The role of mast cells in oral squamos cell carcinoma

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Abstract

The mast cell is a connective tissue cell that has an active role in inflammation, immune modulation, angiogenesis, and more. Apart from its degranulation in allergic reaction, it is associated with "piece meal degranulation", i.e., a selective cellular secretion pathway that aggravates the progression of oral potentially malignant disorders (OPMD) to oral squamous cell carcinoma (OSCC) through angiogenic switch. Angiogenic factor released by mast cells ensures survival and progressive capacity. The tumor microenvironment (TME) is composed of many different cell populations, such as tumor-associated mast cells and various infiltrating immune cells and non-cellular components of the extracellular matrix. These crucial parts of the surrounding stroma can function as both positive and negative regulators of all the hallmarks of cancer development, including induction of angiogenesis and activation of invasion and metastasis. This review will focus on describing the role of mast cells in the tumor microenvironment and the dissection of cancer, especially oral squamous cell carcinoma.

Keywords: mast cells, tumor microenvironment, angiogenesis, oral squamous cell carcinoma

INTRODUCTION

Mast cells, described by Paul Ehrlich in 1876, are connective cells originating in a medullary progenitor cell. They are located in vascularized tissues, especially in connective tissues and mucosal surfaces [1]. The phenotype of mast cells differs according to the microenvironment in which they are located, adjusted to the functions they serve [2]. They have an active role in a wide biological spectrum of inflammation, immune modulation, angiogenesis and more.

There is ample evidence regarding the role of mast cells as a promoter of metastasis in some tumor types, but also as an inhibitor in others [3]. The tendency of mast cells to concentrate in the inflammatory and neoplastic focus in the immediate vicinity of blood vessels was observed, which was later shown to accumulate around tumors before the onset of tumor-associated angiogenesis [4].

Inflammation is responsible for both defense and protection against the carcinogen, but at the same time leads to tissue destruction. Also, the pathogenesis of oral potentially malignant diseases (OPMD) and oral squamous cell carcinoma (OSCC) begins with the inflammatory response, mediated by immune cells such as mast cells, neutrophils, lymphocytes, macrophages and others.

Head and neck cancer is considered one of the malignancies with the most severe impact on patients' quality of life, mainly caused by relatively low response to treatment and severe drug resistance [5.6]. It represents a heterogeneous group of tumors that appear from the mucosal surfaces of the oral cavity, nasal cavity, oropharynx, hypopharynx and larynx. Up to 90% of these tumors are head and neck squamous cell carcinomas (HNSCC), which is the sixth most common type of cancer worldwide. Data from the Global Cancer Observatory (GCO) show that the annual incidence of OSCC in 2020 was 377,713 cases worldwide, with the highest number recorded in Asia, followed by Europe and North America [7].

The most important prognostic determinant of HNSCC tumors is considered the presence of lymph node metastases, as lymphatic metastatic spread correlates with a significant decrease in the survival rate of patients [8]. While the main risk factors are tobacco and alcohol consumption, numerous studies suggest the role of HPV infection as a risk factor for the development of HNSCC [9].

In recent years, the perspective on cancer has changed dramatically and the tumor is no longer viewed as a mass of malignant cells, but rather as a complex tumor microenvironment (TME) in which other cell subpopulations are recruited to form a self-sustaining biological structure. The stromal component of the tumor microenvironment is composed of many different cell types, such as tumor-associated fibroblasts, neutrophils, macrophages, regulatory T cells, natural killer cells, platelets, and mast cells. These cell subpopulations interact both with each other and with cancer cells through various secreted cytokines, chemokines, growth factors and extracellular matrix (ECM) proteins.

This review will focus on describing the role of mast cells in the tumor microenvironment and cancer staging, especially oral squamous cell carcinoma.

The role of mast cells in the tumor microenvironment

In the late 1870s, Paul Ehrlich described the existence of MCs in tumor microenvironments (TME). Since then, convincing evidence has confirmed the presence of mast cells in cancerous tissues, now called tumor-associated mast cells (TAMCs) [10]. Remarkably, TAMCs can adopt the “Dr. Jekyll and Mr. Hyde", because they can be both pro- and anti-tumorigenic, or just neutral spectators [11, 12]

Mast cells can promote tumor development by mediating tumor vasculature and by inducing the release of various growth factors such as SCF (stem cell factor) [13]. The increased number of MCs in the tumor mass correlates with a poor prognosis, metastasis and reduced survival rate in several tumor types, including oral squamous cell carcinoma [14]. Mast cell accumulation can occur due to the chemotactic activity triggered by RANTES (regulated upon activation, normally T-expressed) or MCP-1 (chemokine monocyte chemoattractant protein 1).

Mast cell activation is mediated by cross-linking of the IgE receptor (FcεRI) expressed on their surface, which leads to the release of mediators from intracytoplasmic granules. Among the mediators released in the extracellular space are: heparin, histamine, tryptase, chymase, cathepsin G, prostaglandin D2, carboxypeptidase A, leukotriene C4, TNF-α, GM-CSF, chondroitin sulfate and various interleukins [15]. Mast cells release their granule content selectively through piecemeal degranulation [16]. This type of mast cell degranulation has been observed in areas of chronic inflammation or tumors and has been reported to be a preferred secretory pathway of tumor-associated mast cells (TAMC) [17].

Histamine can induce cancer proliferation through H1 receptors and simultaneously suppress host immune defense through another H2 receptor [18]. It should be noted that both histamine receptor binding sites are present on the surface of tumor cells.

Mast cells release fibroblast growth factor 2 (FGF-2) and vascular endothelial growth factor (VEGF) to induce angiogenesis [19, 20]. Therefore, mast cells are often present near CD31+ cells and blood vessels [21]. Mast cells also release tryptase, which contributes to extracellular matrix degradation and vascularization, thereby mediating angiogenesis and tumor growth as well as metastasis [22].

Mast cells can also facilitate tumor progression by modulating the tumor microenvironment (TME) and developing resistance to anticancer drugs. Mast cells can also promote cancer development by releasing specific cytokines. For example, inflammatory IL-6 release can occur independently of histamine [23].

In contrast, MCs can also mediate anticancer responses. For example, MC accumulation in a mammary gland tumor and surrounding lymph nodes can mediate tumor regression. In certain tumor types, mast cells can inhibit the growth of cancer cells by releasing proteolytic enzymes and some cytokines. Mast cell tryptase can also promote protease-activated receptors, such as PAR-1 or PAR-2, stimulated by thrombin and trypsin [24]. Protamine, which neutralizes the anticoagulant properties of heparin, can trigger thrombosis of blood vessels in the tumor mass.

The profile of mediators secreted by tumor-associated mast cells, mentioned above, suggests that tumor-associated mast cells may have both pro-tumorigenic and anti-tumorigenic roles in cancer development. The tumor-promoting functions of TAMC include: angiogenesis through the production of vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2) [25]; degradation of the extracellular matrix through the production of metalloproteinases (MMPs) and various proteases, which results in the invasion and migration of tumor cells [26]; inducing the proliferation of tumor cells through the production of histamine [27]. In addition, mast cells produce a variety of chemotactic factors through which they recruit other immune cells to the tumor [28]. Conversely, in some tumor types, tumor suppressive effects of TAMC have been reported, mainly by mediating tumor cell apoptosis through the production of IL-4 and TNF-α [29].

The role of mast cells in the pathogenesis of oral squamous cell carcinoma

Primary tumor growth is associated with the presence of immune cells, which cause inflammation commonly seen in head and neck squamous cell carcinomas (HNSCC). Mast cells influence the primary tumor mainly by producing many pro-angiogenic factors, such as

VEGF, bFGF, TGF, TNF-α, tryptase, heparin and various MMPs, which are associated with ECM degradation, angiogenesis, progression and growth of oral squamous cell carcinoma [30, 31].

The role of mast cells in potentially malignant oral diseases (OPMD), including oral leukoplakia, oral lichen planus [32] and oral submucosal fibrosis [33], has been widely documented. In the presence of a carcinogenic environment, a continuous oncogenic signal drives the conversion of normal cells to OPMD and then OPMD to OSCC [34].

A recent study showed an increase in mast cell density in both OSCC and OPMD compared to normal oral mucosa. Also, the authors observed that the number of mast cells was more reduced in OSCC than in OPMD [35]. A similar observation was presented in the study by Oliviera et al., where it was concluded that once the tumor microenvironment was established, there was a high probability for failure of mast cell migration to the tumor site [36]. Following these results, several hypotheses were formulated by the authors regarding the relevance of mast cell migration. Thus, the authors state that the failure of mast cell infiltration at the tumor level could be due either to reduced chemotactic factors to attract mast cells, or to down-regulation of the c-kit activation pathway, which are prerequisites for mast cell migration. A similar finding was also observed by Singh et al. while evaluating mast cells in OPMD and OSCC using toluidine blue staining [37].

In contrast to the mentioned studies, Iamaroon et al. [38] and Michailidou et al. [39] found a significant increase in the number of mast cells in cases of OSCC compared to OPMD. These findings were correlated with the "angiogenic switch" that could occur in the early stage of malignant transformation. Also, the authors emphasized the role of mast cells in the progression of normal tissue to dysplasia which then leads to the appearance of OSCC. Rojas et al. also observed an increase in mast cell density in squamous cell carcinoma of the lip [40].

The association of mast cells with the pathogenesis of OSCC has been controversial due to the dual role played by these cells. A group of experts believed that mast cells favor tumor progression through angiogenesis and neovascularization. On the contrary, another group of experts supports the cytotoxic function of mast cells that suppresses the tumor growth potential [41,42]. The cytotoxic effect of mast cells is present in the initial stage of tumor infiltration. However, once the tumor is established, the altered tumor microenvironment suppresses mast cell infiltration through various mechanisms, whereby its cytotoxic effect is suppressed favoring its angiogenic potential for tumor growth. This likely mechanism is potentiated with the finding that the cytotoxic effect of mast cells is actively associated with a mast cell-to-tumor ratio greater than 20:1 that reverses when the ratio changes from 10:1 to 1:100 [43].

In oral squamous cell carcinoma, a significant correlation was observed between mast cell density (MCD) and microvascular density (MVD). Following these observations, it was suggested that mast cells can regulate angiogenesis in OSCC, possibly by releasing tryptase from intracytoplasmic granules. Tumor angiogenesis is a complex event mediated by angiogenic factors released by cancer cells and/or host immune cells. Among host immune cells several observations have indicated the role of mast cells in tumor progression by promoting angiogenesis. Tryptase, FGF, IL 4, IL 8, TNF α and β are among the mediators released by mast cell granules and are strong inducers of angiogenesis [44]. The increased densities of mast cells and microvessels in oral squamous cell carcinoma indicate that mast cells may play a role in the upregulation of angiogenesis in this tumor type.

However, three studies in the literature showed no positive correlation between mast cell density and microvessel density in oral squamous cell carcinomas [45, 43, 46]. On the other hand, a study revealed a positive correlation between mast cell and microvessel densities in well-differentiated types, but not in moderately or poorly differentiated types of oral squamous cell carcinoma [47]. On the contrary, one study observed a statistically

significant correlation between mast cell and microvessel densities in poorly differentiated OSCC [44]. However, Sharma et al., in 2010, investigated the correlation of microvascular density with mast cell proliferation and revealed a positive correlation in moderately differentiated types, but not in well or poorly differentiated types [43]. On the other hand, another study stated that there was a significant correlation between mast cell and microvessel density in normal oral mucosa, but not in oral squamous cell carcinoma, regardless of histological grade [48].

Studies in the literature have shown that mast cells in the perilesional and intratumoral area of oral squamous cell carcinoma express CD105, VEGF, VEGFR1 and VEGFR2 and have shown a positive correlation with the angiogenic activity of the tumor [31]. Thus the authors suggest that mast cells influence tumor progression and growth.

Another study investigated the population of cancer stem cells expressing CD44, CD133, and CD117 at the invasion front and intra-tumor areas. Their results suggest that CD 133 and CD117 positive cells were of mast cell origin and could influence angiogenic activity [49].

Mast cells cause much debate today regarding their role in a variety of physiological and pathological processes, including cancer. They act as guardians of the immune system and, in turn, respond to many signaling pathways, thus contributing to the process of carcinogenesis and metastasis. Many studies have shown that the number of mast cells definitely increased with tumor progression. New therapies targeting mast cell mediators and receptors play an important role in controlling the process of tumor progression and metastasis, thus favoring a good patient prognosis.

CONCLUSIONS

Evidence for the crucial contribution of various stromal components, including mast cells, in regulating OSCC development implicates a fundamental role of the tumor microenvironment in providing a supportive niche, thereby substantially promoting OSCC development and metastasis.

While research has previously focused mainly on altered gene expression and aberrant genetic mutations in tumor cells, it is becoming increasingly clear that investigating differences in the stromal composition of the tumor microenvironment in OSCC and their impact on cancer development and progression may help to further better understanding of the mechanisms behind different responses to therapy.

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