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Review

The mast cell: an active participant or an innocent bystander?

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Summary. Mast cells (MC) are phylogenetically old cells which are distributed throughout the human organism and, on the whole, occupy roughly the volume of the spleen. MC have long been recognized as key cells of type I hypersensitivity reactions. Several lines of evidence, however, indicate that they not only express critical effector functions in classic IgE-associated allergic disorders, but also play important roles in host defence against parasites, bacteria and perhaps even viruses. Indeed, it is now clear that MC can contribute to host defence in the context of either acquired or innate immune responses through the release of a myriad of pro-inflammatory and immunoregulatory molecules and the expression of a wide spectrum of surface receptors for cytokines and chemokines. Moreover, there is growing evidence that MC exert distinct non-immunological functions, playing a relevant role in tissue homeostasis, remodeling and fibrosis as well as in the processes of tissue angiogenesis. In this review, we provide a small insight into the biology of human MC and their potential implications in clinical pathology.

Key words: Mast cell, Structure, Function, Pathology

Introduction

Mast cells (MC) were first described by Paul Ehrlich (1878) in his doctoral thesis. He named these cells Mastzellen (from the greek μαστός, breast) because he believed that the intracellular granules, which appeared purple in colour when stained with aniline blue dyes, contained phagocytosed materials or nutrients. This change in colour, or metachromasia, we now know represents the interaction of the dyes with the highly acidic heparin contained within mast cell granules. MC are unique secretory cells with a well documented role in immediate hypersensitivity reactions. However, the presence of these cells in various cell-mediated reactions, in tissues from multiple diseases, and as a component of the host reaction to parasite, bacteria and even virus infections as well as their participation in angiogenic and tissue repair processes after injury, render MC most frascinating protagonsists in the fields of cell biology and ultrastructure research.

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General biology of mast cells

The MC is a multi-functional long-lived secretory cell, characterized by its content of numerous large cytoplasmic granules. MC is a phylogenetically old cell, which apparently occurs in all species with blood circulation. All mammalian MC express common characteristics, including high affinity plasma membrane receptors (FcεRI) binding IgE antibodies and cytoplasmic granules storing biogenic amines, proteoglycans, cytokines and neutral serine proteases. However, MC populations show marked differences in their phenotypic expression in different species as well as distinct anatomical sites, a phenomenon called "MC heterogeneity" (Galli, 1990).

There is general consensus that MC develop, like other leukocytes, from haematopoietic stem cells but do not mature before exiting the bone marrow and circulate as committed progenitors (Gurish and Austen, 2001). In humans, MC derive from $CD34^+$, $CD13^+$, FcεRI-, $c\text{-}kit^+$ multipotential precursors (Kirschenbaum et al., 1991). Committed progenitors, circulating as mononuclear agranular cells, traverse the vascular space and complete their maturation after moving into diverse peripheral tissues (Rodewald et al., 1996). Here, they acquire concomitant phenotypic diversity. Local differentiation and maturation of MC are most likely regulated by tissue micro-environmental factors, in particular the c-kit ligand (stem cell factor, SCF) secreted by fibroblasts, stromal cells and endothelial cells, which represents the most important cytokine involved in MC development. In humans, tissue MC survival and differentiation are also enhanced by other cytokines including interleukin

(IL)-4, IL-6 and IL-10 (Conti et al., 2002). Committed progenitors are supposed to populate peripheral tissues functioning as a local reservoir. These undifferentiated but committed progenitors do not develop into mature MC unless adequate inflammatory stimuli ensue. In the adult mouse, for instance, it has been shown that the mucosa of the intestine contains the largest peripheral pool of these committed progenitors (Guy-Grand et al., 1984).

MC are found in almost all of the major organs and tissues of the body, particularly in association with connective tissue structures such as blood vessels, lymphatic vessels and nerves, and in proximity to surfaces that interface the external environment such as those of the respiratory and gastrointestinal system and the skin. This selective accumulation at tissue sites where foreign material attempts to invade the host suggests that MC are among the first cells to initiate defence mechanisms. MC are not found in avascular tissues such as mineralized bone, cartilage and the cornea. Human MC are conventionally divided into two types depending on the expression of different proteases in their granules (Irani et al., 1986). MCT cells, also regarded as "immune cell-associated", contain tryptase and are predominantly located in the respiratory and intestinal mucosa, where they co-localize around T lymphocytes. MCTC cells contain both tryptase and chymase, along with other proteases such as carboxypeptidase A and cathepsin G. They are predominantly found in connective tissue areas, such as skin, submucosa of stomach and intestine, breast parenchyma, myocardium, lymph nodes, conjunctiva and synovium. Recently, a third type of MC, MCC cell has been identified: this MC expresses chymase without tryptase and resides mainly in the submucosa and mucosa of the stomach, small intestinal submucosa and colonic mucosa (Irani and Schwartz, 1994).

General morphology of mast cells

Viewed by light microscopy, human MC usually present as round or elongated cells with a diameter ranging between 8 and 20 μm, depending on the organ examined. Their single nucleus shows a round or oval shape and the cytoplasm contains numerous secretory granules that metachromatically stain with thiazine dyes such as toluidine blue. By electron microscopy, these cells exhibit a non-segmented monolobed nucleus with peripherally condensed chromatin. The cytoplasm contains a few mitochondria, short profiles of the rough endoplasmic reticulum and numerous free ribosomes.

The most characteristic cytoplasmic organelle in human MC is the membrane-bound, moderately electron-dense secretory granule (Dvorak, 1991). Secretory granules are very abundant and correspond to the metachromatic granules of the light microscopy. They have an average diameter of 1.5 μm and present different types of substructural patterns: homogeneous, crystalline, scroll, particle or thread-like or a combination of them (Figs. 1, 2). Granule ultrastructure has been partly related to their content of serine protease. Indeed, granules with the chymase protease preferentially exhibit homogeneous or crystalline substructures whereas granules lacking this protease show mainly a scroll pattern. However, significant granule heterogeneity can be found in any particular tissue and even between granules of a single MC. Besides the typical secretory granules, human MC also contain non-membrane-bound, highly osmiophilic granules, called lipid bodies (Dvorak, 1991) (Fig. 1). They are fewer in number and generally larger than secretory granules, and serve as a significant storage site for arachidonic acid. Recently, both secretory granules and lipid bodies have implicated in RNA metabolism in human MC (Dvorak and Morgan, 2000; Dvorak et al., 2003).

Preformed mediators stored in the secretory granules can be released by two morphologically distinct secretory pathways, referred to as exocytosis (also called "anaphylactic degranulation") and piecemeal degranulation (Dvorak, 1991; Crivellato et al., 2002). Exocytosis consists of a rapid and massive secretory process, characteristically occurring during IgE-dependent hypersensitivity reactions. In exocytosis, cytoplasmic granule membranes fuse with each other and with the plasma membrane, giving rise to open secretory channels which allow the release of granule contents into the local extracellular environment. Piecemeal degranulation, conversely, represents a particulate mode of MC secretion, characterized by a slow discharge of granule contents in a "piecemeal" fashion, without membrane fusion events and granule opening to the cell exterior (Fig. 1). This degranulation pattern has frequently been observed in MC infiltrating areas of chronic inflammation or tumours.

Biochemical composition of mast cell secretory granules

Secretory granules of human MC contain crystalline complexes of preformed inflammatory mediators ionically bound to a matrix of proteoglycan. Histamine, the first discovered mediator in MC, is present at a concentration of 1 to 4 pg/cell. Histamine exerts many effects pertinent to the immediate phase of allergic response, including vasodilation, increased vasopermeability, contraction of bronchial and intestinal smooth muscle cells, and increased mucus production. It has been shown that the dominant proteoglycan in human MC is heparin, which constitutes some 75% of the total, with a mixture of chondroitin sulfates making up the remainder (Church and Levi-Schaffer, 1997). Within the granule, proteoglycan may be viewed as a storage matrix because the acidic sulphate groups of the glycosaminoglycans provide binding sites for the other preformed mediators. Released heparin exerts different actions such as anticoagulant, anticomplement and antikallikrein effects as well as some angiogenic activity

(Ribatti et al., 1987).

Human MC are a rich reservoir of neutral proteases. The major MC protease is tryptase, a 130 kd serine protease, which is stored in a fully active form in the granule. It represents the most abundant constituent of human MC. Some 10 pg/cell has been detected in MC in

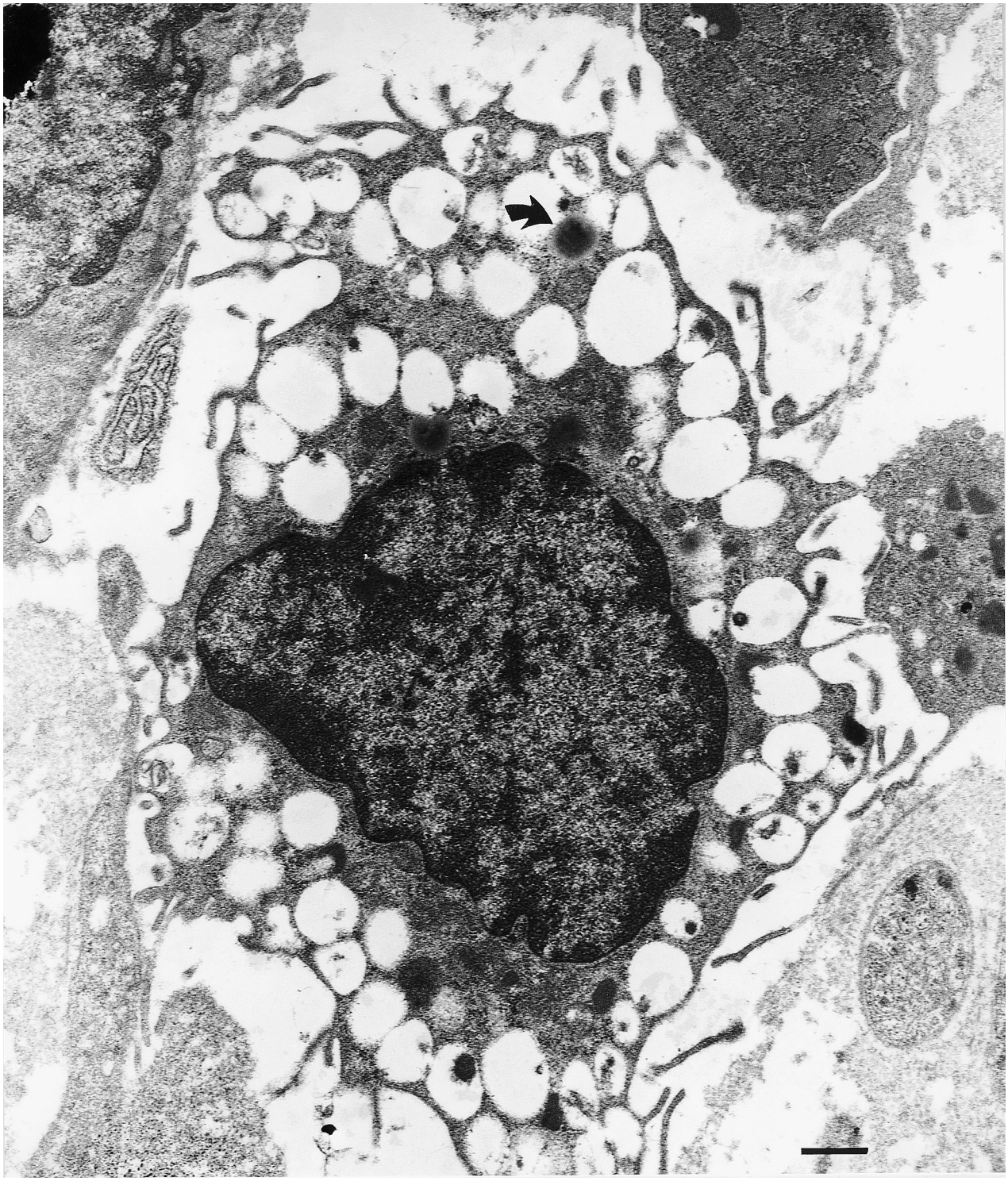

Fig. 1. Electron micrograph of a human skin MC, exhibiting piecemeal degranulation. The cytoplasm is filled by numerous, non-fused, almost empty granule containers. The arrow indicates an osmiophilic granule (lipid body). Bar: 1.5 μm.

the lung and up to 35 pg in skin MC (Schwartz et al., 1987). Tryptase cleaves various bronchial and intestinal neuropeptides, and matrix components. In addition, it is emerging as a potent growth factor for fibroblasts, endothelial cells and muscle cells (Blair et al., 1997; Gruber et al., 1997). Chymase, a 30 kD protease, is

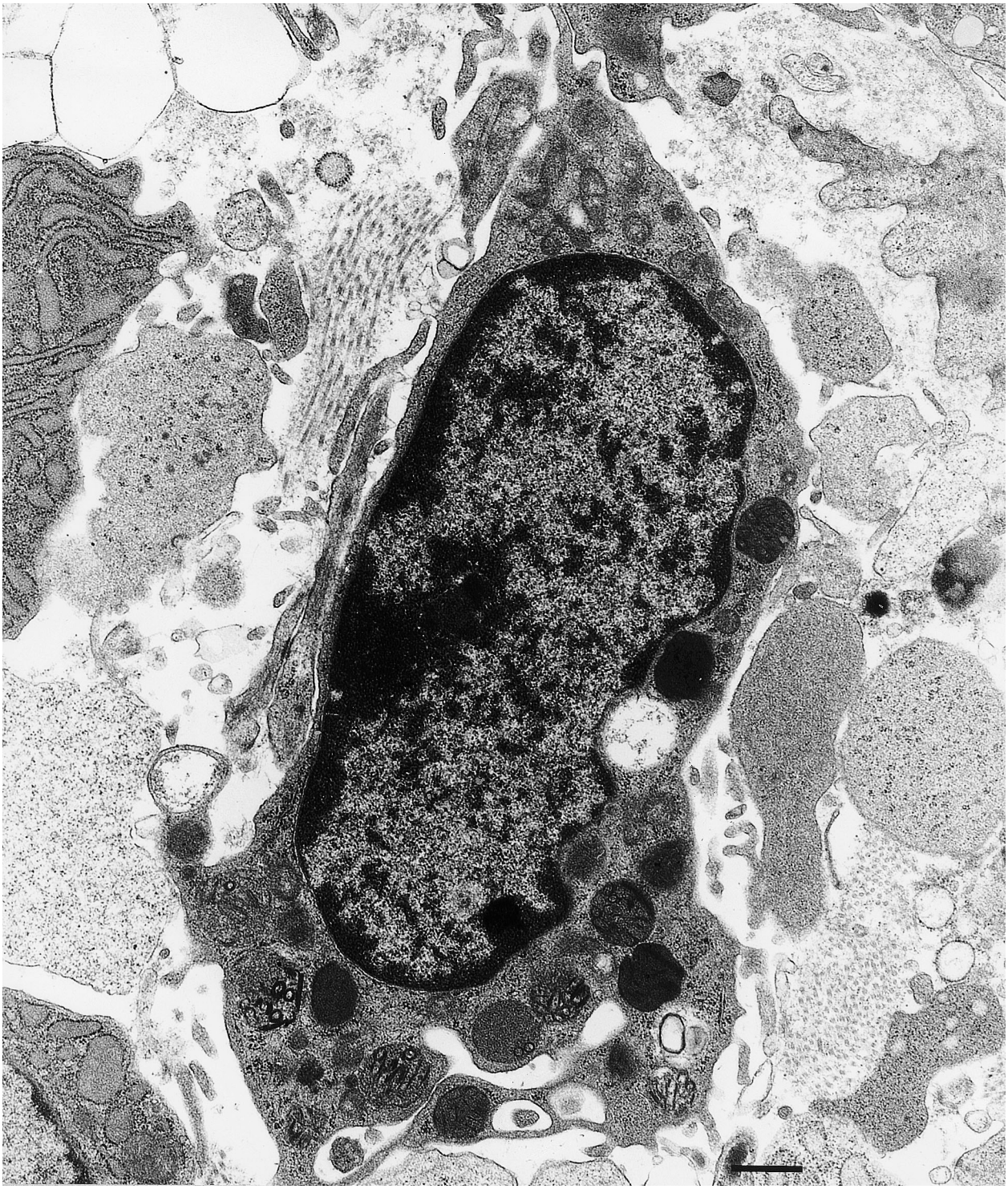

Fig. 2. Electron micrograph of a human intestinal MC from the duodenal mucosa. Secretory granules show the characteristic scroll-like pattern. Bar: 1.5 μm.

present within the granules of the MCTC subset of MC, in an estimated concentration of 4.5 pg/cell (Schwartz et al., 1987; Metcalfe et al., 1997). Like tryptase, it degrades some neuropeptides and interleukins, and cleaves collagen and other matrix components. Two other proteases, carboxypeptidase and cathepsin G, have been associated with the MCTC subset of human MC.

Mast cell membrane receptors

MC express the high affinity receptor FcεRI, which binds the Fc region of an IgE antibody molecule. Cross-linking of FcεRI receptors by specific IgE molecules binding multivalent antigens causes initiation of MC activation.

Besides FcεRI receptors, human MC express a large array of adhesion molecules and chemotactic factor receptors. Adhesion molecules on both progenitors and mature MC are certainly important factors controlling MC distribution within tissues (homing) (Vliagolftis and Metcalfe, 1997) as well as MC activation. Studies with *ex vivo* MC obtained from human tissues demonstrate surface expression of ß1 integrins such as VLA-3, VLA-4, VLA-5 and αvß3 integrin (Valent and Bettelheim, 1992; Columbo et al., 1995). The natural ligands of VLA-3, VLA-4 and VLA-5 and αvß3 integrin are laminin, type I collagen and fibronectin; fibronectin and vascular cell-adhesion molecule (VCAM-1); fibronectin; and vitronectin, fibronectin, thrombospondin and fibrinogen, respectively. It has been reported that ß1 integrins are involved in MC activation, up-regulation of cytokine expression and survival (Ra et al., 1994). As far as non-integrin adhesion molecules are concerned, human MC have been reported to express low levels of intracellular adhesion molecules 1 and 3 (ICAM-1, ICAM-3) as well as leukocyte function-associated antigen-1 and 3 (LFA-1, LFA-3) (Bochner and Schleimer, 2001). Additional adhesion molecules expressed by MC are CD44, a hyaluronic acid receptor, and singlec-8, a molecule which binds to sialic acid moieties (Bochner and Schleimer, 2001).

With respect to chemotactic factor receptors, MC express the chemokine receptor CCR3, the ligand for eotaxin, eotaxin-2 and eotaxin-3. This receptor can also bind to other chemokines such as monocyte chemoattractant protein (MCP)-3, MCP-4 and RANTES (Nickel et al., 1999; Romagnani et al., 1999). Indeed, most if not all of these chemokines cause MC migration in vitro.

Another structure found in MC is the C3a receptor. Known primarily for its ability to act as a secretagogue on skin MC, C3a is also a potent chemoattractant for these cells (Hartmann et al., 1997).

Mature MC do not express IL-3 and granulocyte monocyte-colony stimulatory function (GM-CSF) receptors which, conversely, are characteristically expressed by human basophils and blood monocytes (Valent and Bettelheim, 1992). Human MC, but not basophils, express the c-kit receptor for SCF and this represents a key feature for distinguishing between the two cell types. The expression of the tyrosine kinase c-kit receptor on the surface of the MC is very important for MC functional activity. Indeed it does not only drive terminal differentiation of the MC but has also other important roles in regulating MC biology, such as survival, activation and degranulation of mature MC.

MC also express the urokinase receptor which may be related to the specific pro-angiogenic function of MC, urokinase being an enzyme involved in processes of tissue remodeling such as fibrinolysis, fibroblast and endothelial cell migration and local repair. The finding that angiogenic factors, such as fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF) and platelet-derived endothelial cell growth factor (PD-ECGF) stimulate MC migration suggests that MC would express surface receptors for these pro-angiogenic cytokines (Gruber et al., 1995).

Table 1. Cytokines produced by human mast cells.

Interleukin-1 (IL-1)
Interleukin-3 (IL-3)
Interleukin-4 (IL-4)
Interleukin-5 (IL-5)
Interleukin-6 (IL-6)
Interleukin-8 (IL-8)
Interleukin-9 (IL-9)
Interleukin-10 (IL-10)
Interleukin-12 (IL-12)
Interleukin-13 (IL-13)
Interleukin-14 (IL-14)
Interleukin-16 (IL-16)
Interleukin-18 (IL-18)
Interleukin-25 (IL-25)
Stem Cell Factor (SCF)
Granulocyte Monocyte-Colony Stimulatory Factor (GM-CSF)
Tumor Necrosis Factor-α (TNF-α)
Tumor Growth Factor-ß (TGF-ß)
Fibroblast Growth Factor-2 (FGF-2)
Nerve Growth Factor (NGF)
Vascular Endothelial Growth Factor (VEGF)
Platelet Derived Growth Factor (PDGF)
Macrophage Inflammatory Protein-1α (MIP-1α)
Monocyte Chemoattractant Protein-1 (MCP-1)
Lymphotactin

Mast cell cytokines

MC produce an impressively broad array of mediators and cell-cell signalling molecules. The recognition that MC produce a large number of cytokines upon activation suggests that they may influence other cells within the microenvironment, thus playing a central role in inflammatory processes as well as non-immunological functions. Cytokine and chemokine production by MC is closely regulated and may occur independently from classical FcεRI receptor-mediated MC activation. Now, about thirty different cytokines have been shown to be produced by human MC (Table 1). Human MC secretory granules contain

tumor necrosis factor (TNF)-α which has pleiotropic pro-inflammatory effects. TNF-α has been implicated in neutrophil recruitment, inducing up-regulation of the endothelial-leukocyte adhesion molecule (ELAM-1) (Walsh et al., 1991). TNF-α has also been known to enhance the bactericidal activities of neutrophils (Kenny et al., 1993). Mice that either have a targeted disruption of the TNF-α gene or are MC deficient due to a functional inactivation of their c-kit (w/wv) are highly susceptible to death after cecal ligation and puncture (Malaviya et al., 1996). In addition, human MC have the capacity to generate IL-8, thus contributing to neutrophil recruitment (Moller et al., 1993). Under allergic conditions MC produce significant amounts of IL-1 that may contribute to lymphatic infiltration (Bochner et al., 1990) and IL-4, essential for the triggering of Th2 lymphocytes that themselves produce IL-4 to initiate inflammatory cell accumulation and B lymphocyte immunoglobulin class switching to IgE (Bradding et al., 1993). Other cytokines involved in MC found in normal and in asthmatic airways are IL-5 and IL-6 which, together with IL-4 and IL-13, would enhance Th2-type immune response and eosinophil chemotaxis, thus indicating that MC may play an important role in initiating and maintaining the inflammatory response in asthma (Bradding et al., 1995; Galli, 1997).

Interestingly, a unique profile of cytokines is induced depending upon the nature of the stimulus or type of infection. Human intestinal MC have been shown to spontaneously produce pro-inflammatory cytokines such as TNF-α, IL-6 and IL-8 at low levels without stimulation of the cell (Lorentz and Bischoff, 2001). Stimulation by IgE receptor cross-linking leads to an enhanced production of pro-inflammatory cytokines and de novo production of Th2 cytokines such as IL-3, IL-5, IL-10 and IL-13. Gram-negative bacteria, in contrast to IgE receptor cross-linking, do not induce the release of Th2 cytokines but enhance that of pro-inflammatory cytokines.

Functional heterogeneity of mast cells

It is now well established that MC have phenotypically distinct subpopulations and exhibit not only species-specific but also site-specific heterogeneity. This implies that MC from different tissues are slightly distinct in their protease content, surface markers, cytokine release and response to some external stimuli (Kitamura, 1989; Galli, 1990; Bradding et al., 1995). We have already seen that human MC can be distinguished on the basis of their neutral protease content into MCT and MCTC cells. A third type, MCC cells, has been identified recently. However, MC from different anatomical sites are also able to generate distinct profiles of cytokine expression. In the tissues of bronchial and nasal mucosae from normal, asthmatic and allergic rhinitis patients, MCT release IL-5, IL-6 and some IL-4, whereas MCTC preferentially express IL-4 but little IL-5 and IL-6. A similar predominant IL-4 pattern is recognizable in skin MC which contain both tryptase and chymase (MCTC). Such differences in the distribution of cytokine expression between subsets of MC suggest a difference in the capacity of MC subsets to produce various cytokines and therefore a difference in their specific roles in allergic inflammation. In addition, human MC from different sites express some different responses to secretagogues. Indeed, MC from skin seem to be very sensitive to stimulation with substance P, compound 48/80 and morphine, all leading to histamine release, whereas heart and lung MC only react to compound 48/80 (Fureder et al., 1995). Intestinal MC do not react to compound 48/80 whereas uterine MC fail to respond to substance P (Shanahan et al., 1985).

Immunological functions of mast cells

MC are known to be the primary responders in allergic reactions, orchestrating strong responses to minute amounts of allergens. Because of the high affinity (10^{-10}M) of the FcεRI for IgE, MC are constantly coated with antigen-specific IgE and are, in essence, masquerading as cells of the adaptive immune system (Benoist and Mathis, 2002). Exposure to specific multivalent antigens results in the bridging of IgE molecules bound to FcεRI on the MC surface. This event causes a rapid discharge of pre-formed inflammatory mediators from secretory granules, as well as the release of newly-formed mediators, which all act on distinct effector cells to produce the symptoms of allergy and anaphylaxis (Ishizaka and Ishizaka, 1984; Serafin and Austen, 1989). Indeed, MC reaction to allergens may be imaged as a two-wave response. The cross-linking of surface-bound IgE by antigen leads to the rapid release of histamine, specific proteases and TNF-α from rich intracellular stores. On activation, MC also rapidly synthesize bioactive metabolites of arachidonic acid, prostaglandins and leukotrienes. A specific program of gene expression is also activated, leading to the de novo synthesis of several cytokines (IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, IL-14 and nerve growth factor [NGF]), chemokines (macrophage inflammatory protein 1α [MIP-1α], MCP-1 and lymphotactin) and, again, TNF-α. This second-wave response comes after the immediate hypersensitivity reaction, which it amplifies. It may also influence the type of secondary events, for example, by stimulating specific subsets of T lymphocytes.

A number of studies, however, have recently provided experimental evidence that MC not only express critical effector function in classic IgE-associated allergic disorders, but also express a variety of IgE-independent functions, which lead to cell activation and initiation of inflammatory responses (Stassen et al., 2002). Collectively, these studies have demonstrated that MC play a key role as sentinels of the immune system in host defence against parasites, bacteria and perhaps even viruses. A great contribution to the formulation of this concept has derived from studies using MC deficient w/wv mice. Indeed, it is now

clear that MC can contribute to host defence in the context of either acquired (adaptive) or innate immune responses (Mekori and Metcalfe, 2000). It has been found that rodent MC have the capacity to recognize and phagocytose bacteria and subsequently serve as antigen-presenting cells to T lymphocytes in an MHC class I restricted fashion (Malaviya and Abraham, 2001). In humans, bacterial and fungal pathogens are able to induce a highly selective production of MC mediators (IL-1ß, GM-CSF, leukotrienes) through Toll-like receptor stimulation (Mc Curdy et al., 2003). Very recently, it has been shown that human MC can be activated by different HIV-1 proteins (gp120 and Tat) and thereby represent a potentially important source of Th2 cytokines during HIV-1 infection (Marone et al., 2000).

Mast cells and angiogenesis

Angiogenesis is a multistep, highly orchestrated process not only involving vessel sprouting but also endothelial cell migration, proliferation, tube formation and survival. Angiogenic growth factors can be produced by a number of cells such as embryonic cells (endoderm, astrocytes, Müller cells), adult resident and inflammatory cells (fibroblasts, macrophages, T lymphocytes, plasma cells, neutrophils, eosinophils) and tumor cells. MC have been implicated in the regulation of both physiological and pathological neovascularization mostly on the basis of histological studies. In fact, in many organs MC are particularly prominent in close vicinity to capillaries and lymphatic channels under physiological conditions. In addition, an increased number of MC have been reported in angiogenesis associated with haemangiomas, neoplasm, rheumatoid arthritis, nasal polyps, wound healing and ovulation. Tissue ultrastructural analyses have demonstrated profound MC involvement in the form of MC degranulation, according to the particulate, "piecemeal" pattern (Dvorak, 1991). There is now emerging evidence that MC release a variety of factors known to enhance angiogenesis. MC from human tissues with chronic inflammation release preformed FGF-2 from their secretory granules. Human cord blood-derived MC release VEGF upon stimulation through FcεRI and c-kit. Both FGF-2 and VEGF have also been identified by immunohistochemistry in mature tissue MC (Qu et al., 1995; Grutzkau et al., 1998). A role in angiogenesis for the proteolytic enzymes tryptase and chymase has been established. Tryptase, in particular, stimulates the proliferation of human vascular endothelial cells, promotes vascular tube formation in culture and is likely to play an important role in neovascularization in human tumors, such as B-cell non-Hodgkin's lymphomas, multiple myeloma, myelodysplastic syndromes, chronic lymphocytic leukemia, and cutaneuos melanoma (Ribatti et al., 1999, 2000, 2002, 2003a,b). Other MC-specific mediators with angiogenic properties include histamine and heparin. Both molecules have been shown to stimulate proliferation of endothelial cells and to induce the formation of new blood vessels in the CAM-assay (Ribatti et al., 1987; Sorbo et al., 1994). In addition, other cytokines produced by MC, such as TNF-α transforming growth factor (TGF)-ß and IL-8, have been implicated in normal and tumor-associated angiogenesis (Blair et al., 1997). Endothelial cells might exert maintenance functions on MC since it is known that human dermal endothelial cells express MC growth and chemotactic factor SCF (Meininger et al., 1995). Furthermore, SCF may induce urokinase-type plasminogen-activator-receptor (uPAR)-expression in MC, and cells stimulated in this way could also chemotactically respond to uPA released by endothelial cells (Sillaber et al., 1997).

Mast cells and tissue remodeling

There is now emerging evidence that MC exert relevant functions in tissue homeostasis, remodeling, repair and fibrosis (Dvorak and Kissel, 1991; Gruber et al., 1997; Metcalfe et al., 1997; Artuc et al., 1999, 2002). These functions are accomplished by a direct MC stimulation of specific connective tissue cell types, in particular fibroblasts, and by the release or activation of a series of matrix-degrading enzymes. The presence of MC in connective tissues has been linked to the development of fibrosis through the production of cyokines and growth factors, such as histamine, heparin, tryptase, FGF-2, TNF-α and TGF-ß, which stimulate the proliferation of myofibroblasts and fibrosis. TGF-ß has a variety of effects on wound repair including the induction and/or facilitation of directed cell migration, angiogenesis and granulation tissue formation. TGF-ß exerts a potent chemotactic effect on MC (Gruber et al., 1994). MC are capable of both responding to and producing TGF-ß. Moreover, latent TGF-ß bound to matrix can be released but not activated by MC-derived chymase (Taipale et al., 1995). During the process of wounding, MC granules released into the tissue are phagocytozed by fibroblasts and endothelial cells and might thus contribute to persistently increased tissue histamine levels (Seibold et al., 1990). MC release platelet-derived growth factor (PDGF) into wounded tissue and thereby influence the healing process from very early stages onward. Tryptase and FGF-2 are potent activators of fibroblast migration and proliferation (Rouss et al., 1991; Artuc et al., 2002)). In an *in vivo* model of wound healing, an increased number of MC positively stained for FGF-2 was detected during the fibroproliferative stage (Liebler et al., 1997). Of particular interest is the observation that tryptase can stimulate the synthesis and release of collagen from fibroblasts in culture, as well as provoking secretion of collagenase (Cairns and Walls, 1997). Moreover, tryptase cleaves fibronectin and type VI collagen. In addition, it has the ability to activate the pre-enzyme forms of some metalloproteases and urinary

plasminogen activators. Indeed, these enzymes have been implied to have a major role in tissue degradation. The ability of tryptase to induce the proliferation of airway smooth muscle cells could be of relevance in conditions such as bronchial asthma, in which smooth-muscle cell hyperplasia is a feature (Thabrew et al., 1996). Tryptase may also have a role in tissue repair processes as a growth factor for epithelial cells. Chymase may contribute to the role of MC in tissue remodeling by cleaving type IV collagen and by splitting the dermal-epidermal junction. The production of type VIII collagen by human MC *in vivo* may influence repair processes since this collagen is believed to facilitate the assembly of endothelial cells and tubes and its synthesis precedes that of pro-collagen type I. In addition, MC contain NGF which actively stimulate neurogenesis after injury. Indeed, in the rat intestinal mucosa, reconstitution of nerve fibers after experimentally-induced inflammation and nerve fiber degeneration is accompanied by a significant increase in mucosal MC density (Stead et al., 1991). We have recently shown that low densities of both total and tryptase-reactive MC in the human intestinal mucosa from different inflammatory bowel disorders are associated with defective villous architecture (Crivellato et al., 2003).

Mast cells and the neural network

Numerous micro-anatomical and ultrastructural investigations over the past years have demonstrated the presence of close nerve-MC contacts in different organs of various species, including man (Stead et al., 1987, 1989; Crivellato et al., 1991). It has also been reported that electrical stimulation of nerve fibers causes degranulation of tissue MC and that these effects are inhibited by atropine or prior treatment with capsaicin (Javed et al., 1992). These findings have prompted further studies on a possible functional interaction between the peripheral nerve system and the tissue MC populations. It has subsequently been shown that several neurotransmitters and neuropeptides are able to modulate MC function and to induce granule release (Foreman and Jordan, 1980). MC in turn are able to stimulate nerve fibers through histamine release, thus amplifying the nerve-MC loop, or conversely decrease the local effects of nerve mediators by releasing neuropeptide-degrading proteases such as tryptase and chymase. A key link between the neural tissue and MC is NGF. The first evidence that MC are receptive to NGF showed that exogenous administration of NGF in newborn rats induced a marked increase in the number and size of MC in peripheral tissues (Aloe and Levi-Montalcini, 1977). The effect of NGF on MC includes stimulation of proliferation, differentiation, survival and mediator secretion. Furthermore, proliferation and differentiation of connective tissue-type murine mast cells has been shown to be dependent on the MC degranulation property of NGF (Matsuda et al., 1991). It has been ascertained that MC, in turn, synthesize and release NGF (Nilsson et al., 1997). NGF appears to be increased in the circulation in a variety of inflammatory and autoimmune conditions; it most consistently appears to be elevated in the circulation of patients with multiple allergic diseases, including asthma (Bonini et al., 1996).

MC have long been identified in the central nervous system. They are most numerous and most consistently present in the infundibulum, pineal organ, area postrema and choroid plexuses (Dropp, 1979). They are also numerous in the leptomeninges surrounding the pineal organ and infundibulum. Occasional MC are also seen within the supraoptic crest, the subfornical organ and the ventricles. They are not detectable elsewhere in the brain or spinal cord. MC have recently been implicated in the regulation of permeability of the blood-brain-barrier (Esposito et al., 2002). In addition, it has been suggested that MC in the central nervous system may function as a gate to the hypothalamic-pituitary-adrenal axis, thus participating in the counter-regulation of inflammatory immune responses (Matsumoto et al., 2001). This effect would be accomplished through histamine secretion, activation of histamine H1 receptors at the hypothalamus and induction of the corticotrophin-releasing factor. Glucocorticoids secreted by the adrenal cortex downmodulate immune reactions. Thus MC, which have a broad armamentarium of pro-inflammatory mediators, would also be able to express anti-inflammatory functions.

Mast cells and human diseases

Besides the classical IgE-mediated allergic disorders, involving the respiratory, cutaneous and gastro-intestinal compartments, MC have repeatedly been linked to a series of human diseases of uncertain aetiology. We have already shown that MC respond to a large array of stimuli and produce a great number of activatory molecules. Thus, when we consider the role of MC in a given pathological process, the key point would be to understand if they are primary protagonists or more or less active as by-standers. Growing evidence suggests that MC play a crucial role in the inflammatory process and subsequent demyelinization observed in patients suffering from multiple sclerosis. Indeed, recent results from animal models clearly indicate that these cells act at multiple levels to influence both the induction and the severity of the disease (Zappulla et al., 2002). A potential role for MC in rheumatoid arthritis has also been highlighted recently. An increased number of MC are found in the synovial tissues and fluids of patients with rheumatoid arthritis and at the site of cartilage erosion, reflecting the presence of MC chemotactic or survival factors, such as SCF and TGF-ß, in the synovial fluid (Olsson et al., 2001). The invading MC show ultrastructural signs of piecemeal degranulation and produce several inflammatory mediators, notably TNF-α, IL-1ß, and VEGF. TNF-α reportedly plays a pivotal role in the pathogenesis of rheumatoid arthritis, especially in its ability to regulate IL-1, expression, this

being important for the induction of prostanoid and matrix metalloproteinase production by synovial fibroblasts and chondrocytes. Bullous pemphigoid is another human disease whereby MC have been proposed to exert a relevant pathogenic role. This autoimmune skin disease is characterized by subepidermal blisters resulting from auto-antibodies against two hemidesmosomal antigens, BP230 and BP180. Intradermal injection of antibodies against BP180 into neonatal mice causes a blistering disease mimicking bullous pemphigoid. Injection of antibodies against BP180 into w/wv MC-lacking mice does not induce bullous pemphigoid, nor does the injection into wild-type mice pre-treated with the MC stabilizer cromolyn sodium induce it (Chen et al., 2002). Interstitial cystitis has gained increasing attention for an MC role in its pathogenesis. Indeed, the presence of activated MC in close proximity to suburothelial nerves is a consistent feature of this yet-to-be-clarified urological pathology (Elbadawi, 1997). MC involvement in the pathogenesis of coronary spasm, cardiomyopathy, atherosclerosis and myocardial ischemia has been suggested. It has been shown that chymase cleaves angiotensin I to angiotensin II more effectively than the angiotensin-converting enzyme (Church and Levi-Schaffer, 1997). Studies in the canine model of myocardial ischemia and reperfusion, indicate a role for MC mediators in initiating the cytokine cascade which is ultimately responsible for neutrophil accumulation in the ischemic area. In addition, MC have been claimed to play a crucial role for leading to the subsequent fibrotic process (Frangogiannis et al., 1998).

Mast cell neoplasia

Neoplasia of MC are rare and their diagnosis is difficult and frequently mistaken. Proliferation of MC may be limited to the skin (cutaneous mastocytosis), or may involve more extracutaneous organs ("systemic" or "generalized" mastocytosis: SMCD). The classification of MC Diseases (MCD) is controversial, but recently the WHO presented a consensus classification system developed after a Working Conference (WHO, 2001) (Table 2). Interesting is the observation that in the majority of MCD of the adult, a somatic mutation of the protooncogene encoding for the SCF receptor (c-kit) is present, with activation of the c-kit protein.

Table 2. Classification of mastocytosis (WHO, Vienna 2000).

Cutaneous Mastocitosis (CM)
Indolent Systemic Mastocytosis (ISM)
Systemic Mastocytosis with Associated clonal, Haematological Non-Mast cell lineage Disease (SM-AHNMD)
Aggressive Systemic Mastocytosis (ASM)
Mast Cell Leukemia (MCL)

Concluding remarks

MC are multifunctional effector cells of the immune system, capable of producing a great variety of pre-formed and newly-formed mediators. They are involved in a spectrum of activities that are not strictly confined to immunological functions but also concern non-immunological processes. Due to this ample potential involvement in a large array of reactions, MC have recently focused the interest of both basic and clinical researchers for their possible involvement in human pathology. Further studies on the structure and functional activity of MC will hopefully shed new light on the different aspects of this fascinating cell.

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