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Review

Lipid abnormalities and lipid-based repair strategies in atopic dermatitis☆

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ABSTRACT

Prior studies have revealed the key roles played by Th1/Th2 cell dysregulation, IgE production, mast cell hyperactivity, and dendritic cell signaling in the evolution of the chronic, pruritic, inflammatory dermatosis that characterizes atopic dermatitis (AD). We review here increasing evidence that the inflammation in AD results primarily from inherited abnormalities in epidermal structural and enzymatic proteins that impact permeability barrier function. We also will show that the barrier defect can be attributed to a paracellular abnormality due to a variety of abnormalities in lipid composition, transport and extracellular organization. Accordingly, we also review the therapeutic implications of this emerging pathogenic paradigm, including several current and potentially novel, lipid-based approaches to corrective therapy. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier. Guest Editors: Kenneth R. Feingold and Peter Elias.

1. Introduction

Because both a defective epidermal permeability barrier [1–4], as well as a propensity to develop secondary infections [5] are well-recognized features of AD, we and others proposed several years ago that the barrier abnormalities in AD are not merely epiphenomena, but rather the 'driver' of disease activity (i.e., an 'outside-to-inside' view of disease pathogenesis) [6–8] (Fig. 1), because: 1) the extent of the permeability barrier abnormality parallels severity of disease phenotype in AD [1,2,4]; 2) both clinically uninvolved skin sites, as well as skin cleared of inflammation for several years, can continue to display significant barrier abnormalities [2]; and 3) emollient therapy comprises effective ancillary therapy for AD [9]. Much more is now known about inherited and acquired abnormalities in AD, which have fortified this 'outside-to-inside' view of disease pathogenesis, with broad implications for what should comprise rational therapy.

2. Basis for the permeability barrier in normal skin

The epidermis generates a set of protective/defensive functions, mediated by its unique differentiation end-product, the stratum corneum [10] (see also article by Feingold & Elias in this volume). These functions include the *permeability barrier*, which retards transcutaneous evaporative water loss, allowing survival in a potentially desiccating external environment, while simultaneously impeding the ingress of noxious substances, including toxins, allergens, and pathogenic microbes. Yet, the permeability barrier shares many features with the *antimicrobial barrier*, which impedes the growth of pathogenic organisms, while simultaneously encouraging colonization by non-pathogenic 'normal' flora (see article by Wertz, et al., in this issue). This antimicrobial system comprises a key distal component of the cutaneous innate immune system [11].

The stratum corneum (SC) comprises a multilayered tissue composed of flattened, geometrical, anucleate corneocytes, surrounded by multiple stacks of board, planar lamellae, enriched in ceramides, cholesterol, and free fatty acids (FFA) [12]. It is the localization of these highly hydrophobic lipids within the extracellular domains of the SC that inhibits both the outward movement of water and the access of noxious substances and pathogenic microbes from the environment (Ibid.). These lipids are delivered to the SC as their precursors through secretion of a unique organelle, the epidermal lamellar body [13]. As the SC forms, this organelle delivers lipid precursors (e.g., glucosylceramides and phospholipids), as well as a set of hydrolytic, lipid-processing enzymes, such as β-glucocerbrosidase,

Abbreviations: AD, atopic dermatitis; AMP, antimicrobial peptide; Cer, ceramide; EFAD, essential fatty acid deficiency; FLG, filaggrin; FFA, free fatty acid; GC, glucocorticoid; hBD, human β-defensin; hCAP, human cathelicidin; IV, ichthyosis vulgaris; KLK, kallikrein; LEKTI, lymphoepithelial Kazal-type trypsin inhibitor; NS, Netherton syndrome; PAR2, plasminogen activator type 2 receptor; SP, serine protease; SC, stratum corneum

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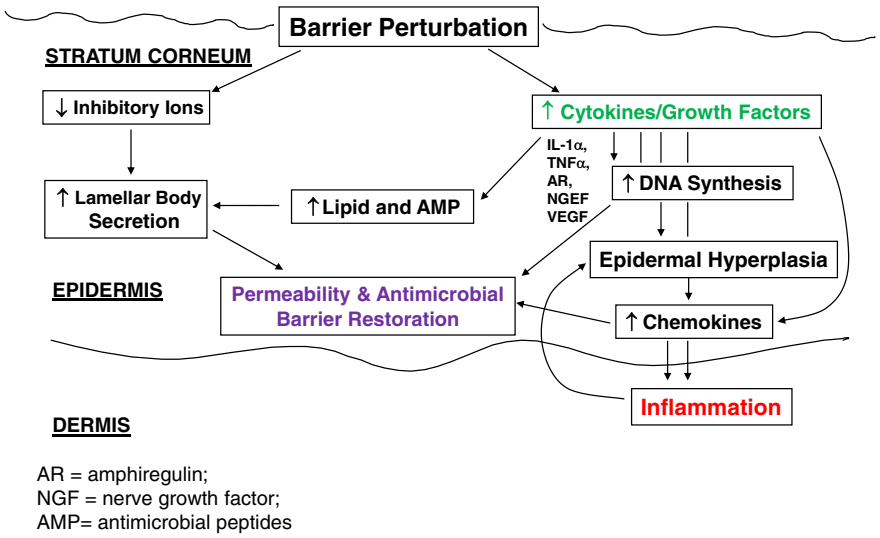

Fig. 1. 'Outside-inside' homeostatic responses can also provoke a cytokine cascade leading to inflammation.

acidic sphingomyelinase, secretory phospholipase A_2 and steroid sulfatase, required to generate ceramides (Cer), free fatty acids (FFA), and much of the cholesterol that is required for the organization of these non-polar lipids into mature lamellar membrane structures [13] (see also article by Feingold & Elias, and K. Sandhoff in this issue). In parallel, lamellar body-derived proteases and their inhibitors orchestrate the orderly digestion of corneodesmosomes, transient intercellular rivets that are progressively degraded, initiating the invisible shedding of corneocytes from the skin surface [14–16]. Finally, at least two antimicrobial peptides, human β-defensin 2 and the carboxyterminal cathelicidin peptide, LL-37, are delivered to the SC intercellular domains through secretion of lamellar body contents [17–19]. Thus, the epidermal lamellar body is a multi-functional organelle, whose contents influence not only permeability barrier status, but also at least two other key functions, SC cohesion/desquamation and cutaneous antimicrobial defense.

2.1. Inherited causes of a barrier abnormality in atopic dermatitis

2.1.1. Deficiency of filaggrin and other S100 proteins

The strongest evidence that a primary structural abnormality underlies the pathogenesis of AD derives from the recent work that links loss-of-function mutations in the gene encoding, *filament aggregating protein* (filaggrin, FLG) in humans with AD [20,21]. Up to 50% of northern European kindreds with AD reveal either single or double allele mutations in the gene encoding for FLG, which is located in the differentiation complex on chromosome 1q21. The initial product of FLG translation is pro-FLG, a large, histidine-rich, highly cationic phosphoprotein, consisting of ten to twelve FLG repeats, connected by peptide segments enriched in hydrophobic amino acids [22–24]. Pro-FLG contains an amino-terminal sequence, including a calcium-binding A domain as well as a B domain of uncertain function, with a putative S100-like, calcium binding domain. In contrast to the cytoplasmatic location of the C-terminal FLG monomers, the N-terminal portion of pro-FLG tethers to the nucleus, consistent with its nuclear localization sequence. During cornification in normal, non-atopic humans, pro-FLG is dephosphorylated and proteolytically processed to FLG monomers. Immunolocalization studies suggest that processed FLG peptides associate with, and induce aggregation of keratins within the corneocyte cytosol, while also attaching to the cornified envelope, a unique structure that forms under the plasma membrane as granular cells transform into corneocytes [25,26]. The CE provides an inflexible, mechanically resistant *physical* barrier. However, as the water content of the SC drops in the mid-to-outer stratum corneum of humans, FLG detaches from the cornified envelope, with the C-terminal portion of FLG proteolyzed by caspase 14 into its constituent amino acids. These amino acids subsequently are further deiminated into polycarboxylic acids that comprise the 'natural moisturizing factor' of the SC (Fig. 2) [27,28].

FLG deficiency in AD has been ascribed to both nonsense and frameshift mutations that result in partial or complete loss of FLG expression, as well as the reduction-to-loss of keratohyalin granules in the epidermis. Although more than 40 different mutations are now reported [29], 4 mutations predominate in northern and central Europeans [30,31]. These mutations exhibit an allele-dose effect, wherein heterozygous patients show diminished FLG expression with a mild IV phenotype, as well as minor abnormalities in surface pH, hydration, and barrier function [32]. But IV patients with homozygous and compound heterozygous *FLG* mutations, who lack FLG expression, exhibit more severe scaling, more pronounced abnormalities in stratum corneum structure and function [32], and a further propensity to develop AD [29]. Yet importantly, a substantial proportion of these double-allele IV patients still do not exhibit inflammation (AD), emphasizing the role of exogenous (acquired) factors in AD pathogenesis.

FLG is the main component of keratohyalin granules located in the outer nucleated layers of the epidermis, that account for the designation of this cell layer as the stratum granulosum. Accordingly, decreased FLG expression results in a paucity of keratohyalin granules, a hallmark of ichthyosis vulgaris (IV) [33,34], the *forme fruste* of AD, and often accompanied by allergic rhinitis and/or asthma. But an acquired reduction in epidermal FLG expression also occurs in AD [3,35–37], in part due to Th2-induced down-regulation of a broad range of proteins associated with epidermal differentiation [38,39].

Yet, there is increasing evidence that inherited abnormalities not only in FLG, but also in other proteins that are important for barrier maintenance, also can lead to AD. It is important to note that inherited abnormalities in FLG occur primarily in populations of northern European descent [29]. AD in other populations will likely prove to be associated with other inherited abnormalities. Very recent studies have shown an association of AD with other S100 proteins, including hornerin [40] and FLG-2 [41]. But a still broader view might be that any inherited abnormality that leads to a chronic barrier abnormality could predispose to AD. Note the association of AD with loss-of-function mutations in the fatty acid transporter, *FATP4* [42]. It is also likely that any mutations that occur in the lamellar body secretory system should predispose to AD, as suggested by the association of the trans-membrane, trans-Golgi-associated protein, Tmem, with