

Editorial

The skin as a target for allergic diseases

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Introduction

Over the past two decades, it has been clearly shown that the skin is much more than just a covering and protecting coat. Indeed, it represents an integral component of the immune system, and, like other interface organs such as the lungs or gut, it could in many ways be considered the front line of immune defense. The mechanisms of skin immune defense can be broadly divided into two categories: innate, or *nonadaptive*, immune responses and *adaptive* immune responses (1, 2). The innate immune response of the skin is achieved through the presence of evolutionary, highly conserved antimicrobial peptides such as β -defensin (3). The adaptive component contains the full repertoire of immune mechanisms employed by the immune system in the other organ systems. In contrast to innate immunity, this type of immune defense is antigen-specific and is amplified upon re-exposure to the same antigen. Thus, specificity and memory are key features of the adaptive immune system and are mediated by various cellular components of the epidermal and dermal compartments.

The concept of the skin as an immunologic organ – a short review

In 1970, Fichtelius et al. (4) suggested that the skin may be considered a “first-level lymphoid organ” comparable to the primary lymphoid tissue thymus. They suggested that lymphoepithelial microorgans in the skin of neonates, localized at the orifices of the body, reflect educational lymphoid environments in which systemic immunity to exogenous antigens is formed. In 1978, Streilein et al. (5–7) coined the term “skin-associated

lymphoid tissues (SALT)”, including keratinocytes, intraepidermal Langerhans cells (LC) as antigen-presenting cells (APC), skin-seeking T cells, endothelial cells of the skin directing these skin-seeking cells into the dermis, and the skin-draining lymph nodes, this complex being the specific localization of the induction of immunity by the antigens processed and transported by LC. Later, Bos et al. (1, 2) proposed the term “skin immune system (SIS)” to denote the complex of immune-response-associated cells present in normal human skin, and Sontheimer (8) completed this concept by his notion of the “dermal immune system (DIS)”, referring to the center of immunologic reactivity in most immunodermatoses. More recently, in 1993, Nickoloff (9) suggested that the DIS is the cellular and humoral counterpart of the SALT. It includes fibroblasts, mainly because they are intrinsically related to the homeostasis of other skin components such as the epidermis. With the exception of SALT lymph nodes and DIS fibroblasts, these two concepts might also be considered functional subsystems of the SIS.

Functional architecture of the skin immune system (SIS)

The SIS is an organ-related immunologic unit which has to fulfill various protective and effector functions due to the interface status of the skin (10). This system comprises a static component and a more dynamic component.

The cellular elements of the static component are those cells which are anatomically part of the skin architecture, such as keratinocytes, fibroblasts, and endothelial cells, and which provide the necessary background for the immune reaction by producing proinflammatory cytokines.

The dynamic component is composed of leukocytes, i.e., APC such as LC, dendritic cells (DC), and macrophages, as well as T cells, which are committed to spending a limited time in the skin. Schematically, these cells, being equipped with immune recognition receptors, e.g., TCR and FcR, provide the specificity of the immune reaction. A circulating pool of skin-homing T cells, identified by the CLA antigen, represents the cellular basis of the immunologic memory of the skin. The great variations in the clinical appearance of skin diseases are the product of complex and subtle interactions between the static and dynamic components. Hence, the characteristic lesions of a defined condition, such as psoriasis, most probably reflect a distinct and unique immunologic microenvironment.

Clinical expression of various immunoallergic reactions in the skin

IgE-mediated reactions

Urticaria is the paradigmatic IgE-mediated disease of the skin. It is estimated that up to 20% of the general population will experience an episode of urticaria. Clinically, urticaria is subdivided into an acute form, with a duration of less than 6 weeks, and a chronic form. Whereas the acute form usually is a self-limiting condition that requires no or only short-term medical intervention, chronic urticaria follows an unpredictable course and remains a diagnostic and therapeutic challenge. A cause can be determined in only 5–20% of chronic urticaria cases. This contrasts strongly with acute urticaria, for which a cause can often be established. On a pathophysiologic basis, urticaria can be subdivided into IgE-dependent (11–15), complement-mediated (16–24, nonimmunologic (25–29), and idiopathic forms (11–13).

The fact that all types of urticaria share a similar clinical presentation is related to the fact that all causative pathophysiologic mechanisms eventually lead to the degranulation of mast cells. The typical triple response of Lewis comprising of vasodilation, axon reflex, and wheal formation (e.g., edema) that is seen in all forms of urticaria is the macroscopic consequence of the release of histamine and other mediators stored in mast cells (30–34).

In his forthcoming review article for *Allergy* (Review Series V), “Chronic urticaria in childhood”, M. Greaves will discuss the latest developments of this provocative theory that most cases of chronic urticaria in fact reflect an autoimmune disease in which the key element seems to be sensitization targeting the high-affinity receptor for IgE, Fc_εRI.

Autoimmune blistering diseases

Among the IgG-mediated hypersensitivity reactions, pemphigus vulgaris and its variants belong to the so-

called autoimmune blistering diseases. In these disorders, the immune system has produced autoantibodies against various components of the so-called desmosomes, which are the connection points between keratinocytes in the skin epithelium. These antibodies can be demonstrated by direct immunofluorescence of skin biopsy specimens. Several antigens, e.g., desmoglein I and desmoglein III, have been characterized biochemically and at the molecular biologic level. Their distinct localization among the different strata of the epidermis explains the various clinical forms of pemphigus reported so far. These autoantibodies seem to alter the intercellular cohesion between keratinocytes directly, but the participation of the complement system in this phenomenon remains unclear (36, 37).

Arthus reactions

Purpura is the clinical sign of an allergic and destructive (leukocytoclastic) allergic reaction occurring in the upper skin vessels. Direct immunofluorescence of lesional skin usually shows deposits of IgG, IgM, complement, and fibrinogen in the vessel walls. Such an allergic reaction may have several different causes, ranging from viral hepatitis or streptococcal angina to drug intolerance, or it may appear in the hemopathic context as in the monoclonal gammopathies or autoimmune diseases such as lupus erythematosus. Antigens injected intradermally combine with specific antibodies from the blood immune complexes. These complexes activate complement and act on platelets, which release vasoactive amines (9, 38, 39). Complement activation leads to recruitment and activation of inflammatory cells, predominantly neutrophils, which cause tissue injury. This gives rise to local cutaneous vasculitis with necrosis.

Allergic contact dermatitis (ACD)

ACD is the archetypal cell-mediated hypersensitivity reaction in which a distinct type of DC, i.e., epidermal LC, plays a pivotal role in the sensitization phase. To describe the process very schematically, while the contact of irritant compounds on the skin leads to the secretion of TNF- α and GM-CSF by keratinocytes, low-molecular-weight haptens (e.g., nickel, DNCB, or oxazolone) stimulate the additional release of IL-1 β , IL-10, and MIP-2. These chemokines activate LC, DC, and endothelial cells, leading to an accumulation of even more DC at the site of antigen contact. Moreover, application of hapten induces the release of IL-1 β by epidermal LC and thereby promotes their egress from the epithelium.

After the uptake of the antigen, the LC process it while migrating to the regional lymph nodes, where it will be presented to antigen-specific naive T cells. Little is known about the mechanisms which enable LC to be the most efficient stimulators of naive T cells. Another

remarkable property of LC and DC is their ability to present exogenous antigens on MHC class I as well as class II molecules. This cross-priming leads to the activation of both CD4+ and CD8+ hapten-specific T cells (40, 41). Whereas classical delayed-type hypersensitivity reactions are mediated by CD4+ cells, contact dermatitis to haptens is mediated by CD8+ cells (42–44). Other cytokines released during the sensitization process have been implicated in directing the type of immune response mounted by T cells. It has been shown that IL-10 converts LC/DC from potent inducers of a primary immune response to hapten-specific tolerizing cells. A significant decrease in mRNA signals for IL-1 α , IL-1 β , and TNF- α confirms the immunomodulatory role of this cytokine in contact hypersensitivity reactions (45, 46). On the other hand, IL-12, which is released by LC/DC themselves (47), is known to be a strong inducer of the Th1 response.

Upon the second contact of the skin with a hapten, i.e., during the elicitation phase of ACD, other APC such as macrophages, dermal DC, or even less professional APC such as MHC class II-expressing endothelial cells, may stimulate the antigen-specific memory T cells and contribute to the initiation of the local inflammatory response; i.e., the dermatitis reaction.

More insights into the molecular aspects of hapten presentation and its role in the development of contact hypersensitivity reactions, focusing on one of the most common sensitizers, are presented by L. Büdinger and M. Hertl in their review article in Series V, “Immunologic mechanisms in hypersensitivity reactions to metal ions”, in this issue of *Allergy*.

Atopic dermatitis – an IgE-mediated, delayed-type hypersensitivity reaction

The emergence of atopic eczema (i.e., a cell-mediated inflammation) in atopic patients (i.e., individuals prone to have increased IgE production and to develop IgE-mediated hypersensitivity reactions) remained puzzling until, in the mid-1980s, the presence of IgE molecules on the surface of LC from patients presenting atopic eczema was first reported (48, 49). Then, a new pathophysiologic concept was proposed whereby LC armed with allergen-specific IgE trigger eczematous inflammation. One of the key elements in this concept is the expression of the high-affinity receptor for IgE (Fc ϵ RI) on these APC (50, 51). In fact, it appeared that the structure of the receptor differs from classical Fc ϵ RI in that it lacks the beta-chain. Moreover, its expression and the function may be highly variable, depending on

the microenvironment. Receptor ligation on DC in the skin putatively triggers the synthesis and release of mediators which may initiate a local inflammatory reaction, as has been demonstrated for mast cells. Thus, from a pathophysiologic point of view, Fc ϵ RI expressing DC, and particularly LC and related DC in the epidermis, have been suspected to play a crucial role in atopic dermatitis since they may represent the missing link between aeroallergens penetrating the epidermis and antigen-specific cells infiltrating the skin lesions (47, 52–55).

The role of IgE-receptor-bearing DC in the pathophysiology of atopic dermatitis will be discussed in more detail by A. Wollenberg in his review article in Series V, “Atopic dermatitis: from the genes to the lesions”.

In this context, it is of interest to consider the possibility that sensitization to aeroallergens may occur through the skin. This issue has been successfully studied by J. Saloga and coworkers in a mouse model, and the arguments for this attractive concept will be expounded in his review in this series, “Sensitization to aeroallergens through the skin: does it exist?”

Concluding remarks

Immunodermatologic investigations of the past two decades have shown that the skin represents an immunologically crucial organ and exhibits a characteristic architecture capable of complex interactions between various cellular components of the epidermis and dermis. The skin is a target of various types of allergic reactions, and it responds to allergic agents in a highly varied manner and covers a broad spectrum of clinical immune phenomena. In response to various agents, the skin represents an important source of all kinds of mediators, including proinflammatory cytokines, prostaglandins, leukotrienes, and neuropeptides. The recent progress made in understanding the ontogenesis of antigen-presenting DC and their role in the immune response has clarified some aspects of allergic skin diseases and opened new therapeutic strategies specifically designed to downmodulate ongoing inflammatory reactions. The most important goal of an effective allergy treatment seems to be to target the cells that trigger and control the key aspects of the allergic cascade, and provide the basis for new therapeutic strategies specifically designed to modulate proinflammatory events and amplify natural anti-inflammatory signals.

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