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Immunologic Aspects of Atopic Dermatitis

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SUMMARY Atopic dermatitis/eczema is a chronically relapsing, pruritic, and inflammatory skin disease. The term "atopic eczema/dermatitis syndrome" covers the "extrinsic" and "intrinsic" atopic dermatitis. The pathogenesis of atopic dermatitis includes complex interaction between the genetic background, skin barrier defects, abnormalities in innate and adaptive immunity, abnormalities of humoral and cellular immunity, and environmental influences. Understanding the immunopathogenesis of atopic dermatitis leads to new diagnostic and therapeutic approaches. The targets in atopic dermatitis are innate immunity including improvement of skin barrier defects by supplementing lipids or inhibiting proteases, and regulating antimicrobial peptides, adaptive immunity, and induction of regulatory T cells.

KEY WORDS: atopic dermatitis, atopic eczema/dermatitis syndrome, immunopathogenesis of atopic dermatitis, regulatory T cells, adhesion molecules

INTRODUCTION

Atopic dermatitis (AD) or atopic eczema is a chronically relapsing, pruritic, and inflammatory skin disease. AD is associated with a personal or family history of atopy such as asthma and/or allergic rhinitis, or AD itself (1,2). The term "atopic eczema/dermatitis syndrome" (AEDS) covers the "extrinsic" and "intrinsic" AD (3-5). The "extrinsic" form of AD is associated with IgE-mediated sensitization and involves 70%-80% of patients. The "intrinsic" form of AD, also called "nonatopic eczema", does not imply IgE-mediated sensitization, does not include associated respiratory disease, and involves 20%-30% of patients (3-5). Eosinophilia is associated with both forms of AD, as well as IgE to *Staphylococcus aureus (S. aureus)* (3,6). AD may affect 20% or more children in westernized societies, making it one of the most common of all noninfectious childhood ailments (7). Around 85% of affected individuals develop the disease before 5 years of age (1). More than 25% of children in northern Europe are affected (8). There is an especially high prevalence in children and infants (9,10). AD may persist into adulthood in up to 60% of patients (2,11). The prevalence of AD

Acta Dermatovenerol Croat
2009;17(3):226-234

in adults is 1%-3%. Its prevalence has increased two- to threefold during the past three decades in industrialized countries but remains much lower in countries with predominantly rural or agricultural areas (3,12). The Eczema Area and Severity Index (EASI) is used by dermatologic investigators worldwide to assess the eczema disease severity. The Self-Administered EASI was found to be a valid measure of AD severity in old age groups (13).

THE PATHOGENESIS OF ATOPIC DERMATITIS

The pathogenesis of AD is a complex interaction between genetic aberrations, skin barrier defects, abnormalities in innate and adaptive immunity, and abnormalities of humoral and cellular immunity, environmental influences, and stress.

Polygenetic aberrations include predisposition to immune system dysregulation and genetic aberration of epidermal barrier that is nowadays seen as the primary event (14). Defects in innate immunity are clinically expressed by increased susceptibility to bacterial, fungal and viral infection, and include decreased antimicrobial peptides derived from keratinocytes such as B-defensins 2 and 3, LL-37, and dermocidin from sweat; defects in receptors such as TLR2 gene, soluble CD14 and interleukin-1 (IL-1) receptor; defects in stratum corneum barrier function such as mutations of genes of the keratin cytoskeleton such as the filaggrin (FLG), involucrin and loricrin, neutrophil defects with impaired chemotactic and phagocytic functions, and decreased levels of the intercellular lipids like sphingosine and ceramide, and epidermal proteases (3,14,15). The epidermal differentiation complex (EDC) on chromosome 1q21, where the FLG gene is located, is a shared susceptibility locus for both AD and psoriasis (16,17). The EDC contains a dense cluster of genes, such as loricrin, trichohyalin, and involucrin, all of which play a role in terminal differentiation of the epidermis. FLG is a major susceptibility gene for AD. The FLG gene encodes profilaggrin, a protein that is essential for the formation and hydration of the skin barrier as it contributes to the water-binding capacity of the stratum corneum. It has been demonstrated that null mutations in the FLG gene cause the common keratinizing disorder ichthyosis vulgaris (18). The mutation of FLG gene is loss-of-function mutation (17,19,20). Two highly prevalent null mutations of the FLG gene are R501X and 2282del4, and they significantly predispose European individuals to early-onset, severe, and persistent AD, and also to the form of asthma that is associated with AD (19). Several prevalent FLG mutations are coupled with the addition of multiple rarer family-specific mutations which, when combined, have a significant influence on AD susceptibility (17,20). The mutations are found in 50% of all AD patients indicating that defects in barrier proteins other than FLG contribute to barrier dysfunction and that there are compensatory mechanisms (14). Additionally, two novel FLG mutations have been described in Japanese patients as the first non-European FLG mutations (21). Impaired barrier allows the entry of allergens and microbial colonization of AD skin. Microorganisms produce proinflammatory cytokines, which amplify the inflammatory response in the skin. IL-4 that is responsible for the expression of fibronectin that binds *S. aureus*, topical corticosteroids, topical immunomodulators and deficiency of antimicrobial proteins are responsible for higher colonization of *S. aureus* on non-lesional, and both acute and chronic AD skin lesions (15). Scratching and microbial toxins activate keratinocytes to release proinflammatory cytokines and chemokines that induce expression of adhesion molecules and amplify the inflammation (3,15).

Moreover, intrinsic and extrinsic AD show immunologic differences in cell and cytokine pattern in peripheral blood and in the affected skin (3).

Extrinsic AD is mainly affected by environmental factors and is therefore associated with higher levels of IL-4 and IL-13 that are responsible for IgE production by B-lymphocytes and for hypersensitivity type I and IgE-mediated delayed hypersensitivity reactions, and IL-5 (3-5).

Intrinsic AD has mainly hereditary influence and other internal procedures that are involved and is therefore less associated with IL-4 and IL-13, and this observation can be in relation with no IgE sensitization. Also, a proportion of these patients react on atopy patch test with aeroallergens, meaning that an antigen T-cell response is observed without specific IgE production (3-5). Intrinsic AD type may switch to an IgE-associated type over time, which underlines the necessity of repeat allergologic testing over years.

IMMUNOLOGIC BACKGROUND

Early hypersensitivity type I, IgE-mediated delayed hypersensitivity and delayed hypersensitivity type IV (cell-mediated immunity) are involved in the pathogenesis of AD. The pathogenetic aspects of AD include imbalance of Th1 and Th2 cells (Th1/Th2 responses), delayed eosinophil apop-

Acta Dermatovenerol Croat
2009;17(3):226-234

tosis, IgE-mediated facilitated antigen presentation by epidermal dendritic cells (DCs), altered prostaglandin metabolism, and intrinsic defects in keratinocyte function (3). The concept of extrinsic *versus* intrinsic AD type is attractive (22). In extrinsic AD, there is exogenous elicitation by contact with aero- or food allergens, which are important for initiating adaptive immune response.

In both types of AD, there is sensitization to human proteins with IgE production. The sensitization to Hom S 1 has been postulated as the basis of intrinsic AD and it may play a part in the chronicity of AD in the absence of actual exogenous allergens (23). A stress-inducible enzyme, manganese superoxide dismutase of human and fungal origin, might also act as an autoallergen in intrinsic AD. Such sensitization may be induced primarily by exposure to *Malassezia sympodialis*, by molecular mimicry leading to cross-reactivity (23,24). In these cases, other effector mechanisms such as T cells or eosinophils play a critical role.

The concept of AD implies Th2 cytokines in acute phase, becoming Th1 cytokines in chronic phase, and finally progressing to an autoimmune disease with IgE antibodies against autologous epidermal proteins. Th2 cells are characterized by IL-3, -4, -5, -9 and -13 secretion. Th1 cells are important in inflammatory delayed hypersensitivity producing IFN-γ, granulocyte macrophage-colony stimulating factor (GM-CSF), and IL-12 (23).

REGULATORY T CELLS

Furthermore, the role of regulatory T cells (Tregs) in AD pathogenesis has yet to be determined (25,26). Tregs are a specialized subset of T cells that actively suppress activation of the immune system and thereby maintain immune system homeostasis and tolerance to allergens. Tregs may directly prevent the activation and function of non-regulatory effector T cells, either Th1 or Th2 effector cells and/or Tregs may inhibit antigen presentation by DCs to effector T cells (25,27-29).

The subtypes of Tregs are natural CD25+Tregs (nTregs) and adaptive/inducible Tregs.

nTregs develop in the thymus; they are specific for auto/self-antigens; they express the CD25 (IL-2 receptor) molecule, cytotoxic T-lymphocyte antigen-4 glucocorticoid-induced tumor necrosis factor receptor, and the transcription factor forkhead fox protein 3 (Foxp3) (27). The expression of Foxp3 highly correlates with suppressor activity, primarily in mice and less clearly in humans (28).

In some patients with AD, nTregs can be higher than in non-atopic and asthmatic patients (25,29). However, when stimulated with staphylococcal enterotoxin B superantigen, which is present at high levels on the skin of AD patients, the nTregs lose their suppressive function, suggesting that environmental factors inhibit their function. Also, it may be that the increase in the number of nTregs is irrelevant. It may be that adaptive Tregs are of greater importance, and that adaptive Tregs are deficient in AD (29).

Adaptive Tregs are Th1 and Th3; they expand after encounter with exogenous allergens in the periphery from naïve CD4+ T cells under the influence of semi-mature DCs, or derive from the same dedicated Treg lineage as do nTregs by differentiation in the thymus, but then expand in the periphery after encounter with allergen. They secrete high levels of IL-10 and transforming growth factor-beta (TGF-β), and exert suppressive action on both Th1 and Th2 (30). Th3 cells secrete TGF-β with various amounts of IL-4 and IL-10, suppressing both Th1 and Th2 cells (31,32). IL-4 has been shown to act as a differentiation factor for TGF-β-secreting Th3 cells (33).

The suppressive effects of IL-10 and TGF-β may be due to direct effects on effector T cells or possibly by direct cell-to-cell contact of suppressors with effector T cells. Alternatively, IL-10 may inhibit effector T cells by effects on antigen-presenting cells with increased monocyte production of indoleamine 2,3 dioxygenase, which catabolizes tryptophan (29,34). IL-10 and TGF-β might inhibit DC function by reducing the expression of co-stimulatory molecules and increasing the production of IL-12.

Both types of Tregs actively regulate Th2 responses to allergens in healthy donors, whereas their suppressive function is impaired in allergic individuals, and therefore Tregs could play a major role in maintaining a healthy immune response to allergens (35).

IMMUNOHISTOPATHOLOGY AND BIPHASIC PATTERN OF T-CELL ACTIVATION

Immune responses in AD include a biphasic pattern of T cell activation. There are different immunologic manifestations in the unaffected, acute and chronic AD skin.

Nonlesional AD skin shows sparse dermal perivascular cellular infiltrate consisting primarily of T lymphocytes. Immunohistologic analysis shows a significantly greater number of Th2 cells express-

ing IL-4 and IL-13 but not IL-5 and IFN-γ messenger ribonucleic acid (mRNA) compared to normal nonatopic skin (3,36-38).

Acute AD skin shows sparse epidermal infiltrate primarily consisting of T lymphocytes, and there is marked perivenular inflammatory cell infiltrate in the dermis consisting predominantly of Th lymphocytes and in less number of Langerhans cells (LCs), inflammatory dendritic epidermal cells (IDECs) and macrophages (3,39). Immunohistologic analysis of cells shows a significant increase in the number of cells expressing IL-4, IL-5 and IL-13 mRNA but not IFN-γ and IL-12 mRNA compared to nonlesional AD skin or normal nonatopic skin (3,36,40). However, acute skin lesions have a predominance of IL-4 and IL-13 expression (3). This is called Th2-type cytokine pattern (36). The authors demonstrated specific regulatory function of CD30+ T cells in acute AD, in accordance with the results reported by Caproni et *al*. (41-43).

Recently, the influx of CD4+ lymphocytes has been related to the up-regulation of IL-16 in AEDS skin lesions. The presence of circulating beta-chemokines (Eotaxin and RANTES) and IL-16, which were investigated in children with AEDS, correlates with the disease severity (36,44). Soluble CD30 in peripheral blood is a marker of Th2 immune response related to AEDS disease activity, and so is the presence of CD30 molecules in the skin (42,44).

LCs play a predominant role in the initiation of the allergic immune response and conversion of prime naïve T cells into T cell of the Th2 type (42).

Many other inflammatory cells and cell types including keratinocytes, vascular endothelial cells are involved in the inflammation. Keratinocytes, eosinophils and basophils stimulate Th2 response.

The keratinocyte-derived IL-7–like cytokine thymic stromal lymphopoietin (TSLP) is critically needed for evoking Th2 response (3,14). TSLP could significantly activate DCs to induce an inflammatory Th response characterized by high tumor necrosis factor-alpha (TNF-α) and low IL-10 (45). Furthermore, human TSLP can potentially activate CD11c+ DCs and induce the production of Th2-attracting chemokines thymus and activation-regulated chemokine (TARC), also known as CCL17; and macrophage-derived chemokine (MDC), also known as CCL22 (46,47). Therefore, TSLP expression is associated with LCs migration and activation *in situ*.

Moreover, eosinophils and basophils derive IL-25, a distinct member of the IL-17 cytokine family, which enhances the expansion and functions of TSLP-DC-activated Th2 memory cells, thus augmenting allergic tissue inflammation (48). Also, there are substantial numbers of Th17 cells in acute, but not in chronic AD, indicating that IL-17 and IL-22 could play important roles in acute AD (49,50). Furthermore, Th17 cells are a subset of T cells producing IL-17 and are highly proinflammatory and induce severe autoimmunity. The role of Th17 cells in allergy is still largely unclear, but these cells could be important in regulating neutrophilic inflammation in acute airway inflammation (51). Therefore, in acute AD there is Th2/Th17 response.

There is also over-expression of IL-16 (3). IL-16 is an LC cytokine that attracts Th cells in acute lesions and therefore plays a role in the initiation of inflammation (3,36,52). IL-13 and IL-4 stimulate B lymphocytes for IgE synthesis, and also induce the expression of vascular cell adhesion molecule-1 (VCAM-1) (3,36). Therefore, they may play a role in the migration of eosinophils and mononuclear cells in acute AD skin lesions (3,41). IL-4 also inhibits the production of IFN-γ. IL-5 plays an important role in differentiation, vascular adhesion and survival of eosinophils. Eosinophils also intermediate and release cytotoxic granules and contribute to tissue injury but also modulate T cell function by its own cytokines.

There is an elevated production of prostaglandin E2 (PGE2) by peripheral monocytes (53). PGE2 has at least two potential roles in the initiation of AD. Firstly, it reduces IFN-γ production by Th cells, thereby favoring the initial, dominant Th2 immune response (53). Secondly, it directly enhances IgE production by B lymphocytes with an increased secretion of IL-4, IL-5 and IL-13. Mast cell chymase may induce eosinophil infiltration into AD lesional skin. IgE is further involved in early hypersensitivity type I.

Chronic AD skin shows IgE-bearing LCs and IDECs in the epidermis. Dermal mononuclear infiltrate is predominated by macrophages, whereas T cells, eosinophils and mast cells are also increased but to a lesser extent. Immunohistologic analysis of cells shows a significant increase in the number of cells expressing a significantly greater number of IL-13, IL-4, IL-5 and IFN-γ mRNA cells than in normal or nonlesional skin of AD patients, while there is a greater number of IL-5, IL-12, GM-CSF and IFN-γ mRNA cells and fewer IL-13 and IL-4 mRNA compared to acute AD skin lesions (3,36). T cells constitute the majority of IL-5 expressing

Acta Dermatovenerol Croat
2009;17(3):226-234

cells. There is also a significantly greater number of activated IL-5 mRNA-expressing eosinophils than in acute lesions (3,36). IL-5 plays an important role in differentiation, vascular adhesion and survival of eosinophils.

IL-12 is produced by eosinophils and/or macrophages, and its function is to induce Th cells to differentiate and mature into Th1 cells (36,54). Therefore, IL-12 may account for the termination of the Th2-type cytokine pattern or Th2/Th17, which is observed in acute lesions, and it also initiates the switch to Th1 cell development in chronic lesions (36,54,55).

However, not all responsible factors for the switch from a Th2/Th17 to a Th1-dominated allergic tissue response are fully understood. FcεR1 engagement of IDECs also induces IDECs to produce the Th1-promoting cytokines IL-12 and IL-18 (56). A role of TSLP in this switch has been implicated as TSLP- and CD40 ligand-activated DCs induce IFN-γ-producing proallergic cytotoxic cells. Such cells have also been implicated in apoptosis of keratinocytes in eczematous dermatitis (57,58).

TGF-β and IL-11, mainly produced by eosinophils, are the major profibrotic cytokines with type I collagen deposition during chronic AD (3,49).

Pruritus in AEDS is not only caused by histamine, neuropeptides, neurotransmitters, proteinases, arachidonic acids derivatives, kallikrein 7 and cytokines. IL-31, a Th2 cytokine, could be a major factor of pruritus. Its receptor is abundantly expressed in dorsal root ganglia (59-61).

GM-CSF, produced by keratinocytes, enhances eosinophil and macrophage survival in chronic lesions (36). Therefore, Th1-type cytokines, IL-2 and IFN-γ, account for the persistence of inflammatory response in AD (36).

In chronic AD lesions LCs are present in increased numbers and have increased amounts of IgE bound to FcεR1. Also, LCs have been shown to be hyperstimulatory to T helper cells and can activate T helper cells to Th2 phenotype in the initiating phase of the disease.

ANTIGEN-PRESENTING DENDRITIC CELLS, ADHESION MOLECULES AND CHEMOKINES

Indigenous and non-indigenous DC subpopulations in AD skin are IDEC, LCs, interstitial/dermal DC (IDDC), immature and mature plasmacytoid DC (pDCs) and dermal DC (DDC), and they differ in immunophenotype. pDCs are an important component of the innate response. The skin of AD patients harbors relatively small numbers of pDCs when compared with the skin of patients with other inflammatory skin diseases (62).

pDCs with toll-like receptors recognize microbial structures and acquire apoptotic and cytotoxic properties (63). This partial deficiency of pDC in AD might also contribute to the impaired host defense of atopic skin against microbial assault.

It appears that both LC cells and IDECs are pathophysiologically relevant antigen-presenting cells in AD and the majority of these cells exhibit surface-bound IgE, with FcεR1 being the critical IgE-binding structure (3,38,64). Therefore, the immediate (IgE-mediated mast cell type), late (IgE-mediated Th2-type) and delayed (IgE-independent Th1 type) allergic reactions are involved.

IDEC in AD is a major population in lesional skin. There is MR-mediated endocytosis, processing and presentation of mannose-rich pathogens such as *Malassezia furfur*. There is IgE-facilitated allergen presentation.

pDC comprise a minor subpopulation with major phenotypic features CD4+, CD11c, CD123+, CD45RA+, BDCA-2+. Depending on their state of activation pDC can stimulate different T cell subsets such as Th1, Treg (14).

The LC's major phenotypic features are CD1a+, Birbeck granules/Lag/Langerin, CD207+, HLA-DR+ and less FcεR1. The IDEC's major phenotypic features are FcεRI, HLA-DR, CD36+, CD206+ and less CD80+ and CD86+ (15).

Activated LCs with antigen *via* FcεR1 contribute to the Th2 response in acute skin lesions as LCs play a predominant role in the initiation of the allergic immune response with migration of LCs into regional lymph nodes and conversion of prime naïve T cells Th2 cells (23,65). Furthermore, activated LCs induce the release of chemotactic signals and recruitment of IDECs, monocytes and T cells *in vitro* with high amount of proinflammatory signals (23).

Additionally, IDECs can skew prime naïve T cell immune response in the Th1 response by IL-12 and IL-18 (56). Therefore, IDECs are also responsible for the switch of the initial Th2 response into Th1 response.

Natural killer (NK) cells are bone marrow derived lymphocytes which constitute a major component of the innate immunity (66). NK cells stimulate DC maturation and function upon direct con-

tact between these cells. The yeast *Malassezia* can act as an allergen in AEDS and induce the maturation of DCs. Therefore, NK cells and DCs can interact in the skin and *Malassezia* affects the interaction between the two cell types (66). NK cells may play a role in regulating DCs in AEDS.

Memory T cells are generated from activated/effector T cells following an initial antigen encounter and memory T cells are distinguished by their ability to mediate rapid effector responses upon antigenic recall. In contrast to naïve responses, memory responses can be elicited by lower antigen concentrations and reduced co-stimulatory requirements, enabling rapid effector functions (67).

Memory T cells that express the homing cutaneous lymphocyte-associated antigen (CLA) are called skin-homing T cells. This is essential for recruitment of these cells to the skin where they contribute to inflammation in the skin (15).

Adhesion molecules also additionally play an important role in the homing of T cell subsets into allergen-exposed skin of atopic individuals. These are E-selectin on endothelium, L-selectin on leukocytes, P-selectin on endothelium and activated platelets, intercellular adhesion molecules (ICAM-1, ICAM-3) and VCAM-1 (68).

Keratinocytes, mast cells and dendritic cells derive TNF-α and IL-1α and induce the expression of ICAM-1 and VCAM-1 (68).

IL-4 and IL-13 also induce the expansion of VCAM-1 and facilitate the migration of eosinophils and mononuclears (3,41).

Chemotactic cytokines are chemokines that participate in the specific leukocyte subset recruitment to the sites of inflammation. These are CCL27 with its receptor CCR10 on memory T cells, CCL20 with its receptor CCR6 on dendritic cells, CCL17 of vascular endothelium with its receptor CCR4 and CCR10 ligand on memory T-cells, CCL8 with receptor on a subset of T cells and dendritic cells, CCL11, CCL5 with its receptors CCR2 and CCR3 on eosinophils, and CCL18 that interact with CLA-bearing T-cells. They are derived from different cells such as keratinocytes, LCs, IDECs, endothelium and macrophages, while receptors are on memory T cells, DCs and eosinophils (15).

CONCLUSION

Despite conventional therapy, immunopathologic findings in AD lead to new diagnostic and therapeutic approaches. The targets are innate immunity with restoring the skin barrier by supplementing lipids or inhibiting proteases, regulating antimicrobial peptides, IgE-blocking antibodies or with infliximab targeting TNF-α. Additionally, targeting adaptive immunity with alefacept or efalizumab on T cells, with rituximab on B-cells; targeting IL-4, IL-13, IL-17, IL-31 or TSLP could lead to inhibition of Th2 cells, pruritus, and improvement of skin barrier and expression of antimicrobial peptides. Novel therapeutic approaches could also include induction of Tregs as a promising approach to limit abnormal Th2 immune responses.

Despite the progress in the pathogenesis, therapeutic options are still limited and far from optimal.

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