Assembly of the epidermal cornified cell envelope

Andrey Kalinin, Lyuben N. Marekov and Peter M. Steinert*

Laboratory of Skin Biology Branch, NIAMS, NIH, Bethesda, MD 20892, USA

*Author for correspondence (e-mail: pemast@helix.nih.gov)

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The cornified cell envelope structure is formed beneath the plasma membrane in terminally differentiating stratified squamous epithelia. It provides a vital physical barrier to these tissues in mammals and consists of a 10 nm thick layer of highly crosslinked insoluble proteins. In the specialized case of the epidermis, a 5 nm thick layer of ceramide lipids is covalently bound to the proteins. These organize extracellular lipids into orderly lamellae and, together, the cell envelope and extracellular lipids are essential for effective physical and water barrier function in the skin.

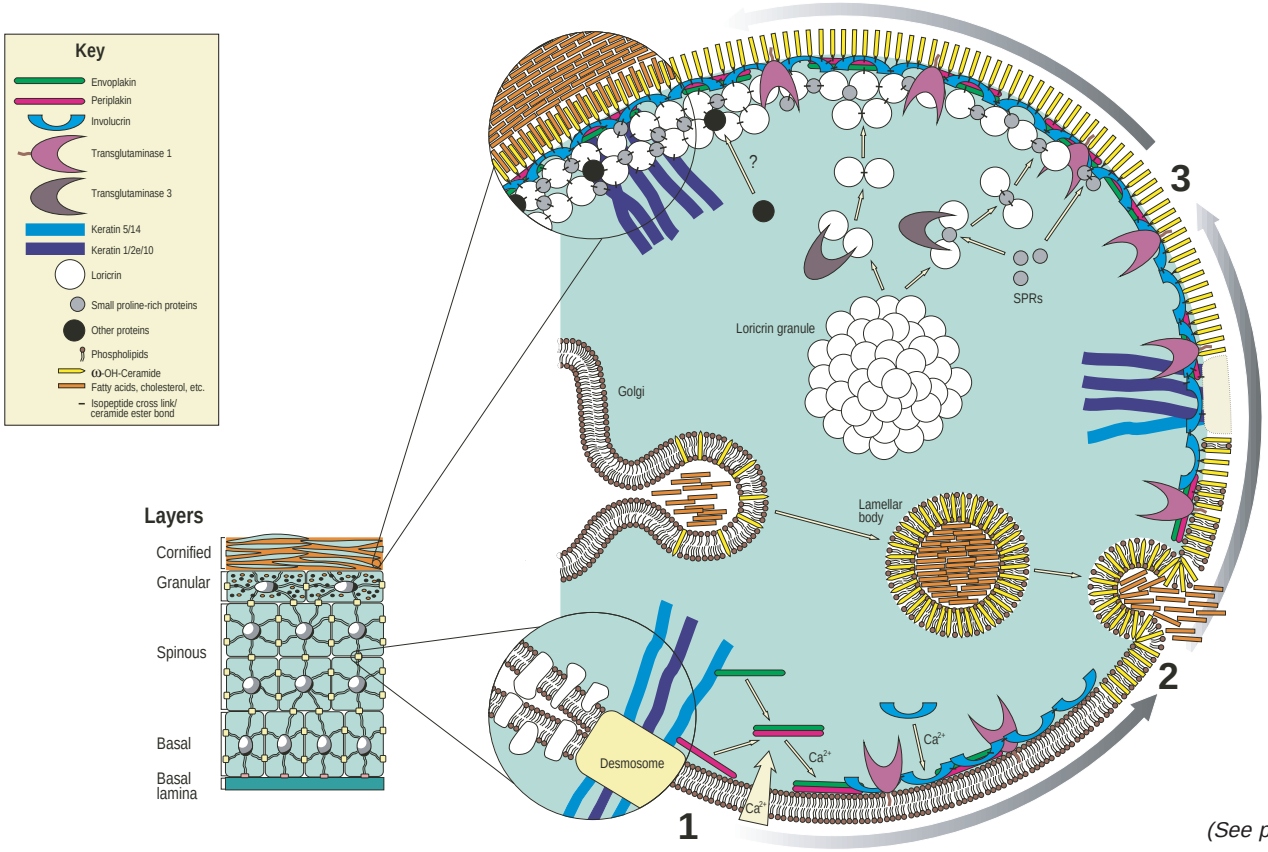
The assembly of the cornified cell envelope proceeds in three principal stages, starting in the upper spinous cell layers of the epidermis.

1. Initiation

As intracellular Ca^{2+} levels rise in suprabasal cells, envoplakin (green), periplakin (red) and involucrin (blue) are expressed. Envoplakin and periplakin form stable heterotetramers, and in vitro data have shown that involucrin and envoplakin-periplakin heterotetramers associate with the plasma membrane in a Ca^{2+}-dependent manner. Coincidently, the transglutaminase 1 enzyme (purple) is expressed, and it spontaneously assembles onto membranes by way of its acyl lipid adducts. As intracellular (or localized micro-environmental) Ca^{2+} levels continue to rise, the enzyme joins together the plakins and involucrin by forming N^{ϵ}-(γ-glutamyl)lysine isopeptide crosslinks. The enzyme also crosslinks other membrane-associated and desmosomal proteins, which drastically changes the dynamic properties of cell junctions and cytoskeletal interactions. Gradually, the involucrin-envoplakin-periplakin proteins form a monomolecular layer along the entire inner surface of the plasma membrane, including over desmosomes, to form a scaffold. This scaffold formation appears to be common to the assembly of cell envelope barrier structures of many other stratified squamous epithelia. Assembly in epidermal cells, however, differs in the two subsequent steps.

2. Formation of the corneocyte lipid envelope

In the granular layer, epidermal cells accumulate lamellar bodies that develop from and bud off the Golgi complex. Specialized ω-hydroxy-ceramides that possess a very-long-chain fatty acid moiety (yellow) are packaged, along with large amounts of other barrier lipids (free fatty acids, cholesterol and its esters, and other ceramides), into both their limiting membrane and central core (orange). At a later stage of differentiation, at the interface of the granular and cornified layers, fusion of the lamellar body limiting membranes with the apical plasma membrane delivers the contents into the extracellular milieu. This process



(See poster insert)

enriches the plasma membrane with ω-OH-ceramides, whose fatty acid chains are long enough (>C_{30}) to span the lipid bilayer, so that the ω-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 the scaffold proteins. Eventually, the ceramides replace the bilayer plasma membrane and are thought to serve to interdigitate with and organize the extracellular lipids into characteristic lamellae. We believe that fusion of the lamellar bodies and extrusion of their contents occurs before the third and final reinforcement stage of cell envelope assembly, for simple physical reasons: if so, then ceramide lipid esterification might occur at this time as well.

3. Reinforcement

In the case of the epidermis, about 80% of the cornified cell envelope constitutes of loricrin (white), complexed with various amounts of the small proline-rich (SPR) protein family members (gray). Loricrin is an insoluble protein and is initially sequestered into loricrin granules, whereas SPRs are very soluble. In vitro data suggest that the cytosolic transglutaminase 3 enzyme (brown) crosslinks them together primarily to form homodimers and heterodimers. This results in the net solubilization of loricrin. At some point, these oligomers are translocated to the cell periphery - again, in vitro data suggest that the transglutaminase 1 crosslinks them onto the pre-existing scaffold. Varying amounts of SPRs are used in the epidermis of different body sites. One hypothesis is that the SPRs alter the biomechanical properties of the tissue in accordance with specific localized physical requirements and functions. Also, minor amounts of other proteins, including repetin, trichohyalin, cystatin α, elafin and LEP/XP-5 proteins (black) become crosslinked to the CE.

Meanwhile, most other cell organelles/structures, microtubules, micro-filaments, other junctional proteins including desmosomes, etc. are degraded. However, keratin intermediate filaments, at late stages consisting almost entirely of keratin 1, keratin 2e and keratin 10, become crosslinked to the cornified cell envelope to desmoplakin and envoplakin remnants, as well as involucrin, loricrin and SPRs. The final dead cornified cell thus consists mostly of bundled intermediate filaments covalently attached to and enclosed within the cell envelope. The resulting durable but flexible dead cells imbedded in the lipid lamellae provide the vital mechanical and water-permeability barrier functions necessary for the survival of mammals in the terrestrial environment.

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