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Immunological and molecular targets of atopic dermatitis treatment

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Conflicts of interest

A.W. has received honoraria, has performed clinical trials sponsored by, or is a paid consultant for ALK-Scherax, Amgen, Astellas, Bayer, Biocon, Galderma, Glaxo-Smith-Kline, Hickma, Janssen, Karrer, Leo, L'Oreal, MEDA, Merz, Merck-Sharp-Dohme, Novartis, Pierre Fabre, Roche and Therakos. A.S. and A.S.A. have no conflicts of interest to declare.

Summary

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease with a highly variable clinical phenotype and heterogeneous pathophysiology. Its pathogenesis is associated with alterations to both the skin barrier and the immune system, which may in turn be influenced by genetic mutations and the patient's environment. Basic and translational research, as well as clinical trials, has helped broaden our knowledge of the molecular mechanisms underlying the development of AD and to identify potential treatment targets and approaches. These include new ways of reducing transepidermal water loss and the shedding of corneocytes, new ways of interacting with established molecular targets (such as histamine receptors and interleukins and other T-cell cytokines), and the identification of new molecular targets (such as toll-like receptors and tight junction proteins). Well-established treatment options such as emollients, corticosteroids and topical calcineurin inhibitors will clearly continue to have a role in treating AD. Among the new agents that could be joining them in the near future are sphinganolipids (a precursor of ceramides 1 and 3), cannabinoids, highly targeted monoclonal antibodies and subcutaneous immunotherapy.

Atopic dermatitis (AD) is a common, clinically defined, chronic inflammatory skin disease frequently associated with allergic rhinitis, asthma and immunoglobulin E (IgE)-mediated food reactions.¹ The high variability of the clinical phenotype and severity, genetic background and known pathomechanisms strongly suggest a high degree of pathophysiological heterogeneity.² The clinical pattern of eczematous skin lesions is relatively uniform and results from interactive alterations of the skin barrier, and the innate and adaptive immune systems.³ Some of the mechanisms linking specific reaction patterns in these three major areas of AD pathogenesis are well understood on a molecular level.

A number of these alterations are caused by mutations in the genes encoding immune and barrier function proteins, which may alter the regulation or the structure of the gene product itself. Other alterations may be consequences of environmental factors such as stress, scratching behaviour, allergen exposure or washing habits. Hence, the development of AD can be understood as a result of gene–environment interaction. This paper reviews selected aspects of AD pathogenesis and highlights current and future treatment targets for AD.

Barrier function in atopic dermatitis

The epidermal barrier consists of a thin layer of vital keratinocytes, which slowly differentiate into flat corneocytes while moving upwards in the epidermis. The thin layer of dead keratinocytes that make up the stratum corneum covers the vital parts of the epidermis and protects it against water loss and microbe invasion. The complex process of epidermal differentiation is disturbed in AD lesions, and offers many potential targets for therapeutic intervention.^{4,5}

The corneocytes are attached to one another by corneodesmosomes. Stratum corneum chymotryptic enzyme (SCCE) is a human enzyme capable of degrading these corneodesmosomes. It becomes active in higher layers of the stratum corneum once the

function of its natural inhibitor, the protease inhibitor lymphoepithelial Kazal-type-related inhibitor (LEKTI), is lost.⁵ In normal human skin, this leads to invisible shedding of single keratinocytes from the stratum corneum. In AD skin, the SCCE is more active, which leads to fewer corneodesmosomes, less cohesion of cells and more shedding of the uppermost corneocytes. The barrier dysfunction of AD skin is characterized by increased transepidermal water loss and lower hydration of the stratum corneum. The slightly acidic pH of the stratum corneum is due to the natural moisturizing factor (NMF), which consists of the filaggrin degradation products, lactic acid and urocanic acid (UCA). As the optimal pH for SCCE is in the alkaline region, the slightly acidic pH of the stratum corneum will protect it from overdegradation. Liberal use of alkaline soap bars will raise the stratum corneum pH and subsequently increase the shedding of corneocytes. This is the scientific basis behind the recommendation that patients with AD use pH neutral synthetic detergents instead of classic soap bars. The consequences of a complete lack of the protease inhibitor LEKTI is demonstrated by the clinical phenotype of Comel–Netherton syndrome: maximal skin barrier dysfunction and AD-like skin inflammation.

Barrier dysfunction in atopic dermatitis

Alterations in genes affiliated with epidermal barrier function, such as the profilaggrin gene (*FLG*), are risk factors for AD and the susceptibility of patients with AD to bacterial and viral skin infections. Many genetic studies of *FLG* have confirmed an association between this gene, responsible for ichthyosis vulgaris, and clinical AD manifestations – an association which has been clinically well known for decades.⁶ As T-helper type 2 (Th2) cytokines infiltrate AD lesions and downregulate filaggrin production on the protein level,⁷ filaggrin protein deficiency also contributes to AD development in patients with AD who do not present with filaggrin mutations.

Filaggrin is the main source of several major components of NMF in the stratum corneum, including pyrrolidone carboxylic acid (PCA) and UCA. Hence, a reduced level of PCA, UCA and histidine in patients with *FLG* deficiency or non-filaggrin-mutated AD⁸ may be regarded as an expected finding. Multiple regression analyses have confirmed that NMF levels are independently associated with the *FLG* genotype and severity of AD.⁸ Hence, the addition of filaggrin components to moisturizing agents seems a useful treatment strategy.

On clinical grounds, it is well known that the small molecules, urea and glycerol, improve the skin barrier function. The addition of petrolatum to barrier-stabilizing creams has a water-sealing effect and reduces transepidermal water loss.⁶

Ceramides are an essential component of the lipid double layer of the stratum corneum, and the ceramide content of the stratum corneum correlates with transepidermal water loss. As lesional AD skin contains significantly less ceramide 1 and ceramide 3 compared with normal human skin, the supplementation of ceramides could be a therapeutic goal.⁹ The addition of the ceramide compound, sphinganine, which is metabolized into ceramide 1 and ceramide 3, is also considered a promising therapeutic strategy.

Defects in tight junction formation contribute to the barrier defects in AD.¹⁰ Tight junctions function as gates for the passage of water, ions and solutes through the paracellular pathway, but the detailed structure and function of tight junctions remains an enigma. A number of claudins, as well as junctional adhesion molecule A, occludin and tricellulin are transmembrane molecules present in tight junctions. Whereas claudin-1 and -4 tighten the epidermal barrier, claudin-2 and -6 disrupt it. The physiological relevance of claudin-1 to the function of tight junctions is supported by the fact that claudin-1 knockout mice die from dehydration within 1 day.¹⁰ Drugs targeting impaired barrier function on the tight junction level seem to be a promising treatment for AD.⁶

Dendritic cells, IgE and adaptive immunity in atopic dermatitis

A tendency towards Th2-dominated immune responses and the predominance of the associated Th2 cytokines and interleukins (IL)-4, IL-5 and IL-13 in the cutaneous microenvironment is the most cited explanation for allergic diseases,¹¹ but clearly not the only cause of AD.¹² Some novel treatment options targeting the Th2 direction of the cutaneous immune response in AD may emerge from current studies involving novel monoclonal antibodies, which target the IL-4 receptor alpha chain or the cytokine thymic stromal lymphopoietin (TSLP).^{13,14}

IgE-mediated facilitated antigen presentation by epidermal dendritic cells that express the high-affinity IgE-receptor (FcεRI)^{15,16} seems to be relevant to the pathogenesis of extrinsic AD (Fig. 1).¹⁷ As patients with intrinsic AD lack detectable IgE against common aero- and food allergens, AD pathogenesis is probably best understood as a primarily cell-mediated, delayed-type hypersensitivity disease with an optional component of IgE-mediated sensitization.³ Being clinically similar, patients with extrinsic AD express higher levels of FcεRI on their cell surface compared with those patients with intrinsic AD.¹⁸ However, patients with clinically severe AD seem 'more atopic' than patients with mild AD.¹⁹ Monoclonal antibodies which block the binding of IgE to FcεRI have been investigated as a treatment for AD, but the results were not clinically convincing.²⁰

Cannabis sativa, and its active constituent 9-tetrahydrocannabinol (THC), exerts some of its effects via the G-protein-coupled cannabinoid receptor types 1 (CB1) and 2 (CB2).²¹ In a 2,4-dinitrofluorobenzene (DNFB)-mediated allergic contact dermatitis model, topical THC decreased ear swelling, chemokine ligand 2 (CCL2) production by keratinocytes, interferon (IFN)-γ production by T cells and myeloid immune cell infiltration in wild-type and CB1/2 receptor-deficient mice.²¹ Cannabinoids may form the basis for the treatment of inflammatory skin diseases in the future.

Vitamin D and antimicrobial peptides in atopic dermatitis

Vitamin D is a key player in innate and adaptive immunity by the stimulation of toll-like receptors (TLRs), which increase pro-inflammatory cytokine production and possibly enhance Th2 responses.²² Vitamin D is an essential factor for the expression of the antimicrobial peptide LL-37 in keratinocytes.²³ It is the only human cathelicidin known so far

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and LL-37 deficiency plays a role in the pathogenesis of eczema herpeticum (EH).²⁴ In clinical studies regarding AD, both high and low vitamin D levels have been linked to an increased susceptibility to disease.²² Synthetic vitamin D receptor agonists, which mediate immunomodulatory activities without the adverse hypercalcaemic effects of the natural receptor ligand calcitriol, suppress IgE production by human peripheral B cells.²⁵ This effect is possibly mediated by reduced activation-induced deaminase and IgE-secreting cells.²⁵

Targeting mast cells and histamine

Mast cells release histamine following allergen-specific and unspecific (e.g. physical or thermal) activation. Binding of histamine to one of the four different histamine receptors (HRs) will trigger a wide variety of effects in the skin's immune system.

Specific targeting of the four described HRs is an emerging strategy for achieving AD control. Although HR1 antagonists are widely used to treat AD, their efficacy remains poor.²⁶ The treatment strategy of combining HR1 antagonists with HR4 antagonists seems effective regarding clinical scores, pathology and skin cytokine levels, at least in a murine model, and reaches the therapeutic efficacy of prednisolone.²⁷ This combined approach may significantly reduce chronic dermatitis by synergistic inhibition of pruritus and skin inflammation.²⁷

A novel function of HR1 in AD was identified using a human skin model of epidermal differentiation: histamine reduces the differentiation capacity of cultured keratinocytes, the expression of the tight junction proteins zona occludens-1, occludin, claudin-1 and claudin-4, and of the desmosomal junction proteins corneodesmosin and desmoglein-1.²⁸ These findings suggest that mast cell activation and histamine release may be clinically relevant to skin barrier dysfunction in AD.

Colonization and infection with *Staphylococcus aureus*

Patients with AD are clinically susceptible to cutaneous colonization and infection with *S. aureus*, as they have an imbalance in innate and acquired immunity connected to staphylococci.²⁹ *S. aureus* may produce exotoxins with superantigenic properties. The overgrowth of staphylococci during AD flares is clearly associated with a loss of diversity in the skin microbiome of patients with AD.³⁰

TLRs, especially TLR-2, recognize the cell wall components of *S. aureus*, such as lipoteichoic acid and peptidoglycan.²⁹ Monocytes of patients with heterozygous TLR-2 polymorphisms clinically associated with severe AD produce significantly more IL-6 and IL-12 upon TLR-2 activation.

S. aureus produces extracellular, protein-containing vesicles in culture, which increase the production of various pro-inflammatory mediators like IL-6, TSLP and eotaxin by dermal fibroblasts.³¹ The application to tape-stripped skin results in epidermal thickening and dermal infiltration by mast cells and eosinophils, as well as increased cutaneous production of IL-4, IL-5, IFN- γ and IL-17. Contact with these extracellular vesicles alone seems sufficient to induce AD-like skin inflammation.³¹

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A novel treatment targeting *S. aureus* colonization without affecting the resident epidermal microflora would be a promising approach to treatment. However, oral antibiotics are indicated only in infected patients,^{26,32,33} and topical antibiotics have limitations due to resistance or contact allergy.³⁴ A promising alternative to the currently favoured topical antiseptics is evolving with emollients containing an active principle from microflora isolated from thermal spring water.³⁵

Herpes infection in atopic dermatitis

Eczema herpeticum (EH) is clinically defined as the disseminated infection of eczematous skin disease with the herpes simplex virus (HSV), which in clinical reality is almost exclusively AD.³⁶ Unmasking of the HSV entry receptor nectin-1,³⁷ a lack of plasmacytoid dendritic cells in AD lesions³⁸ or cathelicidin production *in situ*,²⁴ and an abnormal IFN- γ response to HSV³⁹ all contribute to EH pathogenesis. Clinical risk factors for EH were identified in 2003 by a study involving 100 EH cases and 105 controls, and include early onset and high clinical severity of the underlying AD and high total serum-IgE levels.⁴⁰ A recent study including 52 EH cases confirmed that patients with AD, recurrent HSV infection and a history of EH showed higher total serum-IgE levels, more severe AD and higher IgE sensitization profiles than those without a history of EH.⁴¹ The alpha-toxin produced by *S. aureus* contributes to EH by increasing the HSV load, even in sublytic doses.⁴² As most patients with EH are in AD flare during their EH episode, treatment of acute AD inflammation should also reduce the risk of EH.

Anti-inflammatory therapy for atopic dermatitis

Targeting the cutaneous inflammation of AD is pivotal to achieving clinical control of AD, because most symptoms and complications of AD appear secondary to the inflammation. Topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) differ in their mode of action and their effects on skin barrier function⁴³ and inflammatory cell infiltrate.^{44,45}

Reactive treatment with TCSs and TCIs following the presence or absence of visible lesions was the traditional mainstay of AD treatment. This strategy is well established with good short-term results; however, it is difficult to achieve long-term remission between flares, because normal-looking nonlesional skin of patients with AD is not normal – there is invisible inflammation and barrier defect.⁴⁶

Proactive therapy is defined as the low-dose, intermittent application of anti-inflammatory therapy to previously affected skin, together with ongoing, long-term emollient treatment of unaffected skin.⁴⁷ This approach targets invisible inflammation in the usually relapsing ‘problem zones’ of patients with AD. Recent clinical trials with the TCSs fluticasone propionate and methylprednisolone aceponate, and the TCI tacrolimus, following this approach have been reviewed.⁴⁸

Systemic anti-inflammatory treatment of AD is indicated only if topical therapy fails: ciclosporin A, methotrexate, mycophenolate mofetil and azathioprine are the most commonly used agents.^{32,33,49} In the future, possible disease-modifying strategies targeting the Th2-

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dominated immune response in the skin may enter routine use in AD management, and may achieve the goal to stop, or even reverse, the development of atopic comorbidities.⁴

Itch in atopic dermatitis

Itch and neuroplasticity are additional factors of chronic AD, which are frequently overlooked in the understanding of the disease. T cells can produce IL-31, a cytokine inducing histamine-independent pruritus.⁵⁰ Effects are signalled through a heterodimeric receptor expressed on epithelial cells including keratinocytes. Signal transducer and activator of transcription 3 phosphorylation is activated by IL-31 in human keratinocytes, and augmented after pre-activation with Pam3Cys or IFN- γ .⁵¹ IL-31 enhances the secretion of CCL2 after upregulation of the receptor with Pam3Cys or IFN- γ in a TLR-2-dependent mechanism.⁵¹ The new link between TLR-2 ligands and IL-31 may be important for AD lesions colonized by *S. aureus*.⁵¹ Targeting the IL-31 receptor may be another promising strategy for AD treatment.

Conclusion

A wide variety of treatment modalities have already been described for AD, but none are causative. A combination of emollient therapy, anti-inflammatory therapy and antimicrobial therapy seems optimal for most patients.^{34,49} Disease-modifying strategies, such as subcutaneous immunotherapy,⁵² or targeted therapy with AD-targeting biologics are just emerging. The current position paper of the European Task Force on Atopic Dermatitis,²⁶ as well as the current European Dermatology Forum guideline on AD management provide excellent sources of information for the clinician.^{32,33} Basic and translational research, as well as clinical trial work, will continuously broaden our knowledge of potential treatment targets and identify those treatment approaches that are clinically useful for daily practice.

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Figure legends

Fig 1. The vicious circles of atopic dermatitis. A powerful, superantigen-driven vicious circle involving a T-helper type 2 (Th2)-dominated antimicrobial immune response, downregulation of antimicrobial peptides, staphylococcal overgrowth, and production of immunoactivating toxins with superantigenic properties. This interacts with an antigen-specific vicious circle involving immunoglobulin E (IgE) production and binding to high-affinity IgE receptors expressed on skin dendritic cells, followed by IgE-mediated, facilitated antigen presentation. An interaction of dysfunctional innate and adaptive immune responses in atopic dermatitis lesions may cause severe disease flares. Adapted from Wollenberg and Feichtner.⁶

