29 Extrinsic and Intrinsic Atopic Eczema

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29.1 Introduction

29.1.1 Atopy and Allergy

"Atopy" is an inherited condition which makes individuals more likely to develop a familiar group of diseases of rising incidence in the western world, including rhinitis, asthma, and atopic eczema (AE) [1, 2]. In contrast, the word „allergy" was used to describe all kinds of unpredictable reactions in the skin and the mucosa [3]. Today, the term „allergy" is frequently used synonymously for immunoglobulin E (IgE)-mediated allergic diseases. However, it has also been observed that serum IgE levels may lie within the normal range even in a few cases of severe AE, such as severe AE without concomitant asthma or rhinitis. Due to these observations, today AE can be divided into two distinct variants: the intrinsic, nonallergic variant, with no detectable sensitization and with low serum IgE levels and the extrinsic, allergic variant, which occurs in the context of sensitization toward environmental allergens and is accompanied by elevated serum IgE levels and positive skin prick test reactions to aero- and food allergens [4]. This questions the role of allergens as trigger factors for AE, particularly in infants where the non-IgE mediated form seems to be most frequent. In the view of these findings AE might represent a complex syndrome which evolves through different stages, beginning from the pure/intrinsic form and developing into the mixed/extrinsic form.

It has become increasingly clear that the extrinsic and intrinsic form of AE, in addition to a high number of common features, exhibit specific immunological characteristics which are different in each of these subtypes of AE.

29.2 Allergic Atopic Eczema

29.2.1 Clinical and Epidemiologic Parameters

With regard to the diagnosis of AE, an elevated serum IgE level is not an essential parameter for the diagnosis and AE can be defined by a syndrome of skin lesions, which are not strictly associated with IgE sensitizations [5–8].

It has been repeatedly demonstrated that in patients with the nonallergic, intrinsic form of AE, 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 [9].

In contrast, in about 70% of the adult patients AE goes along with sensitizations, high serum IgE levels, and positive skin prick test reactions to common environmental allergens such as food- or aeroallergens [9].

As a characteristic feature of this subgroup of patients, intranasal or bronchial inhalation challenge with aeroallergens such as house dust mite or animal dander can lead to the development or worsening of AE skin lesions. Further on, the degree of IgE sensitizations to aeroallergens is directly associated with the severity of the disease, while the reduction of exposure to some common allergens such as house dust mite is associated with a significant improvement of AE [10].

For the intrinsic form of AE, recent studies have found that the frequency of the nonallergic, intrinsic form of AE in adult patients ranges from 16% to 45%, depending on the country and the criteria for definition [11, 12]. A higher prevalence of intrinsic AE in preschool children in former East Germany and an increase in allergic forms of atopic disorders in this

region in parallel to profound changes of the life style since the reunification indicate that environmental factors might play an important role in triggering the development of the extrinsic or intrinsic form of AE. Interestingly, a predominance of female patients has been observed among intrinsic AE patients in several studies, but the pathophysiologic background of this phenomenon is totally unclear.

29.2.2 The Transition Between the Intrinsic and the Extrinsic Forms of Atopic Eczema

The hypothesis of a dynamic relationship between the two forms of AE is supported by data from studies investigating the persistence of AE during the development of respiratory allergic diseases during childhood. In this study, children suffering from AE who were negative to the skin prick test became positive to the skin prick test within a time period of 10 years [13]. It is therefore reasonable to hypothesize that intrinsic AE can be considered as the pure or transitional form in the natural history of AE [13]. The influence of environmental factors, in combination with a respective genetic predisposition might contribute to the development of the mixed extrinsic form of AE, which is accompanied by sensitization to environmental factors and increasing IgE serum levels (Fig. 29.1).

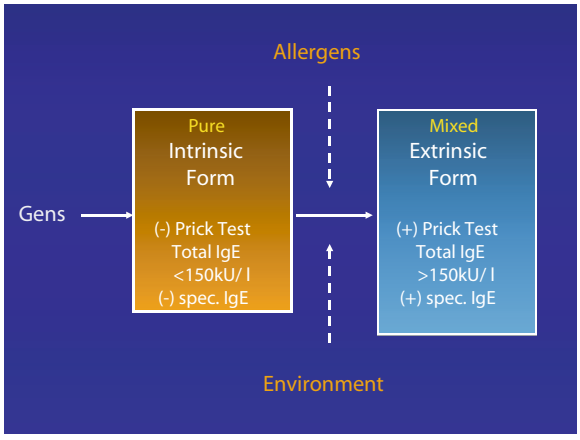

Fig. 29.1. The transition between IAE and EAE

29.2.3 Genes

Preliminary results from genetic studies strongly support the concept of common shared loci for all subtypes of AE, which may also be shared by other chronic inflammatory skin diseases such as psoriasis and have been found to be linked to loci on chromosomes 1q21 and 17q25 [14]. These loci might encode general factors which underlie the chronic-inflammatory immune responses in the skin. On the other hand, some more specific loci seem to be restricted to extrinsic atopic dermatitis patients and elevated serum IgE levels. In the past, linkage analysis showed that the IL-4 receptor alpha gene (IL4RA) at 16p11.2-12 is linked to the elevated total serum-IgE level. Recent studies support the hypothesis that single nucleotide polymorphisms (SNPs) in the IL4RA gene might underlie the distinct IL-4R expression and response to IL-4 in extrinsic and intrinsic AE patients [15]. Whether there exist more genetic similarities than differences between patients with the extrinsic and the intrinsic form of AE remains to be elucidated.

29.3 Skin

29.3.1 Keratinocytes

Dysregulated signal transduction in epithelial cells could favor an exaggerated response to inflammatory stimuli. It is supposed that an intrinsic defect of keratinocytes found in AE leads to an enhanced secretion of GM-CSF, IL-1, and TNF-α and might result in main part from the altered transcriptional control and activation of the signal transduction cascade [16]. As a consequence of the altered cytokine synthesis in AE, keratinocytes also release high amounts of the proinflammatory cytokines, tumor necrosis factor (TNF)-α and Interleukin (IL)-1β. Furthermore, in response to TNF-α and Interferon (IFN)-γ, epidermal KC of AE patients overexpress soluble epidermal growth factors, which induce the release of monocyte-chemotactic protein (MCP)-1, the chemokine regulated upon activation normal T cell-expressed and -secreted (RANTES), IP-10, and IL-8. So far, no phenotypical or functional differences between keratinocytes from patients with intrinsic or extrinsic AE have been found. This

implies that the intrinsic defect of keratinocytes might represent one of the common features of the intrinsic and extrinsic subforms of AE and might form the basis of both the reduced epidermal skin barrier in these patients and the chronic-inflammation of the skin.

29.3.2 T Cells

AE is a biphasic disease, in which cutaneous T cells of the Th2 type which produce soluble factors such as interleukin (IL)-4, IL-5, and IL-13 predominate in the acute phase. In contrast, T cells of the Th1 type which produce interferon (IFN)-γ predominate in the chronic phase [17].

Cutaneous T cells of intrinsic AE patients produce similar amounts of IL-5 and IFN-γ, but less of the Th2 cytokines IL-4 and IL-13, which regulate the IgE synthesis, than cutaneous T-cells of extrinsic patients [18]. This distinct cytokine pattern might be both cause and effect of the lower IgE levels found in intrinsic AE patients (Figs. 29.1, 29.2) [18].

29.3.3 Dendritic Cells

One of the most important features of AE 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 AE patients, Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC), which bear the high affinity receptor for the Fc region of IgE (FcεRI) on their cell surface [19]. It has been suggested that FcεRI plays a pivotal role in antigen focusing, by enabling epidermal dendritic cells to take up allergens invading the impaired epidermal skin barrier via FcεRI-bound IgE, leading to efficient antigen presentation to T-cells. While the surface expression of FcεRI is high on dendritic cells in the lesional skin of extrinsic AE patient, in contrast the skin of intrinsic AE patients harbors a large number of epidermal dendritic cells, which characteristically display lower surface expression of the high affinity receptor for IgE (FcεRI) than in extrinsic AE [20] (Fig. 29.3). Nevertheless, the FcεRI surface expression in intrinsic AE patients is higher than in the normal skin of healthy individuals. This

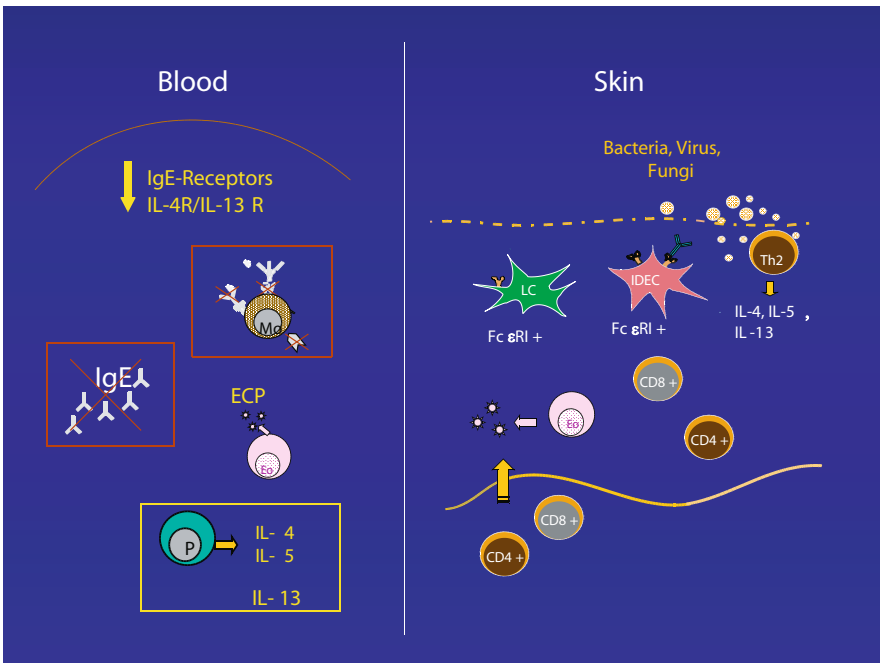

Fig. 29.2. Summary of the pathophysiological characteristics in the blood and the skin of extrinsic AE patients

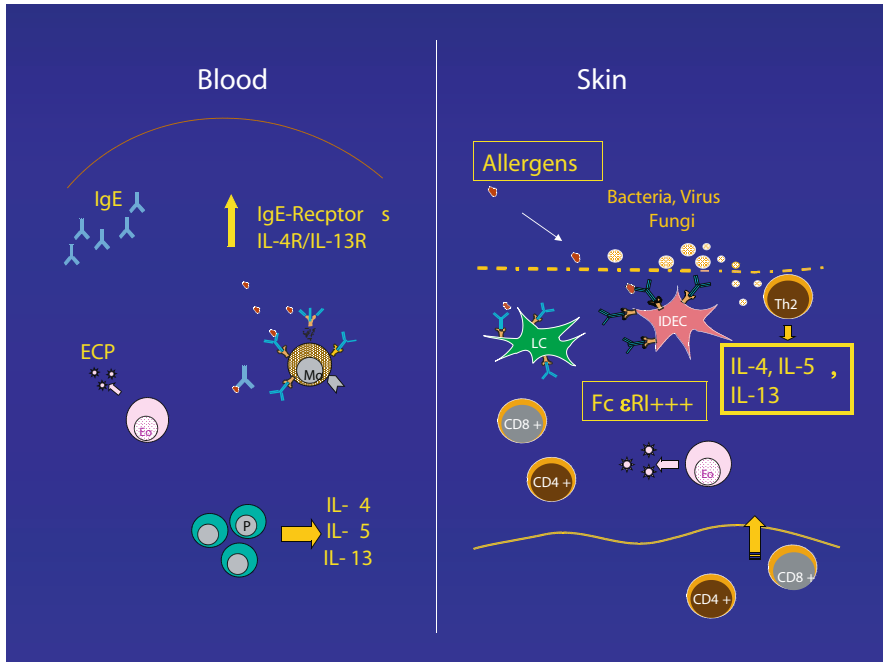

Fig. 29.3. Overview of the pathophysiological characteristics in the blood and the skin of intrinsic AE patients

lower FcεRI surface expression on the surface of skin dendritic cells in the intrinsic form of AE can be used to distinguish patients with extrinsic and intrinsic AE by immunophenotyping of dendritic cells and building a ratio of the surface expression of the high affinity receptor for IgE and the IgG receptor FcεRI/FcγRII, which is higher than 1.5 in extrinsic AE and lower than 1.5 in intrinsic AE [20, 21].

29.3.4 Eosinophils

Eosinophilic granule proteins are characteristically deposited in the skin lesions of AE [22]. As eosinophils and their granule proteins have potent inflammatory functions and are supposed to contribute by their IL-12 production to the switch of the initial Th2 immune response in the acute phase of AE into an immune response of the Th1 type in the chronic phase, they may play a critical role in the skin lesions of both extrinsic and intrinsic AE patients.

29.4 The Role of Aeroallergens and Food Allergens and the Atopy Patch Test

The application of aeroallergens such as cat dander in the so-called atopy patch test shows that it is possible to elicit eczematous skin lesions by solely external application of aeroallergens to the skin [23]. In support of this concept, in patients with positive atopy patch test reactions, a higher number of IgE-bearing dendritic cells can be found in the epidermis and dermis than in patients with negative atopy patch test reactions [24]. In kinetic studies, a rapid influx of IDEC within only 48 – 72 h after the allergen challenge has been observed in atopy patch test lesions [25]. The observation of positive atopy patch test reactions to aeroallergens, which are inducible even in the absence of elevated allergen specific serum IgE in some of the intrinsic AE patients, provides evidence for a role of local IgE and other so far uncharacterized factors in AE [24].

29.5 The Role of Microbial Infections

Similar to rhinitis or asthma, inflammatory processes in consequence of microbial infection play a major role in both the extrinsic and intrinsic form of the disease. The skin of patients with AE exhibits a striking susceptibility to colonization and infection with microbial components, such as *Staphylococcus aureus, Pityrosporum ovale,* or *Candida albicans,* which may be an important trigger factor in the proinflammatory process [26, 27]. *Staphylococcus aureus* bacteria secrete toxins, which are known to act as superantigens, such as *S. enterotoxin A* or *B* (SEA, SEB) and *toxic shock syndrome toxin-1* (TSST), 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 AE patients [28]. Together these mechanisms contribute to the increased susceptibility of atopic skin infection. The reduced amount of Th2 cells producing IL-4 and IL-13, together with the lower FcεRI expression of epidermal dendritic cells in intrinsic AE, indicate that proinflammatory mechanisms are predominant in this subtype of AE. Recently it has been shown that in 50% of the AE patients with low IgE serum levels, exclusively allergen-specific IgE against microbial components could be found. This observation raises the question, whether a hyperreactivity to microbial components might be a trigger factor especially in the intrinsic subtype of AE [19].

29.6 Blood

Several abnormalities in soluble factors, cellular characteristics, and other mediators in the blood are characteristics of the complex pathogenesis of AE.

An elevation in total serum IgE and in the serum levels of specific IgE to aero- and food allergens is characteristic of extrinsic AE. 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 extrinsic AE patients (Figs. 29.1, 29.2).

Eosinophils play a major role in AE and become active by releasing their toxic eosinophilic granules, which constitute a major portion of their cellular protein content. Notably, in both forms of AE, 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 extrinsic AE [29, 30].

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 extrinsic AE display enhanced surface expression of the high and low affinity receptor for IgE (FcεRI and FcεRII) and the interleukin-4 receptor (IL-4R)α chain and in this way can be distinguished from monocytes in patients with intrinsic AE [15].

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 intrinsic form of AE. In contrast to the extrinsic form, in intrinsic AE, 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 [15]. Recent studies support the hypothesis that single nucleotide polymorphisms (SNPs) in the IL4RA gene might underlie the distinct IL-4R expression and response to IL-4 in extrinsic and intrinsic AE patients [15].

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 develop atopic diseases later on in life [31].

In view of these data, the increased level of IL-13 in the sera of patients with intrinsic AE [15] indicates that IL-13 might be involved in the pathogenesis of this form of AE by stimulating eosinophils, interacting with B-cells, altering the IL-13R signal transduction pathway, or activating other unknown mechanisms [32]. Increased peripheral blood IL-4 and IL-13 production in intrinsic AE even in the absence of enhanced IgE levels indicates the predominance of an immune response of the Th2 type even in this subtype [15].

29.7 Conclusion

In the light of recent developments the existence of extrinsic and intrinsic subtypes of AE might be the reason for the high number of contradictory results of studies, which were aimed to identify gene regions or immunological parameters of AE patients in the past. Therefore, it would be important for future studies to attach great importance to a clear-cut and detailed phenotypical and immunological evaluation of the affected individuals investigated to be able to differentiate between intrinsic and extrinsic AE patients and to analyze and interpret the data in this context. At present, it has not been evaluated yet whether patients with extrinsic AE, in contrast to patients with intrinsic AE have a higher risk to develop allergic rhinitis or allergic asthma. In addition, it would be interesting to evaluate the frequency of concomitant intrinsic rhinitis and intrinsic asthma in the intrinsic subgroup of AE.

Future directions of research in AE 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 the intrinsic to the extrinsic form of AE in the same individual. This might enable us to optimize our treatment strategies of both extrinsic and intrinsic subforms of AE.

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