Atopic dermatitis is a chronic inflammatory skin disease that causes significant morbidity in affected individuals. It is characterized by dysregulated immune responses that consist of an increased systemic Th2 response and a combination of Th2 and Th1 responses in the skin lesions. In this article, we review factors that contribute to these abnormal responses, including key effector cells of the immune system, chemokines, defective skin barrier, genetic predisposition, and environmental triggers. Understanding these pathomechanisms may improve our current therapies for atopic dermatitis.

Introduction
Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with genetic predisposition, cutaneous hyperreactivity to environmental triggers, and immune dysregulation [1•]. It affects approximately 10% to 20% of children and 2% of adults. Persistent AD is characterized by pruritus and an eczematous rash in the flexural areas. In young children, the rash may be distributed primarily on the extensor areas and on the face. In severe patients, the eczematous rash may be generalized, covering most of the body and extremities. AD patients, particularly those with moderate-to-severe disease, are affected by significant morbidity, including sleep loss, emotional abnormalities, social dysfunctions, and school or work loss. Because there is currently no cure for this disease, a precise understanding of the underlying mechanisms is critical for development of more effective treatments. In this review, we summarize the current progress in our understanding of the pathophysiology of AD and implications for therapy.

Systemic Immune Response in AD
In young children, AD is a major risk factor for the development of allergic rhinitis and asthma. AD is frequently the initial manifestation of a process known as the “atopic march,” which progresses from AD to the development of allergic rhinitis and asthma. In experimental models of AD, the induction of allergic skin inflammation by epicutaneous application of allergens has been found to augment the systemic allergic response and airway hyperreactivity characteristic of asthma [2].

There are at least two forms of AD. The majority of patients have increased total serum immunoglobulin (Ig)E and allergic sensitization to food or inhalant allergens. This form of AD is known as extrinsic AD (EAD). This is in contrast to a minority (20%–30%) of patients with so-called intrinsic AD (IAD), who have normal total serum IgE without apparent allergen sensitization. EAD patients have been found to have a higher expression of the high- and low-affinity receptor for IgE (FcεRI and FcεRII/CD23) on their monocytes than IAD patients [3]. Because it is known that interleukin (IL)-4 plays a crucial role in upregulating IgE receptors on monocytes, these differences may be attributed to an increased frequency of genetic polymorphisms in the IL-4 and IL-4–receptor α chain (IL-4RA) of EAD as compared to IAD patients [3]. However, both forms of AD have increased eosinophilia and serum IL-13 [3], suggesting the importance of Th2 cells in the pathogenesis of atopic diseases. The reasons for the increased Th2 responses (eosinophilia and IL-13 production) in AD patients are not clear. Possible mechanisms include increased Th1 cell apoptosis or an increased expression of suppressor of cytokine signaling-3 (SOCS-3), which inhibits Th1 cell differentiation, skewing the immune responses in these patients toward a Th2 response [4].

Immune Responses in AD Skin
Clinically unaffected skin in AD demonstrates an increased number of Th2 cells expressing IL-4 and IL-13, as compared with normal nonatopic skin [5]. The predominance of Th2 cytokines in unaffected AD skin may be due in part to the presence of a specialized subtype of Th cells expressing the skin-homing receptor, cutaneous...
lymphocyte-associated antigen (CLA). It has recently been shown that up to 98% of these CLA+ Th cells reside in the skin and that most of them are IFN-γ-expressing Th1 cells under normal conditions [6••]. In AD, however, CLA+ Th cells are predominantly Th2 cells, expressing IL-4 and IL-13. In addition, antigen-presenting cells (APC) in unaffected AD skin have been shown to have increased expression of FcεRI, compared to those in normal non-atopic skin [7]. Therefore, the presence of abnormal CLA+ Th2 cells and FcεRI-expressing APC are likely the main contributors to a Th2 predominance in unaffected AD skin.

The skin lesions of EAD patients contain a higher expression of Th2 cytokines (IL-5 and IL-13) than that of IAD patients [8]. However, both groups of patients have an increased expression of Th2 cytokines (IL-4, IL-5, and IL-13) in their skin lesions, compared to that in the normal skin of nonatopic controls [5,8]. In acute AD lesions, the expression of IL-4 and IL-13 has been shown to be significantly higher than that in chronic lesions. IL-4 is important for the differentiation of Th2 cells. IL-13 has also been shown to be important in generating a cutaneous Th2 response, independent of IL-4 [9•]. IL-13 may directly induce the expression of IL-5 and infiltration of eosinophils in the skin [9•]. IL-13 also induces keratinocytes to produce macrophage-derived chemokine (MDC/CCL22), which further attracts CCR4+ Th2 cells [10]. IL-16 and thymus and activation-regulated chemokine (TARC/CCL17), produced by epidermal APC, may also contribute to influx of Th2 cells into AD lesions [11,12].

Chronic AD lesions have been found to have an increased expression of both Th2 cytokines (IL-5) [5] and Th1 (IL-12 and IFN-γ) cytokines compared to normal skin. The chronic lesions of EAD patients also have an increased infiltration of eosinophils compared to that of IAD patients [13]. This difference may be due to an increased expression of IL-13 and IL-5 in EAD lesions [8]. IL-11, a cytokine associated with tissue remodeling, has been found to be increased in chronic AD lesions and may, therefore, be involved in collagen deposition and remodeling of AD skin lesions [14]. The expression of a chemokine, cutaneous T cell-attracting chemokine (CTACK/CCL27), is increased in the subacute lesions of AD [15]. The expression of this chemokine is induced in keratinocytes by the combined action of tumor necrosis factor (TNF)-α and TARC [16]. CTACK attracts a mixture of CCR10+ Th1/Th2 cells that are characteristics of chronic AD lesions [17]. Activation of keratinocytes by interferon (IFN)-γ leads to the production of other chemokines, including IFN-γ-inducible protein-10 (IP-10/CXCL10), monokine induced by γ-IFN (MIG/CXCL9), and IFN-γ-inducible α-chemoattractant (I-TAC/CXCL11) [18]. These chemokines, attract more Th1 cells via the CXCR3 receptor to perpetuate inflammation of chronic AD lesions. Another chemokine, fractalkine (FKN/CX3CL1), may also contribute to the chemotaxis of T cells into chronic AD lesions via its receptor, CX3CR1 [19]. The increased expression of chemokines such as RANTES/CCL5, monocyte chemotactic protein-4 (MCP-4/CCL13), and eotaxin/CCL11 in AD lesions are likely to contribute to the infiltration of CCR3+ eosinophils, macrophages, and Th2 cells into AD lesions.

Key Effector Cells in AD Skin

T cells

These cells are a major source of cytokines that contribute to the pathogenesis of acute and chronic AD lesions. The sequential role of Th2 and Th1 cytokines in the development of acute and chronic AD lesions, respectively, was initially shown by atopy patch testing (APT) with house dust mite (HDM) allergens on AD skin: an initial phase with predominantly IL-4-expressing Th2 cells and a subsequent phase after 24 to 48 hours characterized by IFN-γ-expressing Th1 cells [20]. This switch in cytokine profile involves a local production of IL-12 from surrounding eosinophils and/or APC. IFN-γ produced by Th1 cells activates keratinocytes to express Fas (CD95), which predisposes keratinocytes to apoptosis, leading to the formation of eczematous lesions [21].

In addition to CD4+ Th cells, CD8+ T cells may also contribute to the pathogenesis of AD. In a murine model, CD8+ T cells account for a major fraction of IFN-γ expression in atopic skin lesions [22]. Recent data suggest that the influx of CD8+ into AD lesions may be mediated through the interaction between CCR8 chemokine receptors on these cells and the cutaneous expression of the chemokine I-309/CCL1 [23].

There is increasing evidence that the effector functions of Th cells in allergic diseases are downregulated by a specialized population of Th cells known as the T regulatory (Treg) cells. A subgroup of naturally occurring Treg cells are characterized by a CD4+CD25+ phenotype and their development under the control of the transcription factor gene, FoxP3 [24,25]. Recently, it has been found that the AD lesions are deficient in this subgroup of Treg cells [26•]. Because it has been shown that Treg cells were capable of suppressing allergen-specific T-cell activation, it was postulated that the lack of CD4+CD25+FoxP3+ Treg cells in AD lesions may contribute to the cutaneous inflammation of AD [26•]. Although Treg cells from AD patients have been consistently shown to be capable of suppressing effector T-cell proliferation, CD4+CD25+ Treg cells and another subgroup of Treg cells, known as the adaptive Treg cells (high IL-10-expressing T cells) were shown to be ineffective in preventing T-cell–induced keratinocyte apoptosis [26•]. The reason for this failed function of Treg cells in AD is not fully understood, but one possible mechanism may be attributed to a subversion of Treg cell function by staphylococcal superantigens, which are frequently present on the lesions of AD patients [27].