Therapy of Skin Diseases

A Worldwide Perspective on Therapeutic Approaches and Their Molecular Basis

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Immune Mechanisms

1.2

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Key Features

- Innate immunity is nonspecific and required to combat infections
- Adaptive immunity regulates antigen-specific responses
- Langerhans cells are important antigen-presenting cells of the epidermis
- Keratinocytes control skin immunity via production of mediators

Abbreviations

APC	Antigen presenting cells
CHS	Contact hypersensitivity
IL	Interleukin
LC	Langerhans cells
TLR	Toll-like recpetors
TNF	Tumor necrosis factor

The skin is endowed with the capacity to generate immune responses, which gave rise to the term "skin-associated lymphoid tissues" (SALT) [22]. The classical immune response, also referred to as the adaptive immune response, is characterized by specificity that is due to immunological memory (specific immunity) [16]. In addition, there exists another more primitive defense system, which acts in a rapid but nonspecific manner [4]. The latter is called innate immunity. Both types of responses can be generated in the skin. Adaptive immune reactions in the skin, however, are not always protective and can also be harmful in nature, e.g., allergic or autoimmune reactions. Numerous skin diseases are caused by T lymphocytes and are therefore immunologically mediated.

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1.2.1 Innate Immunity

Innate immune responses are characterized by the lack of immunologic memory. These immune reactions are less complicated than adaptive responses and therefore developed earlier in evolution [13]. Nevertheless, failures in these "primitive" immune responses may be associated with severe, even fatal health problems. Essential components of the innate response are neutrophils, eosinophils, natural killer cells, mast cells, cytokines, complement, and, as recently discovered, antimicrobial peptides. The innate response is rapid and less controlled than the adaptive immune response.

1.2.2 Activation of Innate Responses via Toll-Like Receptors

Innate immunity recognizes invading microorganisms and induces a host defense response. The molecular mechanisms that underlie innate immune recognition remained quite unclear until recently. It is now recognized that a family of pattern recognition receptors

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exists, which mediate responses to pathogen-associated molecular patterns (PAMP) that are conserved among microorganisms. Human Toll-like receptors (TLR) are one such family of pattern recognition receptors. TLR4 recognizes lipopolysaccharide and TLR9 bacterial CpG DNA sequences. The signaling pathway of TLR is highly homologous to that of the receptor for interleukin-1 (IL-1). It has been recently recognized that dendritic cells express several of the TLR. Upon activation of these receptors by microbial components, dendritic cells mature and present pathogen-derived antigens to naïve T cells, thereby inducing an adaptive immune response. Therefore, TLR are regarded as molecules, bridging the gap between innate and adaptive immunity [1]. This crosstalk between innate and adaptive immunity was further confirmed by the observation that TLR8 signaling appears to control the function of regulatory T cells [17].

1.2.3 Protection from Cutaneous Infection by Antimicrobial Peptides

To cope with an environment that is full of microorganisms, plants and invertebrates produce a variety of highly effective antimicrobial proteins. Vertebrate epithelia can also function as a source of such antimicrobial proteins. Accordingly, it was demonstrated that human epithelia, including the epidermis, secrete such antimicrobial peptides, and thereby, exhibit the capacity to mount an innate chemical defense. The first antimicrobial peptide isolated from human skin was human β-defensin-2 (hBD-2) [9]. Constitutive expression of these peptides may protect skin form bacterial superinfection, as recently demonstrated for psoriasin, which effectively protects from infection with *E. coli* [5]. Many of the peptides can be induced by bacteria and bacterial products or by proinflammatory cytokines. Bacteria may induce antimicrobial peptides via TLR, but this is certainly not the only mechanism. Enhanced expression of these peptides in psoriasis may explain the rare frequency of superinfections in this disease, whereas the expression appears to be downregulated in atopic skin, which is quite frequently superinfected [15].

1.2.4 Monocytes/Macrophages

Macrophages are phagocytic cells derived from blood-borne monocytes. Macrophages carry receptors for carbohydrates that are usually not expressed on vertebrate cells, e.g., mannose. Through this recognition pathway, macrophages can discriminate between "foreign" and "self" molecules. Furthermore, macrophages possess receptors for antibodies and complement. Hence, coating of microorganisms with antibodies and/or complement enhances phagocytosis. After phagocytosis, the microorganisms are exposed to a variety of toxic intracellular molecules, including superoxide anions, hydroxyl radicals, hypochlorous acid, nitric oxide, lysozyme, and antimicrobial cationic proteins. Macrophages can also present processed antigens to T and B cells. However, their T cell stimulatory capacity is much less effective than that of other dendritic cells.

1.2.5 Adaptive Immunity

The characteristic features of an adaptive immune response are its specificity and its improvement with each successive encounter with the same antigen due to the accumulation of a kind of memory [4, 16]. A crucial event during the generation of an adaptive immune response is antigen presentation.

1.2.6 Antigen-Presenting Cells of the Epidermis

Within the epidermis, Langerhans cells (LC) are the relevant antigen-presenting cells (APC). Ultrastructurally, LC are specifically identified by the existence of rod-shaped organelles, termed Birbeck granules. For a long time, the function of Birbeck granules was a matter of debate. A recently identified Ca^{2+}-dependent lectin with mannose-binding specificity, called Langerin, was found to be associated with Birbeck granules and even to induce formation of Birbeck granules [24]. Hence, induction of Birbeck granules appears to be a consequence of the antigen-capture function of Langerin, allowing routing of antigen into

these organelles and providing access to a nonclassical antigen-processing pathway.

CD1a is the most useful marker for detecting human LC, since within the epidermis, it is exclusively expressed on LC, both in normal and inflamed tissues [20]. This does not apply for HLA-DR antigens, since they can also be expressed on keratinocytes in inflamed skin, and thus are not suitable for detecting LC under these conditions. In addition, LC were found to express the high-affinity IgE receptor (Fc∈RI) that was initially thought to be exclusively expressed on mast cells and basophils [21, 25]. The density of LC decreases with age and is reduced in chronically UV-exposed skin [20].

To initiate sensitization, antigens must be presented to lymphocytes by APC [2]. LC play a crucial role in the presentation of antigens, which are generated in or enter the skin. Initial evidence for this assumption was provided by the observation that contact sensitization could not be induced in skin areas that were devoid of LC or in which LC had been depleted, e.g., by ultraviolet radiation [23]. However, other APC must be able to replace LC, since transgenic mice in which LC are completely depleted via the diphtheria toxin receptor technique reveal a diminished, but not abrogated, sensitization response [3]. In another study using a similar model, the sensitization response was not inhibited at all [11]. While the experimental model of these two studies allows a short-term inducible ablation of LC in vivo, another knock-out model yielding constitutive and durable absence of epidermal LC was created [10]. Unexpectedly, these mice also have an enhanced sensitization response, suggesting that LC may exert a kind of regulatory function. This "LC paradigm" proposes that LC may act in both ways: may be tolerogenic when they present antigens under steady-state noninflammatory conditions andt sensitizing upon stimulation by inflammatory mediators [12, 14].

For the MHC class II-dependent antigen presentation to T cells dendritic cells, including LC, B cells and monocytes/macrophages are required. MHC class II-associated antigen presentation primarily targets exogenous (and rarely endogenous) antigens [8, 26, 27]. Exogenous antigens are taken up via macro- or micropinocytosis or via receptor-mediated endocytosis. One example for the latter is the DEC-205 receptor (CD205), which guides antigens into deeper endocytic vesicles containing MHC class II molecules. As a consequence of this unique intracellular targeting, antigens endocytosed by the DEC-205 receptor stimulate respective T cells up to 500-fold better than antigens taken up by pinocytosis or by other receptors. The finding has fostered speculations on the use of this receptor to target antigens to DC for induction of antigen-specific immune responses, e.g., against melanoma antigens or leishmania antigens. Finally, the MHC class II molecule with the bound antigen peptide is expressed on the cell surface allowing antigen recognition by T cells carrying the appropriate T cell receptor.

1.2.7 Contact Allergy

Allergic contact hypersensitivity (CHS) is highly relevant for dermatologists, since it is the pathogenic basis for allergic contact dermatitis, one of the most frequent inflammatory dermatoses. CHS has always been highly relevant for basic immunologists as well, since numerous immunologic discoveries have been made utilizing the model of CHS [6].

Most of the contact allergens are low-molecular weight chemicals, which after penetrating into the skin, have to couple with host proteins to be able to act as full antigens. This process is called haptenization, and therefore, these low-molecular allergens are called haptens. Upon epicutaneous application to a naïve host, LC take up the hapten, process it and migrate towards the regional lymph nodes, where the antigen is presented to naïve T cells. During the emigration, LC convert from a "resting" into an "activated" functional state. This process is initiated by keratinocytes, which secrete inflammatory cytokines as a result of hapten application, and is possibly also due to direct effects of haptens on LC themselves. LC activation is associated with an induction of cytokine secretion (interleukin [IL]-1β, IL-6, IL-12, chemokines), enhanced cell surface molecule expression (MHC class I and II molecules, adhesion molecules, costimulatory molecules), antigen uptake, processing, and presentation [6].

Activation and induction of emigration of LC seems to be dependent on the capacity of haptens to induce IL-1β secretion in LC. Induction of IL-1β is an immediate effect of epicutaneous hapten application and appears to be specific for haptens, since it is not observed with irritants or tolerogens. In addition,

other cytokines including chemokines, tumor necrosis factor (TNF)-α, and GM-CSF may also contribute to LC activation and migration. Hence, the hapten itself, through its capacity to induce a specific cytokine pattern, seems to be the initial trigger factor that activates LC and induces sensitization. However, it is important to note that LC are not absolutely required for sensitization, since other cutaneous APC, such as dermal dendritic cells, may also contribute to priming of naïve T cells, after the epicutaneous application of haptens [3].

Presentation of the hapten in the regional lymph nodes causes activation of naïve T cells carrying the appropriate T cell receptor and finally results in the generation of effector cells. In contrast to other types of delayed type hypersensitivity responses, which are mediated by $CD4^+$ T cells, most haptens induce a T cell response in which mainly $CD8^+$ effector T cells are involved [6]. In addition, T cell populations are induced which downmodulate the CHS response. These inhibitory T cells, that were initially called suppressor T cells, appear to belong to the group of regulatory T cells. The balance between effector T cells and regulatory T cells seems to depend on the dose of the antigen applied, since application of extremely low doses of the hapten does not result in sensitization, but rather in tolerance [19].

T cells that have been primed in the draining cutaneous lymph nodes express the skin homing marker cutaneous lymphocyte antigen (CLA) and, thereby, exhibit the capacity to enter the skin [18]. These T cells become activated when they encounter their relevant hapten presented by LC within the skin. However, in contrast to the sensitization phase, antigen presentation can now be taken over by cells other than LC including keratinocytes, dermal mast cells and macrophages, all of which are readily capable of presenting antigens at least in an MHC class I-restricted fashion [6]. Alternatively, inflammatory cells that infiltrate the site of hapten application very early during the response may function as APC.

The earliest histopathologic findings during a CHS response are mast cell degranulation, vasodilatation, and an influx of neutrophils, followed by mononuclear and T cells. However, the pathophysiologic events that result in allergic contact dermatitis are clearly T cell-dependent, since T cell-deficient mice are unable to mount a CHS response. Yet low doses of hapten that are sufficient to stimulate hapten-specific T cells have been found to be insufficient to elicit a CHS response. This indicates that the elicitation of a CHS response requires, in addition to hapten-specific recognition, some type of proinflammatory stimulus that appears to be provided by the hapten itself and to be quite dose-dependent [7].

1.2.8 Keratinocytes are Important Regulators of Skin Immunity

Although LC are undoubtedly the major immunologic cells within the epidermis, keratinocytes are also vital contributors to the generation of a cutaneous immune response. Due to their close physical proximity, keratinocytes can affect LC by the expression of specific surface molecules. In addition, keratinocytes are able to provide signals to LC in a contact-independent manner via the release of soluble mediators, in particular, cytokines, eicosanoids and neurohormones.

For decades, keratinocytes were regarded as primitive cells endowed only with the capacity to produce keratins to provide a mechanical barrier to the outside. Therefore, it was quite surprising when it was discovered that keratinocytes could secrete immunologic and inflammatory mediators. The first cytokine identified as being released from keratinocytes was IL-1. Subsequently, keratinocytes were shown to have the capacity to secrete a multitude of soluble mediators. These included pro- and anti-inflammatory, immunomodulatory, and immunosuppressive cytokines. Among the inflammatory mediators released by keratinocytes are IL-1, IL-6, TNF-α, IL-8 and other members of the chemokine family. Anti-inflammatory activity can be mediated by keratinocytes via the release of IL-10, IL-1 receptor antagonist and TGF-β. Keratinocyte-derived immunomodulatory mediators include IL-7, IL-12, IL-15, IL-18, IL-19, IL-20, GM-CSF, G-CSF, and M-CSF, while cytokines with immunosuppressive properties include IL-10 and TGF-β. Especially, IL-10 has been successfully developed for the systemic treatment of psoriasis. Of interest is also IL-15, which appears to strengthen antimircobial immunity. Nevertheless, there are cytokines that are certainly not produced by keratinocytes, e.g., IL-2, IL-4 and interferon-γ.

Although some cytokines are produced in tiny quantities by keratinocytes, such low concentrations may suffice to exert an effect in the topical microenvironment. Any perturbation of the skin may induce the release of these mediators by the keratinocytes.

For example, UV radiation is a potent inducer of cytokine production and release. Chemicals with the potential for inducing either irritant or allergic reactions also cause cytokine release from keratinocytes.

In addition to cytokines, keratinocytes release prostaglandins and leukotrienes. Leukotriene B4 is a potent neutrophil chemoattractant. Prostaglandin E_2 possesses both inflammatory and immunosuppressive properties. The erythema caused by UV radiation is partially mediated by prostaglandin E_2. There is additional evidence that the skin, and especially keratinocytes, can function as a source of neuropeptides, in particular, substance P and pro-opiomelanocortin (POMC)-derived peptides including alpha-melanocyte stimulating hormone.

Take Home Messages

- TLRs are important receptors that induce activation of innate immune responses.
- Antimicrobial peptides are produced in the skin and protect from microbial infection.
- Langerhans cells play a role in the induction as well as suppression of immunity depending on their activation status.
- Contact allergy is a classical adaptive immune response to epicutaneously applied antigens.
- Keratinocytes can produce cytokines and thereby regulate topical as well as systemic immunity.

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