Molecular Immunology 63 (2015) 113–124

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

Mast cells as targets for immunotherapy of solid tumors☆

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ARTICLE INFO

Article history:
Received 12 December 2013
Received in revised form 26 February 2014
Accepted 27 February 2014
Available online 31 March 2014

Keywords:
Mast cells
Tumor immunology
Immunotherapy
Cell recruitment
Chemokines
Histamine

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.

☆ This article belongs to Special Issue on Mast Cells and Basophils in Innate and Acquired Immunity.

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http://dx.doi.org/10.1016/j.molimm.2014.02.020

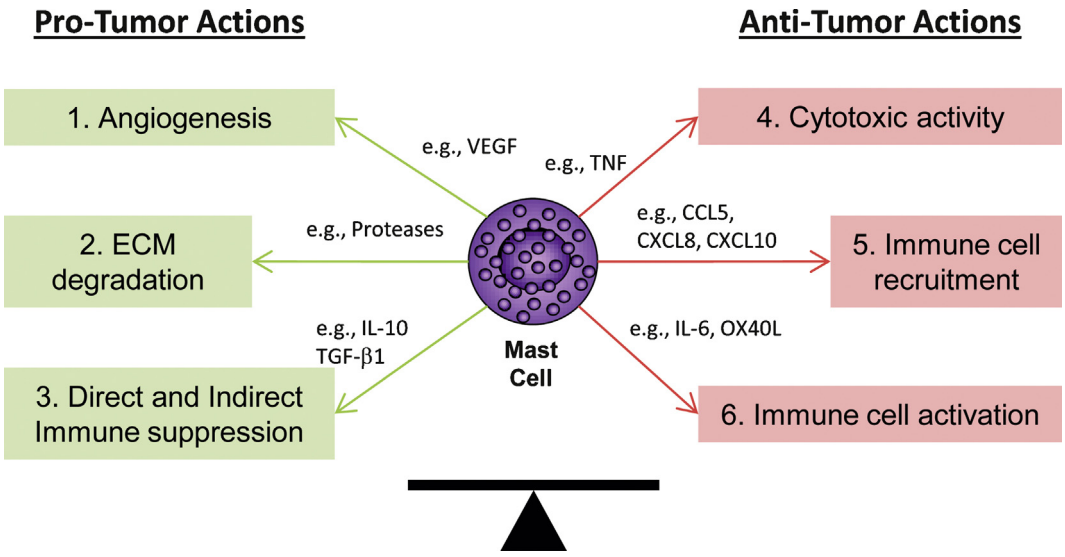

Fig. 1. Mast cell modulation of the solid tumor microenvironment. Activated mast cells can potentiate the deregulated tissue homeostasis of the tumor microenvironment and favor tumor growth and spread through (1) the release of pro-angiogenic factors which enhance endothelial cell migration, proliferation 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