The role of mast cells in inflammatory and malignant lesions of the oral cavity

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Abstract

Mast cells (MC) were described over 100 years ago by Paul Erlich. They are located in the connective tissue in the immediate vicinity of the blood vessels. Mast cells originate from a medullary progenitor cell. It presents in the cytoplasm numerous granules with a variable content of mediators. Different subpopulations of mast cells are described depending on their content in proteases and localization. They are multifunctional cells, being involved both in the body's physiological processes, but also in the pathogenesis of many diseases. Mast cells are involved in the initiation of inflammatory processes in the oral cavity by releasing proinflammatory cytokines. The role of mast cells in cancer is still debatable whether they contribute to tumor progression or have an antitumor effect.

In the future, more in-depth research on mast cells may provide not only insights into their biology, but also a better understanding of their role in various diseases. Mast cells still cause many debates regarding their role in cancer, including oral cancer. The presence of mast cells in oral squamous cell carcinomas has been noted by many authors, but their role remains unclear. However, new therapies targeting mast cells could play an important role in controlling tumor growth and metastasis.

Keywords: Mast cells, inflammation, squamous cell carcinoma

INTRODUCTION

Mast cells form a component of the immune system, playing an important role in host defense. They were first described by Paul Ehrlich in 1878 as cells belonging to the connective tissue. In histological sections, mast cells are round or oval-shaped cells with diameters between 8 and 20μ and have a large number of granules in the cytoplasm.

The content of mast cell granules is very varied. They can produce and secrete a series of substances such as: bFGF (basic fibroblast growth factor), chymase, tryptase, heparin, histamine, TNF-α (tumor necrosis factor alpha), various interleukins (IL-3, 4, 5, 6, 8, 10,13,16), chemokines, matrix metalloproteinases (MMP-2 and 9), TGF-β (transformation growth factor beta), NGF (nerve growth factor), PDGF (platelet-derived growth factor) and VEGF (vascular endothelial growth factor) [1].

They are present throughout the body and play an important role in the maintenance of many physiological functions as well as in the pathophysiology of diseases. Mast cells have been shown to be involved in the initiation of a number of inflammatory conditions. Inflammation is a double-edged sword, responsible for both defense and protection against the carcinogen but at the same time leads to tissue destruction. Also, the pathogenesis of potentially malignant oral diseases and oral squamous cell carcinomas (OSCC) begins with the inflammatory response, mediated by immune cells such as mast cells, neutrophils, lymphocytes or macrophages.

Apart from their role in maintaining homeostasis and inflammation, the association of mast cells with various tumors has been described. In several malignancies, mast cell density has been found to correlate with increased risk of metastasis and poor prognosis. Currently the functional significance of mast cells in various tumors is not yet clearly understood.

Although the presence of mast cells in tumors was recognized more than 100 years ago, only recently has more attention been directed to the role of this cell in neoplastic processes. In the oral cavity, there are few studies on the involvement of mast cells in squamous cell carcinomas, and the results reported in the literature are contradictory.

Back to the history

Mast cells were first described by Paul Erlich in 1878. He called these cells mastzellen because of the tinctorial properties and the intracytoplasmic granules [2-4]. Ehrlich also shows that these cells are located in the immediate vicinity of blood vessels and nerves. He also notes that the number of mast cells is increased in tumors and especially in carcinomas. Studies on the role of mast cells in normal and pathological conditions have a long way to go, Erlich initially suggests that these cells with their granules have the role of "feeding" the surrounding tissues. Today, the role of mast cells in some physiological reactions of the body, wound healing and angiogenesis, defense against pathogens, innate and acquired immunity is known.

Apart from Erlich, other authors also pay special attention to the study of this cell. Among them is Westphall, who in 1891 demonstrated that mast cell granules are soluble in water, and for their preservation the tissues must be fixed in 50% alcohol and stained with alcoholic thionine [5].

In 1935 Jorpes observed the metachromasia of the toluidine blue solution in contact with substances from the heparinoids group and hypothesized that the main component of mast cell granules is heparin [6,7].

The modern literature on the mast cell indicates its active participation in the pathogenesis of numerous diseases, but also in the body's general defense reaction. Among the prestigious personalities who drew attention to this topic was Hans Selye in 1965 [8].

About a century after the discovery of mast cells, Enerback describes, in 1966, two subpopulations of mast cells distinct from a histochemical point of view, thus demonstrating the heterogeneity of the mast cell system [9,10].

Recently, specialized literature pays special attention to the involvement of mast cells in tumor angiogenesis. Thus Grützkau suggests in 1998 that mast cells could contribute to angiogenesis by releasing proangiogenic factors such as VEGF [11]. Since 2009, the idea has been circulating that mast cells could be a therapeutic target for cancer treatment.

The origin of mast cells

For a long time the origin of mast cells was controversial. The origin of mast cells in a medullary progenitor cell, which expresses CD34, is now accepted [12]. In 1978 Kitamura demonstrated for the first time the origin of mast cells. Kitamura also shows that the transcription factors GATA-1 and GATA-2 are involved in the differentiation of pluripotent stem cells into mast cells, and microphthalmia-associated transcription factor (MITF) has an important role in the localization, phenotype and survival of these cells [13,14].

During prenatal development, hematopoietic cells appear in several distinct waves. The first mast cells differentiate from primitive erythromyeloid progenitors in the extraembryonic yolk sac [15]. A second wave of MCs appears together with the first definitive hematopoietic progenitors. The first two waves are mainly connective tissue MCs (CTMCs) [16]. The third hematopoietic wave comes from the aorta-gonado-mesonephros region. Cells formed during this wave produce hematopoietic stem cells that have mast cell-forming potential.

It has long been assumed that MC develops from hematopoietic stem cells in the bone marrow. However, it is now clear that the hematopoietic stem cells in the bone marrow produce only a fraction, not all, of the mast cells. A number of experiments show that bone marrow-derived MCs mainly complement the mucosal MC population (MMC) [17].

Mast cell heterogeneity: how different are they from each other?

Mast cell heterogeneity was first described in the mid-1960s and was based on different characteristics in histochemical staining. Thus the concept of connective tissue mast cells (CTMC) and mucosal mast cells (MMC) was born.

In humans, different subpopulations of mast cells have been defined by their protease content. Thus mast cells containing tryptase (MCT), mast cells containing tryptase and chymase (MCTC) and mast cells containing only chymase (MCC) in cytoplasmic granules are described [18]. The latter were, for a long time, controversial, and the presence of mast cells positive only for chymase remained ignored and practically unstudied. The two distinct subpopulations of mast cells, MCTs and MCTCs, as well as MMCs and CTMCs, differ in localization and mediator content [19].

In addition to dividing mast cells into distinct subpopulations based on their localization or protease content, there are also definitions of mast cells that are either constitutive or inducible, inflammatory (iMC), or pro- or anti-tumorigenic (MC1 or MC2) [20-22]. While the division into constitutive and inducible subpopulations could be related to the prenatal origin of MC, the latter is likely dependent on microenvironmental changes during an inflammation. It is clear that mast cells from different organs differ in receptor and mediator expression, but even within a single tissue there is considerable heterogeneity [23].

The origin and development of different subpopulations of mast cells has raised many questions. For hematopoiesis in the adult, the question was whether there are several different populations of progenitor MCs in circulation or whether there is a progenitor population that has the ability to differentiate and mature into any of the MC subtypes. In other words, heterogeneity is driven by locally produced factors or is driven by the

recruitment of different types of designated progenitors. In a study addressing this question, the results suggested the existence of a common progenitor that gives rise to all subpopulations of mast cells [24]. However, single-cell RNA sequencing and single-cell cultures will likely provide further evidence and insights into this process.

Mast cells in oral inflammation

Mast cells are involved in the initiation of a number of inflammatory conditions in the oral cavity. Gingival inflammation can lead to periodontal disease, where cytokines activate and stimulate mast cells to secrete proinflammatory molecules that play a critical role in inducing inflammation [25]. Increased levels of proinflammatory cytokines, such as IL-1, TNF, and IL-6, are secreted by various cells of the immune system, including mast cells. The role of MC in periodontal disease is not yet clear. However, in this condition, an increase in the number of mast cells and the production of inflammatory cytokines is observed, thus demonstrating their involvement in alveolar bone resorption. In oral tissue, MCs producing cytokines and proteases (tryptase and chymase) favor leukocyte infiltration, causing degradation of the extracellular matrix and leading to gingivitis and periodontitis [26]. In acute inflammation, MCs release various proinflammatory molecules such as histamine, proteoglycans, arachidonic acid metabolites, TNF, and tryptase, a serine proteinase that promotes inflammation. Histamine, acting on the endothelium, mediates vascular permeability and favors platelet adhesion through the adhesion molecule P-selectin.

Mast cells are able to process microbial antigens intervening in acquired immunity and play a key role in inflamed periodontal tissue by producing IL-33 and other pro-inflammatory cytokines. Mast cells play a crucial role in the pathogenesis of allergic and systemic diseases by producing proinflammatory cytokines of the IL-1 family, effects that can be suppressed by IL-37 by forming an extracellular complex with IL-18Rα and IL1R8. In periodontitis, there is a higher expression of pro-inflammatory cytokines, such as IL-33 produced by MC, associated with the pathogenesis of periodontal disease.

Today, IL-37 is known to inhibit innate and acquired immunity and consequently inflammation, an effect that could complement the treatment of acute and chronic gingival inflammation, including periodontal disease [27]. Because IL-37 is a potent blocker of IL-1 and a pro-inflammatory cytokine in periodontal disease, it has been hypothesized that IL-37 treatment of periodontal disease could be an additional therapeutic adjunct to traditional drugs [28].

Mast cells in oral squamous cell carcinoma

The role of mast cells in cancer is still debatable whether they contribute to tumor progression or have an antitumor effect. The presence of mast cells in tumors has been shown to be an independent prognostic factor in prostate cancer, malignant melanoma, pancreatic cancer and leukemia [29]. Increased expression of c-Kit and stem cell factor, which in turn are required for mast cell migration, maturation and survival, has been observed in breast tumors [30]. In addition, increased mast cell numbers and mast cell infiltration in the peritumoral stroma have been observed in Merkel cell carcinoma, lung cancer, hepatocellular carcinoma, colorectal cancer, and Hodgkin's lymphoma [31]. Several cell types, such as tumor cells, endothelial cells, macrophages, and mast cells are involved in increased vascularity in neoplasms [32]. Mast cells are directly involved in the evolution of neoplasia because, beyond their defense functions, they participate in regulating the homeostasis of blood vessels [33]. Their participation in this microenvironment has been suggested in various malignant tumors [34]. Regarding oral squamous cell carcinoma (OSCC) it has been observed that there is an increased density of microvessels and an increased density of mast cells in these tumors, which may be a reason for a poor prognosis [35,36].

Squamous cell carcinoma is the most common malignant lesion in the head and neck region, representing 95% of all malignant lesions in this area. Despite the great progress made in the field of cancer research, the availability of sophisticated diagnostic techniques and improvements in the therapeutic options of patients, the prognosis remains reserved in OSCC. This is probably due to the unpredictable behavior of these tumors, which show a variable aggressiveness independent of the clinico-pathological and histological grade [37].

Because oral squamous cell carcinoma is associated with chronic inflammation in the adjacent connective tissue, immune reaction, and angiogenesis with the progression of dysplastic changes, there is a need to evaluate the role of mast cells in these carcinomas.

Mast cell density in oral squamous cell carcinoma has been reported differently in the specialized literature. Studies by Oliveira-Neto et al. and by Teófilo et al. showed a decrease in the number of mast cells in OSCC [38,39]. The study carried out by Zaidi et al. show that mean mast cell density/mm2 was significantly increased in OSCC cases ($P < 0.05$) compared to normal tissue [40]. This was also demonstrated by the study of Iamaroon et al. and Michailidou and Antoniades. These authors suggested that mast cells release potent pro-angiogenic factors, such as tryptase, which play a significant role in angiogenesis associated with oral squamous cell carcinoma [41,42].

Many studies have been conducted on the role of mast cells in oral cancer and their accumulation in the peritumoral stroma. The involvement of mast cells is linked to the release of important pro-angiogenic factors, which help the interaction of the tumor with the host, thus supporting tumor progression. Not only was its involvement in tumor progression identified, but the progression of leukoplasia with and without dysplasia in oral squamous cell carcinoma was also established. The main factors released are heparin, histamine, chymase, tryptase, bFGF (basic fibroblast growth factor), VEGF (vascular endothelial growth factor) [43].

Other data from the specialized literature show a significant increase in mast cell density in well-differentiated oral squamous cell carcinomas compared to moderately or poorly differentiated ones [44]. A molecular epidemiological study of the mast cell population revealed a significantly higher number of mast cells in squamous cell carcinoma in the skin than in the oral mucosa. In addition, the number of mast cells was higher in squamous cell carcinoma of the lip than in normal oral mucosa. Another study showed that the increase in the mast cell population is not related to the degree of tumor differentiation [45].

The increased density of mast cells and microvessels indicates that mast cells play an important role in regulating angiogenesis in oral squamous cell carcinoma [46]. However, some studies have shown that there is no significant correlation between mast cell density and microvessel density in oral squamous cell carcinoma [47]. On the other hand, Kathuriya et al. showed a significant correlation between mast cell and microvessel density in well-differentiated types, but not in moderately or poorly differentiated types [44]. On the contrary, another study reported a significant correlation between mast cell and microvessel density in poorly differentiated OSCC [35].

On the other hand, another study stated that there was a significant correlation in mast cell and microvessel density in normal oral mucosa but not in oral squamous cell carcinoma regardless of histological grade [48]. However, another study showed that in oral squamous cell carcinomas mast cells in the peritumoral and intratumoral stroma express CD105, VEGF, VEGFR1 and VEGFR2 and showed a positive correlation with the angiogenic activity of the tumor. Also, this study shows that a mast cell influences tumor progression and growth [49].

As can be seen from the studies presented, the results from the specialized literature are controversial so that the exact role of mast cells in oral squamous cell carcinomas is not known. The presence of mast cells in oral squamous cell carcinomas has been observed by many authors, but their role in tumor progression and metastasis still remains unclear.

CONCLUSIONS

The biology and function of mast cells, both under normal and pathological conditions, has been a fascinating topic for many researchers over the years. Many fundamental discoveries have been made since the discovery of mast cells in the late 19th century, shedding light on the function of this ingenious cell. However, there are many questions that still await an answer. With the rapid developments in methodology, systems biology in combination with experimental studies and clinical investigations, a rapid development of mast cell research can be foreseen in the coming years. This research will not only provide insights into the biology of mast cells, but also a better understanding of their role in various diseases.

Arguably, mast cells cause much debate 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 revealed that the number of mast cells definitely increased with tumor progression. New therapies targeting mast cell mediators and receptors could play an important role in controlling the process of tumor progression and metastasis, thus favoring a good prognosis for the patient.

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