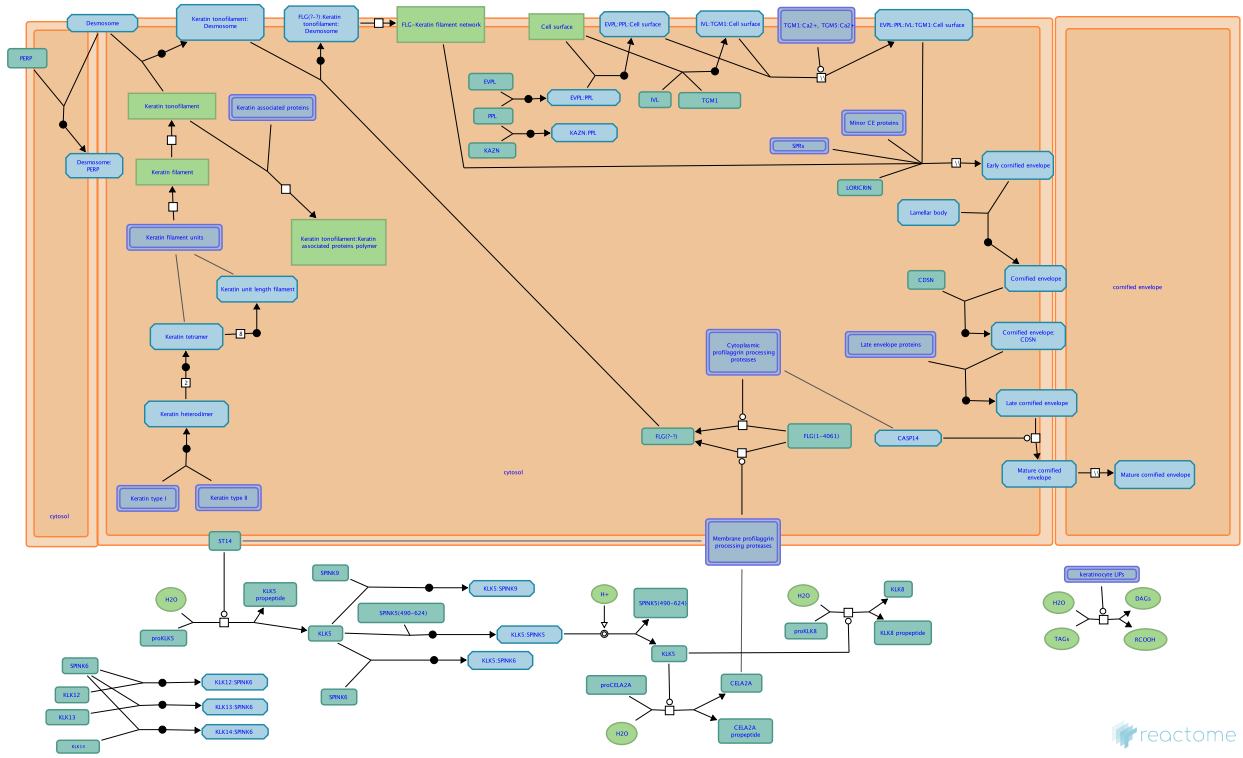
Keratinization



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03/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

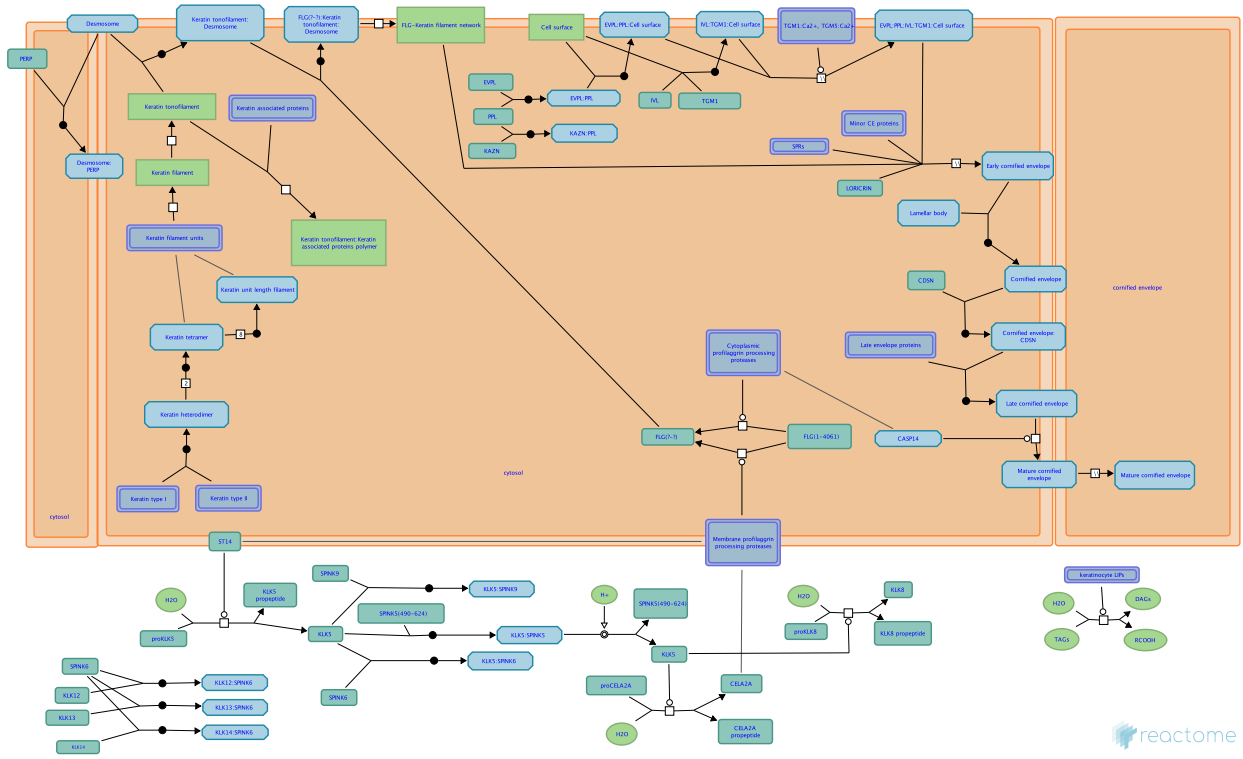
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Keratinization ↗

Stable identifier: R-HSA-6805567



Keratins are the major structural protein of vertebrate epidermis, constituting up to 85% of a fully differentiated keratinocyte (Fuchs 1995). Keratins belong to a superfamily of intermediate filament (IF) proteins that form alpha-helical coiled-coil dimers, which associate laterally and end-to-end to form approximately 10 nm diameter filaments. Keratin filaments are heteropolymeric, formed from equal amounts of acidic type I and basic /neutral type 2 keratins. Humans have 54 keratin genes (Schweitzer et al. 2006). They have highly specific expression patterns, related to the epithelial type and stage of differentiation. Roughly half of human keratins are specific to hair follicles (Langbein & Schweizer 2005). Keratin filaments bundle into tonofilaments that span the cytoplasm and bind to desmosomes and other cell membrane structures (Waschke 2008). This reflects their primary function, maintaining the mechanical stability of individual cells and epithelial tissues (Moll et al. 2008).

Literature references

Moll, R., Divo, M., Langbein, L. (2008). The human keratins: biology and pathology. *Histochem. Cell Biol., 129*, 705-33. ↗

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2016-03-10	Authored	Jupe, S.
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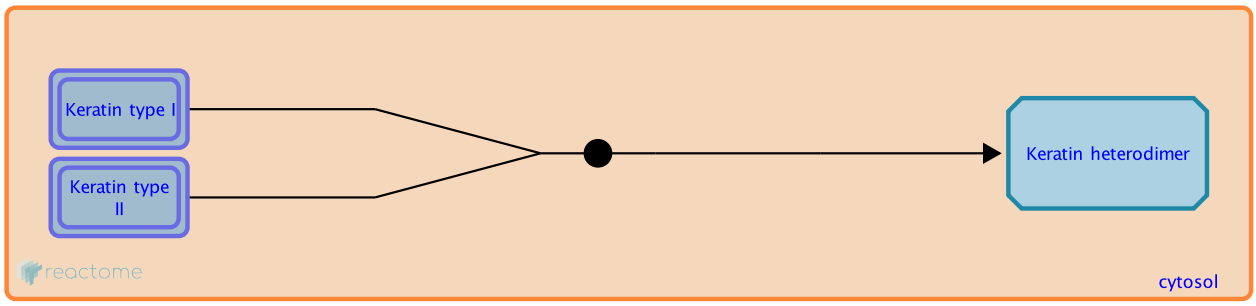
Keratin type I binds keratin type II ↗

Location: Keratinization

Stable identifier: R-HSA-6805546

Type: binding

Compartments: cytosol



The first step in keratin assembly is the formation of coiled-coil heterodimers consisting of an acidic type I keratin and a basic or neutral type II keratin (Coulombe & Fuchs 1990, Hatzfeld & Webber 1990, Steinert 1990). In humans, the type I keratins are K9-24, K25-28, which are specific to the inner root sheath of hair, and the hair-specific keratins K31-K38. The type II keratins are K1-8, K71-80 and K81-86 (Bragula & Homberger 2009). Binding between dimer pairs is remarkably strong and can form even in 9M urea (Coulombe & Fuchs 1990). The ~50 nm long middle rod region of keratin protein aligns with its partner in a parallel orientation (Pauling & Corey 1953, Hanukoglu & Fuchs 1983, Parry et al. 1985, Steinert et al. 1994). The rod region is sufficient to form a heterodimer and subsequent tetramers, but the assembly of keratin filaments requires the non-helical head and tail regions (Wilson et al. 1992). The assembly of rod domain heterodimers has asymmetric salt bridges, hydrogen bonds and hydrophobic contacts, and surface of the heterodimer interface exhibits a notable charge polarization (Lee et al. 2012).

In vitro, virtually any type I keratin can dimerize with any type II keratin, leading to the formation of 10-nm long filaments (Franke et al. 1983, Hatzfeld et al. 1987). In vivo, the composition of keratin heterodimers is probably determined by expression. Differing keratin combinations are not characteristic of entire tissues, but probably confer particular functional properties to cells and tissue regions (Bragulla & Homberger 2009). Certain combinations are characteristic of a cell type, e.g. K18/K8 in simple epithelia. At least some keratins can be replaced with no loss of functionality of the keratin filament, e.g. K1/K10, K1/K9, K2/K9, K2/K10 in epithelia (Coulombe & Omary 2002). Suprabasal cells of stratified epithelia express different keratin pairs in different tissues, e.g. skin epidermis predominantly expresses K1/K10, the anterior corneal epithelium produces K3/K12, esophageal epithelium produces K4/K13 (Eichner & Kahn 1990) while hyperproliferative suprabasal cells are characterized by K6/K16 (Sun 2006).

Followed by: Keratin type I/type II heterodimers form tetramers

Literature references

Coulombe, PA., Fuchs, E. (1990). Elucidating the early stages of keratin filament assembly. *J. Cell Biol., 111,* 153-69. ↗

Hatzfeld, M., Franke, WW. (1985). Pair formation and promiscuity of cytokeratins: formation in vitro of heterotypic complexes and intermediate-sized filaments by homologous and heterologous recombinations of purified polypeptides. *J. Cell Biol., 101,* 1826-41. ↗

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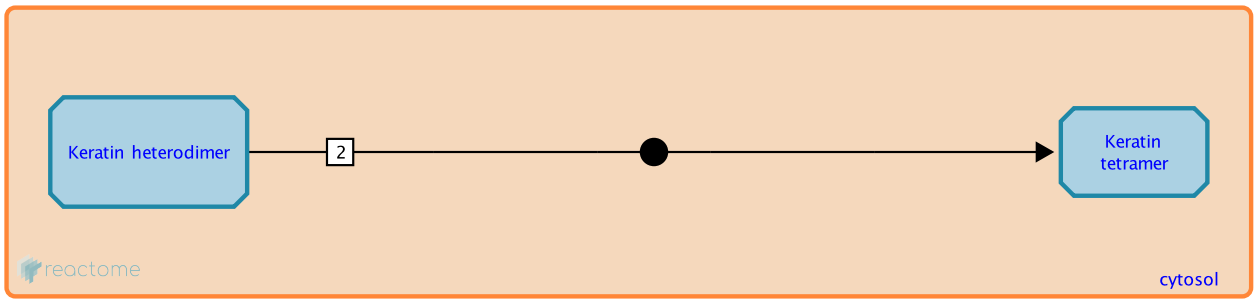
Keratin type I/type II heterodimers form tetramers ↗

Location: Keratinization

Stable identifier: R-HSA-6805573

Type: binding

Compartments: cytosol



Keratin dimers associate in antiparallel orientation to form tetramers (Wood & Inglis 1984, Quinlan et al. 1984). The rod regions of heterodimers align, but alignment of the head and tail regions differs between keratin types. Soft-keratinizing-cornifying cell keratins are slightly out of phase, by 7-8 amino acids, while keratin heterodimers of hard-keratinizing-cornifying cells are in register and consequently there is no overlap between the head and tail domains when a tetramer is formed (Jones et al. 1997). Protofilament tetramers have a diameter of about 2 nm (Aebi et al. 1983, Eicher & Kahn 1990). Heterodimers and tetramers represent the stable building blocks of larger octamers (Herrmann & Abei 2004) and Unit Length Filaments (ULFs), which have a diameter of 20 nm (Parry et al. 2001, Hermann et al. 2007). The tetramers are stabilized by a hydrophobic stripe exposed at the surface of coiled-coil keratin heterodimers (Bernot et al. 2005).

Preceded by: Keratin type I binds keratin type II

Followed by: Keratin filament formation, Keratin tetramers bind to form unit length filaments

Literature references

Eichner, R., Kahn, M. (1990). Differential extraction of keratin subunits and filaments from normal human epidermis. *J. Cell Biol., 110*, 1149-68. ↗

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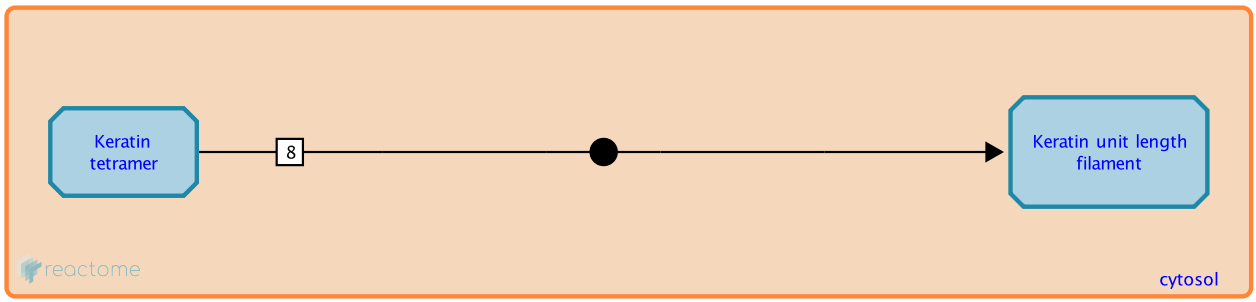
Keratin tetramers bind to form unit length filaments ↗

Location: Keratinization

Stable identifier: R-HSA-6806613

Type: binding

Compartments: cytosol



Mammalian keratins form soluble short full-width filaments called unit length full-width particles (Parry et al. 2007), unit length filaments (ULFs) (Herrmann et al. 2002) or intermediate filament-like particles (Steinert 1991). These are formed by the lateral association of tetramers. ULFs are ~ 70 nm long, with a diameter of ~20 nm. The diameter shrinks during formation of filaments (Parry et al. 2001). X-ray diffraction suggests that ULFs are tube-like structures formed from eight tetramers in non-cornified cells (Parry et al. 2007). In cornified hair cells, the tetramers are thought to be arranged in a seven-member ring, with an eighth in the centre (Parry et al. 2007).

Preceded by: Keratin type I/type II heterodimers form tetramers

Followed by: Keratin filament formation

Literature references

Eichner, R., Kahn, M. (1990). Differential extraction of keratin subunits and filaments from normal human epidermis. *J. Cell Biol., 110*, 1149-68. ↗

Parry, DA., Strelkov, SV., Burkhard, P., Aebi, U., Herrmann, H. (2007). Towards a molecular description of intermediate filament structure and assembly. *Exp. Cell Res., 313*, 2204-16. ↗

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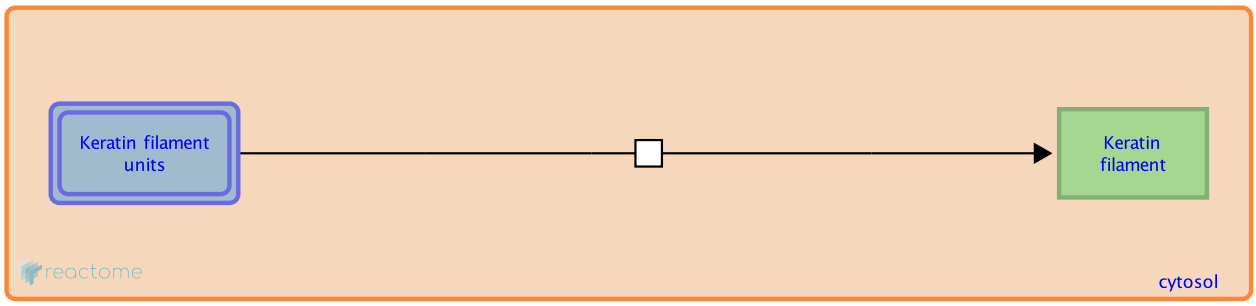
Keratin filament formation ↗

Location: Keratinization

Stable identifier: R-HSA-6806610

Type: transition

Compartments: cytosol



Mammalian keratin filaments are produced by the lateral and longitudinal aggregation of subunits, such as tetrameric protofilaments and octameric protofibrils (Aebi et al. 1983). The extent of aggregation depends on the pH and osmolarity of the surrounding cytoplasm (Yamada et al. 2002, Magin et al. 2007). Filaments have a cross-section of 32 keratin molecules (Jones et al. 1997).

Preceded by: Keratin type I/type II heterodimers form tetramers, Keratin tetramers bind to form unit length filaments

Followed by: Formation of tonofilament bundles

Literature references

Jones, LN., Simon, M., Watts, NR., Booy, FP., Steven, AC., Parry, DA. (1997). Intermediate filament structure: hard alpha-keratin. *Biophys. Chem., 68*, 83-93. ↗

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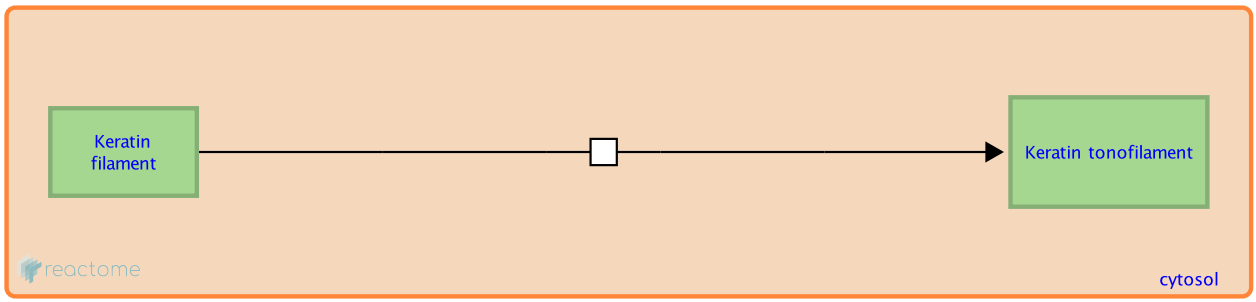
Formation of tonofilament bundles ↗

Location: Keratinization

Stable identifier: R-HSA-6806629

Type: transition

Compartments: cytosol



Keratin filaments are packed into bundles of varying diameter, called tonofilament bundles. These are the building blocks of the cytoskeleton in epithelial cells. Each bundle is surrounded by polyribosomes and multivesicular or folded membrane complexes that form a branched, tubular network (Norlen et al. 2003). In the stratum corneum, keratin bundles are thought to pack in a cubic rod pattern (Norlen & Al-Amoudi 2004). In living cells, X-ray diffraction studies of keratin intermediate filaments indicate a filament radius of 5 nm, hexagonal geometric arrangement with an interfilament distance of 14 nm and bundle diameters of 70 nm (Hémonnot et al. 2016).

Keratin filaments can rapidly disassemble and reassemble, allowing flexibility for the cytoskeleton. Keratin building blocks accumulate at the cell periphery near focal adhesions. Polymerization is regulated by signaling molecules, e.g. heat shock proteins, 14-3-3 proteins, kinases and phosphatases (Magin et al. 2007, Kayser et al. 2003).

Preceded by: Keratin filament formation

Followed by: Formation of hair keratin fibres, Keratin filaments bind cell-cell adhesion complexes

Literature references

Norlén, L., Al-Amoudi, A. (2004). Stratum corneum keratin structure, function, and formation: the cubic rod-packing and membrane templating model. *J. Invest. Dermatol., 123*, 715-32. ↗

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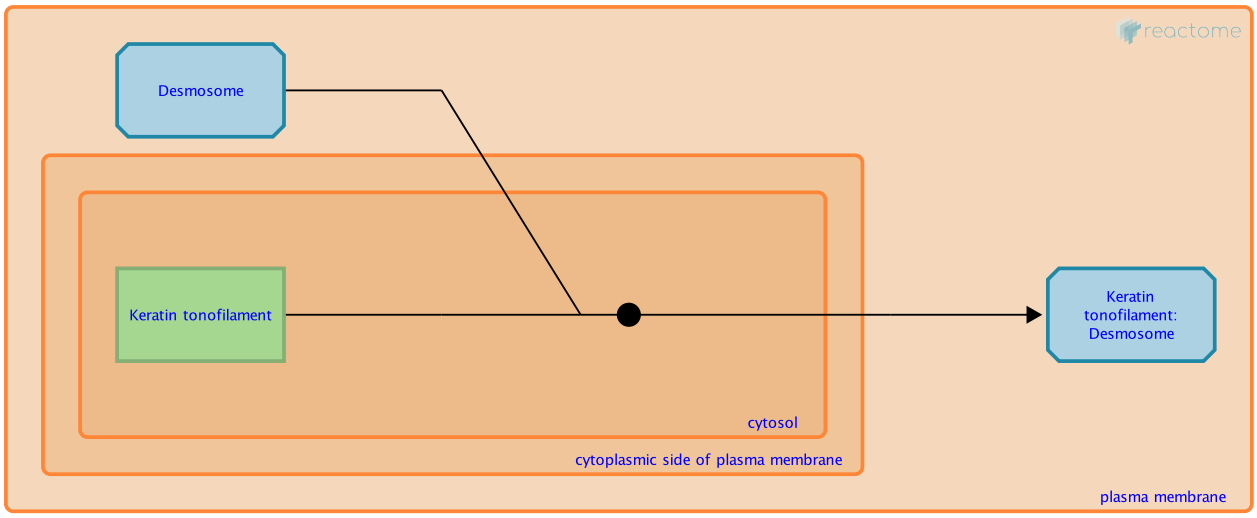
Keratin filaments bind cell-cell adhesion complexes ↗

Location: Keratinization

Stable identifier: R-HSA-6809393

Type: binding

Compartments: cytosol, plasma membrane



Keratin filaments bind cell-cell adhesion complexes such as desmosomes and hemidesmosomes, transferring mechanical forces between cells and maintaining cytoskeletal integrity (Hanakawa et al. 2002). The stability of the tonofilament-desmosome interaction depends, in part, on the type of keratin present in the cell (Loschke et al. 2016).

At the ultrastructural level, desmosomes appear as electron dense discs approximately 0.2-0.5 µm in diameter, which assemble in a mirror-image arrangement at cell-cell interfaces (North et al. 1999, Al-Amoudi et al. 2011, Kowalczyk & Green 2013). Large bundles of filaments extend from the nuclear surface and cell interior out towards the plasma membrane, where they attach to desmosomes by interweaving with the cytoplasmic plaque of the adhesive complex. The head domains of keratins bind the tail domains of desmosomal cadherin molecules such as plakoglobin (Dusek et al. 2007), plectin, periplakin, envoplakin and desmoplakin (Bornslaeger et al. 1996, Kazerounian et al. 2002), thereby anchoring the cytoskeleton to the cell membrane.

The five major desmosomal components are the desmosomal cadherins, represented by desmogleins (DSG1-4) and desmocollins (DSC1-3), the armadillo family members, plakoglobin (PG) and the plakophilins (PKP1-3), and the plakin linker protein desmoplakin (DSP), which anchors the intermediate keratin filaments.

Certain adhesion complex proteins are expressed only when cornification commences. These include desmoglein-1, desmocollin-1, envoplakin, periplakin, plakophilin-1 and corneodesmosin (Candi et al. 2005). This expression is associated with changes in desmosome mophology whereby the cytoplasmic plaque integrates with the cornified envelope (Serre et al. 1991, Simon et al. 2001). Deregulation of desmosome formation can lead to degenerative cutaneous diseases (Brooke et al. 2012, Cirillo 2014).

Preceded by: Formation of tonofilament bundles

Literature references

Kowalczyk, AP., Green, KJ. (2013). Structure, function, and regulation of desmosomes. *Prog Mol Biol Transl Sci, 116*, 95-118. ↗

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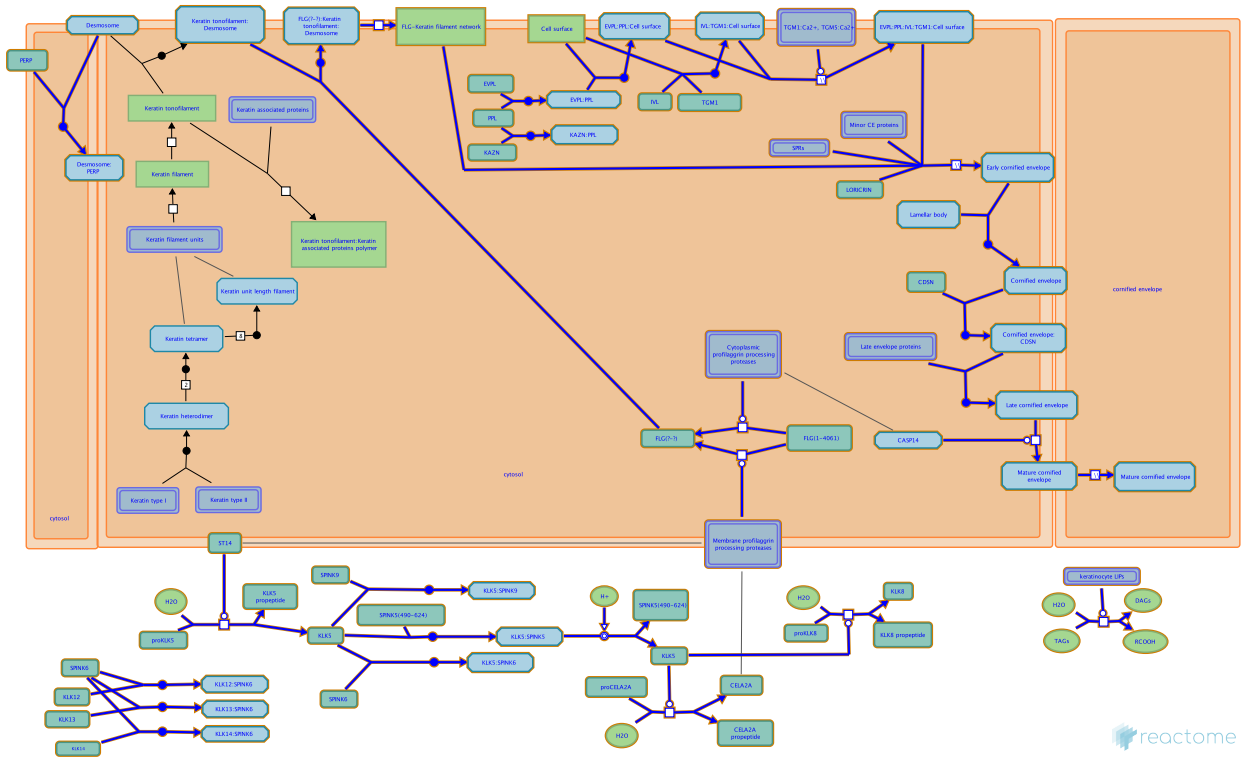
Formation of the cornified envelope ↗

Location: Keratinization

Stable identifier: R-HSA-6809371



As keratinocytes progress towards the upper epidermis, they undergo a unique process of cell death termed cornification (Eckhart et al. 2013). This involves the crosslinking of keratinocyte proteins such as loricrin and involucrin by transglutaminases and the breakdown of the nucleus and other organelles by intracellular and secreted proteases (Eckhart et al. 2000, Denecker et al. 2008). This process is strictly regulated by the Ca2+ concentration gradient in the epidermis (Esholtz et al. 2014). Loricrin and involucrin are encoded in 'Epidermal Differentiation Complex' linked to a large number of genes encoding nonredundant components of the CE (Kypriotou et al. 2012, Niehues et al. 2016). Keratinocytes produce specialized proteins and lipids which are used to construct the cornified envelope (CE), a heavily crosslinked submembranous layer that confers rigidity to the upper epidermis, allows keratin filaments to attach to any location in the cell membrane (Kirfel et al. 2003) and acts as a water-impermeable barrier. The CE has two functional parts: covalently cross-linked proteins (10 nm thick) that comprise the backbone of the envelope and covalently linked lipids (5 nm thick) that coat the exterior (Eckert et al. 2005). Desmosomal components are crosslinked to the CE to form corneodesmosomes, which bind cornified cells together (Ishida-Yamamoto et al. 2011). Mature terminally differentiated cornified cells consist mostly of keratin filaments covalently attached to the CE embedded in lipid lamellae (Kalinin et al. 2002). The exact composition of the cornified envelope varies between epithelia (Steinert et al. 1998); the relative amino-acid composition of the proteins used may determine differential mechanical properties (Kartasova et al. 1996).

Literature references

Candi, E., Schmidt, R., Melino, G. (2005). The cornified envelope: a model of cell death in the skin. *Nat. Rev. Mol. Cell Biol., 6*, 328-40. ↗

Editions

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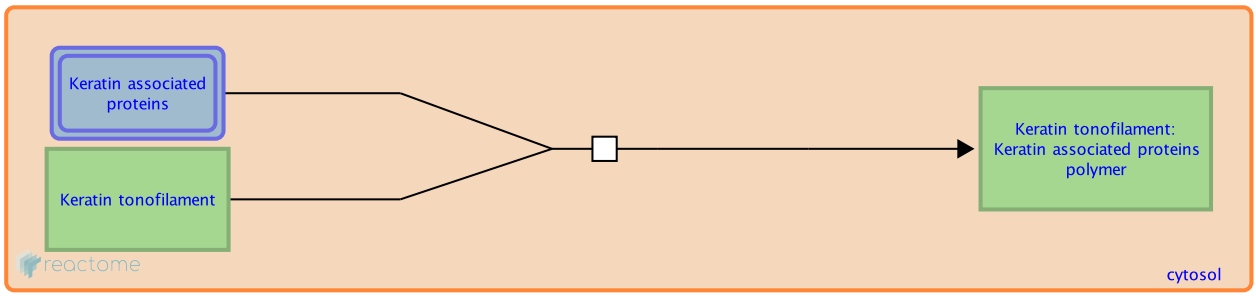
Formation of hair keratin fibres ↗

Location: Keratinization

Stable identifier: R-HSA-6809663

Type: transition

Compartments: cytosol



Hair consists of three major structural components: the cuticle, the cortex and the central medulla. Approximately 90% of cortical cells contain longitudinally arrayed keratin filaments. These filaments have a surrounding matrix that contains keratin-associated proteins (KAPs) that are involved in the formation of cornified, resilient hair shafts (Shimomura & Ito 2005, Lee et al. 2006, Harland et al., 2010, Gong et al. 2016). KAPs forming extensive disulfide cross-links with keratin filaments (Marshall et al. 1991).

The proliferative cells that give rise to hair fibres are located in the bulb at the base of the hair follicle. As they leave the germinative compartment, trichocytic differentiation begins and in matrix, cuticular, and cortical cells, the genes for keratins and KAPs (KRTAPs) are expressed. In the lower and middle cortex, keratin filaments are embedded in a matrix that consists of KAPs. Based on amino acid composition, three classes of KAPs have been described, the high sulfur KAPs (<30 mol % cysteine content), the ultrahigh sulfur KAPs (>30 mol % cysteine content), and the high tyrosine/glycine KAPs (Rogers et al. 2001). KAPs can be divided into subfamilies based on amino acid composition and phylogenetic relationships (Wu et al. 2008). Humans have approximately 100 KAP genes (Wu et al. 2008). Compared to the conserved structure and modality of keratins within mammals, KAP genes differ significantly between species and are likely to explain the variety of characteristics seen in hard keratin appendages such as feathers, claws, scales and hair (Wu et al. 2008, Khan et al. 2014). KAPs are crucial for the assembly of keratin intermediate filaments into arrays and likely to affect attributes of hair such as strength, rigidity and chemical inertness (Parry & Steinert 1999, Koster et al. 2015).

Preceded by: Formation of tonofilament bundles

Literature references

Marshall, RC., Orwin, DF., Gillespie, JM. (1991). Structure and biochemistry of mammalian hard keratin. *Electron Microsc. Rev., 4*, 47-83. ↗

Khan, I., Maldonado, E., Vasconcelos, V., O'Brien, SJ., Johnson, WE., Antunes, A. (2014). Mammalian keratin associated proteins (KRTAPs) subgenomes: disentangling hair diversity and adaptation to terrestrial and aquatic environments. *BMC Genomics, 15*, 779. ↗

Shimomura, Y., Ito, M. (2005). Human hair keratin-associated proteins. *J. Investig. Dermatol. Symp. Proc., 10*, 230-3. ↗

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