

REVIEW

Role of T cells in the pathogenesis of atopic dermatitis

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Summary

Our understanding of the pathogenesis of atopic dermatitis has been dramatically enhanced following the identification of the association with loss of function mutations in filaggrin, an epidermal protein thought to be important for cutaneous barrier integrity. However, it has also emerged that Th2 cytokines can influence barrier function, including through modulation of the expression of filaggrin, other structural proteins and peptides important for microbial barrier function. A picture is developing of a complex interplay between epidermal and non-epidermal susceptibilities that contribute to disease. Understanding the key components involved will be important for the identification of new approaches to treatment.

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Introduction

Atopic dermatitis (eczema) is a chronic pruritic inflammatory skin disease frequently associated with adaptive Th2 immune responses to common environmental allergens. Recent advances in our understanding of the importance of primary epithelial abnormalities have shifted emphasis away from a putative role of the immune response in disease pathogenesis. Is barrier dysfunction alone sufficient to cause atopic dermatitis? Are infiltrating T cells an epiphenomenon or are they actively involved in contributing to the lesional inflammation? Do they still represent a valid treatment target or should we now switch to identifying approaches to structural repair of barrier function? Here the author discusses these questions and reviews the accumulating evidence that, in turn, supports a role of T cells and altered immune defence in the development of compromised epithelial function and clinical disease.

Barrier function

The permeability barrier function of skin is largely contained within the stratum corneum (SC) which is derived

from corneocytes within a lamellar matrix enriched by lipids, including free fatty acids, ceramides, phospholipids and cholesterol. The lipids are predominantly sourced from the secretion of epidermal lamellar bodies (LB) which also contain antimicrobial peptides and enzymes required for lipid generation and eventual corneocyte desquamation. The cornified envelope is also important for normal barrier function. This structure lies beneath the membrane of terminally differentiated keratinocytes and is composed of cross-linked keratin filaments, filaggrin, loricrin, involucrin, trichohyalin and small protein-rich proteins. The components of normal skin barrier function have been recently well reviewed elsewhere [1].

There is longstanding evidence of compromise in epidermal permeability in individuals with atopic dermatitis, which is characterized by increased transepidermal water loss [2–4], increased penetration of exogenous substances [5] and decreased SC hydration [6, 7]. Several outstanding publications have provided genetic support for a role of barrier dysfunction in the pathogenesis of atopic dermatitis, and are allowing the pieces of the jigsaw to begin to fall together. The most compelling evidence comes from the work of McLean and colleagues who were the first to

document the association of loss-of-function mutations in the gene encoding filaggrin with atopic dermatitis. This has been confirmed in a number of subsequent studies, including associations with early onset and persistent disease, asthma (when associated with eczema) and elevated IgE [8–17]. The mechanism underlying the influence of filaggrin abnormalities on epidermal permeability is still unknown, but it is speculated that there may be disruption of corneocyte structure through altered keratin aggregation, loss of water-retaining filaggrin products (including *trans*-urocanic acid and pyrrolidine carboxylic acid), and altered SC pH. It is not yet clear to what degree each of these functions contributes to relative barrier permeability, or indeed whether there are other, as yet unidentified, functions of filaggrin. The flaky tail mouse expresses a lower molecular weight form of profilaggrin (220 kDa) that is not proteolytically processed to profilaggrin intermediates or filaggrin [18]. Interestingly, the ichthyotic changes are transient and/or site restricted, and existing reports do not document significant associated inflammation, which raises the possibility that other factors may be important for the generation and persistence of inflammatory disease. It seems likely that in due course, disease associations will be identified for other structural skin components as well.

Netherton syndrome is caused by loss of function mutations within LEKTI which encodes a serine protease inhibitor (SPINK5) that is thought to be important in controlling lipid and protein processing within the epidermis. Single nucleotide polymorphisms within SPINK5 have been associated with atopic dermatitis in some but not all cohorts [19–23]. It has been proposed that dysregulated epidermal serine protease activity may lead to increased corneodesmosome degradation, enhanced lipid-processing enzyme degradation, elevated SC pH and down-regulation of lamellar body secretion [24–28]. All these effects would be predicted to influence the lipid and antimicrobial composition of the epidermis with consequent reductions in permeability and antimicrobial barrier function.

However, whilst it has been suggested that altered barrier function promotes penetration of allergens and microbes, it is clear that other factors must also be critically involved in order to develop disease. In the original study by Palmer et al., 55% of filaggrin heterozygotes did not present with atopic dermatitis [12]. Furthermore, in a population-based case-control study in UK children aged 7–9 years, 12.9% of healthy controls had one or more filaggrin mutations compared with 18.4% of those with mild-moderate eczema [14]. This suggests that other factors beyond barrier dysfunction are also important in order to develop inflammatory disease. Genetic, epidemiological and functional data predict that abnormal innate and adaptive immune responses are also pre-requisites for development of atopic dermatitis [29].

Influence of T cells and cytokines on barrier function

Lesional skin has been shown to express lower levels of filaggrin than non-lesional skin within the same individuals, including in those with wild-type filaggrin and in those heterozygous for the 2282del4 mutation [30–37]. It is therefore likely that filaggrin expression is tightly regulated, and indeed IL-4 and IL-13 have been shown to contribute to such regulation through reduction in filaggrin expression in primary keratinocytes *in vitro* [37]. Furthermore, IL-4 and IL-13 can lead to down-regulation of loricrin and involucrin, two other components of skin barrier [38]. In contrast, IFN- γ was shown to increase filaggrin expression within keratinocytes [37]. IL-4 reduces the recovery of barrier function after acute disruption [39–41]; and desmoglein 3 expression is inhibited by IL-4 [42]. When IL-4 is expressed under the keratin-14 promoter, a chronic pruritic inflammatory skin disease develops that satisfies the appropriate diagnostic criteria [35, 36]. Th2 cytokines are also known to reduce the expression of antimicrobial peptides in the skin [43, 44] which may predispose to a compromised antimicrobial barrier function and further epithelial damage. Other studies have shown that Th2 cytokines can influence antimicrobial activity through different mechanisms: for example, by increasing the expression of potential *Staphylococcus aureus* adhesion molecules [45, 46] and reducing potentially damaging cutaneous Th1 cytokine responses [47]. Furthermore, IL-4 down-regulates the expression of cutaneous lymphocyte-associated antigen on pathogen-specific CD8⁺ T cells [48]. Th2 cytokines have been shown to reduce the superantigen-induced death of reactive T cells [49] and superantigens themselves can inhibit the activity of regulatory T cells [50, 51]. Once a Th2 environment has been established, then IL-4 can promote the further generation of Th2 polarization both directly and also indirectly through induction of other cytokines including epithelium-derived thymic stromal lymphopoietin (TSLP) [52], which further enhances Th2 cell generation through a number of mechanisms including modulation of dendritic cell function [53–55]. In addition, the Th2-induced class switching to IgE provides amplification via Fc ϵ RI-mediated enhancement of antigen presentation by dendritic cells [56, 57].

T cells may also be able to influence barrier function independent of Th2 cytokines. For example, human leucocyte antigen (HLA)-expressing keratinocytes may become targets for T cell-mediated lysis. Keratinocytes have been shown to up-regulate HLA class II and intercellular adhesion molecule 1 (ICAM-1) in lesions of atopic dermatitis and other inflammatory dermatoses [58] and also in response to injection of IFN- γ into normal skin [59]. HLA class I and II expressing keratinocytes can present antigen to both CD8⁺ and CD4⁺ T cells, respectively, and in both cases, this can lead to keratinocyte death [60–66]. Indeed

T cell-induced keratinocyte apoptosis is thought to contribute to spongiosis which may be in part related to altered cadherin function [67–69]. Recently, it has been shown that staphylococcal superantigen can facilitate keratinocyte presentation of allergen to CD4⁺ T cells, thus linking two of the most common atopic dermatitis disease associations [63]. Perforin and granzyme B are strongly expressed in lesional skin and show significant correlation with the degree of spongiosis [70]. Furthermore, apoptotic keratinocytes can be observed in close proximity to perforin- and granzyme B-positive T cells [70]. Thus, it is possible that keratinocytes can represent a target for infiltrating T cells, potentially leading to keratinocyte death and further barrier dysfunction.

Disorders of regulatory T cells also appear to predispose to dermatitis and an allergic phenotype, as shown by the IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) which is associated with mutations within FoxP3, a critical transcription factor for regulatory T cells. Affected individuals may have autoimmune enteropathy, endocrinopathy, dermatitis, food allergy and other autoimmune phenomena [71, 72]. FoxP3-deficient scurfy mice develop spontaneous cutaneous inflammation that is thought to be dependent on dysregulated skin-homing T cells [73].

Overall, these data show that through a number of mechanisms, barrier function is variable within an individual. It is clear that adaptive immune responses represent one such influence and that this may well be important for disease and indeed for the targeting of new approaches to treatment.

Role of infection and T cells

Individuals with atopic dermatitis have increased susceptibility to particular bacterial, viral and fungal challenges. In particular, there is strong evidence supporting a role for *S. aureus* infection in the pathogenesis of atopic dermatitis. Most affected individuals have *S. aureus* identifiable on the skin, often at very high density and present on both lesional and non-lesional tissue [74]. *S. aureus* present on the skin of atopics with active disease is significantly more likely to express superantigen and the levels have been shown to correlate with disease severity [75–77]. Lower levels of antibody to *S. aureus* superantigen have been associated with more severe disease [78], and keratinocytes have been shown to up-regulate HLA class II and ICAM-1 after application of staphylococcal superantigen to the skin [79]. Bacterial products have been shown to stimulate epithelial production of TSLP, which is typically expressed in keratinocytes from lesional tissue [80]. *S. aureus*-derived ceramidase increases the permeability of the SC [81], and indeed cutaneous challenge with superantigen can induce eczematous changes [82]. Furthermore, there is evidence that some individuals recovering

from TSST-1-induced toxic shock syndrome can develop a chronic eczematous phenotype [83]. *S. aureus* can also express desmoglein-binding exotoxins (e.g. ET-A) which disrupt keratinocyte interactions and have been shown to be important in the pathogenesis of staphylococcal scalded skin syndrome [84, 85].

S. aureus also has a significant influence on the local T cell response which can further compromise barrier function. Several investigators have now shown that *S. aureus* promotes a Th2 environment [63, 86–88], and this may provide a bacterial survival advantage through the mechanisms described above.

Taken together, these studies suggest that *S. aureus* can promote a microenvironment that contributes to an eczematous phenotype, and perhaps provides a bacterial survival advantage.

Role of allergens and T cells

There is convincing evidence that allergic reactivity to environmental challenge has a role in the pathogenesis of atopic dermatitis. The histology of atopic dermatitis shares many features with classic allergic contact delayed-type hypersensitivity, including spongiosis and a predominantly dermal T cell infiltrate. Approximately 80% of individuals with atopic dermatitis have circulating specific IgE recognizing one or more of house dust mite, cat, dog, grass and other ubiquitous environmental allergens. Numerous studies have documented the presence of allergen-specific CD4⁺ and CD8⁺ T cells in the peripheral blood and lesional skin of affected individuals [89–91]. T cell epitopes have been described within many allergens, and the accompanying HLA restrictions have been characterized for a proportion of these [63, 92, 93]. House dust mite extract application to the skin of individuals with atopic dermatitis can reproduce eczematous changes [94] and allergen avoidance has been shown by some to be partially effective [95]. Animal models also support such a role for allergen-specific Th2 reactivity in contributing towards the pathogenesis of eczema. Epicutaneous exposure of murine skin with ovalbumin or house dust mite extract can induce an eczematous phenotype which is thought to be dependent on T cells [96–98].

In addition to indirect T cell-mediated influences on barrier function, allergens may have direct effects as well. For example, Der p 1 has been shown to directly influence tight junction structure and indeed its protease activity is thought to be important in allergenicity [99–104]. Overall these data and numerous other studies show that allergens can directly and indirectly influence components of the cutaneous barrier and skin inflammation.

No barriers to T cell help

How can we put these studies together [12]? The clinical phenotype of those who are heterozygous for filaggrin

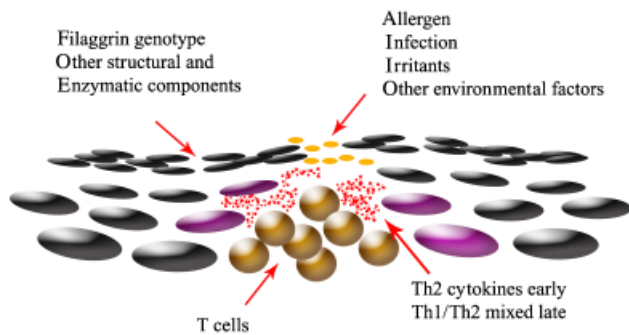


Fig. 1. Genetic and acquired factors combine to contribute towards cutaneous barrier dysfunction. Barrier dysfunction may allow greater penetration of allergens, infection and other inflammatory drivers. Following priming in regional lymph nodes, skin-homing T cells (brown) potentially infiltrate and respond to such stimuli, potentially presented by keratinocytes that have up-regulated human leucocyte antigen class I/II and costimulatory molecules, e.g. intercellular adhesion molecule 1 (purple). This leads to Th2/Th1 cytokine production and to keratinocyte death. These further contribute to barrier dysfunction as described.

mutations is highly variable, and it is therefore likely that other susceptibilities are required, particularly those related to an atopic phenotype. The data presented above show that a Th2-biased response, which may be partly driven by infections, allergens and other factors, can also contribute to barrier dysfunction and probably to clinical disease. The picture that emerges is one of tight regulation of barrier function with numerous inherited and acquired factors (Fig. 1). Under different types of inflammatory state, the barrier can be significantly modulated, perhaps to facilitate defence against microbial challenge with particular organisms. Such a survival advantage may be implicated by the high frequency of loss-of-function mutations in the gene encoding filaggrin in healthy Europeans. However, certain organisms, such as *S. aureus*, have in turn capitalized on this for their own selective advantage. By inducing a Th2-polarized environment, there is reduction in barrier function, which provides a site for good replicative potential, and one which is permissive for surface contact transmission to neighbouring hosts.

Implications for treatment

How can we translate these exciting new findings for patient benefit? It is clear that approaches to enhance barrier function must be pursued. This may be through direct barrier repair, and also through approaches such as immunomodulatory and antimicrobial strategies that are important for reducing the influence of the immune system and infection on altered barrier function. It is likely that interventions will need to be started early in order to limit disease establishment and hopefully the progression towards other atopic disease.

Conclusions

Atopic dermatitis is a complex disease involving multiple gene-gene and/or gene-environment interactions. Over the last 2 years, several important publications have contributed significantly to our understanding of the role of epidermal determinants in the pathogenesis of atopic dermatitis. Interactions clearly exist between these structural barrier determinants and factors that modulate both site and temporal variations in barrier function. These variations are likely to be influenced by non-epithelial genetic determinants and environmental challenges. The aims of future approaches to treatment should not miss opportunities to target the epidermis both directly and indirectly.

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