Current perspectives

Allergic and nonallergic forms of atopic diseases

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Atopic dermatitis, allergic rhinitis, and asthma are atopic diseases that develop on a complex genetic background, the so-called atopic diathesis. Although they target different organs, in most patients they are characterized by the presence of elevated total serum IgE levels. However, a subgroup of atopic patients exhibits normal IgE levels and mechanisms contributing to the so-called "intrinsic" or "nonallergic form" have been the matter of intensive research work in the last years. Because of the rapid advancements in the research field of atopic diseases, it now becomes possible for the first time to delineate a new disease classification of allergic and nonallergic subtypes of atopic diseases, thereby bringing hope to the clinician for a more specific treatment approach for each subgroup of these patients. (J Allergy Clin Immunol 2003;112:252-62.)

Key words: *Atopic diseases, atopic dermatitis, asthma, rhinitis, allergic, nonallergic, IgE*

Atopy is an inherited condition that makes individuals more likely to have a familiar group of diseases of growing importance in Western societies develop, including rhinitis, asthma, and atopic dermatitis.[1,2] It is thought that the key factors behind this rising incidence are increased exposure to sensitizing allergens and reduced stimulation of the immune system by parasitic and microbial components, which are believed to switch the T_H2 profile of the immune response in a T_H1 profile, related to a steady decline in infectious diseases during critical periods of development such as early infancy.[3,4] In addition to these environmental factors, the genetic basis of atopy is still a matter of intensive research, and efforts have been expended in mapping the chromosomal locations of genes involved in the susceptibility to atopic diseases.[5]

THE ROLE OF IgE

Since Prausnitz and Kustner described the existence of a human serum factor that reacts with allergens in 1921, much effort has been made to characterize the effector molecule of immunologic hypersensitivity responses in depth.[6] Today, we know that the antibody called IgE, which was discovered in 1967 by Ishizaka et al[7] is composed of 2 identical heavy and 2 identical light chains. These chains form the variable antigen binding and the constant Fc domain, through which the IgE molecule binds to its cell surface receptors. Most individuals react with an increase of serum IgE levels as a defensive response to parasitic infections. However, some individuals also display an abnormally enhanced ability to produce IgE antibodies in response to certain allergens, such as house dust mite, ragweed, or cat dander, which activate the immune system after ingestion, inhalation, or diffusion through the skin.

Abbreviation used
FcεRI: High-affinity receptor for IgE

Although the theory describing atopic diseases as highly IgE dependent has persisted over a long time, new data have raised the question of the precise role of IgE in atopy.

ALLERGIC OR NONALLERGIC DISEASE?

The term "allergy" was introduced in 1906 by Clemens P. Pirquet, who used it to describe the reactions of protective immunity and hypersensitivity.[8] Later there was a tendency to use the word "allergy" to describe all kinds of unpredictable reactions in the skin and the mucosa.[9] Today, the term "allergy" is frequently used synonymously with IgE-mediated allergic diseases and will be used in this sense here. However, it has also been observed that serum IgE levels might lie within the normal range in mild, moderate, or even in a few cases of severe atopic diseases, such as severe atopic dermatitis without concomitant asthma or rhinitis. A cornerstone in this context was the contribution of Rackemann,[10] in the middle of the 20th century, who first recognized that patients with negative skin prick tests to inhalants have a late onset of disease and have the intrinsic form of asthma. Today atopic diseases can be divided into 2 distinct variants: the extrinsic, allergic variant, which occurs in the context of sensitization toward environmental allergens and is accompanied by elevated serum IgE levels, and the intrinsic, nonallergic variant, with no detectable sensitization and with low serum IgE levels.[11] Since then, it has become increasingly clear that allergic and nonallergic forms exhibit specific clinical and immunologic characteristics.

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ALLERGIC AND NONALLERGIC ATOPIC DERMATITIS

Allergic atopic dermatitis

Clinical parameters. With regard to the diagnosis of atopic dermatitis (AD), numerous scoring strategies and diagnostic criteria have been developed. The criteria of Diepgen et al,[12] Hanifin,[13] the United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis,[14] and the Millennium Criteria for the Diagnosis of Atopic Dermatitis[15] are most often used. In the definition of Hanifin, an elevated serum IgE level is not essential for diagnosis, and it can be defined by a syndrome of skin lesions, which are not strictly associated with IgE sensitization.

Most patients with atopic dermatitis have the allergic form, characterized by high serum IgE levels and positive skin prick test reactions to common environmental allergens such as food or aeroallergens (Table I).[16]

Intranasal or bronchial inhalation challenge with aeroallergens such as house dust mite or animal dander can lead to the development or worsening of AD skin lesions, and the degree of IgE sensitization to aeroallergens is directly associated with the severity of the disease, whereas the reduction of exposure to some common allergens such as house dust mite is associated with a significant improvement in AD.[17]

Parameters in the skin. Numerous studies have demonstrated the importance of activated $CD4^+$ T cells in skin lesions of patients with AD. Immunohistologic investigations have shown that the dermal infiltrate in the skin lesions is mainly composed of $CD4^+$ and $CD8^+$ cells, with a CD4/CD8 ratio similar to that observed in peripheral blood.[16,18,19] It is well known that the human immune system harbors a powerful army of cutaneous T cells. In both the allergic and nonallergic form of AD these T cells seem to be highly activated and bear the cutaneous lymphocyte antigen on their surface, which enables them to be immediately recruited into the skin on invasion of foreign antigens.[20-22] Cutaneous T cells that produce soluble factors such as IL-4, IL-5, and IL-13 predominate in the acute phase of AD. In contrast, T cells that produce IFN-γ predominate in the chronic phase.[23]

Eosinophilic granule proteins are characteristically deposited in the skin lesions of AD.[24] Because eosinophils and their granule proteins have potent inflammatory functions, this finding indicates that they might play a critical role in AD (Fig 1).

One of the most important features of allergic AD is the prominent skin infiltration with hyperstimulatory cells of the dendritic lineage. Dendritic cells play a primary role in cutaneous immune surveillance. Two different dendritic epidermal cell populations have been identified in the skin of AD patients, Langerhans cells and inflammatory dendritic epidermal cells, which bear the high-affinity receptor for the Fc region of IgE (FcεRI) on their cell surface (Fig 1).[25] It has been suggested that FcεRI plays a pivotal role in antigen focusing by enabling epidermal dendritic cells to absorb allergens invading the impaired epidermal skin barrier by means of FcεRI-bound IgE, leading to efficient antigen presentation to T cells. In support of this concept, the successful application of aeroallergens such as cat dander in the so-called atopy patch test shows that it is possible to elicit eczematous skin lesions solely by external application of aeroallergens to the skin.[26] In patients with positive atopy patch test reactions, a higher number of IgE-bearing dendritic cells were found in the epidermis and dermis than in patients with negative atopy patch test reactions.[27] Therefore, an intermittent or a continuous flow of aeroallergens into the process of facilitated antigen presentation might define the pathophysiologic basis of the recurrent or self-perpetuating course of allergic AD, as frequently seen in untreated patients.

Similar to rhinitis or asthma, inflammatory processes as consequences of microbial infection play a major role in both the allergic and nonallergic form of the disease. The skin of patients with AD exhibits a striking susceptibility to colonization and infection with microbial components such as *Staphylococcus aureus, Pityrosporum ovale,* or *Candida albicans.*

S aureus is found in more than 90% of patients with chronic AD skin lesions, reaching a density of approximately 1 million/cm^2 and might be an important trigger factor in the proinflammatory process.[28,29] These bacteria secrete toxins, which are known to act as superantigens, such as *S enterotoxin A* or *B* and toxic shock syndrome toxin-1, and amplify the inflammatory reactions of the skin. The level of endogenous antimicrobial peptides, such as cathelicidins and β-defensins, is reduced on the skin of patients with AD,[30] which together contribute to the increased susceptibility of atopic skin infection. Recently it has been shown that exclusively allergen-specific IgE against microbial components could be found in 50% of the patients with AD with low IgE serum levels. This observation raises the question whether a hyperreactivity to microbial components might be a trigger factor of this subtype of AD.[25]

Parameters in the blood. Research during the last decade has established that several abnormalities in soluble factors, cellular characteristics, and other mediators in the blood are characteristic of the complex pathogenesis of AD.

An elevation in total serum IgE and in the serum levels of specific IgEs to aeroallergens and food allergens is characteristic of allergic AD. In addition, elevated levels of soluble mediators such as IL-4, IL-5, and the soluble form of the low-affinity receptor for IgE are characteristic features of patients with allergic AD. Recently, IgE autoantibodies directed against human proteins have been observed exclusively in the peripheral blood and skin of patients with allergic AD. These IgE-reactive autoantigens are designated as *Hom s* 1-5 and *DSF70* and have been cloned from human epithelial cDNA expression libraries. They are primarily intracellular proteins found in IgE-immune complexes from sera of patients with AD.[31] It is assumed that they increase allergic responses and in this way contribute to the severity and exacerbation of AD.

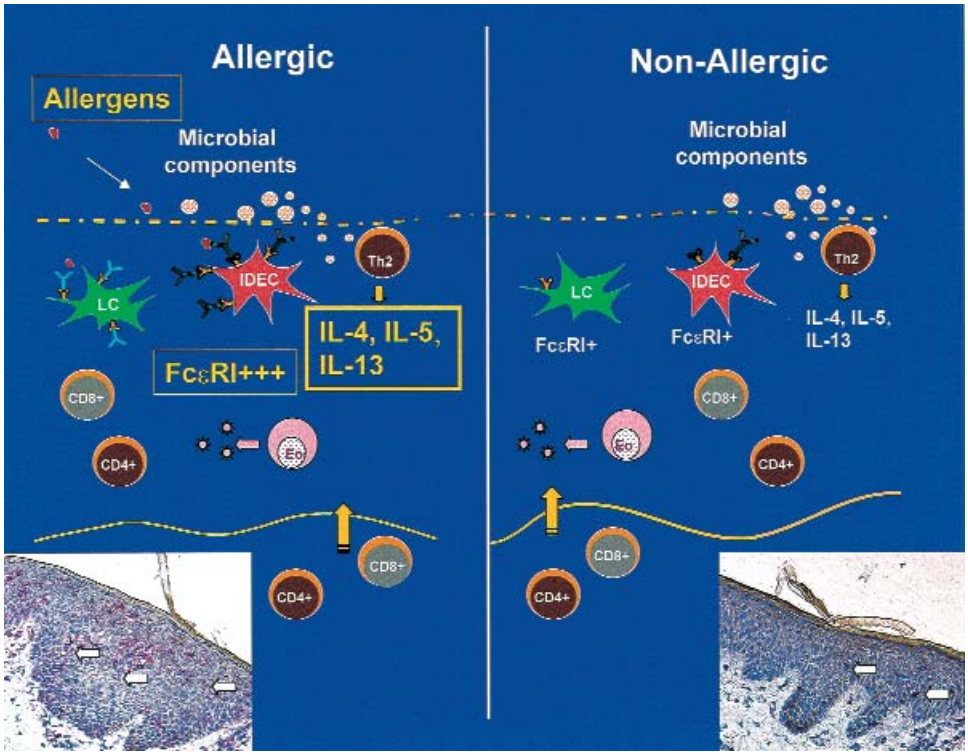

FIG 1. Pathophysiologic puzzle of atopic dermatitis. Differences between the allergic subtype of atopic dermatitis (AD) *(left side)* and the nonallergic subtype of AD are indicated in *yellow.* In addition, immunohistochemical stainings of the FcεRI on CD1a+ Langerhans cells and inflammatory dendritic epidermal cells (indicated by *arrows*) are shown on the bottom of each figure. *FcεRI,* High-affinity receptor for IgE; *Eo,* eosinophils.

Another phenomenon observed in the allergic form of AD is increased activity of cyclic adenosine monophosphate-phosphodiesterase. This leads to reduced intracellular levels of cyclic adenosine monophosphate, which has a permissive effect on various cell functions in patients with AD.[32]

Eosinophils play a major role in AD and become active by releasing their toxic eosinophilic granules, which constitute a major portion of their cellular protein content. Notably, in both forms of AD, increased serum levels of eosinophils with enhanced survival are found. In contrast, the expression of the functional CD137 receptor, which stimulates T-cell activation and differentiation, is restricted exclusively to eosinophils in patients with allergic AD.[33,34]

The question of a defect on the level of monocytes has been an issue of intensive research for a long time. It has been suggested that monocytes in atopic individuals display enhanced survival and release distinct soluble mediators. Monocytes of patients with allergic AD display enhanced surface expression of the high-affinity and low-affinity receptor for IgE (FcεRI and FcεRII) and the IL-4Rα chain and in this way can be distinguished from monocytes in patients with nonallergic AD.[35]

Nonallergic atopic dermatitis

Clinical parameters. In patients with the nonallergic form of AD, the disease is not associated with sensitization to food or aeroallergens, and serum IgE levels lie within the normal range, even though these patients display exactly the same skin lesions as patients with increased serum IgE levels.[16] Recent studies have found that the frequency of the nonallergic form of AD ranges from 16% to 45%, depending on the country and the criteria for definition.[36,37] A higher prevalence of nonallergic AD in preschool children in the former East Germany and an increase in allergic forms of atopic disorders in this region as a consequence of "westernization" since reunification indicate that environmental factors might play an important role in triggering the development of both forms of AD. Interestingly, a predominance of female patients has been observed among patients with nonallergic AD in several studies. These gender differences might be due to the influence of sex hormones, which influence mucosal allergic reactivity.[38,39]

The hypothesis of a dynamic relationship between the 2 forms of AD is supported by data from a study investigating the persistence of AD during the development of respiratory allergic diseases. In this study, children with AD who were negative to the skin prick test became positive to the skin prick test within a period of 10 years.[40] Nonallergic AD might therefore be considered as the pure or transitional form in the natural history of AD.[40] The influence of environmental factors might contribute to the development of the allergic, mixed form of AD, accompanied by sensitization to

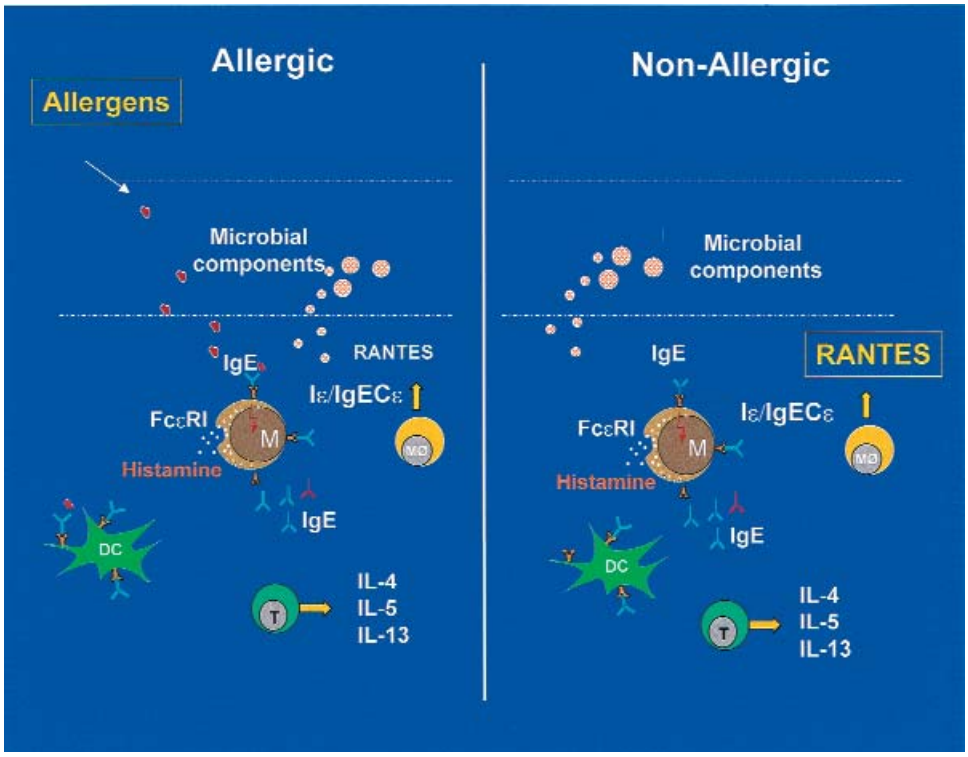

FIG 2. Characteristic features of asthma. Differences between the allergic and nonallergic asthma variant in bronchial mucosa are marked in *yellow*. Increased levels of Iε and Cε RNA+ cells can be found in the bronchial mucosa of both allergic and nonallergic patients with asthma. The amount of RANTES in the bronchoalveolar fluid of nonallergic patients with asthma is higher than in patients with allergic asthma. *M,* Mast cells; *T,* T cell; *MØ,* macrophage.

environmental factors and increasing IgE serum levels. At present, it has not been evaluated whether patients with allergic AD, in contrast to patients with nonallergic AD, have a higher risk of allergic rhinitis or allergic asthma developing. In addition, it would be interesting to evaluate the frequency of concomitant nonallergic rhinitis and/or nonallergic asthma in the nonallergic subgroup of AD in the future.

Parameters in the skin. Atopic skin is characterized by a perivascular infiltrate of highly activated T cells. Although cutaneous T cells seem to be similar in the 2 forms of AD, the nature of their soluble signals varies. Cutaneous T cells of patients with nonallergic AD produce similar amounts of IL-5 and IFN-γ but less of the T_H2 cytokines IL-4 and IL-13 (known to increase IgE synthesis) than cells of allergic patients.[19] This distinct cytokine pattern might be both cause and effect of the lower IgE levels found in patients with nonallergic AD.[19]

The reduced amount of T_H2 cells producing IL-4 and IL-13, together with the lower FcεRI expression of epidermal dendritic cells in nonallergic AD, indicate that proinflammatory mechanisms are predominant.

As with patients with allergic AD, the skin of patients with nonallergic AD harbors a large number of epidermal dendritic cells, which characteristically display lower surface expression of the high-affinity receptor for IgE (FcεRI).[41] Interestingly, positive atopy patch test reactions to aeroallergens can also be induced even in the absence of elevated allergen-specific serum IgE in some of the patients with nonallergic AD, indicating a putative role of local IgE in AD.[27]

Parameters in the blood. The common presence of peripheral blood eosinophilia and elevated serum levels of eosinophilic granule proteins suggests that eosinophil degranulation also plays a major role in the nonallergic form of AD. In contrast to the allergic form, in nonallergic AD, serum levels of both total and allergen-specific IgE lie within the normal range. In addition, the IgE-binding receptors, FcεRI and FcεRII, are not elevated on monocytes. This might be due to lower serum IgE levels, which, in combination with low IL-4Rα expression, result in reduced IL-4 responses from monocytes in these patients.[35]

Another approach suggests that IL-13 plays an unexpected and crucial role in atopic diseases. This is underlined by the finding that T cells producing IL-13 (the earliest indicator of atopy) can be found in large amounts in the cord blood of children who have atopic diseases develop later on in life.[42]

In view of these data, the increased level of IL-13 in the sera of patients with nonallergic AD[35] indicates that IL-13 might be involved in the pathogenesis of this form of AD by stimulating eosinophils, interacting with B cells, altering the IL-13R signal transduction pathway, or activating other unknown mechanisms.[43] Increased

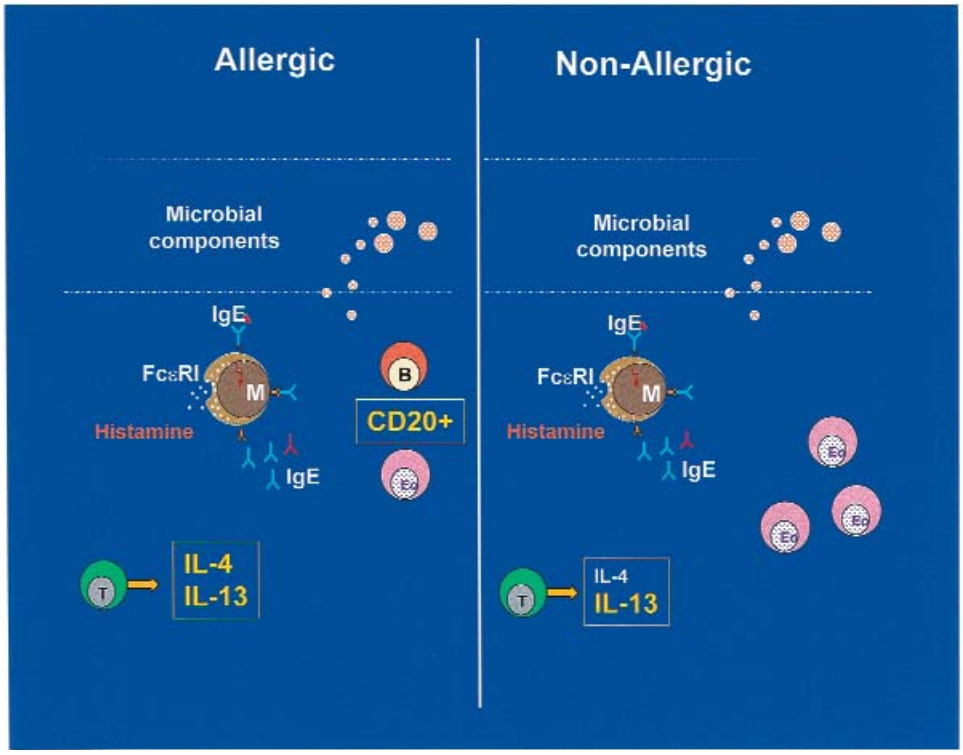

FIG 3. Differences in the nasal mucosa of patients with allergic and nonallergic forms of rhinitis are indicated in *yellow*. Nasal epithelium exhibits mast cells and IgE-positive cells in both the allergic and nonallergic form of rhinitis. In contrast to nonallergic rhinitis, allergic rhinitis is associated with an elevated mRNA expression of IL-4 and IL-13 in combination with augmented numbers of CD20+ B cells and cells expressing Iε and Cε in sinus biopsy specimens. *M,* Mast cell; *B,* B cell; *T,* T cell; *Eo,* eosinophil.

peripheral blood IL-4 and IL-13 production in nonallergic atopic dermatitis even in the absence of enhanced IgE levels indicates the predominance of an immune response of the T_H2 type in this subtype.[35]

ALLERGIC AND NONALLERGIC ASTHMA

Allergic asthma

Clinical parameters. In general, asthma can be subdivided into 3 forms: the extrinsic/allergic asthma, which is clearly caused by an allergen, the intrinsic/nonallergic asthma, which is not linked to such an allergen, and the mixed form. It is well accepted that in all 3 variants local phenomena occurring in the mucosal tissue, such as bronchoconstriction of the smooth muscles as a consequence of local or systemic inflammation of the airways, are the central pathophysiologic mechanisms of asthma.

The sensitivity of extrinsic/allergic patients with asthma to allergens such as pollen, house dust mite, or food is clearly documented by positive skin prick test reactions and elevated IgE/allergen-specific IgE serum levels, which document sensitizations to environmental allergens in these patients (Table II).[44,45]

Parameters in the bronchial mucosa. In biopsies of the respiratory mucosa, enhanced expression can be found of T_H2 type cytokines and chemokines such as IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, which trigger the T-cell response.[46,47] In addition, mRNA for the germline transcript (Iε) and the ε heavy chain of IgE (Cε)[48-51] and increased numbers of cells expressing the high-affinity receptor for IgE (FcεRI) predominate in these tissues (Fig 2).[50,52,53] It is well known that activation of FcεRI on the effector cells of anaphylaxis (ie, mast cells and basophils) induces the release of preformed vasoactive mediators, which rapidly elicit edema of the bronchial mucosa, mucus production, and smooth muscle constriction. Together, these factors cause the local inflammation in the mucosal tissue, which is assumed to play a pivotal role in the development of the disease. Persistent airflow inflammation might develop in response to bacterial infection such as *Mycoplasma pulmonis* or *Chlamydia pneumoniae* infection, in particular in severe longstanding allergic and nonallergic asthma.[54] In addition, it has been speculated that, analogous to atopic dermatitis and rhinitis, *S aureus* might play a role as a trigger factor in asthma, and IgE antibodies to *S aureus* enterotoxins were found more frequently in patients with severe asthma than in normal control subjects and were linked to the severity of the diseases (ie, eosinophilic inflammation).[55] Moreover, an enhanced level of T cells expressing the selected T-cell receptor β-chain variable region, which is known to be induced by microbial superantigens, was detected in bronchoalveolar lavage fluid of patients with asthma.[56,57] Another immunologic key factor in both forms is the recently described local IgE production, which is a pathognomic parameter in both allergic and

TABLE I. Characteristics of allergic and nonallergic atopic dermatitis

	Nonallergic atopic dermatitis	Allergic atopic dermatitis	Reference
Clinical parameters			
Skin manifestation	Similar	Similar	12-16,36
Onset of eczema	Early (in childhood)	Early (in childhood)	16
Sex	Female predominance	No female predominance	16,35,36
Frequency	16%-45% of atopic dermatitis patients	55%-84% of atopic dermatitis patients	16,37
Skin prick test	Negative	Positive	16
Parameters in the peripheral blood			
Total serum IgE	<150 kU/L	>150 kU/L	16
Specific IgE	Negative	Positive	16
Blood eosinophilia	↑	↑	34,35
Eosinophil survival	↑	↑	34,35
CD137 expression of eosinophils	↑	↑↑	34,35
Eosinophilic cationic protein in the blood	↑	↑	34,35
T cells in the peripheral blood	HLA-DR expression similar	HLA-DR expression similar	18-20
Cytokines in the peripheral blood	↑IL-5	↑IL-5	35
	↑IL-4	↑IL-4	
	↑↑ IL-13	↑IL-13	
	↑sIL-4R	↑sIL-4R	
B-cell activation	$CD23^+$ B cells ↑	$CD23^+$ B cells ↑↑	16
Stimulated PBMCs	↑↑IL-13 release	↑IL-13 release	43
Phenotype of monocytes	↓FcεRI, FcεRII	↑↑FcεRI, FcεRII	35
	↓IL-4Rα	↑IL-4Rα	
	↓CD40	↑CD40	
Parameters in the skin			
Phenotype of epidermal dendritic cells	↑FcεRI	↑↑FcεRI	43
	FcεRI/FcγRII\ ratio < .5	FcεRI/FcγRII ratio > 1.5	
Cytokines derived from lesional skin	↑IL-5, IL-13	↑↑IL-5, IL-13	18-20
Parameters on the genetic level			
IL-4Rα promoter polymorphism C-3223-T	↑↑frequency	↓ frequency	36
IL-4 promoter polymorphism C-590-T	↓frequency	↑frequency	35

nonallergic diseases of the respiratory tree, such as asthma and rhinitis.

Furthermore, the increase in FcεRI-bearing cells in mucosal tissues, in combination with the increase in mRNA for the germline transcript (Iε) and the ε heavy chain of IgE, in the absence of an increase in B-cells supports this hypothesis of a local IgE synthesis in both subtypes of asthma.[58] To initiate the synthesis of IgE, inhaled allergens must encounter FcεRI-bearing antigen-presenting cells that line the airway. After successful antigen uptake, these antigen-presenting cells migrate to the draining lymph nodes, where they present their processed antigens to T cells and B cells.

Parameters in the blood. Many more differences between patients with allergic and nonallergic asthma can be found in peripheral blood than in mucosal tissue. The most important inducers of the increase in serum levels of total and allergen-specific IgE in patients with allergic asthma are the cytokines IL-4 and IL-13, which are found at increased concentrations in the sera of these patients.[59] Moreover, these cytokines initiate transcription of the ε-class constant region of the IgE heavy chain and trigger the production of IgE. In addition, the surface expression of the low-affinity receptor for IgE (FcεRII/CD23) on B cells, which is capable of augmenting the serum levels of IL-4 and IL-13, is enhanced in patients with allergic asthma. There is ample evidence that chemokines found in high concentrations in the sera of patients with asthma such as RANTES and monocyte chemoattractant protein-1 and -3 play a role in ongoing lung inflammation, lung leukocyte infiltration, bronchial hyperresponsiveness, and the recruitment of eosinophils in the pathogenesis of asthma.[60]

Other cellular characteristics that can be detected exclusively in the blood of patients with allergic asthma are an increase in the $CD4^+$ T-cell sublineage, an elevated expression of the β-1 integrin CD11b on $CD4^+$ cells, and an elevated number of suppressor cells expressing $CD8^+$.[61,62]

Nonallergic asthma

Clinical parameters. In contrast, 10% to 33% of all patients with asthma have the nonallergic form, which has a later onset, a more severe clinical course in adults, and is significantly associated with nasal polyps in combination with aspirin idiosyncrasy.[48,49,63,64] Precipitating factors in the nonallergic variant of asthma are viral or bacterial infections such as chlamydia or fungal infections, for example, with dermatophytes that cause local inflammation.[54,65,66] The lower levels of IL-10 and IL-12 and the lack of a putative homeostatic mechanism to decrease lung inflammation in the nonallergic form of this entity might predispose these subjects to bronchial inflammation.[67] In addition, irritants such as smoke or fumes, physical or emotional stress, gastroesophageal reflux, and exercise represent the cause of the nonallergic

TABLE II. Characteristics of allergic and nonallergic asthma

	Nonallergic asthma	Allergic asthma	Reference
Clinical parameters			
Onset of the disease	Later	Earlier	44,46,47,51,65
Severity of the disease	Higher	Lower	46,47,51,65
Sex	Female predominance	No female predominance	46,47,51,65
Frequency	About 30%	About 70%	44-47,51,65
Total serum IgE	Low	High	44-47
Specific IgE	Negative	Positive	44-47
Skin prick test	Negative	Positive	44-47
Parameters in the peripheral blood			
Perforin-positive lymphocytes in the peripheral blood	↑↑	↑	77
$CD4^+CD11b^+$ lymphocytes in the peripheral blood	↓	↑	63,64
Phenotype of B cells	↓CD23	↑CD23	60
Number of $CD8^+$ lymphocytes in the peripheral blood	↑	↑	60,61
Number of blood eosinophils	↑	↑	60
$CD68^+$ macrophages	↑↑	↑	69
Parameters in the bronchial tissue			
IL-3, IL-4, IL-5, IL-13, GM-CSF	↑	↑	46,47
Number of GMSFRα-positive cells	↑↑	↑	49,74,75
FcεRI-positive cells	↑	↑	50,52,53
Iε/Cε in bronchial biopsies	↑	↑	58-61

TABLE III. Characteristics of allergic and nonallergic rhinitis

	Nonallergic rhinitis	Allergic rhinitis	Reference
Clinical parameters			
Skin prick test	Negative	Positive	78,79
Sex	Female predominance	No female predominance	45,84,86
Frequency	9% to 42%	91% to 58%	78
Frequency of ASA triad	↑		83-85
Parameters in the peripheral blood			
Total serum IgE	Low	Low to high	81,82
Specific IgE	Negative	Positive	81,82
Eosinophil count	↑↑	↑↑	81,82
Parameters in the nasal mucosa			
Mast cells in the tissue	↑	↑	78,79
IgE-positive cells	↑	↑	80,81
Cytokines in the nasal mucosa	↑ IL-13 mRNA	↑ IL-4 and IL-13 mRNA	80,81
Number of $CD20^+$ B cells	↑	↑↑	80,81
Number of $I\varepsilon/C\varepsilon^+$ cells	↑	↑↑	80,81
Imbalance of nervous system	↑		83

form of asthma. As with AD and rhinitis, a clear female predominance can be observed.

Parameters in the bronchial mucosa. Increases in Iε and Cε RNA^+ cells in the bronchial mucosa provide evidence for a local IgE synthesis in patients with asthma[58] even in the absence of a known antigen or allergen triggering this process.[48,58,68] One of the few differences between the mucosal tissue of patients with allergic and nonallergic asthma is the concentration of the chemokine RANTES,[69-71] which is known to be produced by specific macrophage subtypes.[69] Interestingly, the amount of RANTES in the bronchoalveolar lavage fluid of patients with nonallergic asthma is higher than in patients with allergic asthma. This might be 1 reason for the enhanced number of eosinophils infiltrating the mucosal tissue in the nonallergic form and indicates a distinct predominance of specific tissue macrophage subtypes in nonallergic versus allergic asthma.

Parameters in the blood. Nonallergic asthma is seen with a marked eosinophilia. Some studies found lower IL-4 production in patients with nonallergic asthma than in patients with allergic asthma, which might explain the low circulating IgE serum levels.[72] In contrast, other studies did not detect any difference in IL-4 levels between the asthmatic subgroups.[73] In addition, in nonallergic asthma a marked increase in macrophages was found, which was demonstrated on the basis of the increase in the expression of the monocyte/macrophage specific marker CD68 in combination with GM-CSF receptor α-subunit bearing cells.[49,74,75] An inverse correlation between the number of GM-CSF receptor α-bearing cells and the FEV_1 (FEV_1 % predicted) suggests that these parameters mirror the sever-

ity of disease in the nonallergic form.[75] In contrast, sputum macrophage numbers were not higher in patients with nonallergic asthma.[67] In addition, some differences in the expression of transcription factors have been described. The number of cells expressing the transcription factor GATA-3 and cMAF, which are involved in the mediation of the IL-4 and IL-5 synthesis, was high in patients with allergic and nonallergic asthma. In contrast, reduced signal transducer and activator of transcription 6 expression and consequently a reduced IL-4R signaling is a feature of nonallergic asthma.[76]

Furthermore, analyses of lymphocyte subpopulations in the peripheral blood of patients with nonallergic asthma show that an increased percentage of $CD4^+$ cells expresses the cytotoxic molecule perforin. This molecule has been shown to play a pivotal role in autoimmune diseases[77] and seems to be of major relevance in nonallergic asthma.[77]

Taken together, in consideration of the inflammatory processes in both forms of asthma, there seem to be more similarities than differences between the allergic and nonallergic form of this disease.

ALLERGIC AND NONALLERGIC RHINITIS

Allergic rhinitis

Clinical parameters. Seasonal or perennial allergic rhinitis, which has an overall prevalence of 9% to 42%,[78] arises in atopic individuals with an increased tendency to generate IgE antibodies against common environmental allergens, such as ragweed, pollen, or house dust mite. This form is characterized by mucosal infiltration and activity of plasma cells, mast cells, and eosinophils.[78,79] Typically, positive skin prick test reactions toward aeroallergens can be observed in these patients (Table III).

Parameters in the mucosal tissue. Allergic rhinitis is associated with an elevated mRNA expression of IL-4 and IL-13 in combination with augmented numbers of $CD20^+$ B cells and cells expressing Iε and Cε in sinus biopsy specimens (Fig 3).[80]

Parameters in the blood. Although most patients with allergic forms of rhinitis display an increased serum (IgE) level of total and allergen-specific IgE, in some patients IgE levels are only slightly elevated or lie within the normal range. In addition, serum levels of IL-4, IL-5, and the soluble form of the low-affinity receptor for IgE (sCD23) are elevated in the sera of these patients, indicating a pivotal role of these parameters in IgE-mediated immunologic pathways.[45,81] Most interestingly, endogenous signals for cell death, such as the serum-soluble *Fas ligand* in concentrations often associated with autoimmune diseases, have been shown to be specifically increased in patients with allergic forms of rhinitis.[82]

Nonallergic rhinitis

Clinical parameters. In contrast, nonallergic rhinitis is a diagnosis of rhinitis without any IgE mediation, as documented by allergen skin testing. Similar to atopic dermatitis and asthma, sex might be a risk factor in nonallergic rhinitis, because 58% to 74% of patients with nonallergic rhinitis are female. It is assumed that nonallergic rhinitis is a heterogeneous syndrome consisting of at least 2 subtypes: the noneosinophilic and eosinophilic type. The noneosinophilic type includes various subtypes of rhinitis such as occupational, hormonal, drug-induced, gustatory, and vasomotor rhinitis. The eosinophilic type, also known as nonallergic rhinitis with eosinophilia syndrome, is characterized by nasal eosinophilia and frequent evolution to nasal polyposis or the triad of intrinsic asthma, nasal polyposis, and aspirin idiosyncrasy (ASA triad).[83-85] This syndrome has an overall prevalence of 10% to 15% and a clear female predominance.[45,84,86]

Although nonallergic rhinitis is a well-recognized diagnosis, its prevalence has not been studied definitely. It frequently occurs in combination with allergic diseases and is seen as the so-called mixed rhinitis.[78]

Parameters in the mucosal tissue. The nasal epithelium exhibits mast cells and IgE-positive cells in both the allergic and nonallergic form of rhinitis.

Although IgE-positive cells are also found in the nonallergic form of rhinitis, IL-13 is the predominant cytokine detectable in the sinus biopsy specimens of patients with nonallergic rhinitis.[87] A distinguishing feature of nonallergic rhinitis with eosinophilia syndrome is an elevated eosinophil count of 5% to 25% in nasal smears.

Although the exact pathophysiology of nonallergic rhinitis is not fully understood, in some cases it might result from an imbalance between the nasal sympathetic and parasympathetic nervous system.[83] In general, autonomic stimuli such as isotonic exercise or changes in temperature have a greater effect on patients with nonallergic rhinitis. Similar to asthma, there has been a debate about the relationship of the allergic and nonallergic variant of rhinitis in the context of bacterial infections, which might trigger the pro-inflammatory process in this disease.

Because the role of staphylococcal superantigens in other atopic diseases has recently been recognized, new evidence suggests that similar mechanisms might be relevant in airway diseases such as rhinitis. It is hypothesized that the higher carrier rate of *S aureus* in patients with allergic and nonallergic rhinitis might aggravate the clinical course of the disease.[88] In recent studies it has been suggested that there is an association between increased levels of total IgE, specific IgE, and eosinophilic inflammation in nasal polyps and the presence of specific IgE to *S aureus* enterotoxin A and *S aureus* enterotoxin B. Together these findings might link to a possible role of bacterial superantigens in this disease.[89]

Parameters in the blood. Patients with nonallergic rhinitis display low total and allergen-specific IgE serum levels and negative skin prick test reactions to food allergens and aeroallergens. Several lines of evidence support the hypothesis of local IgE synthesis at mucosa sites. IgE can be found located in the mucosal tissues even in patients with the nonallergic subtype. In addition, concentrations of IgG subclass 1 and IgG subclass 4 anti-IgE autoantibodies are far lower than those found in patients

with allergic rhinitis.[90] In contrast to the allergic form, *Fas ligand* is not detectable in sera of patients with nonallergic forms of rhinitis.

CONCLUSION

The genetic, humoral, and cellular differences between patients with allergic and nonallergic forms of atopic diseases mirror a complex network of distinct properties, which together determine the outcome of the allergic or nonallergic variants of atopic diseases. As a common feature, local IgE production in the affected tissue and the relevance of allergic and nonallergic (infectious) inflammatory processes seem to play a major role in all subtypes of atopic diseases.

Perhaps the most interesting aspect is the characterization of the underlying pathomechanisms of each of these forms, which is indispensable for the development of clear-cut diagnostic criteria and exact definitions of atopic disorders in clinical and scientific practice. Promising future directions of research in the nonallergic forms of atopic diseases include the possible identification of novel allergens or autoantigens, detailed descriptions of the mechanisms involved in local IgE production within inflammatory tissues, and long-term studies to investigate the putative transition of nonallergic to allergic forms of atopic diseases in the same individual. Moreover, effective new treatment strategies for the allergic and nonallergic form would then become a real possibility. These might be quite different from most of the recent therapeutic strategies, which are based on the concept of a predominance of IgE-mediated mechanisms, as the treatment with anti-IgE antibodies.[91]

In addition, the data reviewed here show that it is necessary to reassess the role of IgE and to consider a redefinition of our current terminology.

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