

Review:

Role of Mast Cells in Tumor Growth

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Abstract. The growth of malignant tumors is determined in large part by the proliferative capacity of the tumor cells. Clinical observations and animal experiments have established that tumor cells elicit immune responses. Histopathologic studies show that many tumors are surrounded by mononuclear cell and mast cell infiltrates. Mast cells are ubiquitous in the body and are critical for allergic reactions. Increasing evidence indicates that mast cells secrete proinflammatory cytokines and are involved in neuro-inflammatory processes and cancer. Mast cells accumulate in the stroma surrounding certain tumors, especially mammary adenocarcinoma, and the molecules they secrete can benefit the tumor. However, mast cells can also increase at the site of tumor growth and participate in tumor rejection. Mast cells may be recruited by tumor-derived chemoattractants and selectively secrete molecules such as growth factors, histamine, heparin, VEGF, and IL-8, as well as proteases that permit the formation of new blood vessels and metastases. Tumor mast cell intersections play regulatory and modulatory roles affecting various aspects of tumor growth. Discovery of these new roles of mast cells further complicates the understanding of tumor growth. This review focuses on the strategic importance of mast cells to the progression of tumors, and proposes a revised immune effector mechanism of mast cell involvement in tumor growth.

Keywords: mast cells, cancer, tumor cell growth, cytokines, histamine, heparin, angiogenesis, proteases

Introduction

Despite the major financial and manpower resources that have been invested in basic research on cancer biology, mortality rates for the most frequent forms of cancer have not been reduced significantly [1,2]. The prevailing somatic mutation theory of carcino-

genesis calls for stable DNA mutations. Nevertheless, only about 1% of all breast cancers have so far been explained by mutations, and those identified involve either a lack of resistance gene product or presence of the Her-2 susceptibility antigen [3-5].

Several research groups have proposed that epigenetic mechanisms, similar to those occurring during histogenesis and organogenesis, may be critical for carcinogenesis [6-8]. For instance, endometrial stroma cells have been shown to regulate epithelial cell growth in vitro. The role of

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stromal-epithelial interactions in early events in carcinogenesis was proposed almost 30 years ago. Such interactions regulate the migration, morphogenesis, modulation of proliferation, and differentiation of many specialized cell types. This alternative tissue organization field theory of carcinogenesis assumes that (a) carcinogens disrupt the normal flow of information between stroma and parenchyma and (b) such disturbances result in functional and structural changes leading to proliferation of certain affected or even normal mammary gland epithelium.

For instance, irradiated mammary gland stroma promoted carcinogenesis of unirradiated epithelial cells [9]. Manipulation of the micro-environment, as with a stromal matrix metalloproteinase, rather than the target cell, was shown to promote mammary tumorigenesis [10]. More recently, using tissue recombination techniques, it was unequivocally demonstrated that mammary carcinogenesis in Wistar/Furth rats occurs when only the stroma of the mammary gland (fat pad) is exposed to the carcinogen nitrosomethylurea (NMU). The earliest effects of carcinogen administration in mammary gland carcinogenesis are manifested in the stroma with infiltration of inflammatory cells and desmoplastic reaction [11,12].

There is increasing evidence that mast cells are associated with tumor growth [1,3]. In particular, mast cell numbers are increased in areas of early mammary adenocarcinomas [13]. Moreover, a correlation between accumulation of mast cells and tumor aggressiveness has been established [14]. An increased number of mast cells has also been noticed in rat mammary tumors when another carcinogen, *cis*-hydroxyproline, was used in Buffalo rats [15]. Interestingly, rat mammary adenocarcinoma induced by 7,12-dimethylbenz(a)anthracene is associated with a high number of mast cells, but these are resistant to degranulation [16]. This latter finding suggests that mast cells may either be unable to destroy the tumor or are affected by the tumor, which blocks their degranulation [1,17].

Biology of Mast Cells

Mast cells derive from a specific bone marrow progenitor and are important not only in allergic

reactions, but also in inflammation, autoimmunity, and T cell-mediated immune responses [18,19]. Mast cells are located perivascularly and in close proximity to neurons. Mast cells are an important source of various cytokines and chemokines [1,20-22]. Mature rodent mast cells vary considerably in their cytokine and proteolytic enzyme content: (a) connective tissue-like mast cells (CTMC) that in rats contain rat mast cell protease-I (RMCP-I); (b) mucosal-like mast cells (MMC) that contain RMCP-II [1].

Two mast cell subtypes have been characterized: In humans, one type (CTMC) contains tryptase and chymase (CT mast cells), while the other type contains only tryptase (T mast cells). Phenotypic expression of the mast cells does not appear to be fixed, meaning that MMC can develop into CTMC given appropriate micro-environmental stimuli, such as stem cell factor (SCF), NGF, IL-6, and IL-4 [18]. In addition to IgE and antigen, anaphylatoxins, cytokines, hormones, and neuropeptides can trigger mast cell activation, leading to degranulation and secretion of preformed, granule-stored mediators [20].

Mast cells along with T lymphocytes produce several cytokines, such as IL-4 and IL-4 receptors (IL-4Rs) that are expressed by non-hematopoietic cells, including human breast carcinoma cells (Fig. 1). IL-4 can induce apoptosis in breast cancer and this phenomenon is reversed by insulin-like growth factor, suggesting that the mechanism of IL-4 induced growth-inhibition in human breast cancer is the induction of programmed cells death. TNF- α , which can also induce tumor cell death, is secreted from mast cells and induces leukocyte infiltration.

Costa et al [14] reported that recombinant human SCF (kit ligand) promotes human mast cell and melanocyte hyperplasia and functional activation *in vivo*. These findings suggest that the interaction between SCF and its receptor represents a potential therapeutic target for regulating the numbers and functional activity of mast cells.

Tumors can surprisingly alter T cells to depress the immune response, an interesting process that may be mediated through mast cells, since the latter are necessary intermediates in regulatory T cell tolerance [1,24]. Mast cells and macrophages

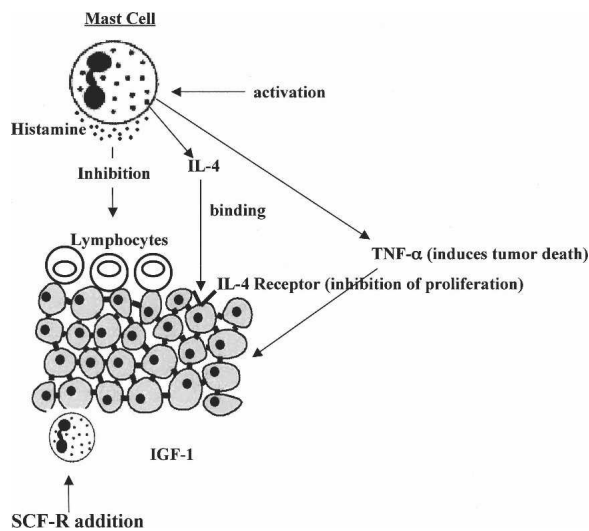


Fig. 1. Schematic diagram of the impact of mast cells on tumor cell proliferation.

are rich in metalloproteases that contribute the majority of proteolytic components necessary for tumor invasiveness [1,18,23]. Mast cells can disturb normal stromal-epithelial communication, as was shown for matrix degradation at sites of tumor invasion in rat mammary adenocarcinoma. Mast cells also generate and secrete IL-8, which can act as an angiogenic factor, as well as a tumor cell chemotactic factor and tumor mitogen [25]. In fact, inhibition of IL-8 by use of neutralizing antibodies reduced human non-small cell lung carcinoma progression in mice [26].

We recently reported that IL-1, a cytokine generated by macrophages, can induce selectively the secretion of IL-6 from human cultured mast cells without degranulation through small vesicles [1,21,27]. IL-1 can also stimulate secretion of VEGF as well as promote angiogenesis and tumor growth [28]. Mast cells also secrete VEGF [29]. Increased mast cell density correlated with increased VEGF expression and poor prognosis in 33/53 non-small cell lung carcinomas. Moreover, increased VEGF-C (tumor cell) and VEGFR-3 (microvessel) expression are independent negative prognostic factors in patients with T1 lung adenocarcinoma.

Mast Cells and Cancer

Mast cell accumulation can either be beneficial or detrimental for tumor growth (Table 1). Mast cells

can promote mammary tumor development by: (a) disturbing the normal stroma-epithelium communication, as was shown for matrix degradation at sites of tumor invasion in rat mammary adenocarcinoma, (b) facilitating tumor angiogenesis, and (c) releasing growth factors such as stem cell factor (SCF) and nerve growth factor (NGF) [1].

It is therefore of interest that mast cells can be recruited at the sites of tumor growth by tumor-derived peptides. Mast cell accumulation may also be due to chemotactic activity elicited by RANTES or MCP-1 [31-34]. Moreover, histamine can induce tumor cell proliferation through H1 receptors and suppress the immune system through H2 receptors [1]. H1 and H2 receptor binding sites are present in human carcinomas. In fact, mast-cell-deficient W/W^v mice exhibit a decreased rate of tumor angiogenesis [35].

Mast cell mediators may also promote brain metastases because they regulate the permeability of the blood-brain-barrier (BBB) [1,36]. Specifically, it was recently shown that acute stress increased BBB permeability in a mast cell-dependent manner [37]. It is noteworthy that acute stress has been shown to increase metastases of breast and other tumors, especially since >30% of breast cancer patients develop brain metastases with poor associated prognosis.

The way that mast cells could be beneficial for tumor cells is if secretion of cytokines and other molecules from mast cells could occur without degranulation. This has been termed "differential release," "intragranular activation," or "piecemeal degranulation," and may be associated with the ability of mast cells to release some mediators selectively without degranulation [38]. For instance, IL-6 can be released without histamine. In certain diseases (eg, scleroderma and interstitial cystitis) mast cells can be almost totally depleted of their granule content and they cannot be recognized by light microscopy (phantom mast cells) [38]. Tumor infiltrating fibroblasts [39] and macrophages [40] are also important.

On the other hand, mast cells can increase at sites of breast cancer and associated lymph nodes in order to participate in tumor rejection, but may be inhibited from doing so by tumor-derived blockers. Recently, it was reported that down-regulation of

Table 1: Effects of mast cell mediators on cancer.

Mediators	Main Pathophysiologic Effects
Positive effect on cancer	
Histamine	Vasodilation, angiogenesis, mitogenesis
Chemokines	
MCP-1, RANTES	Chemoattraction for mast cells
Enzymes	
Chymase	Tissue damage
Kinogenases	Synthesis of vasodilatory kinins
Tryptase	Tissue damage, metastases
Growth Factors	
CSF, FGF, NGF, TGF	Tumor growth
Proteoglycans	
Heparin	Angiogenesis, NGF stabilization
Negative effect on cancer	
Chemokines	
IL-8, MCP-3, MCP-4	Chemoattraction for leukocytes
Proteoglycans	
Chondroitin sulphate	Acts as decoy and prevents metastases
Cytokines	
Interleukins (IL)-1,2,3,4,5,6,9,10,13,16	Inflammation, leukocyte migration
INF- γ ; MIF	Inflammation, leukocyte proliferation/activation
TNF- α	Inflammation, vascular adhesion molecule expression, tumor cell death
Arachidonic acid products	
Leukotriene B ₄ (LTB ₄)	Leukocyte chemotaxis
Platelet Activating factor (PAF)	Platelet activation and serotonin release
Prostaglandin D ₂ (PGD ₂)	Vasodilation
Leukotriene C ₄ (LTC ₄)	Vasoconstriction
Nitric oxide (NO)	Vasodilation, neurotransmission

CSF, colony stimulating factor; TGF, transforming growth factor; INF- γ , Interferon- γ ; TNF- α , tumor necrosis factor- α ; MIF, macrophage inflammatory factor; SRIF, somatostatin; FGF, fibroblast growth factor; NGF, nerve growth factor.

VEGF expression is insufficient for resistance to mammary carcinogenesis and that an enhanced immune response, as evidenced by intramammary lymph node enlargement with mast cell infiltration, may be more important.

Perivascular mast cells in adenocarcinomas can secrete several cytokines and proteolytic enzymes that may be detrimental to the tumor cells, as well as compounds such as heparin, which has both anticoagulant and angiogenic properties (Fig. 2). Mast cell tryptase can stimulate protease-activated receptors (PAR-1 and -2), which are also activated by thrombin and trypsin [41-43]. Protamine, which binds avidly to heparin and neutralizes its anticoagulant properties, can induce selective thrombosis of blood vessels within the tumor. The main sulphated glycosaminoglycans (s-GAGs) found in mast cells are those that accumulate in

mammary gland tumors and in metastatic lesions in dogs: chondroitin sulphate (CS) and heparin/heparan sulphate (HEP/HS). The heparin-related GAG, HS, binds to and modifies the function of a multitude of molecules and cell types involved in the inflammatory process under several conditions [44,45]. It is therefore of interest that tumor cells metastasize by binding to CS and that exogenous administration of CS inhibits metastasis of ovarian carcinoma [48,49]. Moreover, heparan sulfate proteoglycans can block binding of heparin to the cell surface and prevent neovascularization [41,50-53].

In conclusion, increasing evidence indicates that breast adenocarcinoma is associated with a large number of mast cells. It is interesting that a flavonoid, quercetin, has been shown to inhibit mast cell activation and proliferation [50], as well

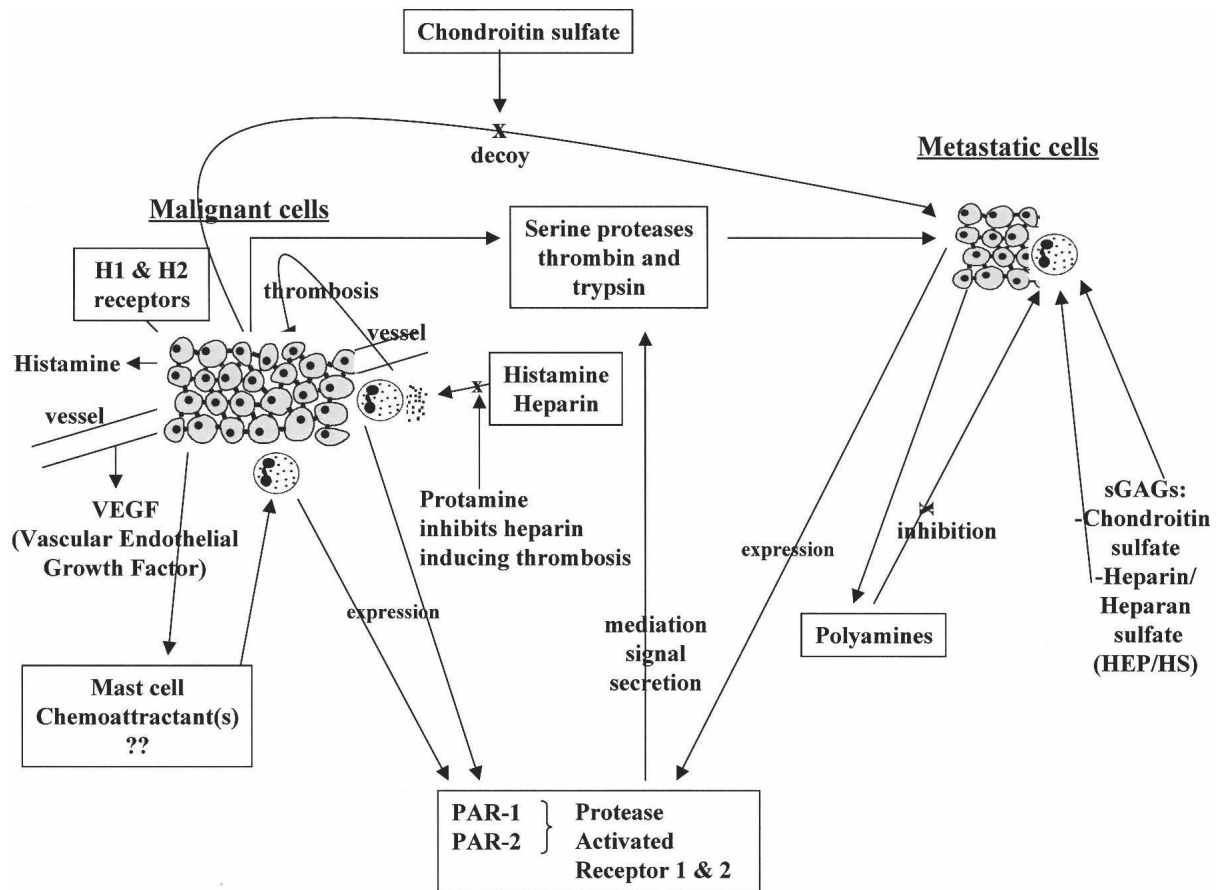


Fig. 2. Schematic representation of two possible reasons why there is an increased number of intact mast cells in human breast adenocarcinoma: (A) Mast cells are recruited by tumor-derived chemoattractants and then stimulated by the tumor to selectively secrete molecules beneficial to the tumor. (B) Mast cells accumulate around breast adenocarcinoma cells in reaction to tumor growth and in an effort to destroy the tumor by secreting molecules such as IL-4 (that induces apoptosis), TNF- α (that kills tumor cells), or trypsin (that stimulates protease-activated receptor-induced inflammation); however, the secretion of these molecules is inhibited by tumor-derived oxidized polyamines.

as to inhibit breast cancer growth [51]. Chondroitin sulphate has also been shown to inhibit mast cells and to block ovarian cancer cell metastases [52]. One might speculate that a combination of mast cell and tumor cell inhibitory molecules could be of help treating breast carcinoma, along with anti-anxiety/anti-depressant agents to reduce stress [52-55]. However, more studies are needed to clarify the relationships between mast cells and tumors.

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