


REVIEW

Controversial role of mast cells in NSCLC tumor progression and angiogenesis

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Abstract

Mast cells (MCs) are multifunctional immune cells implicated in both physiological and pathological processes. Among the latter, MCs play a crucial role in cancer. Many studies have shown a correlation between MCs and tumor progression in several solid and hematological malignancies. In particular, MCs can directly promote tumor growth via c-kit/stem cell factor–dependent signaling and via the release of histamine, which modulate tumor growth through H1 and H2 receptors. At the same time, MCs can increase tumor progression by stimulating angiogenesis via both proangiogenic cytokines stored in their cytoplasm, and by acting on the tumor microenvironment and extracellular matrix. With regard to NSCLC, the role of MCs has not yet been established, with studies showing a correlation with a poor prognosis on the one hand and suggesting a protective effect of MCs on the other hand. These controversial evidences are at least, in part, due to the heterogeneity of the studies exploring the role of MCs in NSCLC, with some studies describing only the MC count without specification of the activation and degranulation state, and without reporting the intratumoral localization and the proximity to other immune and cancer cells. A better knowledge of the role of MCs in NSCLC is mandatory, not only to define their prognostic and predictive properties but also because targeting them could be a possible therapeutic strategy.

INTRODUCTION

Mast cells (MCs) are multifunctional immune cells which play several roles in both physiological and pathological contexts, including cancer. However, the role of MCs in non-small cell lung cancer (NSCLC) remains controversial. Mast cells exert both tumorigenic and antitumoral effects on the basis of the biological context, tumor stage, and tumor histotype. Moreover, the studies conducted on the interactions between MCs, angiogenesis, and tumor progression assessed both inter- and intratumor heterogeneity. Notably, in the same analysis of data, several studies reported on different histotypes and tumor stages. On the other hand, the studies exploring the role of MCs in NSCLC patients have focused on different tumoral zones; some studies examined the peripheral tumoral zone and others examined the central tumoral zone, and many studies did not specify the tumoral zone examined. At the same time, the state of degranulation

and the products of degranulation are not always specified. As a result, the role of MCs in NSCLC has not yet been established but understanding the cellular and molecular mechanisms governing the interactions between MCs, cancer cells and other components of the tumor microenvironment could contribute to the development of a novel strategy to indirectly disrupt cancer cell interplay. This review explores the major aspects concerning the role of MCs in tumor progression and angiogenesis of NSCLC patients, and at the same time also describes aspects related to tumor surveillance and the potential role of MCs as prognostic biomarkers.

A MULTIFACETED CELL

Mast cells are multifunctional immune cells which exert several roles in both physiological and pathological contexts.

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Functional heterogeneity of MCs correlates with biological differences of their compounds.¹ MC specific proteases are the major components of MC secretory granules, and are classified according to their protease content. Tryptase⁺ chymase⁺ MCs (MC_{TCs}) contain tryptase, chymase, carboxypeptidase, and cathepsin G, and are predominantly located in the skin and intestinal submucosa. Tryptase⁺ chymase⁻ MCs (MC_{Ts}), contain only tryptase, and are located in the alveolar wall and small intestinal mucosa. The presence of a third phenotype, expressing tryptases and carboxypeptidase, has been also reported in airway epithelium and esophageal samples of patients with asthma and eosinophilic esophagitis.² Finally, tryptase⁻ chymase⁺ MCs (MC_{Cs}) is a rare MC subtype that only contains chymase and is found in endometrial tissue.³ MCs heterogeneity is not only due to the characteristics of their proteases, but also to different stimuli activating MCs, such as IgE-dependent activation, crosslinking of FcγRIII by IgG immune complexes, complement receptor activation by C3a and C5a, c-kit receptor binding by stem cell factor (SCF), and TLR2 (toll-like receptor 2) activation.¹ At the same time, MCs express and release several different cytokines and chemokines. The pattern of mediators released by MCs is variable, depending on the tissue, context and kind of activation.¹ Concerning IgE-dependent activation of MCs,^{4,5,18} the relationship with cancer is controversial, with chronic inflammation and Th2

immune skewing, increasing cancer risk and on the other hand, immunosurveillance decreasing cancer risk.⁵ This heterogeneity, at least in part, explains the controversial role of MCs in a tumor setting.

TUMORIGENIC EFFECTS OF MAST CELLS

Mast cells play a critical role in tumor development (Figure 1), and express a large number of molecules inducing tumor cell proliferation and survival also contributing to metastasis and modulation of the tumor microenvironment. The tyrosine kinase receptor kit (c-kit) is upregulated in tumor cells and its mutation is associated with mast cell leukemia, mastocytosis, and gastrointestinal stromal tumors.^{6,7} MCs express high levels of both c-kit and SCF, its ligand. SCF may contribute to cancer cell migration⁸ and tumor progression by increasing the production of vascular endothelial growth factor (VEGF), IL-6, IL-10, tumor necrosis factor (TNF)-α, and histamine.⁹⁻¹³ The latter modulates tumor growth through H1 and H2 receptors¹⁴ and is also capable of promoting NSCLC epithelial-mesenchymal transition (EMT) via increasing the phosphorylation of PI3K/Akt/mTOR and MEK/ERK signaling pathways.¹⁵ Moreover, MCs promote tumor growth by expanding its vascular supply. As a result, MCs directly produce a plethora of

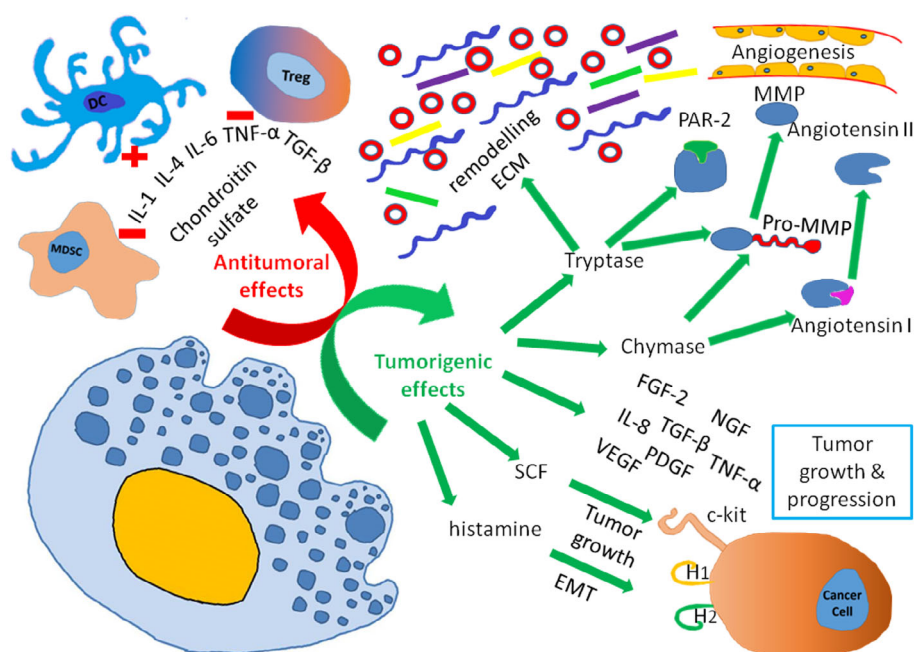


FIGURE 1 Multiple roles of mast cells (MCs) in non-small cell lung cancer (NSCLC). MCs have the capability to play both protumor and antitumor roles according to the tumor context. MCs express a large quantity of molecules which promote tumor progression such as histamine, SCF, FGF-2, IL-8, VEGF, PDGF, and NGF. At the same time, MCs secrete TGF-β and TNF-α, molecules with ambivalent features, able to exert both antitumoral and tumorigenic effects based on the context. Moreover, MCs produce serine proteases activating metalloproteinases and remodeling extracellular matrix (ECM). In particular, tryptase degrades the ECM increasing the space of neovascularization and releasing angiogenic factors included in the matrix. At the same time, tryptase activates PAR-2 inducing endothelial cells proliferation. Another serine protease, namely chymase, induces angiogenesis by converting angiotensin I to angiotensin II. On the other hand, MCs can contribute to tumor rejection by activating dendritic cells and inhibiting Treg cells and myeloid-derived suppressor cells (MDSCs). Moreover, chondroitin sulfate, secreted by MCs, inhibits the development of metastasis

angiogenic factors, such as fibroblast growth factor (FGF)-2, IL-8, transforming growth factor beta (TGF)- β , nerve growth factor (NGF), and already mentholated VEGF and TNF- α . At the same time, MCs can act indirectly to induce tumor angiogenesis. For example, tryptase, which is able to induce endothelial cell proliferation, can also stimulate angiogenesis which acts on the extracellular matrix.^{2,16} Tryptase digests isolated extracellular matrix and also activates metalloproteinases, which are mandatory in the angiogenic process.² The degradation/remodeling of the extracellular matrix increases the space for neovascularisation and releases angiogenic factors included in the matrix, such as VEGF and FGF2. Moreover, tryptase, through its proteolytic activity, acts as an agonist of the protease-activated receptor-2 (PAR-2), a G protein expressed on endothelial cells that is involved in their proliferation. Likely tryptase, and another MC serine protease, namely chymase, are able to act indirectly to induce tumor angiogenesis. In particular, chymases activate MMP-9 and convert angiotensin I to angiotensin II.² Therefore, MCs are able to induce tumor progression in a multimodal manner.

ANTITUMORAL EFFECTS OF MAST CELLS

Mast cells not only have a role in tumor progression but also in tumor surveillance (Figure 1). The mechanisms concerning this dual role of MCs are not completely understood. Several hypotheses have been reported concerning tumor type, biological context, and tissue of origin.^{12,17-20} Mast cells can contribute to tumor rejection by producing molecules such as IL-1, IL-4, IL-6, INF- α , and others, inhibiting tumor growth and tumor cell apoptosis. Moreover, chondroitin sulfate, which is secreted by MCs, inhibits the development of metastasis. Interestingly, some molecules produced by MCs have both beneficial and detrimental effects with regard to tumor growth.¹² As a result, TNF- α , the most widely studied MC associate cytokine, has an emblematic behavior. In a similar context, TNF- α from MCs has been previously reported to show direct cytotoxicity.^{21,22} At the same time, TNF- α from MCs may contribute to dendritic cell (DC) mobilization,²³⁻²⁵ to CD3-T cell proliferation²⁶ and Tregs modulation reducing their suppressive function.^{27,28} Mast cells may also express TNF-related apoptosis-inducing ligand (TRAIL) which is able to induce apoptosis of tumor cells. Finally, MC tryptase, which is renowned for its tumorigenic role by promoting angiogenesis, appears to have a dual outcome, also exerting antitumor effects. Rabelo Melo et al.²⁹ demonstrated that MC tryptase drives nuclear remodeling in human melanoma cells, inhibiting their proliferation and altering their expression of antigens. According to these data, a high number of tryptase-positive MCs have been found in the melanoma regression zones.³⁰ The dual features of MCs, at least in part, explain their controversial role in NSCLC. Of note, higher MCs count have been reported to correlate with better prognosis in some studies as well as with poor prognosis in others.

MAST CELLS AND PROGNOSIS IN NSCLC

In several malignancies, MCs are protumorigenic and have been found to correlate with poor prognosis.^{10,29,31-33} In NSCLC the link between MCs and prognosis is controversial, with studies reporting associations with good prognosis,^{34,35} compared with studies showing a detrimental effect of MC infiltration³⁶ (Table 1). Imada et al.³⁸ showed a correlation with a higher MC count and poor prognosis in patients with resected NSCLC, in particular in stage I lung adenocarcinoma. On the other hand, Carlini et al.⁴⁰ showed that low MC density in the peritumoral zone of stage I NSCLC correlates with worse prognosis. In contrast, Tataroğlu et al.³⁷ reported a higher MC concentration in earlier stage NSCLC, but without a prognostic role. At the same time, no correlation with outcome or other features was reported by Niczyporuk et al.³⁹ in a cohort of 90 resected NSCLC patients, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma histotypes. This discordance is almost in part explained by the high heterogeneity of the studies concerning MCs and NSCLC. These studies used different methodologies and often nonsquamous and squamous histotype were evaluated together as a unique disease. In fact, few studies have separately explored adenocarcinoma and squamous lung cancer. Recently, Tamminga et al.⁴¹ compared adenocarcinoma and squamous cell carcinoma, reporting a higher MC concentration in adenocarcinoma, which correlated with longer OS. Moreover, the studies concerning MCs and NSCLC explored different tumoral zones, some studies examined peripheral tumoral zone and other studies examined the central tumoral zone, and many studies did not report the tumoral zone examined, making it difficult to compare them. In this regard, a link between MC distribution and clinical outcome has been reported in NSCLC patients. The presence of tumor islet MCs and an increased islet/stromal MC ratio resulted in favorable independent prognostic factors. In particular, MCs infiltrating tumor islets and expressing TNF- α , seem to have a favorable prognostic value, suggesting an antitumoral role.⁴² Interestingly, increased tumor islet TNF- α density resulted in a favorable prognostic factor, while stromal TNF- α density resulted in a predictor of poor survival. Furthermore, in NSCLC patients with better prognosis, 100% of TNF- α cells were macrophages and mast cells,

TABLE 1 Mast cells as a poor or good prognostic marker in non-small cell lung cancer (NSCLC)

Good prognosis	Poor prognosis	Indeterminate prognosis
Pang et al. ³⁴	Takanami et al. ³⁶	Tatarglu et al. ³⁷
Tomita et al. ³⁵	Imada et al. ³⁸	Niezyporuk et al. ³⁹
Carlini et al. ⁴⁰		
Tamminga et al. ⁴¹		
Shikotra et al. ⁴²		
Leveque et al. ⁴³		

compared to only 28% in the islets and 50% in the stroma of patients with a poor prognosis, thus confirming the role of MC microlocalization.⁴⁴ In addition to the microlocalization of mast cells, degranulation status also plays a major role in the relationship between tumor cells and tumor microenvironment. In a cohort of surgically-resected NSCLC patients, MCs were more degranulated in patients with extended survival than patients with poor survival. These results are at least partially in contrast to the tumorigenic activities of some products released during MC degranulation.⁴² For example, the tumorigenic effect of histamine, which is able to increase NSCLC proliferation acting on ERK phosphorylation.¹³ At the same time, the cross-talk between MCs and lung cancer cells is not unidirectional, but tumor cells also activate MCs to release cytokines, and affect their migratory ability by tumor-derived microvesicles.⁴⁵ Recently, Leveque and coworkers⁴³ described two distinct phenotype of MCs in NSCLC, based on the expression of an alphaE integrin, namely CD103. In particular, CD103⁺ MCs seem to have a higher interplay with CD4⁺ T cells and a localisation closer to cancer cells than CD103⁻ MCs. However, no different prognostic role has been reported for these distinct phenotypes, while a higher concentration of total MCs correlated with a better prognosis. Further studies, focusing not only on the MC count, but also on MC microlocalization, state of degranulation, characterization of products of degranulation, and cross-talk between lung tumor cells and MCs may contribute to a better knowledge of how MCs affect NSCLC prognosis.

MAST CELLS AND ANGIOGENESIS IN NSCLC

Similarly, to other malignancies, angiogenesis appears to play a role in tumor progression of NSCLC. The majority of studies report a correlation between microvessel density (MVD), VEGF expression, and poor prognosis in NSCLC.^{46–48} However, there is a high heterogeneity between the different studies, with studies also suggesting that angiogenesis has little or no predictive value in NSCLC.^{49,50} Moreover, some studies have reported disappointing results for different histotypes; for example, Pajares et al. reported a correlation with VEGF, VEGFR1, and VEGFR2 expression and lower risk of tumor progression in patients with earlier squamous tumors of the lung, but no correlation has been found in adenocarcinoma histotype.⁵¹ More recently, Qin et al. reported an association of VEGFA and angiopoietin 2 with tumor size and lymph nodes metastasis, only in adenocarcinoma, and not squamous tumors of the lung.⁵² Notably, studies concerning angiogenesis in NSCLC used different assessments to examine tumor vascularity, with endothelial cells identified by different immunohistochemical factors, CD31, factor VIII, and CD34. Moreover, MVD varies within a tumor, and at the same time the significance of MVD changes on the basis of tumor localization. Notably, several studies showed a correlation

between peripheral but not central MVD and poor prognosis and also a correlation between high peripheral MVD, high VEGFA expression, and poor prognosis.⁵³ As is already known, MCs are able to promote tumor angiogenesis in several malignancies, both directly by angiogenic mediators, including IL-8, TNF- α , TNF- β , histamine, bFGF, and heparin, as well as indirectly by acting on the tumor microenvironment and extracellular matrix.¹⁶ However, data concerning the link between MCs and angiogenesis in NSCLC patients are controversial and there are also few studies on this subject. First, Tomita et al. described a direct correlation between the number of mast cells and tumor angiogenesis in patients with NSCLC, independently by VEGF expression.³⁵ In agreement with studies reporting a correlation of high MVD in the border region of NSCLC and poor prognosis, Ibaraki et al. demonstrated a higher count of MCs in the peripheral zone of the tumors than in the central zone, correlating with a higher MVD and a poor prognosis.⁵⁴ Ullah et al. reported a correlation between MC count and MVD, but only high MVD showed a correlation with poor prognosis.⁵⁵ On the other hand, Niczyporuk et al. did not show a correlation between MC count and angiogenesis, except for patients with stage I adenocarcinoma of the lung.³⁹ A similar correlation was found by Imada et al. in a cohort of 53 patients with stage I adenocarcinoma of the lung.³⁸ However, some authors described higher MC counts in the early stages of NSCLC without an analysis of angiogenesis, suggesting a role of MCs in the fight against cancer. Further studies with a more uniform assessment of angiogenesis and MC infiltration are needed. In particular, these studies should define the tumor area examined and also consider the different subtype of NSCLC as well as the tumor stage.

CONCLUSIONS

MCs are crucial players in cancer, affecting outcome and therapy efficacy. However, despite many studies describing the role of MCs in several malignancies, the role of these multifaceted immune cells in NSCLC is far from being understood. Unfortunately, a number of studies focusing on the link between MCs and NSCLC is limited in reporting the count of these cells without describing other major features, such as the degranulation state, localization, characterization of secretory cytokines and proteases, as well as the cross-talk between other immune and lung cancer cells. This is a major limitation in the era of single cell sequencing, and further studies with higher quality methodology for a deeper understanding of MC biology in NSCLC patients are urgently needed.

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