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Review Article

Molecular Pathways of and the Future Therapeutic Implications for Atopic Dermatitis: A Review

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Abstract

No available treatments can provide long-term remission for patients with moderate to severe Atopic Dermatitis (AD) creating a large unmet need for effective systemic treatment. The important factors and related mechanisms for AD are the following: (a) Genetic, (b) Neurohumoral, (c) Skin barrier dysfunction and (d) Immunological mechanisms.

The cellular interactions, molecular events and pathways for the pathogenesis of AD was integrated into a hypothesis and reported recently. As the new insights into the immune and molecular pathways of AD increase, a variety of experimental agents, particularly biological agents that target pathogenic molecules bring promise of safe and effective therapeutics. Some of the most promising biological therapies that are in development or in clinical trials are based on principles as the following: Barrier repair, Allergen specific immunotherapy, Targeted Immunomodulating Therapies (TIT) (Anti-IgE therapy, Anti-CD20, Inhibition of T-cell responses, Th2-cell inhibition strategies/ Anti IL-4 therapies, Anti IL-5 strategies, Anti IL-31), Targeting Th22, Targeting Th17/IL-12/IL-23 pathway, Recombinant IFN-y, Anti IL-6R, Anti TNF agents, Phosphodiesterase inhibitors, PPAR-gamma agonists.

All these biological therapies are at different phases of clinical trials. These biological agents would potentially hold great promise for the treatment of AD if they can offer advantages, i.e. low toxicity, good efficacy, improved patient compliance via given weekly/biweekly/and even monthly administration, reduction of disease activity, relapse prevention, etc. In Summary, the recent advances in understanding of the immunopathogenic mechanisms provide an opportunity for development of biological therapies directed at pathways driving AD. This is possibly the beginning of an exciting era in AD therapeutics with impending availability of drugs having low toxicity and increased patients' compliance. These expected drugs will not only treat this disease, but also prevent the development and relapse of new skin lesions. In this article, attempts have been made to provide an updated account of these new possibilities.

Keywords: Atopic dermatitis; Eczema; Biologics; Therapeutics; Cytokines; Anti-cytokines

Introduction

Atopic Dermatitis (AD) is a common, chronic, relapsing inflammatory skin disease affecting increasing number of people up to 25% of children and up to 3% of the adult population [1-3]. AD, also named eczema in some countries, is considered as the most common, itchy and relapsing inflammatory skin condition. Together with asthma and allergic rhinitis,

it constitutes the "Atopic Triad". Approximately 80% of patients have a personal or family history of atopy, associated with high serum Immunoglobulin E (IgE) level and/or elevated eosinophil count referred to as extrinsic AD in contrast to intrinsic AD that lacks these characteristics [4,5]. Despite its increasing prevalence worldwide, no available treatments can provide long-term remission for patients with moderate to severe AD, creating a large unmet need for effective systemic treatment [6-8]. Much progress has been made in the understanding of its genetic background and pathophysiology through studies in genetics, epidemiology and immunology. These studies have provided new important insight of the complex puzzle and dramatically changed our view on the pathogenesis, its natural history and the future ways to control the disease AD in the context of the so-called atopic march [2,9-12].

Pathogenetic Mechanism

Among the various factors involved in the pathogenesis of AD, the important ones are the following:

a) Genetic factors

b) Neurohumoral factors

c) Skin barrier dysfunction and

d) Immunological mechanisms [2]

Genetic factors

The importance of genetic factors in AD is underlined by the finding that a positive parental history is the strongest risk factor for AD; the incidence rate is double if AD is present in one parent and tripled if both parents are affected. In the modern era of genomics, linkage analysis and association studies have greatly contributed to our understanding on the genetic background of AD [8,9]. The important chromosomal region harboring possibly several important genes is 1q21.

This area includes most of the genes regulating the epidermal homeostasis, the epidermal differentiation complex (EDC). The recent demonstration of loss-of-function mutations of the profilaggrin/filaggrin gene, a key protein in terminal differentiation of the epidermis, can be considered as a breakthrough [2,10,11]. It is expected that other yet-to-be-defined genetic variants from epidermal structures such as those localization in the EDC on chr. 1q21 may also play a role in these phenomena [13,14]. The other set of candidate genes includes the numerous structures related to immunological mechanisms operative in AD. For example, on chromosome 5q31-33, the locus containing genes for the TH2 cytokines interleukin (IL)-3, IL-4, IL-5, IL 13, and granulocyte macrophage colony stimulation factor (GM-CSF) has been suggested. Further studies identified variants of the IL-13 encoding region, functional mutations of the promoter region of the chemokine RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) (17q11) and gain-of function polymorphisms in the alpha subunit of the IL-4 receptor (16q12) [14]. The disbalance between TH1 und TH2 –immune responses in AD may be elucidated by the detection of polymorphisms of the IL-18-gene, resulting in TH2 predominance [15].

Neurohumoral factors

Neuropeptides and neurotropins mediate different actions such as vasodilatation, oedema, itch and pain or sweat gland secretion and have a minor ability to regulate T-cell activation [16,17]. They can be detected in blood and within the epidermal nerve fibres in close association with mast cells or epidermal Langerhans cells, suggesting a tight link between the immune system and the nervous system. Recent studies have documented increased levels of nerve growth factor and substance P in plasma of AD patients while growth factor, detected recently in sera and plasma of patients with AD, enhances the survival of eosinophils, increasing their chemotactic response in vitro [16].

Skin barrier dysfunction

One of the major hallmarks of AD is xerosis which affects lesional and non-lesional skin areas as due to increased trans epidermal water loss. It may favour the penetration of high-molecular weight structures such as allergens, bacteria, and viruses [17]. Several mechanisms have been postulated: (i) a decrease in skin ceramides, serving as the major water-retaining molecules in the extracellular space, (ii) alterations of the stratum corneum pH[18]. (iii) over expression of the chymotryptic enzyme (chymase), (iv) defect in Filaggrin as well as molecules of the EDC the protein family (see genetic factor).

Immunological mechanism:

Both the components of the immune system i.e. (i) innate immunity and (ii) adaptive/acquired immunity are important in the pathogenesis of AD.

Innate immunity: The innate immunity system of the epidermis presents the first line defense against cutaneous infections. Once the epidermis is invaded by micro-organisms, anti-microbial peptides are activated and form part of the defense system [19]. AD skin is characterized by a significant decrease in expression of anti-microbial peptide, explaining the susceptibility of AD patients for bacterial infections [2,20]. The innate skin defence system of patients with AD may be further reduced by the deficiency of dermcidin-derived antimicrobial peptides in sweat, which correlates with infectious complications [21].

Acquired immunity: A predominant TH2 disbalance with increased IgE levels and eosinophilia is widely accepted in the pathogenesis of AD [22-24]. The production of TH2 mediated cytokines, notably IL-4, IL-5, and IL-13, can be detected in lesional and non-lesional skin during the acute phase of disease. IL-4 and IL-13 are implicated in the initial phase of tissue inflammation and may mediate an isotype switching to IgE synthesis, and up regulation expression of adhesion molecules on endothelial cells. IL-5 increases the survival of eosinophils and a systemic eosinophilia with an increase of the eosinophil cationic protein (ECP) correlate to disease severity [25]. Although TH2 mediated cytokines seem to be predominant in the acute phase of AD they are less important during its chronic course. The maintenance of chronic AD involves further on the production of the TH1 like cytokines IL-12 and IL-18, as well as several remodeling-associated cytokines such as IL-11,

IL-17 and TGF-β1 [26]. Role of different chemokines have gained interest in the pathogenesis of AD.

Many chemokines like TARC/CCL17, PARC/CCL18, MDC/CCL22, and CCL1 seem instrumental in the development of acute and chronic lesions [2,22]. C-C chemokines (RANTES, exotaxin, etc) contribute to the infiltration of macrophages, eosinophils, and T-cells into acute and chronic AD skin lesions. Dendritic cells (DC) are highly specialized professional antigen presenting cells and are essential for the allergen uptake and its presentation to T-cells in the context of primary and secondary immune responses. The role of DC in AD has been extensively discussed elsewhere [27,28]. Lesional and normal skin of patients with AD is highly colonized with toxins-production staphylococcus aureus (S. aureus) [29].

This colonization is due to the decreased production of anti-microbial peptides which are down-regulated by the particular inflammatory micro-milieu in AD [30]. Interestingly, S. aureus enterotoxines A (SEA), B (SEB), C (SEC) and D (SED) gained increasing importance in the pathogenesis of AD since they exhibit a large spectrum of biological activities including the induction of a specific (IgE) sensitization, acting as super antigens and altering the function of Treg [2,6]. These cellular interactions, molecular events and pathways for the pathogenesis of AD has been integrated into a hypothesis and reported by Guttman-Yassky et al (Figure-1) [6,31].

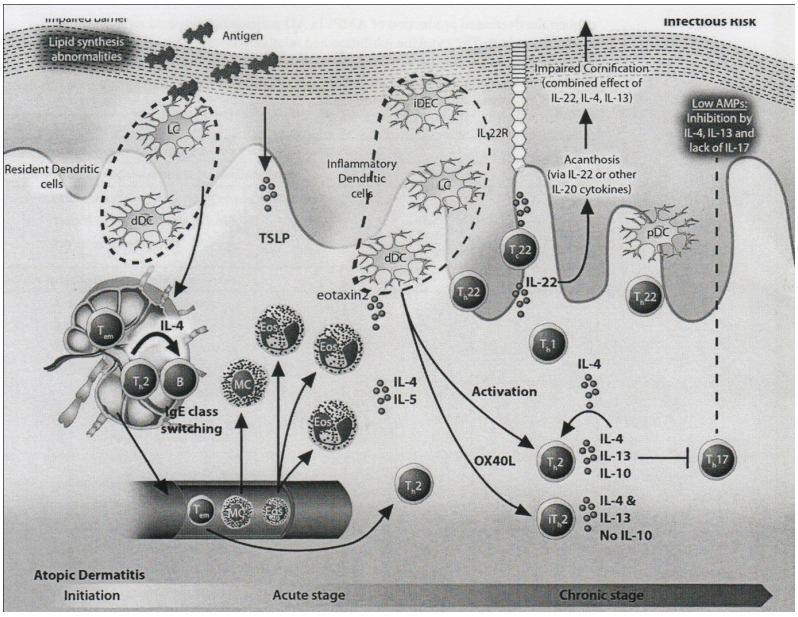

Figure 1: The immunopathogenesis of Atopic Dermatitis (AD).

The disease has three main phases, i.e. initiation, acute and chronic stages. Defects in the epidermal barrier lead to the penetration of the skin by epicutaneous antigens, which in turn encounter Langerhans and dermal dendritic cells that activate Th2 cells and IL-4 and IL-13 production. These cytokines result in two major effects: IgE class switching and increased Th2 cell survival having several direct effects on the epidermis. These include inhibition of anti-microbial peptide (AMP) production, and impaired epidermal differentiation. In addition, the inflammatory mediators of Th2 T-cells and DCs induce peripheral eosinophils and mast cells. Also, of significance is an increase in Th22 cells in AD skin; this subset produces IL-22, which is most significantly increased in chronic AD skin. IL-22 inhibits terminal differentiation and induces epidermal hyperplasia, which is an important characteristic of chronic disease. Thus, the barrier defect in AD most likely results from a combined effect of Th2 and Th22 cytokines. Similarly, to T-cells, there is a progressive increase in dendritic cells and Langerhans cells from non-lesional through chronic AD Adapted from: Guttman-Yassky et al. [6,31].

Biological therapeutics in development

One might hypothesize that in AD epidermal reaction may be largely restored to normal with selective immune suppression. A recent study of AD patients that were treated with Narrow Band (NB) UVB therapy, showed that reversal of clinical disease activity was associated with reversal of the epidermal pathology including reduction in epidermal thickness and expression of proliferation markers [32]. As the new insights into the immune and molecular pathways of AD increase, a variety of experimental agents, particularly biological agents, that target pathogenic molecules bring promise of safe and effective therapeutics for long term use. Some of the emerging and most promising biological therapies that are in development or in clinical trials are based on principles as the following: Barrier repair, Allergen specific immunotherapy, Targeted Immunomodulating Therapies (TIT) (Anti-IgE therapy, Anti-CD20, Inhibition of T-cell responses, Th2-cell inhibition strategies/ Anti IL-4 therapies, Anti IL-5 strategies, Anti IL-31, Targeting TSLP), Targeting Th22, Targeting Th17/IL-12/IL-23 pathway, Recombinant IFN-γ, Anti IL-6R, Anti TNF-α agents, Phosphodiesterase inhibitors, PPAR-gamma agonists. However,

further developments in future targeting and inhibiting cytokines, chemokines and signal transduction are strong possibilities. [31,33-38]. All the above stated biological therapies are at different phases of clinical trials. However, trials showed effectiveness of these treatments differentially in only subset of patients.

Barrier repair: Skin barrier function is linked to the innate immune system. The therapeutic strategies which improve innate immunity might ultimately lead to repair of the epidermal barrier. A meta-analysis of trials of probiotics, however, did not show that they benefitted patients with AD. The findings that vitamin D3 supplements up regulated production of AMPs should be confirmed in larger population of patients with AD. Topical protease inhibitors were also being tested for treatment of AD, although there was no evidence for their benefit. Recently, another approach aims to restore and increase the expression of epidermal differentiation proteins, e.g. filaggrin and loricrin, in order to repair the barrier [31,39-43].

Allergen specific immunotherapy: Double-blinded, multi-centre, randomized trials with house dust mites have been reported to significantly improve the eczema in patients with AD who are sensitized to house dust might allergen. Allergen specific immunotherapy represents the important causative therapeutic approach. With regard to AD only limited, and often contradictorily information is available. A study, re-examining the efficacy of a subcutaneous immunotherapy (SCIT) in atopic patients sensitized to house dust mites (HDM), demonstrated effectiveness improving eczema and allergic sensitization to HDM and reduction of topical corticosteroids required to treat eczema. Oral immunotherapy (OIT) protocols are also being optimized for patients with a history of AD and food allergy [31,44-46]. Further studies are needed to evaluate the comparative benefits of SCIT and OIT in AD patients in the near future.

Targeted Immunomodulating Therapy (TIT)

TIT (Anti-IgE therapy): Although the role of IgE in the pathogenesis of AD is not clear, omalizumab, a humanized IgG1 monoclonal antibody against IgE, has been tested in AD mainly in patient's refractory to conventional therapy. Omalizumab has not been observed to have consistent significant clinical effects in most patients with AD, despite its ability to down regulate FceRI on DCs. This may be in part due to the very high serum IgE levels which may be difficult to neutralize in AD as compared to asthmatics who have lower serum IgE. Alternatively, IgE might only play a secondary role to the primary cellular mechanisms in atopic dermatitis, in which case the therapeutic efficacy of omalizumab would be limited. Overall, this highlights the heterogeneity and complexity of allergic diseases suggesting that more work is needed to characterize AD patients into defined immunologic profiles and phenotypes which may benefit from specific biological therapies [7,31,47].

TIT (Anti-CD20 therapy): Small studies of rituximab, an antibody against CD20 that depletes B cells which was developed for hematologic disorders, have had contradictory results in patients with AD. One study showed that treatment with rituximab resulted in a rapid and sustained decrease of skin inflammation in patients with AD, suggesting a possible role for B cells in its pathogenesis. However, IgE levels remained unchanged during treatment. Further studies are required to determine whether reagents that inhibit or deplete B cells might be used to treat AD.31,48,49

TIT (Anti IL-4 therapy): Few inhibitors of the IL-4R are currently available. An inhibitor of IL-4R signaling (pitrakinra /pascolizumab) that competitively binds to IL-4RA to inhibit binding of IL-4 and IL-13 has shown efficacy in trials of patients with asthma but has not been tested for patients with AD. Of great interest is REGN668, an anti-IL-4R antibody currently evaluated in clinical trials for AD and eosinophilic asthma (phase 2 in eosinophilic asthma and completing phase 1 in AD). The clinical impact of the Th2 cytokines IL-4 and IL-13 on atopic dermatitis has recently been documented in clinical studies with dupilumab, a monoclonal antibody, which blocks the IL-4/IL-13 receptor and in fact, dupilumab has been already approved in 2017 for use in AD [31,50-52].

TIT (Anti IL-5 strategy): Eosinpphils are important mediators of the inflammatory process in AD, so agents that block IL-5 might be developed as therapeutics. However, mepolizumab, a fully humanized monoclonal antibody against IL-5, reduced blood and tissue eosinophilia but did not show clinical efficacy in patients with moderate to severe AD. Mepolizumab reduced the numbers of eosinophils in patients with asthma, but had no effects on T-cell responses, arguing against its role in treatment of AD [31,53,54].

TIT (Anti IL-31 therapy): IL-31 is a cytokine produced by Th2 cells that is believed to promote itching in AD. Recently it has been shown that IL-31 is one of the markers that are most significantly increased, possibly correlating with the increased pruritis in acute AD. Treatment with anti-IL-31 might hold promise for eczema as well as other itch-related dermatoses. Therapeutics that target IL-31 are under development and in phase I clinical trials [31,55,56].

TIT (Anti Th22/Anti IL-22 therapy): The recently described Th22 T-cell subset was shown to have correlation with disease activity in AD. Th22 cells and IL-22 are increased in patients with acute as well as chronic AD. These were taken as high indication that IL-22 might be a therapeutic target for patients with AD [31,57,58].

TIT (Th17/IL-12/IL-23 pathway): As the levels of IL-17 and its related factors are increased in patients with AD, agents directed against IL-17 cytokine or its receptor (such as Ixekinumab, Brodalumab, AIN457) and/or IL-23 (such as MK-3222) might be effective for patients with acute exacerbations of AD. Anti-p40 (such as Ustekinumab/Stelara) might also be effective by targeting multiple pathways involved in AD, including Th17 and Th22 pathways [31,57,59,60].

TIT (Recombinant interferon gamma): Th1 subset of T cells from AD patients has been shown to produce lower levels of IFN-G. Administration of recombinant IFN-G to patients with AD might restore the balance of Th1 and Th2 cell responses, and lower IgE production. However, trials showed effectiveness of this treatment in only a subset of patients and did not reduce levels of

IgE. This treatment might still have a potential role in patients with concomitant skin infections such as herpes simplex, and molluscum contagiosum [31,61].

Anti-IL-6R therapy: Anti IL-6R treatment with Tocilizumab seemed to be promising. Tocilizumab is an IL-6 receptor (IL-6R) antagonist approved by FDA, USA in 2008. Recently, this antagonist was used to treat 3 AD patients, refractory to other treatments, including cyclosporine A. All patients showed significant clinical improvement, with more than 50 % reduction in the Eczema Area and Severity Index (EASI) score. However, bacterial infections were observed in two of the three patients. Further studies are needed to evaluate the potential efficacy and the safety of Tocilizumab in patients with severe AD [31,37].

Anti TNF-α therapy: Anti TNF-α agents have been successful in treating psoriasis probably because TNF and its synergistic interaction with IL-17 mediate the pathogenesis of psoriasis. Furthermore, TNF-α antagonists inhibit the pathogenic Th1- and Thl7-cell responses that contribute to psoriasis. However, a pilot study of the effects of the TNF-α antagonist, infliximab, in patients with moderate-to-severe AD, and another study of etanercept in two children, demonstrated disappointing results, possibly because TNF-induced inflammatory responses have only a minor role in AD. Although clinical improvement was obtained, the patients did not show sustained responses [31,38,62].

PPAR-gamma agonists (Thiazolidinediones): Thiazolidinediones activate the nuclear receptor, PPAR-y, which is expressed on adipocytes and immune cells. Activation of PPAR-Y decreases production of pro-inflammatory cytokines (i.e. TNF-α and IL-6) and also increases responses to insulin. These agents were first approved for treatment of diabetes mellitus and recently also explored for inflammatory skin diseases, such as psoriasis and AD. Few clinical studies with systemic PPAR-y agonist, Rosiglitazone, led to clinical improvement and reduced number of flares in few patients with recalcitrant AD, and topical PPAR-α agonist showed beneficial clinical effects in pediatric AD. Both PPAR-y and PPAR-α are thought to have anti- inflammatory and barrier-normalizing properties and might be useful for treatment of established AD skin lesions and also possibly for prevention of new lesions [31,63].

Chymase inhibitor therapy: Chymase is an inflammatory molecule produced by mast cells which might be associated with AD. After being successful in mice, clinical trials were initiated in humans with chymase inhibitor, SUN-C8257, and currently, an oral chymase inhibitor SUN 13834 is in Phase II clinical trial in AD [31,64].

Conclusion

There has been a growing trend forwards the use of targeted therapies in treating AD in recent years. The systemic biological agents are potentially great promise for the treatment of AD if they can offer the following advantages: low toxicity, good efficacy, improved patient compliance via given weekly/biweekly/and even monthly administration, reduction of disease activity, relapse prevention, etc. Since there is a very close relationship between elucidation of molecular disease pathways and development of targeted systemic therapeutics, academic institutions and researchers will need to work closely and cooperatively with the industry to assure rapid drug development to benefit AD patients. Furthermore, regulatory and funding authorities will need to acknowledge the large unmet need and current lack of safe and adequate treatments for such a common disease in adults and children and support the efforts for translational and drug development for this disease. The recent advances in our understanding of the immunopathogenic mechanisms implicated in AD provide an opportunity for development of biological therapies directed at pathways driving AD. We believe that this is the beginning of a new and exciting era in AD therapeutics with impending availability of narrow-targeted drugs with low toxicity and increased patients' compliance. These expected drugs will not only treat this disease, but also prevent the development and relapse of new skin lesions given the current therapeutic challenges of treating AD.

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