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A Brief Review of Mast Cells in Microbial Infection (Inflammation) and Tumor-Associated Angiogenesis

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Abstract

Mast cells are among cells of the immune system and participate in various physiological and protective immune functions in the body. Association of mast cells with allergic reactions and parasitic infections is well-documented. Various studies indicate that mast cells also play an important role in non-allergic phenomenon. Mast cells are reported to phagocytize and process antigens and play a protective role in immune response against bacterial infections. Mast cells not only act as the first line of defense against parasitic and bacterial infections but exert similar protective functions in viral infections through intracellular and extracellular antiviral defense mechanisms. Additionally, studies in human and animal neoplasms indicate that mast cells and several mast cell mediators are angiogenic, promote tumor-associated angiogenesis and facilitate progress of tumor malignancies and metastasis. This brief review gives a concise account of the role of mast cells in tumor angiogenesis and in microbial (bacteria and virus) infections.

Keywords: Bacteria; Infection; Mast cell; Tumor-angiogenesis; Virus

Introduction

Mast cells are found in several tissues in the body, particularly in those exposed to external environment such as the skin, and the gastrointestinal tract; and are likely among the first inflammatory cells to encounter pathogens and toxic agents [1]. Mast cells possess several unique properties that enable them to initiate rapid and sustained immune reactions [2]. Mast cells are variable in terms of their morphology, function, and metabolic products. Different types of mast cells with variable functions are recognized. Their function varies depending on the tissue micro-environmental milieu, and antigen encountered at a given location in the body. Mast cells release preformed products that are stored in their granules and rapidly liberated upon degranulation, denovo synthesized lipid mediators, and many cytokines, chemokines and growth factors [3]. Through the release of various cytokines, growth factors and enzymes mast cells exert a broad spectrum of physiological functions varying from involvement in tissue homeostasis, and vascular proliferation to the involvement in host defense mechanisms against pathogens. Mast cell function is largely governed by a local stromal microenvironment, which could alter their phenotypic behaviour and their secretory processes and function. The role of mast cells in parasitic infection and allergic reactions is well recognized. Recently, more consideration is also given to their role in immune response against bacterial and viral infections. Furthermore, mast cells and their secretory products are known to promote neovascularization in neoplasm development and progression. This concise review briefly describes the role mast cells play in immune response against bacterial and viral infections and tumor-associated angiogenesis.

Mast Cells in Microbial Infection (Inflammation)

Mast cells are involved in various physiological and immunological functions in the body. They are important effecter cells providing membrane mediators as well as cytokines in allergic and inflammatory diseases [4,5]. Recently, their role in non-allergic phenomena has drawn more attention [6]. Evidences indicate that mast cells exert important functions in both innate and acquired immune responses [3]. As part of their role in innate immunity, mast cells release various cytokines through the recognition of specific molecular patterns on bacteria and viruses by TLR expressed on the mast cell surface [7]. An increasing amount of experimental evidence supports the hypothesis that mast cells are essential for pathogen containment and clearance. Due to their cytoplasmic granules containing preformed mediators, mast cells have the potential to respond within seconds to minutes following recognition of an invading pathogen. Because of their ability to instantly release several pro-inflammatory mediators from intracellular stores and their location at the host-environment interface, mast cells have been shown to be crucial for optimal immune responses during infection. Mast cells seem to exert these effects by altering the inflammatory environment after detection of a pathogen and by mobilizing various immune cells to the site of infection and the draining lymph nodes [8].

Mast cells phagocytize and process antigens [5] and are reported to play an important role in gastrointestinal pathology in humans, especially in the intestinal response to bacterial infections and in antigen presentation to T-cells [9]. Mast cell-derived leukotriens contribute to host defense by mediating early neutrophil influx and bacterial clearance at sites of infection [10]. Activation of mast cells by lipopolysaccharide (LPS) of Gram-negative bacteria results in production of inflammatory cytokines, leading to rapid infiltration of neutrophils, expanding the inflammatory responses, and leading to sufficient bacterial eradication [5].

Mast cells not only act as the first line of defense against parasitic and bacterial challenges but similarly respond to certain viral challenges through specific induction of intra-cellular and extra-cellular programs tailored for antiviral defense [11]. However, in contrast to their well-defined contributions to surveillance for bacteria and parasites, mast cell responses to viruses have hardly been examined [8]. Higuchi and coworkers [12] reported the critical and important role of mast cells in the pathogenesis of viral myocarditis. Increased mast cell and subsequent tryptase and histamine release are also described as major contributing factors in the proventriculus mucosal injury induced by Newcastle Disease Virus infection [13].

Evidence also shows that human mast cells might be involved in host defense against viruses that directly infect human mast cells, such as human immunodeficiency virus (HIV), and also against double-stranded RNA viruses recognized by toll-like-receptor-3 (TLR3) [14]. St. John and co-workers [11] reported that rodent, monkey, and human mast cells detect Dengue virus that results in mast cell activation and degranulation. The authors described the involvement of mast cells in the immune response against Dengue virus through the activation of antiviral, intracellular, multifaceted, host response pathways, which are consequential to the containment of Dengue virus in vivo. This was demonstrated by subcutaneous infection of mast cell-deficient mice, which showed increased viral burden within draining lymph nodes known to be target organs during Dengue virus spread, compared with mast-cell-sufficient mice. The study further indicated that mast cell immune-surveillance include viral pathogens and that mast cells not only resist Dengue virus infection themselves, but also appear to enhance the recruitment of natural killer (NK) and natural killer T-cells (NKT) to facilitate viral clearance [11]. In addition to being able to recognize pathogen associated molecular patterns (PAMPs), mast cells can detect a range of products through the expression of other receptors that sense pathogens such as Fc-receptors (FcRs), which bind pathogen-specific antibodies and receptors for inflammatory factors produced at the site of infection [8]. A novel role for mast cells in the recruitment of human NK cells to sites of early viral infection via CXCL8 and the mechanism by which mast cells provide the chemotactic stimulus necessary to induce NK cell recruitment to sites of viral infection is described [15].

TLR expressed on the surface of mast cells, responds to a variety of bacterial and viral components to induce and enhance high affinity IgE receptor (FcεRI)-mediated cytokine production [16]. Direct pathogen recognition by mast cells occur both in responses to factors that are common to classes of pathogens such as through Toll-like receptors (TLRs) and those that are specific to only a certain infectious challenge such as through binding of antibodies specific for pathogen-associated epitopes. Mast cells have the ability not only to affect immediate innate processes to clear pathogens but also to influence the long term host responses to pathogens. Together with local responses to pathogens, mast cells have long-distance and long-term effects in the host by modulating draining lymph nodes, influencing cell trafficking to the draining lymph nodes and promoting the development of adaptive immunity to pathogens [8].

The role of mast cell in bacterial and viral infections in veterinary medicine is not well documented. There are a few reports on the involvement of mast cells in idiopathic inflammatory bowel disease and canine lymphoplasmacytic and eosinophilic enteritis [17,18]. A significant increase in mast cell count was recorded also in canine enteritis with crypt abscess associated with Canine parvovirus infections as compared to those in the control [19]. The study indicates involvement of mast cells in Canine parvovirus-induced enteritis with crypt abscess and suggests a possible role mast cells could play in other virus-induced immune responses in animals.

All in all, mast cells are reported to play an important role in inflammatory bowel disease in dogs and humans [1,18,20]. In the animal model, increased number of mast cells in the gastrointestinal tract was observed in dogs with inflammatory bowel disease in comparison with healthy dogs [21]. The definitive cause of inflammatory bowel disease is still unknown [18], and the mechanisms through which mast cells play a role in the pathogenesis of inflammatory bowel disease are not yet elucidated. However, inflammatory bowel disease is suggested to be an immune-mediated phenomenon with immunological, environmental, and genetic factors contributing to expression of the disease [22]. While pathogenesis of inflammatory bowel disease remains unclear, mast cells are a key cell type actively involved in the pathogenesis of inflammatory bowel disease, and their key role in this group of diseases strongly demonstrates that inflammatory bowel disease is a mast-cell-associated disease [23].

Generally, the number of mast cells in inflammatory process appears to vary depending on the stage and degree of inflammation. Usually, lesser numbers of mast cells are encountered in areas where other inflammatory cells are abundant. This suggests that mast cells may decrease in number after initial phase of mobilizing various inflammatory cells to the site of infection through their mediators [8]. Kleinschmidt and co-workers [18] reported a more conspicuous decrease in mast cell count with increasing histologic grade in dogs with inflammatory bowel disease and suggested that a higher variability in mast cell counts were due to the differences in disease stage between different dogs. In human patients with systemic mastocytosis, Siegert and co-workers [24] found no increase in mucosal mast cells, but recorded markedly increased histamine content in the gastric tissue. The authors suggested that the decrease in mast cell numbers might be due to a negative feedback phenomenon, in which normal tissue mast cells are reduced as a consequence of high tissue histamine levels derived from the increased neoplastic mast cells in the bone marrow and other tissues. Further investigation should determine if similar negative feedback described above or other mechanisms underlie the decrease in mast cell counts usually observed in areas of inflammation where other inflammatory cells are abundant.

Recent studies in humans using mast cell activators as effective vaccine adjuvants showed the potential of harnessing these cells to confer protective immunity against microbial pathogens [8]. Higuchi and co-workers [12] reported that mast cells participate in acute inflammatory reaction and onset of ventricular remodelling associated with acute viral myocarditis and that inhibition of mast cell-function may be therapeutic in this disease. Detailed studies on the role of mast cells in immune response against viral and bacterial infections would help to envisage similar therapeutic approach in the management of other virus- and bacteria-induced infections in humans and animals.

Mast cell in tumor-associated neovascularization (angiogenesis)

Angiogenesis is a growth of new blood vessels (neovascularization) from pre-existing vasculature. Tumor-associated angiogenesis aids in the progression and metastasis of malignant tumors. Angiogenesis is a complex event mediated by multiple angiogenic factors released from cancer cells and host immune cells [25]. Mast cells accumulate in many angiogenesis-dependent situations including tumor growth, rheumatoid arthritis, ovulation, wound healing, and tissue repair [26]. Mast cells are a component of cancer microenvironment, the role of which is complex and poorly understood [27]. Accumulated evidences show that angiogenesis is related to mast cells. Mast cells are involved in neoplasm development and neovascularization, support tumor progression and potentiate metastasis by stimulating angiogenesis [25]. Several mast cell mediators are angiogenic and regulate endothelial cell proliferation [26]. The role of mast cells in tumor-associated angiogenesis in human malignancies is reported for several neoplasms including basal cell carcinoma [28], plasma cell tumor [29], squamous cell carcinoma [25,30] and lung cancer [31].

Information on the role of mast cells and associated angiogenesis in neoplastic progression and malignancies in veterinary medicine is scarce. Few reports are available on the correlation between higher numbers of mast cell and angiogenesis in canine neoplasms. Mast cell-associated angiogenesis is reported in the development and progression of canine transmissible venereal tumors [32] canine melanomas [33] canine nodal lymphomas [34], cutaneous and non-cutaneous hemangioma, hemangiosarcoma, mammary adenoma and mammary adenocarcinoma in dogs and other domestic animals [35-37]. From the reports available so far [32,33,35-37] it is plausible to suggest that mast cells could possibly be involved also in the neovascularization and progression of other malignancies in animals.

How mast cells exert an effect in neoplasm development and progression is intriguing. Mast cells promote cancer growth by stimulation of neovascularization, tissue remodelling and modulation of the host immune response. The mediators of cancer promotion include protease-activated receptors, mitogen activated protein kinases, prostaglandins and histamine. Histamine may induce tumor proliferation and immunosuppression through H1 and H2 receptors, respectively. Mast cell-derived modulators of immune response include interleukin 10 (IL-10), tumor necrosis factor α (TNF-α) and CD30L. Furthermore, mast cells release potent proangiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β), TNF- α and IL-8, and enzymes such as tryptase and chymase and metaloproteinases (MMPs), which participate in vessel formation [27]. Among mast cell associated factors, vascular endothelial cell growth factor (VEGF), interleukin-8 (IL-8), heparin, and tryptase facilitate angiogenesis and others such as platelet-derived growth factor (PDGF), nerve GF (NGF), stem-cell factor (SCF), and proteases disrupt the surrounding matrix and facilitate tumor metastases [38]. Tryptase released by mast cells degrades connective tissue matrix and provide space for neovascular sprouts [26]. It is also reported that tryptase directly induce endothelial cell proliferation in a dose dependent manner through formation of capillary structures either by directly acting on endothelial cells or by facilitating the early stages of angiogenesis [39].

Mast cells are multifarious in terms of their morphology, function, and metabolic products [40]. Mast cell count varies with the biological behavior and type of a given neoplasm and type of pathogen encountered in infectious processes. Their function in tissues associated with benign and malignant tumors or non-neoplastic lesions may be influenced by the tissue micro-environmental milieu and types of the neoplastic cells.

Hagiwara and co-workers [41] reported increased density of mast cells in human malignant as well as benign vascular proliferating tumors. A significantly increased number of mast cells were reported in human angiosarcoma compared with normal skin [42]. Higher mast cell count is usually seen on the invasive edges of tumors than within the tumor stroma particularly in malignant neoplasms. Higher mast cell count was reported in the stroma on the invasive edges in canine cutaneous hemangioma, hemangiosarcoma, mammary adenoma, mammary adenocarcinoma and canine nodal lymphoma than in the stroma within the neoplastic masses [34,37]. In their study on human squamous cell carcinoma of the esophagus, Elpek and co-workers [30] suggested that in a particular tumor, the number of microvessels and mast cell count could be related to the amount of stromal components. Consequently, tumor with more stroma might have more microvessels and mast cells. Similar observations were recorded for canine

cutaneous vascular and mammary tumors [37]. Sabattini and Bettini [35] reported comparatively higher numbers of mast cells in 25 cutaneous, and 4 visceral hemangiomas than in 29 visceral, and 11 cutaneous hemangiosarcoma. The variation in the examined tissues with more cutaneous tumors in hemangioma group (86%) and more visceral tumors in hemangiosarcoma group (72%) with the consequent variation in the amount of the stromal components and the microenvironment might have influenced the mast cell count. The authors further reported that 25% (10/40) of hemangiosarcoma had a low to moderate number of infiltrating mast cells; and in one tumor there were numerous mast cells. Mast cells were not detected in the remainder of the samples. Infiltrating mast cells were seen in the stromal compartment of all hemangiomas except one splenic hemangioma in which no mast cells were detected. Other report [36] recorded accumulations of mast cells in the stroma of 21% (16/76) of hemangiosarcomas from 66 dogs and 10 cats involving various tissues (skin, eye and bone). Mast cell count may vary depending up on the variation in the type of tissues involved, species of animals examined, number of the examined patients and the counting methods employed. Consequently, careful interpretation should be considered in determining the role of mast cells in the development and progression of each neoplasm in different tissues and patients. Although detailed study and further explanation is needed to elucidate why mast cells were not seen in some neoplasms, it could be due to variation in the developmental stages of the neoplasms as described for human hemangiomas [40], in which mast cell count is reported to vary depending upon the phases of development.

Mast cells are known to accumulate at sites of angiogenesis [43] and promote angiogenesis as previously described in various canine [32-34,37] and in human [28-31] neoplasms. Mounting evidence, however, indicates that mast cells accumulating around tumors could either promote or inhibit tumor growth depending on the local stromal conditions [38] and the stage of tumorigenesis. Mast cells may play both angiogenic and antiangiogenic roles in different stages of hemangioma [44] and intestinal tumorigenesis [45]. In contrast to the large body of evidence showing the proangiogenic role of mast cells, Tan and co-workers [40] reported highest total number of mast cells during the involuting phase, less in the involuted phase, and the least in the proliferative phase of human hemangiomas, suggesting that the increased number of mast cells during the involuting phase indicates that these cells may play a role in the regression of hemangiomas. Sun and co-workers [44] also reported that mast cells may also secrete antiangiogenic modulators in the involuting stage of hemangiomas. The authors postulated that mast cells may play both angiogenic and antiangiogenic roles in different stages of hemangiomas. Therefore, the roles of mast cells in hemangioma are likely to be complex and may involve stimulators of angiogenesis in the proliferative phase and inhibitors in later phases of hemangiomas [40]. Mast cells are also reported to function in a pro-tumorigenic capacity through the promotion of angiogenesis in late stage malignancy in intestinal tumorigenesis in humans, in contrast to early stage tumorigenesis, during which they function in a protective role by promoting apoptosis of tumor cells [45].

It is also recorded that mast cells have anticancer role. The anti-cancer actions of mast cells include direct growth inhibition, immunologic stimulation, and decreased cell mobility; the mediators of these processes include chymase, tryptase, TNF-α, IL-1 and IL-6. The very same mediators may exert both pro- or anti-cancer effects depending on concentration, presence of cofactors or location of secreting cells [27]. Therefore, the discordant results between mast cell

density and tumor progression in different tumors may be due to differences in effect of mast cell chemotactic factors released from cancer cells on stromal mast cells reactions [30]. In fact, peri-tumoral and intra-tumoral mast cells may have dissimilar effects [27]. Although mast cell density has been found to correlate with increased risk of metastasis and prognosis in several human and animal malignancies [30], because mast cells are highly heterogeneous in terms of their morphology, function, and metabolic products [40] the results of mast cell count in different neoplasms, tissues and species involved should be interpreted carefully.

Conclusion

Diverse mast cell functions in normal and pathological phenomenon varying from response in allergic and parasitic infection to neoplasm development and progression are studied. Their role in allergic reactions and parasitic infection is well-documented. In recent years, more studies on the involvement of mast cells in bacterial and viral infection are emerging. Mast cells are reported to be important cells in response to some bacterial and viral infections and play a vital role in immune response during infection. Mast cells detect pathogens, alter the inflammatory micro-environmental milieu and mobilize various immune cells to the site of infection. Their role in the development of angiogenesis in various human and animal malignancies is described. Mast cell density has been found to correlate with increased risk of metastasis and prognosis in various malignant neoplasms. Others proposed that one of the functions of mast cells is to release factors leading to regression of some neoplasms such as hemangioma, warranting a careful interpretation of neoplasm-associated mast cell count. Mast cells are not readily visible in routine hematoxylin-eosin (H & E) stain, particularly in areas where large numbers of other inflammatory cells are present. This leads to an easy overlook of these cells undermining their possible role in inflammatory processes and neoplasm angiogenesis in H & E stained sections. Special metachromatic stains such as toluidine blue or immunohistochemistry against mast cell tryptase should be used to clearly visualize mast cells. From information available so far and increasing studies on mast cells, it is reasonable to envision that future studies will further discover other so far unknown roles of mast cells in infectious processes and tumor progression in humans and animals.

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