Review Article

Contemporary updates on the role of mast cells in oral lesions: A review

Abstract:

Mast cells (MCs) are the immune cells of myeloid lineage and make a crucial role in the inflammatory process in several types of tissues which contain 50–200 large granules which are inflammatory mediators, including rich in histamine and heparin. They are circulating in the body especially in the connective tissues of the oral mucosa like nerve, blood vessel, and subepithelial area. These cells have a major role in the maintenance of many physiologic functions of the body and thus their number is altered in various pathophysiologic diseases of the oral cavity such as a benign and malignant tumor, reactive lesions, autoimmune disease, odontogenic cyst, and tumors, etc. The present paper is focused on the current concept and updates of mast cells in physiologic and pathologic conditions along with alteration in the number of mast cells.

Keywords: Mast cells, Normal oral mucosa, Oral lesions, Histamine, Interleukin, Angiogenesis

Introduction:

Mast cells (MCs) (also known as mastocytes and labrocytes) are large connective tissue cells that containing numerous basophilic granules in their cytoplasm and obscure the nucleus. (1) MC was discovered by Paul Ehrlich in 1878 and used the term “mastzellen” a word derived from German which refers to feeding. Ehrlich described the association of MCs with inflammation as well as with blood vessels and neural tissue. (2) MCs have exhibited both pro-inflammatory and anti-inflammatory effects and are considered specialized cells of the immune system. (3)

Mast cells are originated from a multipotent CD34 precursor in the bone marrow and circulate in peripheral blood. The size of the mast cells ranges from 8 μm to 20 μm in diameter and often appears ovoid, tadpole/spindle-shaped cells in the histologic section. The mast cells contain metachromatically staining secretory cytoplasmic granules which are determined by metachromatic dyes such as toluidine blue, methyl violet, Azure B, safranin, and azure A.(3) (4) The granules vary in size from 0.2 to 0.5 μ diameter, namely rich in histamine and heparin, interleukin-4, chymase, basic fibroblast growth factor, MMPs, vascular endothelial growth factor (VEGF), transforming growth factor-beta and tryptase. (5) The existence of mast cells in various lesions of the oral cavity gives observation of degranulation activity indicates both destructive role and repair process also. The mast cell releases both primary and secondary chemical mediators (degranulation) which exert a direct effect on inflammation and indirectly act by recruiting other cell types like lymphocytes to the site. (3)

MCs also release different proinflammatory cytokines, various interleukins (IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, and IL-16), tumor necrosis factor-alpha (TNF-α), that promote leukocyte infiltration in various oral lesions of the oral cavity. These cells contain a rich

source of proteases, especially tryptase and chymase, which has a direct action on the extracellular matrix by degradation through proteolytic activity, and on another hand, it indirectly stimulates angiogenesis and further helps in the invasion and metastasis of the lesion. (4),(6)

Based on the granular cell morphology of mast cell, divided into three types. The first type, mast cells appears as round or oval in shape with well-demarcated cell borders and the nucleus cannot be seen due to the rich of cytoplasmic granules in the cytoplasm. The mast cell is often located in the deep connective tissue and named “intact cells”. The second type, MCs are flattened or irregular in shape with faint and not well-marked cell borders. The nucleus is partially seen because the cytoplasm presents a lesser granular aspect. Mast cells located in the superficial part of the connective tissue and those situated close to the blood vessels and named as “spreading cells”. The third cell type is represented by the degranulated mast cells with indistinct cell border and seen at cell infiltrates of the connective tissue. (7),(4)

The mast cell is divided into two types depending on the phenotype and functions of the cell. In rodents, two types of mast cell phenotypes have been explained. One is CTMCs (connective tissue MCs) and the other is MMCs (mucosal MCs) which differ through their localization, mediator content, and response to different stimuli. The two phenotypes of mast cells have been explained based on their heterogeneous expression of proteases i.e. mast cell tryptase and chymase. CTMCs contain tryptase and chymase, while MMCs contain the only chymase.

Based on the content of the mast cells which are divided into two types. 1. Few mast cells contain only tryptase in their granules (MCT), found in the lung interalveolar septate, and in the small intestine mucosa. 2. Some mast cells contain both tryptase and chymase (MCTC), found in the skin and the intestinal submucosa. (4)

The role of MCs in an immunologic disorder like allergic diseases, anaphylaxis, autoimmunity, and other reproductive disorders has been well-reported in the medical literature. However, its role in the etiopathogenesis of oral pathologies is still debatable. Oral mucosa is accessible to external and internal stimuli; hence this article is interesting and aiming towards the current concept and role of mast cells in the initiation and progression of oral lesions which manifests in a broad spectrum, ranging from developmental, reactive, and inflammatory to neoplastic.

The review of mast cells in the oral lesion was taken from the electronic database PubMed, MEDLINE, and Clinical key was searched for words: MCs and an oral lesion. Relevant articles in the English language were considered for this review article.

Mast cell in health and pathology:

In the head and neck region, the mast cells are usually found in all connective tissue of the oral mucosa, including the periodontal ligament, the dental pulp, and the gingiva. The

presence of mast cell in this connective tissue of the oral mucosa is very difficult to detect, hence special stains like toluidine blue staining, immunohistochemical staining methods are required to visualize under bright field microscope and another special microscopy such as electron microscopy to demonstrate mast cell degranulation. (4)

The mast cell count (MCC) in normal mucosa (NM) 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.(10) MCC was found to be 71 ± 16 in normal healthy gingiva using monoclonal antibodies specific for tryptase.(11)

MCs number is altered in various oral pathological conditions. Some of the studies related to common oral conditions are as follows:

Mast cells in common dental conditions:

The expression of mast cell in the dental pulp was an incredible face because of the way that the tissue injuries that happen during dental pulp removal require degranulation, and, then again, dental pulp also expresses the progenitor MCs and sometime degranulated cells also. In the human dental pulp tissue that has high convergences of TNF-α have been recognized during inflammation. The concentration of mast cells focuses on the decline when the aggravation of the dental pulp advances towards putrefaction, while the least number of mast cells is found in the sound dental pulp tissue.

A critical concentration of mast cells has been found in gingival inflammation, yet no clarification concerning their suggestion in the support and movement of the provocative inflammatory cycle has been disclosed. Also, there is no information on the relation between the density of MCs and the inflammatory cells in the connective tissue.

Huang et al. exhibited a correlation between MCs degranulation and various periodontitis grade. The authors noticed that the number of the positive-tryptase degranulated MCs is altogether higher in severe periodontitis compare to mild periodontitis and the normal mucosa. It was difficult to conclude whether degranulation had been initiated by the inflammation or by the inflammatory cells. (12)

Interestingly, another investigation was reported that there is a decline in MCs density (MCD) along with the severity of periodontitis. (13)In periodontal infection, MCs are ensured that it is associated with inflammatory cells and in the development of budding capillaries. MCs influencing angiogenesis and lymph-angiogenesis has been proven in clinical conditions. This viewpoint is proved and upheld through the vascular endothelial development factor (VEGF) by the endothelial cells of the micro vessel number in various oral pathologic conditions. (4)

Mast cells in inflammatory reactive conditions:

Kfir et al have explicitly ordered reactive hyperplastic lesions into pyogenic granuloma (PG), peripheral giant cell granuloma (PGCG), peripheral ossifying fibroma (POF), and fibrous

hyperplasia (FH). Mast cells have the main responsibility in the initiation and aggravation of inflammation in the oral mucosa, both in early vasoinductive functions and in the change from acute to chronic irritation recommending that mast cells may assume the main role in enlisting of inflammatory cells and angiogenesis. (5)

A diminishing in MC was accounted for in acute necrotizing and chronic marginal gingivitis as when contrasted with ordinary gingival.(14) there is an increase in the MC density in gingival hyperplasia has been found. (15)

Farahani led an investigation to look at the MC in different responsive lesions, for example, irritation fibroma, inflammatory fibrous hyperplasia (IFH), peripheral giant cell granuloma (PGCG), and peripheral ossifying fibroma (POF). They found an increase in quantities of MCs in reactive lesions contrasted to normal healthy gingival tissues. MCs were essentially diminished in the PGCG when compare with the IFH and POF lesions. Based on this study, MCs recommend and assume some part in collagen formation and therefore in the variety of microscopic highlights of oral reactive tissue lesions.(16) Vandana et.al studies demonstrated the number of mast cells was more in POF and FH followed by pyogenic granuloma and PGCG proposing that mast cell is a trademark for persistent aggravation of inflammatory cells and it may prompt the formation of collagen fibres by fibrosis leading to fibrosis. (5)

Oral pyogenic granuloma is considered a responsive/reactive lesion because of etiologic components like an injury. MCs' check has been seen to be increased in the connective tissue of pyogenic granuloma.(17) Murata et al. examined that the development of granulation tissue which is by all accounts by different cytokines, especially basic fibroblast growth factor (bFGF) seen during wound healing after injury. Certain authors recommend that the neovascularisation during granulation formation in which bFGF is synthesized and delivered from certain macrophages and MCs into the extracellular matrix. Hence, MCs are considered as the main function in the pathogenesis of oral pyogenic granuloma.(18) Kamal et al. assessed the mast cells in the normal mucosa and oral pyogenic granuloma using 1% toluidine blue and stated that the MCs were high in pyogenic granuloma compare to normal mucosa.(19)

Hamideh et.al investigated the mast cells' role in peripheral ossifying fibroma and irritational fibroma and normal mucosa and opined that it has induction of collagen fibres resulting in fibrosis in these lesions. (20)

Mast cells in Odontogenic Cysts:

MCs were keenly observed in periapical cyst as well as an inflammatory periapical cyst. MCs and lymphocytes were found to be 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 resulting in the stimulation of osteoclast activity, neovascularisation, and aggravation of inflammatory cells in these lesions.(21) (22)

Patidar et al. examined the presence of MCs using toluidine blue stain in various odontogenic cysts like radicular cysts (RC), dentigerous cysts (DC), and odontogenic keratocyst (OKC).

He found that the number of MCs/mm2 was higher in RC compare to other odontogenic cysts and also explained that the density was higher at upper connective tissue than the deeper connective tissue. (23)

Mast cells in Benign and Malignant tumors:

Hagiwara et al. investigated MCs quantity in different vascular proliferated tumors like cutaneous pyogenic granuloma, port-wine stain, cavernous haemangioma, cherry angioma, Kaposi's sarcoma, and malignant haemangioendothelioma utilizing IHC with tryptase stain. There was the increased density of MCs were discovered in a cutaneous pyogenic granuloma, malignant haemangioendothelioma, cavernous haemangioma when compare to port wine stain, cherry angiomas, and Kaposi's sarcoma. By this result, he concluded that there is no difference in MCs density between benign, low-grade malignant, and malignant vascular tumors. It appears to be difficult to decide if an alternate MC thickness is answerable for various vascular tumors because of the significantly high level of MC thickness in three sorts of vascular expansions, they estimated that there might be a limit level of MC thickness for its induction, however, this speculation requires further clarification. (24)

Mast cells in premalignant lesions and conditions:

The number of MC was investigated under toluidine blue stain in normal mucosa, oral leukoplakia, OSMF, oral lichen planus (OLP), and OSCC which showed a higher number in theses lesions compared to normal mucosa. (8)

Biviji reported the MC was increased and contribute to an inflammatory reaction in leukoplakia. The MCs may release interleukin-1, which causes expansion of epithelial and histamine may cause expanded permeability of mucosa which could encourage expanded antigenicity to connective tissue. (25)

Sathyakumar et al. evaluate and compare the mast cell density (MCD) and microvascular density (MVD) in NM and various grades of dysplasia to assess the role of these cells and progression of the disease by using MC tryptase and Factor VIII related von Willebrand factor. The number of MCD and MVD were high in dysplasia compare to normal mucosa, based on this result, he stated that MC and microvessel density were the indicator of disease progression in leukoplakia. (26)

Some studies on the density of MCs in OSMF by Bhatt et al. as well as who noted plentiful MCs compare to the normal buccal mucosa. Similarly, Sabarinath *et al*. did a study on MCD and MVD in NM and different grades of OSMF and he found that there was a positive relationship between them. The author also described that the formation of vesicle and tingling sensation is due to histamine released from the MCs which is the main signs and symptoms of OSMF. (27) The histamine could likely ascribe to submucosal oedema seen in the beginning phases of OSMF. Because of expanded vasopermeability, the eosinophilic chemotactic factor is delivered from the MCs.

The other mediators of MC like prostaglandins and leukotrienes are intense secretagogues of the salivary gland which lead to an increase in salivation of OSMF patients. Interleukin-1 from the MCs could cause an increase in fibrosis i.e. formation of type-1 collagen and fibronectin. (27,28)

MC number was raised in OLP in contrast with normal oral mucosa which was explained by Jontell et al. (29) Zhao et al. recommended that MCs assume a significant role in the pathogenesis of OLP. The interaction between MCs and T-cells, which are identified from initiation till effector periods of OLP. They considered MC was the main reason for the degeneration of the basement membrane. TNF-alpha is delivered from MCs which causes an increase in the synthesis of matrix metalloproteinases like collagenase, which leads to the destruction of the basement membrane layer. This could most likely reason for leukocytic migration. (30) TGF-β and tryptase from MCs can stimulate the fibroblast cells to lead to fibrosis of the lesion. Iamaroon A proposes that MC can increase endothelial cells, fibroblasts, epithelial cells, and macrophages lead to angiogenesis. (3) Histamine causes vasopermeability prompting submucosal oedema and antigen-induced T-cell proliferation. The cytotoxic lymphocytes and MCs cause the basal cell degeneration, keratinocyte apoptosis, and consequently trademark Civatte bodies seen in OLP. (30)

Sharma et al. discovered that there was an increase in MC number in OLP and oral lichenoid response (OLR) in contrast with NOM. (31) There are numerous investigators like Ankle MR et al., Shilpa et al., and Janardhanan M and Ramesh V conducted research on recognition and enumerate the mast cells by using toluidine blue and Azure A stain but they appreciate more with toluidine blue. (3)

Mast cells in squamous cell carcinomas:

Many types of research explained the relationship between mast cell thickness and various malignant tumors of the oral cavity, among which the oral squamous cell carcinoma is explained appropriately. There are various studies indicated a there is a connection between the density of mast cells and their degranulation in various stages of hyperkeratosis, dysplasia, in situ carcinoma, and various grades of oral carcinoma.

Rojas *et al*. observed that MC density was increased in squamous cell carcinoma (SCC) compare to benign tumors. (32) Iamaroon *et al*. observed under IHC using an anti-tryptase antibody and stated that MC numbers were increased in SCC compared to normal mucosa. A significantly increased in the number of the MC and microvascular counts in oral SCC, as well as the relationship between them, was also observed. The authors suggested that MC tryptase was released by MCs and also upregulate during angiogenesis in oral carcinoma's carcinogenesis which may be used as key indicators of oral carcinoma disease progression.(10) But Jahanshahi et al. reviewed and explained that there is an increase in the MC and microvacularity in SCC compare to normal mucosa but there is an association between them. (33)

Gomes *et al*. studied and reported that the number of MCs in NOM was less compare to mild dysplasia in actinic cheilitis (MDAC), severe dysplasia in actinic cheilitis (SDAC), and LSCC and he suggests a role of the MCs in the development of these lesions.(9)

Molouk Torabi et al and Mohtasham *et al*. compared the MCC and MVD among NOM, oral dysplastic epithelium, and low- and high-grade OSCC evaluated by immune-histochemical staining. The results showed a statistically significant increase in mean MCC and MVD between NOM and epithelial dysplasia, NOM and OSCC, and epithelial dysplasia and OSCC and they concluded that MCs promote tumor progression via up-regulation of angiogenesis.(34) Therefore, angiogenesis can be used as an indicator of the development of the disease. In contrast to the above study, there is a decrease in MCs count in specimens of 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. (35)

Mast cells in Salivary gland tumors:

Vidal et al. evaluate 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, adenoid cystic carcinoma. The microvessel density (MVD) was higher seen in mucoepidermoid carcinomas and adenoid cystic carcinoma when compared to pleomorphic adenoma and polymorphous low-grade adenocarcinoma. (36)

Mast cells in immunological disorders:

The pathogenesis of aphthous ulcer was explained, there is increased MC numbers in aphthous ulcers and induced the degranulation tissue resulting in the healing of it. (14)

Conclusion:

Mast cells are a defence cell and play an important character in the development of inflammation in the dental pulp and oral mucosa as well as both in normal condition as well as in the pathologic condition. Based on this, the MCs have a part in the progression from acute to chronic inflammation of oral lesion 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.

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