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Contemporary Updates on the Role of Mast Cells in Oral Lesions: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Mast cell (MCs) is considered the immune cell of myeloid lineage and make a crucial role in the inflammatory process in several types of oral diseases. This mast cell contains 50–200 large granules which are inflammatory mediators, including rich in histamine and heparin. It is mainly found in the connective tissues of the oral mucosa like nerves, blood vessels, and subepithelial areas of the human body. These cells have a key role in the maintenance of many physiologic functions of the body and thus their number was altered in various pathophysiologic diseases

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of the oral cavity such as benign and malignant tumors, reactive lesions, autoimmune diseases, odontogenic cyst, tumors, etc. The present paper is focused on the current concept and updates on the role and function of mast cells in physiologic and pathologic conditions of the oral cavity.

Keywords: Mast cells; oral mucosa; oral pathology; histamine; interleukins; angiogenesis effect.

1. INTRODUCTION

Mast cells (MCs), also known as mastocytes and labrocytes, are a type of cell found in the human body. It's most common in connective tissue, which has a lot of basophilic granules in their cytoplasm that covers over the nucleus [1]. In 1878, Paul Ehrlich discovered the mast cell and named it "mastzellen," a German word that means "to feed." It's mostly associate with blood vessel, neural tissue, and inflammatory disease, according to Ehrlich. Mast cells are thus specialized immune cells that have both pro-inflammatory and anti-inflammatory properties [2,3].

Mast cells, which are produced from bone marrow and are a multipotent progenitor of CD34, disseminate and flow into the peripheral circulation. Mast cells are ovoid, tadpole/spindle-shaped cells that range in size from 8 to 20 m in diameter and appear in histologic sections as ovoid, tadpole/spindle-shaped cells. Metachromatic dyes such as toluidine blue, methyl violet, Azure B, safranin, and azure A indicate the presence of metachromatically stained secretory cytoplasmic granules in mast cells [3,4]. The granules range in size from 0.2 to 0.5 m in diameter, and they are high in histamine and heparin, interleukin-4, chymase, basic fibroblast growth factor, MMPs, vascular endothelial growth factor (VEGF), transforming growth factor-beta, and tryptase [5].

Mast cells indicate either a destructive or a healing phase, depending on the type of the oral lesions. Mast cells secrete both primary and secondary chemical mediators (degranulation), which cause inflammation both directly and indirectly by attracting other cell types, such as lymphocytes, to the site [3].

Different proinflammatory cytokines, interleukins (IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and IL-16), and tumor necrosis factor-alpha (TNF-α), as well as tumor necrosis factor-alpha (TNF-α), are released by MCs and increase leukocyte infiltration in diverse oral lesions. These cells are also high in proteases, including tryptase and chymase, which act on connective tissue with proteolytic activity and encourage angiogenesis, which aids in lesion invasion and metastasis [4,6].

Mast cells can be classified into three categories based on their granular cell shape.

1. Mast cells, have a distinct border of numerous cytoplasmic granules in the cytoplasm and no visible nucleus. Mast cells, often known as "intact cells," are commonly found in deep connective tissues.
2. Degranulated mast cells with a poorly defined cell boundary, sometimes known as "granulating cells," are observed in connective tissue cell infiltrates.
3. The mast cell which has a flattened or irregular form with faint and poorly defined cell borders. The nucleus is only partially visible because the cytoplasm is less granular. Mast cells also referred to as "spreading cells," are present in the intestines [7,4].

Mast cells are divided into two groups based on their chemical composition.

1. Mast cells (MCT) are found in the interalveolar section of the lungs and the mucosa of the small intestine and release solely tryptase in their granules.
2. Mast cells produce both tryptase and chymase in the epidermis and the intestinal submucosa (MCTC) [4].

The mast cell is classified into two categories based on its phenotypic and functions.

1. Connective tissue MCs (CTMCs) contain tryptase and chymase,
2. Mucosal MCs (MMCs) contain chymase [4].

The importance of MCs in immunologic illnesses such as allergic diseases, anaphylaxis, autoimmunity, and other reproductive diseases has been extensively reported in the medical

literature. However, its role in the etiopathogenesis of oral lesions is still being contested, as shown below. The current concept and role of mast cells in the initiation and progression of oral lesions, which can range from developmental to reactive to inflammatory to neoplastic, was examined in this research since the oral mucosa is subjected to both external and internal stimuli.

The review of mast cells in the oral lesion was found by searching PubMed (34 articles), MEDLINE (30 articles), and Clinical key (26 articles) for the terms mast cells and an oral lesion.

2. MAST CELL IN ORAL HEALTH AND PATHOLOGY

Mast cells can be found in abundance in the oral mucosa's connective tissue, such as the periodontal ligament, tooth pulp, and gingiva. Mast cells are difficult to detect in this connective tissue of the oral mucosa, so special stains such as toluidine blue staining and immunohistochemical staining methods are needed to visualize them under a bright field microscope, as well as another special microscopy such as electron microscopy to demonstrate mast cell degranulation [4].

In normal mucosa (NM), the mast cell count (MCC) is 25.50/sq.mm [8] and 12.2/microscopic field at 400X using Toluidine blue stain [9] and 41.67 15.38 cells/sq.mm using MC tryptase antibody. Using monoclonal antibodies specific for tryptase, MCC was shown to be 71 16 cells/ sq.mm in typical healthy gingival [10].

In diverse oral pathological conditions, the number of MCs changes. The following are some examples of studies on common oral conditions:

3. MAST CELLS IN COMMON DENTAL CONDITIONS

The expression of mast cells in the dental pulp was incredible due to mast cells degranulating after dental pulp removal and also expressing progenitor MCs. During inflammation, high TNF-α convergences in human tooth pulp tissue have been identified. The concentration of mast cells starts decline when the aggravation of the dental pulp advances towards putrefaction, while the least number of mast cells is found in the intact dental pulp tissue.

Although a crucial concentration of mast cells has been discovered in gingival inflammation, little information is known about their role in the support and development of the stimulating inflammatory cycle. In addition, there is no data on the association between MC density and inflammatory cells in connective tissue.

Huang et al. discovered a link between MC degranulation and different stages of periodontitis. The number of positive-tryptase degranulated MCs in severe periodontitis is much higher than in mild periodontitis and normal mucosa, according to the researchers. It was unable to identify whether the inflammatory cells' inflammation was the cause of the degranulation [11].

Interestingly, another study found that the severity of periodontitis correlates with a decrease in mast cell density (MCD) [12]. MCs are proven to be related to inflammatory cells and in the development of emerging capillaries in periodontal infection. Clinical evidence of MCs regulating angiogenesis and lymphangiogenesis has been established. The endothelial cells of the microvessel number in various oral pathologic circumstances produce vascular endothelial development factor (VEGF), which proves and supports this viewpoint [4].

4. MAST CELLS IN INFLAMMATORY REACTIVE CONDITIONS

Kfir et al. discovered four forms of reactive hyperplastic lesions: pyrogenic granuloma (PG), peripheral giant cell granuloma (PGCG), peripheral ossifying fibroma (POF), and fibrous hyperplasia (FH). Mast cells play a role in the onset and progression of inflammation in the oral mucosa, both in early vasoinductive functions and in the transition from acute to chronic aggravation, implying that mast cells are involved in inflammatory cell migration and angiogenesis [5].

When compared to normal healthy gingiva, chronic marginal gingivitis and acute necrotizing gingivitis showed a decrease in MC [13]. Gingival hyperplasia has been linked to an increase in MC density [14].

Irritation fibroma, inflammatory fibrous hyperplasia (IFH), peripheral giant cell granuloma (PGCG), and peripheral ossifying fibroma were among the response lesions studied by Farahani (POF) and detected an increase in the quantity of MCs in reactive

lesions as compared to healthy gingival tissues. MCs in the PGCG were substantially lower than in the IFH and POF lesions. MCs are thought to play a role in collagen formation and, as a result, in the range of microscopic highlights found in oral reactive tissue lesions, according to the research [15]. According to Vandana et al., the number of mast cells was highest in POF and FH, followed by pyogenic granuloma and PGCG, implying that mast cell is a trademark for pyogenic granuloma and PGCG [5].

Oral pyogenic granuloma is considered a responsive lesion because of etiologic components like an injury. MCs' seen to be higher density in the connective tissue of pyogenic granuloma as compared to healthy mucosa [16]. Murata et al., examined the development of granulation tissue which is accounts by different cytokines, especially basic fibroblast growth factor (bFGF) seen during wound healing after injury. According to some authors, mast cells play a key part in the pathogenesis of oral pyogenic granuloma, in which neovascularization occurs during granulation formation as a result of bFGF being produced and released into the connective tissue by MCs and macrophages [17]. Similarly, Kamal et al. found that mast cells were abundant in pyogenic granuloma compared to normal mucosa by using 1% toluidine blue [18].

Hamideh et al. investigated the mast cells' role in irritational fibroma, peripheral ossifying fibroma, and normal mucosa and opined that it has induction of collagen fibres resulting in fibrosis in these lesions [19].

5. MAST CELLS IN ODONTOGENIC CYSTS

MCs were keenly observed in periapical cyst as well as in inflammatory periapical cyst. MCs and lymphocytes were found to be in a close relationship to each other and this will help us to explain the immune response which facilitates the pathogenesis of odontogenic cysts. A few authors propose that TNF- alpha is released from MCs which act as an antigen-presenting cell in periapical cysts and result in the stimulation of osteoclast activity, neovascularisation, and aggravation of inflammatory cells in these lesions [20,21].

Patidar et al. examined the odontogenic keratocyst (OKC), dentigerous cysts (DC), and radicular cysts (RC) for the existence of mast cells using toluidine blue stain and they found that the density and number of MCs/mm2 of connective tissue section were higher in RC compared to other odontogenic cysts and also explained that the density was higher at superficial connective tissue compared to deeper connective tissue [22].

6. MAST CELLS IN BENIGN AND MALIGNANT TUMORS

Hagiwara et al. investigated the number of MCs in numerous vascular proliferating tumors, including cutaneous pyogenic granuloma, port-wine stain, cavernous hemangioma, cherry angioma, Kaposi's sarcoma, and malignant hemangioendothelioma, using IHC with tryptase stain. A cutaneous pyogenic granuloma, malignant hemangioendothelioma, and cavernous hemangioma had a higher density of MCs than port wine stain, cherry angiomas, and Kaposi's sarcoma. Based on this observation, they concluded that there is no difference in MC density between benign, intermediate malignant, and malignant vascular tumors. It appears to be difficult to ascertain if a distinct MC density is responsible for different vascular tumors due to the extremely high level of MC thickness in three types of vascular expansions. They speculated that there might be a limit to how much MC density can be inducted, but this conjecture has to be confirmed [23].

7. MAST CELLS IN PREMALIGNANT LESIONS AND CONDITIONS

Toluidine blue stain was used to assess the number of MC in normal mucosa and premalignant illnesses such as oral leukoplakia, oral submucous fibrosis (OSMF), and oral lichen planus (OLP), which demonstrated that these lesions had a higher number of MC than normal mucosa [8].

According to Bhatt et al. [24], the density of MCs in OSMF was higher than in normal buccal mucosa. Similarly, Sabarinath et al. [25] discovered a favorable association between mast cell density (MCD) and microvascular density (MVD) in normal mucosa (NM) and different grades of OSMF in a study. The authors also stated that histamine produced from the MCs causes the production of vesicles and tingling sensations, which are the hallmark indications and symptoms of OSMF [26]. Submucosal oedema seen in the early stages of OSMF could

be to blame for the histamine. The eosinophilic chemotactic factor is supplied from the MCs due to enhanced vasopermeability.

Sathyakumar et al. investigated the involvement of mast cells in NM and various grades of dysplasia by measuring mast cell density (MCD) and microvascular density (MVD). In dysplasia, the density of mast cells and microvascular density was higher than in normal mucosa. Mast cell MC tryptase and Factor VIII associated von Willebrand factor causes the disease to start and progress. Sathyakumar et al. concluded that MC and microvessel density were indications of disease progression in leukoplakia based on this finding [27].
According to Biviji, the MC level in leukoplakia, which causes the inflammatory reaction, was elevated. Mast cells may release interleukin-1 and histamine, resulting in increased mucosal permeability and increased antigenicity to connective tissue [25].

Prostaglandins and leukotrienes, for example, are powerful salivary gland secretagogues that lead OSMF patients to salivate more. Interleukin-1 produced by the MCs may promote fibrosis by inducing the production of type-1 collagen and fibronectin [28,29].

Jontell et al. elucidated that OLP had a greater MC number than normal oral mucosa [30]. According to Zhao et al., MCs and T-cells interact from the initiation of OLP, therefore MCs play a critical role in the pathogenesis of OLP. They also concluded that basement membrane degeneration was caused primarily by MC. MCs, release tumor necrosing factor (TNF-alpha), which promotes an increase in the synthesis of matrix metalloproteinases such as collagenase, causing the basement membrane layer to degenerate and lead to leukocytic migration [31]. TGF and tryptase from MCs can cause fibrosis by stimulating fibroblast cells. MC can promote angiogenesis via expanding endothelial cells, fibroblasts, and epithelial cells, according to Iamaroon.

Sharma et al. found an increase in MC number in OLP and an oral lichenoid reaction, in contrast to normal mucosa (OLR) [32]. Many researchers, like Ankle et al., Shilpa et al., and Janardhanan and Ramesh, have studied mast cells using toluidine blue and Azure A, but they prefer toluidine blue is the best staining for recognition of mast cells [3].

8. MAST CELLS IN SQUAMOUS CELL CARCINOMAS

The association between the density of mast cells and numerous epithelial/connective tissue malignant tumors of the oral cavity was explained in a variety of ways, with the oral squamous cell carcinoma being one of them. Several studies have found a link between the density of mast cells and their degranulation at different stages of oral cancer.

Squamous cell carcinoma (SCC) has a higher MC density than benign tumors, according to Rojas et al. [33] Gomes et al. Jahanshahi et al. reviewed and explained that SCC has a higher MC and microvacularity than normal mucosa, that there is a link between the two, and that the MCs may play a role in the progression of these lesions [34]. Mohtasham et al., Molouk et al., and Iamaroon et al. detected higher MC numbers and microvascular counts in SCC compared to normal mucosa utilizing immunohistochemistry (IHC) using an anti-tryptase antibody. According to the researchers, MC tryptase is secreted by MCs during angiogenesis, suggesting that it could be employed as a crucial biomarker of oral cancer progression [35]. In contrast to the above study, there is a decrease in MCs count in OSCC and premalignant oral hyperkeratosis (leukoplakia) which was reported by Oliveira-Neto HH. This decrease in the number of MCs might be related to the migration failure of these cells, possibly reflecting an important modification in the microenvironment during tumor initiation and progression [36].

9. MAST CELLS IN SALIVARY GLAND TUMORS

Vidal et al. evaluated the density of MCs and microvessels in minor salivary organ tumors of the oral cavity by utilizing immunohistochemistry of MC tryptase and von-Willebrand factor. The density of MCs was higher in mucoepidermoid carcinoma when compared to another minor salivary gland tumor-like pleomorphic adenoma, polymorphous low-grade adenocarcinoma, or adenoid cystic carcinoma [35]. The microvessel density (MVD) was higher and seen in mucoepidermoid carcinomas and adenoid cystic carcinoma when compared to pleomorphic adenoma and polymorphous low-grade adenocarcinoma [36].

10. MAST CELLS IN IMMUNOLOGIC DISORDERS

The pathophysiology of an aphthous ulcer was described; increasing MC numbers in aphthous ulcers cause degranulation tissue, which leads to healing [14]. In an immunohistochemistry investigation, Natah SS et al. investigated the number and distribution of MCs in traumatic ulcers (TUs), recurrent aphthous ulcers (RAU), and healthy oral mucosa as a control group and conclude that MC counts were considerably higher in the recurrent aphthous ulcers connective tissue than in the connective tissue of traumatic ulcers and control samples. These MC numbers show evidence of activation/ degranulation, implying that this cell type is actively involved in RAU pathogenesis [37].

11. CONCLUSION

Mast cells are a type of defence cell that plays a key role in the development of inflammation in the tooth pulp and oral mucosa in both physiologic and pathologic conditions. Based on this, the MCs have a part in the progression from acute to chronic inflammation of oral lesions but it is remaining controversial in the oral squamous cell carcinoma regarding development and metastasis. It needs further molecular level research in the mechanism of activation and progression of mast cells with a larger sample study. There should be an evaluation of immunomodulation capacity through therapeutic strategies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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