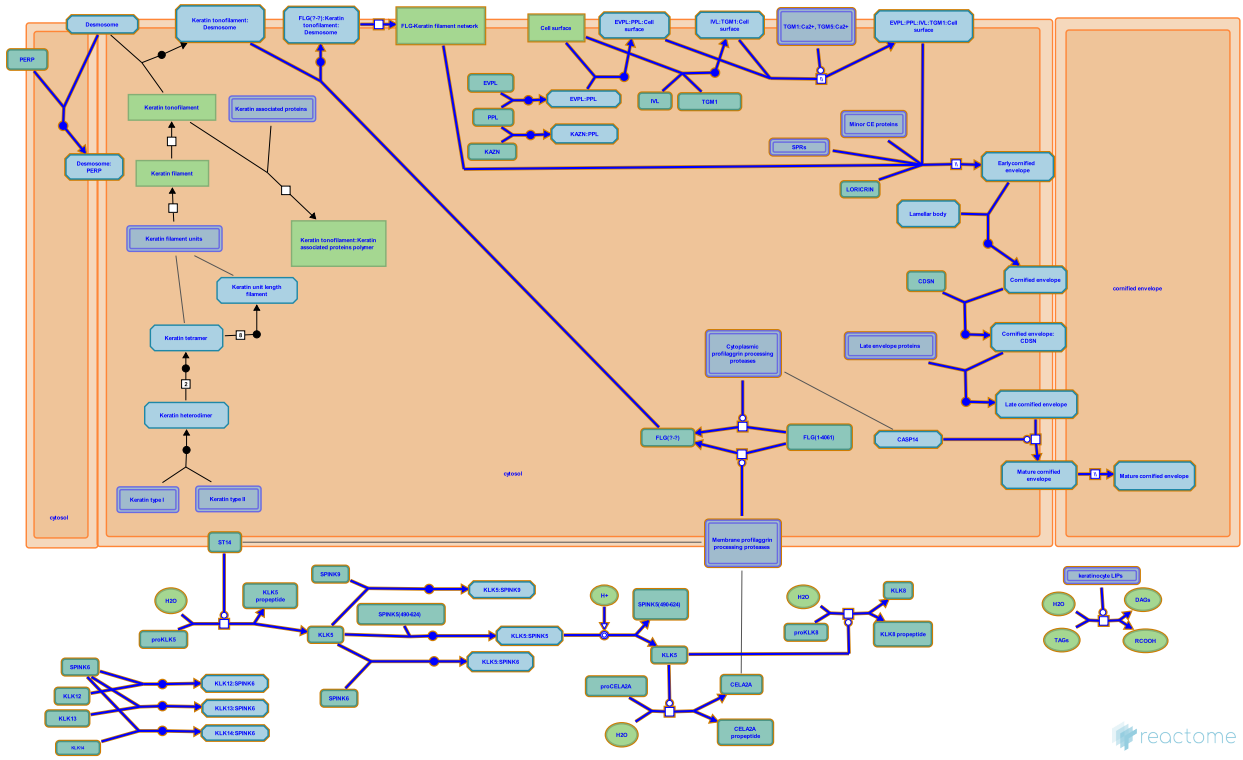
Formation of the cornified envelope



Blumenberg, M., D'Eustachio, P., Jassal, B., Jupe, S.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

10/10/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

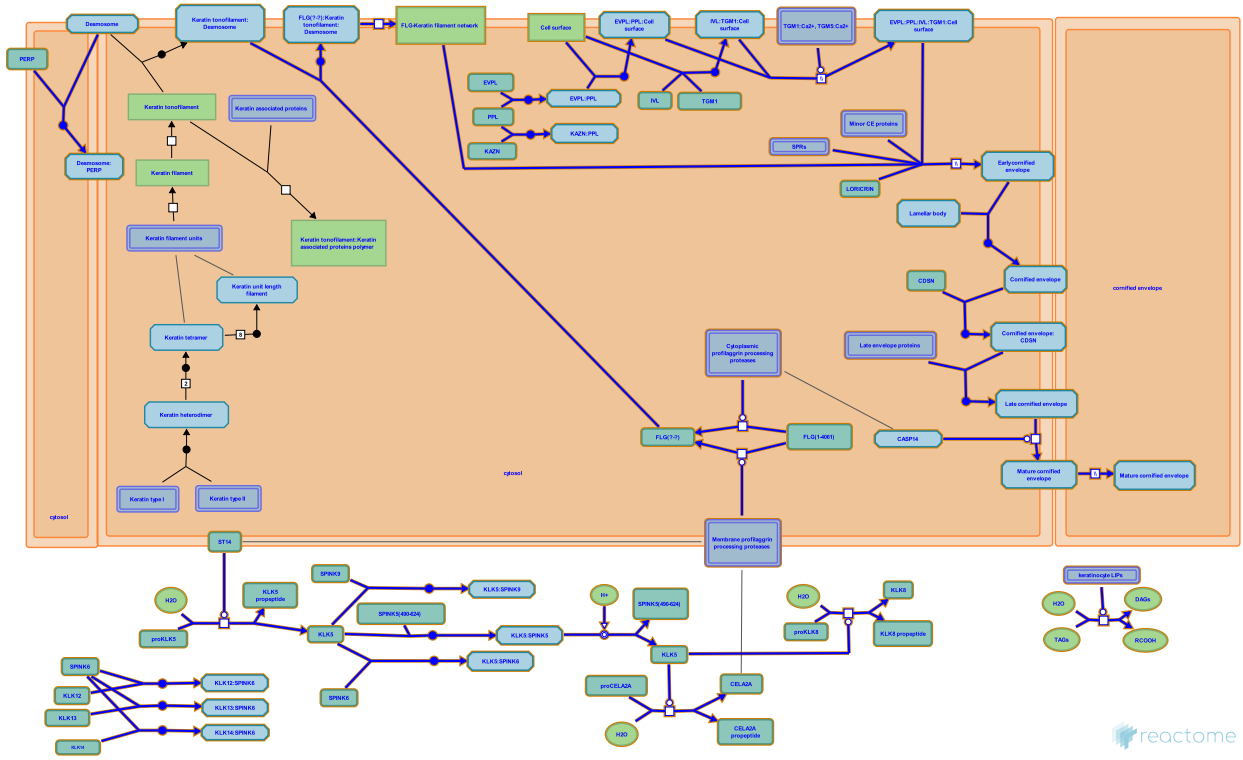
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Formation of the cornified envelope ↗

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

Editions

2016-03-10	Authored	Jupe, S.
2016-08-10	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

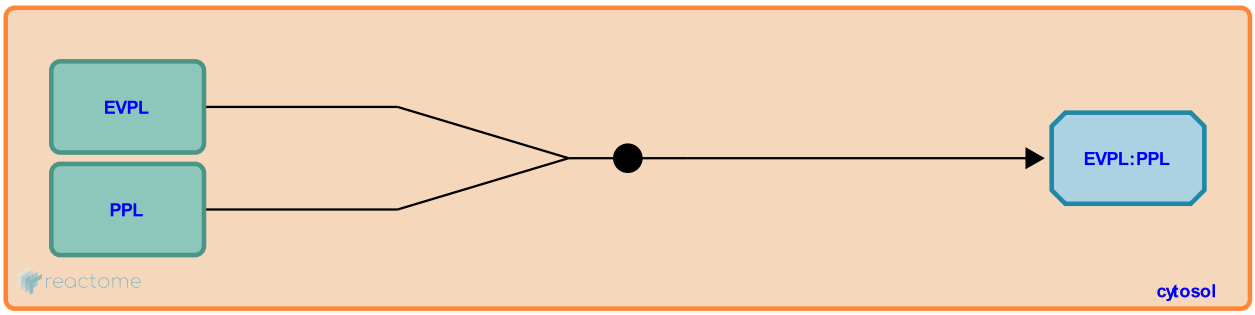
Envoplakin binds periplakin ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6810843

Type: binding

Compartments: cytosol



Envoplakin (EVPL) is insoluble under physiological conditions but soluble as a heterodimer with periplakin (PPL) (Kalinin et al. 2004). The heterodimers provide a firm but flexible structures (Al-Jassar et al. 2013). EVPL and PPL deposition and crosslinking are amongst the earliest events of cornification (Kalinin et al. 2002, Candi et al. 2005). They partially colocalize with desmosomal proteins and keratin intermediate filaments (Ruhrberg et al. 1996, DiColandrea et al. 2000), linking the cornified envelope to desmosomes and keratin filaments (Ruhrberg et al. 1996, 1997). PPL also associates with cortical actin at the interdesmosomal plasma membrane (DiColandrea et al. 2000, Groot et al. 2004).

Followed by: EVL:PPL heterodimer binds the inner surface of the plasma membrane

Literature references

Idler, WW., Steven, AC., Kalinin, AE., Steinert, PM., Bowers, B., Marekov, LN. et al. (2004). Co-assembly of envoplakin and periplakin into oligomers and Ca(2+)-dependent vesicle binding: implications for cornified cell envelope formation in stratified squamous epithelia. *J. Biol. Chem., 279*, 22773-80. ↗

Editions

2016-03-10	Authored	Jupe, S.
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2016-08-12	Reviewed	Blumenberg, M.

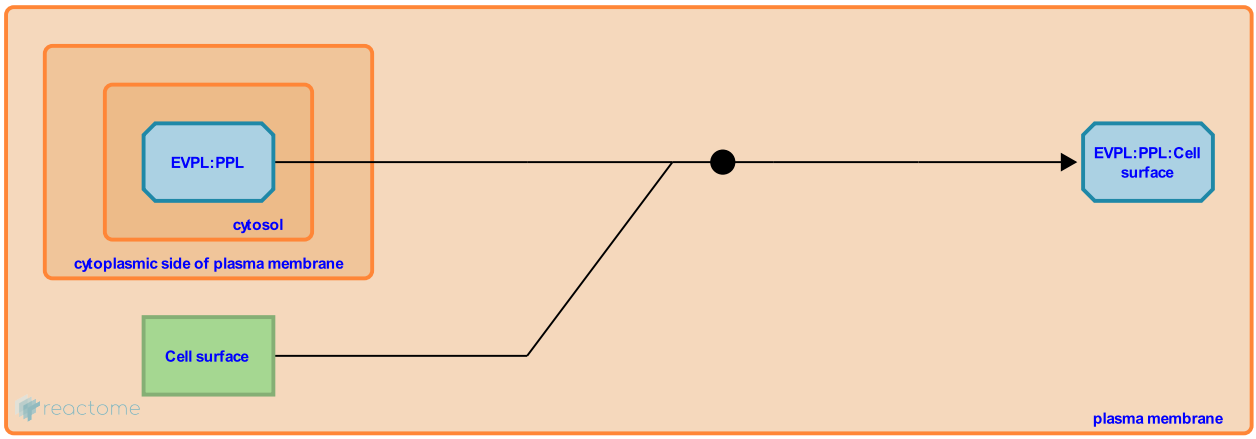
EVL:PPL heterodimer binds the inner surface of the plasma membrane ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6814187

Type: binding

Compartments: plasma membrane, cytosol



Envoplakin:periplakin heterodimers (EVPL:PPL) bind the plasma membrane. In vitro, EVPL:PPL can bind lipid vesicles in response to increasing Ca2+, suggesting that translocation and binding to the plasma membrane is regulated by elevation of intracellular Ca2+ (Kalinin et al. 2004).

Preceded by: Envoplakin binds periplakin

Followed by: Envoplakin, periplakin, involucrin, SPR binding mediated by TGM1 crosslinking

Literature references

Idler, WW., Steven, AC., Kalinin, AE., Steinert, PM., Bowers, B., Marekov, LN. et al. (2004). Co-assembly of envoplakin and periplakin into oligomers and Ca(2+)-dependent vesicle binding: implications for cornified cell envelope formation in stratified squamous epithelia. *J. Biol. Chem., 279*, 22773-80. ↗

Editions

2016-03-10	Authored	Jupe, S.
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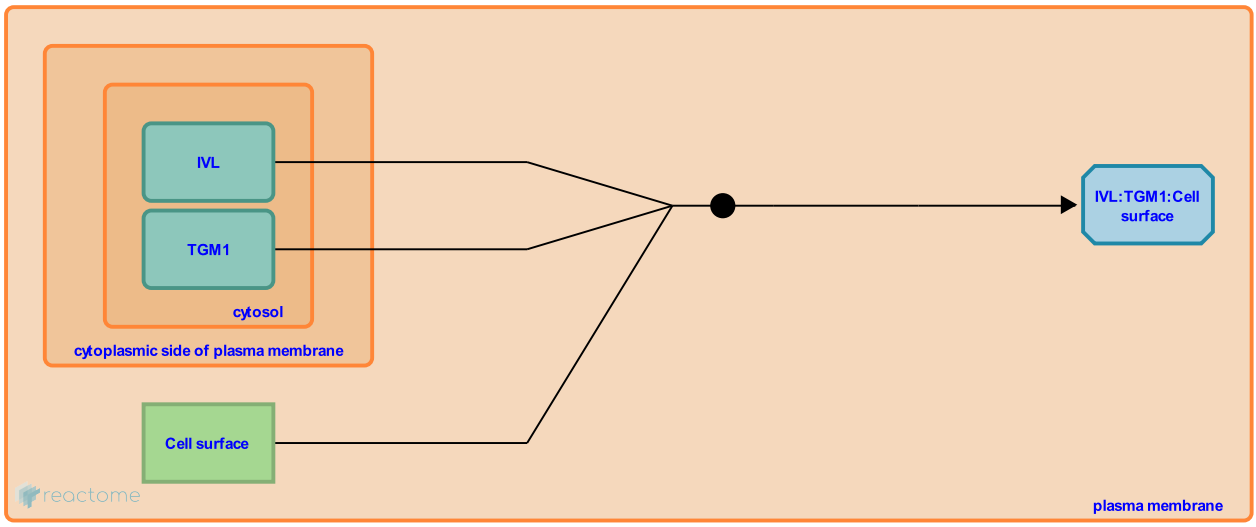
TGM1 and involucrin bind the plasma membrane ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6810899

Type: binding

Compartments: plasma membrane, cytosol



Transglutaminase-1 (TGM1) and involucrin (IVL) are expressed shortly after envoplakin and periplakin. TGM1 associates with the plasma membrane via C14-16 fatty-acid adducts on its C-terminus (Steinert et al. 1996). IVL deposition precedes that of most other cornified envelope proteins (Nemes & Steinert 1999). It can bind the plasma membrane in a calcium and phosphatidyl-serine dependent manner, where it becomes a substrate for membrane-bound TGM1 and TGM5 (Nemes et al. 1999, Candi et al. 2001).

Followed by: Envoplakin, periplakin, involucrin, SPR binding mediated by TGM1 crosslinking

Literature references

Steinert, PM., Nemes, Z. (1999). Bricks and mortar of the epidermal barrier. *Exp. Mol. Med., 31*, 5-19. ↗

Kim, SY., Steinert, PM., Chung, SI., Marekov, LN. (1996). The transglutaminase 1 enzyme is variably acylated by myristate and palmitate during differentiation in epidermal keratinocytes. *J. Biol. Chem., 271*, 26242-50. ↗

Steinert, PM., Nemes, Z., Marekov, LN. (1999). Involucrin cross-linking by transglutaminase 1. Binding to membranes directs residue specificity. *J. Biol. Chem., 274*, 11013-21. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-10	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

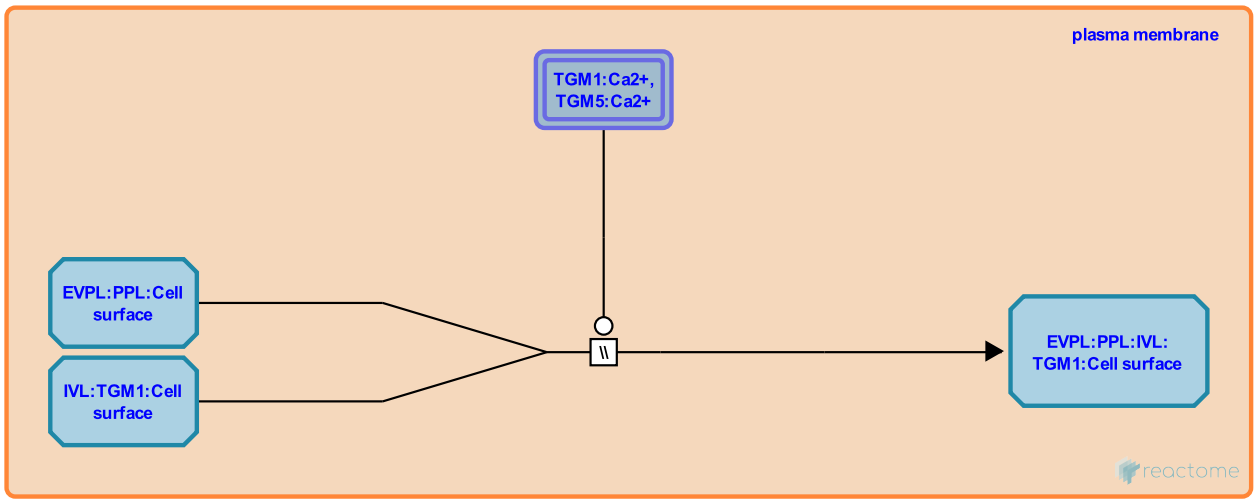
Envoplakin, periplakin, involucrin, SPR binding mediated by TGM1 crosslinking ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6810894

Type: omitted

Compartments: plasma membrane, cytosol



The current model of cornified envelope (CE) formation suggests that crosslinking between envoplakin (EVPL), periplakin (PPL), involucrin (IVL) and small proline-rich proteins (SPRs) results in the formation of a layer along the entire inner surface of the plasma membrane, including desmosomes, forming a scaffold to which other precursors are added to form the mature CE (Steinert & Marekov 1999, Kalinin et al. 2002, Candi et al. 2001).

Transglutaminases (TGs) are believed to mediate the intramolecular bonds involved in CE formation. They catalyze inter-protein bond formation by forming a thiolester acyl-enzyme intermediate and subsequently transferring the acyl residue to a primary amine (Folk & Finlayson 1977, Folk 1980). The amine acceptor is generally provided by the epsilon-amino group of a protein-bound lysine and the link formed is an N6-(gamma-glutamyl)lysine isopeptide bond.

CE assembly is thought to be initiated on the inner face of the plasma membrane between desmosomes by the cross-linking of involucrin to itself, to envoplakin and perhaps to periplakin (Steinert & Marekov 1999). The extent of homo- and heterologous cross-linking varies as the CE matures. In the immature CE, EVPL, IVL, SPR1, and SPR2 are largely cross-linked to themselves; EVPL-IVL and IVL-SPR crosslinks are common while cross-links between desmoplakin (DSP) and IVL or DSP and EVPL are not. Later there are many more cross-links between DSP and IVL, DSP and EVL, or IVL and type II keratins. Loricrin (LOR) cross-linking to other protein partners appears later.

Transglutaminase-1 (TGM1) can crosslink IVL (Simon & Green 1988, Nemes et al. 1999), LOR (Candi et al. 2001), SPR3 (Steinert et al. 1999) and is thought to be responsible for EVPL crosslinking to itself and to IVL (Steinert & Marekov 1999). TGM5 can catalyse homo-crosslinking in LOR, SPR1, SPR2, and IVL, and hetero-crosslinks between LOR-SPR3 (Candi et al. 2001).

Preceded by: EVL:PPL heterodimer binds the inner surface of the plasma membrane, TGM1 and involucrin bind the plasma membrane

Followed by: Reinforcement of the Cornified Envelope

Literature references

Steinert, PM., Marekov, LN. (1999). Initiation of assembly of the cell envelope barrier structure of stratified squamous epithelia. *Mol. Biol. Cell, 10*, 4247-61. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-10	Edited	Jupe, S.
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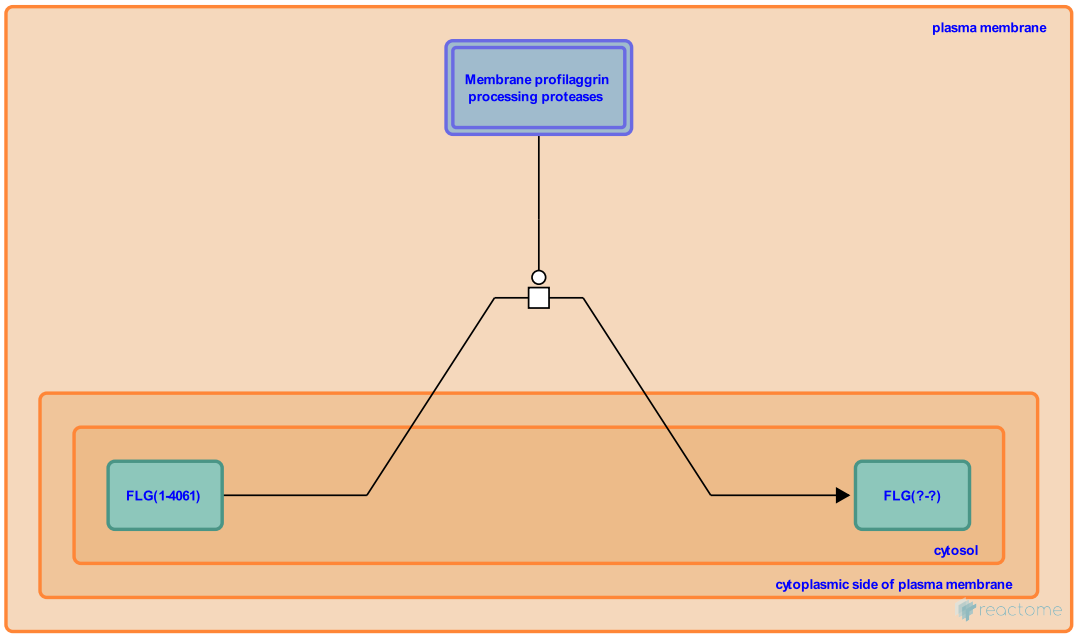
Membrane proteases cleave Profilaggrin producing Filaggrin ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8849797

Type: transition

Compartments: plasma membrane, cytosol



Filaggrin is initially synthesized as a large, insoluble, highly phosphorylated precursor containing many tandem copies of 324 residues. This precursor is dephosphorylated and proteolytically cleaved by several proteases, including the undefined protease PEP1 (Resing et al. 1996), mu-calpain (Yamazaki et al. 1997), furin, PCSK6 (PACE4) (Pearton et al. 2001), PRSS8 (cap1) (Leyvraz et al. 2005), ST14 (matriptase) (List et al. 2003), CELA2 (Bonnart et al. 2010), CASP14 (Denecker et al. 2007) and Kallikrein-related peptidase 5 (KLK5) (Sakabe et al. 2013). Filaggrin is further processed and proteolytically degraded by CASP14 (Eckhart & Tschachler 2011).

Followed by: Filaggrin binds Keratin tonofilament:Desmosome

Literature references

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

Dale, BA., Pearton, DJ., Nirunsuksiri, W., Presland, RB., Rehemtulla, A., Lewis, SP. (2001). Proprotein convertase expression and localization in epidermis: evidence for multiple roles and substrates. *Exp. Dermatol., 10*, 193-203. ↗

Guitard, M., Breiden, B., Rubera, I., Charles, RP., Leyvraz, C., Hummler, E. et al. (2005). The epidermal barrier function is dependent on the serine protease CAP1/Prss8. *J. Cell Biol., 170*, 487-96. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-10	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

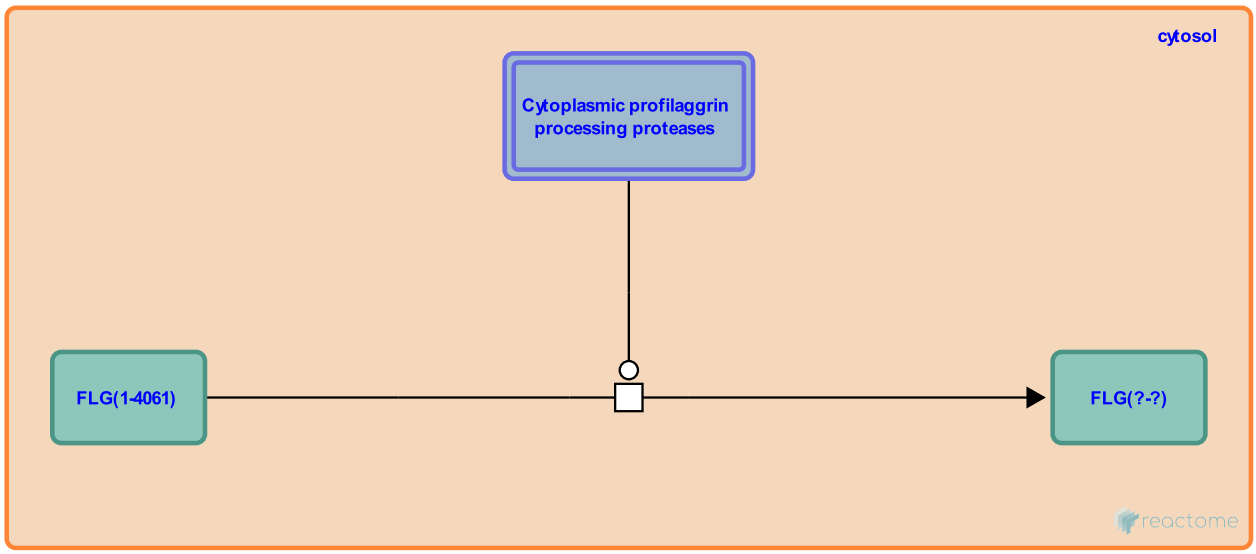
Cytoplasmic proteases cleave Profilaggrin producing Filaggrin ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8934819

Type: transition

Compartments: cytosol



Filaggrin is initially synthesized as a large, insoluble, highly phosphorylated precursor containing many tandem copies of 324 residues. This precursor is dephosphorylated and proteolytically cleaved by several proteases, including the undefined protease PEP1 (Resing et al. 1996), mu-calpain (Yamazaki et al. 1997), furin, PCSK6 (PACE4) (Pearton et al. 2001), PRSS8 (cap1) (Leyvraz et al. 2005), ST14 (matriptase) (List et al. 2003), CELA2 (Bonnart et al. 2010), CASP14 (Denecker et al. 2007) and Kallikrein-related peptidase 5 (KLK5) (Sakabe et al. 2013). Filaggrin is further processed and proteolytically degraded by CASP14 (Eckhart & Tschachler 2011).

Followed by: Filaggrin binds Keratin tonofilament:Desmosome

Literature references

Eckhart, L., Tschachler, E. (2011). Cuts by caspase-14 control the proteolysis of filaggrin. *J. Invest. Dermatol., 131*, 2173-5. ↗

D'Herde, K., Libert, C., Gilbert, B., Borgonie, G., Lippens, S., Declercq, W. et al. (2007). Caspase-14 protects against epidermal UVB photodamage and water loss. *Nat. Cell Biol., 9*, 666-74. ↗

Hovnanian, A., Robin, A., Besson, C., Deraison, C., Briot, A., Bonnart, C. et al. (2010). Elastase 2 is expressed in human and mouse epidermis and impairs skin barrier function in Netherton syndrome through filaggrin and lipid misprocessing. *J. Clin. Invest., 120*, 871-82. ↗

Yamamoto, M., Tokura, Y., Hirakawa, S., Kabashima, K., Ohta, I., Sakabe, J. et al. (2013). Kallikrein-related peptidase 5 functions in proteolytic processing of profilaggrin in cultured human keratinocytes. *J. Biol. Chem., 288*, 17179-89. ↗

Editions

2016-03-10	Authored	Jupe, S.
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2016-08-12	Reviewed	Blumenberg, M.

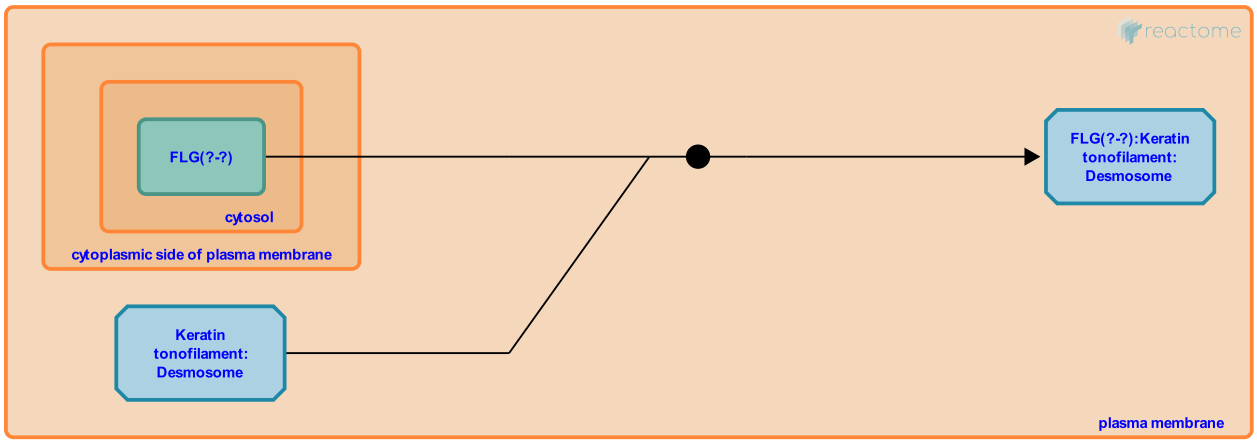
Filaggrin binds Keratin tonofilament:Desmosome ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8942224

Type: binding

Compartments: plasma membrane, cytosol



During cornification, a network of keratin intermediate filaments (KIF) and filaggrin (FLG) becomes crosslinked to the cornified envelope (CE). The FLG-KIF linkage occurs primarily through a specific lysine residue on the head domain of type II keratin chains, which can crosslink with several CE proteins including loricrin, SPRs, envoplakin and involucrin (Dale et al. 1978, Manabe et al. 1991, Mack et al. 1993, Steinert et al. 1995, Candi et al. 1998). This FLG-KIF crosslinking is believed to organise intermediate filaments into bundles, which stabilize the keratin network (Steinert et al. 1981, Candi et al. 2005) and facilitate the collapse and flattening of cells in the outermost stratum corneum to produce squames. Cell flattening can occur in the absence of FLG, but at the ultrastructural level loss-of-function mutations in FLG are associated with disorganized keratin filaments, impaired lamellar body loading and abnormal architecture of the lamellar bilayer (Gruber et al. 2011).

Preceded by: Cytoplasmic proteases cleave Profilaggrin producing Filaggrin, Membrane proteases cleave Profilaggrin producing Filaggrin

Followed by: Fillagrin and keratin intermediate filaments polymerize forming a network

Literature references

Steinert, PM., Marekov, LN. (1995). The proteins elafin, filaggrin, keratin intermediate filaments, loricrin, and small proline-rich proteins 1 and 2 are isodipeptide cross-linked components of the human epidermal cornified cell envelope. *J. Biol. Chem., 270*, 17702-11. ↗

Editions

2016-08-12	Reviewed	Blumenberg, M.
2016-09-23	Authored	Jupe, S.

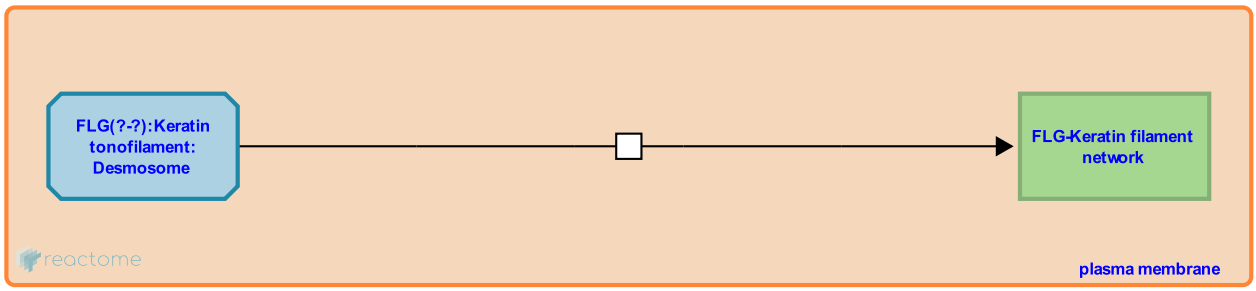
Fillagrin and keratin intermediate filaments polymerize forming a network ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6810357

Type: transition

Compartments: plasma membrane



During cornification a network of keratin intermediate filaments (KIF) and filaggrin (FLG) becomes crosslinked to the cornified envelope (CE). This facilitates the collapse and flattening of cells in the outermost stratum corneum to produce squames (Dale et al. 1978, Mack et al. 1993, Candi et al. 2005, Gruber et al. 2011).

Preceded by: Filaggrin binds Keratin tonofilament:Desmosome

Followed by: Reinforcement of the Cornified Envelope

Literature references

Steinert, PM., Marekov, LN. (1995). The proteins elafin, filaggrin, keratin intermediate filaments, loricrin, and small proline-rich proteins 1 and 2 are isodipeptide cross-linked components of the human epidermal cornified cell envelope. *J. Biol. Chem., 270*, 17702-11. ↗

Editions

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2016-08-10	Edited	Jupe, S.
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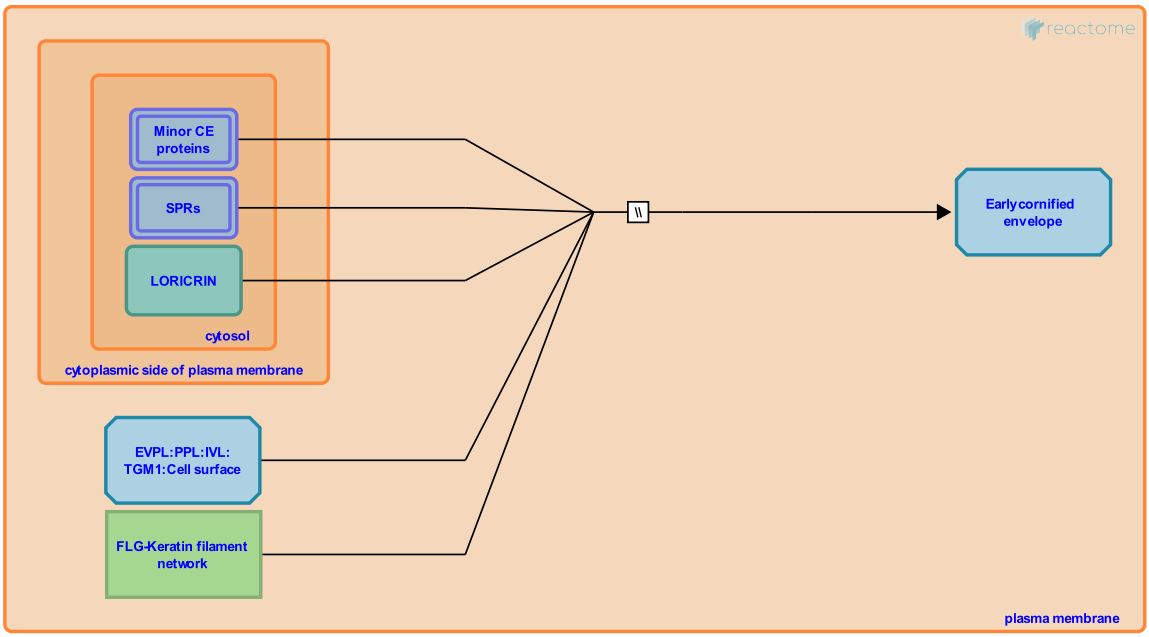
Reinforcement of the Cornified Envelope ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6811539

Type: omitted

Compartments: plasma membrane, cytosol



The inital scaffold of the cornified envelope (CE) is reinforced by the inclusion of loricrin (LOR) and small proline-rich proteins (SPRs), which together comprise about 75% of the total mass of the CE. Other proteins include filaggrin (FLG) (8%), elafin (6%), cystatin A (5%), involucrin (IVL) and keratin intermediate filaments (KIFs) (about 2% each) (Steinert & Marekov 1995). Other minor proteins include repetin (RPTN), trichohyalin (TCHH) and elafin (PI3) (Steinert & Marekov 1997, Steinert et al. 1998).

LOR is poorly soluble in vivo, while SPRs are very soluble. Both are preferred substrates of cytosolic transglutaminase-3 (TGM3) (Candi et al. 1999, Steinert et al. 1999, Tarcsa et al. 1999), which suggests that TGM3 may cross-link LOR and SPRs to create soluble complexes that are more easily translocated to the cell periphery (Kalinin et al. 2002). These cross-linked oligomers are good substrates for TGM1 (Candi et al. 1999, Steinert et al. 1999) which may link the LOR-SPR complexes to the CE scaffold. LOR can also be crosslinked by TGM5 (Candi et al. 2001). SPR content varies in epithelia from different body sites and increasing SPR content correlates with mechanical requirements of the tissue (Steinert et al. 1998). In humans LOR is initially deposited in the granular layer of the epidermis in keratohyalin granules, intermixed with profilaggrin (Yoneda & Steinert 1993). These are encoded in a linked 'Epidermal Differentiation Complex.' (Kypriotou et al. 2012, Niehues et al. 2016).

As the main component of the CE (Steinert & Marekov 1995), LOR is thought to function as the main reinforcement protein. LOR proteins are extensively crosslinked through isopeptide bonds but also crosslinked to SPRs, which may function as bridging proteins between LOR molecules (Candi et al. 2005). LOR can also form crosslinks with keratin and filaggrin (Steinert & Marekov 1995). CE crosslinking involves TGM1, TGM3 and TGM5 (Lorand & Graham 2003). The type-II keratin chains (K1, K2e and K5) are crosslinked at a specific Lys residue that is located in a conserved region of the V1 subdomain of the head domain (Steinert & Marekov 1995). IVL can be crosslinked by TGM1, which preferentially crosslinks Gln495 and Gln496 (Simon & Green 1998). In vitro, LOR is a substrate for TGM1-3 and 5 (Candi et al. 1995). In the epidermis, TGM1, TGM5 and TGM3 are believed to crosslink LOR sequentially; an initial attachment by TGM1 and 5 forms interchain crosslinks followed by a compaction process that involves TGM3 (Candi et al. 2005). SPRs are also TGM substrates, particularly TGM3 (Candi et al. 1999, Tarcsa et al. 1998, Steinert et al. 1999).

FLG binds KIFs, aggregating them into tight bundles. As a component of the CE, FLG 'glues' KIFs to the CE and coordinates the structure of cornifying cells (Steinert & Marekov 1995, Candi et al. 2005).

Preceded by: Envoplakin, periplakin, involucrin, SPR binding mediated by TGM1 crosslinking, Fillagrin and keratin intermediate filaments polymerize forming a network

Followed by: Lamellar bodies bind the early cornified envelope

Literature references

Steinert, PM., Marekov, LN., Kartasova, T. (1998). Biochemical evidence that small proline-rich proteins and trichohyalin function in epithelia by modulation of the biomechanical properties of their cornified cell envelopes. *J. Biol. Chem., 273*, 11758-69. ↗

Steinert, PM., Marekov, LN. (1997). Direct evidence that involucrin is a major early isopeptide cross-linked component of the keratinocyte cornified cell envelope. *J. Biol. Chem., 272*, 2021-30. ↗

Steinert, PM., Idler, WW., Candi, E., Marekov, LN., Kartasova, T., Tarcsa, E. (1999). Transglutaminase cross-linking properties of the small proline-rich 1 family of cornified cell envelope proteins. Integration with loricrin. *J. Biol. Chem., 274*, 7226-37. ↗

Steinert, PM., Marekov, LN. (1995). The proteins elafin, filaggrin, keratin intermediate filaments, loricrin, and small proline-rich proteins 1 and 2 are isodipeptide cross-linked components of the human epidermal cornified cell envelope. *J. Biol. Chem., 270*, 17702-11. ↗

Editions

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2016-08-12	Reviewed	Blumenberg, M.

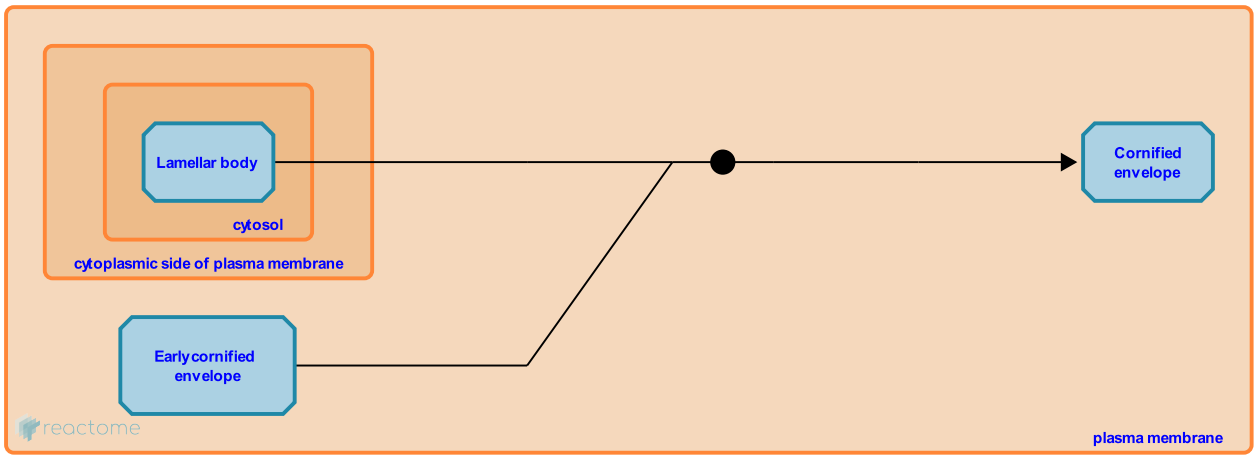
Lamellar bodies bind the early cornified envelope ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6810937

Type: binding

Compartments: plasma membrane, cytosol



Lamellar bodies (LBs)) are lipid-rich organelles produced by keratinocytes and secreted to form an impermeable water barrier (Feingold & Elias 2014). The lipids in LBs contain phospholipids, glucosylceramides, sphingomyelin and cholesterol (Feingold 2007). These lipids, some of which are keratinization specific, are synthesized and accumulate in the trans Golgi apparatus, budding off as LBs that accumulate in the granular layer (Wertz & van den Bergh 1998).). LB lipids also organize into characteristic intercellular lamellae (Kalinin et al. 2002). LBs fuse with the plasma membrane (Schmitz & Muller 1991, Chattopadhyay et al. 2003) delivering lipids which become ester-linked to involucrin and probably other cornified envelope proteins by TG1 (Nemes et al. 1991) and possibly TG5 (Candi et al. 2005), forming a monomolecular layer termed the lipid envelope. Eventually these lipids replace the plasma membrane lipid bilayer, which is reabsorbed. Extracellularly, the LB lipids are further metabolized to have a unique composition and are 50% ceramides, 25% cholesterol, and 15% free fatty acids (Feingold 2007).

Preceded by: Reinforcement of the Cornified Envelope

Followed by: Late envelope proteins bind cornified envelope:CDSN

Literature references

Wang, P., Liu, L., Chattopadhyay, S., Abonyo, B., Cross, NL., Sun, P. (2003). Fusion of lamellar body with plasma membrane is driven by the dual action of annexin II tetramer and arachidonic acid. *J. Biol. Chem., 278*, 39675-83. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

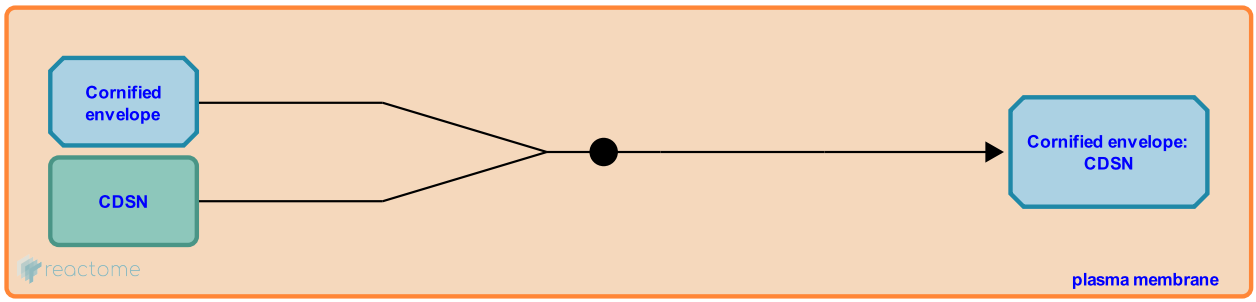
CDSN binds the cornified envelope ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6814734

Type: binding

Compartments: plasma membrane, cytosol



Corneodesmosomes (CDS) are an ultrastructurally modified form of desmosomes (DS) (Chapman & Walsh 1990). When DS are transformed into CDS between the stratum granulosum and the stratum corneum, the desmoglea loses its trilamellar structure and becomes homogeneously electron dense. On the cytoplasmic side, the attachment plaque (desmosomal plaque) becomes incorporated into the cornified cell envelope (CE). Keratin filaments are connected to the attachment plaque in DS; this association is no longer visible in CDS.

Like DS, desmoglein and desmocollin constitute the extracellular parts of CDS (Simon et al. 1997), but there is an additional unique extracellular component known as corneodesmosin (CDSN). CDSN is a 52- to 56-kDa glycoprotein produced by keratinocytes that is incorporated into the desmoglea of DS shortly before their transformation into CDS during cornification (Serre et al. 1991). It is stored and secreted by Lamellar bodies. After secretion CDSN localizes to the extracellular structures of CDS and covalently cross-links to the CE. This step coincides with the morphological transformation of DS into CDS. In vitro studies suggest that CDSN mediates homophilic binding to counterparts on adjacent corneocytes (Ishida-Yamamoto & Kishibe 2011). Cleavage of desmoglein, desmocollin and CDSN is a key step in desquamation.

Literature references

Guerrin, M., Montézin, M., Serre, G., Durieux, JJ., Simon, M. (1997). Characterization and purification of human corneodesmosin, an epidermal basic glycoprotein associated with corneocyte-specific modified desmosomes. *J. Biol. Chem., 272*, 31770-6. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

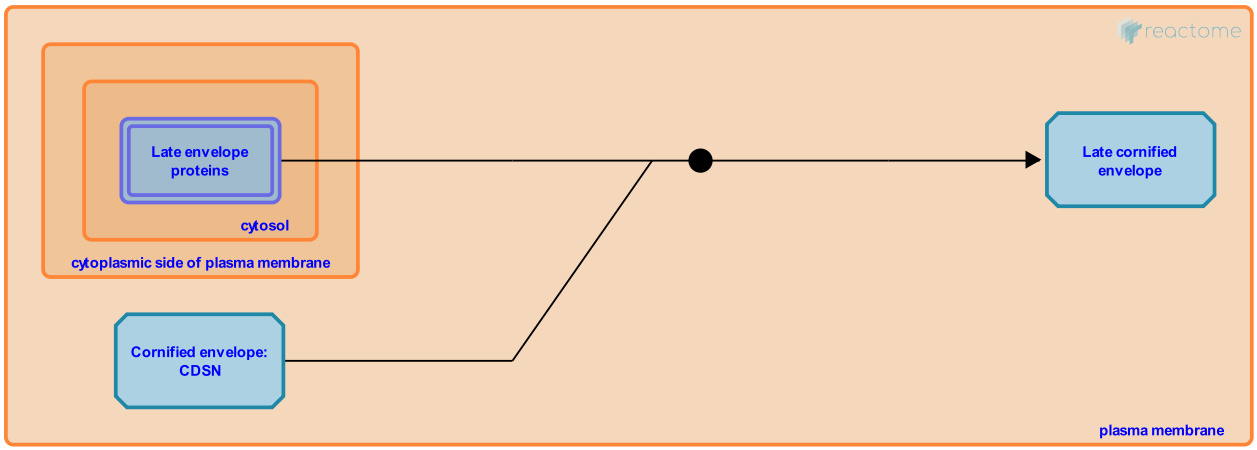
Late envelope proteins bind cornified envelope:CDSN ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6814298

Type: binding

Compartments: plasma membrane, cytosol



Late envelope proteins or late cornified envelope proteins (LCEs) are a family of 18 proteins that are expressed after assembly of the cornified envelope (CE) is advanced (Marshall et al. 2000, Kypriotou et al. 2012). They are incorporated into the CE late in the process of envelope maturation during epidermal differentiation. They are probable substrates for epidermal transglutaminases and proposed to link CE proteins and mediate differences in barrier quality, perhaps through interaction with cytoplasmic components of the cornified cell (Marshall et al. 2001).

Human LCEs fall into distinct structural groups, encoded by genes which form clusters on the genome at 1q21 (Marshall et al. 2001, Niehues et al. 2016). Group 1 are expressed predominantly in epidermis. Group 4 (LEP 13-17) have highest expression in internal epithelia (Wang et al. 2001, Marshall et al. 2001).

Preceded by: Lamellar bodies bind the early cornified envelope

Followed by: CASP14 cleaves filaggrin, Plasma membrane resorption

Literature references

Byrne, C., Hardman, MJ., Marshall, D. (2000). SPRR1 gene induction and barrier formation occur as coordinated moving fronts in terminally differentiating epithelia. *J. Invest. Dermatol., 114*, 967-75. ↗

Wang, A., MacLeod, MC., Johnson, DG. (2001). Molecular cloning and characterization of a novel mouse epidermal differentiation gene and its promoter. *Genomics, 73*, 284-90. ↗

Pflugfelder, SC., Li, DQ., Beuerman, R., Chen, Z., De Paiva, CS., Tong, L. et al. (2006). Expression and regulation of cornified envelope proteins in human corneal epithelium. *Invest. Ophthalmol. Vis. Sci., 47*, 1938-46. ↗

Editions

2016-03-10	Authored	Jupe, S.
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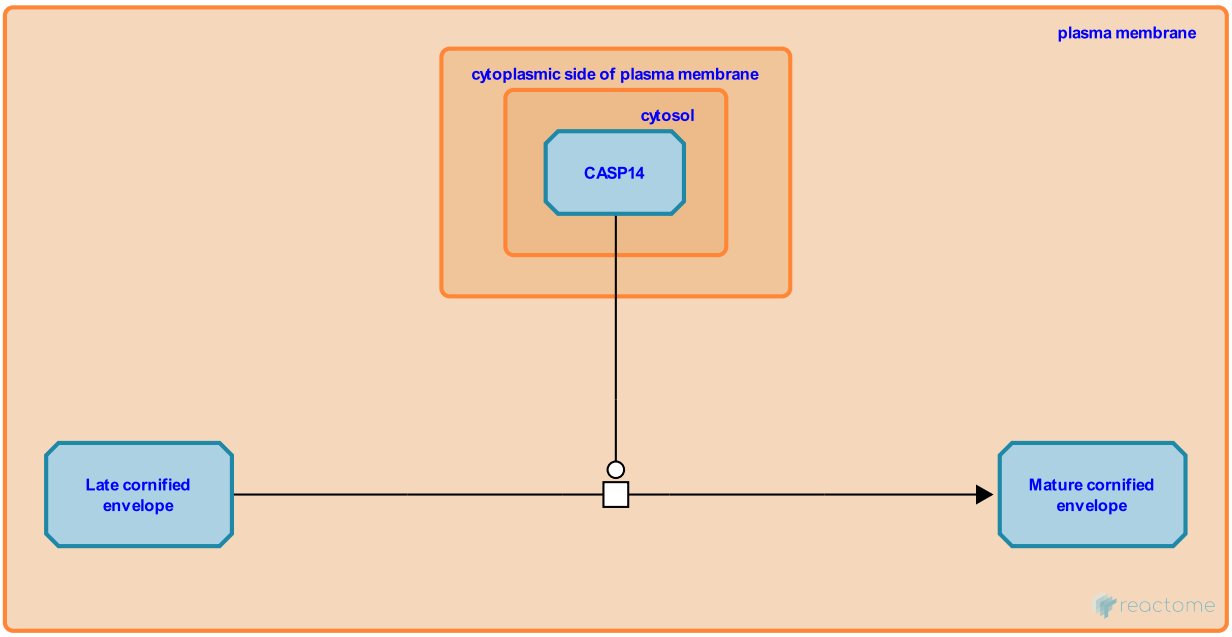
CASP14 cleaves filaggrin ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6814387

Type: transition

Compartments: plasma membrane, cytosol



In fully cornified cells, filaggrin is degraded into free amino acids. This high concentration of hydrophillic amino acids is essential for water retention and contributes to the osmolarity, and consequently the flexibility of the cornified layer (Candi et al. 2005). Filaggrin monomers are a direct target for cleavage by the aspartate-specific protease caspase 14 (Denecker et al. 2007, 2008, Hoste et al. 2011, Eckhart & Tschachler 2011). Proteases able to process profilaggrin into fillagrin in vitro include microbial ST14 (Profillagrin endopeptidase 1, PEP1), CAPN1 (mu-calpain), furin, PACE4 and matriptase MT-SP1 (Reising et al. 1995, Yamazaki et al. 1997, Pearton et al. 2001, List et al. 2003, Candi et al. 2005), but these proteases do not appear to have a role in the degradation of filaggrin that occurs at a late stage in keratinization.

Preceded by: Late envelope proteins bind cornified envelope:CDSN

Literature references

Roelandt, R., Kemperman, P., Takahara, H., Gilbert, B., Lippens, S., Declercq, W. et al. (2011). Caspase-14 is required for filaggrin degradation to natural moisturizing factors in the skin. *J. Invest. Dermatol., 131*, 2233-41. ↗

D'Herde, K., Libert, C., Gilbert, B., Borgonie, G., Lippens, S., Declercq, W. et al. (2007). Caspase-14 protects against epidermal UVB photodamage and water loss. *Nat. Cell Biol., 9*, 666-74. ↗

Editions

2016-03-10	Authored	Jupe, S.
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2016-08-12	Reviewed	Blumenberg, M.

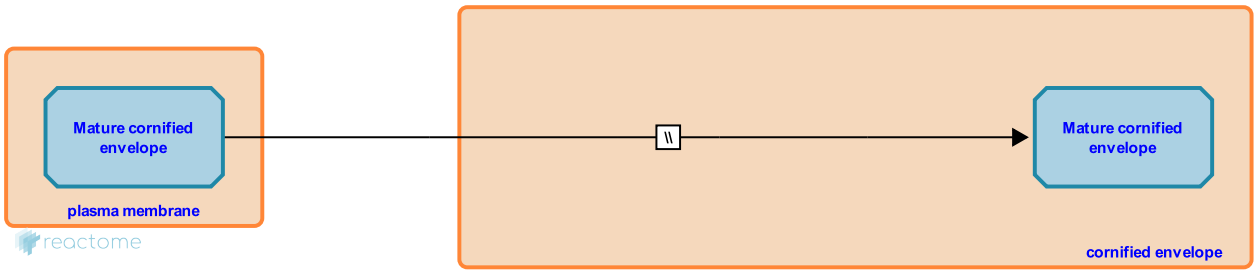
Plasma membrane resorption ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6814764

Type: omitted

Compartments: cornified envelope, plasma membrane



In differentiating keratinocytes, fusion of lamellar body (LB) membranes with the plasma membrane enriches the plasma membrane with lipids including omega-OH-ceramides. Their fatty acid chains are long enough to span the lipid bilayer, so that the omega-OH projects into the cell. In vitro data have shown that the membrane-anchored transglutaminase 1 enzyme can covalently esterify these ceramides onto glutamine residues of cornified envelope scaffold proteins (Nemes et al. 1999). Eventually, the ceramides replace the bilayer plasma membrane and are thought to serve to interdigitate with and organize the extracellular lipids into characteristic lamellae (Kalinin et al. 2001).

Preceded by: Late envelope proteins bind cornified envelope:CDSN

Literature references

Steinert, PM., Kalinin, A., Marekov, LN. (2001). Assembly of the epidermal cornified cell envelope. *J. Cell. Sci., 114*, 3069-70. ↗

Fésüs, L., Steinert, PM., Nemes, Z., Marekov, LN. (1999). A novel function for transglutaminase 1: attachment of long-chain omega-hydroxyceramides to involucrin by ester bond formation. *Proc. Natl. Acad. Sci. U.S.A., 96*, 8402-7. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

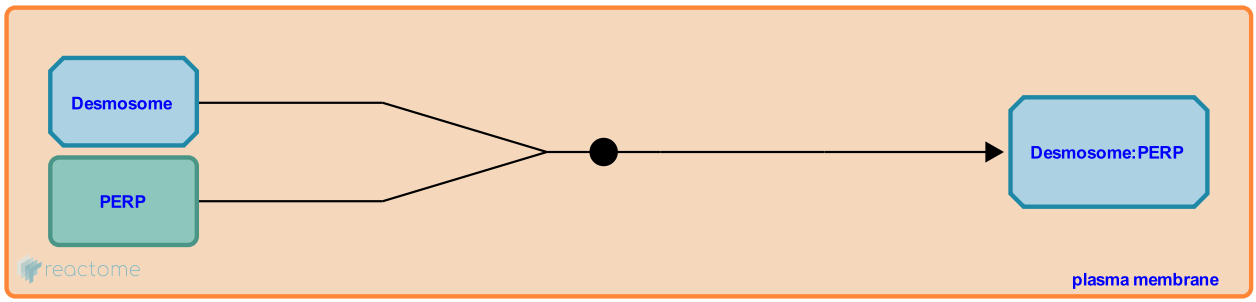
PERP binds desmosomes ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6814695

Type: binding

Compartments: plasma membrane



PERP (p53 effector related to PMP-22) is a p53/p63 target gene involved in DNA damage-induced apoptosis (Flores et al. 2002). It is a tetraspan membrane protein,distantly related to members of the claudin/PMP-22/EMP family of four-pass membrane proteins (Attardi et al. 2000). It has an epithelial-specific expression pattern during embryogenesis and localizes to desmosomes. Perp -/- knockout mice exhibit numerous desmosomal structural defects, suggesting a role for Perp in promoting the stable assembly of desmosomal adhesive complexes (Ihrie et al. 2005).

Literature references

Horner, JS., Nguyen, BT., Papazoglu, C., Marques, MR., Attardi, LD., Bronson, RT. et al. (2005). Perp is a p63-regulated gene essential for epithelial integrity. *Cell, 120*, 843-56. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

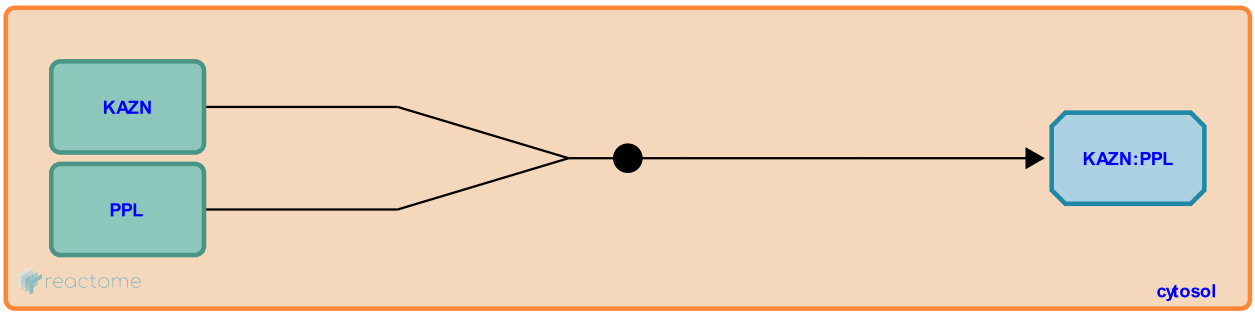
Kazrin binds periplakin ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6814374

Type: binding

Compartments: cytosol



Kazrin (KAZN) is an evolutionarily-conserved cytoplasmic and nuclear protein that was identified as a binding partner of periplakin (PPL), a component of epidermal desmosomes (DS) and the cornified envelope (CE) (Groot et al. 2004).

Kazrin has at least 5 different isoforms. Overexpression of the short isoform kazrinE stimulates the terminal differentiation of cultured human keratinocytes and is associated with a reduction in F-actin content, disruption of DS assembly, and changes in cell shape. Overexpression of activated RhoA rescues the effects on cell shape and adhesion. Conversely, knockdown of the longest isoform kazrinA impairs terminal differentiation, independently of RhoA activity (Sevilla et al. 2008a). KazrinE colocalizes with stabilized microtubules in differentiating keratinocytes (Nachat et al. 2009). All KAZN isoforms can form complexes with one another (Nachat et al. 2009), suggesting that like periplakin and envoplakin, it may form part of the cortical scaffold that integrates the actin cytoskeleton with DS (Ruhrberg et al. 1997, Kalinin et al. 2001, Groot et al. 2004). In Xenopus embryos, depletion of endogenous KAZN results in striking defects in axial elongation, muscle and notochord differentiation, and epidermal morphogenesis. These effects are believed to be due to disruption of cell-cell junctions (Sevilla et al. 2008b, Cho et al. 2010). However, mice with a knockout that removes exons 5-15 of KAZN had normal epidermal morphogenesis and homeostasis (Chhatriwala et al. 2012).

Literature references

Groot, KR., Nishi, K., Sevilla, LM., Watt, FM., DiColandrea, T. (2004). Kazrin, a novel periplakin-interacting protein associated with desmosomes and the keratinocyte plasma membrane. *J. Cell Biol., 166*, 653-9. ↗

Editions

2016-03-10	Authored	Jupe, S.
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ST14 hydrolyzes and activates KLK5 ↗

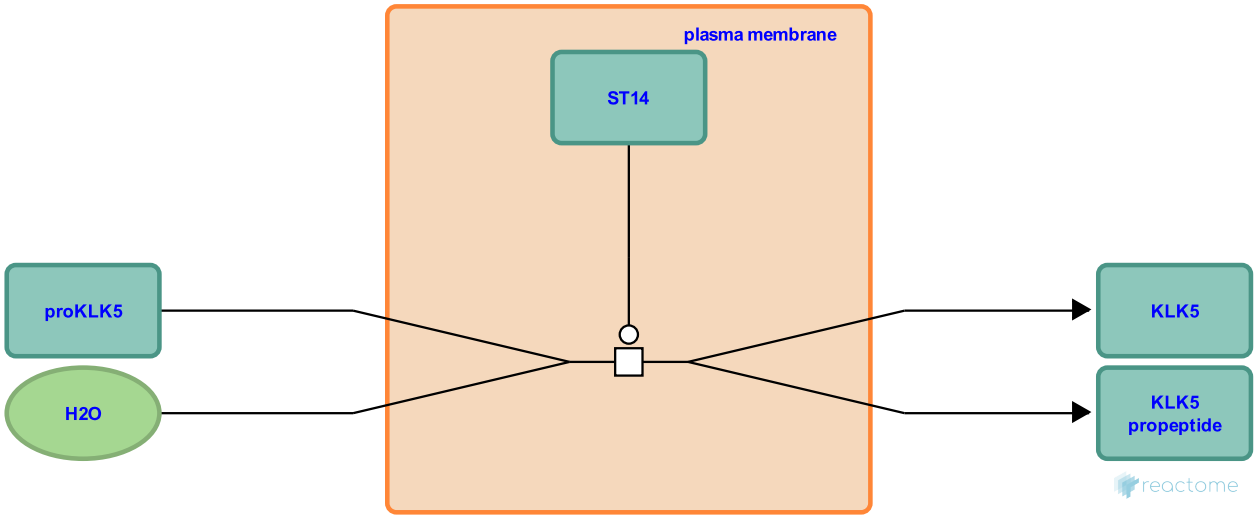
Location: Formation of the cornified envelope

Stable identifier: R-HSA-8849826

Type: transition

Compartments: plasma membrane, extracellular region

Inferred from: St14 hydrolyzes and activates Klk5 (Mus musculus)



ST14 (Suppressor of tumorigenicity 14, also known as matriptase) associated with the plasma membrane catalyzes the hydrolytic cleavage of proKLK5 (pro-Kallekrein-5) to yield active KLK5 enzyme. The activity of human ST14 enzyme is inferred from that of its well-characterized mouse homolog (Sales et al. 2010). Consistent with this inference, deficiencies of the human enzyme are associated with an ichthyosis syndrome (MIM 602400) as is a knockout mutation of mouse St14 (Alef et al. 2009).

Followed by: SPINK5(490-624) binds KLK5

Literature references

Sales, KU., Weigert, R., Bey, AL., Bugge, TH., Szabo, R., List, K. et al. (2010). Matriptase initiates activation of epidermal pro-kallikrein and disease onset in a mouse model of Netherton syndrome. *Nat. Genet., 42*, 676-83. ↗

Lestringant, GG., Metze, D., Hausser, I., Alef, T., Hennies, HC., Türsen, U. et al. (2009). Ichthyosis, follicular atrophoderma, and hypotrichosis caused by mutations in ST14 is associated with impaired profilaggrin processing. *J. Invest. Dermatol., 129*, 862-9. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

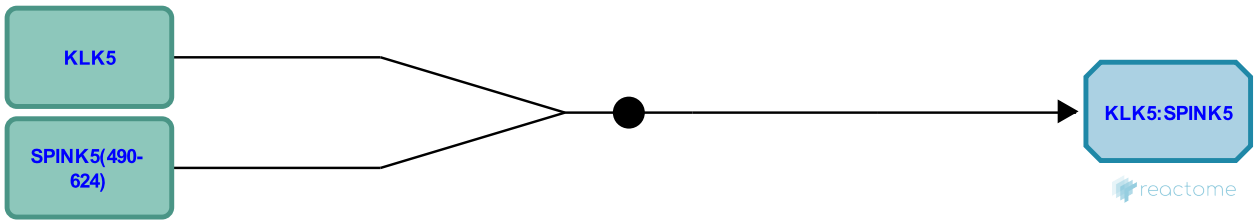
SPINK5(490-624) binds KLK5 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8849646

Type: binding

Compartments: extracellular region



The D8D9 fragment of SPINK5 (Serine protease inhibitor Kazal-type 5, also known as LEKTI, Lympho-epithelial Kazal-type-related inhibitor), consisting of residues 490 - 624 of the full-length protein, binds to KLK5 (Kallikrein-5), inactivating the latter. At neutral pH, complex formation is effectively irreversible. In normal skin, this event occurs extracellularly in the stratum corneum of the skin. As the complex is carried into layers nearer the surface of the skin, falling pH triggers its dissociation and release of active KLK5. Mutations that inactivate SPINK5 are associated with a severe skin disorder, Netherton syndrome (NS, MIM 256500), whose symptoms include premature desquamation (Deraison et al, 2007; Fortugno et al. 2011). Consistent with the hypothesis that SPINK5-mediated inhibition of KLK5 activity is a key feature of regulating normal desquamation, the NS-like phenotype of mice whose SPINK5-homologous gene has been knocked out is reversed in mice missing both SPINK5 and KLK5 activitiies (Furio et al. 2015).

Preceded by: ST14 hydrolyzes and activates KLK5

Followed by: Dissociation of the SPINK5:KLK5 complex at low pH

Literature references

Hovnanian, A., Furio, L., Sotiropoulou, G., Pampalakis, G., Michael, IP., Nagy, A. (2015). KLK5 Inactivation Reverses Cutaneous Hallmarks of Netherton Syndrome. *PLoS Genet., 11*, e1005389. ↗

Hovnanian, A., Jayakumar, A., Wagberg, F., Besson, C., Deraison, C., Bonnart, C. et al. (2007). LEKTI fragments specifically inhibit KLK5, KLK7, and KLK14 and control desquamation through a pH-dependent interaction. *Mol. Biol. Cell, 18*, 3607-19. ↗

Editions

2016-03-10	Authored	Jupe, S.
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2016-08-12	Reviewed	Blumenberg, M.

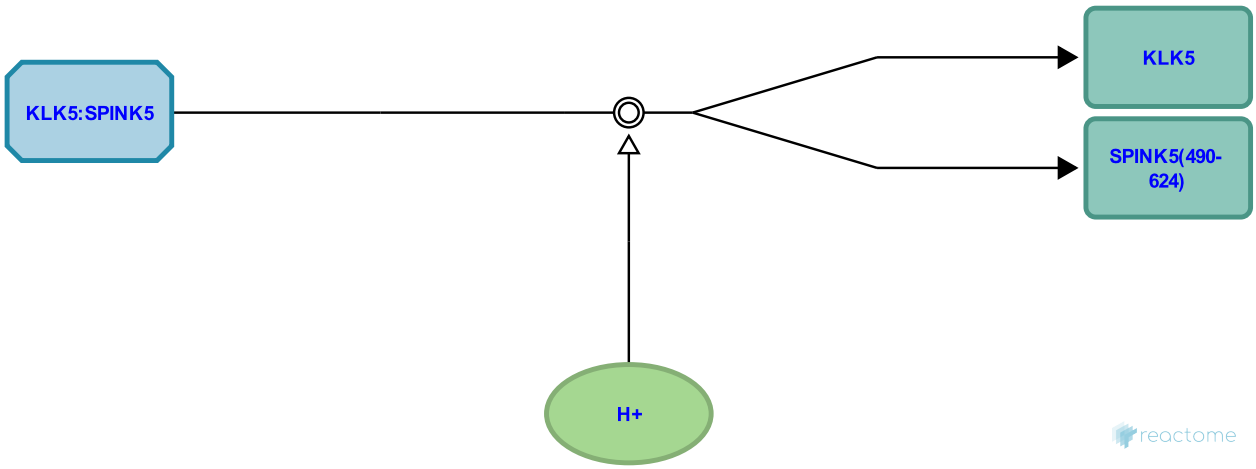
Dissociation of the SPINK5:KLK5 complex at low pH ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8849638

Type: dissociation

Compartments: extracellular region



At low pH, the complex of the D8D9 fragment of SPINK5 (Serine protease inhibitor Kazal-type 5, also known as LEKTI, Lympho-epithelial Kazal-type-related inhibitor), consisting of residues 490 - 624 of the full-length protein, and KLK5 (Kallikrein-5) dissociates, releasing active KLK5 protease. In normal skin, this event occurs extracellularly in upper layers of the skin (Deraison et al. 2007).

Preceded by: SPINK5(490-624) binds KLK5

Followed by: KLK5 cleaves and activates CELA2

Literature references

Hovnanian, A., Jayakumar, A., Wagberg, F., Besson, C., Deraison, C., Bonnart, C. et al. (2007). LEKTI fragments specifically inhibit KLK5, KLK7, and KLK14 and control desquamation through a pH-dependent interaction. *Mol. Biol. Cell, 18*, 3607-19. ↗

Editions

2016-03-10	Authored	Jupe, S.
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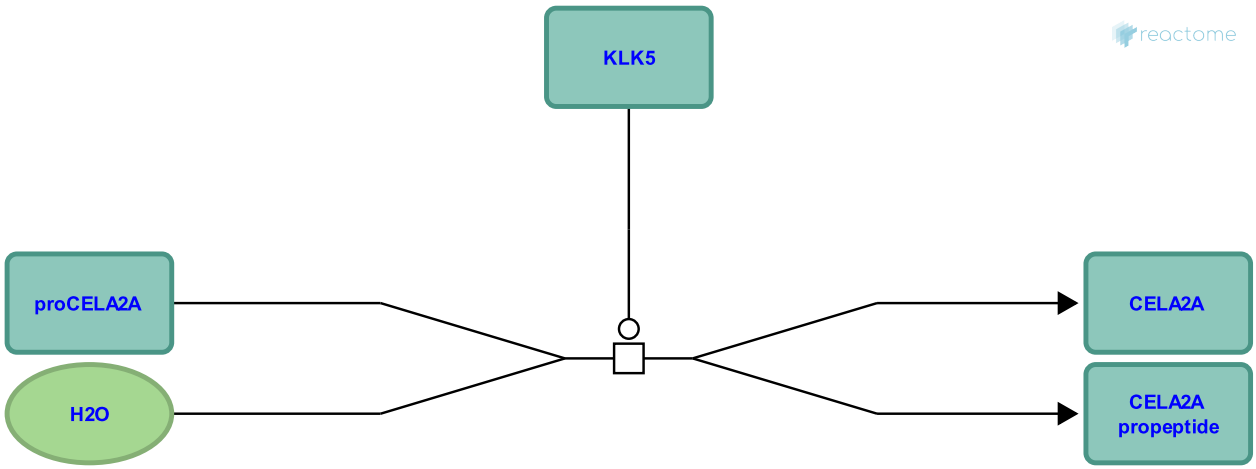
KLK5 cleaves and activates CELA2 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8849857

Type: transition

Compartments: extracellular region



In the low-pH environment of the upper layers of the stratum corneum, KLK5 (Kallikrein 5) dissociates from its complex with SPINK5 (Serine protease inhibitor kazal-type 5) (Deraison et al. 2007) and is free to cleave proCELA2 (Elastase 2), activating it (Bonnart et al. 2010).

Preceded by: Dissociation of the SPINK5:KLK5 complex at low pH

Literature references

Hovnanian, A., Robin, A., Besson, C., Deraison, C., Briot, A., Bonnart, C. et al. (2010). Elastase 2 is expressed in human and mouse epidermis and impairs skin barrier function in Netherton syndrome through filaggrin and lipid misprocessing. *J. Clin. Invest., 120*, 871-82. ↗

Hovnanian, A., Jayakumar, A., Wagberg, F., Besson, C., Deraison, C., Bonnart, C. et al. (2007). LEKTI fragments specifically inhibit KLK5, KLK7, and KLK14 and control desquamation through a pH-dependent interaction. *Mol. Biol. Cell, 18*, 3607-19. ↗

Editions

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2016-08-12	Reviewed	Blumenberg, M.

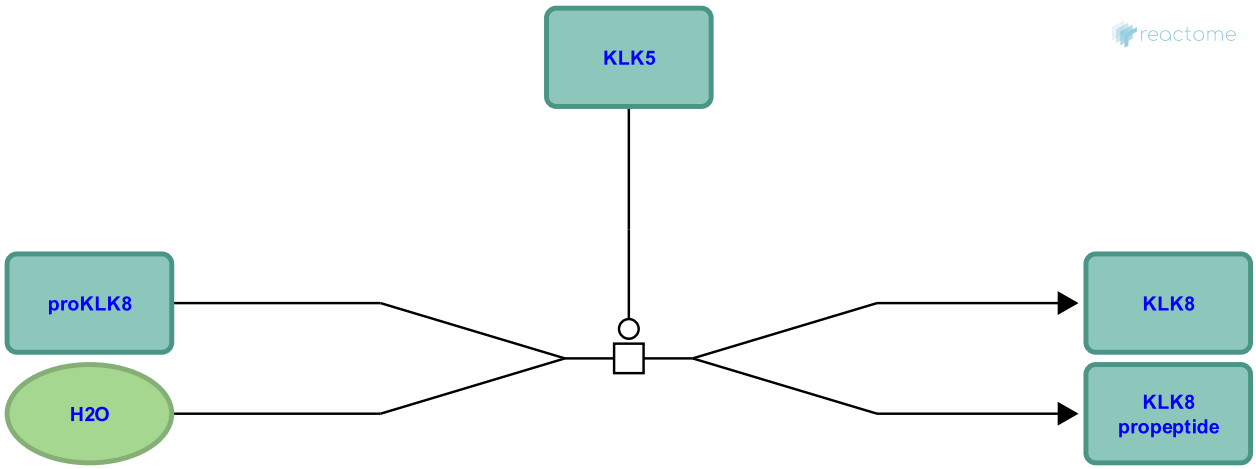
KLK5 cleaves and activates KLK8 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8850831

Type: transition

Compartments: extracellular region



In vitro, KLK5 (Kallikrein 5) catalyzes the slow cleavage of a four-residue aminoterminal propeptide from proKLK8 (pro-Kallekrein 8), to generate active KLK8. The abundance of KLK8 in the stratum corneum and its serine endopeptidase activity are consistent with a role for KLK8 in formation of the stratum corneum, desquamation, or both. Physiological substrates for KLK8 remains to be identified, however, as do possible additional activators of it (Eissa et al. 2011). A possible pathogenic role for KLK8 is suggested by the recent demonstration that it can mediate the extracellular cleavage of the L1 capsid protein of human papilloma viruses, facilitating their infection of human host cells (Cerqueira et al. 2015).

Literature references

Samperio Ventayol, P., Cerqueira, C., Vogeley, C., Schelhaas, M. (2015). Kallikrein-8 Proteolytically Processes Human Papillomaviruses in the Extracellular Space To Facilitate Entry into Host Cells. *J. Virol., 89*, 7038-52. ↗

Eissa, A., Diamandis, EP., Amodeo, V., Smith, CR. (2011). Kallikrein-related peptidase-8 (KLK8) is an active serine protease in human epidermis and sweat and is involved in a skin barrier proteolytic cascade. *J. Biol. Chem., 286*, 687-706. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

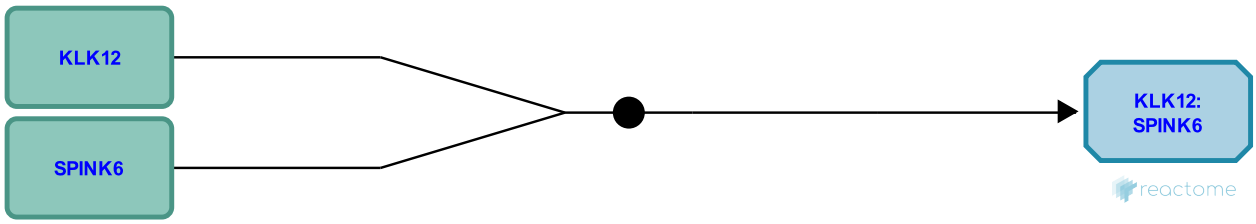
SPINK6 binds KLK12 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8850786

Type: binding

Compartments: extracellular region



Extracellular SPINK6 (Serine protease inhibitor Kazal-type 6) binds KLK12 (kallekrein-related peptidase 12), inactivating the latter (Kantyka et al. 2011).

Literature references

Kantyka, T., Schröder, JM., Meyer-Hoffert, U., Wu, Z., Reiss, K., Declercq, W. et al. (2011). Inhibition of kallikrein-related peptidases by the serine protease inhibitor of Kazal-type 6. *Peptides, 32*, 1187-92. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

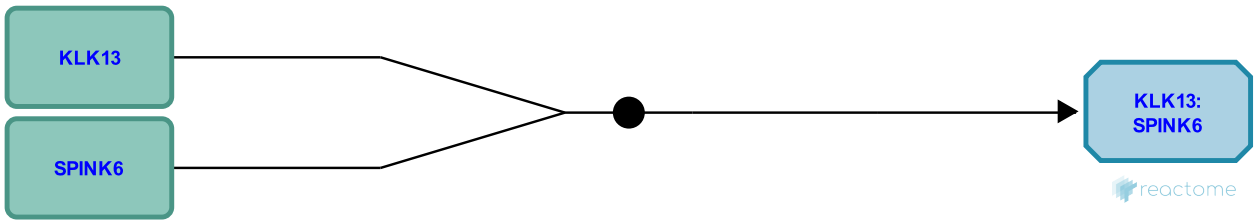
SPINK6 binds KLK13 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8850797

Type: binding

Compartments: extracellular region



Extracellular SPINK6 (Serine protease inhibitor Kazal-type 6) binds KLK13 (kallekrein-related peptidase 13), inactivating the latter (Kantyka et al. 2011).

Literature references

Kantyka, T., Schröder, JM., Meyer-Hoffert, U., Wu, Z., Reiss, K., Declercq, W. et al. (2011). Inhibition of kallikrein-related peptidases by the serine protease inhibitor of Kazal-type 6. *Peptides, 32*, 1187-92. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

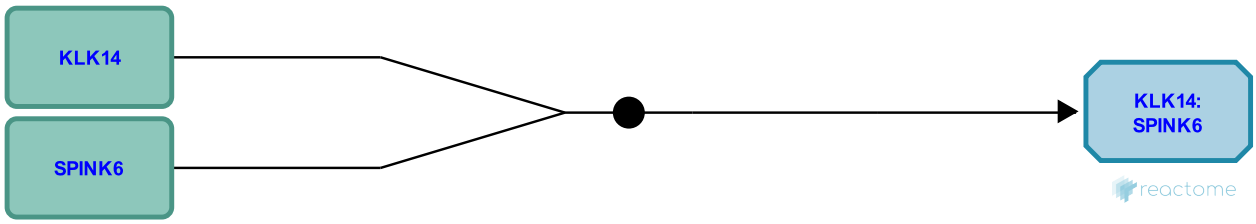
SPINK6 binds KLK14 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8850777

Type: binding

Compartments: extracellular region



Extracellular SPINK6 (Serine protease inhibitor Kazal-type 6) binds KLK14 (kallekrein-related peptidase 14), inactivating the latter. KLK14 activity contributes to the process of desquamation, and SPINK6 binding may play a role in the regulation of that process (Meyer-Hoffert et al. 2010).

Literature references

Hansmann, B., Kantyka, T., He, Y., Schröder, JM., Gläser, R., Meyer-Hoffert, U. et al. (2010). Isolation of SPINK6 in human skin: selective inhibitor of kallikrein-related peptidases. *J. Biol. Chem., 285*, 32174-81. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

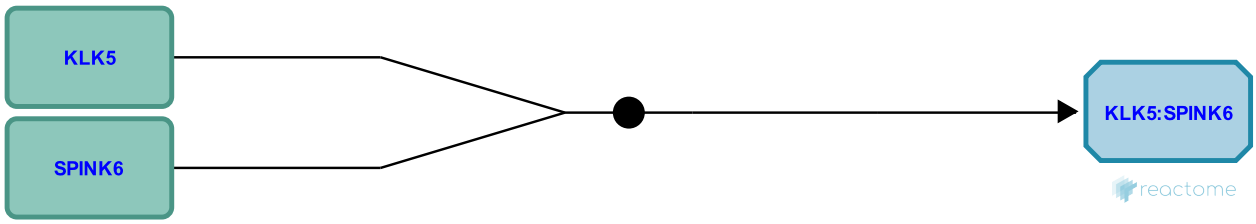
SPINK6 binds KLK5 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8850794

Type: binding

Compartments: extracellular region



Extracellular SPINK6 (Serine protease inhibitor Kazal-type 6) binds KLK5 (kallekrein-related peptidase 5), inactivating the latter. KLK5 activity contributes to the process of desquamation, and SPINK6 binding may play a role in the regulation of that process (Meyer-Hoffert et al. 2010).

Literature references

Hansmann, B., Kantyka, T., He, Y., Schröder, JM., Gläser, R., Meyer-Hoffert, U. et al. (2010). Isolation of SPINK6 in human skin: selective inhibitor of kallikrein-related peptidases. *J. Biol. Chem., 285*, 32174-81. ↗

Editions

2016-03-10	Authored	Jupe, S.
2016-08-09	Edited	Jupe, S.
2016-08-12	Reviewed	Blumenberg, M.

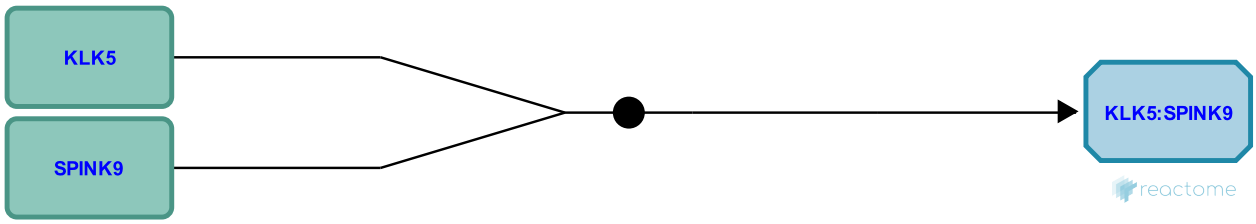
SPINK9 binds KLK5 ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-8850818

Type: binding

Compartments: extracellular region



Extracellular SPINK9 (Serine protease inhibitor Kazal-type 6) binds KLK5 (kallekrein-related peptidase 5), inactivating the latter. KLK5 activity contributes to the process of desquamation, and SPINK9 binding may play a role in the regulation of that process (Brattsand et al. 2009; Meyer-Hoffert et al. 2009).

Literature references

Schröder, JM., Meyer-Hoffert, U., Wu, Z. (2009). Identification of lympho-epithelial Kazal-type inhibitor 2 in human skin as a kallikrein-related peptidase 5-specific protease inhibitor. *PLoS ONE, 4*, e4372. ↗

Nilsson, SK., Hubiche, T., Brattsand, M., Egelrud, T., Stefansson, K. (2009). SPINK9: a selective, skin-specific Kazal-type serine protease inhibitor. *J. Invest. Dermatol., 129*, 1656-65. ↗

Editions

2016-03-10	Authored	Jupe, S.
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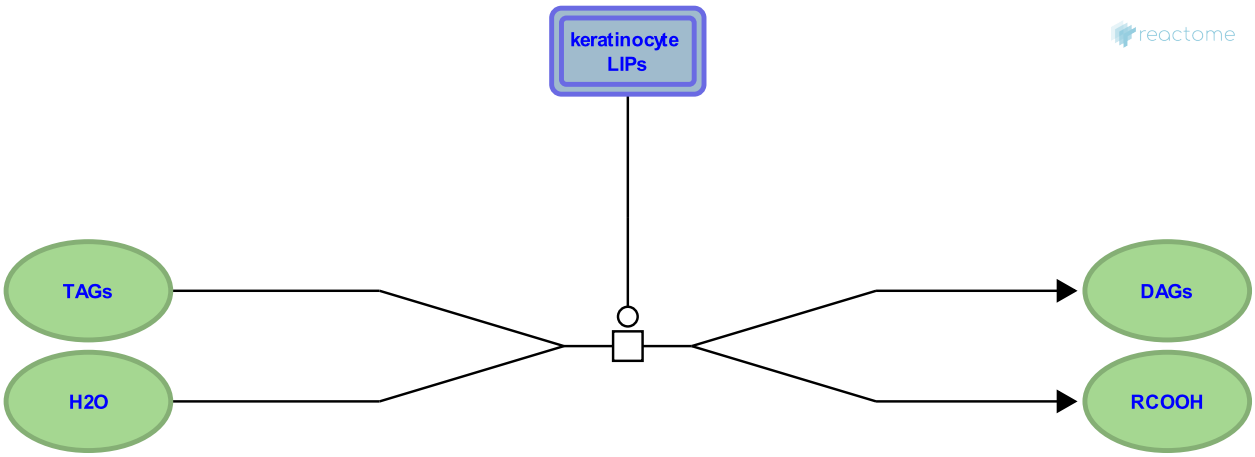
LIPs hydrolyse TG to DAG and RCOOH ↗

Location: Formation of the cornified envelope

Stable identifier: R-HSA-6789310

Type: transition

Compartments: extracellular region



Lipases are enzymes that hydrolyse dietary lipids such as fats, oils and triglycerides. The majority of human lipases are secreted by the pancreas and function mainly in the digestive system. Lipase members K, M and N (LIPK, M and N), however, all appear to play a role in the last step of keratinocyte differentiation where they are proposed to hydrolyse triglycerides to free fatty acids and glycerol which is essential to stratum corneum hydration (Toulza et al. 2007).

Literature references

Serre, G., Guerrin, M., Jacob, D., Dossat, C., Galliano, MF., de Daruvar, A. et al. (2007). Large-scale identification of human genes implicated in epidermal barrier function. *Genome Biol., 8*, R107. ↗

Editions

2015-07-30	Authored	Jassal, B.
2015-09-14	Reviewed	D'Eustachio, P.
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