



Introduction

Psoriasis is a chronic inflammatory skin disorder. It is characterized by pink to red scaly papules and plaques. The lesions are of variable size, sharply demarcated, dry and usually covered with layers of fine, silvery scales (*Elder et al., 2005*).

Mast cells (MCs) are metachromatic cells that reside in vascularized tissues and contain proinflammatory and vasoactive mediators in cytoplasmic granules. These mediators are released in response to IgE receptor cross-linking by receptor-bound IgE interacting with specific allergen or by other stimuli (*Schwartz, 2002*).

Mast cells have been found to play a central effector role in the development of allergic, chronic inflammatory reactions (*Metz et al., 2006*). In response to immunoglobulin E (IgE)-dependent or IgE-independent activation they produce and release a wide variety of preformed mediators including histamine, neutral proteases, proteoglycans and de novo synthesized lipids as leukotrienes, prostaglandins and thromboxanes. MCs were found also to produce many proinflammatory chemokines and immunomodulatory cytokines, such as tumor necrosis factor α (TNF- α), interleukin (IL)-1, IL-2, IL-3, IL-4, IL-6, IL-9 and IL-13 (*Maurer et al., 2006*).

It was suggested that MCs residing in the dermis are among the earliest cells which show activation in the initial



phases of psoriasis leading to MCs degranulation, but the true signal for MCs degranulation is unknown. Further studies are needed to clarify in more details which mediators and cell surface molecules are in fact, expressed in MCs in psoriasis (*Galli et al., 2005; Huttunen and Harvima, 2005*).



Aim of the Essay

The aim of this essay is to clarify the role of MCs in psoriasis and whether it plays a role as an initiator of the inflammatory reaction in psoriasis or is it just an effector cell.

1.0.0.0.0. Human Cutaneous Mast Cells

1.1.0.0.0. Mast cell origin and differentiation

Mast Cells (MCs) are tissue-based inflammatory cells of bone marrow origin that responds to signals of innate and acquired immunity with immediate and delayed release of inflammatory preformed and newly synthesized mediators. MCs are implicated in the pathogenesis of allergic diseases. Human MCs are ovoid or irregularly elongated with an oval nucleus and contain metachromatic cytoplasmic granules. In lungs, MCs are found in bronchial airway connective tissues and in peripheral intraalveolar spaces. In the skin, MCs appear near blood vessels, hair follicles, sebaceous glands and sweat glands (*Prussin and Metcalfe, 2003*).

Mast cells are derived from committed progenitor cells in bone marrow, which circulate as mononuclear leukocytes expressing certain receptors and migrate into tissues and complete their differentiation to mature MCs which express the characteristic secretory tryptase granules and the high-affinity IgE receptor Fc ϵ RI (Fc ϵ RI) under the influence of stem cell factor (SCF) (**Figure 1**) (*Li and Krilis, 1999; Kitamura and Ito, 2005; Kitamura and Oboki, 2006*).

After tissue localization, MCs undergo further differentiation into distinct subsets. Two MCs subtypes have

been described in tissue based on structural, biochemical and functional differences, the mucosal MCs which are MCs Tryptase (MCT) and connective tissue MCs which are MCs Tryptase Chymase (MCTC) [Table 1] (*Krishnaswamy et al., 2006*). Distinctive features help differentiate the two subsets. For example, the MCT MCs predominantly expresses the protease tryptase. This subset is usually localized in mucosal surfaces, often in close proximity to the T-helper 2-type (TH2 secreting IL-4 and IL-5). This subset usually is seen in increased numbers infiltrating the mucosa in patients suffering from allergic and parasitic diseases. Because of their unique T cell-dependence, the numbers of MCT cells are diminished in individuals infected with human immunodeficiency virus (HIV) (*Church and Levi-Schaffer, 1997*). The MCTC MCs, however, expresses tryptase, chymase, carboxypeptidase and cathepsin G. It tends to predominate in the gastrointestinal tract as well as in skin, synovium and subcutaneous tissue [Table 1] (*Krishnaswamy et al., 2006*).

Increased numbers of MCTC MCs are seen in fibrotic diseases whereas its numbers are relatively unchanged in allergic or parasitic diseases and in HIV infection. The presence of these MCTC cells could help explain why patients with HIV infection continue to have allergic reactions (e.g., to medications). For experimental purposes, MCT, which possess only tryptase as a major component of secretory granules, are considered the human identical of mucosal-type MCs of rodents whereas the MCTC which contain tryptase, chymase, carboxypeptidase and cathepsin G in their granules are

considered the human identical of connective tissue-type MCs of rodents (*Irani et al., 1991*).

Mast cell Tryptase reside in intestinal mucosa and lungs, whereas MCTC are located in skin and intestinal submucosa. Although human MCs from all tissues degranulate in response to FcεRI cross-linking and to calcium ionophores (ionophores are used to increase the permeability of biological membranes to certain ions), the difference between these two types of MCs is that MCTC degranulate in response to the basic substances that promote secretion or degranulation such as substance P (SP), C5a and C3a, whereas MCT do not respond to them (*Kambe et al., 2001*).

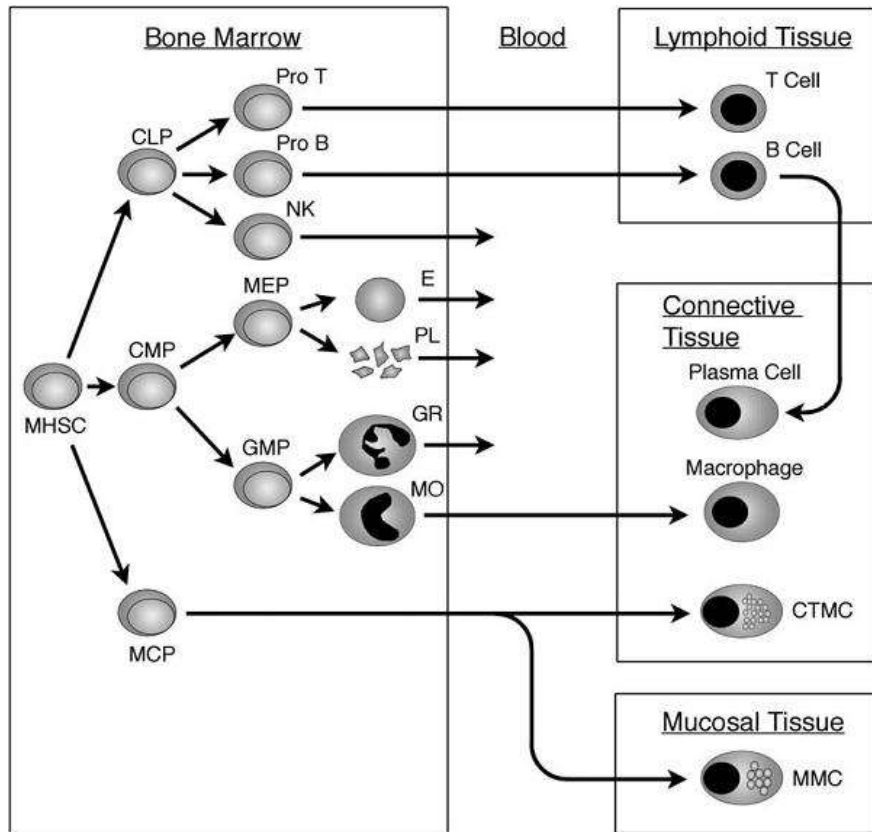


Figure (1): Development of MCs, **CLP**, common lymphoid progenitors; **CMP**, common myeloid progenitors; **CTMC**, connective tissue-type MCs; **E**, erythrocyte; **GMP**, granulocyte/macrophage progenitor; **GR**, granulocyte; **MEP**, megakaryocyte/ erythrocyte progenitor; **MHSC**, multipotential hematopoietic stem cells; **MMC**, mucosal mast cell; **MO**, monocyte; **NK**, natural killer cell; **PL**, platelet (*Kitamura and Oboki, 2006*).

Mast Cell Subtypes		
Feature	MC _{TC} cell	MC _T cell
Structural features		
Grating/lattice granule	++	—
Scroll granules	Poor	Rich
Tissue distribution		
Skin	++	—
Intestinal submucosa	++	+
Intestinal mucosa	+	++
Alveolar wall	—	++
Bronchi	+	++
Nasal mucosa	++	++
Conjunctiva	++	+
Mediator synthesized		
Histamine	+++	+++
Chymase	++	—
Tryptase	++	++
Carboxypeptidase	++	—
Cathepsin G	++	—
LTC ₄	++	++
PGD ₂	++	++
TNF- α	++	++
IL-4, IL-5, IL-6, IL-13	++	++

Table 1: Differences between MCs subtypes (*Krishnaswamy et al., 2006*).

Using light microscopy, MCs occur in the normal dermis in small numbers as oval to spindle-shaped cells with a centrally located round to oval nucleus. They contain in their cytoplasm numerous granules that do not stain with routine stains like hematoxylin-eosin. Therefore, MCs in normal skin

usually are indistinguishable from other perivascular cells. The granules stain metachromatically with methylene blue in the Giemsa stain, toluidine blue and Alcian blue [**Figure 2**] (*Elder et al., 2005; Samoszuk et al., 2005*).

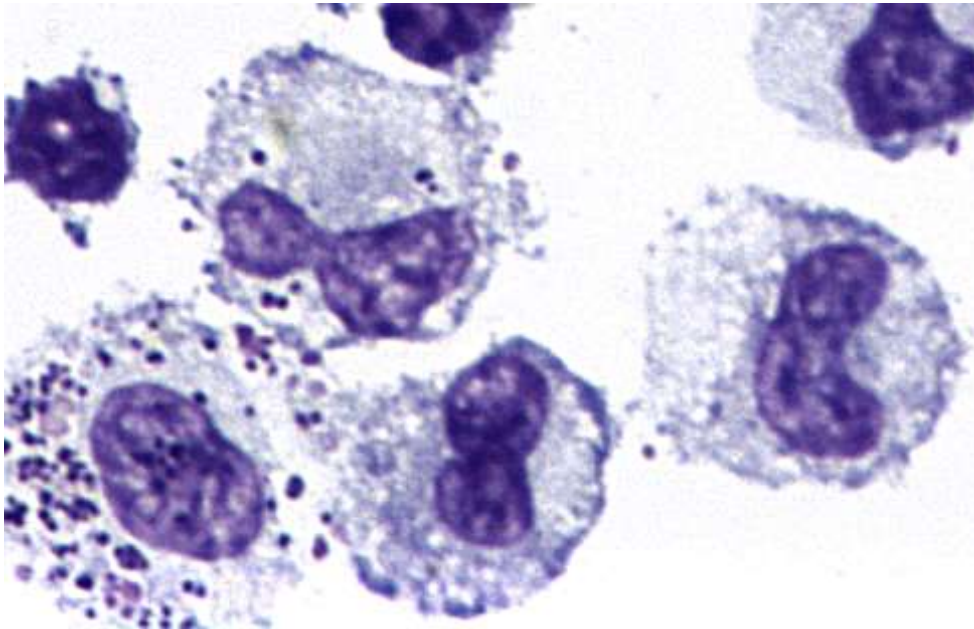


Figure (2): Cultured human MCs using an oil immersion lens and toluidine blue stain at x100 (*Samoszuk et al., 2005*).

The ultrastructural appearance of the tryptase-positive, chymase-positive connective tissue MCs are cores of electron-dense crystal network surrounded by rims of curvilinear lamellae oriented circumferentially around the periphery of the granule (**Figure 3**) (*Kaminer et al., 1995*). In biopsies obtained 15 seconds after antigen injection, there was evidence of degranulation, with global swelling and disorganization

(solubilization) of all granule matrix constituents and fusion of granules with each other and the plasma membrane to form channels to the extracellular space (anaphylactic degranulation) **(Figure 4) (Kaminer et al., 1995)**. All remaining intact granules began to exhibit features of degranulation between 5 and 10 minutes after antigen challenge **(Figure 5) (Kaminer et al., 1995)**. Ultrastructural changes in these granules were characterized by swelling and segmental solubilization of the granule matrix to give a “moth-eaten” appearance. Affected granules were characterized by being amorphous, zonal and electron-dense **(Figure 5) (Kaminer et al., 1995)**. The ultrastructural appearance of non-activated tryptase-positive, chymase-negative mucosal MCs, are cell membrane that is distorted, without major indentation. The granules are numerous, having an even arrangement around the nucleus. Their structure is dense, made up of fine granulations **(Figure 6) (Moneret-Vautrin et al., 1984; Dvorak et al., 1991)**.

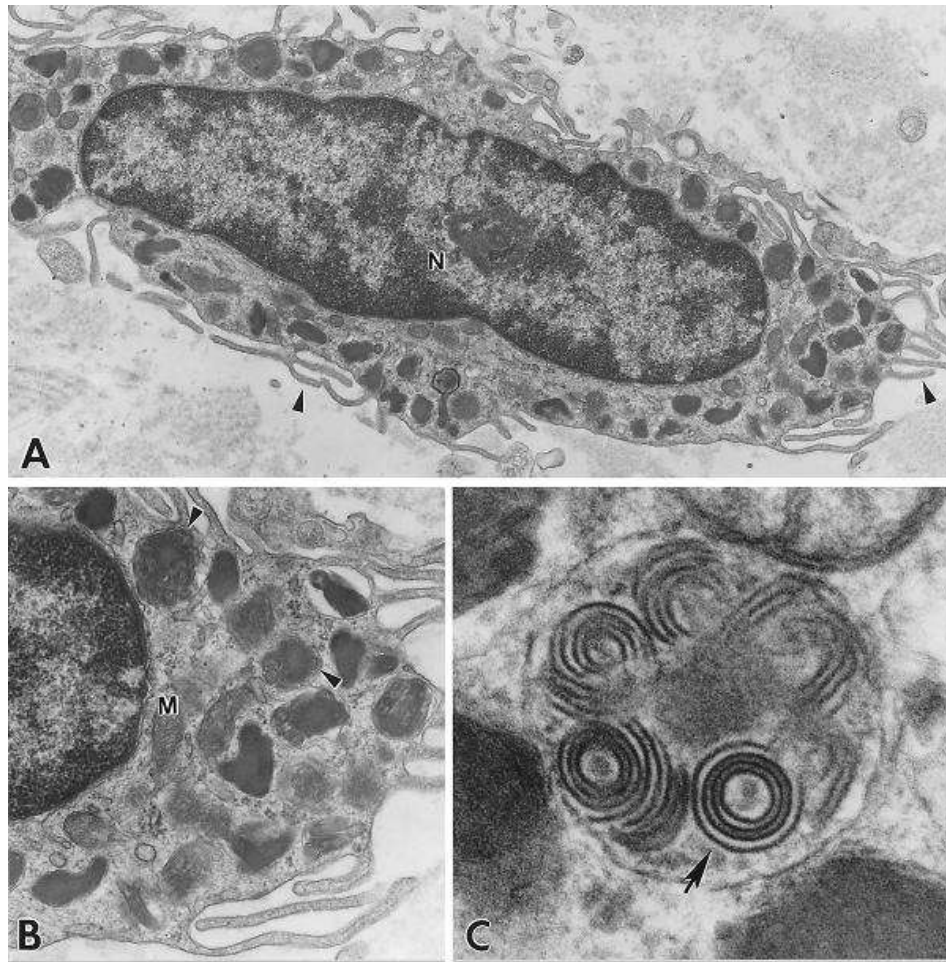


Figure (3): Inactivated human connective tissue MC (MCTC). **(A)** The MC has numerous cytoplasmic processes (arrowheads), a nucleus (N)/cytoplasm ratio of more than 1 and cytoplasm filled with round-to-oval granules. x13, 500. **(B)** Granules exhibit cores with various electron densities, with peripheral rims of curvilinear lamellae (arrowheads). M, mitochondria. x326, 000. **(C)** Membrane-bound connective tissue MC granule with a well-formed scroll substructure (arrow) x3160, 000 (Kaminer *et al.*, 1995).

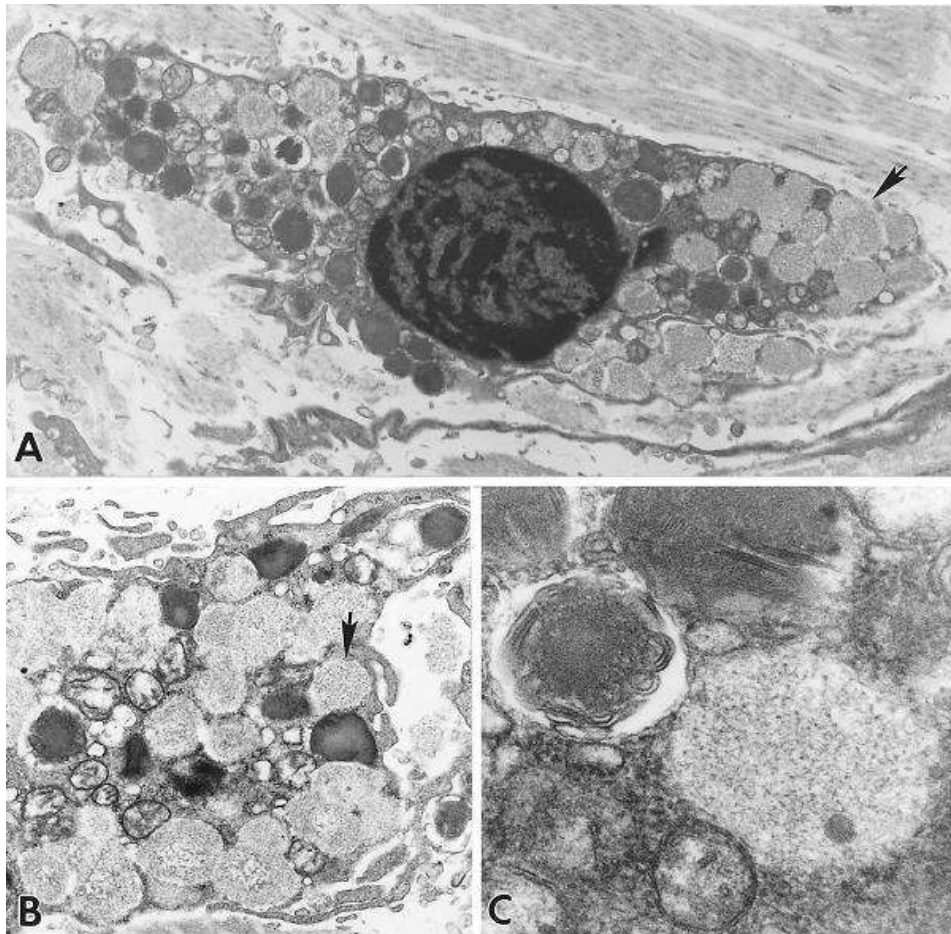


Figure (4): Human connective tissue MC 15 seconds after stimulation exhibiting global degranulation. **(A)** Degranulation is characterized by solubilization and swelling of the entire granule matrix, fusion of granule membranes with each other, and fusion of granule membranes with the plasma membrane to form conduits to the extracellular space (arrow). x312,500. **(B)** The matrix of affected granules is completely solubilized as evidenced by disorganization of the granule ultrastructure and an increase in electron lucency (arrow). x319,800. **(C)** Granules actively involved in degranulation are adjacent with granules that do not exhibit ultra structural features of degranulation. x378,000 (*Kaminer et al., 1995*).

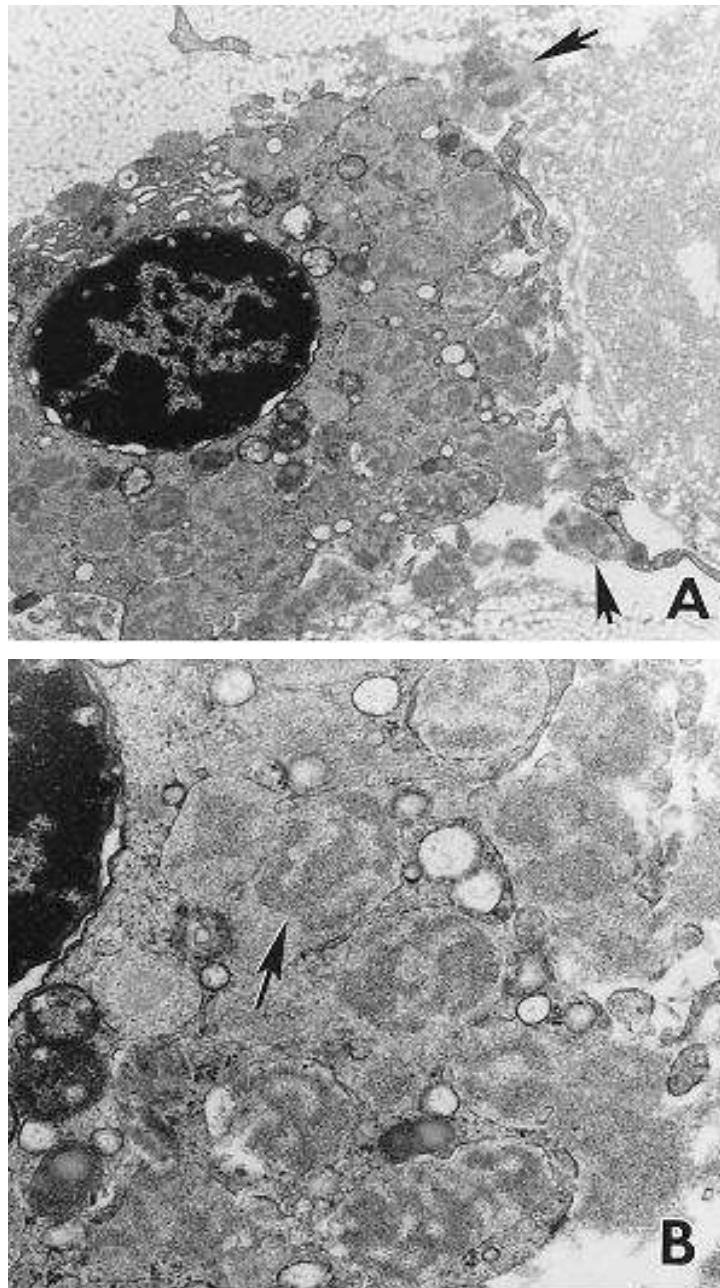


Figure (5): Segmental degranulation in a human connective tissue MC 10 minutes after intradermal injection of ragweed extract. **(A)** The majority of MC granules exhibit features of degranulation. Extracellular non-membrane- bound granule matrix is present in the pericellular space (arrow). x39,300. **(B)** The

granule ultrastructure reveals partial solubilization of granule matrix (arrow). x325,000 (*Kaminer et al., 1995*).

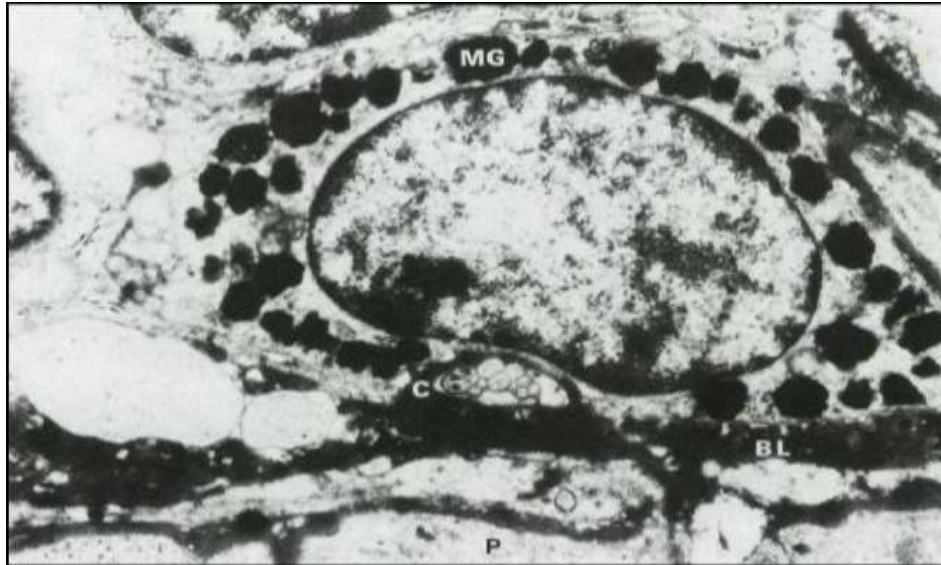


Figure (6): Non-activated mucosal MCs (MCT) under the basal lamina (BL) containing granules (MG) dense with electrons. Collagen (C). Parietal cell (P) E/M x7000 (*Moneret-Vautrin et al., 1984*).

1.2.0.0.0. Function of human mast cells

Mast cells are known for their role in type I hypersensitivity because of their surface expression of FcεR1s. The interaction of an antigen with IgE-occupied FcεR1 results in the activation of downstream signaling molecules that lead to the release of preformed and de novo synthesized mediators (*Galli et al., 2005a*). Histamine and serotonin are preformed, stored in the secretory granules and are released on stimulation of MCs through FcεR1 aggregation and contribute to the immediate-phase reaction by increasing smooth muscle

contraction, vascular dilatation and extravasation of plasma into dermis (**Bradding and Holgate, 1999; Castells, 2006**).

Eicosanoids, prostaglandins and leukotrienes (LTs) are potent factors synthesized from arachidonic acid (AA) after the activation of MCs; they act as leukocyte chemotactic factors and contribute to the development of the intermediate-phase reactions. Subsequently, within hours, cytokines such as interleukin (IL)-3, -4, -5, and 6; granulocyte macrophage colony stimulating factor (GM-CSF); TNF- α are synthesized and released along with other newly formed mediators from antigen-activated MCs (**Kobayashi et al., 2000**). These proinflammatory cytokines possess chemotactic activity towards inflammatory cells as eosinophils and contribute to the late-phase reactions, secreting its cytotoxic granular proteins that have an impact on the development of inflammatory allergic diseases, such as atopic asthma and atopic dermatitis (**Marshall, 2004**). MCs are also involved in innate and acquired immunity, wound healing, cancer development, autoimmune diseases and neurogenic disorders due to psychological stress (**Puxeddu et al., 2003**).

Mast cells have long been incriminated for their initiation and maintenance of anaphylaxis, as effector functions in immunoglobulin IgE-associated allergic disorders and immune responses to parasites. However, these cells and their multiple preformed and de novo-synthesized mediators have been