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New pathogenic and therapeutic paradigms in atopic dermatitis

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ABSTRACT

Atopic Dermatitis (AD) is a common inflammatory skin disease with increasing prevalence in industrialized countries. Up to one-third of adults with AD have moderate-to-severe disease, leading to a large, unmet need for effective treatments. While current therapeutics focus mainly on symptom control, major advances have been made in translational research, with the goal of developing drugs to eradicate disease.

A translational revolution is now occurring in AD, similar to the one that has occurred in psoriasis over the past decade. Research has focused on elucidating immune pathways responsible for AD, including Th2, Th22, and Th17 pathways, with testing of immune antagonists specific to these axes. An IL-4R antagonist, dupilumab, is the first drug that shows great promise in phase II trials. By studying clinical and molecular responses following treatment with specific immune antagonists, our understanding of and ability to treat AD will expand.

1. Introduction

Atopic Dermatitis (AD) is the most common inflammatory skin disease, with rising prevalence in industrialized nations [1,2]. It is present in up to 25% of children in the U.S., and while only one-third of cases persist into adulthood, the vast majority of these children will go on to develop asthma or allergic rhinitis later in life [3,4]. This pattern of onset has been termed the atopic March, and atopic dermatitis represents the earliest possible point of intervention in this series of related diseases.

The lifetime prevalence of AD in adults is 2–10%, but remains lower in rural and non-industrialized countries [5]. This observation has led to controversy surrounding the "hygiene hypothesis", in which lack of exposure to antigens in early life creates immune imbalances favoring a pro-allergic Th2 response, leading to a predilection for atopic disease [6–8]. Of all adults with AD, one-third are classified as having moderate to severe disease, representing a large and unmet need for safe, effective and reliable treatments [9].

Molecular medicine is radically changing the AD pathogenic and therapeutic landscape, similar to the process in psoriasis over the past decade [10,11]. Translational research accelerates therapeutic development by identification of pathogenic pathways that foster development of drugs to target specific components of these pathways. Efficacy can then be proven if suppression of the pathway is associated with improvement of clinical and tissue pathology.

However, several criteria are required for this translational approach to succeed in AD. First, investigators must have a well-defined cellular and molecular disease phenotype and a comprehensive understanding of immune circuits, although testing with targeted inhibitors can certainly contribute to this understanding. Additionally, well-established biomarkers of disease activity are vital to quantifying response to treatment, especially in a disease known to have high rates of clinical improvement in placebo cohorts [12] and diverse clinical phenotypes. Lastly, in order to test

Abbreviations: AD, Atopic Dermatitis; ADSI, atopic dermatitis severity index; AMP, anti-microbial peptide; CCL, chemokine (C–C) motif ligand; CCR, chemokine (C–C) motif receptor; CsA, cyclosporine A; CTRH2, chemoattractant receptor-homologous molecule 2; DC, dendritic cell; DEFB1, defensin, beta 1/HBD1; EASI, Eczema Area and Severity Index; FcεRI, Fc receptor, IgE, high affinity; FLG, filaggrin; iDC, inflammatory dendritic cell; IDEC, inflammatory dendritic epidermal call; IFN-γ, interferon-gamma; IgE, immunoglobulin E; IL-4R, interleukin-4 receptor; IVL, involucrin; K16, keratin 16; LC, Langerhans cell; LOR, loricrin; NOD, nucleotide-binding oligomerization domain; NB-UVB, narrow-band ultraviolet B; PBMC, peripheral blood mononuclear cell; PDE4, phosphodiesterase-4; SCORAD, scoring of atopic dermatitis; SPINK5, serine peptidase inhibitor, Kazal type 5; Th, T-helper; TLR, toll-like receptor; TMEM79, transmembrane protein 79/MATT; TSLP, thymic stromal lymphopoietin.

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an immune-based hypothesis, researchers require access to drugs that will selectively target components of the immune system. The first example of the successful translational model in AD has been recently shown with the IL-4R antagonist, dupilumab [12,13]. This landmark trial marks an important turning point in the study and treatment of AD, demonstrating reversal of epidermal pathology with a specific immune antagonist targeting the Th2 pathway. Additional targeted therapies are currently being studied in the clinic, with the hope of shifting the paradigm of AD management from symptom control to disease eradication.

2. Clinical characteristics/clinical phenotypes

A diagnosis of AD is generally made on clinical criteria alone [14]. The disease is characterized by pruritic, eczematous, erythematous, often excoriated plaques with serous exudate and crusts (Fig. 1). The lesions are poorly demarcated, often involve the face and flexor surfaces, and are prone to development of cutaneous bacterial and viral infections [15]. The appearance of AD varies according to disease phase; the acute stage manifests as bright red, oozing lesions that transform into dull, pink-to-red lichenified plaques in chronic lesions.

With reports of increasing prevalence of AD in both adults and children around the globe [16], it is becoming clear that not all forms of AD are epidemiologically and/or clinically equal. Different AD phenotypes have unique characteristics, including age of onset, areas of involvement, increased skin thickness, levels of serum biomarkers (IgE), and rates of infectious complications [17–19]. For example, in infants AD is common on the face, while in adults, involvement of the hands and folds is often seen [20]. Additionally, roughly 80% of AD patients show reactivity to allergens based on elevated serum IgE or immediate skin test reactivity, while 20% have normal IgE levels and lack of sensitization toward environmental allergens [21]. These "intrinsic" patients have been shown to exhibit lower rates of atopic March and filaggrin mutations compared with their extrinsic counterparts [21,22], although recent studies suggest that these patients may show evidence of sensitization to uncommon antigens that are not assessed on standard panels, such as metal or microbial antigens [21,23]. We have also shown that while both intrinsic and extrinsic AD show similar Th2 polarization, much higher Th17 and Th22 activation is seen in intrinsic AD, with potential therapeutic relevance [24]. These variants are probably influenced by inherent genetic factors and environmentally controlled humoral and cell-mediated immune responses.

3. Genetics

AD has a strong familial component. One recent twin study showed that 82% of AD risk is determined by genetic factors, and only 18% by environmental factors [25]. Genes that have been associated with AD encode factors in the innate and adaptive immune systems as well as proteins that regulate the terminal differentiation of keratinocytes [26–28]. Adaptive immune response genes associated with AD include known Th2 cytokines and chemokines (IL4, IL4RA, IL13, TSLP, CCR5), while several genes have also been identified in the innate immune system, including NOD1, NOD2, TLR2, CD14, and DEFB1, which play an important role in the immune defense against infection. Several barrier genes were also associated with AD, including filaggrin/*FLG* (most common), loricrin/*LOR*, involucrin/*IVL*, *SPINK5*, and *TMEM79/MATT*. Loss-of-function mutations in *FLG*, which encodes an intermediate-filament protein filaggrin, have been found in 10–50% of AD patients, depending on the population [29–32]. AD patients with homozygous null mutations of *FLG* have earlier onset of disease, more

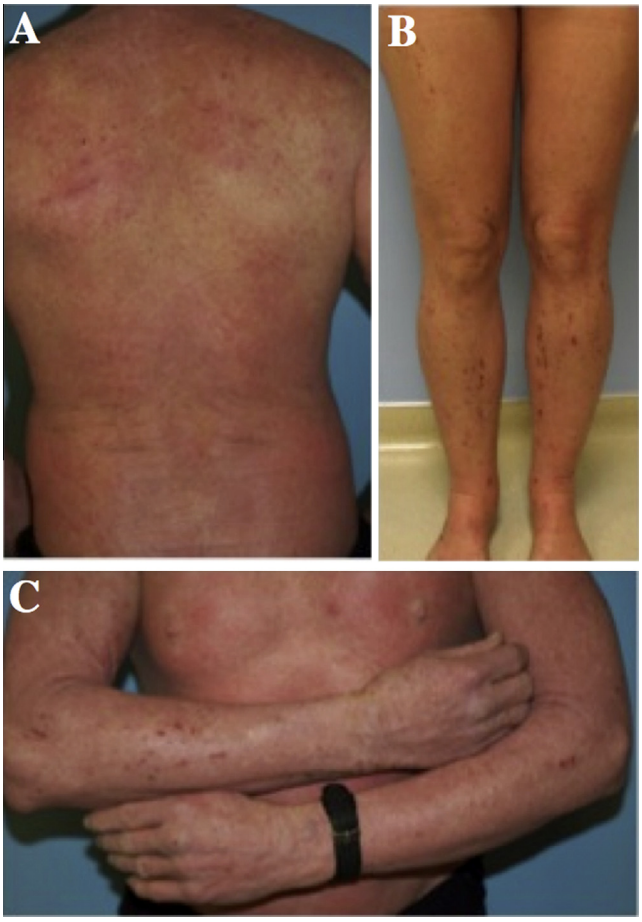

Fig. 1. Clinical images of AD patients with severe disease on the (A) back, (B) legs, and (C) trunk and arms. In contrast to psoriasis, the borders of the lesions are poorly demarcated and blend in with surrounding skin.

palmar hyperlinearity, greater risk of allergen sensitization, and increased pH in their stratum corneum in comparison to those with heterozygous *FLG* mutations. However, the rate of *FLG* mutations in the American AD population is only 10%, suggesting the predominance of other factors in creating the AD phenotype.

4. Epithelial skin barrier dysfunction in AD: "outside-in"

The association of *FLG* mutations with atopic dermatitis has prompted further support of the "outside-in" hypothesis, or the idea that functional disruption of the epidermal barrier is the primary pathogenic process in AD [30,33–35]. In mice, *FLG* mutations result in flaky skin on the tails, with a barrier abnormality that predisposes them to penetration of irritants and allergens, and resulting increased inflammatory processes in the skin [36]. However, the precise cellular implications of this mutation in humans are still being elucidated. It is believed that loss-of-function mutations in *FLG* may change the shape of epidermal corneocytes, therefore disrupting their function and also altering the organization of extracellular lamellar bodies [30,33].

Patients with *FLG* mutations are not only predisposed to the formation of AD, but were also found to have early onset of recalcitrant AD, and disease that is more likely to be associated with asthma, food allergy, and cutaneous infections [37–39].

Recent studies in mice have stressed the interaction of *FLG* with other genes. Mouse models of AD have shown that the propensity to develop eczema spontaneously requires the FLG mutation and a