The epidermal barrier and its role in atopic dermatitis pathogenesis

The main roles of epidermal barrier are to block antigens/pathogens penetration, to protect from UV light, detergents and toxins and also to prevent skin desiccation and trans-epidermal water loss (TEWL). The epidermal barrier is composed of three major components: intracellular keratin filaments, cornified cell envelope and intercellular lipids. The granular layer of the epidermis contains the keratochoyalin granules (storing intracellular components of the stratum corneum (SC) such as filaggrin, loricrin and keratin) and the lamellar granules (containing intercellular components such as lipids, kallikreins (KLK’s) and corneodesmosin). The corneocytes in the SC are kept adjacent to each other by modified desmosomes called corneodesmosomes and another component of the epidermal barrier are tight junctions crucial for keratinocytes adhesion in the upper epidermal layers. In atopic dermatitis pathogenesis, abnormalities in almost each one of epidermal barrier components may be observed including impaired filaggrin metabolism, abnormalities in intercellular junctions, lipids metabolism and desquamation.

Abnormalities in Filaggrin and its metabolism

In the granular layer, the profilaggrin is stored within the keratochoyaline granules as a polymer of 10-12 repeats of filaggrin monomers that are cleaved into monomers in the border between the granular layer and the SC by different proteases including SASPase. Filaggrin monomers are linked to the keratin filaments forming a prominent part of normal corneocytes structure in the SC. In the uppermost layers of the SC, the filaggrin dissociates from keratin filaments and filaggrin monomers are degraded to free amino acids forming urocanic acid and pyrrolidine carboxylic acid. The urocanic acid is a chromophore for UV radiation playing a role in epidermal acidification while the pyrrolidine carboxylic acid is important for skin hydration. These are crucial for normal epidermal barrier function.

Loss of function mutations in FLG are reported in 25-50% of AD patients from Northern European and Asian populations. FLG mutations predispose to early onset severe disease, allergen sensitization and susceptibility to infections. However, abnormalities in other proteins involved in Filaggrin metabolism or in FLG-like genes may be defected in atopic dermatitis. For example, deficiency in SASPase was associated with dry and rough skin in hairless mice and missense mutations in the SASPase gene were identified in atopic dermatitis patients.

In atopic dermatitis, also Th2 skewing and colonization with staph aureus result in abnormal expression of filaggrin and other terminal differentiation proteins.

Abnormalities in tight junctions

Tight junctions are another crucial component of the epidermal layer. They are located at the granular layer sealing intercellular spaces with dynamic regulation of water, ions and protein trafficking, limiting penetration of allergens and pathogenic microbes by regulating langerhans cells dendrites penetration. Tight junctions are composed of transmembrane proteins such as claudins, occludins and cytosolic scaffolds.
Several studies have demonstrated abnormalities in tight junction proteins in atopic dermatitis. Polymorphisms in \textit{CLDN1} were associated with atopic dermatitis onset and severity. In addition, reduced expression of claudins was evident in both adults and pediatric atopic dermatitis patients.

\textbf{Lipids alterations in atopic dermatitis}

Intercellular lipids are produced in the stratum granulosum, stored in the lamellar granules and secreted into extracellular spaces during the transition into SC. Lamellar granules contain different lipid precursors, lipid processing enzymes, KLK’s, anti-microbial peptides and corneodesmosin. Under a normal state, ceramides, cholesterol and free fatty acids have a similar molar ratio in the epidermis. Most free fatty acids are saturated and omega-hydroxy-ceramide is the most abundant ceramide in the epidermis.

In atopic dermatitis there are alterations in the expression of key enzymes involved in SC lipid synthesis contributing to changes in the lipid composition, especially in lesional skin but also in non-lesional skin. These abnormalities correlate with a reduced skin barrier and increased TEWL.

\textbf{Impaired desquamation}

Normal cornocytes desquamation is required for normal SC homeostasis. This process is regulated by different peptidases called KLK’s. The proteolytic activity of these is upregulated in a higher pH of the SC and their activity is inhibited by protease inhibitors such as LEKTI. Both proteases and their inhibitors are stored in lamellar bodies and secreted into the intercellular space between the stratum granulosum and the SC.

In atopic dermatitis there is upregulation in KLK’s activity which results in:

- Degradation of adhesion molecules, filaggrin and lipid processing enzymes
- Secretion of cytokines with increased inflammatory state
- PAR2 activation with inhibition of lamellar granules secretion and neuropeptides release

These result in desquamation, impaired lipid barrier, inflammation and pruritus. Polymorphisms in genes associated with these pathways (for example \textit{SPNK5}, \textit{KLK7}, \textit{PAR2}) serve as risk factors for the development of atopic dermatitis.

\textbf{Pediatric vs. adult atopic dermatitis}

Data gleaned from recent studies revealed that adult long-standing disease and pediatric early-onset disease are probably driven by different mechanism. Abnormalities in terminal differentiation proteins, and in particularly filaggrin, are observed only in adult patients with atopic dermatitis while abnormalities in lipid metabolism and tight junction proteins are evident in both adult and pediatric patients.

\textbf{Estimation of barrier abnormalities}

TEWL is a good functional measure of epidermal barrier function and in pediatric patients it’s a measure of severity (increased levels of 32 g/m$^2$/h were demonstrated in lesional skin as compared to 16 g/m$^2$/h in nonlesional skin). Elevated TEWL in early infancy is associated with a significant risk for atopic dermatitis later in life and it has been shown that the use of a daily moisturizer starting within the first 3 weeks of life in high risk infants lowers the risk of developing atopic dermatitis by 32-50% with altering skin microbiome and pH levels in high-risk newborns.
References:
7. van Smeden J, Janssens M, Kaye EC et al. The importance of free fatty acid chain length for the skin barrier function in atopic eczema patients. Experimental dermatology 2014; 23: 45-52.

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