

J. Ring
M. Thewes

The clinical expression of allergy in the skin

Authors' affiliations:

J. Ring, M. Thewes, Division of Environmental Dermatology and Allergy GSF/TUM, Department of Dermatology and Allergy Biederstein, Technical University Munich, Munich, Germany

Correspondence to:

Prof. Dr J. Ring
Department of Dermatology and Allergy
Biederstein
Technical University Munich
Biedersteiner Straße 29
80802 Munich
Germany

The cutaneous immune system has evolved to protect the organism from potential exogenous pathogens in a complex manner. Recent investigations of the special role of the skin in allergy have focused on the proinflammatory potential of various cells such as Langerhans' cells, keratinocytes, mast cells (MC), endothelial cells, and dermal fibroblasts. Furthermore, in processing and reacting to antigens, infiltrating inflammatory cells (lymphocytes; monocytes; macrophages; and eosinophil, neutrophil, and basophil granulocytes) play an important role both by cell-cell interactions with specific receptors on cell surfaces and via soluble mediators.

Anatomic peculiarities of the skin in influencing the clinical expression of allergy

Keratinocytes (KC)

The process of keratinization, leading to the formation of a stratum corneum as representation of the skin barrier function against environmental influences, distinguishes the epidermis from other epithelial tissues. KC have long been regarded as the structural backbone of the epidermis only. Recently, it has been found that they play an active role in the pathogenesis of allergic diseases (1). They secrete a wide variety of cytokines and various eicosanoids. For example, interleukin (IL)-1 can activate Langerhans' cells (LC) in the epidermis. Fibroblasts are stimulated to proliferate and secrete collagen and collagenase by IL-1. Other cytokines secreted by stimulated KC are IL-6, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), and several chemokines (1, 2).

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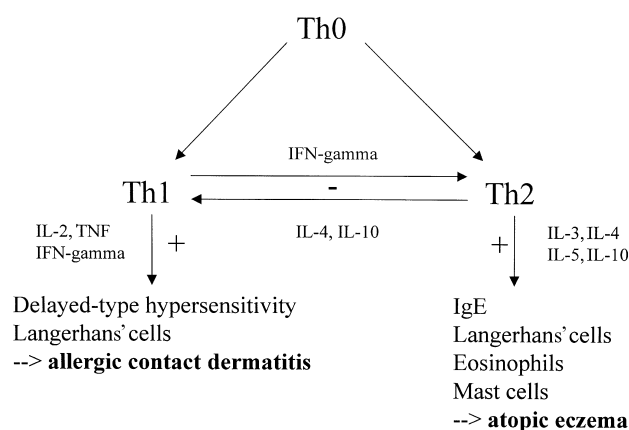


Figure 1. T-cell interactions involved in early phase of induction of atopic as opposed to classic contact dermatitis.

Langerhans' cells (LC)

The bone-marrow-derived LC play an integral role in the processing of antigens and are located primarily within the epidermis in varying concentrations ranging from 400 to 1000 mm². These cells have the capacity to bind small molecular compounds and to present allergens involved in classic allergic contact dermatitis (29). Antigen presentation involves endocytosis as well as cyclic processing from cytoplasm to cell membrane into structures of the major histocompatibility complex (MHC). The increase of the LC-specific intracellular Birbeck granules during this process reflects the functional role in the processing of antigens. LC leave the epidermis after cutaneous immune stimulation to migrate to the draining regional lymph nodes. After a specific interaction between an immune response-associated surface antigen and a specific T-cell receptor in a sensitized individual, additional amplification of the immune response is achieved through release of IL-1 and -2 as well as of interferon (IFN) from participating LC, KC, and T cells.

Recent studies have focused on the role of LC, which have been observed to carry IgE in patients with severe atopic eczema as well as in patients with other, IgE-related, inflammatory skin diseases. There was a positive correlation between the number of IgE-positive LC in the epidermis and the serum IgE concentrations. The IgE-binding site on LC is the focus of current research (3, 4). LC express both the low-affinity IgE receptor (IgE FcεRII [CD23]) and the high-affinity receptor (FcεRI), and the IgE-binding protein (EBP) (3, 5).

Lymphocytes (LyC)

The CD4⁺ LyC play an integral role in cutaneous immune responses and can be subdivided into two major cell types

producing characteristic cytokine profiles (Fig. 1): T cells, which produce IL-2, IFN, and tumor necrosis factor (TNF), are referred to as TH1 cells and are involved as effector cells in cell-mediated immunity reactions such as delayed-type hypersensitivity or allergic contact dermatitis. The TH2 CD4⁺ LyC produce IL-3, IL-4, IL-5, and IL-10 and facilitate humoral immune responses of the IgE type, while down-regulating TH1-mediated responses. TH1 cells preferentially activate macrophages that kill or inhibit the growth of pathogens, whereas TH2 cells facilitate humoral responses and inhibit some cell-mediated immune responses (6–8). Recently, a qualitative distinction between (difficult to stimulate/afferently acting) naive and (easy to-stimulate/ efferently acting) effector memory T cells was confirmed. For example, both types of T cells are essential in allergic contact dermatitis. A high-molecular-weight isoform of the leukocyte common antigen (LCA) characterizes naive T cells (cluster of differentiation [CD45RA]), whereas only a truncated form of the molecule is expressed on effector/memory T cells (CD45RO). T cells with the naive phenotype show excellent proliferative capacity and IL-2 production. CD45 RO LyC, however, tend to home to the same tissue environments where they were first exposed to antigen, as, for example, in allergic contact dermatitis (7).

The paradigm of CD4⁺ LyC with two opposing cytokine profiles is reflected in the pathogenesis of two very common allergic skin diseases, atopic eczema and allergic contact dermatitis (Fig. 1).

In inflammatory skin lesions, 85% of the infiltrating T cells express a surface glycoprotein referred to as the cutaneous lymphocyte-associated antigen (CLA). This antigen binds to E-selectin – a member of the superantigen family specifically expressed in epithelial cells – which is often found in the setting of chronic inflammation in the skin. CLA is found on only 16% of peripheral blood T cells and on 5% of LyC within lymphoid tissues (and noncutaneous sites of chronic inflammation), providing further evidence that this molecule may play a role in lymphocyte homing to the skin (8a).

The complex consisting of LC, cytokine-producing KC, and skin-targeting LyC has been referred to as skin-associated lymphoid tissue (SALT) and appears to be an analog of gastrointestinal tract-associated lymphoid tissue (GALT).

Mast cells (MC)

Another important cell in the skin immune system is the skin MC. These cells originate in the bone marrow from a

pluripotent cell and migrate to peripheral tissue, where they are influenced by the microenvironment to develop into two phenotypes resembling either the mucosal MC or the connective-tissue MC (9). They are never found within the epidermis but are located in the superficial dermis, where they are closely associated with blood vessels, allowing these cells to be uniquely positioned to react to allergens diffusing through the epidermis as well as to allergens hematogenously presented through the cutaneous vascular system. The close association with dermal nerves may explain why MC play a key role in various dermatologic diseases with psychosomatic involvement such as urticaria and atopic eczema (10, 11). Like that of the peripheral blood basophil, the MC membrane contains high-affinity receptors for IgE involved in the mediation of allergic type I disease. Furthermore, these cells characteristically contain potent chemical mediators either preformed or newly generated during the course of MC activation (12). Some of these have vasoactive properties, others exhibit chemotactic or enzymatic activity, and others are proteoglycans. It is not surprising that cutaneous MC are unique in the fact that they display an optimal release of mediators at 30°C, which is slightly cooler than core temperature.

Mediators and chemokines

Histamine is the best-known MC-derived mediator. It is synthesized from amino-acid histidine by histidine decarboxylase and is stored in MC or basophil granules. It acts via specific receptors of the H₁- or the H₂-type. If it is injected into the skin, a wheal-and-erythema reaction in the form of urticaria is produced that is partially blocked by H₁-antagonists, not affected by H₂-antagonists, and inhibited by the synergistic action of both H₁- and H₂-antagonists.

Furthermore, the products of immunologically active cells are cytokines that are effective in modulating proliferation, differentiation, activation, migration, or secretion of other inflammatory cells. The cytokines include at least six distinct families according to their functions or similarities in structure: the interleukins, the colony-stimulating factors (CSFs), the interferons (IFNs [13]), the tumor necrosis factors (TNF), the chemokines, and the growth factors (12).

Among newly generated mediators, the eicosanoids, major metabolites of arachidonic acid including leukotrienes, prostanoids, thromboxanes, and hydroxyeicosatrienoic acids, are essential in the interaction of inflammatory cells. They are thought to have only local

effects because of their rapid degradation after release from cells (autacoids [12]).

The biologic functions of neuropeptides such as substance P, VIP, and CGRP are various and include effects on vascular tone, vascular permeability, cellular proliferation, immunoglobulin production, cytokine production and secretion, mediator release, phagocytosis, chemotaxis, and endothelium adhesion molecule expression (8).

Pathophysiologic peculiarities of the skin in influencing the clinical expression of allergy

Already in 1963, Coombs & Gell (14) had classified the mechanisms of immune tissue injury into four distinct types of reactions. Although partly too simplistic and not reflecting the complex interplay of inflammatory cells and cytokines, this classification is still helpful for didactic reasons.

Anaphylactic or immediate hypersensitivity (type I)

Bivalent antigen binding to preformed IgE antibodies attached to the surface of MC or basophils causes release of the already mentioned inflammatory mediators. The best examples of type I skin disease are urticaria and angioedema. Contact urticaria may occur when the allergen is applied directly to the skin. Skin lesions caused by TH₂-mediated reactions, as in the early phase of atopic eczema, also have a type I hypersensitivity component.

Cytotoxic reactions (type II)

Cytotoxic reactions involve the binding of either IgG or IgM antibody to cell-bound antigens. Antigen-antibody binding results in activation of the complement cascade and the destruction of the antigen-carrying cell. In the skin, cytotoxic reactions are manifested as noninflammatory purpura; e.g., drug-induced allergic thrombocytopenic purpura.

Immune complex reactions (type III)

Immune complexes are usually cleared from the circulation by the phagocytic system. Under certain conditions, immune complex deposits in tissues or in vascular endothelium can produce complement-dependent tissue injury. These reactions occur 4–6 h after interaction of

soluble antigen with (complement-fixing) soluble IgG antibody. The most common example of type III allergy in dermatology is the Arthus reaction of allergic leukocytoclastic vasculitis. Furthermore, erythema nodosum and erythema multiforme may be included as skin-associated type III reactions. The systemic manifestations of serum sickness often include urticarial skin changes.

Delayed-type hypersensitivity (type IV)

These reactions occur 24 h or more ("delayed hypersensitivity") after interaction of soluble antigen with sensitized, cytokine-secreting TH₁ LyC ("cell-mediated immunity"). The best example of type IV allergy in the skin is the classic allergic contact dermatitis. In the late phase of atopic eczema, TH₁ mechanisms also seem to play a role. Other skin-associated type IV reactions include many forms of exanthematous drug eruptions.

Recently, the following two additional types (6) were added to the above-mentioned classification by Coombs & Gell

Granulomatous reactions (type V)

In this type, slowly occurring (2–3 weeks) and long-lasting (up to 1 year) inflammatory skin lesions to exogenous substances with histologic features of epithelioid cell granulomatous infiltrates are seen, as after xenogeneic collagen injection or zirconium contact.

Stimulating/neutralizing hypersensitivity (type VI)

These reactions involve specific hormone-like effects of antibodies without amplifying inflammatory reactions. Examples are autoimmune disease of the thyroid or myasthenia gravis.

Clinical expression of allergy in common selected skin diseases

Urticaria, angioedema, and anaphylactoid reactions

Urticaria and angioedema often occur together (15). They are also often the first part of anaphylaxis or anaphylactoid reactions. Urticaria presents with pruritic, transient, mostly erythematous, sometimes white wheals without postinflammatory hyperpigmentation. A duration longer than 24 h, petechial bleeding, and postinflammatory hyperpigmentation suggest urticarial vasculitis. Angioedema is characterized by deep dermal and subcutaneous swelling, frequently involving the tongue, face, and

genital region, in most severe cases leading to laryngeal edema.

Urticaria is typically classified as either acute (duration of less than 6 weeks), chronic (longer than 6 weeks), or chronic relapsing. Acute disease is most commonly due to infection, medications, foods, or insect bites (16). Chronic relapsing urticaria has been associated with a multiplicity of underlying disorders. In addition, cases of physical urticaria evoked by cold, heat, exercise, pressure, vibration, solar radiation, or water have to be regarded separately (17).

In the pathogenesis of urticaria and angioedema, different mechanisms, including allergic and pseudo-allergic reactions, have to be discussed. Allergic urticaria is mostly an IgE-dependent (type I) hypersensitivity reaction. Contact urticaria is seen after topical application of some antigens (e.g., latex [18]). The urticarial response is not confined to the contact area but can develop into generalized reactions ("contact anaphylaxis").

Apart from IgE-mediated urticaria, there is also immune-complex (type III)-induced urticaria as part of the spectrum of serum sickness and immune-complex anaphylaxis (19).

Complement (C1-esterase) deficiency, i.e., lack or loss of function of the proteinase, is seen in hereditary angioedema and has to be excluded in the differential diagnosis (17).

Pseudo-allergic reactions include nonimmune mediator secretions as in direct MC or basophil release reactions through chemicals, such as radiocontrast media, cyclooxygenase blockers, or food additives (20).

Atopic eczema/dermatitis (AE)

The classic triad of atopy includes AE, allergic bronchial asthma, and allergic rhinoconjunctivitis. AE often starts in childhood but can occur in all age groups, alone or associated with respiratory atopic disorders. In recent years, the prevalence of AE has increased markedly (10–20% in schoolchildren) (21). AE is an inflammatory disorder characterized by chronic relapses of a typically eczematous eruption, usually associated with a family history of atopic diseases. The eruption is typically extensor-predominant in infants and young children, but it involves the flexural surfaces in older children and adults (22).

AE is clearly a disorder with a strong genetic influence, whereas secondary bacterial and viral infections can modify the phenotypic expression. Other trigger factors include physicochemical irritants and emotional and physical stress (22).

The role of allergy in AE has been disputed with the focus on IgE-mediated sensitization. The role of other types of allergic reactions is less well studied. There is a vast amount

Table 1. Classification of exanthematous drug eruption according to form of skin lesions

Urticarial
Erythematous/vesicular (eczematous)
Maculo/papular
Exfoliative dermatitis (erythroderma)
Purpuric
Thrombocytopenia
Vasculitis
Papura pigmentosa progressiva
Bullous
Erythema exsudativum multiforme
Fixed drug eruption
Lyell's syndrome (toxic epidermal necrolysis)
Lichenoid
Acneiform
Psoriasiform
Lymphohistiocytic infiltration

of literature about a decreased tendency for patients with AE to develop contact allergy. However, most of these studies are retrospective and without adequate controls. We found no overall differences in frequency of contact sensitization between atopics and nonatopics (23).

It also has been shown convincingly by provocation tests under double-blind conditions that food allergy plays a role in AE (24). Food additives can also provoke eczematous skin lesions in a placebo-controlled oral provocation test (20).

The markedly elevated IgE-antibody production has been regarded by some authors as a mere epiphenomenon relevant to respiratory symptoms, but not to skin lesions (24). Recently, there is increasing evidence that IgE-mediated sensitization also plays a decisive role in the pathogenesis of the eczematous skin lesions. This has become clear through investigations of IgE on dendritic epidermal LC. Recently, the high-affinity IgE receptor (Fcε RII) has been detected on this cell, whereas it had been previously believed to be present only on MC and basophils (3, 5). The proof of the clinical relevance of these findings is the elicitation of eczematous skin lesions by epidermal application of allergens known to induce IgE responses (e.g., house-dust mite [25]). We have standardized the procedure and called it the "atopy patch test" (26, 27). However, not only allergens can provoke skin reactions in patients with atopic eczema. As with other atopic diseases, one can classify AE, according to the relative role of IgE allergic sensitization on one hand, and nonspecific hyperreactivity on the other hand, into an "extrinsic" and an "intrinsic" form (28).

Allergic contact dermatitis/eczema (ACD)

ACD is one of the most common skin diseases and a major occupational disease. *Allergic* CD has to be distinguished from *toxic (irritant)* CD. While the acute treatment of these diseases is similar, it is essential in ACD to identify the

specific allergen by patch testing. Only then can avoidance and cure be achieved (29).

In histopathology, ACD is characterized by acanthosis, parakeratosis, exocytosis, and spongiotic dermatitis. Spongiosis refers to the accumulation of intercellular edema between KC, in some cases progressing to vesicle formation, especially on the palms and soles (e.g., dyshidrotic eczema). ACD may be acute, subacute, or chronic.

ACD is initiated via LC presenting a chemical substance (hapten) to LyC in a classical TH1 immune response (type IV delayed-hypersensitivity reaction) (Fig. 1) and can be subdivided into five pathophysiologic steps (30):

- 1) binding of allergen to skin components
- 2) recognition of allergen-modified LC by specific T cells
- 3) proliferation of specific T cells in draining lymph nodes
- 4) preparation of specific T-cell progeny over the body
- 5) efferent phase via CLA-positive LyC and cytokines.

The entire process of the afferent limb requires from at least 3 days to several weeks, whereas full development of the elicitation phase requires only 24–48 h.

Photosensitization

A special form of ACD is photoallergic contact dermatitis, which has to be distinguished from phototoxic CD by a photopatch test (31). The mechanisms resemble those in allergic or toxic (irritant) CD except that they require the activation of an ultraviolet light-absorbing substance in the skin. Photosensitization also can occur after systemic drug application, giving rise to symmetric light exposed exanthematous eruptions (32).

Exanthematous drug eruptions

Adverse reactions to drugs are a major problem in clinical medicine. Currently, 15–30% of all hospitalized patients experience at least one adverse drug reaction. The clinical history is the most important tool in evaluating possible drug-related reactions. Because the clinical appearance of exanthematous drug eruptions can be quite variable, they are subdivided according to the form of skin lesions (Table 1).

The pathogenesis of the various exanthematous drug eruptions is not well established. Sensitized LyC and positive LyC transformation tests with eliciting drugs have been described. Therefore, they are commonly classified among type IV reactions (3–36).

The most severe variants of drug-induced exanthematous drug eruption are erythema exsudativum multiforme major

with mucous membrane involvement (Stevens-Johnson syndrome [34]) and toxic epidermal necrolysis (drug-induced Lyell's syndrome [35]). In spite of modern intensive therapy, the lethality of the latter condition is still around 30%. Among the drugs most commonly named as elicitors of drug-induced Lyell's syndrome are antimicrobial drugs (e.g., sulfonamides), analgesics (e.g., pyrazolones), central nervous system-acting drugs (e.g., phenytoin, barbiturate), and allopurinol [34].

Conclusions

Various pathophysiologically different and highly allergic reactions are manifested on the skin. Knowledge of the basic and clinical aspects of skin allergies greatly enhances the understanding and improved practical management of many patients in the interdisciplinary field of allergy.

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