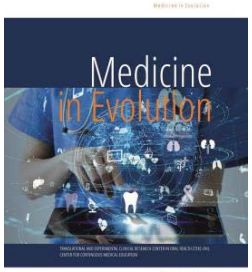
The dark side of mast cells and their role in oral pathology



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Abstract

Mast cells (MC) were discovered over 130 years ago, and their function was almost exclusively related to allergic diseases. It is now well known that MC possesses a wide variety of roles in both physiological and pathological conditions. These cells play a key role in inflammatory processes in the oral sphere (dental pulp, periapical tissue and gums). In oral tissues, MC release various proinflammatory cytokines and tumor necrosis factor-alpha that promote leukocyte infiltration in various inflammatory conditions of the oral cavity. The number of mast cells has been found to be altered in various premalignant and malignant conditions developed in the oral sphere. The present review aims to describe the role of mast cells in the initiation and progression of inflammatory processes, but also in premalignant and malignant lesions of the oral cavity.

Keywords: Mast cells, normal oral mucosa, oral pathologies

INTRODUCTION

Mast cells (MC) are a type of innate immune cell that belong to the myeloid lineage. In both humans and animals, MC derives from hematopoietic stem cells. Mast cell progenitors leave the bone marrow as immature cells and enter the blood circulation and with the help of surface molecules, such as integrin α4β7, MAdCAM-1 and VCAM1, migrate to various target tissues [1,2].

Despite the fact that all mast cells derive from a common precursor and have granular cell morphology, they are extremely heterogeneous in terms of phenotype and function [3]. The heterogeneity of mast cells is most likely influenced by the surrounding microenvironment. In rodents, two phenotypes were described: connective CTMCs (connective tissue MCs) and mucosal MMCs (mucosal MCs) that differ in location, mediator content and response to different stimuli. Human mast cells are also divided into two types depending on their content in proteases [4]. Thus, mast cells that contain only tryptase (MCT) in granules and mast cells that contain tryptase but also chymase (MCTC) are described.

Mast cells are located at the interface between the host and the environment, in the immediate vicinity of blood vessels, lymphatic vessels, nerve fibers, but also in the vicinity of some cells of the immune system, including dendritic cells [5]. This strategic location allows mast cells to act as sentinels against microbial invasion, but they can also quickly respond to any change in the surrounding microenvironment due to interactions with other cells involved in the body's physiological and immunological response. Mast cells are found in all connective tissues of the oral cavity, including the dental pulp, periodontal ligament and gingiva.

The induction of inflammation by MC is a consequence of the release of preformed biological mediators as well as secondary mediators [6]. Mast cells were also detected in the inflammatory infiltrate associated with periapical cysts and granulomas, suggesting their role in the inflammatory mechanism of these lesions. Among the cells present in periodontal tissues are also mast cells, which are present both in healthy and inflamed gums [7].

The role of mast cells in the immunological and non-immunological processes of the body is well known, an aspect reflected by the large number of mediators present in the granules through which they influence other cells. These mediators allow mast cells to carry out their functions at the tissue level [8]. However, the role of mast cells in the pathogenesis of oral pathologies is still debatable. Therefore, we set out in this review to explore the role of mast cells in the initiation and progression of pulpal, periapical, periodontal inflammatory processes, but also in premalignant and malignant oral lesions.

Mast cell: morphology and secretory granules

Examined under optical microscopy, mast cells appear as round or elongated cells with a diameter between 5-25 μm depending on the organ in which they are studied. They present a round or oval-shaped nucleus, and have numerous secretory granules in the cytoplasm. Each MC typically contains between 80 and 300 granules bounded by a double membrane.

Under the influence of some stimuli (physical, chemical, toxins, bacteria, or viruses) mast cells are activated and degranulate explosively, after which they resynthesize their granules or can continuously release solitary granules into the extracellular environment. This process is called "piecemeal degranulation" and has been observed in both the oral mucosa and the skin.

After degranulation, mast cell mediators are deposited in large quantities in the extracellular environment, where they exert effects on endothelial cells, but also on other cell

types. Mast cells can subsequently synthesize and secrete additional mediators that are not preformed in their granules. Preformed mediators are represented by proteases (tryptase, chymase and cathepsin G), histamine, heparin, serotonin, TNF-α (tumor) and interleukin-16 (IL-16). As a result of activation, MCs can synthesize a number of mediators, de novo, such as: IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13 and IL-16, PGD2 (prostaglandin 2), LTC4 (leukotriene C4), MIP 1a (macrophage inflammatory protein), RANTES (regulated on activation, normal T cell expressed and secreted) and PAF (platelet activating factor) [10,11].

Mast cells in dental pulp inflammation

The inflammatory process in the human dental pulp is associated with vascular changes and migration of inflammatory cells to the site of inflammation. Normally in healthy dental pulp

MCs are found in small numbers, but an increase in the number of MCs is observed in pulpitis.

High concentrations of TNF-α, its source, were detected in the inflamed dental pulp being the mast cell granules released after the degranulation of these cells [12] At the pulp level dental substance P can mediate mast cell degranulation after they are activated ca following the bacterial invasion of the dental pulp during the formation of dental caries [13]. Karapanou *et al*. hypothesized that MC activation may occur through neuropeptides which are released locally into the pulp and subsequently pro-inflammatory mediators which are released from mast cell granules can participate in the inflammatory process of the dental pulp and serve as diagnostic markers for inflammatory diseases of the dental pulp [14]. The presence of mast cells in the dental pulp and their role in dental pulp inflammation was a controversial issue because past studies have revealed that mast cells are absent in normal pulp tissue and few cells in inflamed tissue [15]. These controversies can be also related to the technique of sampling and processing the dental pulp. Ali Farnoush suggested that the method used to obtain the dental tissues and the fixation process could change mast cell integrity [16]. Studies by Martins *et al*. and Nica *et al*. [17] showed a complete absence of mast cells in human and rat dental pulp. They assume that the pulp is a single connective tissue surrounded by a mineralized tissue and is considered a low compliance environment. In that situation, the presence of mast cells could generate the release of vasoactive substances that could produces pain. On the other hand, Zachrisson *et al*. reported the presence of a few mast cells intact around blood vessels and adjacent to plasma cells in the pulp of young teeth [18]. Dinakar *et al*. demonstrated the presence of a small number of mast cells on the sections of healthy pulp tissue and a higher number of mast cells in the inflamed pulp tissue, the difference being statistically significant [19]. These results justify the fact that mast cells are activated in during inflammation and releases various vasoactive amines such as histamine, heparin, but also cytokines such as TNF-alpha and interleukin-8 from their granules. Demonstration of increased mast cell density in the inflamed dental pulp throws a shed of light on the fact that mast cells are important in the regulation of pulpal pathology. These cells could have both a protective and destructive role due to the fact that they can cause destruction of connective tissue in inflammation. Because mast cells play an essential role in inflammation, therapies targeting mast cell function may have value in management chronic inflammation of the dental pulp. Moreover, this could also help to treatment planning in pulpitis, because mast cell stabilizers and antihistaminic agents could be used in the future to control pulpal pain and inflammation.

Mast cells in inflammatory periapical lesions

Cysts and granulomas are chronic periapical lesions mediated by a set of mediators of inflammation. The inflammatory infiltrate of periapical lesions is mainly composed of

lymphocytes and plasma cells, but contains other cells such as macrophages and mast cells [20].

Several studies have reported the presence of mast cells in periapical inflammatory lesions. Smith *et al*. demonstrated the presence of mast cells in the thickness of the cyst capsule, and observed that MCs were more widespread under the epithelium than in the deeper areas of the cyst [21]. The study by Oliviera *et al*. demonstrated the presence of a greater number of mast cells in periapical cysts than in granulomas. In periapical cysts MC were more numerous in region with active inflammation. In addition, the authors observed that MCs tended to concentrate in the peripheral regions of the periapical lesions, in close proximity to the lymphocytes [22]. The presence of mast cells in periapical chronic inflammatory lesions is demonstrated by many authors and it is suggested that mast cells play an important role in the pathogenesis of lesions chronic inflammatory [23]. After activation, MCs induce the migration of T lymphocytes either directly through the release of chemokines such as IL-16 and MIP-1 or indirectly by inducing expression adhesion molecules on endothelial cells. Histamine increases vascular permeability and favors the adhesion of leukocytes to the endothelium through the transient mobilization of the molecule de P selectin adhesion to the surface of the endothelium [24]. This functional relationship between MC and T lymphocytes has been shown to be bidirectional, performing reciprocal roles of regulation and/or modulation. In addition, T-lymphocyte-derived mediators such as chemokines directly induce mast cell degranulation. In the periapical granuloma, stimulated mast cells can release IL-1, which causes epithelial proliferation, thus being one of the factors that determine the proliferation of epithelial cells from the remains of Malassez thus leading to the formation of the cyst. Mast cell-derived tryptase can activate matrix metalloproteinases that determine the degradation of the extracellular matrix and bone resorption, which allows an increase in lesions [25]. Mast cells can act as antigen-presenting cells in inflammatory lesions periapical and are also involved in the expansion of periapical cysts because it is the only cell from which tumor necrosis factor alpha is immediately released from stores preformed. The effects of TNF-alpha include stimulation of bone resorption by osteoclasts, growth local vascular response and promotion of chronic inflammation in human periapical lesions [26].

Mast cells in gingival inflammation

Mast cells have been consistently reported to be present in healthy gingival tissue. At the level of the gums, mast cells are located both in the connective and intraepithelial tissue [27]. In gingival lesions, plaque products can directly or indirectly induce mast cell proliferation [28]. Proinflammatory cytokines that are released during the initial stage of inflammation influence mast cell migration. Following degranulation, large amounts of mediators are released into the extracellular environment, where they exert effects on endothelial cells, as well as on other types of cells. TGF β (transforming growth factor-β), FGF (fibroblast growth factor), as well as inflammatory cytokines and chemokines are key factors in the inflammatory process, facilitating the recruitment and activation of mast cells.

Mast cells produce mediators such as histamine, heparin and TNF-α, which can influence the proliferation of fibroblasts, the synthesis and degradation of the extracellular matrix. TNF-α also upregulates RANTES expression, which in turn triggers subsequent mast cell degranulation. MC degranulation can lead to chronic gingival inflammation and fibrosis [27].

Gingival inflammation can lead to periodontal disease, in which cytokines activate and stimulate MC to secrete pro-inflammatory molecules that participate in the pathological state of the tissue and therefore play a critical role in inducing inflammation [29]. Increased levels of proinflammatory cytokines, such as IL-1 and IL-6, are secreted by various cells of the

immune system, including mast cells. The role of MC in periodontal disease is still not very clear. However, in this pathology there is an increase in the number of mast cells, as well as the production of inflammatory cytokines, thus demonstrating their involvement in alveolar bone resorption.

In the gingival tissue, MC releases cytokines and proteases, such as tryptase and chymase. Thus, the infiltration with leukocytes, the degradation of the extracellular matrix and the appearance of gingivitis and periodontosis are favored [30]. In acute inflammation, histamine released by MCs acts on the endothelium, mediates vascular permeability and promotes platelet adhesion through the adhesion molecule P-selectin.

Periodontal cells and inflammatory-immune cells, including MC, produce cytokines and chemokines, thus mediating local inflammation of the gingival tissue, along with the destruction of the periodontal ligament and alveolar bone [31].

IL-1 and IL-33 are inflammatory cytokines released by mast cells that mediate inflammation and contribute to many key features of periodontitis and other inflammatory disorders [30]. IL-37 inhibits innate and acquired immunity and consequently inflammation, an effect that could complement the treatment of acute and chronic gingival inflammation, including periodontal disease [32]. Blocking IL-1 with IL-37 could result in an inhibition of inflammation in periodontal disease, but all these data need to be confirmed in the future. Thus, it can be hypothesized that IL-37, being a blocker of IL-1, one of the main inflammatory cytokines involved in the pathogenesis of periodontal disease, could be helpful in the therapy of this condition [33].

Mast cells in premalignant lesions

In premalignant lesions of the oral mucosa, such as leukoplasia, oral submucosal fibrosis, and lichen planus, an increased density of mast cells has been observed compared to normal oral mucosa. In a study by Biviji *et al*. observed similar aspects in leukoplakia and concluded that active mediators released from mast cell granules might contribute to an inflammatory reaction seen in leukoplakia. Stimulated mast cells can release interleukin-1, which causes the increased epithelial proliferation seen in leukoplasia. Histamine can cause increased mucosal permeability that could facilitate increased access of antigens to the connective tissue [34].

Sathyakumar *et al*. compared and correlated mast cell density (MCD) and microvascular density (MVD) in normal oral mucosa and oral mucosa with varying degrees of dysplasia. The authors concluded that the number of mast cells and microvessels can be used as indicators of disease progression [35].

Studies on MC were also conducted by Bhatt *et al*. who noticed a higher number of MC in oral submucosal fibrosis (OSMF) compared to oral mucosa normal. The authors suggested that some of the signs and symptoms seen in OSMF might be attributed to mast cell hyperplasia [36]. Mast cell histamine could be responsible for the submucosal edema seen in stages beginnings of OSMF. On the other hand interleukin-1 in MC could cause a response increased fibroblast, and mast cell tryptase causes increased production of collagen type 1 and fibronectin, being the cause of increased fibrosis. Sabarinath *et al*. evaluated MCD and MVD in normal oral mucosa and in varying degrees of OSMF. The results showed a significant increase in MCD and MVD in OSMF cases. May much, a positive correlation was found between MCD and MVD [37]. There are many studies in the literature that suggest that mast cells play a role important in the pathogenesis and evolution of oral lichen planus (OLP). The interactions between MC and T cells, which are related to the disease process, are relevant both to the initiation phases, vaso-induction and effectors of OLP. TNF-alpha released from MC causes increased synthesis of matrix metalloproteinases, such as collagenase, which cause membrane destruction basal cells and cause increased expression of adhesion molecules such

as E-selectin and ICAM. This could probably cause increased leukocyte migration [38]. In oral lichen planus, mast cells were observed in increased numbers at the junction epithelial and connective tissue, in areas with basement membrane rupture. It was also observed increase in mast cell degranulation in this condition. Thus establishing a definite role played of mast cells and their degranulation would possibly provide a way of permanent treatment and effective for oral lichen planus [39].

Mast cells in malignant tumors of the oral cavity

Mast cells tend to concentrate around blood vessels, in inflammatory foci and neoplastic and later to accumulate near the tumors before the onset of angiogenesis associated with the tumor [40]. They also have an important function in regulating neovascularization physiological and pathological [41]. Mast cells are a major source of pro-angiogenic factors. In various malignant tumors solid, mast cells are arranged on the periphery of tumor areas to facilitate angiogenesis through release of preformed mediators. Sometimes a large number of mast cells are seen even before from the appearance of neovascularization from certain malignant tumors. A pioneering study by Tomita *et al*. they cited two reasons for the reports contradictory regarding the role of MC in malignant tumors and their associated angiogenesis [42]. First, when MCs infiltrate the tumor tissue, the cytotoxic function of they suppress the activity of tumor cells. However, after infiltration, the cells tumors could instigate the angiogenic properties of MCs while suppressing their functions cytotoxic, thus leading to tumor angiogenesis. Second, the cytotoxic effects of MCs are reported when the MC-to-tumor ratio is > 20:1. Instead, these effects are abrogated when the MC-to-tumor ratio is increased from 10:1 to 1:100, leading to tumor progression. Therefore, the effect of MC against cancer cells might depend on the concentration of mast cell mediators released in the microenvironment. Based on these findings, researchers hypothesized that reversing this process, i.e. improving cytotoxic functions of MCs and suppression of their angiogenic functions, could lead to a new treatment strategy anticancer [43]. Malignant tumors of the oral cavity represent a public health concern at the level world. The most common malignant tumor is oral squamous cell carcinoma (OSCC), which accounts for nearly 90-95% of all oral cancers. It is an invasive malignant epithelial tumor and aggressive. It is often preceded by the development of potentially malignant conditions that present histologically different degrees of epithelial dysplasia. The most important potentially malignant disorder affecting the oral cavity is oral leukoplakia. Some studies on the involvement of mast cells in oral squamous cell carcinomas, show an increase in mast cell density in these malignant tumors. This aspect was noticed by Rojas *et al*. in squamous cell carcinoma of the lip [44]. A significant correlation between MC and density was also observed microvascular in oral squamous cell carcinoma (OSCC). Also in oral squamous cell carcinoma a linear increase in the number of MCs and OSCC progression was also observed. The authors suggested that mast cells may regulate angiogenesis in OSCC, possibly by releasing mast cell tryptase. Through therefore, the number of MCs can be used as an indicator of disease progression [45]. The study by Kalra *et al.* suggested that angiogenesis in OSCC and could be used as an index to express the aggressiveness of the disease, however MC represents only a part of the complex process of angiogenesis, together with other factors secreted by the tumor [46]. Another study by Laishram *et al.* demonstrates a significant increase in microvascular density (MVD) and mast cell density (MCD) in carcinoma cases oral squamous cell carcinoma, followed by cases of leukoplakia with dysplasia, leukoplakia without dysplasia, and normal gingival tissue. Therefore, it is concluded that MC can play a significant role in angiogenesis by releasing pro-angiogenic factors that can favor, in turn, progression premalignant lesion to a malignant one [47]. Patil, in his study, suggests that MC by releasing a variety of mediators have regulatory function on angiogenesis, and inflammation can facilitate the transformation of leukoplakia

into invasive squamous cell carcinoma [48]. Other studies in specialized literature demonstrate a reduced number of mast cells in oral squamous cell carcinomas. Thus, the study carried out by Teófilo *et al*. showed a decrease in the number of mast cells in oral squamous cell carcinomas, but observe a vascularization increased in these malignant tumors. Following these observations the authors suggest that angiogenesis begins when the malignant transformation begins, which seems to be inversely associated with the number of mast cells [49]. MC/OSCC interactions affect tumor cell characteristics and thereforetumor progression, making them interesting candidates for targeted tumor therapy. In his study Hemmerlein *et al*. identified CCL2 for the first time in OSCC as a potential mediator of this interaction. Data suggest that CCL2 may promote tumor cell proliferation. Further studies should characterize the functional relationships [50]. Mast density itary (MCD) and the role of these cells in oral squamous cell carcinoma a has been reported differently in the specialized literature. Some studies have shown an increase in mast cell density, while others demonstrated a decrease in MCD. Thus, the role mast cells in angiogenesis, progression and metastasis of oral squamous cell carcinomas still remains unclear.

CONCLUSIONS

Mast cells play a critical role in the development of inflammation in the dental pulp and periodontium, acting both in the early stages and during the transition from acute to chronic inflammation. In the future, it may be possible to develop new approaches that influence the release of proinflammatory molecules or neuropeptides to ameliorate mast cell-driven inflammation.

Mast cell function can vary depending on the type of cancer and clinical stage. More detailed studies are needed to elucidate the varied roles of MC. However, the present findings indicated the relevance of mast cells as a diagnostic and therapeutic target in oral squamous cell carcinomas.

From the results of this review, it can be concluded that additional research studies on mast cells can improve our knowledge of their exact role in the pathogenesis of various oral pathologies.

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