

Involvement of Mast Cells in Angiogenesis and Chronic Inflammation

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Abstract: Mast cells (MC) are granulated secretory cells that have long been recognized as a rich source of biologically highly active mediators such as biogenic amines, prostaglandins, leukotrienes, proteases, cytokines and chemokines. Most of their biological functions however has been rather elusive. There are now emerging data assigning these cells a relevant role in orchestrating angiogenesis, both in normal and pathological conditions. MC indeed synthesize and release a large array of proangiogenic factors upon different stimulation pathways. In addition, MC have been recognized as key cells in mediating host innate and adaptive immune responses. This review summarizes the most recent acquisitions concerning MC involvement in angiogenic processes and chronic inflammatory reactions.

Keywords: Mast cells, angiogenesis, inflammation, cytokines, human pathology.

INTRODUCTION

Mast cells (MC) are multi-functional long-lived secretory cells, characterized by their content of numerous large cytoplasmic granules. 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 [1]. However, MC populations show marked differences in their phenotypic expression in different species as well as distinct anatomical sites, a phenomenon called "MC heterogeneity" [2].

There is general consensus that MC develop, like other leukocytes, from haematopoietic stem cells but do not mature before exiting the bone marrow [3]. Committed progenitors, circulating as mononuclear agranular cells, traverse the vascular space and complete their maturation after moving into different peripheral tissues, where they acquire phenotypic diversity [4]. 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) [5].

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 [6]. 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.

MAST CELLS AND ANGIOGENESIS

Angiogenesis refers to the formation of capillaries from pre-existing vessels, i.e. capillaries and post-capillary venules [7]. Angiogenesis is a multistep process involving vessel sprouting, endothelial cell migration and proliferation followed by capillary tube formation. It is well established that a number of cells - such as embryonic cells (endoderm, astrocytes, Müller cells), [7,8] adult resident and inflammatory cells (fibroblasts, macrophages, T lymphocytes, plasma cells, neutrophils, eosinophils) [9-12] and tumor cells [13] - can produce and release angiogenic growth factors. MC have long been implicated in the regulation of both physiological and pathological neovascularization mostly on the basis of histological observations [14]. Under physiological conditions, indeed, MC localize close to capillaries and lymphatic channels. Angiogenesis associated with physiological events, such as embryonic development, ovulation and wound healing, has been found to be accompanied by tissue accumulation of MC [15,16]. In addition, an increased number of MC have been reported in angiogenesis associated with chronic inflammatory diseases (rheumatoid arthritis, nasal polyps) [17,18], vascular neoplasms (haemangiomas) [19], as well as solid and haematopoietic tumors (gastric cancer, neurofibroma, lung carcinomas, laryngeal squamous cell carcinoma, cutaneous melanoma, B-cell non-Hodgkin's lymphomas, multiple myeloma, myelodysplastic syndromes, chronic lymphocytic leukemia) [20-31]. In tumor samples, MC density correlates with angiogenesis and poor tumor outcome [20,32,33]. Beside MC

accumulation, ultrastructural analyses of involved tissues reveal profound MC challenge in the form of cell degranulation, according to the particulate "piecemeal" pattern [1,34,35].

There is now emerging evidence that MC release a variety of proangiogenic factors. Human, rat and mouse MC release preformed fibroblast growth factor-2 (FGF-2) from their secretory granules [19,36]. Human cord blood-derived MC release vascular endothelial growth factor (VEGF) upon stimulation through FcεRI and c-kit. Both FGF-2 and VEGF have also been identified by immunohistochemistry in mature MC in human tissues [37,38]. It has recently been shown that human MC are a potent source of VEGF in the absence of degranulation through activation of the EP(2) receptor by prostaglandin E2 [39]. It has also been demonstrated that rat peritoneal MC contain angiogenic factors stored in their secretory granules. Granulated MC and their granules, but not degranulated MC, are able indeed to stimulate an intense angiogenic reaction in the chick embryo chorioallantoic membrane (CAM) assay. This angiogenic activity is partly inhibited by anti-FGF-2 and -VEGF antibodies, suggesting that these cytokines are involved in the angiogenic reaction [40]. Similarly it has been demonstrated, using the rat-mesenteric window angiogenic assay, that intraperitoneal injection of compound 48/80 - a potent MC secretagogue - causes a vigorous angiogenic response [41]. The same treatment in mice also causes angiogenesis [42].

MC store large amounts of preformed active serine proteases, such as tryptase and chymase, in their secretory granules [1,6]. A role in the angiogenic process for these proteolytic enzymes has been established. Tryptase, in particular, stimulates the proliferation of human vascular endothelial cells, promotes vascular tube formation in culture and also degrades connective tissue matrix to provide space for neovascular growth. Tryptase also acts indirectly by activating latent matrix metalloproteinases (MMP) and plasminogen activator (PA), which in turn degrade the extra cellular connective tissue [43]. Tryptase-containing MC are likely to play an important role in neovascularization in human tumors, such as cutaneous basal cell carcinoma [44], squamous cell carcinomas of the oral cavity [45] and uterine cervix [46], cutaneous melanoma [26], B-cell non-Hodgkin's lymphomas [29], multiple myeloma [30], myelodysplastic syndromes [28], chronic lymphocytic leukaemia [27]. Chymase also expresses angiogenic potential [47] and a correlation between tumor progression and accumulation of chymase-positive MC has been found in the small sized adenocarcinoma of the lung [48].

Other MC-specific mediators with angiogenic properties include histamine and heparin [48,49]. Both molecules have been shown to stimulate proliferation of endothelial cells and to induce the formation of new blood vessels in the CAM-assay [50,51]. In addition, other cytokines produced by MC, such as tumor necrosis factor-α (TNF-α), transforming growth factor (TGF)-β and IL-8, have been implicated in normal and tumor-associated angiogenesis [43]. Endothelial cells might exert maintenance functions on MC since it is known that human dermal endothelial cells express the potent MC growth and chemotactic factor, stem cell factor (SCF) [52]. 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 [53]. uPAR-expression in MC may be related to the specific pro-angiogenic function, 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

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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 [54].

It should be underlined that MC can contribute to tissue angiogenesis either directly, by releasing proangiogenic molecules, or by an indirect way. MC mediators stimulate indeed other cells - such as fibroblasts, endothelial cells and macrophages - to secrete angiogenic factors and cytokines as well as extra cellular matrix-degrading proteases [55].

MAST CELLS AND CHRONIC INFLAMMATION

MC have been recognized as key cells of both innate and acquired immunity [56]. They synthesize indeed and release a myriad of pro-inflammatory and immunoregulatory molecules, and express a wide spectrum of surface receptors for cytokines and chemokines. MC are thus largely equipped to exert profound effects on different aspects of inflammatory and immunological reactions [57]. They are a relevant component of the inflammatory infiltrate in the tissues from multiple diseases and participate to various cell-mediated reactions. In addition, they are considered to play a still poorly defined but critical role in host defence against parasites, bacteria and perhaps even viruses [58-60].

MC express the high affinity receptor FcεRI, which binds the Fc region of an IgE antibody molecule. 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 [61]. Cross-linking of FcεRI receptors by specific IgE molecules binding multivalent antigens causes initiation of MC activation. MC indeed have long been recognized as key cells of type I hypersensitivity reactions [1,6]. Besides FcεRI receptors, MC express a large array of adhesion molecules and chemotactic factor receptors. In particular, they 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 [62,63]. Indeed, most if not all of these chemokines cause MC migration *in vitro*.

MC produce an impressively broad array of mediators and cell-cell signalling molecules. Cytokine and chemokine production by MC is closely regulated and may occur independently from classical FcεRI receptor-mediated MC activation. MC secretory granules in humans and rodents contain TNF-α which has pleiotropic pro-inflammatory effects [64]. TNF-α has been implicated in neutrophil recruitment, inducing up-regulation of the endothelial-leukocyte adhesion molecule (ELAM-1) [65]. TNF-α has also been known to enhance the bactericidal activities of neutrophils [66]. Mice that are MC deficient due to a functional inactivation of their c-kit (w/wv) are highly susceptible to death after cecal ligation and puncture [58,64]. In addition, human MC have the capacity to generate IL-8, thus contributing to neutrophil recruitment [67]. Under allergic conditions MC produce significant amounts of IL-1 that may contribute to lymphatic infiltration [68] 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 [69]. 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 [70,71].

In humans, MC have repeatedly been linked to a series of chronic inflammatory diseases of uncertain aetiology. Growing evidence suggests that MC play a crucial role in the inflammatory process and subsequent demyelination 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 [72]. A potential role for MC in rheumatoid arthritis has also been highlighted recently [73]. 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-α, in the synovial fluid [74]. The invading MC show ultrastructural signs of piecemeal degranulation and produce several inflammatory mediators, notably TNF-α, IL-1β and VEGF. TNF-α reportedly plays a pivotal role in the pathogenesis of rheumatoid arthritis, especially in its ability to regulate IL-1β expression, this being important for the induction of prostanoid and matrix metalloproteinase production by synovial fibroblasts and chondrocytes [75]. Interestingly, it has been noted that MC containing tryptase (MC_T subset) are selectively expanded in the early phase of rheumatoid arthritis,

suggesting an active participation in the inflammatory events, whereas MC expressing tryptase and chymase (MC_{TC} subset) predominate during disease progression and thus may be more relevant in connective tissue damage [76]. 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 [77]. Interstitial cystitis is another disease that has gained increasing attention for a 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 [78].

CONCLUDING REMARKS

There is growing evidence that MC play a pivotal role in driving inflammatory responses and organizing both normal and pathological angiogenesis. Recent findings indeed identify MC as sentinels for signalling and mediating host innate and adaptive immune responses. In addition, these cells have increasingly been recognized as a key source of angiogenic cytokines and endothelial cell growth factors in chronic inflammatory diseases and tumors. It is reasonable to speculate that a deeper understanding of MC activation mechanisms, immuno-modulatory capacity and proangiogenic potential will open new perspectives on the development of future therapeutical strategies targeted at such multifunctional cells.

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