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Review

Mast cells as targets for immunotherapy of solid tumors☆

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ABSTRACT

Mast cells have historically been studied mainly in the context of allergic disease. In recent years, we have come to understand the critical importance of mast cells in tissue remodeling events and their role as sentinel cells in the induction and development of effective immune responses to infection. Studies of the role of mast cells in tumor immunity are more limited. The pro-tumorigenic role of mast cells has been widely reported. However, mast cell infiltration predicts improved prognosis in some cancers, suggesting that their prognostic value may be dependent on other variables. Such factors may include the nature of local mast cell subsets and the various activation stimuli present within the tumor microenvironment. Experimental models have highlighted the importance of mast cells in orchestrating the anti-tumor events that follow immunotherapies that target innate immunity. Mast cells are long-lived tissue resident cells that are abundant around many solid tumors and are radiation resistant making them unique candidates for combined treatment modalities. This review will examine some of the key roles of mast cells in tumor immunity, with a focus on potential immunotherapeutic interventions that harness the sentinel role of mast cells.

1. Introduction

Mast cells play multifaceted roles in regulating inflammatory processes, tissue remodeling and host defense. Many of these activities are linked to their function as sentinel cells recruiting innate and adaptive immune effector cells (Galli and Tsai, 2008; Theoharides et al., 2012; Dawicki and Marshall, 2007). Mast cell responses are governed by their wide range of cell surface receptors which regulate the selective release of mediators. Upon activation, via cross-linking of the high affinity IgE Fc receptor (FcεRI), mast cells release pre-formed granule-associated mediators, including histamine. Activated mast cells also produce de novo synthesized lipid mediators (e.g., prostaglandins and leukotrienes), usually within minutes of activation, and a wide range of growth factors, cytokines and chemokines over a more sustained time period. Degranulation is tightly controlled and occurs either by a classical rapid process or via the slower, and potentially more selective, process of piecemeal degranulation (Dvorak and Kissell, 1991). Mast cells can also be activated by other stimuli, including certain cytokines and toll-like receptors (TLR), to selectively release cytokines and chemokines in the absence of degranulation (Fischer et al., 2006; Kandere-Grzybowska et al., 2003; McCurdy et al., 2003). In the context of the tumor microenvironment, multiple stimuli may serve to activate mast cells including anti-tumor antibodies, hypoxia, alarmins, cytokines and chemokines. Therefore, mast cells and their mediators can have profound immunoregulatory effects with both tumor promoting and anti-tumorigenic consequences (Fig. 1).

The overall impact of mast cells in the tumor microenvironment is unclear owing to contradictory reports on the prognostic significance of mast cell infiltration in solid tumors and may be highly dependent on the type and stage of cancer. Increased mast cell density is associated with a poor prognosis in many cancers including Hodgkin's lymphoma, melanoma, endometrial, cervical, esophageal, lung, gastric, colorectal and prostate carcinomas (reviewed in Groot Kormelink et al., 2009). The tumor promoting capacity of mast cells has been attributed to their release of pro-angiogenic and tissue degrading mediators as mast cell infiltration

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; FcεRI, high affinity IgE Fc receptor; FcγRI, high affinity IgG Fc receptor; FcγRII, low affinity IgG Fc receptor; FGF, fibroblast growth factor; H1–H4, histamine receptors 1–4; HIF-1α, hypoxia inducible factor 1 alpha; IFN, interferon; MDSC, myeloid-derived suppressor cell; PDGF, platelet-derived growth factor; PG, prostaglandin; SCF, stem cell factor; TGF-β, transforming growth factor beta; TLR, toll-like receptor; TNF, tumor necrosis factor; T_{reg}, regulatory T cell; VEGF, vascular endothelial growth factor.

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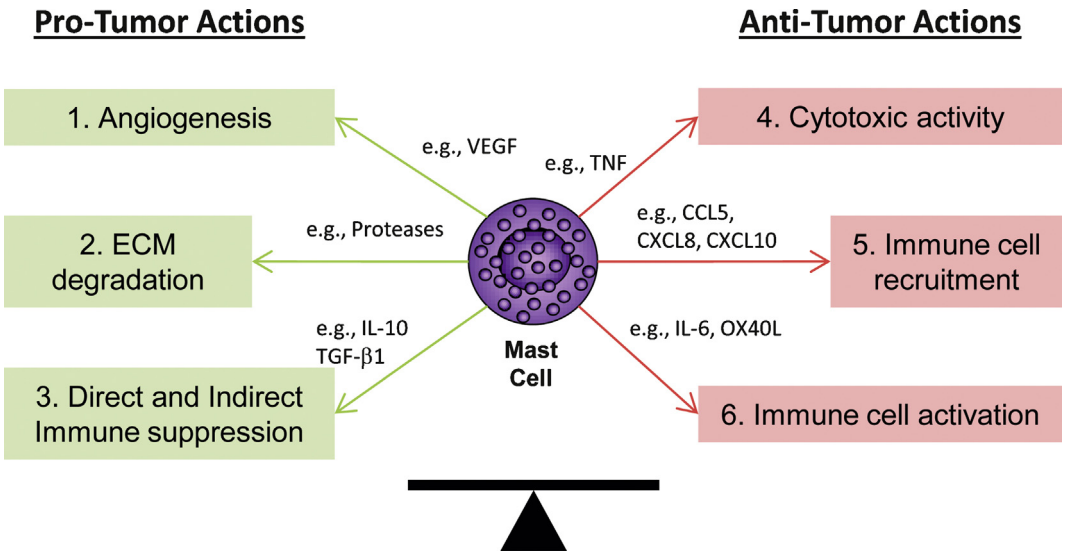

Fig. 1. Mast cell modulation of the solid tumor microenvironment. Activated mast cells can potentiate the deregulated tissue homeostasis of the tumor microenvironment and favor tumor growth and spread through (1) the release of pro-angiogenic factors which enhance endothelial cell migration, proliferation and blood vessel formation, (2) the release of proteases that release growth factors that have been sequestered in the extracellular matrix (ECM) to enhance fibroblast proliferation and the angiogenic response and that degrade the ECM thereby aiding tumor cell invasion of the stroma and (3) mast cells can contribute to the immune suppressive tumor environment through the release of cytokines such as TGF-β1 and IL-10 and indirectly through interactions with MDSC and T_{reg}. Mast cells can also exhibit anti-tumor activity through (4) direct tumor cell cytotoxicity through release of TNF or indirectly via mast cell released heparin actions on fibroblasts, (5) acting as sentinel cells that secrete multiple chemokines that mobilize anti-tumor immune effector cells to tumor sites and (6) modulating immune effector cell responses and differentiation through the release of cytokines or via cell–cell interactions. Effective mast cell targeting immunotherapy will shift the balance toward promoting the anti-tumor activities of mast cells.

positively correlates with microvessel density and tumor progression (Takanami et al., 2000; Yano et al., 1999; Ribatti et al., 2003). In contrast, mast cell infiltration of tumor sites or draining lymph nodes is not always a poor prognostic indicator in cancer (Xia et al., 2011; Hedstrom et al., 2007; Chan et al., 2005; Wang et al., 2013). Moreover, in two large scale tissue microarray studies mast cell infiltration correlated with improved patient survival for prostate carcinoma (Fleischmann et al., 2009) and breast carcinoma (Rajput et al., 2008). The location of mast cells and their activation status within the tumor microenvironment are likely critical to determining their prognostic significance. In support of this, elevated intratumoral tumor necrosis factor (TNF), which is produced in substantial amounts by both mast cells and macrophages, is an independent predictor of survival for non-small cell lung carcinoma, while increased stromal TNF is a negative prognostic indicator (Ohri et al., 2010). In studies of non-small cell carcinoma and prostate carcinoma intratumoral, but not peritumoral, mast cells independently predict improved survival (Welsh et al., 2005; Johansson et al., 2010).

Mediators released from activated mast cells may have direct anti-tumor effects. Mast cells can have direct tumor cytotoxic effects via TNF in vitro (Samoszuk et al., 2005; Benyon et al., 1991; Dery et al., 2000). Mast cell mediators can also be tumor growth inhibitory as heparin can inhibit human breast tumor cell clonogenic growth in the presence of fibroblasts (Samoszuk et al., 2005) and histamine can protect against tumorigenesis as evidenced by the increased susceptibility to carcinogen-induced colorectal and skin tumors in histamine deficient mice (Yang et al., 2011).

Mast cell activation in response to a range of stimuli can have profound effects on immune responses depending on the classes of mediators released from mast cells. Cytokines and chemokines such as IL-6, CCL3, CCL5, CXCL8 and CXCL10 released from mast cells, often in the absence of degranulation, have huge potential for modulating anti-tumor immunity. Signals derived from the tumor microenvironment including those arising from tissue damage, tumor outgrowth or following therapy can also modulate effective anti-tumor immunity through distinct pathways, some of which may involve mast cells. Mast cells are also attractive candidates for targeted tumor immunotherapy as they are found in abundance at the periphery of solid tumors in close proximity to blood vessels. As such, mast cells are poised to act as first responders following local and systemic administration of innate immune activators to help facilitate effective anti-tumor immune responses. This review will discuss potential mechanisms of recruitment to and activation of mast cells at tumor sites and focus on their role as sentinel cells in eliciting effective immune responses and how this activity might be therapeutically targeted.

2. Mechanisms of mast cell recruitment to solid tumors

Mast cells and their committed precursors express numerous chemokine and growth factor receptors which, in response to chemotactic stimuli, drive their migration to inflamed or damaged tissues (reviewed in Halova et al., 2012). Mast cells are often among the first immune cells recruited to solid tumor sites. They are increased in precancerous lesions, found in greater abundance as cancer progresses and their numbers are positively associated with microvessel density (Benitez-Bribiesca et al., 2001; Mohtasham et al., 2010; Kankkunen et al., 1997). Several mediators released within the tumor microenvironment are likely to drive the recruitment of mast cells. Notably, mast cells express high levels of the stem cell factor (SCF) receptor CD117 (c-Kit). SCF is a chemotactic factor for mast cells (Nilsson et al., 1994; Meininger et al., 1992) and has been implicated in mast cell recruitment to experimental models of breast and hepatocellular carcinoma (Zhang et al., 2000; Huang et al., 2008; Kwok et al., 2012).

Chemokines are likely to play a pivotal role in mast cell recruitment to tumor sites. Mast cells express several chemokine receptors, in amounts that vary between immature and mature mast cells and among mast cell subsets. CCL5 is expressed in Hodgkins lymphoma tumor tissue samples and CCL5 released from Hodgkin/Reed-Sternberg cell lines induces human mast cell chemotaxis in vitro (Fischer et al., 2003). Human mast cells also migrate to CCL5 released from human keratinocytes following exposure to UVB radiation (Van Nguyen et al., 2011). CCL5 expression by human uterine smooth muscle tumor cells correlates with

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mast cell density in the tumor tissue and the majority of infiltrating mast cells express the CCR3 receptor for CCL5 (Zhu et al., 2007). These data suggest CCL5 may be an important mast cell chemotactic mediator in several tumor settings. Another chemokine likely to be important for mast cell recruitment to tumor sites is CXCL12, which is abundant in solid tumors and can be produced by both tumor cells and stromal cells (Kryczek et al., 2005). Tumor-associated mast cells express CXCR4 (Polajeva et al., 2011) and CXCL12 induces human mast cell transendothelial migration in vitro (Lin et al., 2001).

Other mast cell chemoattractants that are increased at solid tumor sites include the complement products C3a and C5a (Hartmann et al., 1997), tumor-derived peptides (Niyonsaba et al., 2002), transforming growth factor (TGF)-β isoforms (Olsson et al., 2000; Gruber et al., 1994) and the angiogenic factors vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-2 and platelet-derived growth factor (PDGF) (Gruber et al., 1995). Lipid mediators, including PGE_2 (Weller et al., 2007) and leukotrienes (Duffy et al., 2008) may also have a role in attracting mast cells or their precursors in this context. There may be substantial functional redundancy for this response. Once mast cells or their committed precursors are recruited to a tumor site, the nature of the cytokine microenvironment will influence many aspects of mast cell development including the expression of Fc receptors and TLRs as well as the protease content of the cells.

3. Antibody-mediated mast cell activation within the tumor microenvironment

Mast cells have been studied extensively in allergic disease where allergen specific IgE activates mast cells via cross-linking surface FcεRI. Other human cell types such as basophils, dendritic cells and macrophages can also express FcεRI. However, for the purpose of this review we will limit our discussion to mast cells. Epidemiological studies including multi-center case–control studies, rigorous meta-analysis and pooled analyses have suggested that allergic disease is associated with a decreased cancer risk in several solid tumors including pancreatic cancer and colorectal cancer (Sherman et al., 2008; Olson et al., 2013; Negri et al., 1999). In support of these studies, elevated total and allergen specific serum IgE is associated with a decreased risk of developing glioma (Calboli et al., 2011; Schwartzbaum et al., 2012). In contrast, others have associated lower serum IgE concentrations with improved survival in breast cancer (Ownby et al., 1985), although this was restricted to the subgroup of estrogen receptor positive cancers. Thus, the impact of IgE-mediated activation of mast cells on tumor development and progression may be dependent on the tissue microenvironment. It has been proposed that IgE-mediated mast cell activation may play an important role in anti-tumor immunity (Jensen-Jarolim et al., 2008). In support of this, IgE-activated human skin-derived mast cells have increased anti-tumor cytotoxic activity in vitro (Benyon et al., 1991). There is growing interest in the concept that IgE-mediated immune cell activation may provide opportunities for a targeted cancer immunotherapy (Teo et al., 2012; Singer and Jensen-Jarolim, 2013). In these situations the effector actions of mast cells could determine therapeutic outcome.

In addition to IgE receptors, human mast cells can express the lower affinity IgG receptor FcγRII and the high affinity IgG receptor FcγRI (Okayama et al., 2000). FcγRI expression is upregulated following interferon (IFN)γ treatment and activation of mast cells via crosslinking of FcγRI induces potent mast cell activation similar to that of IgE-mediated activation (Okayama et al., 2001). Thus, in the context of cancer, if the tumor microenvironment contains sufficient IFNγ, anti-tumor IgG containing immune complexes may activate mast cells leading to degranulation, lipid mediator production and cytokine/chemokine generation. Anti-tumor IgG or IgM containing immune complex deposition can also activate mast cells via activation of the complement cascade and mast cell activation through complement receptors. Complement can also enhance IgG-mediated mast cell degranulation (Woolhiser et al., 2004). The impacts of FcγR and complement-mediated mast cell activation on tumor growth are unknown. There is an urgent need for studies aimed at investigating such mechanisms of human mast cell activation, in the face of ever increasing use of anti-cancer antibody-mediated therapies and anti-cancer fusion proteins containing Fc structures.

4. Alternate activators of mast cells within the tumor microenvironment

The tumor microenvironment is rich in soluble mediators which have the potential to activate mast cells (reviewed in Oldford and Marshall, 2013). Mast cells express and are activated via HIF-1α under hypoxic conditions (Sumbayev et al., 2012; Gullikson et al., 2010). Tumor-induced hypoxia also increases adenosine and PGE_2 (Lee et al., 2010; Ghiringhelli et al., 2012). Adenosine activates mast cells to release pro-inflammatory cytokines through A2b and A3 receptors (reviewed in Rudich et al., 2012) and PGE_2 can increase mast cell production of mediators such as IL-6 (Leal-Berumen et al., 1995), VEGF (Abdel-Majid and Marshall, 2004) and CCL2 (Nakayama et al., 2006). Many tumors are also rich in mast cell activating neuropeptides which can enhance tumor growth (Rozengurt, 2002). Tissue damage at tumor sites can activate mast cells via the release of damage-associated tissue breakdown products such as hyaluronan (Horny et al., 1996) that can activate TLRs or via the release of endogenous alarmins. Alarmins that are upregulated in a number of cancers include HMGB1, S100 proteins, and cathelicidin peptides such as LL37 (reviewed in Chan et al., 2012). Alarmins can act directly on cancer cells to induce tumor cell proliferation, migration and angiogenesis or indirectly via actions on immune effector cells, including mast cells. Alarmins can activate mast cells via innate pattern recognition receptors, including TLR and other receptor systems. For example, HSP70 induces IL-6 and TNF production by mast cells in a TLR4-dependent manner (Mortaz et al., 2006), while LL37 induces degranulation, upregulates TLR4 expression and enhances T_H2 and pro-inflammatory cytokine production and CCL4 chemokine production from human mast cells via the MrgX2 G-protein coupled receptor (Yoshioka et al., 2008; Schiemann et al., 2009; Subramanian et al., 2011). Alarmins have a dichotomous role in solid tumors. While they can enhance the chronic inflammatory response of solid tumors, promoting their growth, alarmins are also hallmarks of immunogenic cell death that are required to induce effective anti-tumor immunity (reviewed in Krysko et al., 2013). The factors governing the tumor-promoting or tumor-inhibitory functions of alarmins and the contribution of mast cells to these processes are areas that require further investigation.

Several cytokines and chemokines at the tumor site can also enhance mast cell activation. SCF is important for mast cell differentiation, survival and activation (reviewed in Galli et al., 1993). In experimental tumor models, tumor-derived SCF activates mast cells and enhances tumor growth via increased production of pro-inflammatory mediators, including IL-6 and TNF, pro-angiogenic mediators, including VEGF and immune-suppressive mediators, such as IL-10 (Huang et al., 2008). CXCL12 enhances mast cell secretion of the pro-angiogenic factor and neutrophil and NK cell chemoattractant CXCL8 (Lin et al., 2001) and synergizes with CXCL8 and VEGF to enhance angiogenesis (Kryczek et al., 2005; Matsuo et al., 2009). Thus, within the tumor microenvironment, CXCL12 may promote angiogenesis via the coordinated recruitment of mast cells to the leading edge of solid tumors whereby it can synergize

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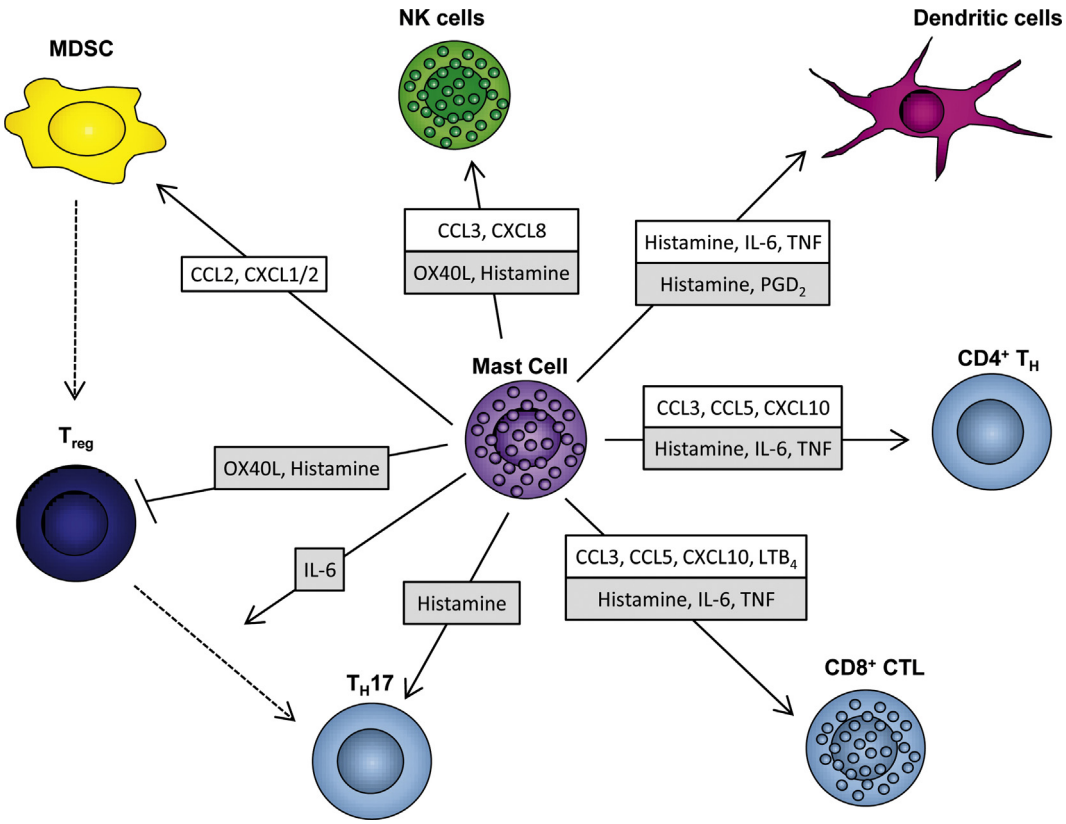

Fig. 2. Major mechanisms by which mast cells may modulate anti-tumor immunity. Mast cells can modulate anti-tumor immunity through the release of granule-associated and de novo synthesized mediators that induce the mobilization of immune cells (white boxes) and their activation and differentiation (gray boxes). Mast cells can contribute to the immune suppressive tumor microenvironment via mobilization of and interaction with MDSC and T_{reg}. With appropriate activation, mast cells may also enhance anti-tumor responses via the recruitment of NK cells, DC subsets and T cells and via their interactions with these cells to enhance their activation. In turn, cells recruited to tumor sites via mast cells can then modulate mast cell activity.

with VEGF and CXCL8 to enhance angiogenesis. The cytokine IL-33 is released in response to tissue damage by many cell types, especially epithelial cells, including many common tumor types (Le et al., 2013). Murine studies have demonstrated that IL-33 is upregulated in squamous cell carcinoma cells that evade immunological destruction (Byrne et al., 2011) and promotes breast cancer cell metastases by enhancing immune suppression (Jovanovic et al., 2013). Both human and murine mast cells express functional IL-33 receptors. Mast cells activated by IL-33, released from necrotic stromal cells, secrete TNF, IL-6 and leukotrienes (Enoksson et al., 2011). Mast cell activation by IL-33 may occur in a number of tumor types and particularly in skin cancers, as mast cells have been shown to accumulate with IL-33 expressing fibroblasts in UV-exposed murine skin samples (Byrne et al., 2011).

The milieu of mediators secreted by tumor cells, stromal cells and infiltrating immune cells affect not only the mast cell activation status but also the type and numbers of mast cells recruited to tumor sites. This milieu is likely to be influenced by the tumor microenvironment. Some of the mast cell recruiting and/or activating factors, abundant at tumor sites, are also released by activated mast cells, including LTB_4, CCL5, LL37 and IL-33 (Wang et al., 2012; Di Nardo et al., 2003; Hsu et al., 2010; Weller et al., 2005; Venkatesha et al., 2005). Thus, mast cells may potentiate their recruitment to and activation at tumor sites, in an autocrine manner. It can be difficult to predict from acute in vitro studies the full nature of the mast cell responsiveness within a tumor microenvironment. Within tumor sites, mast cells are chronically activated by multiple signals which are not readily reproduced in cell culture systems.

5. Mast cell modulation of anti-tumor immunity

In addition to their roles in tumor angiogenesis, mast cells can have profound effects on anti-tumor immunity. The generation of effective anti-tumor immunity requires the recruitment and activation of immune effector cells at tumor sites, including dendritic cells, NK cells, $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T_H1 cells and the simultaneous inhibition of immune suppressive cells including regulatory T cells (T_{reg}), myeloid-derived suppressor cells (MDSC) and alternatively activated M2 macrophages (reviewed in Motz and Coukos, 2013; Butt and Mills, 2013). Mast cells may modulate the recruitment and activity of all of these cell types (reviewed in Galli and Tsai, 2010). Some mechanisms by which mast cells can modulate anti-tumor immune responses have been more extensively studied (Fig. 2). There is evidence that mast cells can contribute to immunosuppression at solid tumor sites, through mediator release and through their interactions with T_{reg} and MDSC. However, in their activated state, mast cells are known sentinel cells that are important for the mobilization and activation of immune effector cells at sites of inflammation (reviewed in Marshall, 2004). Mast cells can also influence the development of acquired immune responses through interactions with dendritic cells and T cells. Each of these processes provides potential opportunities to improve immunotherapy.

5.1. Mast cell-mediated immune suppression

Effective anti-tumor immunity is dependent on overcoming the marked immune suppressive environment of solid tumors. Human

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mast cells can contribute to local immune deficits through release of the immune suppressive cytokines TGF-β1 and IL-10 (Royer et al., 2001; Kanbe et al., 2000). Although the extent to which this process occurs in vivo is unknown, mast cell proteases, released following degranulation, play an important role in releasing extracellular matrix bound latent TGF-β1 and processing it to a bioactive form (Taipale et al., 1995). Degradation of other bioactive cytokines and chemokines by mast cells also contributes to immune suppression (Piliponsky et al., 2012; Zhao et al., 2005; Kato et al., 2009). In addition, histamine can mediate immune suppression by inhibiting both T_H1 and T_H2 responses through H2 receptors (Noubade et al., 2007; Forward et al., 2009; Jutel et al., 2001).

Mast cell interactions with MDSCs can impact the development and functional capacity of effective tumor immunity. In a murine model of liver cancer, a complex interrelationship between mast cells, MDSC and T_{reg} is observed whereby mast cells recruit MDSCs and induce their production of IL-17, which in turn acts to mobilize T_{reg} cells and enhance their suppressor function (Yang et al., 2010). This study suggested an important role for mast cell-derived CCL2 in the recruitment of MDSC. Mast cells also secrete other known MDSC chemoattractants. Mast cell release of CXCL1 and CXCL2 is important for early neutrophil recruitment to sites of inflammation (De Filippo et al., 2013) and likely enhances the recruitment of MDSC subsets as they are known MDSC chemotactic factors (Toh et al., 2011). Studies in a melanoma metastasis model suggest direct mast cell-MDSC interaction is required for monocytic MDSC-mediated immune suppression (Saleem et al., 2012). Mast cells may also regulate MDSC via histamine release. Histamine regulates myeloid cell differentiation and the increased inflammation-associated carcinogenesis observed in histamine deficient mice associates with decreased myeloid cell differentiation and accumulation of immature $CD11b^+Gr1^+$ myeloid cells (Yang et al., 2011). Furthermore, addition of exogenous histamine drives the maturation of these cells and suppresses their ability to enhance tumor growth in vivo (Yang et al., 2011).

Mast cell interaction with local T_{reg} populations within the tumor microenvironment may be of particular importance. Studies in transplantation have suggested an important link between mast cells and T_{reg} in modulating allograft tolerance (Lu et al., 2006). However, mast cells may be able to overcome T_{reg}-induced immunosuppression. Mast cells and T_{reg} cells are able to cross-regulate each other's activity. T_{reg} cells can modulate mast cell activity to inhibit their degranulation in an OX40/OX40L cell contact-dependent manner and enhance their secretion of IL-6 via TGF-β1 (Ganeshan and Bryce, 2012; Gri et al., 2008). In contrast, histamine released from degranulating mast cells can inhibit T_{reg} suppressive function via H1 receptors (Forward et al., 2009). Mast cells can also skew T_{reg} differentiation to a pro-inflammatory T_H17 phenotype via both IL-6-dependent and independent mechanisms (Blatner et al., 2010; Piconese et al., 2009). While T_H17 cells can contribute to tumor promoting chronic inflammation, in some instances T_H17 cells are potent anti-tumor effector cells (reviewed in Zou and Restifo, 2010). Thus, mast cell activation provides a potential avenue for reducing T_{reg} function at mast cell rich tumor sites to enhance the development of effective anti-tumor immunity as an adjunct to tumor immunotherapy.

5.2. The sentinel role of mast cells in immune cell recruitment

Activated mast cells selectively recruit immune effector cells to tissue sites through a multi-step process that can involve increased adhesion interactions, altered vascular permeability and direct chemoattractant actions of mast cell mediators (reviewed in Marshall, 2004). Mast cells can enhance adhesion interactions of recruited cells via up-regulation of adhesion molecules on vascular endothelium (Torres et al., 2002; Zhang et al., 2011). This process has been demonstrated in several models of infection, with both TNF and IL-1β being critical. Several granule-associated mediators, including TNF, heparin and histamine can also increase vascular permeability (Oschatz et al., 2011; Dvorak, 2005; Brett et al., 1989). Similar mechanisms likely occur in response to mast cell activation at tumor sites. The more permeable immature blood vessels, often found at tumor sites, may further increase the mobility of cells in response to chemoattractant signals from mast cells.

Altered chemokine levels have been associated with disease progression and immune activation in experimental tumor models. For example, in a murine melanoma model CCL2 and CCL3 have been demonstrated to have important roles in host immunity and prevention of metastasis (Nakasone et al., 2012). Notably, CCL2 is also active in mast cell recruitment (Collington et al., 2010). CCL3 has also been shown to be critical for the development of immune responses following tumor cell apoptosis (Iida et al., 2008). We have observed that TLR2 activated murine mast cells secrete CCL3 and recruit NK cells and T cells in a CCL3-dependent manner in vitro (Oldford et al., 2010). Mast cell-derived CCL3, CCL5 and CXCL10 may all have roles in T cell recruitment to tumor sites. Other mediators released from mast cells can also induce effector cell recruitment which might be relevant in a tumor context. For example, the leukotriene LTB_4 released from activated mast cells induces $CD8^+$ effector T cell migration (Ott et al., 2003).

Studies of human mast cells have confirmed their importance as regulators of immune effector cell recruitment. Upon engagement with activated T cells, human mast cells induce the migration of neutrophils via CXCL8 (Salamon et al., 2005). CXCL8 is also a potent and selective inducer of NK cell recruitment, following viral activation of human mast cells (Burke et al., 2008). Virally activated human mast cells also recruit $CD56^+$ T cells, including invariant NKT and cytotoxic T cells, via CCR3 and CCR5 ligands (McAlpine et al., 2012) and are an abundant source of CCL4, CCL5 and CXCL10 (Brown et al., 2012). Mast cells at tumor sites are therefore likely to be important contributors to the chemokine milieu of the tumor microenvironment and the ensuing immune cell infiltrate in clinical settings.

5.3. Mast cell dendritic cell interactions

Several mast cell activators mobilize dendritic cells to draining lymph nodes and serve as effective adjuvants to drive antigen specific humoral and T cell-mediated responses (McLachlan et al., 2008) and thus demonstrate the potential of local mast cell activation for cancer therapy. Following bacterial peptidoglycan activation, mast cells enhance the migration to draining lymph nodes of Langerhans cells via TNF (Jawdat et al., 2006), plasmacytoid and myeloid dendritic cells via histamine receptor-dependent pathways and myeloid and $CD8^+$ dendritic cell subsets via IL-6 (Dawicki et al., 2010). In contrast, transplantation studies have suggested that mast cells can enhance tolerance by converting graft-associated dendritic cells into tolerogenic dendritic cells (de Vries et al., 2011). These dendritic cell subsets have important roles in tumor immune suppression by enhancing effector T cell anergy and apoptosis and enhancing T_{reg} activity (reviewed in Janikashvili et al., 2011). Mast cell induction of tolerance can be overcome by degranulation (de Vries et al., 2009). Therefore, local mast cell degranulation may be advantageous to subvert tumor-induced immune suppression and elicit effective anti-tumor immunity. However, IgE-mediated mast cell activation does not always overcome tolerance as it has been shown to be ineffective in altering T_{reg} responses in models of oral tolerance (Tunis et al., 2012). Given these data, it is difficult to predict the outcome of mast cell-dendritic cell interactions in a tumor setting. Mast cells can interact with dendritic cells and drive their maturation leading to enhancement of both T_H1 and T_H17 responses (Dudeck et al.,

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2011). Depending upon the stage of tumor development and location this could either aid in effective tumor immunity development or promote inflammatory changes that enhance local angiogenesis. Histamine released from mast cells is also likely to have major impact on dendritic cell responses in the tumor microenvironment. Studies in $H1R^{-/-}$ mice have demonstrated a requirement for H1 engagement on dendritic cells for their effective priming of IFNγ producing $CD8^+$ T cells in a model of atopic dermatitis (Vanbervliet et al., 2011). If mast cells are activated at tumor sites, similar mechanisms could come into play in regulating $CD8^+$ T cell responses.

Mast cell release of prostaglandins (PG) may also alter dendritic cell function. Mast cells are a primary source of intratumoral PGD_2, which can limit tumor growth via suppressing angiogenesis (Murata et al., 2011) but might also suppress anti-tumor T cell responses. PGD_2 can act on DP1 receptors on dendritic cells to promote their development of T_{reg} cells (Hammad et al., 2007). PGD_2 has also been shown to inhibit IL-12 secretion by dendritic cells leading to increased T_H2 polarization (Theiner et al., 2006). The overall impact of mast cells on dendritic cell function within the tumor microenvironment is likely to be influenced by the type of mast cell activating stimuli, the subsequent mediator release and the balance of expression of receptors for those mediators on tumor-associated dendritic cells. Since dendritic cells are critical modulators of anti-tumor adaptive immune responses, mast cell-induced dendritic cell recruitment and modulation of their function can profoundly impact the generation of effective anti-tumor immune responses.

5.4. Mast cell enhancement of NK cell activity

Activated mast cells can recruit NK cells to tumor sites (Oldford et al., 2010) and mast cells may also enhance NK cell activity against tumor cells. In co-culture experiments mast cells activated with TLR3, 4 or 9 activators enhance NK cell secretion of IFNγ in a cell contact-dependent manner (Vosskuhl et al., 2010). In experimental models of melanoma, NK cell-derived IFNγ is crucial for preventing metastasis (Takeda et al., 2011) and has important roles in anti-tumor immunity following innate immune receptor-targeted immunotherapy (Shime et al., 2013).

Degranulating mast cells at tumor sites can also augment NK cell function via histamine release. Histamine can indirectly modify NK cell activity by signaling through H2 receptors on monocytes and phagocytes to prevent phagocyte-derived ROS down-regulation of NKp46 and NKG2D activating receptors (Romero et al., 2006), block their cell contact-dependent immune suppression of NK cells and enhance both natural and antibody-mediated NK cell cytotoxicity (Hellstrand and Hermodsson, 1991; Hellstrand et al., 1994). Histamine has shown clinical success when combined with IL-2 in randomized phase III clinical trials of acute myeloid leukemia and metastatic melanoma (Brune et al., 2006; Agarwala et al., 2002). The enhanced efficacy of IL-2 immunotherapy in the presence of histamine has been attributed to increased NK cell-mediated killing of tumor cells (Brune et al., 1996; Hellstrand et al., 1997). Importantly, the ability of histamine to augment NK cell-mediated tumor cytotoxicity will be dependent on the histamine receptor status of the tumor cells as histamine can reduce tumor cell susceptibility to NK cell-mediated killing via downregulation of NKG2D ligands on some types of tumor cells (Nagai et al., 2012).

5.5. Mast cell modulation of T cell responses

Mast cells at tumor sites can have multiple impacts on T cell responses. Whereas mast cells can promote tumor growth by inhibiting IFNγ producing $CD8^+$ T cell responses (Wasiuk et al., 2012), activated mast cells may enhance anti-tumor immune responses indirectly through their effects on dendritic cells, as described in Section 5.3, and also directly by enhancing T cell activation. Activated mast cells can enhance T cell activation through cell contact-dependent mechanisms and via TNF release (Nakae et al., 2006). Mast cell-derived histamine can also influence the generation of effective T cell responses (reviewed in Kmiecik et al., 2012). Histamine released from mast cells can enhance T_H1-type responses via the H1 receptor (Forward et al., 2009). In contrast, signaling through H2 can inhibit both T_H1 and T_H2 responses (Noubade et al., 2007; Forward et al., 2009; Jutel et al., 2001). Murine studies have also highlighted an important role for H4 receptor in the generation of T_H2, T_{reg} and T_H17 responses (Cowden et al., 2013, 2010; del Rio et al., 2012).

Another mediator released by mast cells that may alter T cell responses is IL-6, a pleiotropic cytokine with important roles in the induction of effective anti-tumor T cell responses. Mast cells release abundant IL-6 following activation with both degranulating and non-degranulating stimuli. As described in Section 5.1, in the presence of large amounts of IL-6, activated mast cells may enhance anti-tumor immune responses by inhibiting T_{reg} cell immunosuppression (Piconese et al., 2009). In this study, T cell-derived IL-6 was implicated, however, activated mast cells are a particularly potent source of IL-6 (Kruger-Krasagakes et al., 1996; Gomi et al., 2000; Haidl et al., 2011). Elevated tumor IL-6 has been shown to enhance both $CD4^+$ and $CD8^+$ effector/T_{reg} ratios and induce significant tumor reduction in vivo (Hsieh et al., 2010). Strategies that enhance IL-6 production by mast cells at tumor sites might be particularly beneficial in conjunction with T cell-targeted immunotherapies. Indeed, the inclusion of IL-6 in culture media used to generate cytokine-induced killer cells from peripheral blood of hepatocellular carcinoma patients ex vivo, decreased the proportion of T_{reg} cells and enhanced the in vitro cytotoxicity of the resultant killer cells (Lin et al., 2012). However, since mast cell IL-6 can also serve as a growth factor for some tumors, the impact of mast cell IL-6 will certainly differ depending on mast cell types and tumor stage. The overall impact of mast cells on the T cell response to solid tumors is likely to be dependent on the relative numbers of mast cells, T_{reg} cells and effector T cells as well as the cytokine milieu within the tumor microenvironment, but these studies suggest that activated mast cells at tumor sites can reduce local T_{reg} numbers and potentiate anti-tumor effector T cell responses.

6. Methods to modify mast cell function in tumor immunotherapy

Mast cells represent ideal candidates for targeted tumor immunotherapy due to their abundance at the periphery of many solid tumors, their close proximity to blood vessels and ability to selectively secrete distinct profiles of mediators. The specific approach required to target mast cells in cancer therapy will depend on the type of cancer, the stage of progression, the tumor microenvironment and potential interactions with existing conventional therapies. As mast cells are generally considered protumorigenic several groups have suggested that inhibiting mast cell activity is a viable therapeutic approach for the treatment of solid tumors (Groot Kormelink et al., 2009; Maltby et al., 2009). However, given the limited success of several other anti-angiogenic therapies, this may not be an optimal approach. Mast cell activity can also be suppressed indirectly via targeting mast cell mediators using agents such as the anti-TNF monoclonal antibody infliximab or directly through the use of mast cell stabilizing agents. In experimental models, therapeutic interventions that decrease mast cell activity have shown some success. For example, treatment of dextran sodium sulphate-induced colitis with infliximab resulted in decreased TNF, decreased mast cell numbers and significantly reduced the development of colorectal tumors (Kim

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et al., 2010). Mast cell stabilization with sodium cromoglycate in a xenograft model of thyroid cancer significantly reduced tumor growth (Melillo et al., 2010). However, the mast cell specificity of sodium cromoglycate, particularly at high doses, has been questioned (Oka et al., 2012). Others have assessed the impact of mast cell depletion on tumor growth using imatinib mesylate, a tyrosine kinase inhibitor which inhibits signaling through c-Kit (Takeuchi et al., 2003). In a murine model of prostate carcinoma, imatinib mesylate administration significantly decreased the incidence of prototypical prostate carcinoma but increased the incidence of the more aggressive neuroendocrine phenotype prostate carcinomas (Pittoni et al., 2011). Mast cell stabilization was also detrimental in murine model of breast carcinoma where stabilization of mast cells with sodium cromoglycate or depletion with imatinib mesylate enhanced tumor hypoxia, intratumoral blood clotting and tumor growth (Samoszuk and Corwin, 2003a,b). Thus, widespread inhibition of mast cell function may not be advantageous for all tumor types.

Treatments that enhance local mast cell degranulation may induce a variety of anti-tumor immune mechanisms including the enhanced recruitment of effector cells, the direct impact of granule-associated and de novo synthesized mediators on tumor cells and secondary impacts on immune regulation. A major mediator released from degranulating mast cells is histamine. The role of histamine in the tumor microenvironment is complex as histamine can exert diverse biological and immunological effects through the engagement of one of 4 different histamine receptors (H1–H4). Several experimental models have demonstrated that histamine delays tumor growth and enhances survival. In a xenograft model of melanoma, histamine and H4 agonists exerted anti-tumor effects (Massari et al., 2013), histamine administration decreased the development of chemically induced intestinal carcinomas (Tatsuta et al., 1986) and in a murine fibrosarcoma model histamine-mediated anti-tumor effects through H1 which were enhanced in the presence of H2 blockade (Burtin et al., 1982). In contrast, in murine colorectal carcinoma (Adams et al., 1994), murine melanoma (Tomita et al., 2005) and human gastric carcinoma xenograft models (Watson et al., 1993) histamine enhances tumor growth in an H2-dependent manner. As histamine receptors can be expressed on both tumor cells and immune cells, histamine can exert beneficial or detrimental effects on tumor growth and tumor immunity depending on the cell types within the tumor microenvironment and their histamine receptor expression profile.

Anti-tumor IgE may play an important role in anti-tumor immunity as IgE isolated from the serum of pancreatic cancer patients can enhance pancreatic cell ADCC by peripheral blood mononuclear cells (Fu et al., 2008). The anti-tumor potential of IgE-mediated immune cell activation is further supported by experimental models. Tumor specific IgE antibodies can inhibit ovarian cancer growth in a xenograft model when co-administered with human peripheral blood mononuclear cells (Gould et al., 1999; Karagiannis et al., 2003). While these studies demonstrated the ability of IgE-mediated ADCC to inhibit tumor growth, ADCC was examined using peripheral blood mononuclear cells and they did not specifically evaluate the impact of mast cell activation. In humans, multiple cell types can contribute to IgE-mediated ADCC, including mast cells, eosinophils, basophils, and monocytes (reviewed in Singer and Jensen-Jarolim, 2013). The contribution of mast cells to IgE-mediated ADCC at tumor sites will be dependent on their numbers relative to these other immune effectors.

Several IgG monoclonal antibodies are routinely used in the treatment of hematological malignancies and some solid cancers. Others have proposed that anti-tumor IgE antibodies hold promise in the treatment of solid tumors (Singer and Jensen-Jarolim, 2013). Humanized monoclonal anti-Her-2/neu IgE induces antigen specific mast cell degranulation following incubation with Her-2/neu overexpressing cancer cells in vitro (Karagiannis et al., 2009). Humanized anti-CD20 IgE antibodies enhance cytokine secretion, degranulation and mast cell cytotoxicity against lymphoma cell lines in vitro (Teo et al., 2012). In a murine breast cancer model, anti-tumor IgE associates with mast cell degranulation and induces tumor growth inhibition, which is enhanced when co-administered with mast cell attracting chemokines. Furthermore, anti-tumor IgE induces effective anti-tumor memory immune responses as demonstrated by tumor rechallenge experiments (Teo et al., 2012). Mast cells are likely to be critical for the efficacy of anti-tumor IgE. Their location combined with their long lifespan and high expression of FcεRI suggests mast cells can improve the retention of anti-tumor IgE at tumor sites following systemic administration. However, anti-tumor IgE therapies are limited to situations where there is an appropriate tumor antigen to target with antibody.

An alternate strategy that may hold promise in the effective induction of anti-tumor immunity and avoid potential systemic side effects of degranulating mast cell activation is the use of therapeutic strategies that selectively activate the sentinel role of mast cells. TLR-targeted tumor immunotherapy is an active area of clinical investigation (Vacchelli et al., 2013) and has great potential for the treatment of solid tumors. TLR agonists can enhance dendritic cell-mediated activation of T cells and block the immune suppressive and tumor promoting functions of MDSC and tumor-associated macrophages and drive their maturation into immune promoting anti-tumor effector cells (Shime et al., 2013; Zoglmeier et al., 2011; Shirota et al., 2012; Shime et al., 2012; Akazawa et al., 2004). We and others have demonstrated critical roles for mast cells in modulating TLR immunotherapy. Both human and murine mast cells express TLRs (McCurdy et al., 2003; Matsushima et al., 2004) and can be directly targeted in the tumor microenvironment. We have demonstrated a critical role for mast cell-derived IL-6 in tumor growth inhibition following TLR2-targeted immunotherapy in a model of melanoma. The TLR2 activator Pam_3CSK_4 activates mast cells in a degranulation independent manner and TLR2 activated mast cells recruit NK cells and T cells to tumor sites (Oldford et al., 2010). The sentinel role of mast cells was also demonstrated to be critical for melanoma tumor growth inhibition following TLR7-targeted immunotherapy with imiquimod. TLR7 activated mast cells, via CCL2, recruit plasmacytoid dendritic cells to tumor sites and are critical for the regulation of tumor immunity following TLR7-targeted immunotherapy of murine melanoma (Drobits et al., 2012). While these data focused on melanoma and may therefore highlight a particularly important role for mast cells at skin sites, where they are abundant, TLR2 activated mast cells can also decrease the growth of lung carcinoma in vivo (Oldford et al., 2010).

These data suggest that a therapeutic approach that utilizes innate immune activators to target mast cells in the tumor microenvironment and harnesses their immune potential as sentinel cells may hold promise. The success of TLR-targeted immunotherapy requires balancing the potential pro-tumorigenic effects of direct interactions with TLR expressing tumor cells and immune suppressive cell subtypes with the generation of effective anti-tumor responses. Strategies to achieve this include the use of TLR agonists in combination with other tumor antigens, chemotherapy or radiation therapy (reviewed in Kaczanowska et al., 2013). Conventional chemotherapy and radiotherapy can induce immunogenic tumor cell death via the release of tumor-associated antigens and danger signals. This coupled with immunoadjuvants such as TLRs, other innate immune receptor activators or cytokines can augment anti-tumor immunity (reviewed in Ma et al., 2011). In contrast to other immune cells, mast cells are relatively radioresistant (Soule et al., 2007). Mast cells have a slow rate of cell division, which will likely also make them more resistant to several common classes of chemotherapeutic drugs than rapidly dividing immune cells. Mast

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cells are also long-lived and relatively immobile, once mature in the tissue. These attributes suggest that local mast cell activation, leading to selective mediator release and local immune enhancement, might be achievable with minimal systemic side effects.

7. Concluding remarks

While most studied in the context of cancer for their pro-angiogenic and tumor promoting roles, mast cells can also be important regulators of tissue homeostasis and sentinel cells capable of enhancing immune responses to cancer. Several experimental tumor model studies have suggested an important role for mast cells in the tumor microenvironment (Wedemeyer and Galli, 2005; Gounaris et al., 2007; Coussens et al., 1999; Soucek et al., 2007). The majority of studies aimed at investigating the importance of mast cells have utilized mast cell deficient $Kit^{W/W-v}$ or $Kit^{W-sh/W-sh}$ mice. However, the *Kit* mutation in these mice is often associated with other immunological abnormalities (Grimbaldeston et al., 2005; Nigrovic et al., 2008; Michel et al., 2013). These phenotypic defects may affect the interpretation of mast cell dependence in these studies, but can be partially overcome by the use of mast cell deficient mice in which mast cells have been selectively reconstituted in relevant tissues. Additional useful in vivo models, that can be used in fully immunocompetent mice include the use Matrigel basement membrane matrix containing tumor cells with or without the addition of primary mast cells (Oldford et al., 2010). In a further effort to overcome the defects associated with *Kit* mutations, newer mast cell deficient models utilize Cre-lox technology to specifically delete mast cells (Dudeck et al., 2011; Feyerabend et al., 2011). The tumor promoting role of mast cells has been demonstrated in a murine model of cutaneous lymphoma using the $Mcpt5\text{-}Cre^{+}/iDTR^{+}$ mast cell deficient model, which showed delayed tumor growth kinetics compared to wild type controls that was similar to that observed in $Kit^{W-sh/W-sh}$ mice (Rabenhorst et al., 2012). In contrast, the growth of chemically induced skin cancer was independent of mast cells in studies using Cre-Master mice in which mast cell deficiency arises due to insertion of the Cre recombinase into the carboxypeptidase A3 locus (Antsiferova et al., 2013). As we continue investigating the contributions of mast cells to the tumor microenvironment, it will be beneficial to utilize multiple models of mast cell deficiency in conjunction with other relevant and well established experimental approaches to both confirm and identify roles for mast cells and mast cell-derived mediators in the tumor microenvironment.

Comprehensive studies of the impacts of mast cell activation with degranulating and non-degranulating stimuli in a variety of tumor settings are essential for our understanding of the role of mast cells in the generation of anti-tumor immunity. Mast cells can produce a vast array of pre-formed and de-novo synthesized mediators following activation. Activated mast cells are able to initiate multifaceted responses through their interactions with tumor cells, stromal cells and immune cells. The mediator milieu within the solid tumor microenvironment often does not activate mast cells via pathways that lead to a full complement of mediator release. Thus, depending of the microenvironmental or cancer therapy-derived signals mast cells can either inhibit or enhance anti-tumor immunity, through distinct pathways. The increased interest in the use of innate immune activators as well as anti-tumor IgE based cancer treatments highlights novel therapeutic approaches in which mast cells can be targeted to initiate anti-tumor immune events. Mast cells are also prime candidates for combined treatment modalities as they have a long lifespan and low rate of cell division making them resistant to existing cancer therapeutics that target rapidly dividing cells. Therapeutic interventions aimed at harnessing the multifaceted sentinel activities of mast cells hold promise as effective cancer immunotherapies to initiate and enhance effective anti-tumor immunity.

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