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Mast Cells: Potential Positive and Negative Roles in Tumor Biology

Thomas Marichal¹, Mindy Tsai¹, and Stephen J. Galli^{1,2}

Abstract

Mast cells are immune cells that reside in virtually all vascularized tissues. Upon activation by diverse mechanisms, mast cells can secrete a broad array of biologically active products that either are stored in the cytoplasmic granules of the cells (e.g., histamine, heparin, various proteases) or are produced *de novo* upon cell stimulation (e.g., prostaglandins, leukotrienes, cytokines, chemokines, and growth factors). Mast cells are best known for their effector functions during anaphylaxis and acute IgE-associated allergic reactions, but they also have been implicated in a wide variety of processes that maintain health or contribute to disease. There has been particular interest in the possible roles of mast cells in tumor biology. *In vitro* studies have shown that mast cells have the potential to influence many aspects of tumor biology, including tumor development, tumor-induced angiogenesis, and tissue remodeling, and the shaping of adaptive immune responses to tumors. Yet, the actual contributions of mast cells to tumor biology *in vivo* remain controversial. Here, we review some basic features of mast cell biology with a special emphasis on those relevant to their potential roles in tumors. We discuss how using *in vivo* tumor models in combination with models in which mast cell function can be modulated has implicated mast cells in the regulation of host responses to tumors. Finally, we summarize data from studies of human tumors that suggest either beneficial or detrimental roles for mast cells in tumors. *Cancer Immunol Res*; 1(5); 269–79. ©2013 AACR.

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No potential conflicts of interest were disclosed.

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Learning Objectives

Upon completion of this activity, the participant should acquire a basic knowledge of the heterogeneity of macrophages, their roles in homeostasis, infection, and in the maintenance of organ integrity. A better understanding of the cellular ontogeny and tissue regulation of this group of circulating and tissue-resident hematopoietic cells of myeloid origin, how they balance between promoting immune tolerance during steady state, and responding to tissue damage and inflammation during infection will lead to the development of more specific and effective therapeutics.

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General Aspects of Mast Cell Biology

Paul Ehrlich described mast cells in his doctoral thesis in 1878, identifying them in human tissues as connective tissue cells containing purple intracellular granules when stained with aniline blue; Ehrlich also reported that mast cells were

particularly abundant in some tumors (1). In 1891, Ehrlich's student, Westphal, observed that in certain human tumors, mast cells were mainly present at the periphery of the tumor (2). These early observations have been confirmed and extended many times since then (Fig. 1), suggesting that mast cells may be involved in tumor biology.

Today, mast cells are mainly thought of as critical effector cells in antigen-induced anaphylaxis and other acute IgE-dependent allergic reactions, responses initiated when antigen crosslinks antigen-specific IgE antibodies bound to high-affinity FcεRI receptors on the mast cell surface, thereby triggering mast cell activation (3). However, mast cells are also thought to represent versatile cells that can have effector or immunomodulatory functions in both innate and adaptive immunity,

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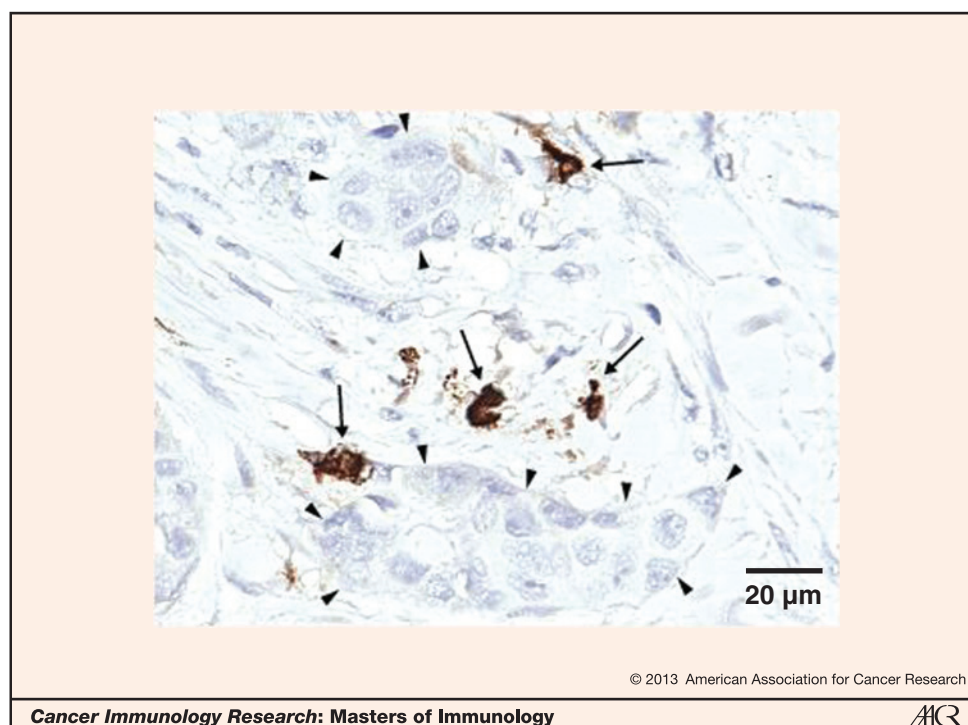


Figure 1. High-power photomicrograph of a specimen of infiltrating ductal carcinoma of the breast stained by immunohistochemistry to detect tryptase, which identifies mast cells as cells with brown-stained cytoplasm. The section depicts at least 4 mast cells (solid arrows) in the tumor stroma, near groups of infiltrating carcinoma cells (the edges of these groups of carcinoma cells are indicated with solid arrowheads). Scale bar, 20 μ m (photomicrograph by Matt van de Rijn).

and a wide variety of additional possible mast cell functions have been proposed, spanning many aspects of health, host defense, and disease (4–6).

Mast cells are long-lived secretory cells derived from hematopoietic precursors that ordinarily are found only in small numbers in the blood but that complete their differentiation and maturation in the microenvironments of almost all vascularized tissues (7–9). Like cells in the monocyte lineage, mast cells can proliferate after appropriate stimulation (10). In addition, increased recruitment, survival, and maturation of mast cell progenitors may also contribute to the local expansion of mast cell populations in the tissues (8). Mature mast cells are particularly abundant in tissues and organs exposed to the external environment, such as the skin, the lung, and the gut, and are often located close to potential targets of their mediators, such as epithelia and glands, smooth muscle cells, fibroblasts, blood and lymphatic vessels, and nerves (8).

During IgE-associated biologic responses, the antigen-dependent cross-linking of antigen-specific IgE bound to Fc ϵ RI on the plasma membrane of mast cells induces the aggregation of Fc ϵ RI, thereby activating downstream signaling events that lead to the secretion of biologically active products implicated in allergic reactions (11). Following antigen binding, mast cells very rapidly release into the extracellular space mediators prestored in their cytoplasmic granules, for example, vasoactive amines (histamine and serotonin), neutral proteases (tryptase, chymase, and carboxypeptidase), proteoglycans (heparin), and some cytokines and growth factors by a process

called degranulation. A second class of secreted products is generated by *de novo* synthesis of proinflammatory lipid mediators, such as prostaglandins and leukotrienes. Finally, mast cells are also able to synthesize and secrete a large number of growth factors, cytokines, and chemokines, many of which have been implicated in tumor biology [e.g., VEGF, angiopoietin-1, TGF- β , interleukin (IL)-1, IL-6, TNF- α , and IL-10; refs. 12–14]. Notably, mast cells can be activated not only by IgE and specific antigen but by a long list of stimuli, including physical agents, products of diverse pathogens, endogenous danger signals, certain endogenous peptides, and components of venoms, and several products of innate and adaptive immune responses, including some chemokines and cytokines and products of complement activation (8).

Mast cells express high levels of the tyrosine kinase receptor Kit (CD117), which is also expressed by other cell types such as hematopoietic stem cells, melanocytes, germ cells, and intestinal interstitial cells of Cajal (15). Kit expression can be upregulated in tumor cells and mutations in *c-kit* have been shown to be a primary event in the development of some nonhematopoietic tumors, such as gastrointestinal stromal tumors, and in neoplastic disorders associated with the development of abnormal expansion of mast cells (such as the various forms of mastocytosis and mast cell leukemia; refs. 15–17).

Stem cell factor (SCF), the ligand for Kit, is produced by structural cells in the tissues (and also by mast cells) and plays a crucial role in mast cell development, survival, migration, and function (7, 18). SCF can be expressed by several types of tumor

cells and tissues (19–22). SCF can induce mast cell migration *in vitro* (20, 21), and inhibition of the SCF/Kit axis *in vivo* has been shown to inhibit the migration of mouse bone marrow–derived cultured mast cells (BMCMC) to tumors in a transplanted tumor model in mice (21).

The Notion of Mast Cell Plasticity

Many key characteristics of mast cells, such as proliferation, survival, and ability to store and/or secrete various products, as well as the magnitude and nature of their secretory responses to particular activation signals, can be regulated or "tuned" by many environmental and genetic factors (8). The properties of individual mast cells thus may be different depending on the genetic background of the host and/or the local or systemic levels of factors that affect various aspects of mast cell biology. This "plasticity" of multiple aspects of the mast cell phenotype can result in the development of phenotypically distinct populations of mast cells in different anatomic sites (or in different animal species). It also may result in the induced alteration of mast cell phenotypes during various biologic responses *in vivo*, and is called mast cell heterogeneity.

The extent to which it is useful to use differences in the phenotype of mast cells to "subclassify" the cells into distinct subtypes, and the extent to which such phenotypic differences are "fixed" as opposed to malleable, has been a matter of debate. However, mast cells in some animal species can be placed into "subpopulations" based on readily identifiable features such as differences in the ability of the mast cells to synthesize and store various proteases or proteoglycans. In humans, mast cells have been classified into those containing mainly tryptase and those containing both tryptase and chymase (23). In mice, connective tissue-type mast cells (CTMC) are distinguished from mucosal mast cells (a population that is more dependent on T-cell–dependent modulation than are CTMCs) according to their anatomic localization, morphology, and content of heparin and proteases (7–9). No matter what criteria are used to identify the subpopulations of mast cells that are present at a particular time in an individual anatomic location, the concept of mast cell plasticity is of particular importance in the context of tumors, as the phenotype (and therefore the function) of mast cells may be influenced by the tumor microenvironment and may change in important ways during disease progression.

Possible Mast Cell Functions in Tumor Biology

Tumors are complex tissues whose fate depends on the levels of pro- versus antitumorogenic signals that are provided by the tumor cells, by the local tumor microenvironment (including by resident and recruited immune cells), and by the host systemically. In particular, the proliferation and survival of tumor cells, angiogenesis, and other aspects of tissue remodeling, metastasis and distant growth of tumor cells, and the ability of tumors to modulate the immune system are especially important for the progression of tumors. All of these processes can potentially be negatively or positively regulated by individual products released by mast cells. For instance, the granule-associated mediator heparin can interfere with the growth of human breast cancer cells (24).

Histamine can inhibit the proliferation of human primary melanoma cells, an effect that is enhanced by IL-6 (25). Angiogenesis is central to tumor development, and tumors often exhibit enhanced vascular permeability and the development of abnormal blood vessels. Notably, the proangiogenic VEGF, which was first described as a potent enhancer of vascular permeability (26), can be produced by mouse and human mast cells (27, 28). VEGF expression has been detected in mast cells within different types of human tumors (29–32). Several proteases released by mast cells [MMP-9 (33) and the serine proteases chymase and tryptase (34–36)] are proangiogenic; they can degrade components of the extracellular matrix and contribute to tumor invasiveness. In addition, host immunity plays a central role in cancer development (elegantly reviewed in ref. 37), and several mouse studies have provided evidence that mast cells have the ability to modulate adaptive immune responses, including effects on the biology of regulatory T cells (Tregs) and immunologic tolerance, thereby potentially modulating the fate of tumors (38–40).

Functions of Mast Cells in Tumor Development: Lessons from Mouse Models

Many biologic functions of mast cells have been discovered using mouse models in which the activities and/or numbers of mast cells can be altered. Each model has its advantages and limitations (5, 6, 41), and mutant mice that specifically lack all mast cell populations as their sole abnormality have not yet been reported. Moreover, to our knowledge, there are no pharmacologic agents that can solely and selectively suppress mast cell activation (5). These points need to be kept in mind when interpreting data derived from studies using such approaches.

Mast cell–deficient mice with mutations affecting *c-kit* structure or expression, especially WBB6F₁-Kit^{W/W^v} (Kit^{W/W^v}) and C57BL/6-Kit^{W-sh/W-sh} (Kit^{W-sh/W-sh}) mice, have been used extensively to study the functions of mast cells *in vivo* (5). These mice are profoundly deficient in mast cells but also exhibit several other Kit-dependent phenotypic abnormalities (42, 43), and differences in the biologic responses of such "Kit-mutant mice" compared with the corresponding wild-type (WT) mice might, in principle, be due to any one of their abnormalities, not solely their deficit in mast cells. However, the lack of mast cells in Kit-mutant mice can be selectively repaired by the adoptive transfer of genetically compatible, *in vitro*-derived mast cells to create so-called mast cell "knock-in" mice (44). These mast cell knock-in mice then can be used to assess the extent to which abnormalities in the biologic responses of Kit-mutant mice can be "normalized" by the adoptive transfer of WT versus genetically altered mast cells. Such genetic and mast cell engraftment approaches have been widely used, in association with tumor models, to investigate the roles of mast cells in tumor development in mice.

Examples of such studies are summarized in Table 1. Highlighting the potential complexity of the roles of mast cells in tumors, a study by Pittoni and colleagues assessed the contribution of mast cells in prostate cancer (45). Well-differentiated prostate adenocarcinoma cells [derived from transgenic TRAMP (transgenic adenocarcinoma of the mouse prostate)]

Table 1. Examples of pro- versus antitumorigenic functions of mast cells based on *in vivo* mouse studies

Tumor model	Mutant mice used	Features analyzed	Main findings/conclusions	References
Transplant model of B16-BL6 melanoma cells	Systemically BM-engrafted (106) or locally BMCMCs-engrafted (107) <i>Kit^{W/W-v}</i> mice	— number of tumor-bearing mice with a macroscopic angiogenic response (this response could also have reflected a contribution of increase blood flow) — number of spontaneous lung metastases	— Parameters lower in <i>Kit^{W/W-v}</i> than in BM- or BMCMCs-engrafted <i>Kit^{W/W-v}</i> mice or WT mice — MCs contributed to the angiogenic and metastatic response	(106, 107)
Transgenic K14-HPV16 mice: a model of dynamic epithelial carcinogenesis (epidermal hyperplasia, angiogenic dysplasia, invasive SCC)	K14-HPV16 mice on the <i>Kit^{W/W-v}</i> and corresponding WT background	— MC numbers and tryptase/chymase activity — keratinocyte proliferation — histologic evaluation of blood vessels	— MC numbers and chymase/tryptase activity increased in angiogenic dysplastic lesions in WT K14-HPV16 mice — <i>Kit^{W/W-v}</i> K14-HPV16 mouse was deficient in MCs, had reduced keratinocyte proliferation and small quiescent blood vessels — MCs contributed to the process of premalignant neovascularization via release of pro-angiogenic proteases	(34)
1,2-DMH-induced colonic epithelial neoplasms	BM-engrafted <i>Kit^{W/W-v}</i> mice	— MC numbers — number of tumor-bearing mice — number and size of tumors	— <i>Kit^{W/W-v}</i> were less susceptible to tumor development than BM-engrafted <i>Kit^{W/W-v}</i> mice or corresponding WT mice — Increased MC numbers in tumor tissue correlated with tumor size — MCs (and/or other hematopoietic cells deficient in <i>Kit^{W/W-v}</i> mice) may contribute to the growth of such chemically induced intestinal tumor	(108)

(Continued on the following page)

Table 1. Examples of pro- versus antitumorigenic functions of mast cells based on *in vivo* mouse studies (Cont'd)

Tumor model	Mutant mice used	Features analyzed	Main findings/conclusions	References
<i>Myc</i> -induced pancreatic islet tumors (β-cell tumors)	C57BL/6-Kit ^{W-sh/W-sh} mice Cromolyn treatment of WT mice	—pancreatic islet tumor expansion (histology, cell proliferation, insulin expression) —intratumor cell death, hypoxia and vascular expansion	—Cromolyn-treated WT mice and C57BL/6-Kit ^{W-sh/W-sh} mice displayed lower pancreatic islet cell tumor expansion than (untreated) WT mice, a phenomenon associated with increased death of β-cells, hypoxia, and diminished angiogenesis — MCs are required for angiogenesis and expansion of such <i>Myc</i>-induced pancreatic islet tumors	(109)
Transgenic C57BL/6/J-APC ^{Min/+} mice: a model of early-stage intestinal adenomas	C57BL/6/J-APC ^{Min/+} mice on the WT and C57BL/6-Kit ^{W-sh/W-sh} backgrounds	—MC number —tumor size —apoptosis —T-cell, eosinophil, and neutrophil infiltration	—C57BL/6/J APC ^{Min/+} ; Kit ^{W-sh/W-sh} mice displayed increased tumor size associated with decreased eosinophils and decreased apoptosis compared to controls — MCs can play a protective role in the growth of such intestinal tumors	(110)
Transplant model of well-differentiated prostate adenocarcinoma cells derived from TRAMP mice: a model of prostate cancer	MC knock-in C57BL/6-Kit ^{W-sh/W-sh} mice (some engrafted with WT or <i>Mmp9</i> ^{-/-} BMCMCs)	—MC number and MMP9 expression —number of tumor-bearing mice —tumor size	—Tumor cells failed to grow robustly in C57BL/6-Kit ^{W-sh/W-sh} mice, even after engraftment with <i>Mmp9</i> ^{-/-} BMCMCs, but did grow strongly in WT mice or in C57BL/6-Kit ^{W-sh/W-sh} mice grafted with WT BMCMCs — MCs and MC-derived MMP9 contribute to the development of such well-differentiated prostate tumors	(45)

(Continued on the following page)

Table 1. Examples of pro- versus antitumorigenic functions of mast cells based on *in vivo* mouse studies (Cont'd)

Tumor model	Mutant mice used	Features analyzed	Main findings/conclusions	References
Transgenic TRAMP mice: a model of prostate cancer	TRAMP mice on the C57BL/6- <i>Ki^{W-sh}/W-sh</i> background or C57BL/6-TRAMP mice treated with cromolyn	—incidence of anaplastic tumors —gene expression profile of the tumors	—TRAMP mice on the C57BL/6- <i>Ki^{W-sh}/W-sh</i> background, or C57BL/6-TRAMP mice treated with cromolyn displayed a high incidence of aggressive cancer variants characterized by a neuroendocrine signature —MCs may play a protective role in prostate neuroendocrine tumorigenesis —C57BL/6- <i>Ki^{W-sh}/W-sh</i> mice are more resistant to tumor development than MC knock-in C57BL/6- <i>Ki^{W-sh}/W-sh</i> or WT mice, an effect that is T cell dependent —MCs can contribute to tumor invasiveness in this model by impairing the development of protective anti-tumor immunity —Both strains of MC-deficient mice display lower tumor growth —MCs promote the growth of EL4 tumors <i>in vivo</i>	(45)
Transplant model of MB49 bladder carcinoma cells	MC knock-in C57BL/6- <i>Ki^{W-sh}/W-sh</i> mice	—MC number and microvascular density —tumor size and survival —T-cell infiltration		(111)
Transplanted T-cell lymphoma EL4 cells	C57BL/6- <i>Ki^{W-sh}/W-sh</i> mice and inducible MC-deficient Mcpt5-Cre/IDTR ⁺ mice	—tumor volume/area		(58)

NOTE: K14-HPV16 mice, mice expressing early region genes of *human papillomavirus type 16* under the control of the promoter of the keratinocyte-associated *keratin 14* gene; Cromolyn, an agent known to "stabilize" certain rodent mast cells (MC), although its effectiveness and selectivity as an inhibitor of mast cell activation recently has been questioned in mice (112). APC^{Min/+} mouse, the Min (multiple intestinal neoplasia) mouse is the result of a single germline mutation in the tumor suppressor gene adenomatous polyposis coli (APC); APC^{Min/+} mice develop multiple intestinal adenomas; Mcpt5-Cre/IDTR⁺ mice, cross between inducible diptheria toxin receptor-floxed mice and transgenic mice expressing the Cre recombinase under the control of the MC-associated Mcpt5 promoter (diptheria toxin treatment results in nearly complete ablation of peritoneal mast cells).
Abbreviations: BM, bone marrow; DMH, dimethylhydrazine; SCC, squamous cell carcinoma.

failed to grow in mast cell-deficient C57BL/6-*Kit*^{W-sh/W-sh} mice but grew normally in WT controls, as well as in C57BL/6-*Kit*^{W-sh/W-sh} mice engrafted with WT BMCMCs. The authors showed that these effects were mediated by MMP-9, as engraftment of C57BL/6-*Kit*^{W-sh/W-sh} mice with *Mmp9*-deficient BMCMCs did not restore tumor growth (45). These results are consistent with the conclusion that mast cells and mast cell-derived MMP-9 contribute to the development of well-differentiated prostate tumors in this model and may therefore represent attractive therapeutic targets. In contrast, the same report showed that when TRAMP mice were crossed with C57BL/6-*Kit*^{W-sh/W-sh} mice that genetically lack mast cells (and which exhibit other abnormalities independent of the mast cell deficiency), or when TRAMP mice were treated with cromolyn, a drug thought to suppress certain mast cell functions but that also affects other cell types, such mice developed a high incidence of aggressive but rare cancer variants characterized by a neuroendocrine signature and *c-kit* expression. These experiments suggested that mast cells might have a protective role in the development of these aggressive types of prostate tumors. Taken together, these findings from Pittoni and colleagues suggest that mast cells can exert different (and indeed opposite) functions in the development of cancers in this model, depending on the stage and subtype (epithelial vs neuroendocrine) of the particular tumor (45).

Other approaches have been used to identify contributions of mast cells to tumor development. By generating polyp-prone (*APC*^{Δ468}) chimeric mice bearing bone marrow derived from WT mice or mice deficient in genes important for mast cell development or trafficking, Gounaris and colleagues provided evidence suggesting that mast cells (and/or other bone marrow-derived cell types also influenced by these mutations) were essential hematopoietic components that favored the development of intestinal polyps (46). Using this mouse model, the same group investigated cross-talk between Tregs and mast cells and reported that mast cells can induce phenotypic changes in classical immunosuppressive and anti-inflammatory Tregs, causing them to become a "proinflammatory Treg" population that can promote tumor growth (47–49).

Evidence of the importance of mast cells and tumor-derived SCF in the development of plexiform neurofibromas has been provided by Clapp and colleagues (20, 50, 51). Plexiform neurofibromas, tumors comprising many cell types including Schwann cells and infiltrating mast cells, are pathognomonic for neurofibromatosis type 1 (NF1), which results from mutations in the *Nf1* gene (52). Zhu and colleagues (53) developed a mouse model of plexiform neurofibroma and studied the mechanisms underlying the formation of these tumors. Notably, in addition to loss-of-function mutations in both copies of the *Nf1* gene in Schwann cells, optimal growth of the neurofibromas also required haploinsufficiency of *NFI* in Kit-dependent bone marrow-derived cells (which the authors concluded probably represented mast cells) within the tumor microenvironment (50). The proposed mechanism is that *Nf1*^{-/-} Schwann cells secrete high levels of SCF that can enhance mast cell migration within the tumor (20). Furthermore, *Nf1*^{+/-} mast cells are more potent than WT mast cells in proliferating, surviving and secreting proinflamma-

tory cytokines within the tumor, therefore promoting tumor development (20).

In 2011, four different groups generated new "Kit-independent" constitutive or inducible models of mast cell deficiency (5, 54–57). While these models do not exhibit abnormalities related to mutations affecting *c-kit* structure or expression, each model has other limitations that should be considered when used for studies of mast cell biology *in vivo* (5). Nevertheless, these new models represent additional tools to analyze possible roles of mast cells in tumor biology *in vivo* (58).

In summary, studies in mice have provided evidence that mast cells may exert either protumorigenic or antitumorigenic functions in different tumor models. Results obtained in an individual tumor model probably depend on such factors as: (i) the type and stage of the tumor (and other features of the "tumor model," such as whether the tumor developed spontaneously or was transplanted); (ii) the signals in the tumor microenvironment (or generated systemically) that can modulate mast cell phenotype and function; and (iii) the approaches used to manipulate mast cell numbers and/or functions.

Studies Linking Mast Cells to Tumors in Humans

It has long been known that mast cells can accumulate at sites of tumors in humans (1, 2). But what are their functions in human tumor biology, and can features of the mast cell response to tumors, such as their numbers, phenotype, or anatomic distribution, be used to predict tumor behavior or prognosis in patients with cancer? The answers to these questions have not yet been fully resolved, but are likely to be complex. Indeed, as in mice, studies in humans have suggested that mast cells can have either protective or deleterious roles in host responses to tumors.

Increased numbers of mast cells have been associated with unfavorable disease features or outcomes (e.g., high tumor grade, increased metastases, and low overall or progression-free survival). The deleterious roles of mast cells were identified in studies of neoplasms affecting the skin, including malignant melanoma (30, 59, 60), Merkel cell carcinoma (61), and primary cutaneous lymphoma (58). Increased numbers of mast cells were also found in pancreatic adenocarcinomas (62–64); squamous cell carcinomas (SCC) of the esophagus (65), mouth (66), and lip (67); and in a long list of hematologic neoplasms (e.g., Hodgkin lymphoma; refs. 68, 69, B-cell chronic lymphocytic leukemia; refs. 70, 71, myelodysplastic syndromes; ref. 72, follicular lymphoma; ref. 73, B-cell non-Hodgkin lymphoma; ref. 74, and multiple myeloma; ref. 75). In many of these studies (29, 30, 58–60, 62, 64–66, 71, 75), the extent of angiogenesis, as assessed by staining of microvessels (in most cases by immunohistochemistry using anti-human CD31 or CD34 antibodies), was positively correlated with the numbers of mast cells per unit area of tissue. In some of these studies, mast cells were shown to express VEGF (29, 30). Such findings have suggested that mast cells may contribute to tumor progression by supporting angiogenesis. However, in an analysis of Hodgkin lymphoma (68, 69), high numbers of either microvessels or mast cells were associated with a poor prognosis, but high numbers of microvessels did not correlate

significantly with high numbers of mast cells, suggesting that mast cells may contribute to tumor progression in these settings by mechanisms unrelated to angiogenesis.

Studies correlating the presence of mast cells in prostate cancer (76–78), colorectal cancer (79–84) and non-small cell lung cancer (32, 85–88) have led to more nuanced interpretations. In prostate cancer, Nonomura and colleagues reported that the number of tryptase⁺ mast cells (that in this study were *only* observed around but not within the cancer foci) positively correlated with a high Gleason score and an advanced clinical stage of the prostate tumor, indicating that high numbers of such mast cells represent a poor prognostic factor for survival following treatment (76). However, Fleischmann and colleagues used tissue microarrays to count numbers of Kit⁺ mast cells in more than 2,300 prostate cancer specimens from patients who underwent prostatectomy at the same institution and found that high intratumoral mast cell density (i.e., number of mast cells per unit area within the tumor) was associated with a good prognosis in prostate cancer (77). A third study, by Johansson and colleagues, of patients with prostate cancer who underwent prostatectomy, showed that mast cell densities within the tumors were an independent favorable prognostic factor, whereas high numbers of peritumoral mast cell were associated with a poor prognosis (78). The findings of Johansson and colleagues therefore suggest that the discrepancy observed in the two preceding studies might be due to the different anatomic location (peritumoral vs. intratumoral) of the mast cells analyzed and that the function(s) of mast cells in this cancer may be strongly dependent on the cells' distribution within the tumor or in its local microenvironment.

Results similar to those in prostate cancer were reported by Fisher and colleagues in 1989 that in colorectal cancer high numbers of mast cells at the tumor border correlated with decreased survival and represented an independent poor prognostic parameter (79). In accord with this finding, subsequent studies have shown that mast cells positively correlated with microvessel density in colorectal cancers, a parameter that independently was associated with a poor prognosis (82–84). However, in 1999, Nielsen and colleagues showed in a study of more than 500 samples from patients with colorectal cancer that high numbers of tryptase⁺ mast cells within the submucosal area with the highest density of inflammatory cells at the boundary zone between the tumor and normal tissue significantly correlated with a favorable prognosis (80). The latter finding is consistent with observations by Tan and colleagues (81), in which the authors correlated the number of chymase⁺ and tryptase⁺ mast cells within the most abundant inflammatory infiltrates with various clinicopathologic factors (histologic grade, depth of invasion, metastasis) and survival, and showed that patients with a low level of mast cell infiltration had a significantly deeper invasion and lower overall survival (81). Increased numbers of mast cells also have been shown to correlate with either a good (85, 87, 88) or poor (32, 86) prognosis in non-small cell lung cancer, and the reasons for these discrepancies may reflect the following factors: (i) differences in the type and the stage of tumors included in these studies (pulmonary adenocarcinoma only; ref. 85, all types of

non-small cell lung cancer; refs. 86, 87, or stage I of non-small cell lung cancer; refs. 32, 88; (ii) the location of the mast cells analyzed (lung parenchyma; ref. 85, regions of highest mast cell infiltration and vascularization; ref. 86, intratumoral stroma; ref. 32, tumor cell islets; ref. 87, or peritumoral zone; ref. 88; and (iii) the methods used to assess and quantify the mast cells (alcian blue and safranin O; ref. 85, tryptase; refs. 32, 86, 87, or tryptase and chymase; ref. 88).

In breast carcinomas, most (89–92) but not all (93, 94) studies have linked mast cells to a good prognosis. In 2004, Dabiri and colleagues used tissue microarrays to study 348 cases of invasive breast carcinoma (each specimen analyzed was from an invasive region of the carcinoma) using immunohistochemical staining of several markers that were then correlated to patient outcome (90). Interestingly, the presence of Kit⁺ mast cells in the stroma (the authors did not observe any Kit expression in the tumor cells, although it has been reported in other studies; ref. 95) correlated with improved survival. This study confirmed previous findings (89) supporting an important favorable role for mast cells in breast carcinomas (90). The same authors then extended their findings by conducting a large microarray study of 4,444 cases of breast cancer and confirmed by immunohistochemical staining of Kit that the presence of any number of mast cells is an independent marker of a good prognosis in invasive breast carcinomas (91).

Mast cells may herald a favorable prognosis in other tumors as well. For example, high numbers of tumor-associated tryptase⁺ mast cells have been reported to be an independent favorable prognostic factor for survival after surgery in patients with malignant pleural mesothelioma (96). Another study reported that high numbers of tryptase⁺ mast cells in tumor tissue in patients with diffuse large B-cell lymphoma who underwent chemotherapy [mainly CHOP (cyclophosphamide, doxorubicin, oncovin, and prednisone)] were positively correlated with a favorable prognosis (97).

Notably, a study of mast cells in samples from various types of renal cell carcinoma showed that toluidine blue⁺ mast cells were more abundant in tumor tissues and at tumor borders than in healthy tissues, and that the number of mast cells correlated positively with the presence of CD31⁺ microvessels; however, no correlation was found between either mast cells or microvessels and the clinicopathologic features of the disease, including survival (98). It is possible that observations like this also may have been made by other groups investigating other types of tumors, but have not been published given the "negative" findings.

Concluding Thoughts

As reviewed briefly above and by others (e.g., refs. 99–102), the literature abounds with studies correlating the presence of mast cells with tumors but it has been challenging to draw simple conclusions from such studies. As we have outlined, both studies of mouse models and observations in human cancer suggest that, depending on the circumstances, including the tumor model (in mice) or the type of tumor (in humans), mast cells can have either favorable or unfavorable net effects on host responses to tumors. Why this is so remains

to be determined. However, mast cells certainly are not the only type of hematopoietic cells that can have disparate effects on host responses in different types of tumors, as the same has been reported for macrophages (103–105). And while it is correct to point out that both mast cell populations and tumors (and their component neoplastic cells) can exhibit heterogeneity of phenotype, defining mechanistically how mast cells interfere with or promote the survival and progression of particular types of tumors is likely to continue to represent a challenge. This may turn out to be a rewarding challenge to address, however, as advancing understanding in this area holds the promise of determining whether critical functions of mast cells might even be harnessed (or restrained) to provide therapeutic benefit to patients with cancer.

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