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The roles of mast cells in anticancer immunity

Dyana K. Dalton and

Department of Microbiology and Immunology, Dartmouth Medical School, 1 Medical Center Drive, Lebanon, NH 03756, USA

Randolph J. Noelle

Department of Microbiology and Immunology, Dartmouth Medical School, 1 Medical Center Drive, Lebanon, NH 03756, USA. Norris Cotton Cancer Center, Lebanon, NH, USA. King's College London, King's Health Partners, Medical Research Council (MRC) Centre for Transplantation, Guy's Hospital, London SE1 9RT, UK

Dyana K. Dalton: Dyana.Dalton@Dartmouth.edu

Abstract

The tumor microenvironment (TME), which is composed of stromal cells such as endothelial cells, fibroblasts, and immune cells, provides a supportive niche promoting the growth and invasion of tumors. The TME also raises an immunosuppressive barrier to effective antitumor immune responses and is therefore emerging as a target for cancer immunotherapies. Mast cells (MCs) accumulate in the TME at early stages, and their presence in the TME is associated with poor prognosis in many aggressive human cancers. Some well-established roles of MCs in cancer are promoting angiogenesis and tumor invasion into surrounding tissues. Several mouse models of inducible and spontaneous cancer show that MCs are among the first immune cells to accumulate within and shape the TME. Although MCs and other suppressive myeloid cells are associated with poor prognosis in human cancers, high densities of intratumoral T effector (T^{eff}) cells are associated with a favorable prognosis. The latter finding has stimulated interest in developing therapies to increase intratumoral T cell density. However, cellular and molecular mechanisms promoting high densities of intra-tumoral T^{eff} cells within the TME are poorly understood. New evidence suggests that MCs are essential for shaping the immune-suppressive TME and impairing both antitumor T^{eff} cell responses and intratumoral T cell accumulation. These roles for MCs warrant further elucidation in order to improve antitumor immunity. Here, we will summarize clinical studies of the prognostic significance of MCs within the TME in human cancers, as well as studies in mouse models of cancer that reveal how MCs are recruited to the TME and how MCs facilitate tumor growth. Also, we will summarize our recent studies indicating that MCs impair generation of protective antitumor T cell responses and accumulation of intratumoral T^{eff} cells. We will also highlight some approaches to target MCs in the TME in order to unleash antitumor cytotoxicity.

Keywords

Mast cells; Cancer; Tumor microenvironment; T cells; AllergoOncology Symposium-in-Writing

Introduction

MCs are among the first immune cells to infiltrate the TME, contributing to tumor progression in multiple aggressive types of human cancer. Their role in tumor progression has been largely attributed to promoting tumor angiogenesis and invasion. However, less is known about how MCs influence adaptive antitumor T cell responses and immune suppression in the TME. Although host immunity can sometimes control cancer, tumors that have become clinically evident have already evaded antitumor immunity, at least in part, by establishing an immunosuppressive TME [1]. The early accumulation of MCs in the TME reflects their role as tissue-resident sentinel cells poised for rapid responses to pathogens and immunogenic antigens [2]. MCs are capable of modulating both innate and adaptive immune responses [3]. Furthermore, MCs have emerged as critical intermediaries in the regulation of peripheral tolerance [4]. Their presence in many precancerous lesions and human tumors is associated with a poor prognosis. This suggests that MCs may contribute to an immunosuppressive TME and thereby impede the development of protective antitumor immunity. Here, we will review studies of MCs and their prognostic significance in human cancers. We will discuss mechanisms of how MCs influence immune responses to tumors from experimental models of cancer. We will also discuss recent studies of MCs and their regulation of T^{eff} cells within immune privileged sites, including the TME.

MCs are correlated with poor prognosis in many human cancers

A high density of MCs in many human cancers is significantly correlated with poor prognosis (decreased survival and increased tumor recurrence). High densities of tumor-associated MCs predict poor prognoses in aggressive skin cancers such as Merkel cell carcinoma and malignant melanoma [5–7]. Similarly, MCs accumulate in nearly all Hodgkin's lymphomas and those patients with highest MC infiltration have significantly worse relapse-free survival rates [8]. MCs accumulate in premalignant lesions of colorectal cancer, that is, adenomatous polyps, suggesting their involvement in these tumors at the earliest stages [9]. MCs also contribute to angiogenesis of colorectal tumors as reflected by increased microvascular density (MVD) in tumor tissues. Thus, high MVD and high MC counts positively correlated with each other and high levels of both histological features were significantly correlated with poor prognosis, that is, a shorter duration of disease-free survival [10]. Supporting this, the invasive fronts of colorectal tumors contain "hot spots" of angiogenesis, which were identified as regions of high MVD with respect to other regions of the tumor. Increased MVD and MC density in hot spots were associated with worse overall survival in patients with colorectal cancer [11].

Similarly, high densities of MCs infiltrating human pancreatic cancers are correlated with poor prognosis. MCs accumulated at the invasive edges of pancreatic tumors and expressed VEGF and bFGF, in regions of high MVD within the tumors. There were significant positive correlations between MC density and MVD; moreover, increased numbers of MCs directly correlated with lymph node metastasis. Although survival was lower in patients with high MC density, the difference did not reach significance [12]. Likewise, high MC density in the invasive margins of pancreatic tumors was correlated with increased vascularization and tumor invasion and increased lymph node metastases; moreover, high MC numbers were independent prognostic indicators for reduced overall survival [13]. Similarly, patients with high MC density in the stroma of pancreatic tumors had significantly worse median disease-free survival times compared with patients with low MC density [14]. In the latter study, in vitro evidence indicated cross-talk between MCs and tumors; pancreatic tumor cells recruited MCs, and MCs promoted growth and invasion of pancreatic tumors [14].

The presence of tumor-associated MCs is correlated with favorable prognosis in some human cancers

In some human cancers, high MC density in tumors is associated with favorable prognosis. A study of over 4,000 breast cancer patients reported that the mean survival time of patients with any stromal MCs was significantly better compared with those lacking stromal MCs: 15 years with MCs compared to 13.9 years without MCs [15]. The presence of MCs also correlated with favorable prognosis in high hormone-responsive breast cancers [16]. Histological images of MCs degranulating near dying tumor cells suggested a cytotoxic effect of MCs on breast cancers. In breast cancers, MCs were suggested as a source of IL-4, which arrests the growth and induces apoptosis of breast cancer cells in vitro [17].

A few studies have reported that the microanatomical location of MCs within the TME was prognostic. In prostate cancer, a high density of MCs within the tumor mass (intratumoral) was associated with favorable prognosis. In contrast, a high density of MCs surrounding (peritumoral) prostate tumors was significantly associated with unfavorable prognosis and poor survival [18]. The peritumoral MCs in human prostate cancer expressed pro-angiogenic bFGF, suggesting that they enhanced tumor angiogenesis [18]. The microanatomical location of MCs was also important in lung cancer. In a study of non-small cell lung cancer patients, the presence of MCs within tumor islets, but not stroma, was a favorable prognostic indicator [19].

The studies above suggest that high MC density can be correlated with either favorable or unfavorable prognostic significance in human cancers depending on the type of cancer, perhaps the methods used to assess MC presence and density, as well as where MCs are located in the TME. For understanding the mechanisms of MC functions in cancer, experimental models of cancer may be valuable and will be discussed next.

Mechanisms of MC-mediated tumor promotion from murine models

The MC growth factor, stem cell factor (SCF), has been implicated in one study in both recruiting and activating tumor-associated MCs and promoting inflammation in the TME [20]. SCF was shown to be produced by many mouse and human tumor cell lines as well as by primary mouse and human tumors. Furthermore, tumors that were engineered to knock down gene expression of SCF were unable to attract MCs to the TME and grew more slowly than normal. Injection of large numbers of bone marrow-derived MCs into tumor-bearing mice resulted in immune suppression (reduced T cell proliferation and NK cell-derived IFN- γ), increased inflammation (expression of IL-6, TNF- α , and VEGF), and increased expression of immune-suppressive TGF- β and IL-10 in the TME. All of these MC-induced alterations of the TME were shown to require SCF. However, since large numbers of exogenous MCs were injected into tumor-bearing mice, the physiological relevance of the latter experiments is unclear.

Mice with genetic deficiencies of MCs have been useful for investigating the function of MCs in various immune responses. SCF binds to MCs through the c-kit receptor, which provides essential growth and survival signals for MCs. Mice with mutations in the c-kit gene, strains WBB6F1-kit^{W/W-v} and ckit^{W^{sh}} (W^{sh}) are mast cell deficient [21, 22]. Both strains exhibit other hematological abnormalities as a consequence of their c-kit mutations. However, the W^{sh} strain has fewer abnormalities than the kit^{W/W-v} strain. Nonetheless, in order to implicate MC deficiency in the phenotype of W^{sh} mice, the role of MCs must be tested by reconstitution of W^{sh} mice with in vitro derived bone marrow-derived MCs. If reconstitution of W^{sh} mice with MCs restores the normal phenotype, this provides strong evidence for a role of MCs in the observed phenotype of W^{sh} mice [21, 22]. These strains of

mice with MC deficiencies have been used in tumor models to define roles for MCs in cancer.

A number of strains of mice have been genetically modified to develop inducible tumors that progress in predictable stages from preneoplasia to malignancy. An advantage of inducible tumors is that the tumor microenvironment can be studied from the earliest stages. Inducible tumor models facilitate identifying leukocyte subsets and their temporal sequence of appearance. Furthermore, inducible mouse tumors offer the opportunity to target cells and molecules during tumor progression in order to understand cause and effect. Insights into the roles of MCs in mouse models of inducible tumors are discussed below.

A transgenic (Tg) mouse model of squamous cell carcinoma was generated by expressing the human papilloma virus gene 16 in basal keratinocytes (K14-HPV-16 Tg mice). Such mice develop epidermal hyperplasia that progresses to squamous cell carcinoma [23]. MCs infiltrated premalignant epidermal lesions at a time coinciding with the angiogenic switch. Moreover, MCs accumulated at the invasive front of tumor–stroma borders, but not within the core of tumors. MC tryptase stimulated proliferation of dermal fibroblasts and MC-chymase-promoted remodeling of the extracellular matrix. Both proteases released pro-angiogenic molecules from the extracellular matrix. Thus, MCs promoted squamous cell carcinoma in this model by stimulating premalignant angiogenesis, tumor cell proliferation, and by MC proteases remodeling the stromal architecture at the invasive front of tumors [23].

A mouse model of pancreatic islet cell cancer was generated by expressing an inducible c-Myc oncogene together with the anti-apoptosis protein Bcl-XL in insulin-producing islet cells (*myc⁺bcl⁺* Tg mice) [24]. Activation of c-Myc in these mice caused rapid proliferation of islet cells and expansion of pancreatic islet tumors. Further investigation showed that within 2 h of c-Myc activation, there was elevated expression of MC-recruiting chemokines within the islets. Within 24 h of c-Myc activation, the invasive margins of the tumors became infiltrated by MCs, which coincided with the onset of tumor angiogenesis. As MCs were the only immune cells present, they were implicated in promoting angiogenesis of pancreatic islet tumors. To further investigate the role of MCs in pancreatic tumors, *myc⁺bcl⁺* Tg mice were bred onto the *W^{sh}* MC-deficient strain. The absence of MCs in *W^{sh} myc⁺bcl⁺* Tg mice completely abolished the expansion of pancreatic tumors; that is, in MC-deficient mice, c-Myc-activated cells divided rapidly and then became hypoxic and died rather than forming tumors. This indicates that MCs are required for c-Myc-driven pancreatic tumor expansion. Similarly, blocking MC degranulation (i.e., release of stored bioactive mediators from MC granules) with cromolyn also abolished c-Myc-driven tumor expansion in *myc⁺bcl⁺* Tg mice. In addition, MCs were required for the survival of previously established pancreatic tumors; mice with established tumors were treated with cromolyn, which induced hypoxia, tumor cell apoptosis, and a dramatic regression of the tumors. Thus, in the *myc⁺bcl⁺* model of pancreatic cancer, MCs were not only essential for angiogenesis, growth, and expansion of nascent pancreatic tumors, but also required to sustain established pancreatic tumors [24].

The roles of MCs were also investigated in several mouse models of colorectal cancer [25]. Mice with inducible overexpression of β -catenin in intestinal cells develop adenomatous polyps, which were densely infiltrated with MCs from the earliest time points. Similarly, two other strains of mice that develop intestinal polyps (APC⁴⁶⁸ and Rag^{-/-} Min) also had a striking accumulation of MCs in polyps [25]. Preventing MC migration in the APC⁴⁶⁸ strain reduced the vascularization, size, and numbers of intestinal polyps. Also, treatment of the APC⁴⁶⁸ strain with cromolyn reduced the size, numbers, and vascularization of intestinal polyps. Therefore, similar to the role of MCs in pancreatic cancer, MCs are

required for the development of polyps and colorectal cancer by promoting tumor angiogenesis and expansion of tumors [25]. In summary, a wealth of evidence from human cancers and mouse models of cancer indicates that MCs contribute to tumor invasion and angiogenesis, both vital for the macroscopic expansion of tumors.

In addition to MCs promoting angiogenesis and expansion of tumors, we propose an immunosuppressive role for MCs in the TME that is analogous to their role of promoting suppression by Foxp3⁺ regulatory T (T^{reg}) cells in the immune-suppressive microenvironment of a tolerated allogeneic skin graft [4]. Within the tolerant skin allograft, one sees the infiltration of alloreactive T^{eff} and T^{reg}, in a dynamic equilibrium that favors immune suppression by the T^{reg} [4, 26]. We propose that MCs suppress the development of protective antitumor immune responses, in part, by promoting Treg suppression in the TME. Also, our studies in allograft tolerance show that MCs “condition” dendritic cells (DCs) (in part by producing GM-CSF and TNF- α) to mediate tolerance by controlling DC migration, longevity, and ability to present antigen in an immunogenic fashion [27].

Potential mechanisms of antitumor activities of MCs in murine models

Although MCs surround many tumors at a high density and support tumor growth, there is some evidence that the pro-tumoral activities of MCs may be subverted by targeting these cells to promote tumor destruction. In one example, TLR2 (Toll receptor) agonist activation of MCs was also used to stimulate MC-mediated antitumor activity in a mouse model of B16 melanoma [28]. Alternatively, triggering MC degranulation can subvert their suppression. As noted above, MCs are in a delicate equilibrium with T^{reg} cells, maintaining immune suppression in established tolerated allografts [4, 26]. MCs can be degranulated by IgE antibody binding and cross-linking their cell surface Fc ϵ R1. Degranulating MCs by IgE antibody in mice with established tolerated allografts resulted in T^{reg} impairment and acute CD4 and CD8 T-cell-mediated tissue destruction [26]. Such acute T-cell-mediated destruction is an important goal of immune therapy for cancer. One promising approach to elicit MC targeting of tumors is to use therapeutic antitumor antibodies of the IgE class. IgE-directed responses against tumors have proven to promote tumor destruction; reviewed in Ref. [29]. IgE antibodies were bound to tumors using biotinylated antitumor IgG bridged to biotinylated IgE with avidin; this resulted in slower growth of IgE-loaded tumors [30]. An anti-ovarian tumor antibody of the IgG class was engineered to express the IgE Fc domain. The IgE antibodies were more effective than the IgG antibodies of identical specificity in promoting tumor cytotoxicity [31]. Mice also have been vaccinated with oral mimitopes (peptides mimicking antibody binding sites on tumors) to generate antitumor IgE antibodies [32–34]. These antitumor IgE antibodies have proven effective in promoting tumor immunity. However, it is not yet clear whether MCs were involved in tumor regression in the models used. Nonetheless, this remains a promising strategy.

Intratumoral T cells in human cancers and their prognostic significance

T cells producing IFN- γ and cytotoxic molecules are important antitumor effector cells. In a number of studies of humans with ovarian cancer, melanoma, colorectal, pancreatic, and lung cancers, a favorable prognosis is associated with the presence of large numbers of intratumoral T cells, particularly CTL and Th1 cells [35–42]. Long-term survival in colorectal cancer is significantly associated with the presence of high densities of intratumoral CD3⁺CD8⁺CD45RO⁺ memory T cells [38]. Moreover, gene expression profiling has identified a coordinately expressed cluster of genes associated with adaptive Th1 immunity; high expression of this cluster was associated with favorable prognosis in colorectal cancer [38]. Further analysis revealed that coordinated high expression of both the CTL-associated gene, granulysin (GNLY) in combination with high expression of the Th1-

associated gene, interferon-regulatory factor-1 (IRF-1) is significantly associated with long-term disease-free survival from colorectal cancer (over a decade) [35]. In contrast, patients with high expression of VEGF genes within their tumors had unfavorable prognoses and reduced survival, even if they had other favorable T cell and gene expression profiles [35]. The detailed analyses of human cancers discussed above have provided important clues on the characteristics of protective and detrimental immune responses to tumors. These clues can be used to develop more effective immune therapies for cancer. However, the cells and molecules that control the balance between protective and non-protective immune responses are still poorly defined. In particular, how MCs influence T cell responses to cancer has not been well studied. For such studies, mouse models of cancer have provided insights.

The effect of MCs on T cell responses in murine cancer models and other immune-suppressive microenvironments

We have recently investigated how MCs influence T cell responses to MB49 carcinomas in W^{sh} and wild-type mice (A. Wasiuk et al., manuscript in revision). The MB49 bladder carcinoma was used because MCs influence both tumor angiogenesis and antitumor T cell responses in this model. Upon injection of MB49 tumor cells into skin, MCs accumulated around tumors and promoted tumor angiogenesis. Tumors growing in the W^{sh} mice (lacking MCs) exhibited significantly reduced angiogenesis compared with those in wild-type mice. The MB49 tumor cell line naturally expresses minor allogeneic male antigens (HY), thereby triggering rapid anti-male Th1/Tc1 responses in tumor-bearing females. Male mice are tolerant of HY antigens and do not make this rapid T cell response against tumor/HY antigens. A comparison of tumor growth in wild-type and MC-deficient male and female mice highlights the synergy between MC deficiency and prompt antitumor IFN- responses. Thus, male mice, including the W^{sh} males with reduced tumor angiogenesis, exhibited rapid growth of MB49 tumors. The failure of male W^{sh} mice to control the growth of MB49 tumor indicates that merely reduced angiogenesis of tumors because of MC deficiency was not sufficient to control tumor growth in the absence of a prompt anti-HY T cell response. Wild-type females generated rapid anti-HY IFN- + T cell responses, but MB49 tumors were poorly controlled; thus, a rapid IFN- response was also not sufficient to control MB49 tumors. In contrast, most MC-deficient female W^{sh} mice, which exhibited decreased tumor angiogenesis and rapid anti-male immune responses, controlled the growth of solid tumors. Taken together, our studies indicate that the absence of MCs (with reduced tumor angiogenesis) and the presence of a rapid antitumor T cell response synergized in promoting tumor regression in female W^{sh} mice. Similarly, systemic MB49 tumors caused the death of wild-type and W^{sh} males and wild-type females within 25–30 days. However, 50 % of MC-deficient female W^{sh} mice survived to the end of the monitoring period of 80 days. Moreover, enhanced survival of female W^{sh} mice with systemic MB49 tumors was abolished by their reconstitution with wild-type MCs, demonstrating an essential role for MCs. Enhanced survival of female W^{sh} mice upon systemic MB49 challenge was also dependent on T cells; thus, depletion of either $CD4^{+}$ or $CD8^{+}$ T cells in female W^{sh} mice abolished their resistance to tumors. The antitumor T cell response was superior in W^{sh} female mice; such mice had significantly increased frequencies of $CD8^{+}$ IFN- + antitumor T cell responses in their tumor draining lymph nodes compared with wild-type females. This finding indicates that MCs impaired the generation of protective antitumor T cells.

Mice with MC deficiency also exhibited significantly increased ratios of T^{eff} cells relative to tumor cells within the TME. Effective antitumor immunity (i.e., tumor regression) was associated with high ratios of T^{eff} cells relative to tumor cells, as measured by quantitative flow cytometry analysis of single cell suspensions from tumors. By this metric, tumors from the W^{sh} female mice had 8-times higher ratios compared with tumors from WT female mice. These findings suggest that MCs impaired antitumor immunity by reducing ratios of T^{eff}

cells to tumor cells in the TME, as well as by impairing the generation of antitumor CD8⁺IFN-⁺ T cells. As noted for human cancers, high densities of IFN-⁺ CD4⁺ and CD8⁺ T cells accumulating within tumors are associated with favorable prognosis. Therefore, it is important to understand how MCs impair these important aspects of antitumor immune responses.

We hypothesize that MCs impair T cell accumulation within tumors indirectly by promoting angiogenesis. Increasing evidence suggests that molecules promoting tumor angiogenesis also impair the accumulation of intratumoral T cells, recently reviewed [43, 44]. For T cells to enter the TME, they must cross the endothelial cell barrier by diapedesis [45]. An initial step in diapedesis is the adhesion of T cells by their integrins, LFA-1 and VLA-1, to the endothelial cell adhesion molecules, ICAM and VCAM, respectively. Angiogenesis in tumors has been shown to reduce ICAM and VCAM expression on endothelial cells. In vitro cultured endothelial cells showed significantly reduced expression of both ICAM and VCAM in the presence of either VEGF or bFGF [46]. Also, in vivo blockade of angiogenesis restored leukocyte adhesion to vessel walls and significantly increased leukocyte infiltration into tumors [47]. Furthermore, intravital microscopy showed that tumor-bearing mice had reduced interactions of leukocytes with blood vessels [46]. Finally, VEGF blockade, not alone, but in combination with antitumor vaccines or adoptive T cell therapy, increased the infiltration and accumulation of intratumoral T cells [48–50]. These studies have prompted the interesting suggestion that blockade of tumor angiogenesis renders tumors more accessible to the immune system [43]. We hypothesize that interfering with or deleting MCs will synergize with anti-tumor vaccines to promote effective killing of tumor cells.

How MCs impair the generation of antitumor IFN-⁺ T cells is under investigation now. MCs produce a plethora of molecules capable of influencing immune responses [51]. MCs are known to produce molecules that can impair dendritic cell-mediated generation of CTL and Th1 cells by suppressing IL-12 production by DCs. These molecules include VEGF, IL-10, histamine and prostaglandins and possibly others yet to be identified [52–56]. MC expression of VEGF in the TME has been well documented [12, 57, 58]. Moreover, VEGF was the first tumor-derived factor reported to inhibit DC differentiation [59], and its critical role in mediating tumor-induced defects in DC differentiation has been proven both in vitro and in vivo [60]. Furthermore, administration of neutralizing VEGF antibody to tumor-bearing animals resulted in improved DC differentiation [61]. Our preliminary studies indicate that blocking VEGFR2 also enhanced the resistance of wild-type female, but not male, mice to MB49 tumors, suggesting a potential role for VEGF impairing tumor immunity in this model. Also, our recent work showed that MC-derived TNF-⁺ and GM-CSF conditioned graft-derived dendritic cells that mediate allograft tolerance [27]. Such tolerogenic dendritic cells accumulated in draining lymph nodes where they dominantly suppressed T cell responses. The role of MCs in promoting tolerogenic DCs in the TME is currently under investigation.

We have observed a novel role of MCs in regulation of antitumor immunity by their expression of tryptophan hydroxylase-1 (Tph-1), an enzyme using tryptophan as a substrate to produce serotonin. Tph-1 is therefore capable of depleting local tryptophan, which may have detrimental effects on antitumor T cells. Mice (females but not males) with a genetic deficiency of Tph-1 were better able to control MB49 tumors, and this was T-cell-mediated; Tph-1-deficient mice lost their superior tumor resistance when CD4 and CD8 T cells were depleted. Moreover, Tph-1-deficient mice had significantly increased IL-17 and IFN-ELISPOT responses to tumor antigens. Also, W^{sh} female mice lost their superior resistance to MB49 tumors when reconstituted with WT, but not Tph-1-deficient mast cells; this implicates MCs as an essential source of Tph-1 in suppressing tumor resistance. Taken

together, MCs inhibit antitumor T cell immunity, at least in part, by their expression of Tph-1 (E. Nowak et al., manuscript in preparation).

MCs may also influence T cell responses by forming immunological synapses with and presenting antigens to T cells [62]. MCs can be induced to express MHC II both in vitro and in vivo. In co-cultures MCs, presented MHC class II-associated antigens to CD4⁺ T cells, and there was a preferential expansion of T^{reg} cells in these in vitro cultures [63]. However, the in vivo occurrence and significance of MCs presenting antigens to T^{reg} cells has yet to be demonstrated. MCs and T^{reg} have regulatory effects on each other. MCs are capable of producing TGF- β [64] which enhances Treg differentiation [65]. T^{reg} recruit MCs to tolerant allografts, and both subsets are essential for maintaining skin graft tolerance [4]. Conversely, in tolerant allografts, degranulation of MCs induced rapid allograft rejection and loss of T^{reg}-suppressive functions [26]. Moreover, in colorectal cancer, MCs promote T^{reg} production of pro-inflammatory cytokines, such as IL-6, that promote tumor progression [66]. The reciprocal interactions of MCs and T^{reg} in cancer are well summarized in a recent review [67]. The molecules made by MCs and their potential suppressive effects on T cells and DCs are shown in Fig. 1.

New mouse models for investigating molecules and mechanisms MCs in TME

A number of studies on the roles of MCs have used mice with c-kit mutations rendering them deficient in MCs. Such mice have provided valuable insights, especially when combined with MC reconstitution studies to validate the roles of MCs and MC-derived molecules. Although MCs produce many molecules capable of influencing the immune responses to tumors, whether MCs are significant biological sources of such molecules remains to be investigated. To address such questions, new strains of mice have been developed that will permit precise deletion of MC subsets and MC-derived molecules. One strain has Cre-recombinase expression driven by the Mcpt5 promoter (Mcpt5-Cre), which promotes the expression of reporter genes in MCs located within the peritoneal cavity, skin, and connective tissues [68]. In Mcpt5-Cre mice, inducible deletion of such MCs can be achieved by introducing a transgene for the inducible diphtheria toxin receptor (iDTR) with Loxp-flanked (floxed) stop sequences. Upon expression of Mcpt5-Cre, DTR will be expressed in those MCs, rendering them sensitive to killing by diphtheria toxin (DT); in mice Mcpt5-expressing MCs in skin, peritoneal cavity, and connective tissues are deleted by DT. On the same principle, constitutive deletion of Mcpt5-Cre⁺ MCs can be achieved by crossing Mcpt5-Cre mice with Tg mice carrying a gene for the active subunit of diphtheria toxin with floxed stop sequences; upon expression of the Mcpt5 promoter, such MCs will be deleted [69]. Similarly, Mcpt5-Cre and floxed IL-10 genes have a targeted deletion of IL-10 expression by Mcpt5⁺-MCs [69]. Another model of MC-specific gene expression contains a promoter that is restricted to chymase-expressing MCs, located in mucosal tissues [70].

Concluding remarks

The roles of MCs in cancer are far from being understood and many questions remain. Current evidence favors the idea that MCs influence tumor angiogenesis, tumor invasion, immune suppression, and contribute to the composition of the immune-suppressive TME. Although MCs have been demonstrated to secrete molecules with angiogenic and immune-suppressive functions, the extent to which MCs are a relevant source of these immune-suppressive molecules in the TME is an unresolved, but important, question. As mentioned above, new transgenic mouse strains allowing the precise deletion of genes within MCs will help elucidate the roles of MCs and MC-derived molecules within the TME. Important future directions will be to identify molecules that provide signals to MCs during initiation

of tumors, to identify the molecules MCs produce in response to the signals, and to understand how MC-derived molecules influence the outcome of antitumor immune responses. MCs have a great deal of flexibility during initiation of immune responses and are capable of enhancing or suppressing adaptive immunity. Preclinical studies suggest that blocking MC functions, degranulating MCs, or depleting MCs in some types of cancer might be an effective therapeutic strategy. However, a better understanding of how MCs influence antitumor responses might also suggest new strategies to therapeutically target MCs in the TME to improve protective immune responses.

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Fig. 1.

Mast-cell-derived molecules and their potential impact on the development of antitumor immunity. Effective antitumor T cell responses have been characterized by immunogenic dendritic cells producing IL-12, priming and expanding T^{eff} cells such as Th1 and CTL. Mast cells are known to produce the various molecules shown. The molecules shown in the diagram are known to impair IL-12 production by DCs, promote Th2 immune responses, suppress maturation of DCs and thereby promote development of myeloid-derived suppressor cells (MDSCs). Other molecules shown are known to inhibit T^{eff} proliferation and function either directly acting on T cells or indirectly by enhancing T^{reg} differentiation. T^{reg} cells inhibit T^{eff} cell expansion and function. It is important to note that the extent to which MCs are a major biological source of immune-suppressive molecules in the TME and lymph nodes has yet to be established; therefore, this is presented as a hypothetical model. *VEGF* vascular endothelial growth factor; *GM-CSF* granulocyte macrophage colony stimulating factor; *T^{reg}* Foxp3⁺ regulatory T cells; *DC* dendritic cell; *MC* mast cell; *Th1* IFN-⁺ CD4⁺ T cells; *CTL* IFN-⁺ Gln⁺ (granulysin) CD8⁺ T cells