From vesicles to barrier: flower's essential role in skin differentiation

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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.

Previously

In the previous episode we have learned about the Flower protein and its role in healthy epidermal barrier formation. We found that Flower is a key contributor during the active construction phase and is crucial for LB trafficking. When Flower is knocked-out, the skin barrier is compromised. We have also seen the authors Rudd et al. hypothesize that Flower controls the intracellular calcium level, which, as we have learned in episode 1, is the master regulator of skin barrier function. In this episode we will reveal how Flower controls barrier formation and which diseases might be related to Flower expression.

FWE vesicles

Rudd et al. isolated FWE-positive vesicles to analyse their composition, cellular origin and transport mechanism to elucidate their role in epidermal proliferation. This proteomic profiling showed their complexity: FWE vesicles contain 180 proteins involved in vesicle trafficking, lipid metabolism, and organelle acidification. They share significant overlap with the lamellar body (LB) proteome (all proteins in a vesicle), confirming their role in skin barrier formation [1].

FWE vesicles are equipped with a sophisticated trafficking toolkit, including Rab GTPases and SNARE complex components, which ensure precise delivery to the apical membrane. Beyond carrying LB cargo like KLK5, SKALP, and CDSN, these vesicles also transport tight junction (TJ) proteins such as TROP2 and JAM-A. This dual function suggests FWE coordinates lipid secretion with junction assembly, both essential for a strong epidermal barrier [1].

Functional studies reinforced this idea: when FWE expression was increased, LB-related proteins were more efficiently delivered to the cell surface. In short, FWE-positive vesicles acted as multi-tasking couriers, delivering the building blocks for barrier lipids and structural proteins that lock keratinocytes together. This discovery positions FWE as a central player in orchestrating late-stage epidermal differentiation and barrier integrity [1].

Calcium

FWE does more than marking vesicles; it actively shapes calcium signals that drive the final steps of keratinocyte differentiation. As discussed in blog 1 calcium (Ca^{2+}) is a master regulator in skin biology, and FWE amplifies its role. When FWE is expressed, keratinocytes showed a stronger rise in free cellular Ca^{2+} after stimulation, indicating that FWE helps release calcium from intracellular stores like the endoplasmic reticulum and lysosome-related organelles [1].

Since LB vesicles carry TJ proteins such as TROP2, their release is essential for barrier function. When intracellular Ca^{2+} is removed, FWE could no longer promote TROP2 delivery to the cell surface. Instead, TROP2 levels dropped, consistent with misrouting to degradation rather than successful trafficking. This demonstrated that FWE-mediated vesicle transport is Ca^{2+}-dependent: without the calcium signal, LB cargo fails to reach the plasma membrane and cannot support TJ assembly [1].

Calcium also influences cell fate. FWE expression triggered G1 cell-cycle arrest, a key step toward terminal differentiation. Removing calcium reversed this effect. In in vitro models, cells overexpressing FWE migrated to the outer layers, confirming accelerated differentiation [1].

In summary, FWE is not just a vesicle marker, it is a calcium-responsive regulator that ensures LBs and TJ proteins reach the right place, while simultaneously pushing keratinocytes toward their final differentiated state. This dual role makes FWE a critical player in building and maintaining the skin barrier.

Skin disorders

As we have discovered, calcium signaling is essential for the final steps of keratinocyte differentiation and cornification, the process that forms the skin's protective barrier. When this calcium balance is disrupted, the consequences are visible in disorders like Darier disease (DD) and Grover disease (GD). Both conditions involve mutations in the SERCA2 calcium pump, leading to impaired calcium handling, loss of cell cohesion, and premature cornification, producing characteristic cells called corps ronds and grains [1], [2].

Recent findings showed that in these diseases FWE is affected as well. RNA-seq analysis revealed higher FWE expression in DD and GD lesions compared to normal skin. But more striking than expression levels was where FWE ended up. In healthy skin, FWE was neatly polarized at the apical side of granular layer cells. In DD and GD, this polarity disappeared: FWE spread into deeper layers, encased entire cell membranes, or appeared in abnormal positions, **Figure 1**.

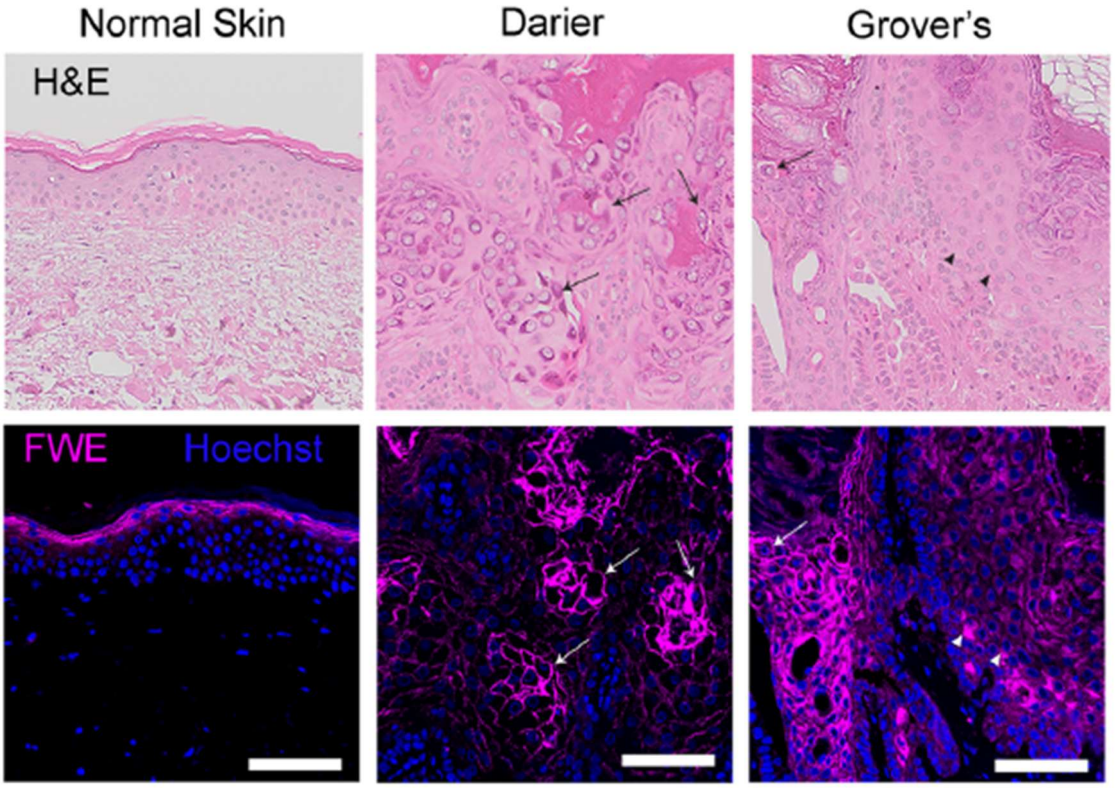

Figure 1. *Representative FWE immunofluorescence performed on normal (n= 5), Darier (n = 3) and, Grover (n = 3) patient samples. Following fluorescent imaging, H&Es were performed on the same section to allow co-registration of FWE signal with histopathology. Arrows show significant elevation of FWE signal in corps ronds and grains of dyskeratotic foci, arrowheads show examples of cells with improper FWE polarization. Scale bars, 100µm.*

Double staining for FWE and LB marker CDSN confirmed that FWE-positive LBs lose their directional delivery, accumulating in the wrong cells instead of reaching the surface. This mislocalization suggests that calcium imbalance disrupts FWE's trafficking role, contributing to defective barrier formation.

Take-home messages

- FWE vesicle proteome is similar to the LB proteome and contains lipids and TJ proteins
- FWE vesicles are apically secreted & efficiently delivered to the cell surface
- FWE helps to release Ca^{2+} from intracellular stores
- Beside correct delivery of essential molecules and regulation of Calcium, FWE pushes keratinocytes to terminal differentiation
- In Darier disease and Grover disease, the location of FWE is distorted, leading to incorrect delivery of vesicle content and defective barrier formation.

Acknowledgement

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References

[1] J. C. Rudd *et al.*, “Flower dependent trafficking of lamellar bodies facilitates maturation of the epidermal barrier,” *Nature Communications* , vol. 16, no. 1, Dec. 2025, doi: 10.1038/s41467-025-62105-1.

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