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The dark side of mast cells and their role in metastasis

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Abstract:
Mast cells are one of the best and least understood components of the immune system. They play a crucial role in inflammatory diseases as well as in the promotion of progression of many types of neoplasms. This review covers the most important pathological conditions associated with mast cell activity focusing on inflammatory diseases, e.g. inflammatory bowel disease, chronic pancreatitis, asthma, and mostly on tumor growth and metastases.

Keywords: mast cells, inflammatory diseases, tumor growth, metastases.

Introduction:
Mast cells (MC) are multi-effectors cells, first described in 1876 by Paul Ehrlich, who named them “Mastzelle” meaning “well-fed cells” because they had a high number of cytoplastic granules [1-3]. Despite having been discovered over 100 years ago, mast cells are one of the best and least understood components of the immune system [4].

Mast cells are long-living, multifunctional immune cells, and due to synthesis and release diverse types of inflammatory mediators. MC affect various organs, leading to the development of different diseases [5]. In the recent decades, the importance and fascinating biology of the mast cells has been described in many physiological and pathological disorders.

I. Mast cells in physiology

Mast cells play a key role in processes such as wound healing, tissue regeneration and remodeling after injury. They are found at sites of wound healing and have different effects on this process. MC may inhibit or stimulate collagen synthesis depending on the local concentration of released histamine [6]. By chymase MC induce a mitogenic effect on fibroblasts [7], and by nerve growth factor coordinate proliferation of epithelial cells. Increased numbers of MCs are also observed at sites of healing fractures [8,9].

Mast cells are found in most tissue, especially in tissue connected with the external environment (gastrointestinal tract, genitourinary and respiratory mucosal epithelial surfaces), where they associate with blood vessels and nerve endings and thus may have immediate and easy contact with the external environment and invading pathogens. This MC subpopulation is called mucosal or reactive mast cells and their numbers are more dynamic compared with the relatively stable MC in connective tissues. Reactive mast cells increase in circumstances of mucosal inflammation.

I.a. Role of MC in the immune system

In the last few decades, increasing evidence suggested that mast cells can induce and modulate adaptive immune responses. They are the first line of defense against pathogens such as bacteria, viruses and parasites. Currently, several data indicate that mast cells can be infected by some viruses, which could replicate in this cells, such as the dengue virus, cytomegaloviruses, and the HIV-1 virus [13-15]. In response to stimulation by viruses, MCs release preformed mediators, chemokines and cytokines, and synthesize de novo eicosanoids. Moreover, MC also express Toll-like receptors responsible for the recognition of virus-derived PAMP molecules [16]. Recent evidence suggests that mast cells not only efficiently recognize and present bacterial antigens, but also phagocytose and kill adherent bacteria [17]. It has long been documented that mast cells can produce reactive oxygen species [18].

They induce the migration of Langerhans cells from the skin to the draining lymph nodes following activation by IgE and an allergen [19] and also following IgE-independent activation [20,21]. In addition, mast cells also activate T cells by cell contact-dependent and independent mechanisms. Through the secretion of mediators, mast cells are able to attract T cells, e.g., to the regional lymph nodes [22], and can process antigens and are able to present them via MHCI or MHCII complexes. What is interesting, they can be stimulated to re-enter the cell cycle and proliferate [23,24].

II. MC in inflammatory diseases

II.a asthma

Traditionally, mast cells are considered major effectors in IgE-associated immediate hypersensitivity and allergic responses such as asthma. Local accumulation of MCs is also observed in rhinitis, pollinosis, as well as psoriasis and atopic dermatitis [25-28].

MC mediators play an important role in the pathogenesis of asthma, bronchoconstriction (cys-LTs, histamine, PGD2), vasodilation and tissue edema (histamine, cys-LTs), leukocyte infiltration (cys-LTs, PGD2, tryptases, cytokines and chemokines), collagen matrix turnover and stromal cell growth (tryptases, cytokines), and hyperplasia of bronchial smooth muscle (tryptases, cys-LTs) [29]. In normal human bronchi, MC are located in submucosal connective tissues, while in asthma MC are both in the epithelial surface and in the smooth muscle [30,31]. Mast cell numbers were increased in the bronchi in people with allergic and non-allergic asthma, although the accumulation of mast cells was more pronounced in those with allergic asthma [32-34]. TNF- alfa, a proinflammatory cytokine, is implicated in the pathogenesis of asthma its levels increase in the airways of patients with mild asthma [35]. Recent studies demonstrated that administration of Etanercept (TNF inhibitor) to patients with severe refractory asthma improved quality of life and lung function [36,37].

Taken together, these findings clearly demonstrate that mast cells are not only effector cells during allergic reactions but also have a complex role in the induction and regulation of adaptive immune responses. Increased numbers of mast cells are commonly observed in many autoimmune diseases, including multiple sclerosis, rheumatoid arthritis and bullous pemphigoid. However, there is still debate regarding the relative role of mast cells in these processes [38].

IIb. Mastocytosis

Mastocytosis is a leading but rare, heterogenous group of rare diseases characterized by abnormal proliferation and acumulation of mast cells and their CD34+ progenitors in one or more organs, such as the skin, bone marrow and internal organs (liver, spleen, lymph nodes) [39-41]. The organ most frequently involved is the skin. Clinical presentation of cutaneous disease is characterized by the progressive appearance of erythematous, pruritic, and urticarial papules that subsequently become pigmented [42]. The severity of skin lesions does not correspond to disease severity [43,44]. The symptoms of mastocytosis are associated with the release of mediators and organ infiltration by mast cells; they often overlap and it is difficult to distinguish them [45].

Systemic mastocytosis mainly affects adults and the symptoms are different depending on the location of the extra mast cells. The most common symptoms of the gastrointestinal tract are: nausea, vomiting, abdominal pain, diarrhea, malabsorption, hepato- and splenomegaly [46], and life-threatening peptic ulcer, ulcerative colitis with massive bleeding. Patients with any form of mastocytosis may experience life-threatening symptoms associated with the rapid release of mast cell mediators, e.g. hypotension, hypertension, anaphylactic reaction, dyspnoea. Triggers of these symptoms may be physical factors such as high and low temperatures, exercise, chemical agents like alcohol, hymenoptera venom, other inhalant and food allergens and drugs (e.g. drugs for anesthesia, antibiotics, opioids, alpha and beta blockers) [47,48]. Weakness, weight loss, cachexia, fever, bone pain, osteopenia and osteoporosis may be the symptoms. Significant liver disease, splenomegaly, and ascites may occur, particularly in advanced cases.

Pathogenesis of the disease is related to mechanisms governing the development, proliferation, differentiation and survival of mast cells [49,50]. MC are derived from CD34+ multipotent hematopoietic progenitor cells, which reside in the bone marrow and in the peripheral blood [51]. Under normal circumstances, MC especially differentiate under the influence of stem cell factor (SCF), which sends the signal to the cells using the receptor Kit (CD117), a transmembranous tyrosine kinase receptor [52]. Somatic activating mutations in the c-kit gene, especially the D816V mutation, lead to continuous signaling in the kit-mediated pathway and thus to abnormal proliferation of mast cells [53]. Other oncogenic mutations recently identified in mastocytosis patients include those in TET2 and N-RAS [54,55]. Despite the continuous development of knowledge on mastocytosis, the pathogenesis of this disease is still not fully understood. The most reliable marker for the severity and extension of mastocytosis is serum tryptase [56–59]. In adults, total serum tryptase levels correlate with the type and severity of mastocytosis [60]. Levels over 20 ng/ml are associated with indolent systemic mastocytosis and can be much more elevated in aggressive systemic mastocytosis. At present, there is no causal treatment for mastocytosis, therefore the purpose of treatment is to relieve symptoms and increase quality of life.

IIc. Interstitial cystitis

Interstitial cystitis (IC) is a specific disease in urology, with the most unknown etiology. It is a heterogeneous syndrome characterized by voiding symptoms of urgency, frequency, nocturia, dyspareunia along with suprapubic and pelvic pain [61]. The pain is one of the most important symptoms, therefore IC is also called bladder pain syndrome (PBS) [62]. What is interesting this pathology affects mostly women. The exact pathogenesis and pathophysiology is still unknown; to make an appropriate diagnosis in men, doctors have to rule other diseases, such as bacterial cystitis, cancer of the urinary tract and genitals, kidney and bladder stones, urethral diverticulum and genital infections. There are so many theories about the etiology of this disease. Erickson emphasize the role of epithelial dysfunction, bladder sensory nerve up-regulation and mast cell involvement in neuroimmunoendocrine inflammation [63]. The presence of mast cells is considered a pathognomonic factor for interstitial cystitis. Patients not only have an increased number of mast cells, but also >70% of them are activated versus 10% in healthy controls [64]. Clinical studies have shown the accumulation and activation of mast cells in the detrusor, lamina propria and submucosa in a pathologically changed bladder [65,66]. It has been suggested that mast cell counts > 20

cells/mm^2 in bladder muscle have an 88% diagnostic specificity and a 95% sensitivity [67]. Vasoactive and inflammatory mediators secreted by mast cells caused, for example, apoptotic lesions in the urothelium and urothelial or mucosal barrier dysfunction and bladder-associated pelvic pain [68], which proves that both the bladder pathophysiology and pelvic pain are mast cell-dependent. Vasoactive, nociceptive and proinflammatory molecules released from activated MC produce neuronal sensitization and secretion of neurotransmitters that further stimulate MC [65]. Many authors pointed out increased levels of MC mediators in urine, e.g. histamine and tryptase [69,70]. Richter et al. described a new biomarker, YKL-40, whose levels increased in the serum and urine [71]. Furthermore, YKL-40 can be evaluated as an inflammatory mediator of bladder fibrogenesis in IC [71]. Another mediator, IL-6, released from mature mast cells is elevated in the urine of IC patients and is highly increased in such patients with severe inflammation [72]. Rudick et al. demonstrated that MC could promote urinary bladder pain through TNF [66], and mast cell activation can also be triggered by neuropeptides, such as substance P and acetylcholine [73]. MCs have a close connection with nerves both in the normal bladder and in the bladder with IC [74]. What is interesting, Nickel et al. confirmed a relationship between IC and other chronic pain syndromes such as irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome [75].

II.d Male infertility

Recent studies suggest a role of mast cells in the pathophysiology of testicular disorders [76]. According to Nistal et al., the number of mast cells in the testis and epididymis increased slightly during infancy, decreased during childhood, and then increased again at puberty [77]. There are two types of MC population in the human testis: interstitial large round shaped and peritubular flattened, relatively poor in granules MC [78]. Hussein et al. found a relationship between increased numbers of MC and impaired spermatogenesis [79]. Other studies reported increased numbers of mast cells in idiopathic infertility and varicole [80-82]. As is well known, fibrotic processes underlay male idiopathic infertility [83] and mast cells stimulate fibroblast migration, proliferation and synthesis of extracellular matrix compounds [84]. Roaiah et al. demonstrated a significant correlation between MC in the seminal plasma and sperm-bound IgA antibodies [76]. Allam et al. did not find a correlation between MC and sperm count, motility or morphology [85] as opposed to Weidinger et al. [86]. Previous studies suggest that different types of MC blockers, such as ketotifen, significantly improve semen quality and spontaneous pregnancies in idiopathic infertility and in patients post varicocelectomy [87-89]. On the other hand, other authors showed that mast cell blockers had no benefit in treating infertile men [90].

II.d Inflammatory bowel disease (IBD)

Mast cells are numerous in the gastrointestinal tract. In the human gastrointestinal tract, mast cell density is highest in the lamina propria mucosae, where they amount to 2–3% of all cells, and slightly less (about 1% of all cells) in the submucosa [91]. In the mucosa mast cells containing tryptase alone (MC_T) dominate the population, and in the submucosa MC containing chymase and tryptase (MC_{TC}) [92]. MCs are close to nerve endings and enteric neurons and this determines mucosal homeostasis and appropriate response to injury. According to King et al., the largest number of MCs is located on the border of healthy and inflamed tissue [93]. The mechanism of inflammatory bowel disease, i.e. ulcerative colitis and Crohn`s disease, is not fully understood. Generally, many authors suggest that IBD is a result of an uncontrolled immune response in genetically predisposed people towards a normal microbial gut flora [94]. There is growing evidence that mast cells play a crucial role in IBD [92]. TNF-alpha is one of the most important mediators in the development of IBD, which increases both inflammation and tissue destruction [95].

II.e Irritable bowel syndrome (IBS)

Irritable bowel syndrome along with functional GI disorders, such as functional dyspepsia (FD) and idiopathic gastroparesis (IGP), are characterized by frequent unexpected chronic abdominal pain and symptoms of gastrointestinal (GI) dysmotility (GID) [96]. Increased numbers of mast cells have been observed in patient with IBS throughout the small and the large intestine [97]. MCs and their mediators play a potential role in the pathophysiology of IBS by causing sensorimotor dysfunction

of the gut through interactions with the enteric nervous system [98-100]. The administration of ketotifen has been shown to
reduce rectal sensitivity, abdominal pain and other IBS symptoms, along with improvement in quality of life [101]. Psychological stress increases the symptoms of IBS. Piche et al. reported that psychological factors play a role in increased colonic mast cell concentration [102]. Moreover, in our past study we observed that the number of MC in mucosa and lamina propria in Hirschsprung's disease was significantly elevated, and in the intestinal wall MC in the aganglionic segment were significantly greater compared with normally innervated colon segments taken from the control groups [103].

II f. Chronic pancreatitis

Chronic pancreatitis (CP) is defined as a progressive, chronic inflammatory disease characterized by irreversible morphologic changes and gradual fibrotic replacement of the gland. Loss of exocrine and endocrine function results from fibrosis and parenchymal damage. According to Esposito et al., mast cells are a relevant component of infiltrating inflammatory cells in chronic pancreatitis [104]. Chronic abdominal pain is the dominant symptom of chronic pancreatitis, but we still do not understand the neurobiological aspects. Some authors indicated the role of anatomical abnormalities, e.g structured pancreatic duct. However, placement endoscopic stent and mechanical decompression do not relieve the pain [105]. Mast cell degranulation products, neurotrophin growth factor (NGF), similar to tryptase and histamine, could be responsible for the plastic changes and modulate neuronal function. Mast cells are increased in number in many fibrotic diseases such as scleroderma and idiopathic pulmonary fibrosis [106,107] and play a crucial role in the development of fibrosis [108]. In CP, mast cells are located both in the fibrotic areas and in the residual acinar parenchyma. The total number of MCs are significantly higher in chronic pancreatitis and correlate with the extent of fibrosis and the intensity of inflammation [109].

II g. MC role in obesity development

Recent studies emphasize that inflammation may play a pivotal role in obesity [110,111]. Mast cells are located in white adipose tissue (WAT) as well as macrophages and CD4+ and CD8+ T cells [112]. Liu et al. observed significantly higher tryptase concentrations in the serum of obese mice than in lean ones [113]. Mast cells may contribute to obesity by producing the inflammatory cytokines IL-6 and IFN-γ, and by promoting angiogenesis. MCs are often localized near the microvessels in WAT and infiltrate WAT before the macrophages [112,114]. On the other hand, patients with mastocytosis are not always obese. Furthermore, mice treated with mast cell-stabilizing agents have shown reduced obesity, improved glucose intolerance and insulin sensitivity, and reduced adipose tissue inflammation with reduced leptin and insulin levels in circulation [113]. Similarly, genetically deficient mast cell mice exhibit reduced body weight gain and improved glucose and insulin sensitivities compared with corresponding wild-type control mice fed a Western diet to induce obesity and diabetes [115]. MC may, by direct cell–cell contact or by releasing inflammatory mediators, act as central receivers mediating the interactions between different T-cell subtypes, dendritic cells and non-inflammatory cells.

II h. MC role in Diabetes mellitus (DM)

Zhang suggests that mast cells directly contribute to insulin resistance and type 2 diabetes [116]. Intraperitoneal administration of ketotifen reduced both body weight and glucose intolerance in mice fed a high-fat diet [117]. Furthermore, mice lacking mast cells are protected from developing type 2 DM [2]. Nephropathy is one of the most common microvascular complications of diabetes. MCs are most abundant in the kidneys of diabetic patients with nephropathy [118] and an increase in their level is associated with fibrosis in the kidneys. MCs produce TGF-β, a fibrogenic cytokine [119]. Furthermore, treatment with an anti-TGF-β antibody [120] or a soluble TGF-β type II receptor [121] reduced proteinuria, inhibited renal fibrosis, and produced renoprotective effects in rats with diabetic nephropathy. Additional tryptase promotes renal fibroblast proliferation and collagen synthesis [122], while chymase and cathepsin G activate TGF-β and MMP-9 [123,124]. More research is needed.

II i. MC in Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the vessel wall characterized by degenerative-productive changes in the intima. Physiologically only a few mast cells appear in normal coronary arteries, while many more MCs are observed in fatty streaks underneath the subendothelium. Additionally, MC clusters have been observed in ruptured areas of the coronary atherosclerotic lesions from patients who have died of acute myocardial infarction [125]. What is interesting, IgE and histamine levels are increased in patients with dyslipidemia and coronary artery disease [126,127]. MCs also play a pro-atherogenic role. On the one hand, they cause cholesterol accumulation in macrophages by an increased uptake of LDL molecules [128]. On the other hand, MCs do not allow HDL3 to remove cholesterol from foam cells by degrading the HDL3 components apolipoprotein (apo) E, apoA-I and apoA-IV [129]. Sun et al. demonstrated that in mast cell-deficient Wsh/W-sh mice, atherogenesis in the aorta was reduced [130]. Recent studies have shown that in ruptured plaques the activation of MC correlates with intraplaque hemorrhage, macrophage and endothelial cell apoptosis and vascular leakage [131]. MCs are also rich reservoirs for cathepsin S, which plays critical role in degrading the vascular wall, generating angiogenic factors and promoting vascular cell apoptosis [132].

II j. MC in abdominal aortic aneurysm

Atherosclerosis is the best known risk factor associated with abdominal aortic aneurysm (AAA). Researchers suggest that MC may influence AAA pathogenesis by promoting inflammation and neovascularization [133,134]. Angiogenesis correlates with the degree of aortic wall inflammation and has been identified as a central process in the pathogenesis of AAA [135]. MC-derived cathepsin G may be involved in tissue degradation within the AAA wall. MCs also release matrix metalloproteinase-9 (MMP-9) and MMP-1, and activate pro-MMP-1 and pro-MMP-3 via chymase and tryptase. MC proteases are capable of degrading the tissue inhibitor of metalloproteinase 1 (TIMP-1) and may in this way promote MMP-mediated destruction of the Extracellular Matrix (ECM), known to be important in aneurysm development. Chymase, secreted by mast cells, has also been shown to promote smooth muscle cell apoptosis [136]. MC- deficient rats and mice have been shown to be protected from experimental AAA [137,138]. Mäyränpää et al. found that in contrast to normal aorta MCs are absent in the AAA intima, but were localized in the media and in the proximity of neovessels with endothelium. Furthermore, the number of MCs were higher in aneurysms than in controls [133]. Interestingly, it has been observed in an animal model that activated MCs may participate in the pathogenesis of neovessel ruptures [139]. Additionally, MCs are involved in the pathogenesis of AAA by activating the rennin-angiotensin system (RAS). Both MC-derived chymase and cathepsin G convert ANG I to Ang II [140,141].

III. The role of mast cells in tumor growth and progression

Mast cells (MCs) are often present in large quantities in the stroma of different neoplasms, for example: mammary adenocarcinoma, colorectal adenocarcinoma, urothelial carcinoma, neurofibroma or melanoma. They accumulate especially at the tumor border rather than in the core and could be a negative prognostic factor. An inflow of MCs is probably stimulated by chemoattractants like RANTES, monocyte chemotactic protein-1 (MCP-1) or stem cell factor (SCF). MCs affect tumor development in a few different ways: (1) by affecting tumor cells directly, (2) by modulating the tumor microenvironment, (3) by activating other inflammatory cells which are beneficial for tumor progression. The effect of that activity depends on the multiplicity of molecules that are synthesized and secreted to the extracellular matrix from MCs' granules. Moreover, it is crucial that these molecules are secreted selectively compared with classic anaphylactic degranulation. This is called piecemeal degranulation and is characteristic of chronic inflammation or cancer. Selective secretion is qualified by substances released from the tumor cells and takes place on different pathways. It shows that the connection between mast cells and the neoplasm is bilateral. MCs could be activated to synthesis and secretion by Fc, c-kit and Toll-like receptor mechanisms, exposure to chemokines, anaphylatoxins C3a and C5a, and fragments of fibrinogen and fibronectin [142]. MCs could induce tumor cell proliferation by secretion of

mitogenic factors: platelet derived factor (PDGF), SCF, colony stimuli factor (CSF) and nerve growth factor (NGF) [143]. Also, histamine could affect tumor progression by inducing proliferation through H1 receptor and suppressing the immune system through H2 receptor. Histamine concentration correlates positively with mast cell count in mammary carcinomas [144]. Suppression of cellular immunity can be dependent on IL-10 and tumor necrosis factor-α (TNF-α) secreted by MCs. Some enzymes produced by MCs, for example metalloproteases (MMPs), chymase and tryptase, disturb components of the tumor stroma and promote tumor invasiveness. MCs directly stimulate connective tissue cells by releasing basic fibroblast growth factor (bFGF). Chronic inflammation stimulates proliferation of residual tissue MCs and promotes the local recruitment of circulating MC precursors. MCs play a role in connecting chronic inflammation with tumourigenesis. MC inflow is mainly mediated by tumor-derived SCF, which act on c-kit receptors on mast cells. SCF-activated MCs increased the transcription of IL-17 gene and the amount of IL-17-producing cells in the tumor mass. IL-17 is a potential candidate for regulating the tumor inflammatory reaction through the production of IL-9, which increases MC inflow. MCs could influence macrophage differentiation and modify them to be more beneficial for tumor development. They also affect dendritic cells and interact with T and B lymphocytes.

III.a Mast cells and pathological angiogenesis

Pathological angiogenesis mainly depends on the release of specific growth factors by inflammatory or neoplastic cells for endothelial cells that stimulate proliferation of the host's blood vessels or the down-regulation of natural angiogenesis inhibitors. Activated MCs synthesize and secrete pro-angiogenic factors such as fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF). There is high VEGF expression in MCs accumulated around tumors. Also, tryptase and chymase, which are serine proteases, promote neovascularysation. Degradation of components of the extracellular matrix results in the release of VEGF or FGF-2 from their matrix-bound state. Moreover, it provides space for newly formatted vessels. In addition, tryptase stimulates endothelial cell proliferation. Histamine and heparin have a similar attribute. Histamine stimulates endothelial cell growth through H1 and H2 receptors. Heparin may act directly on blood vessels or indirectly by inducing release of FGF-2 from the extracellular storage site. some Cytokines produced by MCs – such as IL-8, TNF-α, transforming growth factor-β (TGF-β), NGF and urokinase-type PA – also have an influence on angiogenesis. Despite serine proteases, MCs secrete MMPs (MMP-2, MMP-9) to the extracellular matrix, which degrades connective tissue causing release of matrix-bound angiogenic factors. MCs recruit macrophages and lymphocytes, and activate platelets which secrete pro-angiogenic factors. There are some observations of premalignant lesions with infiltration and activation of MCs. This may suggest that MCs angiogenic potential plays a role in their progression to invasive neoplasm. New formatted vessels enable nourishing of the tumor and therefore its growth and expansion. Association between MCs and new vessel formation has been reported in mammary cancer, colorectal cancer and uterine cervix cancer. MC infiltration correlates with microvessel density. MC could be a prognostic factor in the progression of dysplastic changes to invasive carcinoma, for example. Dyduch et al. suggested a possible role of MCs in the progression from melanocytic nevus to melanoma [145].

IV. Mast cells and metastases

Metastases, especially in the brain, are the chief cause of morbidity and mortality in many cancers [146]. For instance, over 30% of breast cancer patients develop brain metastases with poor prognosis [147]. It is documented that stress promotes cancer growth and increases metastases (of mammary adenocarcinoma of mice).

IV a. MCs and tumor cell invasion

MCs are modulators of the tumor microenvironment, but their role in this process is still not completely clear. It has been suggested that local inflammation could promote tumor growth. Tumor-derived peptides, (SCF) the ligand of receptor c-kit, RANTES and MCP-1, lead to the accumulation of MCs around the tumor. MCs produce and release metalloproteinases and enzymes such as tryptase and chymase, which disturb normal stromal-epithelial communication and lead to matrix and tissue degradation. This causes tumor invasiveness and leads to metastases. Some

studies have reported that metastases were reduced in mast cell-deficient mice, and also when levels of mast cells were inhibited the metastases of rat mammary adenocarcinoma were inhibited [148]. Metastases also appear to be regulated by stromal proteolityc enzymes and chemokines. Proinflamatory factors (IL-b1, IL-18, TNFalfa) lead to hypoxia-induced metastasis [149]. Mediators produced by MCs cause immunosuppression and tumor cells cannot be destroyed by the host's immune system. Vasoactive factors produced by MCs, such as histamine, IL-8, VEGF, PGD2, and SP, lower the endothelial barrier and cause neovascularization, which facilitate metastasis.

IV b. MCs and metastases in the brain

The blood-brain-barrier (BBB) is a complex system separating blood from the brain extracellular fluid in CNS which includes endothelial cells, astrocytic endfeet, pericytes and perivascular mast cells. This "barrier" contains tight junctions between endothelial cells in CNS vessels that restrict the passage of solutions and molecules. Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins. BBB is damaged in some CNS diseases, e.g. neuroinflammatory diseases or multiple sclerosis. Defects of BBB permit tumor spread to the brain, e.g. in mammary carcinoma and melanoma [150].

Mast cells surround the endothelial cells, and pericytes play the role of "gate keepers" of the BBB. MCs also have anatomical and functional connections with neurons [151]. Acute stress can activate MCs by corticotrophin-releasing hormone (CRH) and leads to developing inflammation and increasing BBB permeability [152]. Chronic stress also participates in facilitating cancer metastases by suppressing the immune system. Functional CRH-receptors are expressed on human mast cells and brain vessels. CRH lead to mast cell activation by this receptors and can also be synthesized and secreted by MCs [153]. CRH can also induce selective secretion of VEGF[11]. Activated MCs release mediators that could disrupt BBB, such as bradykinin, CRH, prostaglandin D2, neurotensin, substance P, tryptase, IL-6,IL-8, VIP and VEGF[148].

IV c. MCs and survival of tumor cells in a new localization

Another important thing is the survival of tumor cell metastases in a new localization. MCs may play a crucial role in the initial survival of tumor cells, because they are the first inflammatory cells accumulated around metastatic tumor cells and can remodel the tumor microenvironment. Tumors produce SCF and other substances which stimulate MCs to secrete biologically active products that induce immunosuppression in new places for tumor cells and growth factors causing tumor cell survival. For instance, MCs secrete inhibitory factors, such as IL-10 and TGF-beta, and adenosine, which inhibits tumor-infiltrating T cells and NK cells. MCs also secrete CCL2 and this way recruit MDSCs (myeloid-derived suppressor cells), which secure immune system unresponsiveness in the new localization.

IV d. Mast cells and negative effect on cancer

Apart from their positive role in cancer growth, MCs could be detrimental to tumor cells. The same mediators may have both positive and negative effects, and this depends on MCs ability to degranulate, specific mediators in response to stimuli, the presence of cofactors, and the locations of secreting cells. The mediators could inhibit cell growth directly, increase inflammatory reaction, induct apoptosis, or decrease cell mobility. The main sulphated glycosaminoglycans (s-GAGs) found in mast cells are chondroitin sulphate (CS) and heparin/heparan sulphate. For instance, CS acts as a decoy and inhibits metastases, e.g. ovarian cancer metastases, and heparin sulphate proteoglycans can block binding of heparin to the cell surface and prevent formation of new blood vessels. Chemokines (IL-8, MCP-3, MCP-4) are chemoattractants for leukocytes and cytokines causing leukocyte migration, proliferation and activation resulting in an inflammatory response, which has an unfavorable effect on tumor growth. MCs may destroy the tumor by secreting some molecules such as IL-4 that induce apoptosis, e.g in breast cancer, TNF alfa which can induce tumor cell death, and tryptase which stimulates protease-activated receptor-induced inflammation and provokes apoptosis. But secretion on these mediators could be inhibited by tumor-derived oxidized polyamines. TNF-α, IL-1 and IL-6 have been reported to suppress melanoma growth. Mast cells might recruit both M1 and M2 macrophages, which have the opposite effects on tumor growth and could also recruit NK cells and CD3+[147]. In a mouse melanoma model, recruitment

of eosinophils by tryptase and promotion of their survival by mast cell derived IL-5 lead to tumor regression [150]. Some mediators which are proangiogenic factors paradoxically may inhibit tumor progression. For instance, histamine can increase prostacyclin synthesis and prostacyclin potentially inhibits metastases. Another important factor is the heterogeneity of mast cells, especially the presence of both chymase positive and chymase negative cells; these may differ in their products and also in their response to stimuli.

We confirm that all authors have read and approved the submission of the manuscript, the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract. We also declare no financial relationships with any industry (through investments, employment, consultancies, stock ownership, honoraria). The authors declare no conflict of interests.

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