中国临床研究 Chin J Clin Res, January 2024, Vol.37, No.1

Cite as: Luo Y, Zhang Q, Zhang S, et al. Role and mechanism of mast cells in solid tumors[J]. Chin J Clin Res, 2024, 37(1): 6-11.

DOI: 10.13429/j.cnki.cjcr.2024.01.002

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Role and mechanism of mast cells in solid tumors

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Abstract: Mast cells are a type of innate immune cells, and have been considered to be related to the pathogenesis of allergic and autoimmune diseases in the long term. However, in recent years, a number of studies have elucidated that mast cells play an indispensable role in tumor development, metastasis, infiltration, and angiogenic, providing new ideas for tumor diagnosis and immunotherapy. Once mast cells have infiltrated solid tumors, they are known as tumor-associated mast cells (TAMCs), and one of the most controversial immune cells in tumor tissues with remarkable heterogeneity. In view of important role of mast cells in solid tumor in inflammation and immune system, this paper reviews the mechanisms of mast cells in solid tumor development and their relationship with angiogenesis and lymphangiogenesis, aiming to deepen the understanding of the relationship between mast cells and tumors.

Keywords: Mast cells; Tumor-associated mast cells; Solid tumors; Tumor microenvironment; Angiogenesis; Lymphangiogenesis; Tumor production; Tumor suppression

Fund program: National Natural Science Foundation of China (82273422); Nantong Social Livelihood Science and Technology Plan Project (MS2023067)

The tumor microenvironment (TME) is a tumor growth environment composed of many types of cells and secreted factors. Mast cells are important immune cells in the TME and influence tumor progression by regulating the TME. It has been confirmed that the ability of mast cells to promote or impede tumourigenesis is related to the histological classification of the tumor, the stage of neoplasia, the activation state of mast cells, their spatial distribution within the TME, and net balance of pro- and anti-tumorigenic effects in the tumour cells. Mast cell-induced net balance of tumor-inhibiting and tumor-promoting responses within the tumor, stromal and immune microenvironment ultimately governs the impact of TAMCs on the tumor progression.

1 Overview of Mast Cells

1.1 Origin of mast cells

Mast cells are key effector cells in allergy and are reliable sentinel cells against infection. Mast cells are ancient components of the immune system, and there are three hematopoietic sources of mast cells inherent in fetal tissues: early erythro-myeloid progenitors (EMPs), late-EMPs and fetal hematopoietic stem cells (HSCs) produced in the aorto-gonadal-mesonephric region. They are sequentially differentiated into integrin $\beta7^+$ cells, also known by cell precursors of mast cells, which subsequently complete their final maturation in peripheral tissues. Mast cells from three different sources have different tissue-resident preferences and shape the heterogeneity of mast cells[1].

1.2 1.2 Types of mast cells

In human bodies, mast cells are classified into two

major subtypes based on specific proteases, which are mucosal phenotype mast cells (MC_TS) and conncective tissue phenotype mast cells (MC_TCS), respectively. Among them, MC_TS only contains tryptase-like enzymes and is mainly distributed in mucosal tissues. MC_TCS expresses two tryptase (TPSAB1 and TPSB2), carboxypeptidase A3, and chymase 1, and is mainly distributed in connective tissues[2]. In murine, mast cells are categorized into two prominent subtypes based on their histologic origin. MC_TCS originated from yolk sac-derived precursors, and are situated in small veins and nerve endings and in the pleural cavity of most connective tissues (i.e., skin, tongue, trachea, esophagus, adipose esophagus and peritoneal cavity). The MC_TS derived from HSCs are primarily located in the epithelium of intestinal and respiratory mucosa[3].

2 TAMCs

Mast cells have been implicated in many inflammatory and physiological processes, most widely known to be associated with IgE-mediated type 1 hypersensitivity. The hypersensitivity underlies many allergic diseases. Additionally, mast cells have a variety of additional functions in inflammation, innate and adaptive host defense, wound healing, coagulation, and cancer[4]. The cytoplasm of mast cells is filled with secretory granules, which are their dominant structural feature. These granules contain numerous immunomodulatory and vasoactive mediators, including cytokines [vascular endothelial growth factor (VEGF), nerve growth factor (NGF), fibroblast growth factor (FGF), stem cell factor (SCF), tumor necrosis factor (TNF), transforming growth factor-β (TGF-β)], proteases [matrix metalloproteinase (MMP), trypsin-like enzymes, chymotrypsin-like enzymes, granzymes], biogenic amines (histamine, serotonin), and chemokines [chemokine ligand 3 (CCL3), CCL5, and CCL4] [5]. Some proteins [e.g., interleukin(IL)-2, VEGF, interferon (IFN)-γ, and CCL2] and lipid products (e.g., prostaglandin D2, leukotriene C4, platelet-activating factor, etc.) are synthesized by *de novo* upon mast cell activation. They can be released via the non-degranulation pathway. Mast cells also spontaneously secrete extracellular vesicles (EVs), such as microvesicles, exosomes, and apoptotic bodies. The substances contained in these EVs include proteins, enzymes, RNA, and miRNA, and they are absorbed and transported to other cells in the microenvironment[6].

Mast cells are known to pervade numerous solid neoplasms, and once they are infiltrated, they will be designated as tumor-associated mast cells (TAMCs)[7]. TAMCs are recognized as distinct contributors, and regulators of both pro-tumorigenic and anti-tumorigenic responses, positioning them among the most contentious immune cellular entities within the oncological milieu. On one flank, they are adept at fostering myriad processes that expedite neoplastic progression, inclusive of angiogenesis, lymphangiogenesis, fibrosis, and metastatic dissemination. Furthermore, TAMCs can secrete a cadre of mediators that potentiate the infiltration of additional immune cells into the neoplastic framework. These mediators may exert influences that span the spectrum of tumor-promoting to tumor-inhibiting activities[8]. There are complex interactions between tumor cells and mast cells, and in TME, TAMCs are exposed to and activated by multiple factors[9].

Adenosine produced by neoplastic cells and mast cells is significantly increased in TME and enhances the production of angiogenic factors by human mast cells and macrophages. One of the main characteristics of TME is hypoxia, which activates human mast cells to release IL-6 and VEGF-A.

Prostaglandin E2 is produced by cyclooxygenase 2 (COX-2), which is overexpressed in tumors and stimulates angiogenic and lymphangiogenic factors in human mast cells. Chemokines, such as CXCL1, CXCL10, and CXCL12, activate mast cells and enhance their secretion, thus promoting the cancer cells' epithelial-to-mesenchymal transition (EMT)[10]. In a mouse model of melanoma, it was discovered that increased expression of immunoglobulin-free light chains (FLCs) activated mast cells and stimulated tumor growth. Gastric cancer-derived adrenal medulla induces mast cell degranulation through the PI3K/Akt pathway, which effectively promotes neoplastic cell proliferation, inhibits apoptosis, and promotes tumor growth *in vivo*[11]. TAMCs regulate other immune cells' recruitment and activity of tumor. For instance, myeloid-derived suppressor cells (MDSCs), primarily through immunosuppressive qualities, can stimulate tumor growth when mobilized into TAMCs. In addition, mast cells enhance the function of MDSCs *in vitro* and *in vivo*[12].

3 Role of mast cells in tumor angiogenesis and lymphangiogenesis

3.1 Role of mast cells in tumor angiogenesis

Angiogenesis is essential to promote solid tumors' development, invasion, and metastasis[13]. Mast cells are associated with tumor angiogenesis. Mast cells are attracted to tumor-associated macrophages in the TME. They are promoted by releasing classical angiogenic factors (VEGF, FGF) and non-classical angiogenic factors (proteases) to generate tumor angiogenesis. Tumor angiogenesis is reduced in mast cell-deficient mice[14]. Activation of mast cells releases the bioactive mediators chymotrypsin and trypsin-like enzymes, which can increase endothelial cell permeability[15]. In breast cancer patients, mast cells are implicated in the facilitation of neoplastic proliferation and metastasis. These factors and proteases activate growth factors isolated in the extracellular matrix, which promote fibroblast proliferation and angiogenic responses, induces extracellular matrix degradation, and favors tumor cell invasion[16]. In gastric cancer, mast cells play a pro-tumorigenic role by releasing angiogenic factors (VEGF-

A, CXCL9, MMP-9)[6].

Mast cells are potent inductors of angiogenesis, capable of synthesizing and releasing common angiogenic components[17]. Currently, plenty of evidence suggests that mast cell density (MCD) is closely related to angiogenesis in different human cancer types. The relationship between microvessel density (MVD) and MCD has been demonstrated in various human tumors[18]. In the cases of pulmonary neoplasia and oral squamous cell carcinoma, a positive correlation has been observed between MCD and MVD. Furthermore, in gastric cancer, MCD is associated with angiogenesis, growth, and tumor progression. In breast cancer patients, high serum level of tryptase-like enzymes is correlated with high numbers of TAMCs, strongly correlated with MVD, supporting the involvement of mast cell-derived tryptase-like enzymes in tumor angiogenesis[19].

3.2 Role of mast cells in tumor lymphangiogenesis

Lymphatic vessels can act as a channel for spreading tumor cells and promote the growth of lymph node metastases in malignant tumors. Human mast cells are a source of both pro-angiogenic and pro-lymphangiogenic factors. Mast cells synthesize VEGF-C and VEGF-D, which stimulate lymphangiogenesis. Human mast cells are both a source and a target of VEGF. VEGFs produced at sites of inflammation and tumor may promote mast cell infiltration by interacting with vascular endothelial growth factor receptors 1 and 2 (VEGFR-1 and VEGFR-2) or both[20].

Recent evidence suggests a positive correlation between TAMCs and lymphangiogenesis. It has been shown that in breast cancer, as tumor size increases, there is a corresponding increase in MCD of the metastatic lymph nodes and elevated intratumoral and peritumoral lymphatic vessel density (LVD)[21]. There is a notable positive correlation between lymphovascular invasion, nerve invasion, and the positivity of estrogen receptors (ER) with the MCD. Intratumoural LVD becomes higher with increasing nuclear grading[22]. A recent investigation analyzed the association between TAMCs and lymphangiogenesisacross diverse molecular phenotypes of breast carcinoma. It showed a conspicuous correlation between an abundance of peritumoral mast cells and the emergence of novel lymphatic vessels in the ductal within the tubulointerstitial Type A and basal-like subcategories. Intriguingly, the basal-like subgroup exhibited distinctive patterns of interaction between TAMCs and LVD. This subtype was the only one that showed a significant correlation between overall MCD (peri- and intratumoral mast cell counts) and LVD[23]. These findings suggest that TAMCs respond specifically to each breast cancer molecular subtype and that different subtypes may influence lymphovascular invasion[24]. However, much evidence indicates that the lymphatic system also eases inflammation. It has also been found that lymphatic vessels may play an immunomodulatory role and participate in immunosurveillance.

In summary, more studies are needed to verify that the production of lymphangiogenic factors by TAMCs may contribute to metastasis formation, and lead to the relief of tumor-associated inflammation in some cases[25].

4 Tumor-promoting effects in mast cells

Mast cells promote oncogenesis by facilitating angiogenesis, and contributing to tissue reconfiguration [26]. Mast cells can secrete a cohort of cytokines and growth factors [FGF-2, VEGF, NGF, platelet-derived growth factor (PDGF), IL-8, and IL-10], histamine, proteolytic enzymes, and chylus, further bolstering their role in tumor progression[27]. The following is a list of the tumor-promoting roles of mast cells in some common tumors.

(1) Bladder cancer: Interactions between mast cells and bladder tumor cells may lead to mast cell activation and mediator release. Mast cells produce a variety of growth factors, angiogenic factors, and pro-inflammatory chemicals after being activated, leading to an aggressive phenotype of tumor cells. In addition, mast cells infiltrate the tumor and promote its proliferation and invasion, and their recruitment into the tumor increases the interaction between ERs and CCL2. Among them, CCL2 promotes EMT and MMP, which elucidated that the activation of the ERβ/CCL2/EMT/MMP axis by mast cells increases bladder cancer invasion[28].

(2) Gastric cancer: In patients with gastric cancer, mast cells are implicated in the facilitation of angiogenesis and the metastasis of neoplastic cells. A discernible positive correlation has manifested among mast cell infiltration, IL-17 production, and MVD association with intermediate numbers of neutrophils and regulatory T cells (Tregs). Amount of mast cells increase with tumor progression and predict a decrease in overall survival in patients with gastric cancer[29]. Through the deployment of macrophages, IL-33-mediated mast cell activation stimulates gastric cancer progression. Tumor-derived TNF-α induces mast cells to express programmed cell death ligand (PD-L1), suppressing T-cell immunity and promoting gastric tumor growth. MCTs and tumor-associated macrophages, in a synergistic manner, contribute to tumor angiogenesis in gastric cancer patients[30].

(3) Pancreatic cancer: Mast cells release IL-13 and trypsin-like enzymes that promote the proliferation and invasion of cancer cells. Peripheral mast cells interact with pancreatic cancer cells in a mouse model, and high MCD indicates poor prognosis. By activating the angiopoietin-1 pathway, MCTs play an important role in the angiogenesis and development of tumors in pancreatic cancer[31].

(4) Breast cancer: Mast cells may play a role in primary breast cancer angiogenesis. Infiltrating mast cells secrete trypsin-like enzymes to promote stromal remodelling and α-smooth muscle actin-positive myofibroblast differentiation in breast cancer patients. The killer cell Ig-like receptor 2DL4 expressed in human mast cells promotes cancer invasion and metastasis[32].

(5) Lung adenocarcinoma: Intratumoral mast cells

suggest poor prognosis in advanced human lung adenocarcinoma and advanced tumor. Mast cell-derived exosomes can facilitate the transfer of CD117 to enhance proliferative capabilities[33].

(6) Prostate cancer: MMP-9 is secreted by mast cells to encourage angiogenesis and invasion. In mouse and rat models, mast cells release significant amounts of FGF-2. In human and mouse models, mast cells promote metastasis by regulating the lncRNA-HOTAIR-PRC2-AR-MMP9 signaling complex. Periprostatic mast cells are an early biomarker of prostate tumors, indicating a poor prognosis[34]. Protein kinases can enhance mast cell recruitment and angiogenic factor expression, contributing to tumor angiogenesis. Mast cells regulate the immunoreactivity of polymorphonuclear leukocytes-MDSCs through CD40L-CD40 interaction, contributing to immunosuppression and tumourigenesis[35].

(7) Colorectal cancer: Perivascular mast cells promote early and late angiogenesis and tumor progression. Protease-activated receptor 2-positive perivascular mast cells are associated with advanced colorectal cancer, and the number of mast cells is a prognostic marker for advanced colorectal cancer[36]. Mast cells are recruited and promote human colorectal cancer growth through bidirectional crosstalk[37].

(8) Hepatocellular carcinoma: Mast cell density positively correlates with the number of Tregs in patients with hepatocellular carcinoma. Mast cells contribute to tumor progression and angiogenesis by secreting IL-17[38].

(9) Melanoma: Perivascular mast cells secrete VEGF to promote angiogenesis, which correlates with tumor progression and metastasis in a mouse model. Hypoxia-inducible factor-1α secreted by mast cells induces mast cell migration and contributes to tumor growth. IgE induces mast cells to secrete VEGF and enhances tumor-promoting activity through a pathway dependent on Fyn kinase[39].

(10) Renal cell carcinoma: In human and mouse models, intratumor mast cells promote tumor angiogenesis and accelerate tumor growth. Mast cells are associated with cell growth and recurrence in individuals with renal cell carcinoma[40]. Tumor-infiltrating mast cells are associated with immunosuppression by mediated hypoxia-inducible factor-2α in renal clear cell carcinoma. In renal cell carcinoma, mast cells promote tumor angiogenesisby activating PI3K-Akt-GSK3β signaling[41].

(11) Thyroid cancer: Human mast cells secrete histamine, CXCL1 and CXCL10 to encourage the growth, survival, and metastasis of cancer cells, as well as angiogenesis in vitro. Through the IL-8-Akt-Slug pathway, mast cells induce EMT and stem cell features, increasing human thyroid cancer's invasiveness[42].

(12) Oral squamous cell carcinoma: MCTCs upregulate the expression and catalytic activation of melanoma inhibitory activity (MIA) and MIA2. This upregulation is implicated in facilitating both angiogenesis and lymphangiogenesis[43].

5 Tumor suppression in mast cells

Mast cells exert tumor suppressive effects by generating relevant immune responses to tumors. They can suppress tumor progression through the release of various cytokines and mediators such as interleukins (IL-1, IL-2, IL-4, IL-6, and IL-10, albeit IL-10 is usually expressed at low levels), monocyte chemotactic proteins 3 and 4 (MCP-3 and MCP-4), cytokines (IFN-α, TGF-β, TNF-α and leukotriene B4) and histamine. The following is a list of tumor suppressive roles played by mast cells in some common tumors.

(1) Melanoma: CXCL10 secreted by mast cells upon activation with lipopolysaccharides (LPS), plays a pivotal role in the recruitment of effector T cells to the tumoral milieu. This mechanism is critical in the immune surveillance of melanomas. In addition, CXCL10 upregulation and mast cell signaling at melanoma sites are biomarkers for improved patient survival[44]. To destroy hnRNP A2/B1, trypsin-like enzymes secreted by mast cells translocate to the nucleus of melanoma cells, which is followed by the down-regulation of the oncogene EGR1 expression and other non-coding RNAs to inhibit the growth of tumor cells[45].

(2) Colorectal cancer: Mast cells inhibit colorectal cancer cell growth and induce apoptosis *in vitro* and *in vivo*, but do not affect normal colorectal epithelial cells. Mast cells have been shown to preferentially induce endoplasmic reticulum stress and activate unfolded protein responses in colorectal cancer cells but not in normal cells, which inhibits the progression of colorectal cancer *in vivo*. In addition, secreted cystatin C protein is identified as a key factor in mast cell-induced endoplasmic reticulum stress in colorectal cancer cells[46]. A genetically modified mouse model revealed that different immune responses alter mast cell activity, which directly alters colorectal tumorigenesis. Mast cells produce celiac to attract macrophages, neutrophils, and other immune cells, which improve host immunity to cancer in colorectal cancer patients[47].

(3) Non-small cell lung cancer: The cytotoxicity of TNF-α from mast cells can enhance the survival of patients with non-small cell lung cancer[48]. Mast cells exhibit proinflammatory and chemotactic properties in lung adenocarcinomas enriched with features of ground-glass nodules, whereas mast cells from radiologically solid lung adenocarcinoma are associated with tumor angiogenesis. Mast cells are an important source of CCL2 and correlate with the recruitment of its receptor $CCR2^+$ cytotoxic T lymphocytes[49]. Pronglonged survival is linked to high mast cell abundance in patients with early-stage lung adenocarcinoma[50].

(4) Oral squamous cell carcinoma: A higher density of tumor-infiltrating mast cells can be associated with a more favorable prognosis[51].

(5) Pancreatic neuroendocrine tumors (pNETs): In patients diagnosed with pNETs , a high MCD is prognostic of favorable clinical outcomes. Conversely, a low MCD correlates with high-grade tumor histology, the non-insulinoma phenotype, and the advanced tumor stage. Moreover, an increased infiltration of mast cells is concomitant with augmented counts of $CD4^+$ T

lymphocytes and $CD15^+$ neutrophils[52].

(6) Esophageal adenocarcinoma: The high presence of mast cells was significantly associated with a less tumor stage and a lower frequency of lymph node metastasis. Furthermore, mast cells are associated with a favorable prognosis in individuals with lymph node metastases[53].

6 Conclusion

Mast cells contribute significantly to forming the inflammatory response and solid tumors. There is ongoing debate on mast cell involvement in malignancies. To develop novel treatment strategies that precisely target mast cells and treat tumors, further thorough research on the involvement of mast cells in malignancies must be conducted. As research into mast cells progresses, an expanded repertoire of pharmacological agents is anticipated to substantially enhance the efficacy of treatments for autoimmune disorders and solid neoplasms.

Conflict of Interest None

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Submission received:2023-12-08/**Revised:**2023-12-30

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肥大细胞在实体瘤中的作用及机制

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摘要：肥大细胞（mast cells）是一种先天免疫细胞，长期以来一直被认为与过敏性和自身免疫疾病的发病机制有关。然而近年来不少研究发现，肥大细胞在肿瘤的发生发展、转移、浸润和血管生成中起着不可或缺的作用，为肿瘤的诊断及免疫治疗提供了新思路。肥大细胞一旦浸润实体瘤，就被称为肿瘤相关肥大细胞（TAMCs），是肿瘤组织中极受争议的免疫细胞之一，具有显著的异质性。鉴于肥大细胞在炎症和免疫系统中的重要作用，本文对肥大细胞在实体肿瘤发生发展中的作用机制以及与血管和淋巴管生成的关系作一综述，旨在加深对肥大细胞与肿瘤关系的认识。

关键词：肥大细胞；肿瘤相关肥大细胞；实体瘤；肿瘤微环境；血管生成；淋巴管生成；肿瘤促进；肿瘤抑制

中图分类号：R730.3　**文献标识码**：A　**文章编号**：1674-8182(2024)01-0006-06

Role and mechanism of mast cells in solid tumors

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Abstract: Mast cells are a type of innate immune cells, and have long been considered to be related to the pathogenesis of allergic and autoimmune diseases. However, in recent years, a number of studies have found that mast cells play an indispensable role in tumor development, metastasis, infiltration and angiogenesis, providing new ideas for tumor diagnosis and immunotherapy. Once mast cells have infiltrated solid tumors, they are known as tumor-associated mast cells (TAMCs) and are one of the most controversial immune cells in tumor tissues with remarkable heterogeneity. In view of the important role of mast cells in inflammation and the immune system, this paper reviews the mechanisms of mast cells in solid tumor development and their relationship with angiogenesis and lymphangiogenesis, aiming to deepen the understanding of the relationship between mast cells and tumors.

Keywords: Mast cells; Tumor-associated mast cells; Solid tumors; Tumor micro-environment; Angiogenesis; Lymphangiogenesis; Tumor promotion; Tumor suppression

DOI: 10.13429/j.cnki.cjcr.2024.01.002

基金项目：国家自然科学基金（82273422）；南通市社会民生科技计划项目（MS2023067）

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出版日期：2024-01-20

QR code for English version

Fund program: National Natural Science Foundation of China (82273422); Nantong Social Livelihood Science and Technology Plan Project (MS2023067)

肿瘤微环境(tumor microenvironment, TME)是由多种类型细胞及分泌因子等组成的肿瘤生长环境。肥大细胞是 TME 中重要的免疫细胞,通过调控 TME 影响肿瘤的进展。其促进或阻碍肿瘤发生的能力已被证明取决于肿瘤类型、癌症分期,肥大细胞自身的活化状态及其在 TME 中的位置,以及促肿瘤和抗肿瘤作用对肿瘤细胞的净平衡。肥大细胞诱导的抗肿瘤和促肿瘤信号在肿瘤、基质和免疫微环境中的净平衡,决定了肿瘤相关肥大细胞(tumor-associated mast cells, TAMCs)对肿瘤生长的影响。

1　肥大细胞概述

1.1　*肥大细胞的起源*　肥大细胞是过敏和过敏反应的关键效应细胞,是防止感染的可靠哨兵细胞。肥大细胞是免疫系统的一个古老组成部分,胎儿组织固有的肥大细胞有三种造血来源,胚胎期卵黄囊产生的早期红髓系祖细胞(erythro-myeloid progenitors, EMPs)、晚期 EMPs 以及主动脉—性腺—中肾区产生的胎儿造血干细胞(hematopoietic stem cells, HSCs)。它们相继分化为整合素 $\beta7^+$细胞,即肥大细胞前体细胞,随后在外周组织中完成最终成熟。三个不同来源的肥大细胞具有不同的组织驻留偏好,并塑造了肥大细胞的异质性[1]。

1.2　*肥大细胞的分型*　在人体中,肥大细胞根据特异蛋白酶的不同,被分为两大亚型,分别是 T 亚型(mast cells type T, MCTs)和 TC 亚型(mast cells type TC, MCTCs)。其中,MCTs 亚型仅含有类胰蛋白酶,主要分布在黏膜组织中。MCTCs 亚型则表达两种类胰蛋白酶(TPSAB1 和 TPSB2)、羧肽酶 A3 和糜蛋白酶 1,主要分布在结缔组织中[2]。在小鼠中,肥大细胞根据其组织来源又分为两个主要亚群,由卵黄囊衍生的肥大细胞在出生后构成主要的结缔组织肥大细胞(connective tissue mast cells, CTMCs),位于大多数结缔组织(即皮肤、舌、气管、食管、脂肪、腹膜腔)的小静脉和神经末梢周围及胸膜腔。而 HSCs 来源的肥大细胞主要发育为黏膜肥大细胞(mucosal mast cells, MMCs),位于肠道和呼吸道黏膜的上皮内[3]。

2　TAMCs

肥大细胞与许多炎症和生理过程有关,最广为人知的是其与 IgE 介导的 1 型超敏反应有关,该超敏反应是许多过敏性疾病的基础,此外肥大细胞在炎症、先天性和适应性宿主防御、伤口愈合、凝血和癌症方面具有多种附加功能[4]。肥大细胞的细胞质中充满了分泌颗粒,是其最主要的结构特征,这些颗粒内含有众多的免疫调节和血管活性介质,包括细胞因子[如血管内皮生长因子(VEGF)、神经生长因子(NGF)、成纤维细胞生长因子(FGF)、干细胞因子(SCF)、肿瘤坏死因子(TNF)、转化生长因子 β(TGF-β)]、蛋白酶[如基质金属蛋白酶(MMP)、类胰蛋白酶、类糜蛋白酶、颗粒酶],生物胺[如组胺、血清素]和趋化因子[如 C-C 基序趋化因子配体(CCL)3、CCL5 和 CCL4][5]。一些蛋白质[如白细胞介素(IL)-2、VEGF、干扰素(IFN)-γ 和 CCL2]和脂质产物(如前列腺素 D2、白三烯 C4、血小板活化因子等)在肥大细胞活化后进行从头合成,并可通过非脱颗粒途径释放。肥大细胞还自发分泌细胞外囊泡(EVs),包括微囊泡、外泌体和凋亡体。这些 EVs 中所含的物质包括蛋白质、酶、RNA 和 miRNA,它们被吸收并运输到微环境中的其他细胞中[6]。

肥大细胞可以浸润许多实体瘤,一旦浸润,它们就被称为 TAMCs[7]。TAMCs 被认为是促肿瘤和抗肿瘤反应的可区分参与者和协调者,并且代表了肿瘤中最具争议的免疫细胞类型。一方面,它们可以促进导致肿瘤进展的不同过程,例如血管生成、淋巴管生成、纤维化和转移,另一方面,TAMCs 可释放能诱导其他免疫细胞募集到肿瘤中的介质,这些介质可以执行促或抗肿瘤功能[8]。肿瘤细胞和肥大细胞之间存在复杂的相互作用,在 TME 中,TAMCs 暴露于多种因素并被激活[9]。由肿瘤细胞和肥大细胞产生的腺苷在 TME 中显著增加,并增强人肥大细胞和巨噬细胞血管生成因子的产生。缺氧是 TME 的一个突出特征,可激活人肥大细胞释放 IL-6 和 VEGF-A。环加氧酶 2(COX-2)在肿瘤中过表达,产生前列腺素 E2 促进人肥大细胞的血管生成因子和淋巴管生成因子。趋化因子(即 CXCL1、CXCL10、CXCL12)激活肥大细胞并增强肥大细胞的分泌,从而促进癌细胞上皮向间充质的转化(EMT)[10]。在小鼠黑色素瘤模型中发现免疫球蛋白游离轻链(FLCs)的表达增加,能够激活肥大细胞并促进肿瘤生长。胃癌来源的肾上腺髓质通过 PI3K-Akt 信号通路诱导肥大细胞脱颗粒,有效促进肿瘤细胞增殖,抑制细胞凋亡,促进肿瘤在体内的生

长[11]。TAMCs 调节肿瘤部位其他免疫细胞的募集和激活。例如，TAMCs 动员髓源性抑制细胞（MDSCs），能够促进肿瘤的生长，主要是通过其免疫抑制的特性。此外，肥大细胞增强体外和体内 MDSCs 的功能[12]。

3　肥大细胞在肿瘤血管及淋巴管生成中的作用

3.1　*肥大细胞在肿瘤血管生成中的作用*　血管生成是增强实体瘤的生长、侵袭和转移的必要条件[13]。已有研究证实肥大细胞与肿瘤血管生成有关。肥大细胞在 TME 中被肿瘤相关巨噬细胞吸引并通过释放经典血管生成因子（VEGF，FGF）和非经典血管生成因子（蛋白酶）来促进肿瘤血管生成。在肥大细胞缺陷小鼠中肿瘤血管生成减少[14]。肥大细胞的激活，会释放生物活性介质乳糜和类胰蛋白酶，这可以增加内皮细胞通透性[15]。在乳腺癌患者中，肥大细胞通过释放促血管生成因子和蛋白酶促进肿瘤生长和扩散，这些因子和蛋白酶激活隔离在细胞外基质中的生长因子，进而促进成纤维细胞增殖和血管生成反应，并诱导细胞外基质降解，有利于肿瘤细胞侵袭[16]。在胃癌中，肥大细胞通过释放血管生成因子（VEGF-A，CXCL8，MMP-9）发挥促肿瘤作用[6]。

肥大细胞是血管生成的有效电感器，能够合成和释放常见的血管生成成分[17]。目前，大量证据表明，肥大细胞密度（MCD）与人类不同癌种的血管生成密切相关。在人类各种肿瘤中，微血管密度（MVD）和 MCD 之间的关系已得到证实[18]。在肺癌、口腔鳞状细胞癌中，均发现 MCD 与 MVD 呈正相关。在胃癌中，MCD 与血管生成、生长和肿瘤进展相关。在乳腺癌患者中，血清中高水平类胰蛋白酶与高 TAMCs 数相关，与 MVD 密切相关，支持肥大细胞来源的类胰蛋白酶参与肿瘤血管生成[19]。

3.2　*肥大细胞在肿瘤淋巴管生成中的作用*　在恶性肿瘤中，淋巴管是肿瘤细胞播散的途径，并可促进淋巴结转移的发展。人类肥大细胞不仅是促血管生成因子的来源，也是促淋巴管生成因子的来源。肥大细胞可以合成 VEGF-C 和 VEGF-D，从而刺激淋巴管生成。人类肥大细胞既是 VEGF 的来源，也是 VEGF 的靶标。在炎症和肿瘤部位产生的 VEGFs 可能通过与 VEGFR-1 和 VEGFR-2 或两者相互作用而促进肥大细胞浸润[20]。

最近的证据表明 TAMCs 与淋巴管生成之间存在正相关关系。有研究表明，在乳腺癌中，随着肿瘤大小的增加，转移性淋巴结中的 MCD 相应增加，瘤内和瘤周淋巴管密度（LVD）也随之升高[21]。血管、淋巴管和神经的侵犯及雌激素受体阳性，与肿瘤内 MCD 呈正相关。随着核分级的增加，肿瘤内 LVD 变得更高[22]。最近一项研究分析不同分子亚型乳腺癌中 TAMCs 与淋巴管生成之间的关联，显示管腔 A 型和基底样亚型中大量肿瘤周围肥大细胞与新形成的淋巴管之间存在显著相关性。有趣的是，基底样亚型表现出关于 TAMCs 和 LVD 的特定行为。该亚型是唯一显示总体 MCD（肿瘤周围和肿瘤内肥大细胞计数）与 LVD 之间显著相关性的亚型[23]。这些发现表明，TAMCs 对每种乳腺癌分子亚型的反应具有特异性，不同的亚型可能影响淋巴血管的侵犯[24]。但不少证据表明，淋巴系统也有助于炎症的消退。尚有证据表明淋巴管可发挥免疫调节作用并参与免疫监视。

综上所述，需要更多的研究来验证 TAMCs 产生淋巴管生成因子不仅可能有助于转移形成，而且在某些情况下，还有助于肿瘤相关炎症的消退[25]。

4　肥大细胞的促瘤作用

肥大细胞通过推动肿瘤的血管生成、协助组织重塑等方面而促进肿瘤的生长[26]。肥大细胞通过释放细胞因子和生长因子［如 FGF-2、VEGF、NGF、血小板衍生生长因子（PDGF）、IL-8 和 IL-10］以及组胺、类胰蛋白酶和乳糜来促进肿瘤生长[27]。以下列举肥大细胞在一些常见肿瘤中发挥的促瘤作用。（1）膀胱癌：肥大细胞和膀胱肿瘤细胞之间的相互作用可能导致肥大细胞的激活和介质的释放。激活后，肥大细胞产生多种生长因子、血管生成因子和促炎化学物质，导致肿瘤细胞的侵袭性表型。此外，肥大细胞浸润肿瘤并促进其增殖和侵袭，它们募集到肿瘤中增加了雌激素受体（ERs）和 CCL2 之间的相互作用，其中 CCL2 促进 EMT 和 MMP 的产生，表明肥大细胞激活 ERβ/CCL2/EMT/MMP 轴会增加膀胱癌的侵袭[28]。（2）胃癌：肥大细胞促进胃癌患者癌细胞的血管生成和转移。在胃癌患者中，肥大细胞数量、IL-17 产生和 MVD 与中性粒细胞和调节性 T 细胞（Tregs）的数量之间具有正相关关系。肥大细胞水平随着肿瘤进展而增加，并预示胃癌患者的总生存期降低[29]。IL-33 介导的肥大细胞激活通过巨噬细胞动员促进胃癌生长。肿瘤来源的 TNF-α 诱导肥大细胞表达程序性细胞死亡配体 1（programmed cell death ligand 1，PD-L1），抑制 T 细胞免疫，促进胃肿瘤生长。MCTs 和肿瘤相关巨噬细胞以协同方式促进手术治疗胃癌患者的肿瘤血管生成[30]。（3）胰腺癌：

肥大细胞在体外分泌类胰蛋白酶和 IL-13,促进癌细胞增殖和侵袭。在小鼠模型中,周围肥大细胞通过接触与胰腺癌细胞相互作用,高密度肥大细胞表明预后不良。MCTs 通过激活血管生成素-1 通路在胰腺癌血管生成和肿瘤生长中发挥重要作用[31]。(4) 乳腺癌:肥大细胞可能在原发性乳腺癌血管生成中发挥作用。浸润的肥大细胞分泌类胰蛋白酶以促进乳腺癌患者的基质重塑和 α-平滑肌肌动蛋白阳性的肌成纤维细胞分化。在人肥大细胞中表达的杀伤细胞 Ig 样受体 2DL4 促进癌症侵袭和随后的转移[32]。(5) 肺腺癌:肿瘤内肥大细胞提示人肺腺癌和晚期肿瘤预后不良。肥大细胞外泌体将 CD117 转移到癌细胞并促进其增殖[33]。(6) 前列腺癌:肥大细胞分泌 MMP-9 以促进血管生成和侵袭,并在小鼠和大鼠模型中分泌高水平的 FGF-2。肥大细胞通过调节人类和小鼠模型中的 lncRNA-HOTAIR-PRC2-AR-MMP9 信号传导复合物促进转移。前列腺周围肥大细胞是前列腺肿瘤早期的生物标志物,表明预后不良[34]。蛋白激酶增强肥大细胞的募集和血管生成因子的表达,有助于肿瘤血管生成。肥大细胞通过 CD40L-CD40 相互作用调节多形核白细胞-MDSCs 的免疫活性,有助于免疫抑制和肿瘤发生[35]。(7) 结直肠癌:血管周围肥大细胞促进早期和晚期的血管生成和肿瘤进展。蛋白酶活化受体 2 阳性的体周肥大细胞与晚期结直肠癌相关,肥大细胞的数量可作为患者的预后标志物[36]。肥大细胞被招募并通过双向串扰促进人类结直肠癌的生长[37]。(8) 肝癌:肥大细胞密度与肝细胞癌患者 Tregs 的数量呈正相关。肥大细胞分泌 IL-17 以诱导肝癌患者的血管生成和肿瘤进展[38]。(9) 黑色素瘤:血管周围肥大细胞分泌 VEGF 以促进血管生成,这与小鼠模型中的恶性肿瘤和转移相关。肥大细胞分泌的缺氧诱导因子-1α 促进肥大细胞迁移并有助于肿瘤生长。IgE 诱导肥大细胞分泌 VEGF,并通过 Fyn 激酶依赖性途径增强其肿瘤促进活性[39]。(10) 肾细胞癌:肿瘤内肥大细胞促进人类和小鼠模型中的肿瘤血管生成和肿瘤生长加速。肥大细胞与肾细胞癌患者的细胞增殖和复发有关[40]。肿瘤浸润肥大细胞与肾透明细胞癌中缺氧诱导因子-2α 介导的免疫抑制相关。肥大细胞通过激活肾细胞癌中的 PI3K-Akt-GSK3β 信号传导来促进肿瘤血管生成[41]。(11) 甲状腺癌:人肥大细胞分泌组胺、CXCL1 和CXCL10 促进癌细胞的增殖、存活和转移,以及体外血管生成。肥大细胞通过 IL-8-Akt-Slug 途径诱导 EMT 和干细胞特征来增加人类甲状腺癌的侵袭性[42]。(12) 口腔鳞状细胞癌:MCTCs 促进黑色素瘤抑制蛋白(MIA)和 MIA2 的表达和活化,诱导口腔鳞状细胞癌的血管生成和淋巴管生成[43]。

5　肥大细胞的抑瘤作用

肥大细胞通过对肿瘤产生相关的免疫应答发挥抑制肿瘤的作用。肥大细胞通过释放 IL(IL-1、IL-2、IL-4、IL-6 等,IL10 低表达状态)、单核细胞趋化蛋白 3 和 4、细胞因子(IFN-α,TGF-β、TNF-α 和白三烯 B4)以及组胺,来抑制肿瘤生长。以下列举肥大细胞在一些常见肿瘤中发挥的抑瘤作用。(1) 黑色素瘤:脂多糖激活的肥大细胞产生的 CXCL10 将效应 T 细胞募集到 TME 中,从而对黑色素瘤进行有效的免疫控制。此外,CXCL10 上调和黑色素瘤部位的肥大细胞信号是提高患者生存率的生物标志物[44]。肥大细胞分泌的类胰蛋白酶转运到黑色素瘤细胞核,降解 hnRNP A2/B1,随后,癌基因 EGR1 和多种非编码 RNA 的表达下调,抑制肿瘤细胞增殖[45]。(2) 结直肠癌:肥大细胞在体内外抑制结直肠癌细胞生长并诱导细胞凋亡,但对正常结直肠上皮细胞无影响。已有研究表明,肥大细胞特异性诱导内质网应激并激活结直肠癌细胞中的未折叠蛋白反应,而不是正常细胞,这导致体内结直肠癌发展受到抑制。此外,有研究发现分泌的胱抑素 C 蛋白是结直肠癌细胞中肥大细胞诱导内质网应激的关键因子[46]。通过基因修饰小鼠模型发现,不同的免疫反应会改变肥大细胞活性,而肥大细胞活性直接改变结直肠肿瘤发生。肥大细胞分泌乳糜以募集巨噬细胞、中性粒细胞和其他免疫细胞,进而提高结直肠癌患者对癌症的宿主免疫力[47]。(3) 非小细胞肺癌:来自肥大细胞的 TNF-α 的细胞毒性活性提高了非小细胞肺癌患者的生存率[48]。肥大细胞在富含具有磨玻璃结节特征的肺腺癌中表现出促炎和趋化特性,而放射学实体型肺腺癌的肥大细胞与肿瘤血管生成有关。肥大细胞是 CCL2 的重要来源,并与其受体 CCR2+细胞毒性 T 淋巴细胞的募集相关[49]。肥大细胞高丰度与早期肺腺癌患者的生存期延长相关[50]。(4) 口腔鳞状细胞癌:人口腔鳞状细胞癌中较高的肥大细胞密度与更好的预后相关[51]。(5) 胰腺神经内分泌肿瘤:肥大细胞高密度预示胰腺神经内分泌肿瘤患者预后良好。肥大细胞低密度与高级别、非胰岛素瘤和晚期相关。此外,肥大细胞高浸润与 $CD4^+$ T 细胞和 $CD15^+$ 中性粒细胞计数升高有关[52]。(6) 食管腺癌:肥大细胞的高度存在与肿瘤分期较少和淋巴结转移频率较低显

著相关。此外,肥大细胞是淋巴结转移患者的良好预后因素[53]。

6 结　语

肥大细胞在炎症反应中具有重要作用,在实体肿瘤发生发展过程中同样扮演着重要角色。目前关于肥大细胞在肿瘤中的作用仍备受争议。未来,需要更深入地研究其在肿瘤中的作用机制,开发针对肥大细胞的治疗策略,为肿瘤治疗提供新思路。随着对肥大细胞研究的不断深入,相信会有更多针对肥大细胞治疗的药物用于临床,从而提高对自身免疫性疾病以及实体瘤的疗效。

利益冲突　无

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收稿日期:2023-12-08　**修回日期**:2023-12-30　**编辑**:王国品