

Review Article

The regulatory role and mechanism of mast cells in tumor microenvironment

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Abstract: Mast cells (MCs) have emerged as pivotal contributors to both the defensive immune response and immunomodulation. They also exhibit regulatory functions in modulating pathological processes across various allergic diseases. The impact of MC presence within tumor tissues has garnered considerable attention, yielding conflicting findings. While some studies propose that MCs within tumor tissues promote tumor initiation and progression, others advocate an opposing perspective. Notably, evidence emphasizes the dual role of MCs in cancer, both as promoters and suppressors, is crucial for optimizing cancer treatment strategies. These conflicting viewpoints have generated substantial controversy, underscoring the need for a comprehensive understanding of MC's role in tumor immune responses.

Keywords: Mast cells, tumor microenvironment, immunomodulation

Introduction

Mast cells (MCs) are a kind of immune cell derived from bone marrow precursor cells, with maturation occurring in peripheral tissues [1]. Analogous to basophils, MCs function as the principal effector cells involved in IgE-mediated inflammation. Since their discovery by the eminent German scientist Paul Ehrlich in 1878, a growing body of scholarly research has focused on MC's immunomodulatory functions within both innate and adaptive immune responses. Investigations have also delved into their impact on the progression and prognosis of immune-related disorders [2]. As a constituent of the sentinel immune cell population, MCs have received more and more attention for their immunomodulatory and effector functions in the tumor microenvironment (TME) [3]. Existing evidence highlights the prevalence of MCs across a spectrum of tumors, where they can either promote or inhibit tumorigenesis via distinct regulatory mechanisms specific to each tumor type [2]. Nevertheless, the precise functions and regulatory mechanisms of MCs in various tumor contexts remain subjects of on-

going debate. This research presents a focused review scrutinizing the impact of MCs on both pro-tumorigenic and anti-tumorigenic activities, along with their contributions to the remodeling of the TME through infiltrative interactions.

Biological characteristics of MC

Development, differentiation, and subtypes of MC

Human mast cells (MCs) represent a heterogeneous population of immune cells that originate from the CD34⁺/CD117⁺ hematopoietic stem cells, entering the bloodstream or serous lumen as MC precursors. Subsequent differentiation and maturation ensue at the colonization site [4, 5]. MC development hinges on Kit (CD117) activation, facilitated by Kit dimerization and autophosphorylation induced by stem cell factor (SCF). IL-3, IL-4, IL-9, nerve growth factor (NGF), and transforming growth factor (TGF)- β also play pivotal roles in the maturation and differentiation of MCs [6-8].

At present, mature human MCs can be divided into at least two distinct categories according to

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the type and content of their protease enzymes. MCs that exclusively contain trypsin are referred to as MC_T, whereas those containing trypsin, chymase, carboxypeptidase A, and cathepsin G are termed MC_{TC}. These MC subpopulations exhibit variations in tissue localization, with MC_{TC} predominating in normal skin and the submucosa of the small intestine, while MC_T is the prevailing subtype in the mucosa of the small intestine and bronchi/bronchioles. Functionally, these different MC subtypes also exhibit contrasting responses, with MC_{TC} being responsive to non-immune stimuli such as Compound 48/80 and Substance P, while MC_T does not exhibit this responsiveness [9].

Research has revealed the existence of distinct subtypes among MCs, with their maturation primarily influenced by the tissue microenvironment in which they are situated. Nevertheless, it is precisely due to the heterogeneity and adaptability of MCs that they may exert a dual role, either promoting or inhibiting tumor development.

Biological activity and activation of MC

MCs can play a crucial immune regulatory role by releasing bioactive molecules upon activation. These bioactive molecules can be categorized into three main types: firstly, pre-stored mediators within MC cytoplasmic granules, enabling rapid release within seconds to minutes; secondly, MCs engage in de novo synthesis of lipids, prostaglandins and leukotrienes occurring within a few minutes; and thirdly, various cytokines and chemokines produced through transcription and translation processes, which typically take several hours [7].

Specific stimuli, such as IgE or specific antigens, trigger the activation of MCs, resulting in the secretion of a diverse array of bioactive substances that exert downstream effects [10]. The classical activation pathway of MCs involves downstream signaling mediated by the high-affinity receptor (FcεRI) for IgE on the MC surface. Additionally, MC membranes harbor various receptors activated by their ligands, including cytokine and chemokine receptors, Toll-like receptors (TLRs), and vascular endothelial growth factor receptors [11, 12].

Moreover, studies have showed that MCs can selectively release particulate matter through a

process known as segmental degranulation. This unique process involves vesicle transport from the particle to the cell membrane and is commonly observed at sites of certain chronic diseases [13]. The activation mechanisms of MCs coupled with the diversity of active molecules they release, collectively contribute to their intricate immune regulatory roles within the TME.

Remodeling effect of infiltrating MC on tumor microenvironment

Mast cells (MCs) secrete mediators, including: (1) amines such as histamine and 5-hydroxytryptamine; (2) serine proteases, including tryptase, chymase, cathepsin G, and carboxypeptidase A3; (3) cytokines such as TNF-α, SCF, and prostaglandins; and (4) bioactive substances like proteoglycan (heparin). These mediators play a pivotal role in regulating various physiological functions. Within the TME, MCs have the capacity to remodel the TME by directly influencing the extracellular matrix, collaborating with other immune cells, and controlling the formation of tumor-derived micro vesicles (TMV). Consequently, MCs actively participate in mediating the reshaping effects of the TME [14, 15] (**Figure 1; Table 1**).

Interaction between MCs and immune cells

MCs and dendritic cells (DC): Dendritic cells (DCs) function as professional antigen-presenting cell and play an important role in mediating immune response in the TME. MCs and products act as “adjuvants”, influencing DC migration, maturation, and function to mediate specific humoral or cellular immune responses and exert an anti-tumor effect [16]. Studies have shown that MC enhances DC functionality by producing immunomodulatory factors, promoting the priming of CD8⁺ T cells [17].

Furthermore, MC-secreted granules, when engulfed by DCs during skin inflammation, enhance DC migration and activation efficiency, potentially strengthening the antitumor immune response [18]. Synapse-like structures formed between MCs and DCs facilitate antigen transfer, aiding in T cell activation [19], offering a novel perspective for eliciting immune responses within the TME.

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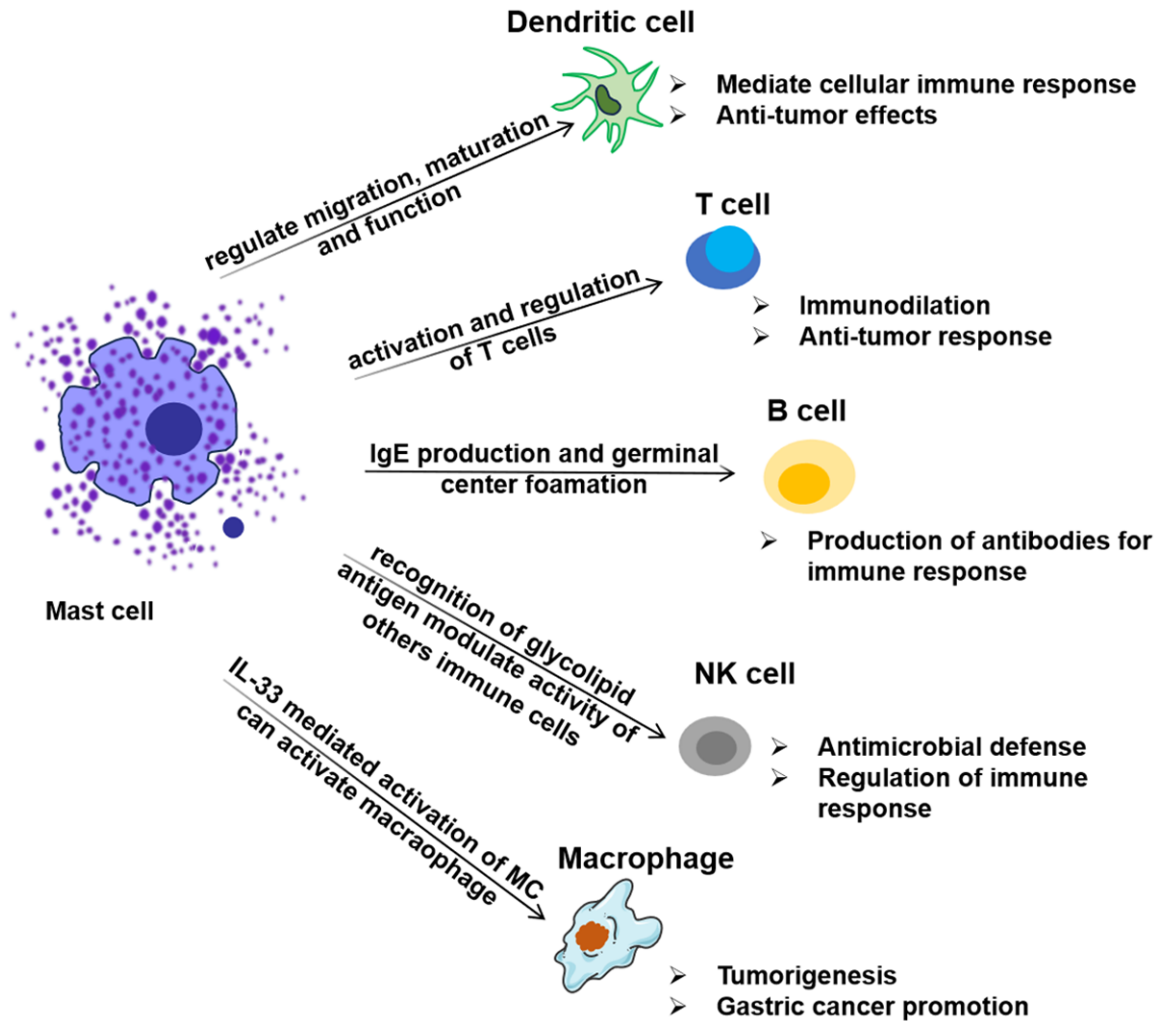


Figure 1. Interaction between MCs and immune cells. Mast cells regulate the metastasis and maturation of DC, thus playing an anti-tumor role and mediating cellular immune response; Recruit and activate T cells to play the role of immune regulation and anti-tumor; Recruit and induce B cells to secrete IgE, promote germinal center formation, and stimulate B cells to secrete antibodies; Recognize antigens, activate other immune cells, promote the antibacterial action of NK cells and regulate their immune response; IL-33 mediated activation of MC can activate macrophage, involve in tumorigenesis and progression.

Furthermore, MCs may play roles in other immune-related domains, such as mediating allograft tolerance [20] and potentially serving pivotal roles in anticancer immunity [21]. The intricate interplay between MCs and DCs significantly contributes to our understanding of tumor immune responses and development of novel immunotherapeutic strategies [15, 16, 22-25]. Consequently, future research should prioritize unraveling the detailed mechanisms underlying these interactions to maximize their potential in tumor immunotherapy.

Mast cells and T cells: MCs are gaining recognition for their pivotal role in the TME, where they intri-

cately shape T cell responses. Recent studies contribute to our understanding of the multifaceted regulatory functions of MCs in the TME. Stassen et al. highlight the presence of MCs within cellular networks in the TME, emphasizing their intricate interactions with various immune cells. These interactions form complex regulatory networks that may influence T cell activity [14]. Moreover, Kambayashi et al. underscore the significance of MCs expressing MHC class II molecules, suggesting their potential antigen-presenting capabilities and involvement in T cell activation [26]. Furthermore, MCs exert their influence through the expression of co-stimulatory molecules and the release of

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Table 1. Interaction between MCs and immune cells

| Mediators | Effects | References |
|---|---|--------------|
| Mast Cells and Immune Cells | | |
| <ul style="list-style-type: none"> • MCs and DC | MC and its derivatives serve as adjuvants, overseeing the regulation of dendritic cell (DC) migration, maturation, and function. This orchestration enables the facilitation of specific humoral or cellular immune responses, ultimately resulting in an anti-tumor effect. | [15-25] |
| <ul style="list-style-type: none"> • MCs and T Cells | MCs and their complex interactions within cellular networks significantly impact T cell activity. | [14, 26, 27] |
| <ul style="list-style-type: none"> • MCs and B Cells | The presence of CD40 on B cells is pivotal for IgE class transition and germinal center formation. MCs, both in lines and specific tissues, express CD154, allowing them to interact with B cells. | [28-30] |
| <ul style="list-style-type: none"> • MCs and NK Cells | MCs play a crucial role in regulating natural killer (NK) cells through chemotaxis, enhancing the anti-tumor activity of NK cells. In cell co-culture, MCs, activated by Toll-like receptor (TLR), induce direct cell-to-cell contact, promoting the secretion of γ interferon by NK cells and facilitating an anti-tumor immune response. | [31-34] |
| <ul style="list-style-type: none"> • MCs and Macrophages | The activation of MCs demonstrates a pronounced association with both the recruitment and polarization of macrophages within the tumor milieu. | [35-37] |
| Interaction between MC and TMV | MCs release tryptase, stimulating capillary growth and reshaping vascular structures while creating space for tumor blood vessels. Contrary to previous views, histamine has dual roles in tumor immunity-both regulatory and pro-angiogenic. Other MC-derived substances, including heparin-like molecules, IL-8, and VEGF, actively promote tumor angiogenesis. | [38] |
| Microenvironmental mechanical forces regulate the interaction between MCs and ECM | ECMs pivotal role in the tumor microenvironment is evident, with MCs contributing to early tumor formation through ECM degradation and later stages by facilitating invasion and metastasis. | [9-40] |

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cytokines. According to Nakae et al. they shed light on the crucial role of MCs in T cell activation, particularly through the expression of tumor necrosis factor (TNF) and other co-stimulatory molecules, potentially contributing to the initiation and proliferation of T cells [27]. Additionally, the secretion of cytokines by MCs may modulate T cell activation, polarization, and migration [27]. These findings collectively illuminate the intricate and multifaceted role of MCs in the regulation of T cell responses within the TME, underscoring their potential impact on immunomodulation and tumor immunotherapy. Further research is warranted to unravel the precise mechanisms governing MC-T cell interactions, offering promising avenues for innovative immunotherapeutic strategies [14, 26, 27].

MCs and B cells: MCs also have the capability to engage in direct interactions with B cells. The expression of CD40 on the surface of B cells plays a crucial role in facilitating the class transition to IgE and the formation of germinal centers [28]. Both MC lines and MCs in specific tissue contexts express CD154, enabling these MCs to interact with B cells. In the presence of IL-4 or adenosine, such interactions with MCs can induce IgE production [29]. Additionally, MCs can influence the maturation and development of B cells through the secretion of various cytokines including IL-4, IL-5, IL-6, IL-13, and others [30].

MCs and NK cells: The interaction between tissue-resident MCs and recruited immune cells plays a pivotal role in facilitating tissue immune surveillance. However, the specific cells, mechanisms, and receptors involved in this cross-talk remain poorly understood. Invariant natural killer T (iNKT) cells, a subset of CD1-restricted innate lymphocytes known for recognizing glycolipid antigens, hold significant importance in immunity. Notably, it has been observed that peritoneal MCs in primary mice express surface CD1d, and following the administration of α -lactoceramide, in vivo up-regulation of CD1d occurs. In contrast, in bone marrow-derived MCs, CD1d was found to be intracellularly stored and subsequently re-localized to the cell surface during IgE-mediated degranulation. This re-localization of CD1d was shown to induce iNKT cell proliferation, resulting in the release of IFN- γ , IL-13, and IL-4 in a

CD1d-restricted manner. Additionally, several co-stimulatory molecules, including CD48, CD-137L, CD252, CD274, and CD275, were found to influence MC-induced IFN- γ release and iNKT cell proliferation [31].

In the context of the TME, NK cells, an integral component, are subject to chemotactic regulation by MCs, which can augment the anti-tumor activity of NK cells. In cell co-culture systems, MCs, when stimulated by TLR activation, promote the secretion of γ interferon by NK cells through direct cell-to-cell contact, thereby facilitating an anti-tumor immune response [32, 33]. Conversely, it has been proposed that histamine, secreted by MCs within the TME, which may down-regulate the expression of NKG2D ligands on tumor cells, thereby influencing the sensitivity of NK cells to tumor [34].

MCs and macrophage: The investigation into the dynamic interplay between MCs and macrophages within the context of gastric cancer has constituted a significant area of scientific inquiry. Empirical evidence derived from studies has elucidated that the IL-33-mediated activation of MCs plays a pivotal role in fostering gastric cancer through the orchestration of macrophage mobilization. This intricate process is initiated by the activation of MCs through IL-33, an alarmin synthesized by the tumor epithelium. Subsequently, activated MCs contribute to the recruitment of macrophages within the TME, thereby substantiating their involvement in tumorigenesis [35]. Pertinently, interventions involving the genetic ablation or therapeutic inactivation of MCs have been observed to exert a suppressive effect on the accumulation of tumor-associated macrophages, resulting in attenuated tumor cell proliferation, diminished angiogenesis, and reduced overall tumor burden [36]. This compelling evidence indicates that the IL-33-mediated signaling cascade, centered around MCs and macrophages, represents a viable therapeutic target for the treatment of gastric cancer, substantiating the potential clinical utility of targeting this intricate IL-33/mast cell/macrophage axis [37].

Interaction between MC and TMV

Infiltrated MCs within cancer tissues and the tumor stroma exhibit potent angiogenic effects upon activation. MCs secrete tryptase, a serine proteolytic enzyme, which exerts multifaceted

influences. Tryptase stimulates the proliferation of capillary endothelial cells and facilitates the reformation of vascular structures, and degrades the connective tissue matrix, creating an adequate space for the development of tumor blood vessels. While histamine was previously considered to be inhibitory to tumors, recent findings reveal its bidirectional regulatory impact on tumor immunity, including pro-angiogenic properties promoting the formation of tumor blood vessels. Additionally, other MC-derived bioactive substances, such as heparin-like molecules, angiogenic factors (e.g., IL-8), and growth factors (e.g., VEGF), actively promote tumor angiogenesis. Observations in the MC-deficient mice substantiate the active role of MCs in tumor angiogenesis [38].

Microenvironmental mechanical forces regulate the interaction between MCs and ECM

Paget's seminal work introduced the "seed and soil" hypothesis, which posits that microenvironmental factors and mechanical forces collaborate in orchestrating the site-specific dissemination of tumor cells [39]. From a physiological perspective, MCs participate in processes such as tissue remodeling, wound healing, and angiogenesis. However, under pathological conditions, MCs can release various mediators that remodel the TME and alter its mechanical properties, consequently influencing tumor metastasis.

The extracellular matrix serves as a crucial component of the TME, exercising a significant influence over the metastatic potential, adhesion, and functionality of both tumor cells and adjacent cells. In the initial stages of tumor formation, MCs contribute to promoting angiogenesis, tissue remodeling, and creating a conducive environment for tumor growth through the secretion of matrix metalloproteinases, specifically matrix metalloproteinase 9 (MMP-9), resulting in the degradation of the extracellular matrix [40]. Conversely, during specific phases of tumor growth, MCs participate in the invasion and metastasis of tumor cells. This process involves the secretion of proteases, such as tryptase, leading to the degradation of the extracellular matrix and expression protease-activated receptor 2 (PAR-2) on invasive tumor cells, thereby facilitating their invasion and metastasis.

Effect of MC on tumor progression

Tumor-associated mast cells (TAMCs) have been reported in a variety of solid tumors and hematologic tumors [41]. A large number of studies have attempted to clarify the role of TAMCs in tumor growth, and it has been found that in most tumors, TAMCs shows its function-promoting or inhibiting the occurrence and development of tumors [42-44]; In a few cases, they may not be functioning and are simply "inert bystanders" [45]. This seemingly contradictory result illustrates the complex role of MCs and their mediators in different types of tumors. Therefore, we analyzed the regulatory role of MCs in different major tumors (**Table 2**).

Gastric tumor

Research on MCs in gastric cancer reveals their multifaceted roles. Lv et al. demonstrates that MCs degranulation, induced by tumor-derived adrenomedullin, is closely associated with gastric cancer progression, potentially serving as a pivotal mechanism driving gastric cancer development [46]. They identify MCs as immune suppressors in gastric cancer, activating TNF- α and PD-L1 pathways, inhibiting immune cell function and promoting tumor progression [36]. Guidolin et al.'s research highlights the spatial distribution of MCs in the gastric cancer microenvironment, aggregating around vessels and glands, impacting tumor vascularization and the microenvironment [47]. Gunjigake et al.'s study suggests that IL-17A derived from MCs contributes to fibrosis in gastric cancer, particularly in cases of peritoneal dissemination [48]. Lin et al.'s indicates that tryptase expression may serve as a prognostic marker in gastric cancer patients [49]. A series of studies by Ammendola et al. reveals a close correlation between MC density and microvascular density, suggesting a potentially pivotal role for MCs in tumor angiogenesis [50-52]. These findings collectively unveil the multifaceted roles of MCs in gastric cancer pathophysiology, offering insights for a deeper understanding of the mechanisms underlying development and related therapeutic strategies.

Colorectal cancer

Recent research has drawn attention to the role of MCs in colorectal cancer, revealing potential significance in both development and

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Table 2. MC mediators in different types of tumor

| Types of Cancer | MCs Role | References |
|--------------------------|--|-------------|
| Gastric Cancer | <ul style="list-style-type: none"> ● MCs as immune suppressors in gastric cancer, activating TNF-α and PD-L1 pathways, inhibiting immune cell function, and promoting tumor progression. ● MC degranulation, induced by tumor-derived adrenomedullin, to gastric cancer progression. | [36, 46-52] |
| Colorectal Cancer | <ul style="list-style-type: none"> ● MCs emerge as key players in colorectal cancer development and treatment, exerting influence through angiogenesis, lymph angiogenesis, and dynamic interactions with immune cells such as T cells, macrophages, and MDSC. | [53-60] |
| Breast Cancer | <ul style="list-style-type: none"> ● MCs play pivotal roles, influencing tumor immune regulation, angiogenesis, and metastatic progression. ● MC interactions with the gut microbiome, their translational significance, and their impact on lymphatic vessels and breast cancer cell apoptosis. | [61-67] |
| Lung Cancer | <ul style="list-style-type: none"> ● Lung cancer-derived exosomes activate MCs, impacting coagulation and cytokine profiles. ● T cell and MC densities in tumor regions are linked to recurrence in early-stage LUAD. ● Elevated MC abundance favorably associated with prognosis in lung adenocarcinoma. | [68-75] |
| Hepatocellular Carcinoma | <ul style="list-style-type: none"> ● Histamine and MC granules' impact on HCC cell growth, offering initial evidence for MC involvement in the hepatic tumor microenvironment. ● Peritumoral MCs and T-regulatory cells exhibit a correlation that has implications for the prognosis of hepatocellular carcinoma (HCC) patients. | [76-78] |
| Pancreatic Cancer | <ul style="list-style-type: none"> ● In vitro studies highlight the dynamic interplay between mast cells and pancreatic cancer cells, actively promoting tumor growth and invasion. ● Mast cell conditioned media, rich in bioactive molecules, induce migration, proliferation, and invasion of pancreatic cancer cells, primarily through matrix metalloproteinase activity. | [79-81] |
| Prostate Cancer | <ul style="list-style-type: none"> ● MC density and distribution in prostate cancer tissues are linked to diverse prognostic implications, with high mast cell numbers inversely associated with cancer recurrence in certain studies. | [82, 83] |
| Leukemia | <ul style="list-style-type: none"> ● Detected pronounced hyperplasia of MCs and eosinophils in NSG-SGM3 mouse models implanted with CD34⁺ hematopoietic stem cells or leukemia xenografts. ● Association between MCs and hairy cell leukemia (HCL) with concurrent marrow reactive plasmacytosis. | [84-86] |

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treatment. MCs impact tumor progression through angiogenesis and lymph angiogenesis within the TME, crucial for growth and metastasis [53, 54]. They also interact closely with immune cells, potentially regulating immune evasion within tumors and influencing patients' immune responses and treatment outcomes [55, 56].

However, the precise role of MCs in colorectal cancer remains a subject of controversy. Some studies suggest that MCs may promote tumor development [57, 58], while others propose that they might have anti-tumor properties [59]. This controversy stems from the multi-functionality and complexity of MCs, exhibiting differential behavior in various stages and types of colorectal cancer [60].

In summary, the role of MCs in colorectal cancer is complex and multifaceted, requiring further in-depth research to elucidate their exact mechanisms in tumor development and treatment. These studies hold potential for developing novel therapeutic strategies and drugs targeting MCs, aiming to improve the prognosis and treatment outcomes for colorectal cancer patients.

Breast cancer

In the realm of breast cancer research, MCs have emerged as a focal point of investigation. Extensive studies have illuminated the multifaceted roles played by MCs within the breast cancer microenvironment. Firstly, Aponte-López et al. underscored the pivotal significance of MCs in orchestrating tumor immune regulation [61]. Subsequently, Cimpean et al. elucidated the pivotal involvement of MCs in breast cancer angiogenesis [62]. The study by Feng et al. delved into the intricate reciprocal interactions between MCs and the gut microbiome, propelling the metastatic progression of hormone receptor-positive breast tumors [63].

Additionally, Marech et al. meticulously explored the potential translational significance of MC tryptase levels in early-stage breast cancer patients [64]. Meanwhile, Raica et al. meticulously investigated the intricate interplay between MCs and lymphatic vessels across distinct molecular subtypes of breast cancer [65]. Complementary research has unveiled the MCs' capacity to selectively target breast cancer cells, thereby inducing apoptosis [66], their

association with breast cancer tumor grading and hormonal receptor status, and their prognostic utility in predicting breast cancer lung metastasis [67].

In summation, these empirical findings impart pivotal insights, engendering a deeper comprehension of breast cancer biology, the development of highly personalized therapeutic modalities, and the refinement of patient prognosis assessment.

Lung cancer

Lung cancer, particularly lung adenocarcinoma (LUAD), is a leading cause of cancer-related deaths. Several studies highlight the crucial role of MCs in lung cancer progression. Ben et al. explored the activation of MCs mediated by lung cancer-derived exosomes, suggesting their potential contribution to cancer-associated coagulation disorders by altering cytokine profiles released by MCs [68]. Bao et al. proposed MC-based molecular subtypes and signatures associated with clinical outcomes in early-stage lung adenocarcinoma [69]. Leveque et al. identified MC heterogeneity in non-small cell lung cancer through phenotypic and histological distribution analysis [70]. Shikotra et al. examined MC phenotype, TNF- α expression, and degranulation status in non-small cell lung cancer [71].

Additionally, Xiao et al. suggested that tryptase released from MCs promotes tumor cell metastasis via exosomes [72]. Recent research has also indicated that the densities of T cells and MCs in tumor regions are associated with recurrence in early-stage lung adenocarcinoma [73]. An elevated abundance of MCs correlates to the enrichment of CCR2+ cytotoxic T cells and a favorable prognosis in lung adenocarcinoma [74].

In summary, these studies underscore the multifaceted roles of MCs in lung cancer, providing substantial evidence for further exploration of their functions in tumor immunity and the microenvironment [75]. These findings hold the potential to offer new insights and strategies for the treatment and prognosis assessment of lung cancer.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) poses a significant challenge in terms of public health and

medical treatment. In recent years, there has been growing research interest in the role of immune cells in HCC. While the focus of this article predominantly centers on hepatic cancer, prior studies have provided some clues regarding the potential involvement of MCs in HCC. The review article by Francis and Meininger underscores the significance of MCs in immune responses and inflammation, offering valuable insights into the role of immune cells in HCC [76]. Furthermore, the study conducted by Lampiasi et al. reveals that histamine and spontaneously released MC granules may impact the growth of HCC cells, presenting initial evidence for the involvement of MCs within the hepatic tumor microenvironment [77]. Ju et al.'s research emphasizes the correlation between peritumoral MCs and T-regulatory cells and the prognosis of HCC patients [78]. These findings suggest that MCs may play a role in the development and treatment of HCC; however, further specialized research is required to delve into their mechanisms of action, enhancing our understanding of this disease and improving treatment strategies.

Pancreatic cancer

The pivotal regulatory role of MCs in pancreatic cancer emerges through their association with tumor progression. Tumor-infiltrating MCs have been implicated in a poorer prognosis for pancreatic cancer, with *in vitro* studies revealing that the interplay between MCs and pancreatic cancer cells actively foster tumor growth and invasion [79]. Notably, MC conditioned media induce pancreatic cancer cell migration, proliferation, and invasion, primarily relying on matrix metalloproteinase activity [80]. The reciprocal communication between MCs and pancreatic cancer cells play a crucial role in recruiting MCs to the TME through pancreatic cancer cell signaling, ultimately influencing cancer cell growth and invasion [81]. This collective evidence accentuates the pivotal regulatory influence of MCs in driving pancreatic cancer progression, emphasizing the potential for targeting MCs as an innovative therapeutic strategy for this challenging disease.

Prostate cancer

The interaction between MCs and prostate cancer tumors is a topic of ongoing research. Some studies have suggested that MCs could pro-

mote the proliferation of prostate cancer cells and the occurrence of epithelial-mesenchymal transition (EMT), which is associated with cancer progression [82]. However, the role of MCs in prostate cancer is complex, and their interaction with prostate cancer cells with different degrees of malignancy requires further investigation to determine the potential for MC targeting in cancer therapy [81]. Additionally, the density and distribution of MCs in prostate cancer tissue have been associated with different prognostic implications, with high MC numbers being inversely associated with prostate cancer recurrence in some studies [83]. Further research is needed to fully understand the specific mechanisms of interaction between mast cells and prostate cancer tumors and their potential implications for the development of novel therapeutic approaches.

Leukemia

The role of MCs in leukemia has gained scholarly attention. Janke et al. found significant hyperplasia of MCs and eosinophils in NSG-SGM3 mouse models with CD34⁺ hematopoietic stem cells or patient-derived leukemia xenografts, indicating a pivotal role of MCs in leukemia pathogenesis [84]. Jia et al. identified MCs as a significant potential target for immunotherapy in acute myeloid leukemia (AML), offering novel avenues for AML treatment [85]. Macon et al.'s study highlighted the association between MCs and hairy cell leukemia (HCL) accompanied by marrow reactive plasmacytosis [86]. These collective research findings underscore the presence and potential roles of MCs in various leukemia types, providing crucial insights for the development of future leukemia treatment strategies.

The opposite function of MC in the TME and their underlying mechanisms

MC is getting more and more attention in cancer-related fields. However, their role has two sides, promoting or inhibiting the development of tumors in different situations.

MCs is known to promote inflammation, inhibit tumor cell growth, and induce tumor cell apoptosis by releasing IL-1, IL-4, IL-6, IL-8, TNF- α , IFN- γ , TGF- β , MCP-3, MCP-4, leukotriene B4 (LTB4), and chymotrypsin. While a key role of MCs in regulating tumor progression is their

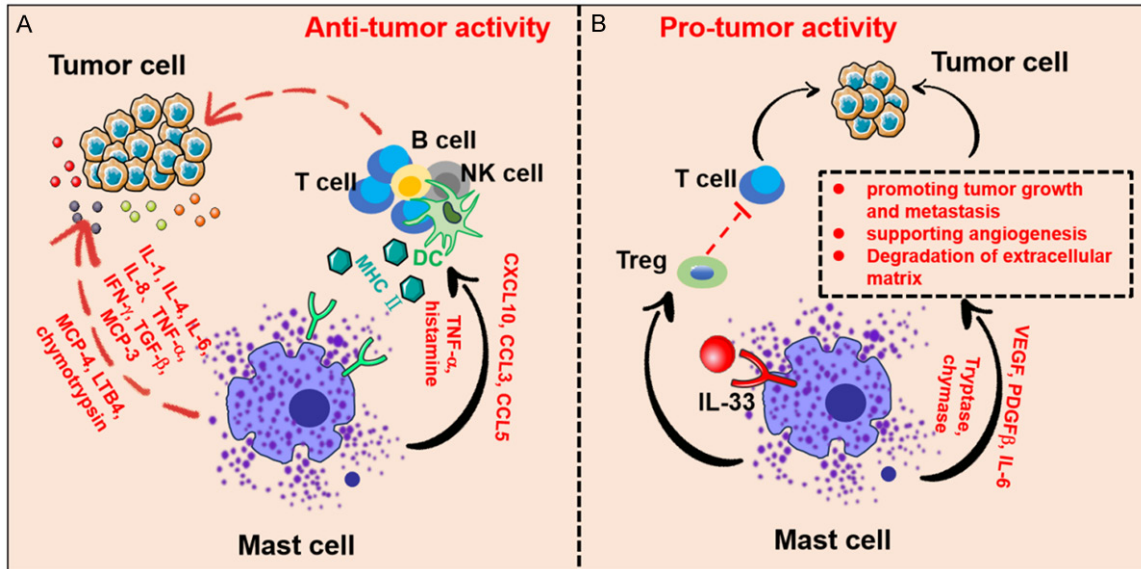


Figure 2. The anti- and pro-tumor function of mast cells in the tumor environment and their underlying mechanisms. A. The anti-tumor function of mast cells: inhibit tumor cell growth and induce tumor cell apoptosis by releasing IL-1, IL-4, IL-6, IL-8, TNF- α , IFN- γ , TGF- β , MCP-3, MCP-4, leukotriene B4 (LTB4), and chymotrypsin; activated mast cells up-regulated MHC-II, co-stimulatory molecules, and chemokines to recruit T cell, NK, DC in the tumor environment; B. The pro-tumor function of mast cells: mast cells degrade extracellular matrix by releasing tryptase and chymotrypsin; promote tumor growth, angiogenesis and metastasis through releases VEGF, PDGF- β , and IL-6; IL33 stimulates mast cells to recruit Treg, so as to inhibit CTL.

role as sentinel immune cells that release chemokines, cytokines, and other factors that recruit other immune cells into the TME and alter their function. MCs release chemokines, such as CXCL10, CCL3, and CCL5, which recruit CD8⁺ T cells and CD4⁺ T cells into the tumor, where they can further regulate T cell activity through TNF- α secretion. Histamine secreted by MCs favors specific T helper cell subtypes or T cell regulatory responses, depending on the receptor being stimulated. Activated MCs have also been shown to up-regulate MHC-II and co-stimulatory molecules, acting as local antigen-presenting cells for T cells. Currently, they are known to be associated with a favorable prognosis for several types of human cancer, such as non-small cell lung cancer, breast cancer, and prostate cancer [87, 88].

MC can support cancer development by supporting angiogenesis, inflammation, and homeostasis. MC can activate matrix metalloproteinases and degrade extracellular matrix and tumor surrounding tissues by releasing tryptase and chymotrypsin, thus promoting tumor growth, angiogenesis, and metastasis. In addition, MC releases VEGF, PDGF- β , and IL-6, promoting angiogenesis, cell proliferation, and

tumor growth. LV et al.'s study verified that TAMCs stimulated Treg through IL-33 and IL-2 axis to promote gastric cancer [89]. MCs can also influence the efficacy of immunotherapy by mediating the formation of inhibitory TME (Figure 2).

The therapeutic potential of MC

Within the domain of cancer immunotherapy, MCs have emerged as a promising subject of investigation. Substantive research has elucidated that MCs, conventionally associated with allergic and autoimmune disorders, exert a noteworthy influence on shaping the cancer microenvironment and modulating anti-tumor immunity. A spectrum of therapeutic strategies has been proffered to target MCs for cancer immunotherapy, encompassing the reduction of mast cell numbers, modulation of MCs activation and phenotype, and alteration of secreted MC mediators. These strategic interventions are designed to harness the inherent anti-tumor properties of MCs, thereby holding the potential to enhance cancer treatment outcomes. Additionally, the discerned abundance of MCs in solid tumors, their proximity to blood vessels, and their capacity to selectively se-

crete distinct profiles of mediators render them ideal candidates for targeted tumor immunotherapy. Furthermore, mast cells have been identified as contributors to the augmentation of anti-tumor responses through the recruitment of natural killer cells, dendritic cells, and T cells. The therapeutic potential of MCs in cancer immunotherapy remains an ongoing subject of rigorous investigation, with a particular emphasis on devising strategies to exploit their role in the TME for optimized treatment outcomes [90-92].

Summary and perspective

In the field of tumor microenvironment research, the role of MCs has garnered significant attention. Studies indicate that MCs exert influence on the tumor immune response by releasing cytokines and mediators, thus potentially serving as a promising therapeutic target. Furthermore, MCs have been associated with resistance to anti-PD-1 therapy, highlighting their significance as potential biomarkers for guiding individualized cancer treatments. However, the role of MCs in cancer is intricate, as they can both promote tumor growth and impact the immune response. Therefore, an in-depth investigation into the regulatory mechanisms of MCs is crucial for achieving precise therapeutic goals, while also addressing the future needs in MC biology to advance the field further.

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Disclosure of conflict of interest

None.

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