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Short Communication

Structural Imprinting of the Cutaneous Immune Effector Function

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ABSTRACT

The epidermal tissue undergoes extensive cross-linkages of the cytoskeleton, ultimately leading to the heavily disulfide cross-linked dead cell layer, the stratum corneum. Therefore, cornification is compared to the anabolic metabolism of sulfur. The leaky para cellular barrier enables antigen-presenting cells to access foreign substances easily and enhanced antigen uptake at the Tight Junction (TJ) is considered the atopic march's culprit. However, the sound epidermal structure cannot be obtained without the thiol-rich cytoskeletal protein loricrin. The down regulation of loricrin not only represents atopic dermatitis pathology but also affects the epidermal metabolism. The metabolic microenvironment genetically reprograms the monocyte-macrophage systems that can tailor-made local adaptive immune responses. Therefore, we reasoned that cornifying keratinocytes, which undergo myriad metabolic pathways above the TJ, could control the distal immune effector functions by directly affecting the gene expression program of cutaneous immune effector function.

Keywords: Epidermal structure; Langerhans cell; Metabolism; Genetic reprogramming

INTRODUCTION

The epidermal barrier function comprises multitiered mechanisms that prevent penetration of foreign substances while preventing dehydration. The Tight Junction (TJ) is an adherens junction conserved across the epithelium tissues and endothelial cells. This primitive barrier defines the apicobasal polarity and primarily prevents the penetration of macromolecules [1]. Once cell-cell adhesion becomes secure, active secretion of protective substances could help protect the cell surface. The Lamellar Granules (LG) is a lipid-secreting organelle also conserved across many cell types. In a similar way that we apply moisturizers, LGs prevent desiccation, lubricate lung gas exchange and protect against aggressive gastric juice. The Stratum Corneum (SC) forms above the uppermost living layer, the Stratum Granulosum (SG), where the TJ and the LGs are located. This terminal differentiation process is termed cornification, which is specialized for the terrestrial lifestyle. The structure of the SC is simplified to the "bricks and mortar," which correspond to enucleated dead cells (corneocytes) and interstitial lipids, respectively [2]. Because evaporation prevention has to be prioritized, the failure to fill in the intercellular space causes pathologies; the condition is termed ichthyosis. Ichthyoses manifest as dry, scaly skin to a hard, plate-like, severe plate-like hyperkeratosis, depending on the extent of the "broken mortar". Notably, the corneocyte "the brick" also moisturizes the SC, and filaggrin, a keratin-aggregating molecule, produces moisturizing factors through proteolytic degradation. The corneocyte is like a sponge that soaks up water (that is why your fingers get wrinkled after a long-time soaking). Filaggrin deficiency is often observed in a common dry skin called ichthyosis vulgaris and it was until the early 2000s that Atopic Dermatitis (AD; eczema) turned out to be an inheritable trait, which drew much attention as to how epidermal differentiation can affect cutaneous immune effector functions [3].

DESCRIPTION

Cornification as anabolic metabolism of sulfur

Another important function of SC is to maintain structural integrity and resilience. It is thought that numerous covalent bonds form within the corneocyte cytoskeleton during cornification until corneocytes detached (desquamation) [6].

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Particularly, disulfide cross-linkage has been regarded as a critical biochemical/biomechanical property of the SC (corneocyte, "the brick"). Epidermal Keratinocytes (KCs) form the gradient of thiol (SH), making the sulfur-rich layer in the SG. Because thiol (SH) quickly becomes disulfide (–S–S–) on the air-liquid interface (above the TJ), terrestrial mammals appear to utilize the lability of sulfur and establish the mechanical stability and resilience. This property endows the epidermis with protection against mechanical damage or ultraviolet. Collectively, cornification is compared to an anabolic metabolism of sulfur. The major player of such cross-linkage/stabilization is the cytoskeletal thiol-rich protein loricrin. Interestingly, unless loricrin harbors nuclear localizing signal and is misplaced into the nucleus, loricrin deficiency causes no ichthyotic phenotype, suggesting that this protein is specialized to stabilize corneocyte cytosol (the "brick"), but not para cellular permeability maintained by the TJ and the LG, which are evolutionary ancient [4].

Antigen priming and SC permeability

Since filaggrin deficiency is identified as a major predisposing factor for AD, a reasonable assumption would be dry, flaky SC makes foreign substances readily accessible to the TJ, where Dendritic Cells (DCs) uptake antigens and present them to T cells in draining lymph nodes. Additionally, it has been known that epicutaneous entry of protein antigens, such as peanuts, through inflamed skin, constitutes the initial part of the so-called atopic march. Some hypothesized that the "leaky" SC might have been advantageous during pandemics, as in eczema vaccinatum following smallpox vaccination. However, not all filaggrin-deficient (Ichthyosis vulgaris) individuals develop AD and percutaneous induction of tolerization (desensitization) either against protein antigen or haptens is feasible. This appears to be because epidermal Langerhans Cells (LCs), which uptake penetrating protein antigens at the TJ, preferentially induce tolerance [5].

LC: The immune sentinel of the squamous epithelium

LCs inhabits the barrier tissue covered with squamous epithelia, such as the skin, the eye, the larynx, the esophagus, the vagina and so forth. The endocytotic receptor CD207/langerin, a mannose-binding lectin, represents the high endocytotic capacity. LCs express the TJ protein and help prevent the entry of viral particles. LCs expresses the conventional DC marker CD11c and requires an autocrine/paracrine loop of transforming growth factor-beta signaling, suggesting that LCs are bonafide antigen-presenting cells that establishes functional adaptive immune system [6].

Conserved features of CD207+DCs

Although LCs exhibit a tissue macrophage-like phenotype in terms of ontogeny and are often compared to the microglia, they can be replaced from bone marrow derived monocytes, depending on the niche in which they reside [7].

In the cutaneous tissue, CD207+DCs, i.e., LCs and CD103+ dermal DCs originate from two distinctive developmental pathways and cooperatively establish the adaptive immunity. By contrast, CD207+/CD103+DCs represent mucosal LCs, which tolerate surface bacteria. Finally, even in the gut tissue that is covered with non-squamous epithelium, Vitamin A-Deficiency (VAD) causes the accumulation of CD207+/CD103+DCs, which establish T helper 17 (Th17)-skewed but somewhat incompetent adaptive immune responses. Given that Th17 immunity is considered to have evolved to cope with body surface commensal microorganisms, DCs with the expression of CD207, which binds to mannans that constitute the bacterial/fungal cell wall, appear to represent a primitive, innate part of immunosurveillance on the body surface. Evolutional significance of the CD207+DC-driven immunity appears to have helped terrestrial animals endure dysregulated epithelial metabolism (such as VAD) above the TJ [8].

CONCLUSION

Cornification is not a passive process. Vitamin A metabolism plays a significant role in the development of epidermal barrier; either the excess (Pt 7) or the deficiency perturbs cornification. From a clinical perspective, VAD dysregulates the barrier homeostasis and causes persistent diarrhea/infection in the gut while drying up the squamous epithelia. Dermatologists rely upon orally administrated RA to alleviate the symptoms of ichthyoses or persistent hand eczema. AD not only comprises broad defect in cornification but also detunes adaptive cellular immune responses. Aberrant cornification not only compromises para cellular permeability (maintained by the "mortar") but also affect corneocyte maturation (maintained by the "brick"). The formation of functional SC para cellular barrier requires KC-intrinsic retinoid acid receptor-alpha signaling, while the maturation of corneocytes requires a rapid conversion of thiol (–SH) to disulfide (–S–S–). Thus, from a structural perspective, LCs, the epidermal resident antigen-presenting cells located beneath the TJ, are under the influence of these metabolic pathways.

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