 1.3% valine, 0.9% leucine, 0.9% threonine, 0.6% phenylalanine, 0.5% isoleucine, 0.5% tyrosine, and 0.4% ornithine.[81] Guinea pigs have two large[96] filaggrin proteins, called *histidine-rich protein B* and *histidine-rich protein C*. These have molecular weights of 200,000 and 250,000, respectively.[163]

A third[81] of the arginine in the filaggrin is turned into citrulline by a process called deimination.[96] This process was first discovered in 1983 when [^{3}H]arginine was labelled in guinea pig skin and then later [^{3}H]citrulline was found.[70][96] This triggers the further break down of the filaggrin into free amino acids[81][93][96] and urocanic acid.[163] These are called *natural moisturising factors*, and are important for the properties of the stratum corneum.[9][48] The glutamine is further turned into pyroglutamic acid through γ-glutamul cyclotransferase[9][116] and magnesium.[116] 70 to 100%, though usually closer to 100%, of the free amino acids of the stratum corneum are derived from this break down of filaggrin.[70][150]

There are no more **tonofilaments**,[181] as they have been turned into *keratin*.[142] The keratin comprises hexagonal or tubal fibres,[41] around 7 nm in diameter,[71] arranged in alternating orientations[41] within an interfilamentous matrix.[251] The ratio of fibres to matrix is 2:3, and known as the *keratin pattern*.[41] The fibres are often coated in phospholipids,[188] increasing the diameter to around 8 nm.[71] The stark contrast between granular keratinocytes and corneocytes is probably due to the conditions for turning keratohyalin and tonofilaments into keratin being achieved spontaneously in the transitional keratinocytes.[41]



Keratin is a group of insoluble proteins that are rich in sulphur and cysteine.[225] They are the most common group of proteins in the epidermis, epidermal appendages (e.g. hair), and other epithelial tissues, and along with collagen is one of the most important biopolymers in animals.[225] Keratins are primarily classed into two groups: *α-keratin* and *β-keratin*.

β-keratin is not as well studied as α-keratin. It has smaller filaments which are arranged as a sheet. This type of keratin is found in the feathers, breaks, and claws of birds, the epidermis, nails, scales, and claws of reptiles, the scutes and eggs of turtles, and the armour of the pangolin. The pangolin is the only mammal known which has both α and β keratin; it is not found in guinea pigs.[225] It may be referred to as 'pseudokeratin' in early literature.[28]

α-keratin is the most heavily studied keratin,[225] with filaments that take the shape of a helix or coil.[225] This type of keratin is found in the hair, nails, claws, horns, and baleen of mammals, the epidermis of reptiles, the slime of hagfish, and the egg capsules of sea snails.[225] The type of α-keratin found in the epidermis is known as *soft keratin*.[61][225] It is poorer in sulphur,[225] richer in lipids,[61] and more flexible than the keratin of the hair and nails. Guinea pig corneocytes express cytokeratin but not vimentin.[97] Guinea pigs also have *α-keratin intraspecies heterogeneity*, meaning they have different subtypes of α-keratin for different parts of the body (e.g. foot thick skin vs. abdomen thin skin).[176] α-keratin may be referred to as 'eukeratin' in early literature.[28]

Intermediate stratum corneum

The intermediate stratum corneum may be grouped with the superficial stratum corneum and referred to as the *stratum disjunctum*.[188] The intermediate corneocytes may look thicker[188] and less flat[192] than deep corneocytes due to uptake of moisture from the environment. They are typically around 1.2 μm high.[41] They are no longer rich in cysteine; the cysteine is now confined to the membranes.[191] Filaggrin has finished breaking down by now,[150] though some deimination may still occur.[96]

There is a sharp change in the appearance of the **cytoplasm** between the deep and intermediate corneocytes.[191] It looks lighter[41] and more hollow,[150] with a somewhat reticulated appearance.[41][181] The light-dark striations disappear.[181]

The **cell membrane** is lighter[41] and thicker[181] here. It is 10 to 30 nm wide.[41][184][209] It contains cysteine.[191]

The **intercellular space** increases, typically to between 20 and 80 nm wide.[41][184][209] The *corneodesmosomes* are more oval in shape here than in the deep stratum corneum.[184] They begin to break down and take on a granular or heterogenous appearance.[184]

There is no more **nucleus**.

As in the deep corneocytes, there may still be a leftover **mitochondrion** corpse visible.[192]

Melanosome complexes are no longer visible, though rarely **melanin granules** are.[181]

The **keratin** fills the cell and takes on a more contrasted appearance, with the fibres appearing darker and the matrix appearing lighter.[192] The cysteine in the keratin is unstable and broken down via hydrolysis,[191] and the phospholipids begin to autolyse.[188]

Superficial stratum corneum

The superficial stratum corneum may also be referred to as the *uppermost stratum corneum*,[181] or be grouped with the intermediate stratum corneum and referred to as the *stratum disjunctum*.[188] The superficial corneocytes may look swollen due to the absorption of moisture from the environment.[192] They range in size from 0.3[41] to 2.0[188] µm high, and may be up to 750 µm long.[244] They have a triangular, rhomboid, or trapezoid shape when viewed from above,[244] and typically follow a roof tile arrangement.[43]

The **cytoplasm** at this stage contains little to no stainable material.[41] It no longer has a reticulated appearance, and instead looks quite empty.[181] It is much lighter and contrasts against the darker cell membrane.[192]

The **cell membrane** is lighter[41] and thicker[181] here, and often has a jagged appearance.[189] It ranges between 10 and 40 nm wide, though is more commonly 20 nm.[184] It still contains cysteine.[191]

The **intercellular space** widens as the cholesterol sulphate hydrolyses and begins desquamation.[60] The cells partially separate,[41] with the intercellular space typically up to 150 nm wide.[184] Larger spaces often give the superficial stratum corneum a vacuolated appearance.[192] Esters from the surface sebum, such as wax esters and triglycerides, may be present,[221] and contribute another layer to the barrier function.[150][212] The *corneodesmosomes* decrease in quantity and are lighter in colour.[41] They have quite a patchy appearance as they break down.[184] By the time a superficial corneocyte has desquamated, its corneodesmosomes have ruptured and dissolved.[184]

There is no **nucleus** or **mitochondria**.

Melanin granules may rarely be visible.[181]

The **keratin** pattern is still noticeable.[41] The bound phospholipids have been autolysed by this stage and no longer present.[188]

Skin surface

The skin surface is where the superficial stratum corneum meets the environment. Generally, the lipids from the lamellar bodies are confined to the intercellular space of the stratum corneum, whereas the lipids from the nearby sebaceous glands are excreted onto the skin surface. These lipids are rich in esters, and are comprised of sterol esters, wax diesters, glycerol diesters, free sterols, and free fatty alcohols.[59]

Sterol esters comprise 33% of the lipids.[59] 40[59] to 75% (average 65%)[67] of these are saturated, 18 to 32% (average 25%) are monunsaturated,[67] and 7 to 13% (10%) are diunsaturated.[67]

Wax diesters comprise 24% of the lipids. Of these, 67% are saturated fatty acids and 33% are unsaturated fatty acids.[59]

Glycerol ether diesters comprise 28% of the lipids. All of them are saturated.[59]

Free fatty alcohols comprise 6% of the lipids.[59]

Free sterols comprise 9% of the lipids.[59] The main free sterol is cholesterol,[59][138] including cholesteryl oleate[138] and cholesterol sulphate.[60] There is some lathosterol.[59] Most of the free sterols are unsaturated.[59]

There are lipids absent from the guinea pig skin surface that are found in other animals. These includes eicosane, squalene, and triolein.[138] Palmitic acid may be present in trace amounts, though is often absent.[138] There may[138] or may not[230] be small amounts of triglycerides present.

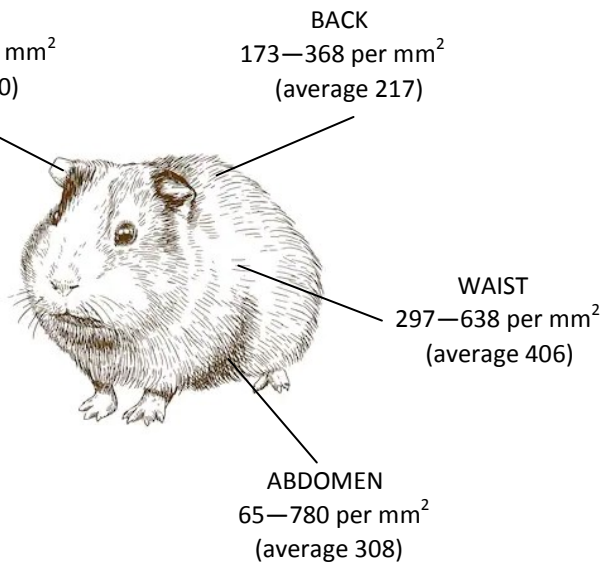
MELANOCYTES

Guinea pigs are relatively unique among rodents in that they have melanocytes in their interfollicular epidermis. Other studied rodents (notably rats and mice) and lagomorphs have no pigmentation in their interfollicular epidermis, and any apparent skin colour is derived entirely from the pigmentation in the follicular epidermis.[19][22] This may be why pigmented hairless guinea pigs are more common than pigmented hairless murids or rabbits.

Melanocytes are found in the stratum basale[17][27][35][63][84][155][185] between basal keratinocytes,[17][27][185] and in the hair follicles.[27][180][185] They are not adhered to surrounding cells by desmosomes, hemidesmosomes, or any other method of attachment.[182][184] In most areas of the body,[22][23] they are found on the sides and hills of the epidermal ridges, but not the valleys;[22][27][155][185] this is probably what causes the speckled appearance of dark guinea pig skin.[155] They are derived from the neural crest.[32] Although melanocytes in the hair bulb may reproduce, those in the interfollicular epidermis rarely or never do.[72] Guinea pig melanocytes do not need to be stained to see them under a microscope. They can still be difficult to see in a cross-section, however, so staining them with dihydroxyphenylalanine (DOPA) makes them stand out more.[23][46]

There is no statistically significant difference in melanocyte numbers between albino,[183] black, and red skin;[23][185] only white-spotted, or piebald, skin lacks melanocytes. However, melanocyte density varies depending on the area of the body. For example, there are 2 to 4 times more melanocytes per mm^2 in the ear and the areola than in the abdomen skin.[185] Below are ranges and averages for melanocyte densities in different body areas.[10][22][23][27][29][63][185][224][241][242]

The purpose of the melanocyte is to produce melanin [80][84][148] and distribute it to nearby keratinocytes. A melanocyte and the surrounding keratinocytes it services are known as an *epidermal melanin unit* (EMU)[78][104][141][107] or an *epidermal proliferative unit* (EPU).[32] The ratio of melanocytes to keratinocytes ranges from 1:17 to 1:38,[104] though averages 1:22 to 1:25.[68][104][126][155] It is hypothesised that the relatively consistent ratio is due to a limitation on how much melanin a single melanocyte can offer. Superficial evidence suggests that melanocytes are repulsed by each other to a certain degree, in order to maintain the ratio in a given area, and prevent denser or sparser areas.[155]

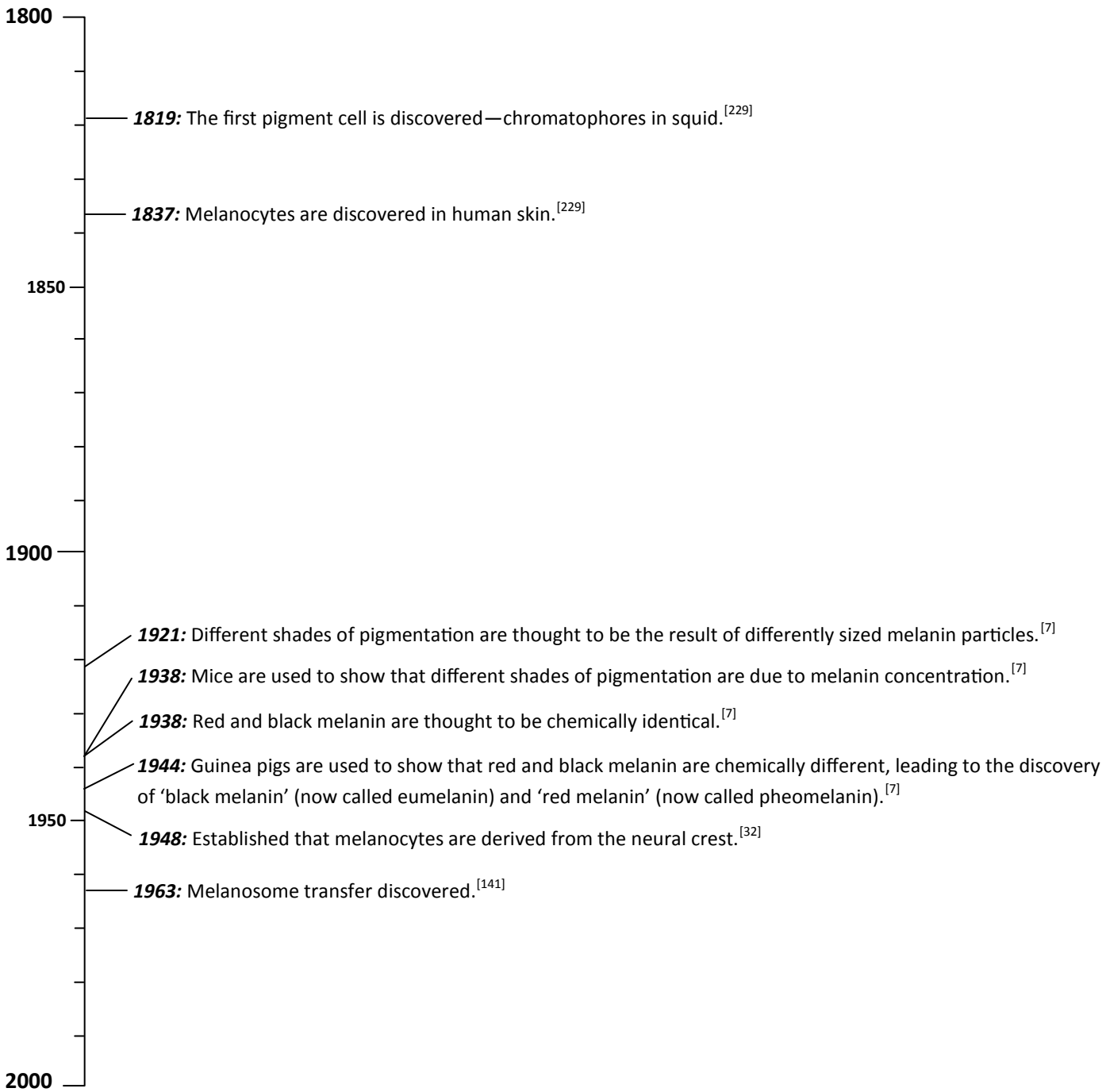


The melanocytes serve two important functions in the epidermis: pigmentation and UV protection.

Pigmentation. The darkness of skin pigmentation is not based on the number of melanocytes, but on how many melanosomes are transferred from the melanocytes to the keratinocytes.[141] Because of this, the actual appearance of pigmentation on a guinea pig is due to the melanin present in the keratinocytes, not the melanocytes; the melanocytes simply make the melanin.[130] Guinea pig skin has more variation in pigment than human skin does.[22] Because albino guinea pigs are acromelanic, even they are capable of producing melanin in at least some of their melanocytes;[183] this is often seen as a dark edge to the pinna or, less commonly, other extremities.

UV protection. The photoprotective effect of melanin is carried out while it is encapsulated in melanosomes in the keratinocytes.[236] The melanin absorbs UV radiation[84] and protects the nucleus, and thus DNA, from radiation.[83] It also works as an oxygen scavenger,[57][141] and a physical sunscreen by preventing UV light from penetrating further into the dermis.[57][212] These photoprotective properties only derive from eumelanin. Pheomelanin, by contrast, is phototoxic and can actually increase the production of free radicals when contacted by UV light.[57][220]

HISTORY



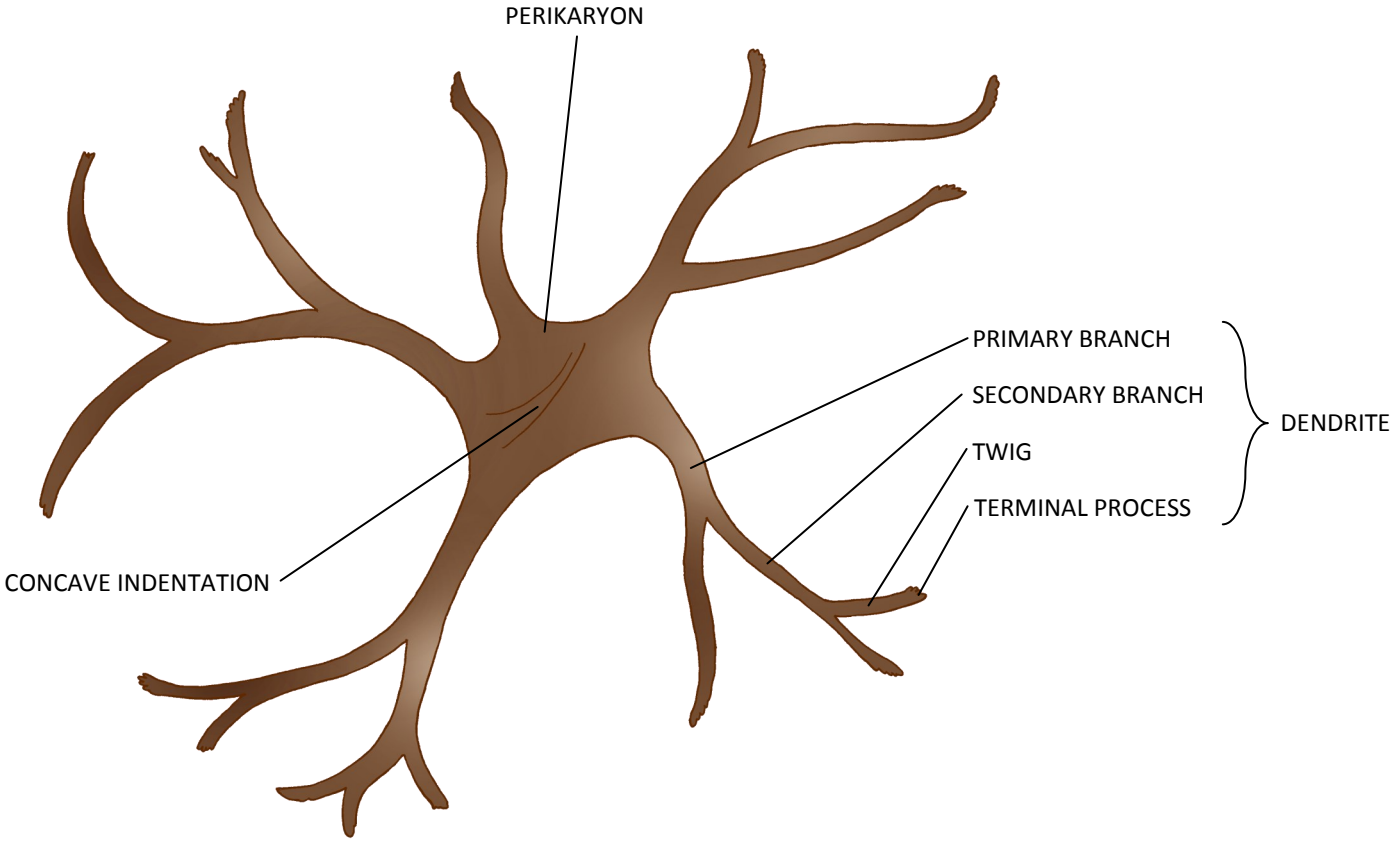
Melanocytes may be round,[172] oval,[27][185] or polygonal[171] in shape. There is often a large concave indentation on the surface of the perikaryon,[171] on the side which split from the parent melanocyte.[169] It may also appear somewhat beaded, which is the melanosomes showing underneath the surface.[120] They are smaller than keratinocytes,[120] ranging from 4 to 18 µm long,[17][171][172] with an average perikaryon diameter of 8 to 10 µm[27] and surface area of 81 to 85 μm^2.[224]

Melanocyte morphology may differ depending on the guinea pig's age, sex, and the area of the body. Melanocytes in females tend to be larger, richer in melanosomes, and contain darker melanin.[185] This is due to estrogen having a melanogenic effect.[185] As guinea pigs mature, males tend to get lighter, whereas females get darker.[185] Ear melanocytes have larger perikarya than abdominal melanocytes.[27] Melanocytes in the ear also tend to have a greater number of dendrites, which are thicker and shorter than those in the abdomen.[27][185]

Dendrites

The dendrites snake between and around the nearby keratinocytes when donating melanosomes.[182] The number of dendrites per melanocyte varies from 2[17] to 10,[172] with averages of 4,[224] 6,[17] and 8[172] reported, depending on the location in the body. Each dendrite forks[170] into gradually tapering branches[27] and twigs.[17] The tips may be ruffled,[120] button-like,[17] or dumb bell-shaped,[171] and are referred to as the *terminal process*[120] or *cap*.[150][17]

The base is between 1[27] and 3 µm[171] thick, with thinner bases in the abdomen and thicker bases in the ears.[27] The tip is around half the thickness of the base.[170] The primary branch is typically around 2.5 µm long,[17] after which point it branches out to lengths up to 30 µm,[171][224] with lengths as long as 48 µm[27] and even 100 µm[20] reported.



There is not much cytoplasm in the perikaryon.[17] The **cytosol** is fairly dark (electron-dense).[63]

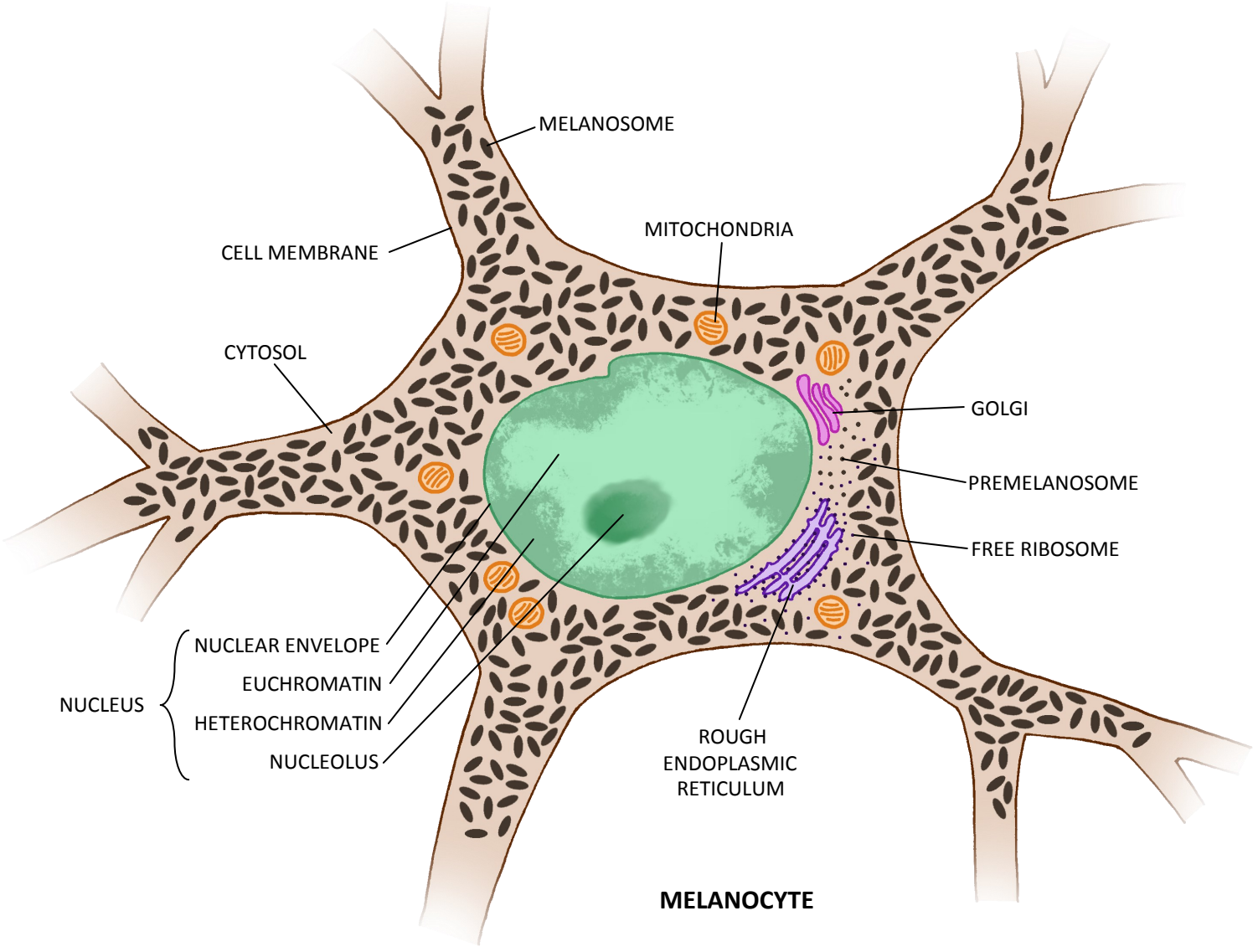
The **nucleus** is located in the centre of the perikaryon and takes up most of the cell.[169] It is similar to the nucleus of the keratinocytes;[120] primarily euchromatic with clumps of heterochromatin beneath the nuclear envelope and throughout the nucleoplasm.[63] It is round[63][172] or oval[169] in shape, with an indentation on one side.[63][170][171][182] It has an average length of 6 µm.[170] It has 1 to 2 nucleoli,[171] though more commonly only one.[120]

The **endoplasmic reticulum** has well-developed rough cisternae[155] but no smooth cisternae.[120]

The **Golgi complex** is well-developed[155][182] and found close to the indentation of the nucleus.[171] There may be more than one Golgi complex.[155]

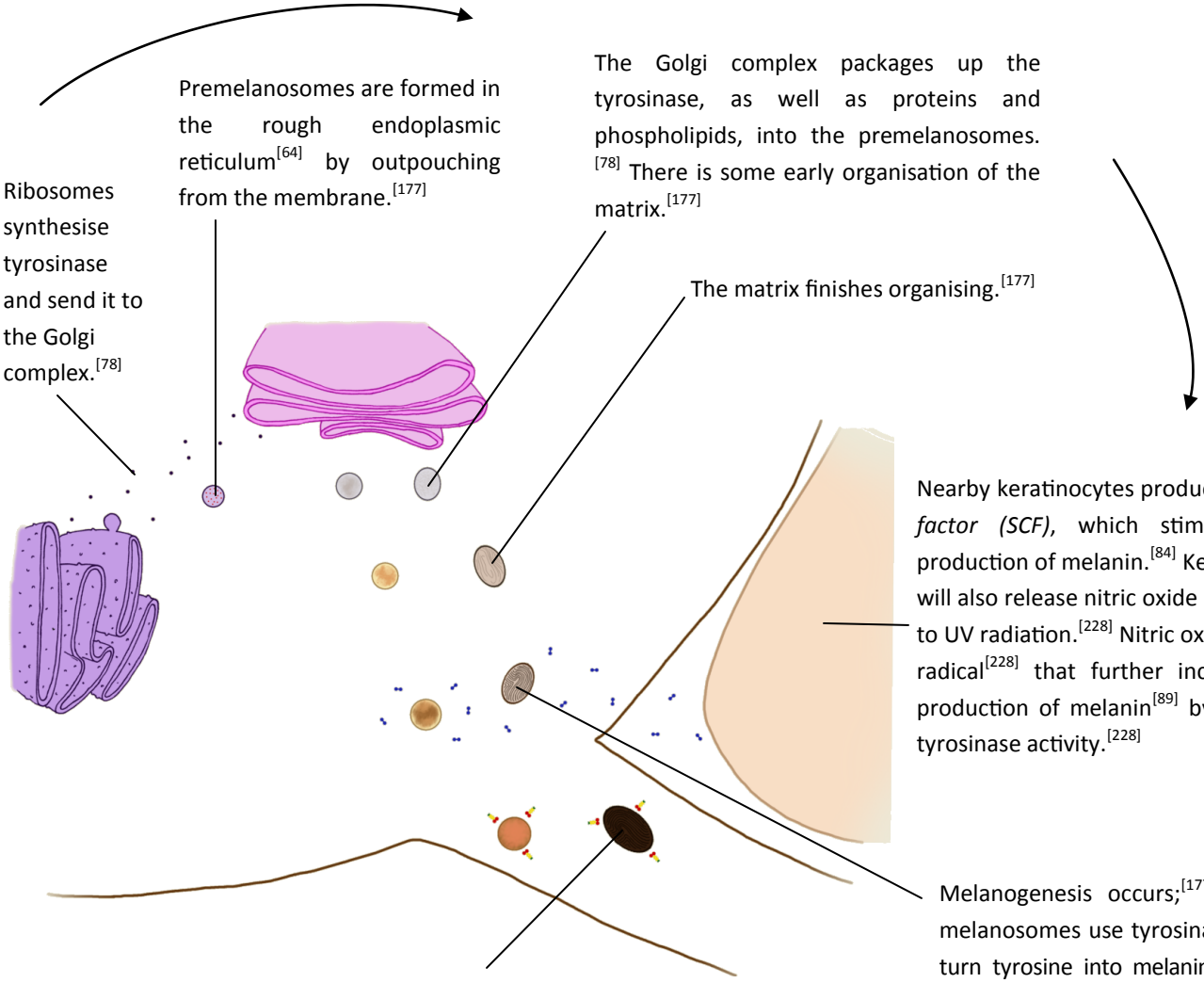
Free ribosomes are present.[247]

There are many **mitochondria**.[63][120][182] They are found primarily in the perikaryon,[171] though will sometimes be seen in the dendrites.[120][171] They are spherical in shape.[171]



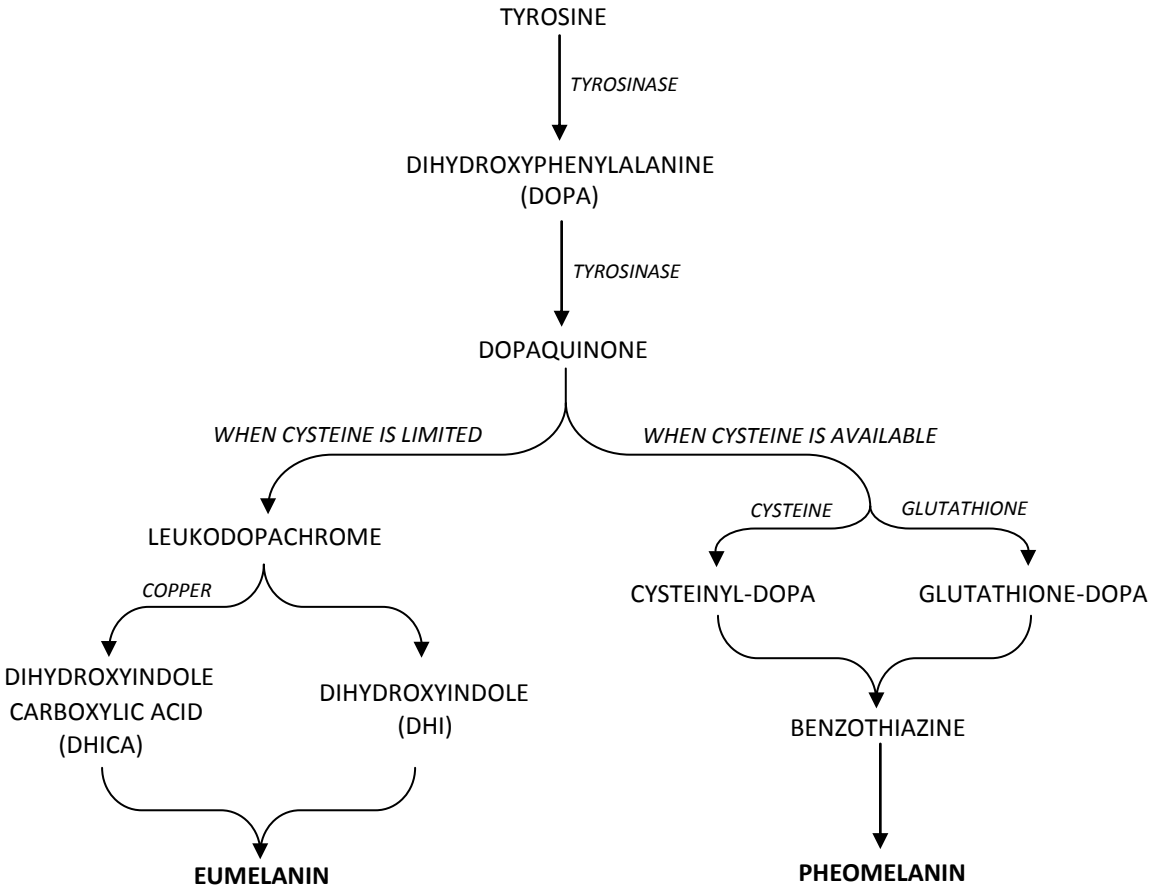
There are many **melanosomes**, scattered in and filling up most of the cytoplasm.[182] They are found in both the perikaryon and the dendrites,[27] but are found in greatest quantity in the dendrites.[120][182] They are oval or round in shape,[120] depending on their type, and have a membrane.[182] They are the organelles responsible for producing and transporting melanin.[57][84][177] An animal's skin colour genes are responsible for the type[84] and size of the melanosomes; small melanosomes are typically 0.1 to 0.5 µm long, whereas big melanosomes are 0.8 to 1.3 µm long.[236] There are two kinds of melanosomes: *eumelanosomes* and *pheomelanosomes*. Eumelanosomes are oval in shape[84] and contain a fibrous matrix.[177] They produce eumelanin.[84] Pheomelanosomes are spherical in shape[84] and contain a granular matrix.[10][177] They produce pheomelanin.[84]

PRODUCTION OF MELANOSOMES



Melanogenesis

Guinea pigs utilise dihydroxyphenylalanine (DOPA) for melanogenesis.[26] There may be up to 0.10 µg of DOPA per gram of coloured skin, by wet weight, whereas there is only 0.03 µg in white skin.[46] The chemical process of melanogenesis has not been specifically studied in guinea pigs, though it can expected to be the same as, or similar to, the process in other DOPA-using mammals. Below is a summation of the likely melanogenic pathway based on available information.[10][23][57][92][177]



Melanin is found in every kingdom and most species of organism.[200] Although other animals utilise many different compounds for pigmentation, mammals only use melanin;[221] this is why mammals are more restricted in their colouration. There are three kinds of melanin: neuromelanin, eumelanin, and pheomelanin.

Neuromelanin is involved in the brain activity of primates, and is not found in guinea pigs.[246]

Eumelanin is responsible for black and brown pigmentation.[57][72][83][84][174] It is composed of dihydroxyindole polymers,[7] and produced from DOPA without cysteine.[83] It is insoluble.[57] It has protoprotective properties,[72] and acts as an oxygen scavenger,[57][141] UV radiation absorber,[84] and physical sunscreen[57][212] in the epidermis. Eumelanin granules are oblong or oval in shape, and are larger than pheomelanin granules.[174]

Pheomelanin is responsible for red and yellow pigmentation.[57][72][83][84][174] It is composed of benzothiazine polymers,[57] and produced from DOPA with cysteine.[83] It is alkali soluble[57] and rich in sulphur.[137] It has phototoxic properties, and can increase free radical production under UV radiation.[57][220] Pheomelanin granules are spherical in shape, and are smaller than eumelanin granules.[174]

There is conflicting information regarding the pheomelanin content of guinea pig skin. Older studies state that eumelanin is the only melanin produced in the interfollicular epidermis of guinea pigs,[174] and that pheomelanin is not produced outside of the hair follicles.[29][220] However, multiple studies on pigment spread in guinea pigs indicate that pheomelanin is regularly found in interfollicular epidermis, and pheomelanin has been found in all skin types in humans.[220]

PIGMENT SPREAD

Pigment spread is a phenomenon discovered in guinea pigs in 1896.[26][155] Since then, it has also been seen in more limited situations in humans,[155] Friesian cattle,[21] spotted pigs,[21] Dalmatian dogs,[23] sheep,[23] and spotted mouse tails.[21]

It is when darker pigmentation encroaches on lighter pigmentation in the epidermis, while leaving the hairs largely unaffected, particularly when the lighter pigmentation takes up a small area.[26] For example, a black guinea pig is born with white spots, where the white spots include white epidermis and white hair. By the time the guinea pig reaches maturity, the surrounding black skin has spread into the white skin, leaving the area with black skin but white hair.[20][21][23][24][26] This skin is called *secondarily blackened*[26] or, less commonly, the *transitional zone*.[99] When the pigment spread is caused by grafts, it is called *artificially blackened*.[20] Occasionally, pigmented hairs will be seen on secondarily blackened skin, though this is relatively rare.[155]

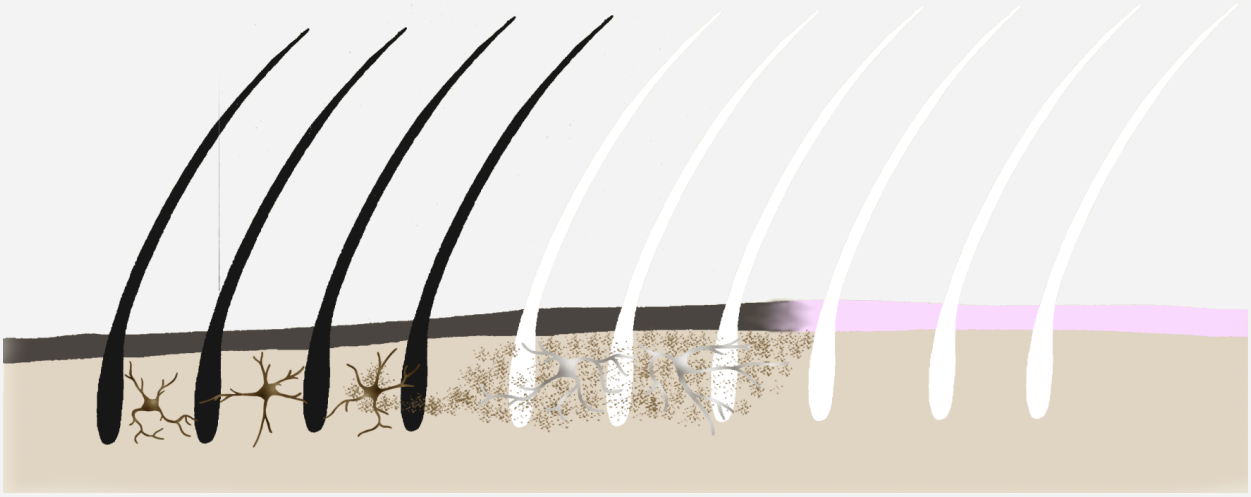
Pigment spread occurs naturally in guinea pigs with the white-spotting, or piebald, gene.[23][155] Black-on-white, red-on-white, and chocolate-on-white encroachment have all been observed naturally in guinea pigs.[21] Encroachment onto non-white skin (including black-on-red,[26] black-on-brown,[24] and black-on-agouti[21]) has also been observed artificially in skin graft experiments. However, it typically takes much longer to encroach on coloured skin than on white skin.[26][21]

Natural pigment spread will result in a secondarily blackened zone of up to 1 cm wide at the reach of adulthood.[20][21][23][24] Artificial pigment spread has reported rates as low as 0.004 mm per day for black-on-red[21] to as high as 0.130 mm per day for one black-on-white study.[26] More commonly, however, the averaged artificial spread rate is fairly consistent with the averaged natural spread rate of around 0.020 to 0.030 mm per day.[21][26][99][155][160] Often the spread will start off rapidly, up to 1.0 mm per week, and then die down to 1.0 mm per month, then 0.5 mm per month, before tapering off completely.[20] Although the mechanisms behind it are unclear, the nervous system appears to inhibit pigment spread; when the nerves serving the relevant area of epidermis are severed, the pigment spread of grafts is much faster.[155]

Over time, four hypotheses have been proposed to explain what causes pigment spread in guinea pigs. Based on all available data, the most plausible scenario is that both the migration and infection hypotheses are correct in different situations: where pigment spreads naturally into white-spotted (or piebald) skin, migration is the culprit; where darker pigment spreads into already-pigmented skin, infection is the cause.

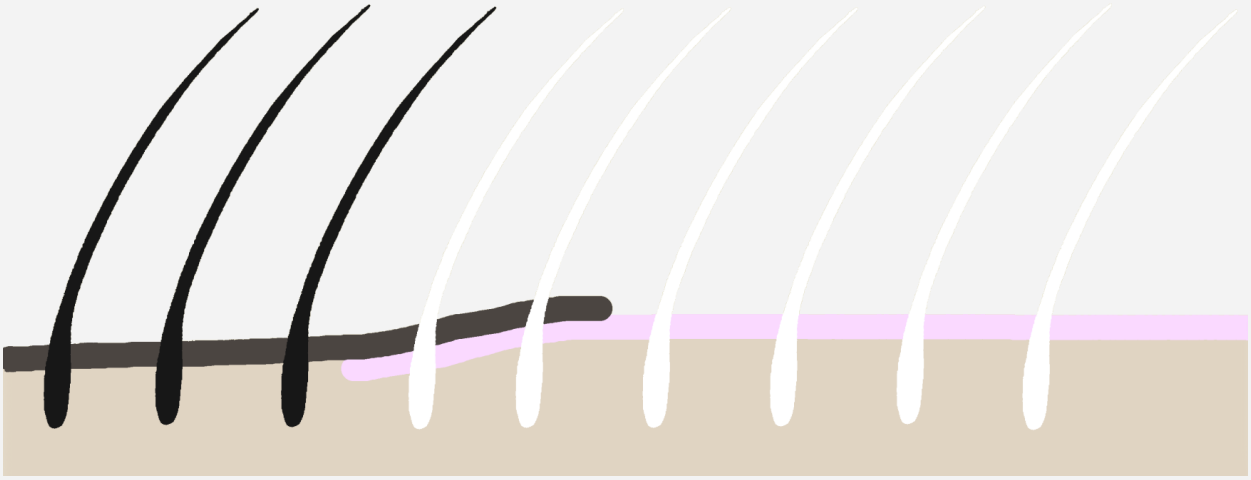
Diffusion hypothesis

This hypothesis states that some compound involved in pigmentation — such as the melanogenic enzymes or the melanin itself – are simply bleeding from the black area into the white area via diffusion.[19] A modified proposal was that the melanin from the black melanocytes migrated into the melanocytes of the white skin.[35] This hypothesis was quickly rejected.



Overgrowth hypothesis

This hypothesis states that the black epidermis itself was growing over the top of the white epidermis and displacing it.[18] It was rejected after studies showed that pigment spread does not affect the keratinocytes, and that grafted skin will remain as whatever type of skin it originated from. For example, grafting foot thick skin onto abdominal thin skin will result in pigment spread, but not any change in skin thickness or layers.[24]



Infection hypothesis

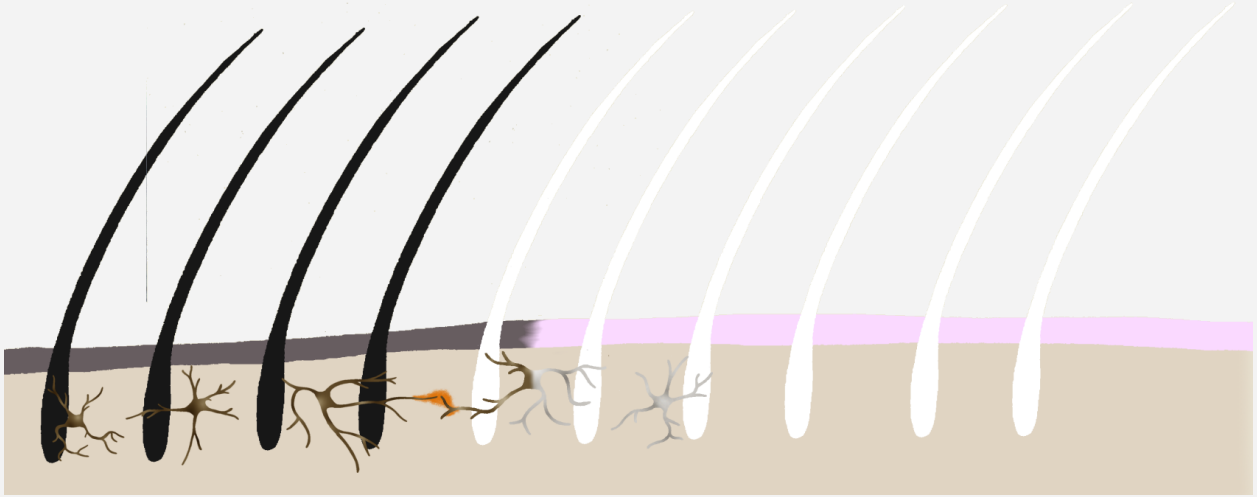
This may also be referred to as *phenotypic transformation*.[26] It states that amelanotic melanocytes are turned into melanin-producing melanocytes, and pheomelanin-producing melanocytes are turned into eumelanin-producing melanocytes.[26] This is done by passing on some kind of infective agent that regulates melanogenesis.[21]

Support #1. Before it was discovered that melanosome transfer is the result of keratinocytes phagocytosing melanocytes, and melanocytes were thought to secrete their melanosomes into the keratinocytes, it was suggested that melanocytes might also secrete their melanosomes into other melanocytes.[24][26] This was further supported by the finding that: melanocytes, of all types, were found capable of creating a network across the epidermis by touching their dendrites together;[24][26] that pigment spread does not occur in non-epidermal epithelia or epidermis where the dendrites are unable to create this network, such as on the tongue;[24] that pigment spread does not spread into the hair follicle, which is also unconnected to the interfollicular dendrite network.[20]

Support #2. Studies in guinea pigs show that secondarily blackened red skin has only eumelanin-producing melanocytes in it, despite having the same density of melanocytes as when there were only pheomelanin-producing melanocytes in the area. If the melanocytes were migrating, one would expect both eumelanin-producing and pheomelanin-producing melanocytes to be present during migration.[24][26]

Support #3. In grafting experiments where eumelanin-producing melanocytes are introduced to light epidermis, in such a way that the melanocytes should not survive, pigment spread still occurs.[24] This suggests that the 'infection' begins upon introduction of the graft, then the grafted melanocytes die, but the 'infection' continues on through the native melanocytes.

Support #4. While pigment spread was studied, no indications were found as to what the infective agent might be, and no studies were able to trigger melanogenesis in amelanotic melanocytes;[24][155] this was a major drawback in the hypothesis. However, in the 1980s a study indicated that various agents, including MSH, cAMP, dbcAMP, and theophylline, were capable of 'throwing the agouti switch' and initiating production of eumelanin in yellow mice.[73] In 1991, a study of lethal yellow (A^y/a) mice showed that α-MSH was capable of altering the melanosome production of hair melanocytes; they produced eumelanosomes instead of pheomelanosomes.[73] These conclusions were further supported by the fact that juvenile mice showed the yellow-to-black switch but adults did not, or did so poorly, just as pigment spread stops as adulthood in guinea pigs.[73] Additionally, MSH receptors have been found in rodents to act as 'molecular switchboards', regulating whether MSH is accepted to create a eumelanin pathway, or rejected to create a



pheomelanin pathway.[177] Certain MSH peptides are capable of stimulating or overriding these pathways;[177] in other words, the infective agent could quite possibly be an MSH peptide that makes unresponsive cells responsive to MSH, thus triggering production from eumelanin to pheomelanin.

Shortcoming #1. White-spotted (or piebald) skin has no melanocytes in it, and thus it would not be possible for an agent to infect amelanotic melanocytes in these areas.[24[[26][155] However, this shortcoming would not apply to skin that has melanocytes in it, such as seen in artificial pigment spread.

Migration hypothesis

This is the most popular hypothesis, and was proven to be the correct one for natural black-on-white spread by 1970.[26] It states that the melanin-producing melanocytes physically migrate from the pigmented to the non-pigmented skin.[26]

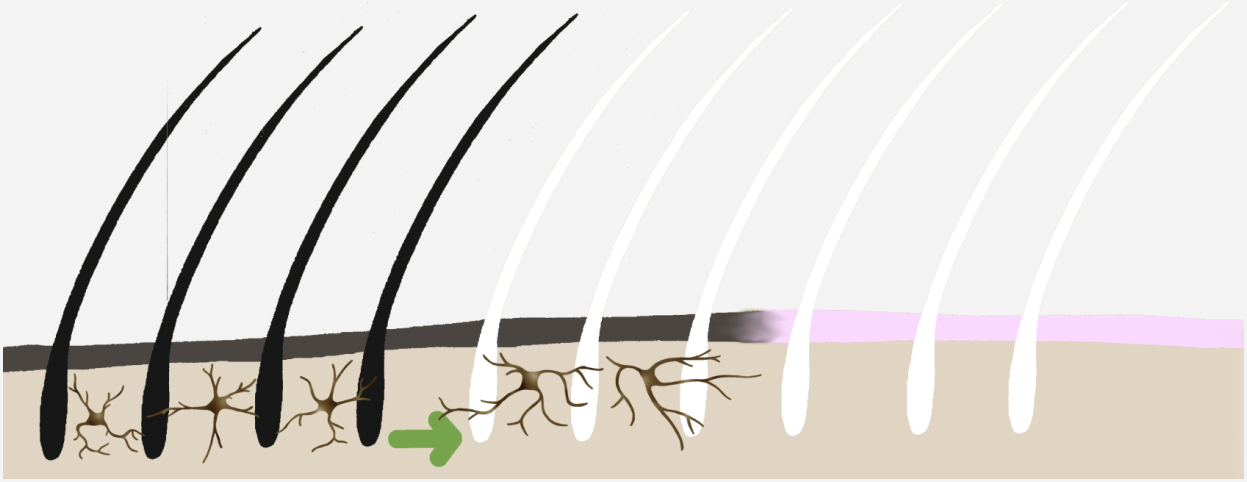
Support #1. Melanoblasts (baby melanocytes) are known to migrate already; during fetal development[20][24] and when fetal melanoblasts are injected into adults.[26] Mature melanocytes are not attached to surrounding cells by desmosomes or other structures,[182][184] and are thus capable of independent movement.

Support #2. Because white-spotting (piebaldism) in guinea pigs is due to a lack of melanocytes, the infection hypothesis can be ruled out for these areas, leaving migration as the most plausible scenario.[24] Grafting experiments consistently and strongly support this.[24][26][155]

Shortcoming #1. For black-on-red encroachment, there is an all-or-nothing appearance in the secondarily blackened zone. Eumelanin-producing melanocytes are not seen partway through migrating into red epidermis, or gradually displacing pheomelanin-producing melanocytes. Instead, only completely eumelanin-producing or completely pheomelanin-producing populations are seen.[21]

Shortcoming #2. This does not explain why pigment spread does not extend into other areas of epidermis, such as the hair bulbs[24][26] or the mouth,[26] even when grafted.[20][24]

Shortcoming #3. This does not explain the mechanism behind why, in the case of black-on-pigmented spread, a population of melanocytes would displace another population of melanocytes.[24][155] This is particularly important when considering the hypothesis that melanocytes are repulsed by each other to maintain a consistent density;[155] there is no biological motive for eumelanin-producing melanocytes to encroach on, and apparently destroy, pheomelanin-producing melanocytes.

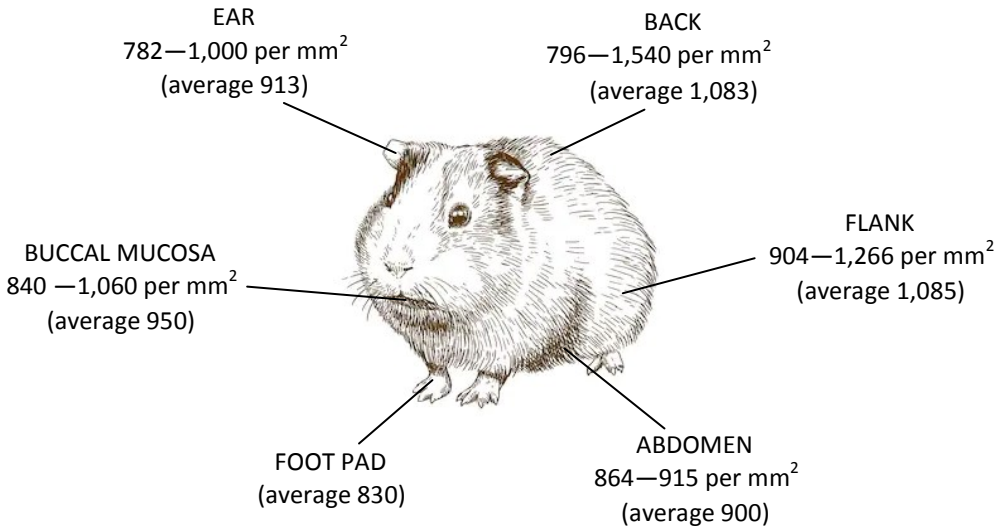


LANGERHANS CELLS

Langerhans cells are found mostly in the stratum spinosum,[35][63][112][201][241] though their dendrites may extend further into the stratum granulosum or even to the basement membrane.[241] Rarely they may be seen in the stratum basale;[35][241] in this case they have less Birbeck granules than those from the stratum spinosum.[35] Unlike in mice, guinea pigs do not have a Langerhans cell situated at the base of each epidermal column; however, the ratio of Langerhans cells to columns is still roughly equal.[115] They are produced by the bone marrow[98][153][240] and then migrate to the epidermis by the lymph vessels.[13] Langerhans cells continuously move from the bone marrow to populate epidermis,[49] crossing through the basement membrane in the process.[240] The lifespan of a guinea pig Langerhans cell has not been studied, though it does take 10 to 15 days for an epidermal population to return to normal after removing them.[240] In humans, the lifespan is around 4 months.[153]

If Langerhans cells are not stained, they will appear clear under the microscope.[231] Historically they have best been stained in guinea pigs with adenosine triphosphate (ATPase).[13][126][240] Gold sodium thiomalate,[95] paraphenylenediamine,[95] cobalt chloride,[95] leucyl aminopepdidase (LAP),[76] leukocyte alkaline phosphatase,[14] and methyl green-pyronon[171] will also stain them, but ATPase brings out the dendrites and makes the cell bodies bolder.[95] Modern staining techniques have started to move away from ATPase, however, and toward green fluorescent protein (GFP) or langerin.[152] Regardless of staining choice, the epidermis is best separated from the dermis for examination of Langerhans cell by a solution of ethylenediaminetetraacetic acid (EDTA), ammonium thiocyanate, or sodium bromide.[95]

Langerhans cells are regularly spaced in the epidermis.[143] They comprise between 2 and 6% of the epidermal cell population,[14][156] though more commonly around 2.6 to 2.8%.[14] In the guinea pig ear, the number of Langerhans cells per mm^2 is typically quite on par with the number of melanocytes per mm^2; so much so that a 1:1 ratio was established in 1960.[23] However, a later study in 1967 showed that the ratio varies depending on the location. Whereas the ear had a roughly 1:1 relationship (specifically, 0.95 Langerhans cells per 1.05 melanocytes), in the abdomen and back it was closer to a 4:1 relationship (specifically 9 Langerhans cells per 2 melanocytes).[241] Generally, the density varies between 500 and 1,500 Langerhans cells per mm^2, depending on the location,[13] with an overall average of around 900 per mm^2.[200] There is no significant difference in density between skin colours.[241] Below are ranges and averages for Langerhans cell densities in different body areas.[11][13][22][76][95][171][241][242]



Guinea pigs were popular laboratory animals for studying the Langerhans cells, and thus important in the process and discovery of their purpose and function.

1868: Discovered by Paul Langerhans.[14][240] They were initially believed to be a sensory cell[240] from the nervous system.[49][201]

1868

A century later they were instead thought to be related to melanocytes:[35][49]

1950

1951-1958: During this time they were believed to be the leftover shell of a dead melanocyte.[22][35][64][153][201] This was primarily for two reasons: because they didn't reproduce in the epidermis and appeared shrunken[64] and moribund;[22] because they were found in the layers above healthy melanocytes[22] and had a relatively equal ratio (when studied in the ears),[64] suggesting they were on their way upward to be desquamated along with the keratinocytes.[22][64]

1955

During the 1960s there was considerable debate against the melanocyte hypotheses:

1959: The shriveled appearance was determined to be due to the method of dying the cells for examination.[64]

1960

1961: The Birbeck granule was discovered by Birbeck.[203]

1963: The evidence that Langerhans cells were melanocytes was questioned and regarded as circumstantial.[37]

1963: Believed to be a melanocyte with retarded or damaged growth.[201]

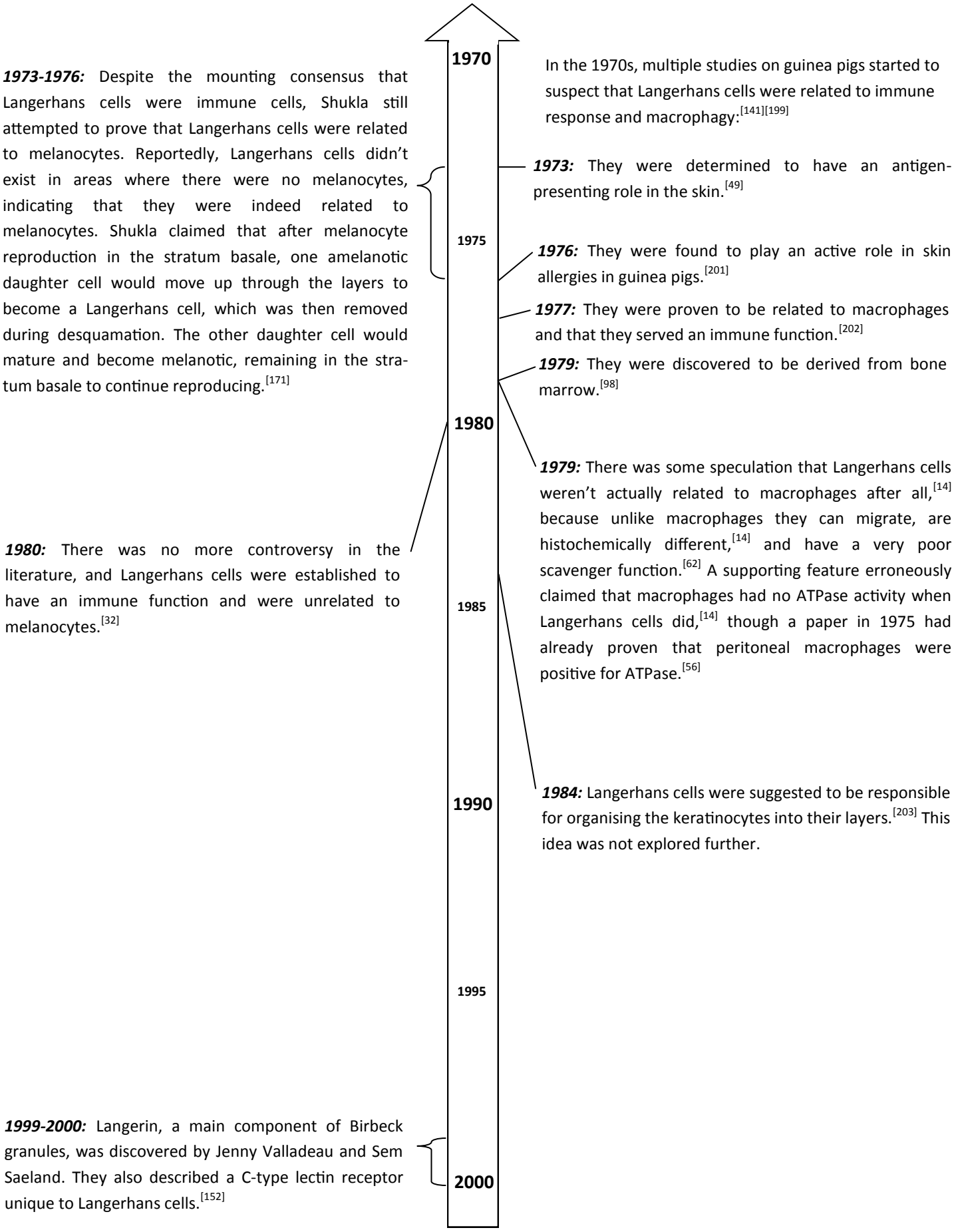
1965

1965-1966: During this time they were believed to be an immature melanocyte[35][141][201] that was amelanotic.[35][182][203] These amelanotic melanocytes reportedly could be stimulated by UV radiation to produce melanin and become proper melanocytes.[182]

1966: It was argued that, even if the origin of guinea pig Langerhans cells was unknown, their morphology—histochemical, ultrastructural, and melanogenic—was indicative enough that they were unrelated to melanocytes.[111]

1968: They were confirmed not to be derived from the neural crest[49] and thus could not be related to melanocytes.[32]

1970


1970
1975
1980
1985
1990
1995
2000
In the 1970s, multiple studies on guinea pigs started to suspect that Langerhans cells were related to immune response and macrophagy:[141][199]
1973: They were determined to have an antigen-presenting role in the skin.[49]
1976: They were found to play an active role in skin allergies in guinea pigs.[201]
1977: They were proven to be related to macrophages and that they served an immune function.[202]
1979: They were discovered to be derived from bone marrow.[98]
1979: There was some speculation that Langerhans cells weren't actually related to macrophages after all,[14] because unlike macrophages they can migrate, are histochemically different,[14] and have a very poor scavenger function.[62] A supporting feature erroneously claimed that macrophages had no ATPase activity when Langerhans cells did,[14] though a paper in 1975 had already proven that peritoneal macrophages were positive for ATPase.[56]
1984: Langerhans cells were suggested to be responsible for organising the keratinocytes into their layers.[203] This idea was not explored further.
1973-1976: Despite the mounting consensus that Langerhans cells were immune cells, Shukla still attempted to prove that Langerhans cells were related to melanocytes. Reportedly, Langerhans cells didn't exist in areas where there were no melanocytes, indicating that they were indeed related to melanocytes. Shukla claimed that after melanocyte reproduction in the stratum basale, one amelanotic daughter cell would move up through the layers to become a Langerhans cell, which was then removed during desquamation. The other daughter cell would mature and become melanotic, remaining in the stratum basale to continue reproducing.[171]
1980: There was no more controversy in the literature, and Langerhans cells were established to have an immune function and were unrelated to melanocytes.[32]
1999-2000: Langerin, a main component of Birbeck granules, was discovered by Jenny Valladeau and Sem Saeland. They also described a C-type lectin receptor unique to Langerhans cells.[152]

FUNCTION

Langerhans cells may be referred to in earlier papers as *migratory cells* because they wander around the epidermis.[148] They interact with the melanocytes and keratinocytes around them to form a keratinocyte-Langerhans-melanocyte (KLM) unit.[141] Langerhans cells function as the skin's immunosurveillance,[231] like sentries, and have three important roles in the epidermis: pathogen surveillance, pathogen prevention, and pathogen response.

Pathogen surveillance

Langerhans cells regulate the immune response by deciding what is and isn't dangerous. In other species they have been observed sensing the external environment by moving the dendrites into the stratum corneum.[53]

Pathogen prevention

Langerhans cells are particularly important for preventing the penetration of pathogens further into the skin. They have three methods of doing this: by phagocytosis, by net, and by cannon fodder.

Phagocytosis. Langerhans cells are capable of ingesting pathogens that enter the skin, though they are less useful in this regard than even the keratinocytes.[85][158][240] As they do not have the phagocytic ability of other macrophages,[8] this is unlikely to be a primary function.[158][173] They have been seen eating their own injured cell parts in response to contact hypersensitivity damage.[173]

Net. Although this has not been observed in guinea pigs, in other species the Langerhans cells will form a network, like a net or trap, termed a *reticuloendothelial system*. This reportedly captures any antigens that penetrate the stratum corneum.[167]

Cannon fodder. Langerhans cells have been seen to act as 'target structures', where antigens damage and attack them instead of other cells.[240] Within 3 hours of exposing guinea pigs to blood fluke larvae in the epidermis, the Langerhans cells surround the larva. Within 12 to 24 hours, they are 'exhausted' by the larva, but after the 24 hour mark, reinforcement Langerhans cells arrive and resume surrounding the larva. In the meantime, other Langerhans cells go to alert the T-cells, which arrive within 2 to 3 days.[159]

Pathogen response

Langerhans cells are critical for initiating the lymphatic immune response in the skin.[159][222][240][75] They stimulate T-cell activation[53][152][173][198] and, to a lesser extent, production.[162][197] They do this by travelling from the epidermis to the dermis,[173] to the lymph,[195] and then into the lymph nodes,[154][199] which are referred to as *skin-draining lymph nodes* (SLN)[159] or *skin-associated lymphoid tissue* (SALT).[203] There they show their antigens[85][203][159] to the T-cells which proliferate there.[159] They present Ia antigens[12][13][62][75][98][162][197][198][200][240] on their plasma membrane,[85] forming a rosette appearance that is appropriate termed *rosetting*.[200][201] They also have Fc-IgG receptors,[62][197][198][203] C3b receptors,[203][15] and B cell alloantigens.[13] C3b rosette formation is temperature-dependent.[15] Langerhans cells are the only cells in the epidermis that express Ia antigens or have Fc-IgG receptors.[199] They are particularly important in contact allergic reactions;[85] In mice, areas with low quantities of Langerhans cells are less likely to reject skin grafts, or when they do the reaction is less aggressive.[13]

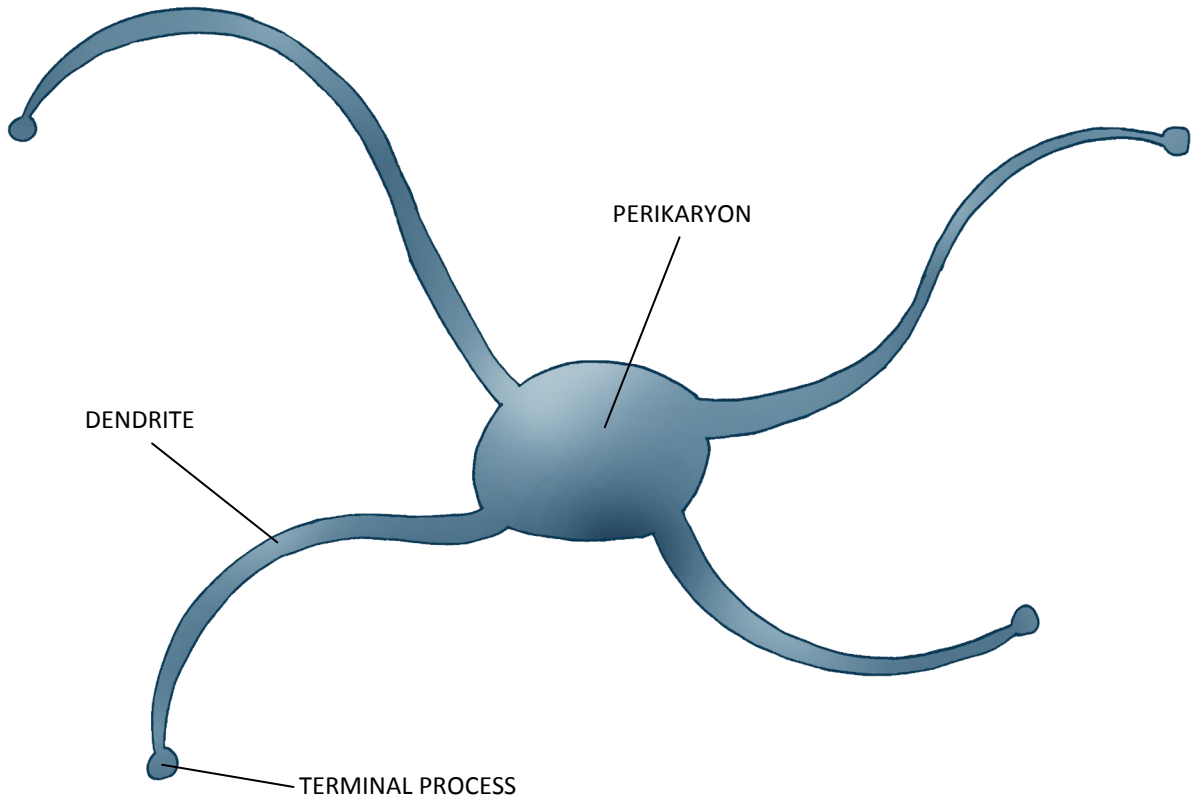
Langerhans cells are responsible for the guinea pig's unique resistance to ixodid ticks, by trapping and presenting the salivary antigens to the lymphocytes.[203]

Langerhans cells have a round or oval body.[168] Because they often lose their dendrites in tissue cultures,[168] early literature considered them to be pleomorphic;[56] however, there is no significant difference in perikaryon size or shape, or dendrite size or shape, in different areas of the body, except for the paw pads.[241] They are considerably smaller than keratinocytes,[115] with a perikaryon length of 7 to 9 µm and width of 5 to 9 µm.[170][171] The surface of the cell is flat and smooth,[171] with Fc-IgG receptors[62][197][198][203] and C3b receptors.[15][203] They do not have any E receptors.[201]

Dendrites

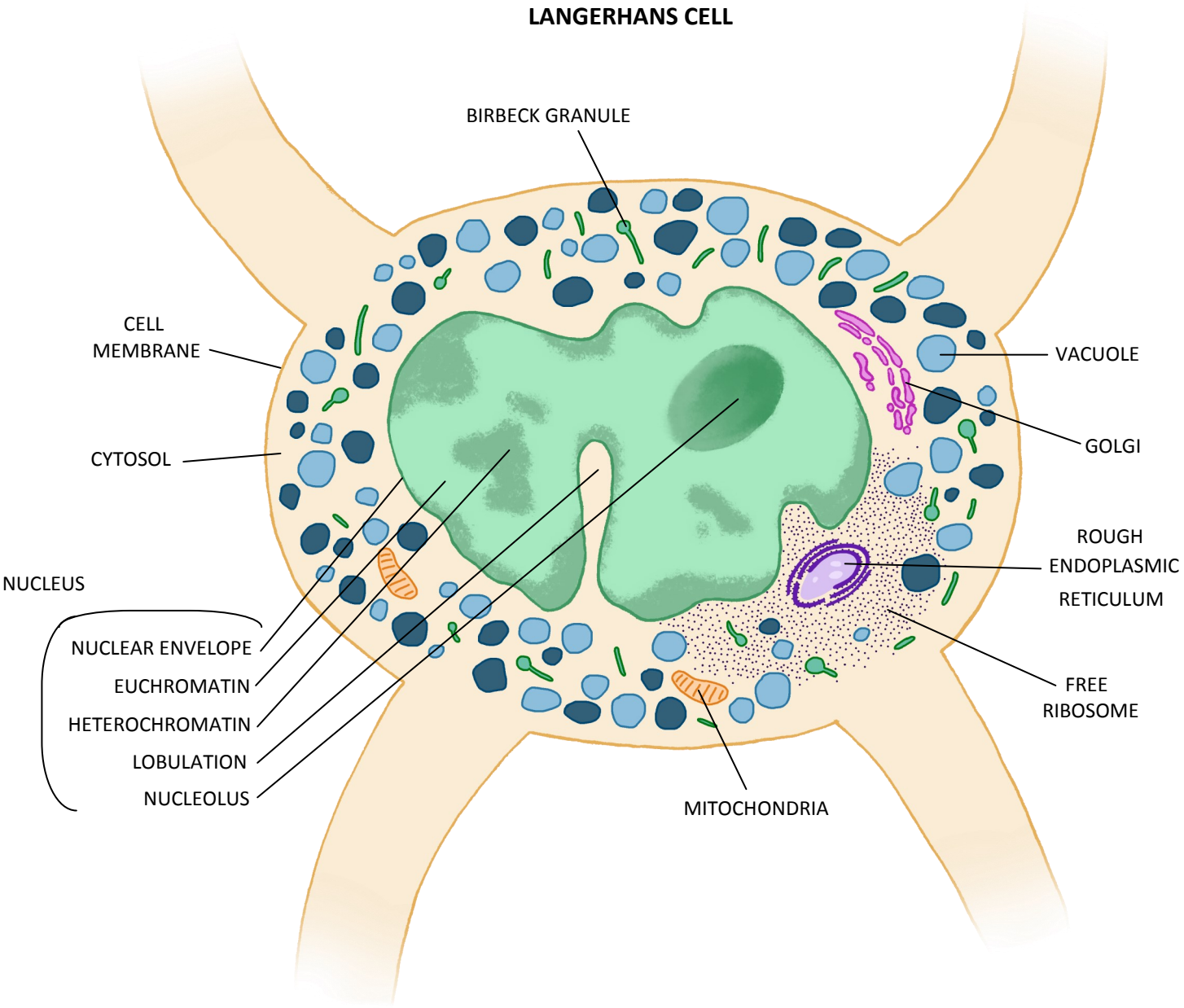
There may be up to 12[56] well-developed[182] dendrites on a Langerhans cell, though normally there is not more than 5.[170][171] They commonly have a somewhat crab-like dendrite arrangement, with two longer dendrites facing upward and two shorter dendrites facing downward.[168] The dendrites are 1 to 2 µm,[171] though more commonly 1 µm,[170] thick at the base, and 13 to 35 µm long.[170][171] There is no branching, but they do have terminal processes at the end.[56]

Langerhans cells use their dendrites to move around; this is referred to as *pseudopodial movement*.[56] The dendrites repeatedly touch keratinocytes by extending and withdrawing,[56] and will weave between[23] or wrap around them. The dendrites can extend for considerable distances,[182] forming a network of sorts around the keratinocytes of the stratum spinosum.[49] Whether the dendrites of different Langerhans cells do[23] or do not[241] touch each other, is conflicted in the literature.



Langerhans cells have a clear **cytosol**.[23][33][49][85][201] They have enzymatic activity in adenosine triphosphatase (ATPase),[14][85][148][222] aminopeptidase,[148][222][241] nucleoside esterase,[241] and alkaline phosphatase.[14] There are low levels of nonspecific esterase[14][222] and sometimes acid phosphatase.[222] They do not have any **desmosomes**[34][63] or **tonofilaments**.[34][63]

The **nucleus** is 3 to 5 µm long.[171] It is mostly euchromatic with clumps of heterochromatin around the periphery.[63] It has 3 to 7[182] heavy indentations[33][34][35][49] or lobulations,[33][63][85][200][201] with an average of 4.[182] In some cases the lobulations are so great that they almost[79][173] or even do[120] cut the nucleus in half. It reportedly does not have a nucleolus,[171] though on personal examination of photographs it does appear to have one.[79][200]



The **endoplasmic reticulum** has not been described in guinea pigs, though personal examination of photographs indicate that it is present in Langerhans cells. The *rough endoplasmic reticulum* is oval in shape, and around 1.5 µm long and 0.8 µm wide.[222] No *smooth endoplasmic reticulum* was personally observed in the photographs.

The **Golgi complex** is large,[82] well-developed,[182] and found near the nucleus.[171] It has a linear or fusiform shape.[171]

There are no or few **mitochondria**.[171] Those that are present are somewhat bean-shaped.[173]

There are many free **ribosomes**.[79][182]

There are many **vacuoles** of varying size, between 0.1 and 1.0 µm in diameter.[79] Some of these appear to be lysosomes.[173]

Birbeck granules

Langerhans cells have a unique organelle[153][201] known as the **Birbeck granule**. It may be referred to as the *Langerhans cell granule* in earlier literature.[200][201] They are composed of langerin,[152] which is a 'mannose-specific C-type lectin.'[153] Cells in the stratum spinosum have more Birbeck granules than those in the stratum basale.[35] They vary in length,[201] though are typically between 0.2 and 0.5 µm long,[79][182] and 30[82] to 36[182] nm wide.

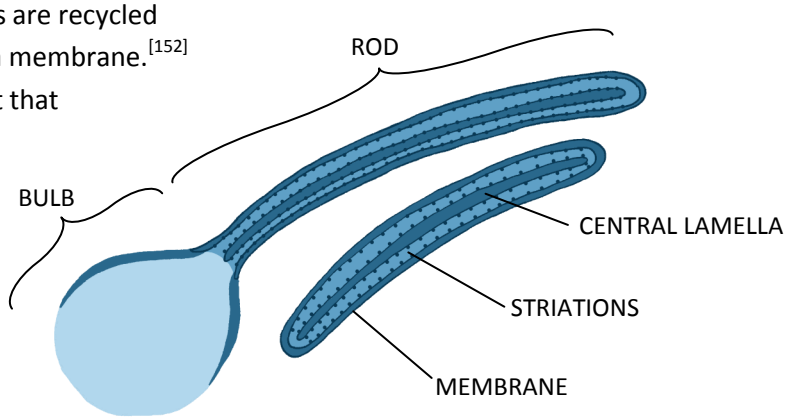
Birbeck granules are rod-shaped with somewhat rounded tips.[35][49][148][182][217][240] One end will sometimes be 'blown out'[35] and look like a tennis racquet.[33][49][217][240] This is called the *bulb*[82] or *saccular terminus*,[231] while the main body of the organelle is called the *rod*.[82] The granule appears to be flat when 3D constructed.[33] Inside there are zipper-like striations.[33][201] on either side of a central line that runs down the length of the granule. This is called the *central lamella*,[217] *linear band*,[182] or *middle layer*.[82]

The granules are usually seen around the periphery of the cell,[63] near the cell membrane[82][148] or the Golgi complex.[49] There are two main hypotheses for their origin: endocytic and Golgi.

Endocytic.[53][217] This hypothesis states that Birbeck granules form via an invagination of the plasma membrane.[62] A study found that a peroxidase marker, when placed outside the plasma membrane, ended up inside the granules, indicating that it was taken up by the granules at the cell surface.[82] However, other studies contradict this, stating that markers do not reappear in the granules.[62]

Golgi. This hypothesis states that Birbeck granules are made by the Golgi complex.[62][158] They then move to the plasma membrane, attach to it, and expel their contents into the intercellular space.[62]

The function of the Birbeck granule is not clear, though it appears to be part of the *endosomal recycling pathway*, where molecules are recycled around the cell, especially when related to the plasma membrane.[152] Proponents of the endocytic origin hypothesis suggest that they are involved in taking in antigens as part of the cell's antigen expression.[153] In any case, the granules likely have some role to play in ATPase activity, because studies in guinea pigs show that Langerhans cells with absent or abnormal Birbeck granules are also negative for ATPase.[79]



MERKEL CELLS

There have been very few studies done on the Merkel cells of guinea pigs. They are known to be a sensory cell for touch,[233] though there is still some debate over exactly what kind of touch they are sensing. They were discovered in 1875[232][233] by Friedrich Merkel,[114] and are found to some extent in all vertebrates.[88] Touch domes and haarscheibe were described in 1902 by Pinkus.[178] They may be simple called *tactile cells*, though this should be avoided because there are other types of tactile cells in the dermis below.

They are best stained immunohistochemically.[31] As they produce the cytokeratin 20 protein,[31] antibodies against cytokeratin 20[31][114] have proven to be useful for staining.[218] Other stains described for guinea pigs include alkaline phosphatase,[232] toluidine blue,[47] hematoxylin and eosin,[63][133] and cholinesterase.[234] In humans, the fluorescent dyes quinacrine and FM1-43 have also proven effective.[31]

There is still conflicting evidence as to where Merkel cells originate from, with some studies supporting a neural origin and some supporting an epidermal origin.[88] The epidermal hypothesis states that, because Merkel cells contain keratin and desmosomes, they must be more closely related to keratinocytes than to melanocytes.[114][233] The neural hypothesis states that they migrate to the skin from the neural crest, like melanocytes do.[31][232][233] The argument is that, because keratinocytes are themselves very specialised, it is illogical to suggest that Merkel cells are modified keratinocytes that developed sensory functions.[32]

Merkel cells are found primarily in glabrous skin[114][233] and in hair follicles.[114]

In glabrous skin they are found at the bottom of the epidermis, in the stratum basale.[63][77][226][231][232] They sit lower in the stratum basale than the basal keratinocytes, protruding a little into the dermis,[114] though typically the neurite will prevent it from actually touching the basement membrane.[233] They are found in large quantities in the ridges of the guinea pig foot pads, at 250 to 650 cells per mm^2.[218] In other mammals they are found in the glabrous skin of the nose [233] and the mouth,[31] though this has not been studied in guinea pigs. Touch domes do not form in glabrous skin.[179]

In hairy skin, they are only associated with the hair follicles and not found in interfollicular areas.

Touch domes are where the epidermis forms a bulge or lump because there is a cluster of Merkel cells underneath.[31] They may also be referred to as: tactile hair disk,[179][233] tactile disk of Pinkus,[234] tactile pad,[179] hair disk,[31][179][233] hair disk of Pinkus,[233] touch spot,[31][179] touch corpuscle,[31][179] tylotrich pad,[179] Iggo disk,[31] Iggo dome,[179] Iggo-Pinkus dome,[179] tastflecke,[179] Merkel tastflecken,[179] or Merkel touch spot.[179] *Haarscheibe* are what touch domes are called when they are associated with a hair follicle.[31] Guinea pigs do not have touch domes in their glabrous skin,[179] and based on available information do not appear to have any in their interfollicular hairy skin. They do have haarscheibe, which will be discussed in the paper on hair follicles and not here.

First and foremost, Merkel cells have a mechanosensory function.[114] Secondarily they are believed to serve an endocrine function.[114]

Mechanosensory

Merkel cells are the only touch receptors found in the epidermis, though there are several other receptors found in the dermis. Their function has not been studied in the glabrous skin of guinea pigs, though it can be extrapolated from other animal studies that they detect when the epidermis has been deformed from touch, and send neurotransmitters to the nerve endings attached to them.[114] In humans, Merkel cells rely on calcium and potassium channels to regulate the triggering of a touch sensation.[31]

There is conflicting information as to what exactly Merkel cells are sensing. In humans, stimulation of them does not elicit a conscious sensation of touch.[114] However, in cats, touching the cells causes them to move, indicating that they can consciously feel it.[179] In humans, they are served by Aβ fibres, which are basic touch receptors and not associated with nociception or proprioception.[31] However, mammalian Merkel cells do produce compounds that are known to be responsible for eliciting a sensation of irritation.[114] Touch domes will also sometimes be served by Aδ or C fibres, which are associated with nociception.[31] In any case, Merkel cells are always concentrated wherever the specific animal requires tactile perception, such as the snouts of pigs[31] or the fingertips of humans.[233]

Endocrine

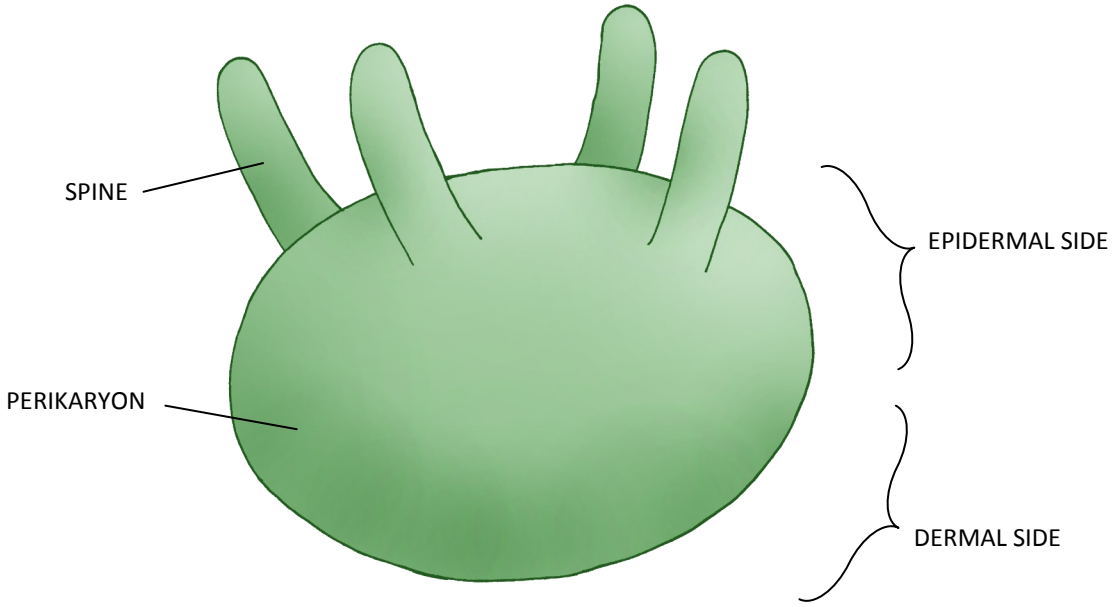
Free, or uninnervated, Merkel cells are those that are not attached to a nerve fibre.[233] In humans these can account for 20 to 30% of total Merkel cells.[218] They are thought to serve some kind of endocrine role,[114] though there is reportedly no evidence of exocytosis in any of these uninnvervated cells.[77] In humans, Merkel cells are rarely found in the bulge area of the hair follicles, so they are thought to have a function in hair development and/or eccrine sweat glands.[114] However, in other mammals, the Merkel cells are often found in the bulge area of the hair follicles,[77] and guinea pigs don't have eccrine sweat glands,[185] so this is unlikely to be the case in guinea pigs.

It is known that innervated Merkel cells serve a neuroendocrine function.[31] They are known to produce hormones,[31] store them in the Merkel cell granules,[114] and secrete them in response to touch.[31][114] As of 2007, there were 75 proteins found to be expressed by Merkel cells among all the species studied.[31] Of these, only the neuropeptide met-enkephalin is known in guinea pigs.[114]

Most Merkel cell morphology and physiology has been studied in humans and rats, with little information available for guinea pigs. As a result, information from the other species has been incorporated in an attempt to paint a better picture of what guinea pig Merkel cells look like.

They are round[232][233] or oval[31][114][232][233] in shape. Based on personal examination of photographs, guinea pig Merkel cells appear to be 5.5 to 6.0 µm high and 9.5 to 10.5 µm wide, not including the spines.[63][218] In humans they are 10 to 15 µm wide;[31][114] around the same size as, or slightly larger than, the basal keratinocytes.[232][233]

Merkel cells have projections of the plasma membrane on the epidermal side of the cell. These are called **spines**,[114][233] protrusions,[233] lobulations,[114] microvilli,[31][114] horns,[232] or roof feet.[233] They are associated with nerve terminations[114] and comprised of cytosol inside.[233] They protrude into the surrounding keratinocytes,[31][77][233] which is often referred to as *interdigitating*.[77] They have not been described much in guinea pigs, though in humans they are up to 2.5 µm long.[114]



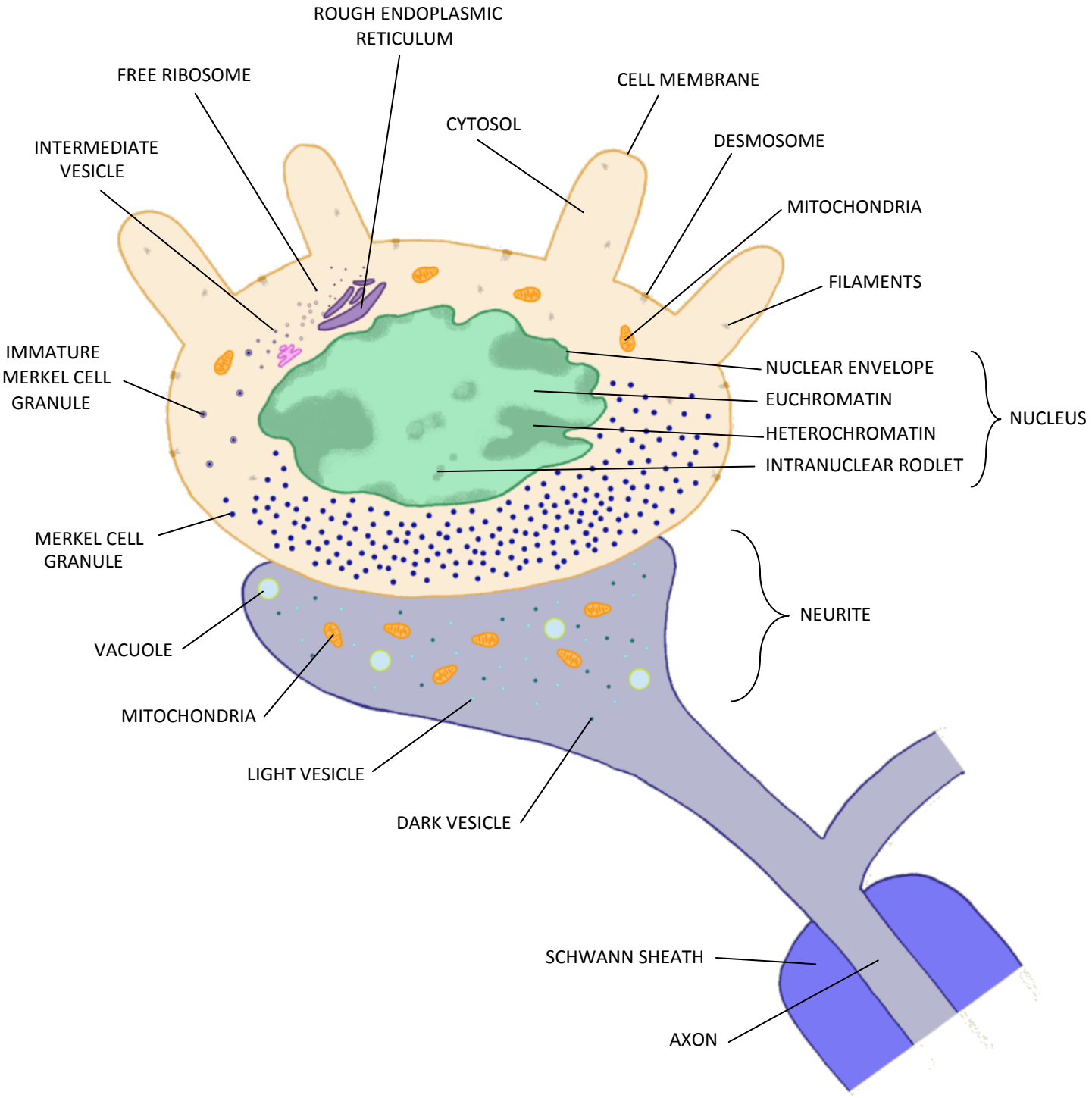
Innervation

Merkel cells are closely associated with a nerve ending.[232] These endings are referred to as a *neurite*,[31][233] a meniscus,[233] a nerve fibre junction,[114] or a nerve plate.[90] The Merkel cell and nerve ending together are often called a *Merkel disk*[31] or a Merkel-neurite complex.[231]

The neurite touches the bottom of the Merkel cell.[232][233] The axon fuses to the basement membrane[233] and the membrane of the Merkel cell.[232] The axon may lose its myelin sheath as it approaches the epidermis.[178] It is a type I slowly-adapting mechanoreceptor.[77][114] Most studies state that the interaction between Merkel cells and their neurites is synaptic.[77][114][226] Free nerve endings are possible when there are no associated Merkel cells.[31][127]

In cats, the neurite is 8 to 10 µm in diameter and 1 to 3 µm thick.[90] Each axon will supply 1 to 2 Merkel cells (average 1.8).[233] The neurite is rich in mitochondria,[218][233] light and dark vesicles,[31][233] vacuoles,[232] and lipids.[232]

MERKEL CELL AND NEURITE (MERKEL DISK)



There are no descriptions about the **cytosol** in guinea pigs; in humans, however, it is clear.[31][114][232][233] Below the nucleus is the dermal or the basal side; above the nucleus is the epidermal side.[233] Most organelles are found on the epidermal side.[233] Organelles described in guinea pig Merkel cells include the nucleus (no nucleolus described), rough endoplasmic reticulum, mitochondria, ribosomes, and Merkel cell granules. Organelles that are seen in other animals but not described in guinea pigs, though they probably still have them, include the Golgi complex, intranuclear rodlet, cytokeratin filaments, vesicles, and desmosomes. Guinea pig Merkel cells are known to have cholinesterase[234] and alkaline phosphatase[232] activity.

The **nucleus** is round in shape[63] and has clumps of heterochromatin around the periphery.[63] Although the nuclear envelope is indented,[63] it seems to be much less lobulated than in other mammal species.[31][77][139][178][232][233] It is around 6.0 µm long and 3.3 µm wide.[63] There is no obvious nucleolus in any of the photographs examined.

An **intranuclear rodlet** has been described in humans, rabbits, and other rodents. In humans it is 0.4 to 1.6 nm long and 0.2 to 1.4 nm wide. It is found in the euchromatin and comprised of filaments and granular masses.[232]

There are no descriptions of the **filaments** in guinea pigs. In humans, the cytoskeleton of the Merkel cell is made of intermediate filaments comprised of cytokeratin.[31][77][114] These filaments are thinner[233] and fewer[114] than in the keratinocytes. They are found close to the desmosomes,[233] sparsely scattered throughout the cytoplasm,[233] and extend into the spines.[114]

There is a poorly-developed **endoplasmic reticulum**.[63] There are a few *rough* cisternae, though there does not appear to be any *smooth* cisternae.[63]

The **Golgi complex** has not been described in guinea pigs. In rats it is situated near the nucleus and rough endoplasmic reticulum, with flat and anastomosing cisternae.[139] It is associated with two kinds of vesicles: coated vesicles that are 70 nm in diameter, and smooth vesicles that are 15 nm in diameter.[139] In humans it is located on the epidermis side,[114][233] with poorly developed cisternae.[233]

There are a few **mitochondria**,[63] though the shape is undescribed. The shape of Merkel cell mitochondria varies considerably between mammal species, so the shape of guinea pig mitochondria cannot be extrapolated.[233] However, in personal examination of photographs of the neurite, the mitochondria there are around 0.7 µm long and have a pear or dumb bell-like appearance.[127] In other mammals, there is a much higher concentration of mitochondria in the neurite than in the Merkel cell.[77] They appear to be located both on the epidermal and dermal side.[114]

There are a few free **ribosomes**.[63]

There are no descriptions of any kind for **vesicles** in guinea pigs. In rats there are intermediate vesicles involved in the production of Merkel cell granules.[139] In humans, there are multivesicular lysosomes and vacuoles.[233]

Melanosome complexes have not been reported in guinea pigs. However, in humans they are occasionally seen.[31][114][232][233] They are always bound by a membrane with mature melanin inside; immature or membrane-less melanosomes are never found.[233] They are typically located on the epidermal side.[31]

Desmosomes have not been described in guinea pigs. However, in other mammals, desmosomes attach the Merkel cells to the neighbouring basal keratinocytes.[31][114][232][233]

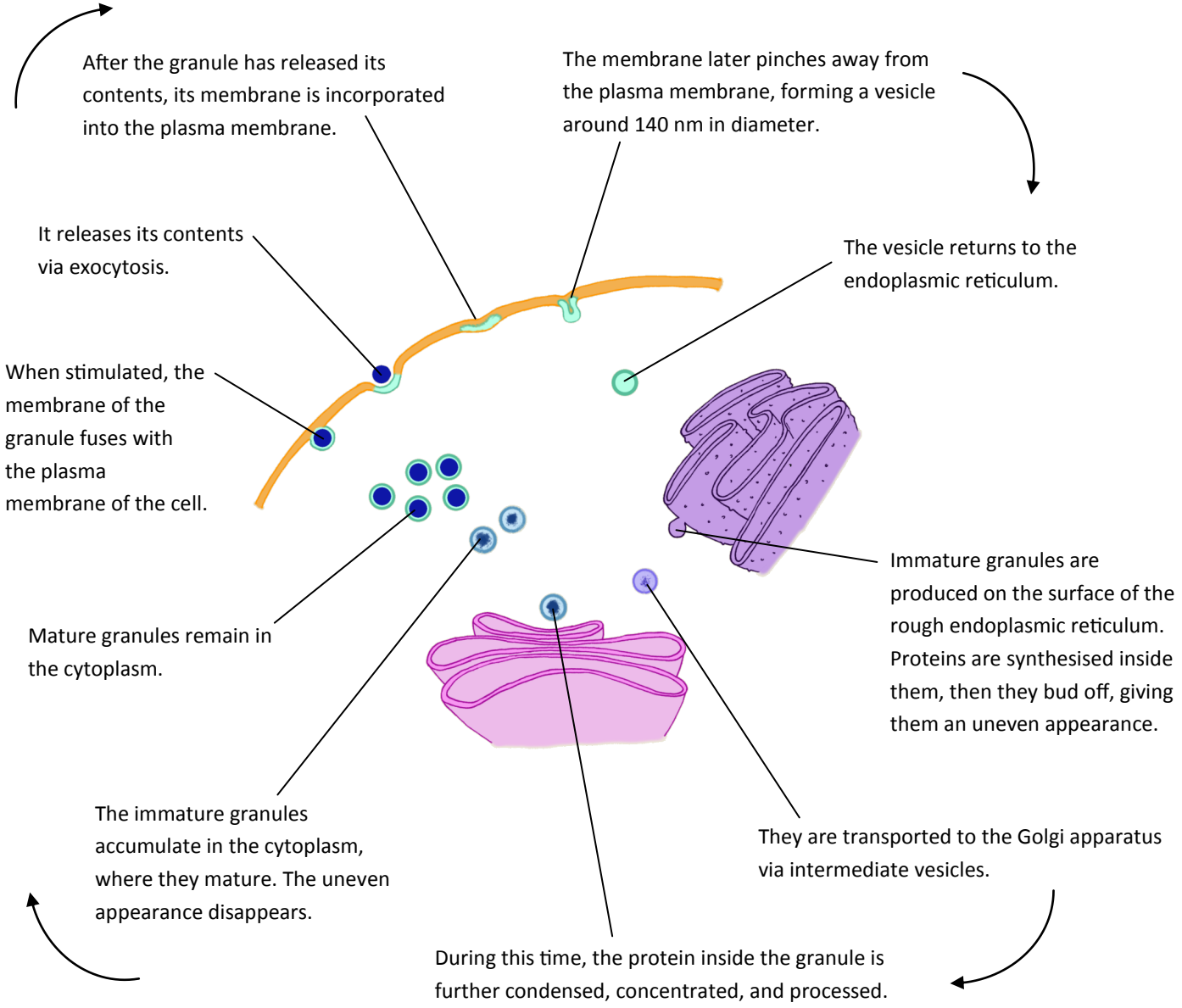
Glycogen particles have not been described in guinea pigs, though they are present in human Merkel cells.[232][233]

Merkel cell granule

These are small, dark-cored granules found in the cytoplasm.[63] They are 80 to 120 nm in diameter[47] and found on the dermal side,[114][232][233] concentrated near where the Merkel cell connects to the neurite.[77][114][232] However, granules at different stages of development may be found attached to the rough endoplasmic reticulum or to the plasma membrane.

Merkel cell granules are considered to be neurological[139][218] secretory granules,[114] which contain neuropeptides.[31] These neuropeptides differ between species.[114] In guinea pigs the only neuropeptide known to be produced is the opioid met-enkephalin,[114][226] used as a stress response and to inhibit pain.[31] It's relative, leu-enkephalin, is not produced in guinea pig granules.[47] The neuropeptides are stored and released from the granules in response to touch.[31]

The life cycle of the Merkel cell granule has not been described in guinea pigs, but it has in rats:[139]

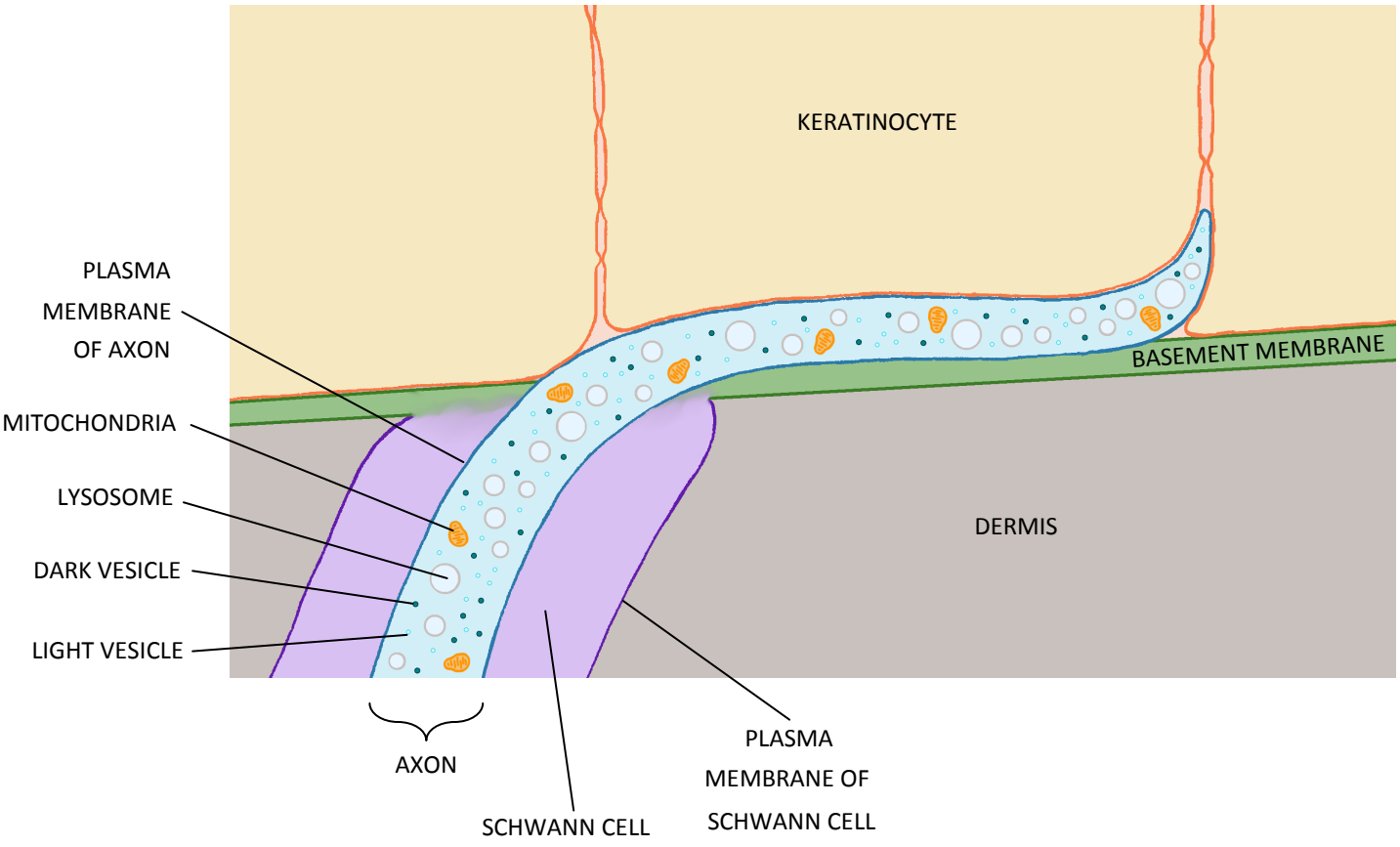


FREE NERVE ENDINGS

Free nerve endings have been found in the epidermis of the guinea pig, unassociated with Merkel cells.[127] They consist of both Schwann cell-axon complexes and naked axons.[127] Most free nerve endings are sensory, though a few of them are adrenergic.[127] They were first discovered in guinea pigs by Mihara, et al., in 1982.[127] Two papers were written by them that year; these remain the only two papers on the topic. They have only been studied in the interfollicular hairy skin of the back.

Free nerve endings are usually situated between the basement membrane and the stratum basale. Rarely they may be found between the basal keratcinoytes.[127] Often the nerve ending will touch a melanocyte.[126] There is no structural difference between black and white skin,[127] though there appears to be a difference in nerve density depending on skin colour.[126] Black, grey, and white skin has an average of 35 (range 6 to 90), 24 (range 4 to 49), and 16 (range 4 to 38) free nerve endings per mm^2, respectively.[126] The researchers propose that the higher concentration of free nerve endings in black skin is because, when subjected to UV radiation, melanocytes reproduce and transfer melanosomes faster; therefore the nerve endings are likely there to allow for signaling when this is necessary.[126] Studies in rabbits and human irises suggest that the nerves are responsible for triggering melanogenesis in melanocytes (when the nerve is rendered unavailable, the area goes white).[126]

FREE NERVE ENDING



Schwann cells envelop the axons.[127]79 The axon-Schwann complexes usually have diameters less than 5 µm,[127] though sometimes they are also encased by perineurial cells, increasing their diameter to 10 µm.[127] Sometimes when the axon enters the epidermis through the dermis, the Schwann cells fuse with the basal lamina of the basement membrane. As a result, the axon is partially enveloped with Schwann sheaths with some part touching the basement membrane. Very rarely does the axon have no Schwann sheath enveloping it and remain naked against the basement membrane.[127]

AXONS

The axons are usually less than 2 µm in diameter.[127]

The axons of the **sensory nerve endings** have the following organelles:

Light synaptic vesicles. They are 40 to 60 nm in diameter.[127]

Dark synaptic vesicles. They are 50 to 80 nm in diameter, and have a dense core.[127]

Mitochondria. They are pear- or dumb bell-shaped, and around 0.7 µm long.[127]

Lysosomes.[127]

Neurotubules.[127]

The axons of the **adrenergic nerve endings** have the following organelles:

Dark synaptic vesicles. They are 40 to 60 nm in diameter, and have a dense core.[127]

Mitochondria. There are many of them.[127]

SCHWANN CELLS

Sometimes, parts of the Schwann cells remain in the dermis, as thin 'cord-like cytoplasmic processes' around 100 nm in diameter.[127] They have the following organelles: rough endoplasmic reticulum, Golgi complex, mitochondria, microfilaments, and multivesicular lysosomes.[127] Glycogen granules may also be seen, which are around 30 nm in diameter, and which accumulate together.[127]

GAPS IN KNOWLEDGE

Because guinea pigs have historically been a popular laboratory animal, quite a lot is known already about their epidermis. However, there are still some areas that have been overlooked in the research. Worthwhile future studies could include:

- The quantity of different lipids in the guinea pig epidermis. Although studies have been done on which types of lipids are present, neither their absolute amounts nor relative ratios have been examined.
- The cell morphology and physiology of the stratum lucidum in guinea pigs. There is currently only one paper on it, which has limited information on the ultrastructure of the cells.
- The β_2 adrenergic receptors in guinea pig keratinocytes and/or melanocytes, as no papers have yet compared them to those of other mammals.
- Whether there is protease-activated receptor 2, or equivalent, present during guinea pig melanosome transfer, as there is in humans.
- The process of melanogenesis in guinea pig melanocytes, and whether it differs from the general melanogenic pathway described in humans.
- The pheomelanin content of guinea pig epidermis, and the ratio of pheomelanin to eumelanin, especially as it relates to different skin colours that look the same to the naked eye (e.g. red, brown, grey, agouti).
- The rate of natural pigment spread, and whether it follows a similar pattern to artificial spread where it encroaches rapidly and then slows down for several months. Natural pigment spread has been largely neglected in the literature in favour of artificial pigment spread. It would be worthwhile to paint a more detailed description and timeline of natural pigment spread in guinea pigs, from birth to maturity, and whether the size of the secondarily blackened zone could be used as an age marker.
- The prevalence and rate of natural pigment spread other than black-on-white. Natural pigment spread studies have focused on black-on-white, with little to no examination of other piebald colours, such as red-on-white, cream-on-white, brown-on-white, grey-on-white, or agouti-on-white.
- A reexamination of the infection hypothesis, in light of the studies on lethal yellow mice, particularly as it pertains to pigmented-on-pigmented spread. Because the establishment of the migration hypothesis only accounted for pigmented-on-white spread, it would be worthwhile to review the infection vs. migration debate as it pertains to pigmented-on-pigmented spread.
- The prevalence and rate of natural pigment spread into white areas that are *not* white-spotted/piebald, such as in acromelanic albinos and calicos. Because non-white-spotted areas contain melanocytes, it would be worthwhile to determine whether pigment-on-white encroachment into melanocyte-containing white areas differs from pigment-on-white encroachment into non-melanocyte-containing white areas.
- The lifespan of the guinea pig Langerhans cell.
- Whether or not Langerhans cells form a reticuloendothelial system in guinea pigs, as they have been seen to do in other mammals.

- The prevalence of interfollicular Merkel cells in different areas of the guinea pig body, including whether they are found in other glabrous skin beside the foot pads.
- The density of Merkel cells based on different demographics, such as age, sex, hairlessness, and location.
- The morphology and physiology of guinea pig Merkel cells. Very little has been described of their appearance or ultrastructure.
- The endocrine role of guinea pig Merkel cells. Very little has been studied on their neuropeptides, and only one such type of neuropeptide has been described.
- The density of free nerve endings based on different demographics, such as age, sex, hairlessness, and location.
- The morphology and physiology of free nerve endings, and the role they play in the epidermis, i.e. whether they only serve to trigger melanogenesis in the melanocytes, or whether they also have a mechanosensory function.

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GLOSSARY AND INDEX

Abutment nexus. See *surface gap junctions*.
Acid anhydride. A group of hydrolase enzyme (ECc 3.6). *15*
Acid phosphatase 1. One of the two types of acid phosphatase found in guinea pig epidermis (ECc 3.1). *16*
Acid phosphatase 2. One of the two types of acid phosphatase found in guinea pig epidermis (ECc 3.1). *16*
Acid phosphatase. A common enzyme in the phosphatase group (ECc 3.1). *16, 21-22, 26, 28, 31*
Acid pyrophosphatase. An enzyme in the phosphatase group (ECc 3.1). *16*
Acidic. Having a pH below 7. *5*
Acromelanic. In guinea pigs, the albino gene is acromelanic, meaning that they still produce pigment in their extremities. This pigment is typically darker in warmer temperatures, and lighter in cooler temperatures. *30, 49*
Actin. A type of contractile protein. In the guinea pig epidermis it forms the epidermal actomyosin complex, along with myosin. *10*
Acylglycosylceramide. A group of ceramide. *43*
Adenosine triphosphatase. A common enzyme in the acid anhydride group (ECc 3.6). Often abbreviated to ATPase. *15, 59, 64*
Adenylate cyclase. An enzyme in the phosphorus-oxygen lyase group (ECc 4.6). *13*
Adenylyl cyclase. See *adenylate cyclase*.
Adrenergic. Relating to adrenaline or noradrenaline. *24, 72-73*
Aerobic. Using oxygen. *14*
Agouti. Hair characterised by a black background and yellow banding. *55, 57*
Alanine. A type of amino acid. *7, 8, 41*
Albino. A gene characterised by lack of pigment. *30, 48*
Alkali soluble. Able to be dissolved in an alkaline solution. *54*
Alkaline 5' nucleotidase. An enzyme in the esterase group (ECc 3.1). *16*
Alkaline phosphatase. An enzyme in the phosphatase group (ECc 3.1). *16, 64, 66, 70*
Alkaline pyrophosphatase. An enzyme in the phosphatase group (ECc 3.1). *16*
Alkaline. Having a pH above 7. *46*
Alloantigen. An antigen that is present in some individuals but not others. *62*
Amelanotic. Not producing melanin. *57-58, 60-61*
Amino acid. A group of molecules that are important protein components. *7, 41-42*
Aminoacyltransferase. A group of transferase enzyme (ECc 2.3). *13*
Aminopeptidase. An enzyme in the protease group (ECc 3.4). *15, 64*
Ammonia. A non-protein nitrogenous compound. *10-11*
Ammonium thiocyanate. A compound used to separate the epidermis and dermis for microscope examination. *59*
Anastomosing. Connection of two or more parts, such as to form a channel or network. *70*
Annular gap junction. A type of gap junction characterised by an invagination moving inwards in a cell. *28-29, 35-37*
Antibody. An immune protein that reacts to an antigen. *66*
Antigen. A foreign body that triggers an immune response. *62, 65*
Antioxidant. A compound that counteracts oxidation. *12, 44*
APase$_1$. Abbreviation. See *acid phosphatase 1*.
APase$_2$. Abbreviation. See *acid phosphatase 2*.
Apposition. Positioning of two things next to each other. *18, 24, 36*
Arachidonic acid. A fatty acid in the ω-6 group. C 20:4. *11-12, 14-15*
Arginase. An enzyme in the ureohydrolase group (ECc 3.5). *15*
Arginine. A type of amino acid. *7-8, 41, 46*
Artificial pigment spread. Pigment spread that occurs as a result of skin grafts. *55, 57-58*
Artificially blackened. *Secondarily blackened*, but as a result of grafting. *55, 57, 58*
Aryl sulphatase A. One of the two types of aryl sulphatase found in guinea pig epidermis. *15*
Aryl sulphatase B. One of the two types of aryl sulphatase found in guinea pig epidermis. *15, 21-22, 26, 33, 35*
Aryl sulphatase. An enzyme in the esterase group (ECc 3.1). 15, *21, 31*
Arylamidase. An enzyme in the protease group (ECc 3.4). *15*
Ascorbic acid. An essential vitamin that is important in regulating enzyme activity. *12, 44*
Asparagine. A type of amino acid. *7*
Aspartic acid. A type of amino acid. *7-8, 41-42*
ATPase. Abbreviation. See *Adenosine triphosphatase.*
Autolyse. When a cell or organelle digests itself or its components. *47-48*
Avascular. Doesn't have its own blood supply. *5*
Axon. The long projection (nerve fibre) of a neuron, which is responsible for sending electrical impulses. *68-69, 72-73*
Aβ fibre. A type of sensory fibre. They identify stretching. *67*
Aδ fibre. A type of sensory fibre. They identify pain. *67*
B cell. A type of white blood cell. *62*
Band. When using electrophoresis to separate and identify molecules, the bands that result indicate the different types or subtypes of proteins. *14*
Basal keratinocyte. A keratinocyte in the stratum basale. *2, 20-24*
Basal layer. See *stratum basale*.
Basal stratum corneum. See *deep stratum corneum*.
Basal zone. See *deep stratum corneum.*
Basement membrane. A thin layer between the epidermis and dermis. *18*
Benzothiazine. A molecule used in pheomelanin production. *54*
Biflavone. A type of phytochemical. *15*
Biopolymer. A large molecule, comprised of repeated subunits, that is found in living things. *47*
Birbeck granule. A unique organelle found in Langerhans cells. *59-61, 64-65*
Black melanin. See *eumelanin*.
Blood fluke. A type of parasitic worm. *62*
Branch. The term given to the forked sections of a dendrite. *51, 63*
Brick and mortar system. A description for the stratum corneum, where the 'bricks' are the keratinocytes and the 'mortar' is the intercellular lipids. *41*
Brick arrangement/pattern. When the keratinocytes are arranged in such a way that each row is offset from the previous one, giving an appearance like layered bricks. *25, 32, 40*
Bulb. In hair follicles, the bulb is the base of the follicle. *49, 58.* In Birbeck granules, the bulb is the 'blown-out' section. *65*
Bulge area. An indented section in the middle of a hair follicle. *67*
C fibre. A type of sensory fibre. They identify pain. *67*
C3b receptor. A type of complement receptor. *62-63*
Ca^{2+}. A calcium ion. *10, 15*
Calcium. An element that functions as an important electrolyte in the epidermis. *13, 21, 24, 26, 33, 37, 43, 67*
Calmodulin. A type of messenger protein. *10, 13*
cAMP. Cyclic adenosine monophosphate. A type of messenger protein. *57*
Cap. See *terminal process*.
Carboxylesterase. A group of esterase enzyme (ECc 3.1). *15*
Carboxylic ester hydrolase. See *carboxylesterase*.
Carboxylic esterase. An enzyme in the carboxylesterase group (Ecc 3.1). *15*
Catalase. An enzyme in the peroxidase group (Ecc 1.11). *14*
Cathepsin B$_1$. One of the three types of cathepsin found in guinea pig epidermis (Ecc 3.6). *15*
Cathepsin C. One of the three types of cathepsin found in guinea pig epidermis (Ecc 3.6). *15*
Cathepsin D. One of the three types of cathepsin found in guinea pig epidermis (Ecc 3.6). *16*
Cathepsin. An enzyme in the protease group (Ecc 3.4). *15, 16*
CE. See *cornified cell envelope*.
Cell body. See *perikaryon*.
Cell membrane. The membrane, typically a plasma membrane, that surrounds a cell. *18, 21, 23-24, 26-27, 30, 32-33, 35, 39, 44-48, 52, 65, 69*
Central lamella. The central line that run downs a Birbeck granule. *65*
Centriole. An organelle that is important during cell division. *22-23, 27-29, 34-35, 37*
Ceramidase I. One of the two types of ceramidase found in guinea pig epidermis (Ecc 3.6). *15, 42*
Ceramidase II. One of the two types of ceramidase found in guinea pig epidermis (Ecc 3.6). *15, 42*
Ceramidase. An enzyme from the hydrolase group (Ecc 3.5). *15, 42*
Ceramide 1. One of the four types of ceramide found in the guinea pig epidermis. *12, 43, 45*
Ceramide. A lipid from the sphingolipid group. *11-12, 43*
Cerebroside. A lipid from the sphingolipid group. *11-12*
Change from order to disorder. The region between 38 and 46 µm thickness in which guinea pig epidermis changes from columnar arrangement to brick or roof -tile arrangement. *40*
Channel. A pore in a membrane, which selectively allows certain ions to pass into or out of the cell. *24, 67*
Chlorine. An element that, when forming chloride, functions as an important electrolyte in the epidermis. *13, 21, 25, 32, 43*
Cholesterol sulphate. A type of esterified cholesterol. *12, 43*

Cholesterol. A lipid from the steroid group. *11-12, 26, 28, 33, 43, 48*
Cholesteryl oleate. A type of esterified cholesterol. *48*
Cholinesterase. An enzyme in the carboxylesterase group (Ecc 3.1). *15, 66, 70*
Chromatophore. A type of pigment cell found in animals other than mammals and birds. *50*
Ciliogenesis. The production of cilia by the centriole. *22-23, 28*
Cisterna. Flattened vesicle in the Golgi complex or endoplasmic reticulum. *21-22, 26, 33, 52, 70*
Cisternae. Plural of *cisterna*.
Citrulline. A type of amino acid. *7-8, 41-42, 46*
Clear layer. See *stratum ludicum*.
Coacervate. An aggregation of droplets. *37*
Cobalt chloride. A compound used as a stain. *59*
Collagen. A protein found in relatively (compared to the dermis) small amounts in the epidermis. *10, 20*
Columnar arrangement/pattern. When the keratinocytes are arranged in such a way that the cells form straight vertical lines. *25, 40*
Commensal. A relationship between two organisms, where one organism benefits and the other remains unaffected. *5*
Complement receptor. A type of receptor, which detects pathogens. *62*
Composite keratohyalin granule. A type of keratohyalin granule, characterised by its profilaggrin content. *37-38*
Concave. Characterised by a surface that curves inward. *51*
Contact allergy. An allergic reaction caused by touching something. *62*
Contact hypersensitivity. An immune response caused by touching something. *62*
Contractile protein. A group of proteins responsible for contracting fibres. *10*
Convex. Characterised by a surface that curves outward. *32*
Corium layer. See *stratum corneum*.
Corneocyte. A keratinocyte in the stratum corneum. *2, 40-48*
Corneodesmosin. A protein found in corneodesmosomes. *46*
Corneodesmosome. A modified desmosome in the stratum corneum. *44-48*
Cornification. See *keratinisation*.
Cornified cell envelope. A tough, insoluble structure that develops in the plasma membrane of corneocytes. *41*
Cornified layer. See *stratum corneum*.
Corny layer. See *stratum corneum*.
Crista. A fold in the membrane of a mitochondrion. *22*
Cristae. Plural of *crista*.
C-type lectin receptor. A receptor that binds to C-type lectins. *61*
Cutaneous layer. See *stratum corneum.*
Cutaneous. Relating to the skin. *5*
Cyclooxygenase. An enzyme from the oxygen receptor group (Ecc 1.14). *14*
Cysteine. A type of amino acid. *7, 20, 32, 38, 41, 42, 44, 47-48, 54*
Cysteinyl-DOPA. A molecule used in pheomelanin production. *54*
Cystine. A type of amino acid, of two cysteine molecules joined together. *7, 42*
Cytokeratin 20. A type of cytokeratin protein. *66*
Cytokeratin. A type of keratin protein. *10, 47, 70*
Cytophagy. The ingestion of a cell, or part of it, by another cell. *30*
Cytoplasm. The material and components inside a cell other than the nucleus. *20-22, 25-26, 28, 30-34, 36, 39, 44, 47-48, 52-53, 70-71, 73*
Cytosol. The fluid in a cell that surrounds the nucleus and organelles. *21, 23, 26-29, 33-34, 36, 38-39, 45, 52, 64, 68-70*
Dandruff. A skin problem characterised by clumped desquamation of the corneocytes. *45*
Daughter. Either of the two cells that result after a parent cell divides. *20, 61*
dbcAMP. Dibuturyl cyclic adenosine monophosphate. An analogue for cyclic adenosine monophosphate. *57*
Deamination. Break down of a molecule by removing an amine group. *11*
Deep corneocyte. A keratinocyte in the deep stratum corneum. *44-47*
Deep stratum corneum. A sublayer of the stratum corneum. *44-47*
Dehydrogenase. A group of oxidoreductase enzyme (Ecc 1.1). *14*
Deimination. Conversion of arginine into citrulline. *46-47*
Dendrite. Long protrusions or extensions from a cell. *30-31, 51-53, 59, 62-63*
Dense body lysosome. A lysosome containing a large amount of dark material. *27-29*
Dense feet. Small protrusions within a centriole. *22*
Dense homogenous deposit. See *single granule*.
Deoxyribonuclease I. One of two types of deoxyribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*

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Cytoplasm. The material and components inside a cell other than the nucleus. *20-22, 25-26, 28, 30-34, 36, 39, 44, 47-48, 52-53, 70-71, 73*
Cytosol. The fluid in a cell that surrounds the nucleus and organelles. *21, 23, 26-29, 33-34, 36, 38-39, 45, 52, 64, 68-70*
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Deoxyribonuclease II. One of two types of deoxyribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Deoxyribonuclease. A type of enzyme in the nuclease group (Ecc 3.1). *17*
Deoxyribonucleic acid. A large molecule, responsible for carrying most of the genetic material. *9*
Dephosphorylation. Break down of a molecule by removing a phosphate group. *38*
Dermis. The section of skin below the epidermis. *3, 18-19*
Desaturase. An enzyme from the oxygen receptor group (Ecc 1.14). *14*
Desiccate. Dry out. *19, 40*
Desmosome. A structure between two neighbouring cells, which adheres them to each other. *23-24, 27, 29-30, 34, 36, 46, 66, 69-70*
Desquamation. The shedding of superficial corneocytes after they have finished their lifespan. *43, 46, 48*
DHI. Abbreviation. See *dihydroxyindole*.
DHICA. Abbreviation. See *dihydroxyindole carboxylic acid*.
Differentiation. The process of the keratinocytes changing as they take on specific or specialised tasks in each layer. *2-4, 20, 40*
Diffusion. Passive migration of molecules from an area of high concentration to an area of low concentration. *56*
Dihomo-γ-linoleic acid. A fatty acid in the ω-6 group. C 20:3. *11-12, 14*
Dihydroxyindole carboxylic acid. A molecule used in eumelanin production. *54*
Dihydroxyindole. A molecule used in eumelanin production. *54*
Dihydroxyphenylalanine. A derivative of phenylalanine that is important in melanin production. *10, 49, 54*
Dimer. Two identical molecules attached to form a larger molecule. *46*
Diunsaturated. An unsaturated fat that has two double bonds. *12, 43, 48*
DNA. Abbreviation. See *deoxyribonucleic acid*.
DNAase I. Abbreviation. See *Deoxyribonuclease I.*
DNAase II. Abbreviation. See *Deoxyribonuclease II.*
DNAase. Abbreviation. See *Deoxyribonuclease.*
DOPA. Abbreviation. See *dihydroxyphenylalanine*.
Dopaquinone. A molecule used in melanin production. *54*
Dry weight. The weight of a substance in a cell, after the water has been removed from that cell. *43-44*
E receptor. A type of receptor, which detects prostaglandin. *63*
Ecc. Enzyme Commission classification.
Eccrine. A type of sweat gland. *67*
Ectoderm. The outermost germ layer in the early embryo. *2*
EDTA. Abbreviation. See *ethylenediaminetetraacetic acid*.
Eicosane. A lipid typically found on the skin surface of mammals. *48*
Electrolyte. Ions which are important in regulating the osmotic content inside and outside of cells. *40*
Electron-dense. Appearing dark under a microscope. *18, 21, 28, 52*
Electron-lucent. Appearing light or clear under a microscope. *18, 28*
EMU. Abbreviation. See *epidermal melanin unit*.
Endocrine. Relating to hormones. *67*
Endocytosis. When a cell invaginates its membrane in order to take in particles from outside. *65*
Endonuclease. An enzyme that breaks non-terminal nucleotides from a polynucleotide chain. *17*
Endopeptidase. An enzyme that breaks non-terminal amino acids from a peptide chain. *15, 16*
Endoplasmic reticulum. An organelle that is important in the production, storage, and transport of proteins and certain lipids. *21, 23, 26-27, 29, 33, 35-37, 52, 65, 70-71*
Endosomal recycling pathway. The process of breaking down defunct organelles or their components and using them for other purposes. *65*
Enzyme. A protein that initiates or speeds up a chemical reaction in the body. *13 -17, 42*
Epidermal actomyosin complex. The cooperation of myosin and actin in the epidermis. *10*
Epidermal appendage. Keratinisied structures on the skin, such as hair or nails. *47*
Epidermal column. The vertical line of keratinocytes that result above a basal keratinocyte. *20, 59*
Epidermal melanin unit. A melanocyte and the surrounding keratinocytes it services. *49*
Epidermal proliferative unit. See *epidermal melanin unit*.
Epidermal ridge. The hills and valleys that are created in the epidermis as a result of the dermal papillae. *2-4*
Epithelia. The thin tissue that forms the outer layer of body surfaces and cavities. *2, 28, 47, 57*
EPU. Abbreviation. See *epidermal proliferative unit*.
Ester. A molecule that has been modified by replacing an –OH group with an –O–alkyl group. *12, 15, 43, 48*
Esterified cerebroside 1. One of the four types of ceramide found in the guinea pig epidermis. *12, 43*
Esterified cerebroside 2. One of the four types of ceramide found in the guinea pig epidermis. *12, 43*
Esterified cholesterol. A cholesterol that has been esterified. *43*
Esterified. The state of becoming an ester. *12, 43*
Estrogen. A group of hormones. *51*
Ethylenediaminetetraacetic acid. A compound used to separate the epidermis and dermis for microscope examination. *59*
Euchromatin. Lightly packed chromosome material. *21, 23, 26-27, 29, 35-36, 52, 64, 69-70*
Eukeratin. See *α-keratin*.
Eumelanin. A type of melanin, responsible for brown or black pigment. *50, 53-55, 57-58*
Eumelanosome. A melanosome that produces eumelanin. *31, 53, 57*
Exocytosis. When a cell attaches a vesicle to its membrane in order to expel its particles outside the cell. *35, 67, 71*
Exonuclease. An enzyme that breaks terminal nucleotides from a polynucleotide chain. *17*
Exopeptidase. An enzyme that breaks terminal amino acids from a peptide chain. *15*
Extracellular space. See *intercellular space*.
Fatty acid. A group of lipids. *11-12, 42-43, 45, 48*
Fatty alcohol. A group of lipids characterised by having long chains of alcohols. *48*
Fc-IgG receptor. A type of Fc receptor that binds to IgG antibodies. *62-63*
Ferritin. An iron-rich protein. *30, 36*
Fibril. A smaller component that makes up a filament. *46*
Fibroblast. A cell found in the dermis, responsible for producing collagen. *11, 20*
Fibronectin. A glycoprotein found in the dermis. *20*
Filaggrin. A group of histidine-rich proteins formed by the breakdown of profilaggrin. *5, 10, 13, 38, 41, 43, 46-47*
Filament. A long chain of proteins that takes on a fibre-like appearance. *24, 26, 34, 46-47, 69-70*
Flavonoid. A type of phytochemical. *15*
FM1-43. A compound used as a stain. *66*
Follicle. See *hair follicle*.
Follicular. Relating to a hair follicle. *33, 49*
Free amino acid. An amino acid that is not bound within a larger protein. *5-7, 41, 46*
Free fatty acid. A fatty acid that has not been esterified. *5, 43, 45*
Free Merkel cell. An uninnervated Merkel cell. *67*
Free nerve ending. A nerve ending that is unassociated with a Merkel cell. *72-73*
Free radical. A molecule that causes oxidative damage by stealing electrons. *14, 42, 44, 50, 53-54*
Free ribosome. A ribosome that is unattached to an organelle and found roaming the cytoplasm. *22-23, 26-27, 33, 52, 65, 69-70*
Free sterol. A sterol that has not been esterified. *48*
Fusiform. Having a shape that is wider in the middle and tapered at the ends. *65*
Galactosidase. An enzyme in the glycoside hydrolase group (Ecc 3.2). *16*
Gap junction. Areas where the membranes of adjacent cells come together. *22, 28, 36*
Geddic acid. A fatty acid in the saturated group. C 34:1. *43*
Germinal layer. See *stratum basale*.
GFP. Abbreviation. See *green fluorescent protein*.
Glabrous skin. Skin that does not contain hair follicles. *7, 66-67*
Glucocerebroside. A lipid in the cerebroside group. *12*
Glucose-6-phosphatase. An enzyme in the phosphatase group (Ecc 3.1). *16, 21, 22, 26, 33*
Glucosidase. An enzyme in the glycoside hydrolase group (Ecc 3.2). *16*
Glutamate. An ion of glutamic acid. *38, 41, 46*
Glutamic acid. A type of amino acid. *7-8, 41-42*
Glutamine. A type of amino acid. *7, 11, 38, 43, 46*
Glutathione. A type of protein. *54*
Glutathione-DOPA. A molecule used in pheomelanin production. *54*
Glyceride. An ester of a glycerol and fatty acid. *22*
Glycerol diester. A type of ester of a glycerol and fatty acid. *48*
Glycine. A type of amino acid. *7-8, 10, 38, 41-42, 46*
Glycocalyx. A 'fuzzy' coating of proteins and sugars on the outside of a cell. *21, 26, 33*

Glycogen. A type of carbohydrate from the polysaccharide group. *12, 28, 32, 70, 73*
Glycolipid. A lipid with a carbohydrate attached to it. *43*
Glycoside hydrolase. A group of hydrolase enzyme (Ecc 3.2). *14, 16*
Glycosphingolipid. A group of glycolipids. *28*
Gold sodium thiomalate. A compound used as a stain. *59*
Golgi apparatus. See *Golgi complex*.
Golgi area. See *Golgi complex*.
Golgi complex. An organelle that is important in the transport and organisation of proteins and lipids. *22, 26, 28, 33, 52-53, 65, 70, 73*
Granular keratinocyte. A keratinocyte in the stratum granulosum. *19, 21, 26, 32-33, 35-38, 46*
Granular lysosome. See *heterogenous lysosome*.
Green fluorescent protein. A protein used as a stain, which appears fluorescent under certain light. *59*
Haarscheibe. A touch dome associated with a hair follicle. *66*
Haarscheiben. Plural of *haarscheibe*.
Hair disk of Pinkus. See *touch dome*.
Hair disk. See *touch dome*.
Hair follicle. The invaginated area in the skin where a hair is produced. *7, 40, 49, 55, 57, 66-67*
Hairy skin. Skin that contains hair follicles. *4, 66, 72*
Halo. The appearance of many ribosomes attached to or surrounding an organelle or other cell structure. *38*
Hard keratin. A type of α-keratin that is found the epidermal appendages.
Hematoxylin and eosin. A compound used as a stain. *66*
Hemidesmosome. A modified desmosome that adheres basal keratinocytes to the basement membrane instead of other keratinocytes. *18, 23-24, 30, 49*
Hepatocyte. A type of cell found in the liver. *10*
HETE. Abbreviation. See *hydroxyeicosatrienoic acid*.
Heterochromatin. Tightly packed chromosome material. *21, 23, 26-27, 29, 33, 35-36, 52, 64, 69-70*
Heterogenous lysosome. A lysosome containing a large amount of heterogenous material. *34, 37*
Heterogenous. Containing particles of differing sizes, shapes, and/or colours. *38, 47*
Hill (of epidermal ridge). The top area of an epidermal ridge. *2-4, 49*
Histidine. A type of amino acid. *7-8, 10-11, 20, 25, 32, 38, 41-43, 46*
Histidine-rich protein A. See *profilaggrin*.
Histidine-rich protein B. One of the two types of filaggrin found in the guinea pig epidermis. *10, 46*
Histidine-rich protein C. One of the two types of filaggrin found in the guinea pig epidermis. *10, 46*
Histochemistry. The use of stains and other markers to identify the composition and structure of cells. *60-61, 66*
Homogenous. Containing particles of identical, or very similar, size, shape, and/or colour. *38, 46*
Hormone. A molecule that has a role in the regulation of cell or organ activity. *67*
Horn. See *spine*.
Horny layer. See *stratum corneum*.
Hydrolase. One of the main groups of enzyme (Ecc 3). *14*
Hydrolysis. Break down of a molecule by water. *11, 17, 42-43, 47-48*
Hydrophilic. Molecules that are attracted to water molecules. *40*
Hydrophobic. Molecules that are repelled by water molecules. *43*
Hydroxyeicosatrienoic acid. A type of lipid derived from arachidonic acid. *14*
Hydroxyproline. A form of collagen, found in the epidermis. *10*
Hyperproliferation. Cell reproduction that is faster than normal. *45*
Ia antigen. A type of antigen. *62*
Iggo disk. See *touch dome*.
Iggo dome. See *touch dome*.
Iggo-Pinkus dome. See *touch dome*.
Indoxyl esterase. An enzyme in the esterase group (ECc 3.1). *22, 33*
Inflammation. An immune response in which a part of the body becomes red and swollen. *14, 45*
Innervated. Served by a nerve fibre. *67-68*
Inosine diphosphatase. An enzyme from the acid anhydride group (Ecc 3.6). *15, 21, 22, 26, 33*
Insoluble. Not able to be dissolved in a solution. *41, 47, 54*
Intercellular body. See *corneodesmosome*.
Intercellular lipid lamella. Lipid sheets from lamellar bodies after they have been excreted into the intercellular space. *43, 45*
Intercellular space. The space between cells. *7, 10, 16, 24, 28, 35, 41, 43, 45, 47-48, 65*
Intercellular. Outside the cell. *7, 17, 43*
Interdigitation. When a cell structure protrudes into a neighbouring cell, often to serve an anchoring role. *68*
Interfilamentous matrix. The cysteine-rich material found between keratin fibres. *38, 46*
Interfollicular. Not relating to the hair follicles; the area between follicles. *33, 40, 49, 55, 57, 66, 72*
Intermediate corneocyte. A keratinocyte in the intermediate stratum corneum. *45, 47*
Intermediate filament. A common type of filament that is important in giving structure to the cell. *46, 70*
Intermediate stratum corneum. The middle sublayer of the stratum corneum. *40, 47-48*
Intermediate vesicle. Temporary vesicles involved in the production of Merkel cell granules. *70-71*
Interposed. When a cell is located between other cells, such as in the roof-tile arrangement. *41*
Interstice. The phospholipid-rich material that surrounds the particles of a composite keratohyalin granule. *38*
Intracellular. Inside the cell. *7, 10*
Intracytoplasmic inclusion. Structures that have entered the cell and remain in the cytoplasm. *28*
Intranuclear rodlet. A small structure found in the nucleus of Merkel cells. *69-70*
Invagination. When a membrane folds in on itself to form a pouch or cavity. *28, 65*
Involucrin. A protein found in the cornified cell envelope. *10, 41*
Ion. A molecule with an electric charge. *28, 41*
Iris. The pigmented circle around the pupil of the eye. *72*
Isoleucine. A type of amino acid. *7-8, 10, 38, 41-42, 46*
Isomerase. One of the main groups of enzyme (Ecc 5). *13*
Ixodid tick. A type of parasite from the Ixodidae tick family. *62*
Keratin pattern. The appearance and ratio of keratin fibres to interfilamentous matrix. *46, 48*
Keratin. A group of proteins that is found in large amounts in the epidermis. *13, 24, 34, 38-39, 41-42, 44-47, 66*
Keratinisation. Transformation of a non-keratinised keratinocyte into a keratinised keratinocyte (corneocyte). *24*
Keratinocyte. The main type of cell found in the epidermis. *2-3, 19-48*
Keratinocyte-Langerhans-melanocyte unit. A melanocyte and the keratinocytes it serves, along with the nearby Langerhans cell that acts as immunosurveillance for that area. *62*
Keratinosome. See *lamellar body*.
Keratohyalin granule. An aggregation of keratohyalin particles. *12, 16, 32, 34, 37-39, 46*
Keratohyalin. An important protein found in granular keratinocytes that is involved in keratin formation. *10, 12, 33, 36, 38-39, 45-46*
Kinesin. A type of motor protein. *10, 53*
KLM unit. Abbreviation. See *keratinocyte-Langerhans-melanocyte unit*.
L-[ureido-^{14}C-]citrulline. The form of citrulline found in guinea pig epidermis. *42*
Lacceroic acid. A fatty acid in the saturated group. C 32:1. *43*
Lactic dehydrogenase. An enzyme from the dehydrogenase group (Ecc 1.1). *14*
Lamella. A thin plate-like or layer-like region in a cell. *24*
Lamellae. Plural of *lamella*.
Lamellar body. An organelle that is rich in lipids. *15, 27, 29, 34, 36*
Lamina densa. The middle layer of the basement membrane. *18*
Lamina lucida. The uppermost layer of the basement membrane. *18*
Lamina reticularis. The bottommost layer of the basement membrane. *18*
Langerhans cell granule. See *Birbeck granule*.
Langerhans cell. A type of cell found in the epidermis, responsible for immunosurveillance. *2-3, 59-65*
Langerin. A protein produced in the Birbeck granules. *59, 61, 65*
LAP. Abbreviation. See *leucinaminopepdidase*.
Large granule. See *composite keratohyalin granule*.
Larger granule. See *composite keratohyalin granule*.
Larva. The immature form of an insect or platyhelminth. *62*
Larvae. Plural of *larva*.
Lathosterol. A type of sterol. *48*
Layer. The horizontal sections of the epidermis that divide it into different stages of differentiated keratinocytes. *2-3*
LDH. Abbreviation. See *lactic dehydrogenease*.
L-dihydroxyphenylalanine. A form of dihydroxyphenylalanine. *10*
L-DOPA. Abbreviation. See *L-dihydroxyphenylalanine*.
Lectin. A group of proteins that bind to carbohydrates. *65*
Leucine. A type of amino acid. *8-10, 38, 41-42, 46*

Leucyl aminopepdidase. An enzyme in the protease group (ECc 3.4). *59*
Leu-enkephalin. A protein that functions as an opioid neurotransmitter. *71*
Leukocyte alkaline phosphatase. An enzyme in the phosphatase group (ECc 3.1). *59*
Leukodopachrome. A molecule used in eumelanin production. *54*
Ligase. One of the main groups of enzyme (ECc 6). *13*
Linear band. See *central lamella*.
Linear. As a line. *65*
Linoleic acid. A fatty acid in the ω-6 group. C 18:2. *12, 14, 43*
Lipogenesis. The production of lipids. *20, 25*
Lipoxygenase. An enzyme from the oxygen receptor group (ECc 1.14). *14*
Lobulation. Used to describe nuclei with multiple indentations in them. Also another term for *spine*. *64, 68, 70*
Lower granular keratinocyte. A keratinocyte in the lower stratum granulosum. *33, 34-36*
Lower spiny keratinocyte. A keratinocyte in the lower stratum spinosum. *25-28*
Lower stratum granulosum. A sublayer of the stratum granulosum. *2-3, 32-33*
Lower stratum spinosum. A sublayer of the stratum spinosum. *2-3, 25-26*
L-pyroglutamic acid. A form of pyroglutamic acid. *11*
L-pyrrolidone carboxylic acid. A form of pyroglutamic acid. *11*
Lyase. One of the main groups of enzyme (ECc 4). *13*
Lymph node. An area of tissue in the lymphatic system. *62*
Lymph vessel. A vessel that serves the lymphatic system. *59*
Lymph. A substance found in the lymphatic system that serves a circulatory and immune role. *62*
Lysine. A type of amino acid. *8-10, 38, 41-42, 46*
Lysosome. A type of vesicle that contains enzymes. *22-23, 28, 31, 33, 65, 70, 72-73*
Macrophage. A type of white blood cell. *61-62*
Macrophagy. The act of a cell taking in a large particle. *61*
Magnesium. An element that functions as an important electrolyte in the epidermis. *13, 21, 25, 32, 37, 43, 46*
Malic dehydrogenase. An enzyme from the dehydrogenase group (ECc 1.1). *14*
Malpighian layer. The stratum basale and the stratum spinosum. *25*
Mannose. A type of sugar. *65*
Margaric acid. A fatty acid in the saturated group. C 17:0. *43*
Matrix. The material that surrounds another larger substance, such as the interfilamentous matrix of keratin, the fibrous matrix of eumelanosomes, or the interstice of keratohyalin granules. *22, 38, 42, 44, 46-47, 53*
MCG. Abbreviation. See *membrane-coating granule*.
MDH. Abbreviation. See *malic dehydrogenase*.
Mechanoreceptor. A sensory cell that reacts to tactile sensation, such as pressure or vibration. *68*
Mechanosensory. Relating to tactile sensation, such as pressure or vibration. *67*
Melanin dust. The loose particles of melanin that result after the melanosomes have degraded inside a melanosome complex. *31, 39, 44*
Melanin granule. The free melanosome that results after the membrane of a melanosome complex has degraded. *31, 39, 44-45, 47-48*
Melanin. The molecule responsible for pigment in mammals. *20, 31, 49-51, 53, 55-58, 60, 70*
Melanoblast. The precursor cell to a melanocyte, found in embryos. *58*
Melanocyte. A type of cell found in the epidermis, responsible for melanin production. *2-3, 30, 49-58*
Melanogenesis. The production of melanin. *53-54, 57, 72*
Melanogenic. The state of being able to produce melanin, or of triggering a nearby melanocyte to produce melanin. *51, 54, 56, 60*
Melanosome complex. A vesicle full of melanosomes that is formed during melanosome transfer. *22, 28, 30-31, 33, 35, 39, 45, 47, 70*
Melanosome dust. See *melanin dust*.
Melanosome transfer. A process in which keratinocytes pinch off part of a melanocyte's dendrite and take in their melanosomes. *22, 28, 30-31, 35, 50, 57*
Melanosome. An organelle that is responsible for the production and storage of melanin. *23, 27-31, 35, 37, 49-53, 57, 70*
Melanosome-lysosome complex. The organelle that forms when a lysosome combines with a melanosome complex. *31, 35, 37*
Membrane-bound. A structure or organelle in a cell that is surrounded by a membrane.
Membrane-coating granule. See *lamellar body*.
Meniscus. See *neurite*.
Merkel cell granule. A structure in Merkel cells that releases neuropeptides when stimulated. *67, 70-71*
Merkel cell. A type of cell found in the epidermis, responsible for mechanosensation. *2-3, 66-71*
Merkel disk. The Merkel cell and neurite together. *68-69*
Merkel tastflecken. See *touch dome*.
Merkel touch spot. See *touch dome*.
Merkel-neurite complex. See *Merkel disk*.
Met-enkephalin. A protein that functions as an opioid neurotransmitter. *10, 67, 71*
Methionine. *8-10, 20, 25, 32, 41-42*
Methyl green-pyronon. A compound used as a stain. *59*
Mg^{2+}. A magnesium ion. *10, 16*
Microfilament. A common type of filament that is important in giving structure to the cell. *73*
Microflora. Microorganisms that live inside or on the surface of a larger organism. *5*
Microtubule. A filament typically involved in the structure of a cell. *22*
Microvilli. See *spine.*
Middle layer. See *central lamella*.
Migratory cell. See *Langerhans cell*.
Mitochondria. An organelle that is important in converting nutrients and oxygen into energy for the cell. *22-23, 26-27, 29, 33-34, 36, 39, 45, 48, 52, 64-65, 68-70, 72-73*
Molar mass. See *molecular weight*.
Mole. A unit of measurement in chemistry, used to determine the number of molecules present in a substance. *7-9, 38, 41-42, 46*
Molecular weight. A unit of measurement in chemistry, used to determine the relative mass of a molecule. *10, 13-15, 17, 38, 42, 46*
Monounsaturated. An unsaturated fat that has one double bond. *12, 43*
MSH. Melanocyte-stimulating hormone. A group of hormones that stimulate or increase melanin production. *57-58*
Multivesicular lysosome. A lysosome containing multiple smaller vesicles. *27-29, 33, 35-36, 70, 73*
Myelin sheath. A type of Schwann sheath, characterised by a protein- and lipid-rich coating around a nerve fibre. *68*
Myosin. A type of contractile protein. In the guinea pig epidermis it forms the epidermal actomyosin complex, along with actin. *10*
Myristic acid. A fatty acid in the saturated group. C 14:0. *43*
Na^{+}/K^{+}-ATPase. An enzyme from the adenosine triphosphatase group (Ecc 3.6). *15, 21, 26, 33*
NADPH. Abbreviation. See *nicotinamide adenine dinucleotide phosphate*.
Naked axon. An axon that does not have any Schwann cells around it. *72-73*
Natural moisturising factor. Proteins and lipids in the stratum corneum that are important in keeping the corneocyte cohesion and barrier function healthy. *38, 43, 46*
Natural pigment spread. Pigment spread that occurs as a result of natural maturation. *55-58*
Na-β-glycerophosphatase. An enzyme in the phosphatase group (Ecc 3.1). *33*
Nerve ending. The terminal portion of a nerve fibre. *67-68, 72-73*
Nerve fibre junction. See *neurite*.
Nerve plate. See *neurite.*
Neural crest. Cells present in the embryo that derive from the ectoderm, which give rise to some of the adult cells of the musculoskeletal and neurological system. *49-50, 60, 66*
Neurite. The flattened end of a nerve ending that contacts the bottom of a Merkel cell. *66, 68-71*
Neuroendocrine. Relating to both the neurological and endocrine system. *67*
Neuromelanin. A type of melanin that is not found in guinea pigs. *54*
Neuropeptide. A group of neurotransmitter molecules. *10, 67, 71*
Neurotransmitter. A molecule that acts as a messenger for the neurological system. *67*
Neurotubule. A microtubule associated with a nerve cell. *73*
Neutral. Having a pH of, or very close to, 7. *38*
Nexus. See *gap junction*.
Nicotinamide adenine dinucleotide phosphate. A molecule that assists with certain enzymatic reactions. *42*
Nitric oxide. A free radical that triggers melanogenesis. *53*
Nitrogenous compound. A molecular containing nitrogen. *10-11*
nm. Nanometre. A thousandth of a micrometre. *18, 21-22, 24, 28, 39, 41, 44-48, 65, 70-71, 73*
Nociception. The sensation of pain. *67*
Non-protein nitrogen. A nitrogenous compound that is not protein. *10, 43*
Nuclear envelope. The two membranes that surround the nucleus. *21, 23, 27, 29, 33, 35-36, 52, 64, 69-70*
Nuclease. A group of esterase enzyme (Ecc 3.1). *17*
Nuclei. Plural for *nucleus*.
Nucleic acid. The group of molecules responsible for genetic material. DNA and RNA. *6, 9, 13, 17, 41*
Nucleoli. Plural for *nucleolus*.

Nucleolus. A structure inside the nucleus that is important for RNA function. *21, 23, 26-27, 29, 33, 35-36, 52, 64, 70*
Nucleoplasm. The material and components inside a nucleus other than the nucleolus. *52*
Nucleoside esterase. An enzyme in the esterase group (Ecc 3.1). *64*
Nucleoside triphosphatase. An enzyme in the acid anhydride group (Ecc 3.6). *26*
Nucleotide phosphatase. An enzyme in the phosphatase group (Ecc 3.1). *16*
Nucleus. A large organelle than contains the cell's DNA. *21-23, 25-29, 31, 33-36, 38-39, 45, 47-48, 50, 52, 64-65, 69-70*
Odland body. See *lamellar body*.
Opioid. A group of molecules that play a role in pain relief. *71*
Organelle. A membrane-bound structure in a cell that performs a particular function. Analogous to organs in a body. *65*
Ornithine. A type of amino acid. *8-9, 46*
Osmiophilic. Able to be stained by osmium tetroxide. *28*
Outermost layer. See *stratum corneum*.
Outpouch. When a membrane folds out from itself to form a bubble; the reverse of invagination. *53*
Oxidoreductase. One of the main groups of enzyme (Ecc 1). *14*
Oxygen receptor. A group of oxidoreductase enzyme (Ecc 1.14). *14*
Oxygen scavenger. A molecule that reduces free radical activity and thus prevents the oxidation of the material it's protecting. *50, 54*
Palmitic acid. A fatty acid in the saturated group. C 16:0. *43, 45, 48*
PAR-2. Abbreviation. See *protease-activated receptor 2*.
Paraphenylenediamine. A compound used as a stain. *59*
Parent. The original cell before it divides and produces daughter cells. *20, 51*
PAS reaction. Abbreviation. See *periodic acid-Schiff staining*.
Pathogen. A microorganism that causes disease. *5, 19, 40, 62*
Pathogenic. The state of being a pathogen. *5*
PCA. Abbreviation. See *pyrrolidone carboxylic acid*.
Pentadecylic acid. A fatty acid in the saturated group. C 15:0. *43*
Pepsin. An enzyme in the protease group (ECc 3.4). *15*
Peptidase. See *protease*.
Peptide. A short chain of amino acids. *15-16, 58*
Perikarya. Plural of *perikaryon*.
Perikaryon. The main part of a cell, where the nucleus is held; not the dendrites or other protrusions. *51-53, 63, 68*
Perineurial cell. A thin protective sheath around an axon. *73*
Periodic acid-Schiff staining. A technique used to stain a sample for polysaccarides. *20*
Peritoneal. Relating to the lining of the abdominal cavity. *61*
Peroxidase. A group of oxidoreductase enzyme (Ecc 1.11). *14, 65*
Peroxidation. When free radicals take electrons from a lipid, causing it to degrade. *44*
pH. The power of hydrogen; determines whether a substance is alkaline, neutral, or acidic. *5, 10, 15-17, 38, 41-42, 46*
Phagocytosis. The ingestion of a cell, or part of it, by another cell. *28, 57, 62*
Phagosome. A type of vesicle that contains phagocytic material. *19, 27-30, 34, 36*
Phenotypic transformation. When the phenotype (appearance to the naked eye) of an animal is altered due to the introduction of a new factor. *57*
Phenylalanine. A type of amino acid. *8-10, 38, 41-42, 46*
Pheomelanin. A type of melanin, responsible for red or yellow pigment. *50, 53-55, 57-58*
Pheomelanosome. A melanosome that produces pheomelanin. *53, 57*
Phosphatase. A group of esterase enzyme (Ecc 3.1). *16*
Phosphodiesterase. A group of esterase enzyme (Ecc 3.1). *15*
Phospholipase A_2. An enzyme from the phosphodiesterase group (Ecc 3.1). *14, 15*
Phospholipid. A group of lipids. *11-12, 14-15, 21, 30, 37-38, 42-48, 53*
Phosphorus. An element that, when forming phosphate, functions as an important electrolyte in the epidermis. *12-13, 21, 25, 32, 38, 43*
Phosphotransferase. A group of transferase enzyme (Ecc 2.7). *13*
Photoprotective. Reduces the damage caused by UV radiation. *40, 50*
Phototoxic. Increases the damage caused by UV radiation. *50, 54*
Piebald. The name often given to the appearance created by *white-spotting*.
Pigment cell. A cell which contributes to the colouration of an organism, such as a chromatophore or melanocyte. *50*
Pigment pattern. The arrangement of melanosomes, and ratio of the types of melanosomes, in a keratinocyte. *31, 35, 39*
Pigment spread. When darker pigmentation encroaches on lighter pigmentation in the epidermis. *55-58*
Pigmentation. The presence and/or degree of colour as seen by the naked eye. *30, 49-50, 54-55*
Pinna. The external flap of the ear. *49*
PLA_2. Abbreviation. See *phospholipase A_2*.
Plaque. A thickening of the cell membrane, which comprises one half of a desmosome. *24, 36, 46*
Plasma membrane. The main membrane that surrounds a cell. *41-42, 44, 62, 65, 68, 71*
Pleomorphic. Varying in size and/or shape. *63*
Polygonal. Having a shape with three or more sides. *51*
Polypeptide. A long chain of amino acids. *10, 37*
Polysaccharide. A group of carbohydrates, whereby multiple sugar molecules are bonded together. *12, 18, 20-21*
Postlysosome. A lysosome with no enzymatic activity left. *33*
Potassium. An element that functions as an important electrolyte in the epidermis. *12-13, 21, 26, 32, 43, 67*
Premelanosome. The precursor to a melanosome. *52-53*
Prickle layer. See *stratum spinosum*.
Primary branch. The area of the dendrite closest to the perikaryon, before it forks into additional branches. *51*
Profilaggrin. A histidine-rich protein found in the composite keratohyalin granules. *10, 32, 38, 46*
Proliferation. Cell reproduction. *4, 20, 24, 40, 62*
Proline. A type of amino acid. *8-10, 38, 41-42, 46*
Proprioception. The perception of space and orientation; where parts of the body are in relation to other parts or the environment. *67*
Prostaglandin D_2. A lipid from the prostaglandin group. *11, 14*
Prostaglandin. A group of lipids. *11*
Protease. A large group of hydrolase enzyme (Ecc 3.4). *15*
Protease-activated receptor 2. A type of receptor in humans that plays a role in melanosome transfer. *30*
Protein nitrogen. A nitrogenous compound that is protein. *6*
Proteinase. See *protease*.
Proteolysis. Break down of a protein into amino acids or polypeptides. *46*
Protransglutimase E. An enzyme in the aminoacyltransferase group (Ecc 2.3). *13*
Pseudokeratin. See *α-keratin*.
Pseudopodial movement. Movement of a cell achieved via arm- or tentacle-like protrusions, such as dendrites. *63*
Psyllic acid. A fatty acid in the saturated group. C 33:1. *43*
Pyroglutamate. See *pyroglutamic acid*.
Pyroglutamic acid. A non-protein nitrogenous compound derived from glutamic acid or glutamine. *5, 11, 13, 43, 46*
Pyrrolidone carboxyl peptidase. An enzyme in the protease group (Ecc 3.4). *15, 42*
Pyrrolidone carboxylic acid. See *pyroglutamic acid*.
Quinacrine. A compound used as a stain. *66*
Receptor. A structure in the cell membrane that activates or deactivates when in contact with specific molecules. *24, 30, 57, 61-63*
Red melanin. See *pheomelanin*.
Reticuloendothelial system. When immune cells form a physical barrier to prevent pathogens from entering an area. *62*
Ribonuclease A. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease B_1. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease B_2. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease B_3. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease C. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease D. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease I. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease II. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease III. One of nine types of ribonuclease found in the guinea pig epidermis (Ecc 3.1). *17*
Ribonuclease. A type of enzyme in the nuclease group (Ecc 3.1). *17*
Ribonucleic acid. . A large molecule, responsible for decoding genetic material. *9*
Ribosome. A small structure in a cell that is important in the production of proteins. *17, 22, 28, 38, 53, 70*
Ridge. See *epidermal ridge*.
RNA Abbreviation. See *ribonucleic acid*.

Rnase A. Abbreviation. See *Ribonuclease A*.
Rnase B_1. Abbreviation. See *Ribonuclease B_1*.
Rnase B_2. Abbreviation. See *Ribonuclease B_2*.
Rnase B_3. Abbreviation. See *Ribonuclease B_3*.
Rnase C. Abbreviation. See *Ribonuclease C*.
Rnase D. Abbreviation. See *Ribonuclease D*.
Rnase I. Abbreviation. See *Ribonuclease I*.
Rnase II. Abbreviation. See *Ribonuclease II*.
Rnase III. Abbreviation. See *Ribonuclease III*.
Rnase. Abbreviation. See *Ribonuclease*.
Rod. The elongated section of a Birbeck granule. *65*
Roof feet. See *spine*.
Roof tile pattern/arrangement. When the keratinocytes are arranged diagonally so that each row is overlapping the one below it, giving an appearance like roof tiles. *40, 48*
Rosetting. When an immune cell presents antigens on their plasma membrane. *62*
Rough endoplasmic reticulum. One of two types of endoplasmic reticulum, characterised by the ribosomes attached to its surface. *21-23, 26-29, 33, 35-36, 52-53, 64-65, 69-71, 73*
Row. A horizontal layer of cells, though the name 'row' is used to distinguish it from the epidermal layers. *20, 28, 32, 39*
Saccular terminus. See *bulb*.
SALT. Abbreviation. See *skin-associated lymphoid tissue*.
Saturated. A fat that has no double bonds. *12, 43, 48*
SCF. Abbreviation. See *stem cell factor*.
Schwann cell. A supporting cell in the neurological system that typically surrounds a neuron. *69, 72-73*
Schwann cell-axon complex. An axon and the Schwann cells that surround it. *72*
Sebaceous gland. A type of skin gland, found in the dermis. *20, 25, 48*
Sebocyte. A cell found in the sebaceous glands. *20, 25*
Sebum. A lipid-rich substance produced by sebaceous glands. *48*
Secondarily blackened. The zone of skin affected by pigment spread. *55, 57-58*
Secondary branch. The thinner area of the dendrite, after forking from the primary branch. *51*
Secondary lysosome. A lysosome that forms when a lysosome combines with another vesicle, such as a melanosome or phagosome. *30*
Serine. A type of amino acid. *7-10, 38, 41-42, 46*
Side (of epidermal ridge). The sloped area of an epidermal ridge, between the hill and valley. *2-3*
Single keratohyalin granule. A type of keratohyalin granule, characterised by its cysteine and sulphur content. *38*
Skin surface. The surface of the topmost layer of skin, where it is exposed to the outside environment. *2-3, 5, 40, 48*
Skin-associated lymphoid tissue. See *skin-draining lymph node*.
Skin-draining lymph node. A lymph node associated with the integumentary system. *62*
SLN. Abbreviation. See *skin-draining lymph node*.
Small granule. See *single keratinocyte granule*.
Smooth endoplasmic reticulum. One of two types of endoplasmic reticulum, characterised by a clean surface with no attached ribosomes. *21, 23, 26-29, 33, 35, 37, 52, 65, 70*
Sodium bromide. A compound used to separate the epidermis and dermis for microscope examination. *59*
Sodium. An element that functions as an important electrolyte in the epidermis. *12-13, 21, 25, 32, 43*
Soft keratin. A type of α-keratin that is found the epidermis. *47*
Soluble. Able to be dissolved in a solution. *11, 13, 54*
Sphingolipid. A group of lipids. *11-12, 43*
Sphingosine. A molecular group found in sphingolipids. *12, 42*
Spine. A protrusion from the epidermal side of a Merkel cell. *68, 70*
Spinous layer. See *stratum spinosum*.
Spiny keratinocyte. A keratinocyte in the stratum spinosum. *2, 19, 21-22, 25-30, 33*
Spiny layer. See *stratum spinosum*.
Splitter. Favouring the separation of groups into subgroups. *3*
Squalene. A type of lipid. *48*
Squame. Appearing like a scale or flake. *5*
Stearic acid. A fatty acid in the saturated group. C 18:0. *43*
Stem cell factor. A protein that is important in triggering melanogenesis. *10, 20, 53*
Steroid. A group of lipids. *11-12, 21*
Sterol ester. An ester of a sterol and fatty acid. *12, 43, 48*
Sterol. A group of steroid lipids. *20, 25*
Strata. See *layer*.
Stratum basale. A layer in the epidermis, which contains basal keratinocytes. *2-3, 20-24*
Stratum conjunctum. See *deep stratum corneum.*
Stratum corneum. A layer in the epidermis, which contains corneocytes. *2-3, 40-48*
Stratum disjunctum. The intermediate and superficial stratum corneum. *40, 47-48*
Stratum germinativum. See *stratum basale*.
Stratum granulosum. A layer in the epidermis, which contains granular keratinocytes. *2-3, 32-38*
Stratum lucidum. A layer in the epidermis, which contains transitional keratinocytes. *2-3, 39*
Stratum spinosum. A layer in the epidermis, which contains spiny keratinocytes. *2-3, 25-31*
Striation. A linear strip, mark, or similar. *44, 47, 65*
Subbasal lamina. See *lamina reticuluaris*.
Sublayer. The further division of epidermal layers. *2-3, 25, 32, 40*
Succinic dehydrogenase. An enzyme from the dehydrogenase group (ECc 1.1). *14*
Sulphatase. A group of esterase enzyme (ECc 3.1). *15*
Sulphur. An element that is important in the composition of keratin. *12-13, 21, 25, 32, 38, 44, 47, 54*
Superficial corneocyte. A keratinocyte in the superficial stratum corneum. *40, 45, 48*
Superficial stratum corneum. The topmost sublayer of the stratum corneum. *2-3, 40, 48*
Superoxide dismutase. An enzyme from the oxygen receptor group (ECc 1.14). *14*
Superoxide. A molecule containing two oxygen atoms. *14*
Suprabasal layer. See *stratum spinosum*.
Surface gap junction. A type of gap junction characterised by a protrusion or divot at the cell surface. *23, 27-28*
Synaptic. Relating to a synapse; a structure between two neurological cells that permits the passage of signals. *68, 73*
Tactile cell. See *Merkel cell*.
Tactile disk of Pinkus. See *touch dome*.
Tactile hair disk. See *touch dome*.
Tactile pad. See *touch dome*.
Tasteflecke. See *touch dome*.
Taurine. A type of amino acid. *8-9*
T-cell. A type of white blood cell. *62* It is also an abbreviation used for *transitional cells*. *39*
Telolysosome. A lysosome that has taken in too much undigestible material and is no longer functional. *33*
Temperature-dependent. The state of having different properties depending on the ambient temperature. *62*
Terminal process. The ruffled or button-like tip at the end of a dendrite. *51, 63*
Theophylline. A type of drug in the xanthine group. *57*
Thiamine pyrophosphatase. An enzyme from the acid anhydride group (ECc 3.6). *15, 21, 22, 26, 28, 33, 35*
Thick skin. Areas of skin where the stratum lucidum is visible as a continuous layer. *4, 25, 39, 47, 56*
Thin skin. Areas of skin where the stratum lucidum is not visible as a continuous layer. *4, 25, 39, 47, 56*
Thioacetic acid esterase. An enzyme in the esterase group (ECc 3.1). *22*
Thioredoxin reductase. An enzyme from the dehydrogenase group (ECc 1.1). *14, 19, 42*
Thioredoxin. A group of proteins. *42*
Threonine. A type of amino acid. *7-10, 38, 41-42, 46*
Tissue culture. The growth of cells in an artificial setting. *63*
Tocopherol. An essential vitamin that functions as a free radical scavenger. *12, 44*
Toluidine blue. A compound used as a stain. *66*
Tonofilament bundle. A close group of tonofilaments. *22-24, 26-27, 29-30, 34, 36*
Tonofilament. A type of filament found in keratinocytes that are precursors to keratin fibres. *21-22, 24, 26, 34, 39, 46, 64*
Touch corpuscle. See *touch dome*.
Touch dome. A cluster of Merkel cells, typically causing a small lump in the epidermis. *66-67*
Touch receptor. A cell that plays a role in mechanosensation. *67*
Touch spot. See *touch dome*.
Transferase. One of the main groups of enzyme (ECc 2). *13*

Transglutaminase C. One of the two types of transglutaminase found in the guinea pig epidermis (ECc 2.3). *13*
Transglutaminase K. One of the two types of transglutaminase found in the guinea pig epidermis (ECc 2.3). *13*
Transglutaminase. An enzyme in the aminoacyltransferase group (ECc 2.3). *13*
Transit time. The time it takes for a keratinocyte to rise up the epidermal column from the stratum basale to the superficial stratum corneum. *19*
Transitional keratinocyte. A keratinocyte in the stratum lucidum. *2-3, 19, 39, 46*
Transitional layer. See *stratum lucidum*.
Transitional zone. See *secondarily blackened*.
Translocase. One of the main groups of enzyme (ECc 7). *13*
Translucent layer. See *stratum ludicum*.
Triglyceride. An ester of glycerol and three fatty acids. *11, 43, 48*
Triolein. A type of triglyceride. *48*
Triplet. An arrangement of three microtubules in a centriole. *22*
Twig. The thinnest area of the dendrite; after forking from the secondary or later branch. *51*
Two-compartment system. See *brick and mortar system*.
Tylotrich pad. See *touch dome*.
Type I slowly-adapting mechanoreceptor. A type of mechanoreceptor. *68*
Type IV collagen. A protein in the collagen group, found in the lamina densa. *18, 20*
Tyrosinase. An enzyme from the oxygen receptor group (ECc 1.14). *53, 54*
Tyrosine kinase. An enzyme in the phosphotransferase group (ECc 2.7). *13*
Tyrosine. A type of amino acid. *8-10, 41-42, 53-54*
Ultrastructure. The use of an electron microscope to identify the physiology of a cell. *60*
Uninnervated. Not served by a nerve fibre. *67*
Unsaturated. A fat that has one or more double bonds. *48*
Upper granular keratinocyte. A keratinocyte in the upper stratum granulosum. *35-38, 46*
Upper spiny keratinocyte. A keratinocyte in the upper stratum spinosum. *25-26, 28-30, 33*
Upper stratum granulosum. A sublayer of the stratum granulosum. *2-3, 32-33, 39*
Upper stratum spinosum. A sublayer of the stratum spinosum. *2-3, 26, 28, 32*
Uppermost stratum corneum. See *superficial stratum corneum*.
Urea. A non-protein nitrogenous compound. *10-11*
Ureohydrolase. A group of hydrolase enzyme (ECc 3.5). *15*
Urocanic acid. A non-protein nitrogenous compound derived from the breakdown of histidine. *5, 11, 40, 43, 46*
UV. Ultraviolet. *12, 14, 19, 40, 42-44, 49-50, 53-54, 60, 72*
UVA. UV light that has a wavelength between 315 and 400 nm. *40, 42*
UVB. UV light that has a wavelength between 280 and 315 nm. *19, 40, 42*
Vacuole. A type of vesicle that is typically used for storage in a cell. *19, 38-39, 64-65, 68-70*
Valine. A type of amino acid. *8-10, 38, 41-42*
Valley (of epidermal ridge). The bottom of an epidermal ridge. *2-4, 20, 49*
Vesicle. A membrane-enclosed bubble- or sac-like organelle. *21-22, 26, 28, 33-34, 68-73*
Vimentin. A type of intermediate filament. *47*
Viscous. Having a thick consistency. *22*
Vitamin C. See *ascorbic acid*.
Vitamin E. See *tocopherol*.
Wax diester. A type of wax ester. *48*
Wax ester. An ester of a fatty alcohol and fatty acid. *11, 43, 48*
Wet weight. The weight of a substance in a cell, while that cell is fully hydrated. *6-7, 9-13, 21, 25-26, 32-33, 54*
White-spotting. A gene found in the guinea pig, characterised by white patches of skin and fur that are lacking in melanocytes. *49, 55, 58*
Zymogen. A precursor to an enzyme. *13*
α-galactosidase. One of two galactosidase enzymes in the guinea pig epidermis (ECc 3.2). *16*
α-glucosidase. One of two glucosidase enzymes in the guinea pig epidermis (ECc 3.2). *16*
α-keratin intraspecies heterogeneity. When an animal has different subtypes of α-keratin for different parts of their body. *47*
α-keratin. The type of keratin found in mammals. *34, 47*
α-mannosidase. An enzyme in the glycoside hydrolase group (ECc 3.2). *16*
α-MSH. A type of MSH. *57*
β_2 adrenergic receptor. A type of receptor that responds to epinephrine. *24*
β-acetylglucosaminidase. An enzyme in the glycoside hydrolase group (ECc 3.2). *16*
β-galactosidase. One of two galactosidase enzymes in the guinea pig epidermis (ECc 3.2). *16*
β-glucosidase. One of two glucosidase enzymes in the guinea pig epidermis (ECc 3.2). *16*
β-glucuronidase. An enzyme in the glycoside hydrolase group (ECc 3.2). *16*
β-keratin. A type of keratin that is not found in mammals. *47*
γ-glutamyl cyclotransferase. An enzyme in the aminoacyltransferase group (ECc 2.3). *13, 42*
Δ5 desaturase. One of two desaturase enzymes missing from the guinea pig epidermis (ECc 1.14). *14*
Δ6 desaturase. One of two desaturase enzymes missing from the guinea pig epidermis (ECc 1.14). *14*
Δ7-cholestene-3-β-ol. A type of lipid in the steroid group. *12*
µm. Micrometre. A thousandth of a millimetre, or a thousand nanometres.
µmole. Micromole. A millionth of a mole. *7, 9, 11, 13, 21-22, 25-26, 32-33, 43-44*