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Potential Treatments for Atopic Dermatitis

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Abstract

Atopic Dermatitis (AD) is the most common pruritic inflammatory skin disease which causes economic and social burden. AD is not curable and therapeutic options are limited. Currently, the therapeutic approaches to AD include topical treatment, phototherapy, and systemic treatment. Although traditional therapeutic strategies are efficacious in ameliorating the symptoms of AD in most patients, sometimes it is a tough challenge for physicians as AD is catastrophic and difficult to treat. Several potential treatments for AD are being studied owing to a clearer understanding of its pathogenesis. Additionally, animal models of AD allow comprehensive and thorough investigation of pathogenesis and provide more options of therapeutic interventions. The purpose of non-classical treatment strategies for AD is to decrease skin inflammation, re-direct the imbalanced immune polarization, and induce immune tolerance to allergens. Generally, the intervention for mouse model of AD can be classified into 1) monoclonal antibodies, 2) anti-oxidants, 3) allergen-specific immunotherapy, 4) herbal medicine, 5) treatment with materials extracted from food or micronutrients, 6) microbiota/probiotics, 7) bio-composites films, and 8) others. Since half of the patients with AD lack specific immunoglobulin E against allergens, the pathogenesis of different phenotypes still needs to be clarified. Through novel therapies such as cytokine-targeting therapy, miRNA or suppression of thymic stromal lymphopoietin, patients with AD could have better quality of life with less morbidity.

Keywords: Atopic dermatitis; Pathogenesis; Inflammation; Homeostasis

Introduction

Atopic dermatitis (AD) is the most common pruritic inflammatory skin disease which causes economic and social burden. AD affects about one-fifth of the world's population [1] and primarily appears under the age of six; half of the patients develop symptoms within one year of birth [2]. The symptoms of AD relieve spontaneously in around 75% paediatric patients before adolescence. However, infants with AD have a higher risk of developing asthma and allergic rhinitis later in life, a phenomenon called atopic march [3,4]. The diagnosis of AD depends on clinical presentation of the skin, and the most widely used diagnostic criteria were developed in 1980, revised by the American Academy of Dermatology [5].

AD is not curable and therapeutic options are limited. Currently, the treatment of AD aims to prevent exacerbations and reduce their duration and severity [6]. Prevention is best achieved by reducing the dryness of the skin and maintaining an intact skin barrier, via daily use of skin moisturizing creams or emollients. Therapeutic approaches to AD include topical treatment, phototherapy, and systemic treatment. Corticosteroid creams are used both for treating acute exacerbation and as maintenance therapy, but their use is associated with cutaneous and systemic side effects, such as thinning of the skin, teleangiectasies, and appearance of striae. Topical calcineurin inhibitors, a newer medicine, can also be used for acute flares and for maintenance therapy of AD [7-9] without the side effects of corticosteroids. UV radiations (UVA1 and UVB311 nm) can treat widespread eczema [10-12] but may cause prematurely aging skin and raises the risk of skin cancer on continual exposure. Oral corticosteroids are recommended only to patients with acute flares of severe, wide spread AD for a short time. A second immunosuppressant drug, for example, azathioprine, methotrexate, or cyclosporine A, should better be added into the treatment when tapering oral corticosteroids [13]. Allergen-specific immunotherapy (ASIT) for patients with AD was considered in some physicians. In opposite to allergic rhinitis and upper airway symptoms, however, the evidence base for the effectiveness of specific immunotherapy on the activity of eczema is controversial [14,15]. Currently, H1 anti-histamines are being used as monotherapy for treatment of AD; its effect is not confirmed due to lack of randomized controlled trials. Although traditional therapeutic strategies are efficacious in ameliorating the symptoms of AD in most patients [16], sometimes it is a tough challenge for physicians since AD is catastrophic and difficult to treat.

Several potential treatments for AD are being studied due to a clearer understanding of the pathogenesis of AD. Additionally, animal models of AD also allow comprehensive and thorough investigation of pathogenesis and provide more options of therapeutic interventions. Currently, mouse models are primarily used. This article reviews some clinically potential trials and therapeutic reports of AD in animal models.

Pathophysiology

The pathogenesis of AD remains incompletely understood. AD is a complex skin disease caused by the interaction between genetic and environmental factors. Colonization of *Staphylococcus aureus* on the skin was also found to be an important factor for aggravating skin lesions. However, two major pathophysiological mechanisms are 1) abnormalities in the epidermal structure and function, and 2) skin inflammation due to different causes such as inappropriate immune response to encountered antigens. The primary and key driver of AD, out of the two mechanisms, is still under debate. It is believed that these two hypotheses are not necessary mutually exclusive but may assist each other. Figure 1 gives the summary of the multifactorial pathogenesis of AD.

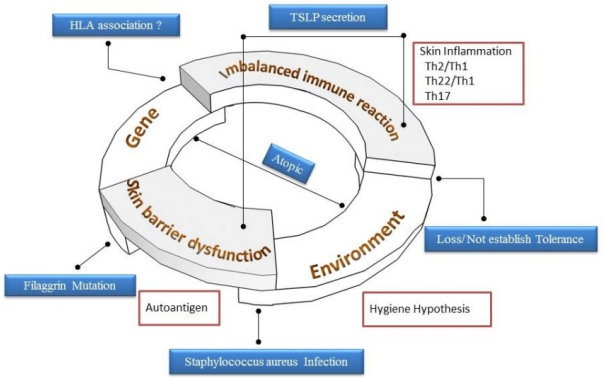

Figure 1: The pathogenesis of atopic dermatitis. AD is caused by the interaction between genetic and environmental factors. Two major pathophysiological mechanisms are 1) abnormalities in the epidermal structure, and 2) skin inflammation due to inappropriate immune response Epidermal TSLP is a factor link the two major pathogenesis.

The skin barrier dysfunction

The skin barrier dysfunction has a key role in the beginning of AD. An impaired and dry skin barrier leads allergens more easily penetrate into the skin, resulting in allergic sensitization [17-19].

Filaggrin is essential for the regulation of epidermal homeostasis [20]; mutations in the filaggrin gene have been associated to increased risk of developing AD [21,22]. In addition to mutations, Th2 associated cytokine interleukin-33 (IL-33) [23] and thymic stromal lymphopoietin (TSLP) [24] were reported to down regulate filaggrin expression. Defects in functions of tight junction (TJ) or enzymatic proteins of the skin can also contribute to enhanced permeability of defective barrier function and impaired anti-microbial defense in patients with AD [25,26]. The polymorphism of Claudin-1, a protein in tight junction, was reported to be associated with AD in early life when exposed to mold [27]. Recently, Pellerin et al. [28] reported that downregulation of bleomycin hydrolase gene expression in patients with AD could lead to dryness of the skin via decreased production of amino acids, which act as natural moisturizing factors.

Immunological hypothesis

The immune responses to antigen/pathogen are imbalanced and differentially polarized in patients with AD. The research involving immunological pathogenesis of AD mainly focuses on T helper/regulatory cells [29] and epidermal cells. In AD, particularly in acute eczema, the Th2 differentiation of naive CD4+ T cells is the predominate immune response. The upregulated Th2-related products including IL-4, IL-5, and IL-13 lead to an increased level of immunoglobulin E (IgE) and inhibited Th1 differentiation with inconsistent increased level of Th17-related cytokine [30]. Although Th2 polarization is the main immunological response, allergic sensitization and elevated IgE are observed in only about half of the patients with AD [31]. In addition to Th2 cytokines, IL-22 was already reported in several studies to be involved in the pathogenesis of AD [32]. Pediatric AD was found to mainly an imbalance of Th2/Th1 immune response, whereas adult patients acquire a stronger Th22 reaction. So that the therapeutic approaches to treat AD in children and adults may different [33,34]. Human mast cells were also studied to understand their role in pathogenesis. A recent study showed that the human skin mast cells are major producers of IL-22 in patients with AD. The authors established that the skin mast cells also produce IL-17 in chronic inflammatory skin disorders [35].

Some researchers suggest that AD is an autoimmune disease. The human skin-associated autoallergen, thioredoxin, which released from dermal or epidermal cells, was found to induce IgE-dependent upregulation of the Th2 cytokine IL-13 and impaired upregulation of IL-10 in sensitized patients with AD [36].

Epidermal TSLP: A factor link two major pathogenesis in AD

The skin plays a critical role in its immuno-pathogenesis. When the skin is damaged, epidermal keratinocytes are activated to release of cytokines, chemokines, and antimicrobial peptides. Among them, TSLP, an IL-7-like chemokine/cytokine promotes the generation and maintenance of Th2 cytokine responses to allergic reaction in the skin and lungs. Over-expression of TSLP in transgenic mice presented an AD-like phenotype [37] and the skin epidermis of AD patients highly secreted TSLP [38,39]. TSLP influences local network of dendritic cells to secrete chemokines like eotaxin and IL-8, and primes naïve T cells into Th2 cells [39-41]. TSLP signaling was also reported to recall the memory of Th2 response in established mouse model of AD [42]. Furthermore, TSLP was found to downregulate filaggrin expression via activating the janus kinase-STAT3 pathway that influenced the skin barrier function [24,43]. The TSLP isoform (short/long) ratio is altered in several inflammatory disorders, which has implications for the treatment and prevention of AD [44]. However, attention in reducing TSLP synthesis or release as a therapeutic strategy is limited.

Non-Classical Treatment Strategies for Atopic Dermatitis

Therapeutic trails of patients with AD

The purpose of therapeutic trails of AD is to decrease skin inflammation, re-direct the imbalanced immune polarization, and induce immune tolerance to allergens. There are few reports that investigated the role of the skin barrier protection in influencing the further immune reaction. Czarnowicki et al. [45] reported that the common moisturizer, petrolatum, used in patients with AD could increase the thickness of the stratum corneum and significantly reduce

skin T-cell infiltration. Interestingly, petrolatum also robustly enhances expression of the skin anti-microbial peptides to prevent skin infection.

Decrease skin inflammation

Wawryzyniak had reported a detailed review about novel treatments linked to mechanisms of AD and allergic disease [46]. From the experience of clinical trial for psoriasis, cytokine-target therapy (IL-23) was reported to have a good therapeutic effect [47]. Human monoclonal antibody specific for cytokines in the pathogenesis of AD may also have a good therapeutic effect in the future. Supplementation of long-chain omega-3 fatty acids, the essential human nutrition, was reported to be a promising way in the prevention of AD since the anti-inflammatory effect. However, this concept still cannot be confirmed and needs more randomized controlled intervention studies [48,49]. MicroRNAs (miRNA) are a class of non-coding RNA molecules that modulate gene expression post-transcriptionally. Few studies have investigated the expression of miRNAs in AD [50]. Recently, Rebane et al. demonstrated that miR-146a alleviates chronic skin inflammation in AD through suppression of innate immune responses in keratinocytes [51]. Besides miR-146a, miR-155 and dozens of other miRNAs have been found to be related to AD lesions [51,52]. Lovendorf wrote an expert review about miRNA in inflammatory skin diseases and concludes that miRNAs will lead to new diagnostic and therapeutic applications in dermatology [53].

Since the properties of sleeping induction and anti-inflammation, melatonin was studied for the management of AD with sleep disturbance [54]. The initial results showed that melatonin supplementation is a safe and effective to improve the sleep onset latency and disease severity in children with AD [55]. Therefore, melatonin has also been regarded as a potential and alternative therapeutic approach in patients with AD [56].

Re-direct the imbalanced immune polarization

Nowadays macrophages are characterized by phenotypical and functional heterogeneity [57]. Functional plasticity of macrophages has emerged as an important aspect of disease progression in several pathologies [58]. Like AD, contact hypersensitivity has complex pathogenesis and mannose receptor-positive M2 macrophages were reported to be associated with the development of it. These results suggest that manipulation of the polarization of macrophages may provide a new strategy for the treatment of AD [59,60].

Vitamin D has known to modulate both innate and adaptive immune systems, which makes vitamin D supplementation a field of interest in the prevention and treatment for AD. However, the literature on vitamin D and AD have resulted in controversial findings; the role of vitamin D in AD is far from clear [61-64].

"Hygiene hypothesis" suggests that changes in immunoregulatory infectious environment and the patterns of microbial exposure of children increase the severity and prevalence of atopic disorders [65,66]. A number of studies have explored the potential efficacy of probiotics in the prevention and treatment of AD. However, there is still no reliable evidence and needs further investigation for clarifications [67].

Induce immune tolerance to allergens

The induction of oral tolerance by oral immunization has been well recognized. Oral tolerance can be mediated by orally activated humoral and cellular factors. In allergy, oral administration of certain allergens may prevent and reduce both contact dermatitis and AD. Numerous independent experiments using different antigens have resulted in a distinct effector for the induction of oral tolerance. The study group of The German Infant Nutritional Intervention (GINI) recently reported their results revealing allergic manifestation after 15 years of early intervention with hydrolyzed formula. The report revealed that in high-risk children, early intervention using different hydrolyzed formulas has variable preventative effects on asthma, allergic rhinitis, and eczema up to adolescence [68]. Furthermore, the results of an animal study conducted by Chiang showed that the preventive oral administration of ovalbumin (OVA) protected β-lactoglobulin (BLG)-conjugated-OVA (B-O)-sensitized mice from BLG-induced airway hyper-responsiveness. The study revealed that non-antigen-specific effect of oral tolerance could be applied as an immunotherapy for allergic disease if the mechanism could be investigated further [69].

Advancement in Potential Treatment using Mouse Model of Atopic Dermatitis

The mouse models of AD can be categorized into three groups [70]: 1) Models induced by epicutaneous application of sensitizers; 2) Transgenic mice that either over-express or lack selective molecules; 3) Mice that spontaneously develop AD-like skin lesions [71]. These models could be used for dissecting mechanisms underlying the pathogenesis of AD. For example, IL-4 over-expressing transgenic mice develop spontaneous pruritus and chronic dermatitis [72]. From this model, IL-4 was also found to have a pronounced negative influence on the wound healing process, even though enhanced epithelial cell proliferation which may help explore new potential therapeutic strategies [73].

Generally, the intervention for mouse model of AD can be classified into 1) Monoclonal antibodies; 2) Anti-oxidants; 3) Allergen-specific immunotherapy; 4) Herbal medicine; 5) Extracted materials from food or micro-nutrition; 6) Microbiota/ probiotics; 7) Bio-composite films; 8) Others. Most of the interventions improved the lesions/symptoms by suppressing Th2 response in local or systemic conditions with various effects on Th1 or Th17 immune response. Few interventions in animal models inhibited the skin secretion of TSLP secretion and suppressed skin inflammation [74,75]. Our group was the first to report that in Th2 environment, the production and secretion of TSLP from human keratinocyes was inhibited by recombinant heat shock protein 70 (rHSP70) [76]. Recently, we further subcutaneously injected rHSP in mouse model of AD (ovalbumin epicutaneous application on BALB/c mice). The initial results showed that rHSP70 improved the histological morphology by decreasing allergic inflammation and TSLP expression of AD-like lesions with increased serum Th1 immune responses (Not published). Our data suggested that rHSP might also be a promising approach for the treatment of AD. From the results of allergen specific immunotherapy via succinylated antigen or high-dose antigen exposure in epicutaneous application mice model, increased IgG titer (IgG1/IgG2 ratio) not IgE was reported to be associated with clinical improvement [77,78]. To find a more efficient way to modify allergen being an IgG inducer and further elucidate role of Fc receptors involved in this intervention could help to develop new strategy for AD. Therefore, ASIT was proved as a promising treatment [76].

Increased reactive oxygen species (ROS) and oxidative stress has been reported in AD. In addition to Th2 suppression and Th1 enhancement, anti-oxidant treatment in mice model demonstrated the increased regulator T cells [79]. The results imply oxidative stress direct the imbalanced immune polarization and which could be the therapeutic target in the future.

Finally, extracted materials from food like algae or chitin were reported to have anti-inflammatory function and were used for treatment of AD in mouse model. Some results showed that the suppressive effects were equal to those induced by corticosteroids and suppress inducible nitric oxide synthase (iNO) synthase [75,80,81].

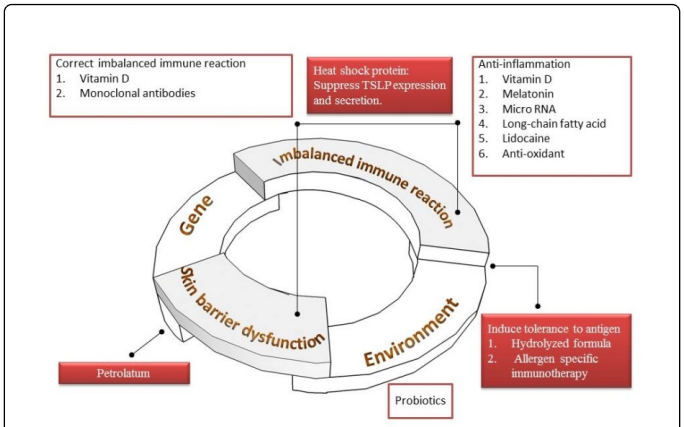

Figure 2: The potential treatments for atopic dermatitis. Therapeutic approaches in the treatment of AD include anti-inflammation, correction of Th2/Th1 or Th22/Th1 imbalance, and induction of oral tolerance to antigen.

Conclusion

AD is a complex genetic disease arising from several gene-gene and gene-environment interactions. A mechanistic advance in AD could be achieved by establishment of mouse models of AD and by oral tolerance. Therapeutic approaches in the treatment of AD include anti-inflammation, correction of Th2/Th1 or Th22/Th1 imbalance, and induction of oral tolerance to antigen (Figure 2). Since half of the patients with AD lack specific IgE against allergen, the pathogenesis of different phenotypes still needs to be clarified. Through novel therapies such as cytokine-targeting therapy, miRNA or suppression of thymic stromal lymphopoietin, patients with AD could have better quality of life with less morbidity.

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