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EDITORIAL

IMPACT OF MAST CELLS ON THE SKIN

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When through the skin a foreign antigen enters it provokes an immune response and inflammatory reaction. Mast cells are located around small vessels that are involved in vasaldilation. They mature under the influence of local tissue to various cytokines. Human skin mast cells play an essential role in diverse physiological and pathological processes and mediate immediate hypersensitive reaction and allergic diseases. Injection of anti-IgE in the skin or other agents that directly activate mast cells may cause the decrease in vascular tone, leakage of plasma and may lead to a fall in blood pressure with fatal anaphylactic shock. Skin mast cells are also implicated as effector cells in response to multiple parasites such as Leishmania which is primarily characterized by its tissue cutaneous tropism. Activated macrophages by IFNγ, cytotoxic T cells, activated mast cells and several cytokines are involved in the elimination of the parasites and immunoprotection. IL-33 is one of the latest cytokines involved in IgE-induced anaphylaxis and in the pathogenesis of allergic skin disorders. IL-33 has been shown in epidermis of patients with psoriasis and its skin expression causes atopic dermatitis and it is crucial for the development of this disease. Here we review the impact of mast cells on the skin.

Skin is the largest organ in the body, and it is an essential physical barrier between internal and external environments, representing an important site of entry of microbes. Skin contains specialized cutaneous immune cells, and when in the skin a foreign antigen enters, it may provoke immune

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responses and inflammatory reactions (1). However, little is known about the physiopathology of immune cells in the skin, even though this organ represents an important portal antigen entry. Many immune responses are initiated in the skin which contains specialized cutaneous immune cells such as lymphocytes, and antigen presenting cells. Mast cells (MCs) are located around the small vessels and are involved in vasodilation (2). They derive from bone marrow, progenitors migrate to the peripheral tissue and undergo differentiation *in situ*. MCs mature under the influence of local tissue, through various cytokines such as stem cell factor (SCF) (3). They are important for both innate and adaptive immunity and they are activated by cross-linking of FcεRI molecules, which are involved in the binding of multivalent antigens to the attached IgE molecules, resulting in a variety of responses including the immediate release of potent inflammatory mediators (4-5). However, knockout mice mast cells lacking IgE have very low levels of FcεRI (6). The antigen binding to IgE cross-link FcεRI in mast cells cause the release of mediators that provoke hypersensitivity reaction, including TNF that can up-regulate endothelial expression of E-selectin and ICAM-1 (7). There are three types of mast cell biological responses: a) secretion of their granules; b) synthesis and secretion of lipid mediators; and c) synthesis and secretion of cytokines (8).

It is well known that mast cell development, *in vivo* and *in vitro*, depends on stem cell factor and IL-3 produced by helper T cells. Cytokine generation by activated mast cells is a consequences of a newly induced cytokine gene transcription in these cells. Stimulation of mast cells leads to NF-kB and AP-1 activation, with the production of many cytokines such as IL-33, TNF-alpha, IL-6, IL-5, IL-4, IL-1, IL-13, and GM-CSF (9) and various chemokines (MIP-1alpha, MIP-1beta, etc.) (10). However, TNF, like biogenic amines and enzymes also can be stored in the granules and be rapidly released after mast cell stimulation. Some of the above-mentioned cytokines are also produced by T cells which are recruited into the site of allergic reactions.

In addition, stimulated mast cells result in the *de novo* synthesis and release lipid-derived mediators, such as prostaglandin D2, platelet-activating factor (PAF) and leukotrienes: LTC4, LTD4 and LTE4, which are called slow-reacting substance of anaphylaxis (SRS-A). When these leukotrienes are injected into the skin they produce a long-lived wheal and flare reaction along with preformed mediators, dependent on mast cell activation (11). Leukotrienes and PAF are thought to be the major mediators of acute broncho-constriction in asthma. Experimental inhibition of mast cells with cromolyn and corticosteroid therapy which inhibits cytokine generation drastically reduce airway inflammation. There are two subsets of mast cells: mucosal mast cells and connective tissue mast cells, however, their phenotypes are not distinct lineages. The human mucosal mast cells are found in intestine and alveolar lung and their presence and reproduction are T cell-dependent. Connective tissue mast cells are little T cell-dependent and are found in the skin and intestinal sub-mucosa. In the skin, human connective tissue mast cells play an essential role in diverse physiological and pathological processes, and mediate immediate hypersensitive reactions

Table I. *Cellular components of the skin.*

EPIDERMIS	Keratinocytes Melanocytes Langerhans cells T Lymphocytes (CD8+)
DERMIS	T lymphocytes Macrophages Perivascular mast cells

Table II. *Biochemical events of mast cell activation.*

ALLERGEN→ FcεRI receptor→Lyn tyrosine kinase →Syk tyrosine kinase PP→Ras-MAP kinases→Cytokine gene expression→Cytokine RNA→ Intracellular cytokines →Secretion of cytokines (TNF).

and allergic diseases along with basophils and eosinophils. The dermatologic side effects are the most common adverse effects associated with epidermal growth factor receptor tyrosine kinase inhibitors and immunological mechanisms are considered to be involved (12).

Immediate hypersensitivity reaction occurs in within minutes after intra-dermal injection of an allergen, the injection site becomes red from dilated blood vessels, with edema and swells as a result of leakage of plasma. Injection of anti-IgE in the skin or agents that directly activate mast cells such as complement fragments C5a, C4a, and C3a, or occurred local trauma, can also activate mast cells even in non-atopic individuals (13). In the skin, the poison injected by an insect sting activates mast cells following mediators, and TNF release which may cause the decrease in vascular tone, leakage of plasma and may lead to a fall in blood pressure with fatal anaphylactic shock (14). The late-phase reaction appears at two to twenty hours later with *in situ* infiltration of Th2 cells, eosinophils and neutrophils, but not mast cells, and may lead to chronic inflammatory diseases such as eczema (atopic dermatitis), allergic rhinitis and asthma (15). Urticaria and eczema, are largely mediated by histamine, therefore using H1 receptor antagonists (antihistamines) can have a great relief effects. In the late-phase reaction, Th2 cells produce TNF-alpha, IL-4 and other cytokines which act on endothelial cells and provoke inflammation. IL-4 is a B cell growth factor, important for the production of IgE. IL-4 knockout mice or mice treated with anti-IL-4 antibody, do not make IgE and seem to be less resistant than normal mice to some infections. Therefore mast cells play an important protective role in infections and innate immunity (16).

Mast cells are effective sentinel cells and have been implicated as effector cells in response to multiple parasites and other organisms. For example, Leishmania is primarily characterized by its tissue cutaneous tropism and ninety percent of all Leishmania infections are restricted to the skin (17). Therefore, protective immunity against Leishmania is critical for the host defense against this parasite. In cutaneous leishmaniasis, and several other parasitosis, development of protective immunity is dependent on the production of IFNγ by T lymphocytes. Infected activated macrophages by IFNγ, cytotoxic T cells, mast cells and several cytokines such as IL-1, TNFα, IL-12, IL-23 and IL-27 are involved in the elimination of parasites and immune protection.

Therefore, in the beginning of skin lesions, resident macrophages occur; while in the second phase immigration and activation of cells of the innate immune system such as resident mast cells, and neutrophils are most prominent. In the third phase there is a migration of dendritic cells and T cells which promote an involution of lesions.

Mast cell–neuronal interactions might be involved in the pathophysiology of psoriasis, which is a prevalent immune-mediated disease involving primarily the skin, and might participate in the exacerbation of symptoms by stress (18). Available evidence indicates that psoriasis, which involves skin inflammation, and infiltrating leukocytes play key roles in driving the disease. Therefore, psoriasis is dependent on cells of the innate and adaptive immune systems interacting with keratinocytes and other resident cells in the skin, including fibroblasts, mast cells and endothelial cells (19).

IL-33 is one of the newest members of the IL-1 family of inflammatory cytokines, and was recently shown to mediate IgE-induced anaphylaxis in mice (20). IL-33 also induces release of IL-6 from mouse bone marrow–derived cultured mast cells, and IL-8 from human umbilical cord blood–derived cultured mast cells (21). It has been reported that IL-33 is involved in the pathogenesis of several allergic disorders such as rheumatoid arthritis, asthma and allergic rhinitis. IL-33 is capable of augmenting the effect of SP on mast cells to release VEGF, thus increasing vascular permeability and contributing to inflammation. VEGF is a major proangiogenic factor involved in many inflammatory diseases and psoriatic plaques in the skin contain increased levels of VEGF compared with normal skin (22). Mast cells can secrete VEGF in response to IgE, and other factors (22) and epidermal overexpression of VEGF in transgenic mice leads to a phenotype nearly identical to that of psoriasis (23). In the affected psoriatic skin, other possible sources of IL-33 may include infiltrating lymphocytes, proliferating keratinocytes, as well as endothelial cells from new vessels. SP-positive nerve fibers has been shown to be denser in psoriatic skin and to have increased numbers of mast cell contacts compared with normal skin. The abil-

ity of IL-33 to augment the effect of SP on inducing mast cell release of VEGF is certainly relevant, as angiogenesis is at the core of psoriasis pathogenesis (24). Activated skin mast cells increase vascular permeability through the activation of CRH receptor-1 which is found to be high in several inflammatory skin diseases such as chronic urticaria, psoriasis and atopic dermatitis (25).

Atopic dermatitis has a neuroimmunological mechanism in the skin and profoundly affects the patient's quality of life. Clinically, mast cells accumulate in the skin lesions of patients with atopic dermatitis, with an elevation of histamine and IgE levels in the blood. Recently, an increase in IL-33 has been shown in the epidermis of patients with psoriasis, a skin disease which is mediated mainly by Th1 and Th17 cells (26). IL-33 skin expression causes atopic dermatitis-like cutaneous manifestations and this cytokine contributes to the pathogenesis of cutaneous inflammation. In addition, the intra-dermal injection of mouse recombinant IL-33 has been shown to elicit a scleroderma-like reaction with an increase in dermal collagen fibers or a psoriasis-like dermatitis. IL-33 levels are upregulated in the epidermis of the patients with atopic dermatitis and allergic diseases (27). Therefore, IL-33 is crucial for the development of atopic dermatitis. However, it is still unclear how IL-33 contributes to those inflammatory conditions involving skin and the exact pathogenesis of psoriasis remains to be elucidated. Further studies should be conducted to elucidate the precise mechanism of mast cell pathophysiology in the skin.

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