

Multilayered business of the skin barrier

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Our skin may seem simple on the surface, but beneath it lies an incredibly coordinated system that protects us from dehydration, harmful substances, and environmental stress. This system depends on precise communication, vesicle transport, and structural remodeling.

In recent years, researchers have uncovered new players involved in this mechanism of communication, transport and remodeling, and one of the most intriguing is a small membrane protein called Flower (FWE). In this 3-part blog series, we take a closer look at the skin barrier and unravel the functions of the FWE protein in depth. In episode 1, we explore how the epidermis, the outermost protective layer of the skin, is organized and how keratinocytes mature as they travel through its layers. Understanding this foundation prepares us for episode 2, where we dive into FWE's role in vesicle transport and calcium regulation. Building on this, episode 3 takes us into how disrupted FWE function may contribute to skin disorders.

Strata of the epidermis

A key part of understanding the skin barrier is following how its main cell type changes over time. Keratinocytes, skin cells, undergo a remarkable journey called terminal differentiation. Starting as active, dividing stem cells, they gradually move upwards, changing shape and function, to eventually end-up as dead cells with a rigid cornified envelope. Every layer of the epidermis has its own specific role in this differentiation [1]:

- **Stratum basale (SB):** The deepest layer of the epidermis, which is separated from the dermis by the basal membrane. This layer consists of continuously dividing stem cells that produce new keratinocytes.
- **Stratum spinosum (SS):** The newly produced keratinocytes move upwards into the stratum spinosum. This 8-10 cell layers consist of irregularly shaped keratinocytes which produce structural proteins and form strong connections with neighboring cells.
- **Stratum granulosum (SG):** Consists of 3-5 cell layers of diamond-shaped keratinocytes that are tightly connected with tight junctions and secrete lipid-rich lamellar bodies from their apical (upper) surface.
- **Stratum corneum (SC):** When the keratinocytes are terminally differentiated they move to the outer most layer, where they lose their nuclei and become corneocytes. This 20-30 cell layers thick barrier is composed of keratin and corneocytes embedded in lipids.

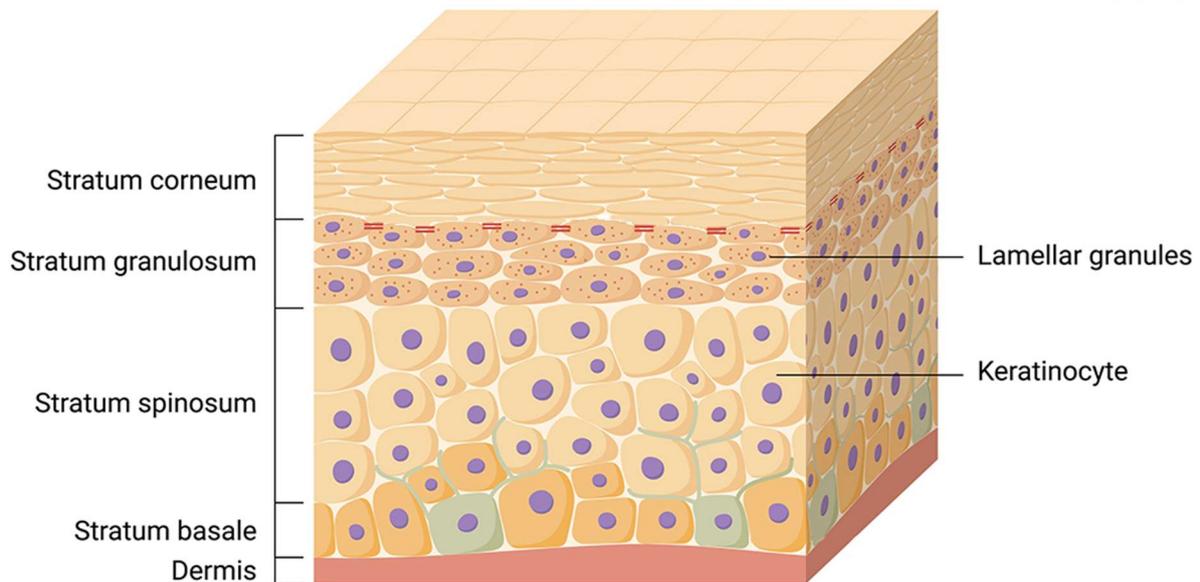


Figure 1. The four layers of the epidermis. Keratinocytes gradually change shape during terminal differentiation as they mature and move upward. Lamellar bodies, also known as lamellar granules, are present in cells of the stratum granulosum and contribute to barrier formation. Adjusted from [6]

Tight junctions

Tight junctions (TJs) are specialized protein complexes located between keratinocytes in the SG that form a selective seal, preventing uncontrolled passage of water, ions, and solutes through the epidermis. TJs maintain tissue polarity and contribute to overall skin integrity. Their assembly and maintenance are highly dependent on calcium signaling, and disruption of TJs - whether by genetic defects, inflammation, or injury- compromises barrier function [2].

Lamellar bodies

Lamellar bodies (LBs) are a type of vesicles (messenger sacs between cells), released from cells that contain many lipids, enzymes, and proteins. These specialized vesicles, predominantly present in keratinocytes of the SG, release a complex cargo essential for barrier formation and renewal: lipid precursors, lipid-processing enzymes, antimicrobial peptides, and proteases. This cargo is secreted at the junction between the SG and SC, where enzymes digest lipid precursors into barrier lipids, which further enhance barrier function. The skin barrier is renewed approximately every month through proteases secreted by LBs, which facilitate corneocyte shedding and replacement by newly differentiated cells from the basal layer. Beyond this routine turnover, keratinocytes also respond to mechanical stress induced on the skin by sensing the stimulus and triggering regulated secretion of existing LBs, while promoting differentiation and new LB formation. These processes create a positive feedback loop in which LB biogenesis, keratinocyte differentiation, and barrier assembly reinforce one another. Thus, LBs are indispensable for the development, maintenance, and homeostasis of the skin barrier [3].

Corneocytes

Corneocytes are dead, nucleus-free keratinocytes in the SC characterized by a covalently cross-linked cornified envelope underlying the plasma membrane. Their cornified envelope and surrounding lipid matrix create a strong, waterproof barrier that protects the body from dehydration, pathogens, and environmental stress. Beyond serving as a physical barrier,

corneocytes actively defend the skin by releasing defensins, small positively charged proteins that are part of the innate immune system [4].

Calcium: The master regulator

The epidermal barrier relies on two structural pillars: the stratum granulosum and the stratum corneum. The SG forms a defense layer through TJs between keratinocytes and the production of LBs, while the SC provides the outer shield of corneocytes embedded in a lipid-rich matrix. Both TJ formation and LB secretion are highly sensitive to intracellular and extracellular calcium (Ca^{2+}) levels. A calcium-dependent differentiation program drives keratinocytes upward to form corneocytes and assemble the cornified envelope, while the same calcium signaling also orchestrates LB trafficking and TJ formation. The interplay between keratinocyte differentiation, lamellar body secretion, and calcium signaling ensures that the skin remains an effective barrier. Disruption of the calcium level component compromises this delicate system and skin health [5].

Take-home messages

- The epidermis consists of 4 layers: stratum basale, stratum spinosum, stratum granulosum, and stratum corneum.
- Lamellar bodies, tight junctions, and corneocytes are essential for barrier function.
- The formation and maintenance of a healthy skin barrier is calcium-dependent.

Coming up next

In the next blog, we are going to talk about Flower (FWE), a tiny protein with a big job in skin biology...

Acknowledgement

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