Mast Cell-A Gatekeeper Of The Microvasculature In The Oral Cavity: A Review
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INTRODUCTION
Mast cells are mobile, bone-marrow-derived, granule-containing immune cells that are found in all connective tissue and mucosal environments, and in the peripheral and central nervous systems. Mast cells are a heterogeneous population which can be divided into two phenotypes on the basis of neutral serine proteases. Mast cells play an important protective role as well as being intimately involved in wound healing and defense against pathogens. They are large spherical or elliptical mononuclear cells. The nuclei are small compared to the size of the cell and in histological preparations they are frequently obscured by the large number of granules in the cytoplasm. Mast cells can be found in a wide variety of tissues, including the skin, submucosa or connective tissues of various organs, and mucosal epithelial tissues. They resemble circulating basophils in containing large number of cytoplasmic granules containing pharmacologically active mediators and IgE receptors.

STAINING PROPERTIES
Mast cells stain with basic dyes like toluidine blue and methylene blue. The stained granules often acquire a color that is different from that of native dye, they are referred to as metachromatic dyes. These basic dyes are not very specific as even some cells like macrophages and fibroblasts also take up the stain due to released mast cell granules from phagocytes; and it may also fail to stain immature mast cells. Tryptase is considered a specific mast cell marker. (a immunohistochemical reaction).
Figure 1
Table 1. Selected hypotheses of physiological mast cell functions

<table>
<thead>
<tr>
<th>Hypothetical mast cell function</th>
<th>Author</th>
<th>Year</th>
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<tbody>
<tr>
<td>Protection from cancer</td>
<td>Ehrlich</td>
<td>1877</td>
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<tr>
<td>Phagocytosis of pathogens</td>
<td>Metchnikoff</td>
<td>1892</td>
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<tr>
<td>Endocrine function</td>
<td>Cajal</td>
<td>1896</td>
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<tr>
<td>Lipid metabolism</td>
<td>Ciacio</td>
<td>1913</td>
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<td>Vitamin metabolism</td>
<td>Tuma</td>
<td>1928</td>
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<tr>
<td>Calcium metabolism</td>
<td>Pautier</td>
<td>1931</td>
</tr>
<tr>
<td>Tissue growth and cell proliferation</td>
<td>Sylven</td>
<td>1941</td>
</tr>
<tr>
<td>Blood clotting and coagulation</td>
<td>Baekeland</td>
<td>1951</td>
</tr>
<tr>
<td>Hair growth</td>
<td>Montagna</td>
<td>1951</td>
</tr>
<tr>
<td>Hemopoiesis</td>
<td>Messerschmidt</td>
<td>1955</td>
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<tr>
<td>Local tissue detoxification</td>
<td>Higginbotham</td>
<td>1956</td>
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<tr>
<td>Regulation of blood pressure</td>
<td>Keller</td>
<td>1957</td>
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<tr>
<td>pH regulation</td>
<td>Caselli</td>
<td>1958</td>
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<tr>
<td>Temperature regulation</td>
<td>LeBlanc</td>
<td>1959</td>
</tr>
<tr>
<td>Aging</td>
<td>Spicer</td>
<td>1960</td>
</tr>
<tr>
<td>Response to stress</td>
<td>West</td>
<td>1962</td>
</tr>
<tr>
<td>Fixation of blood-borne particles</td>
<td>Selye</td>
<td>1963</td>
</tr>
<tr>
<td>Sweat secretion</td>
<td>Szabo</td>
<td>1964</td>
</tr>
<tr>
<td>Peripheral “memory bank”</td>
<td>Padawer</td>
<td>1978</td>
</tr>
</tbody>
</table>

ROLE OF MAST CELLS

HYPERSENSITIVITY REACTIONS

Mast cells are central to the development of immediate hypersensitivity reaction, which are mediated by IgE antibodies. IgE - secreting B cells differentiate by the activity of helper T cells. Mast cells express Fc portion of IgE and avidly binds IgE antibodies. When such an armed mast cell is exposed again to the specific allergen, there is mast cell degranulation discharging pre-formed (primary mediators) and de novo synthesis and release of secondary mediators such as arachidonic metabolites. These mediators are directly responsible for the initial, sometimes explosive symptoms of type-I hypersensitivity reactions and they also set into motion the events that lead to the late-phase response.2

INFLAMMATION

The mast cells are widely distributed in connective tissues and participate in both acute and persistent inflammatory reactions. Many of these cytokines promote neutrophil aggregation, eosinophil aggregation, T-lymphocyte stimulation, which in turn stimulates B-lymphocytes, acts on endothelial cells, acts on platelets by stimulating platelet activating factor, directly or indirectly the mast cells have an effect on the modulating inflammation.2

REPAIR AND WOUND HEALING

Repair begins early in inflammation. Sometimes as early as 24 hours after injury, fibroblast and vascular endothelial cells begin to proliferate forming a specialized type of tissue that is the hallmark of healing. There is formation of new small blood vessels and proliferation of fibroblasts.2

PMNLs along with macrophages, lymphocytes and mast cells play a major role in inflammation and wound healing. TGF-beta when released helps in stimulating fibroblasts to proliferate and synthesize extra-cellular matrix proteins.3

Mast cells degranulate during wound healing releasing mediators like heparin, histamine tryptase, chymase, VEGF, TNF-alfa. Mast cells derived pro inflammatory and growth promoting peptide mediators VEGF, FGF-2, PDGF, TGF-beta, NGF, IL-4, IL-8 contribute to neoangiogenesis, fibrinogenesis or re-epithelization during process of repair.5

MAST CELLS IN COMMON ORAL DISEASES

PULPITIS

The spatial association of nerves and mast cells facilitates the effects of neuropeptides that are secretagogues for mast cells. The stimulation of nerve fibres results in mast cell degranulation resulting in increased blood flow and permeability of microvessels. This promotes vasodilatation and inflammation.6

GINGIVITIS AND PERIODONTITIS

Degranulated mast cells increase within the gingival connective tissue as gingival inflammation increases, and mast cells transcribe TNF, interleukin and interferon. A central feature of periodontitis is the remodeling of connective tissue that leads to a net loss of local soft tissues, bone and periodontal ligament attachment apparatus. The transition from gingivitis to periodontitis is the loss of soft tissue attachment to the tooth and subsequent loss of alveolar bone. Mediators produced as a part of host response that contribute to tissue destruction include proteinases, cytokines, TNF, IL-1, IL-6.7 (some of which are secreted by mast cells).

CYSTS

Mast cells are widespread in the connective tissue wall of all
cyst types, particularly adjacent to the epithelium. Degranulating mast cells release heparin and hydrolytic enzymes and the latter facilitated the breakdown of glycosaminoglycans and proteoglycans. Mast cells are recognized in nonkeratinizing and keratinizing odontogenic cysts. Alteration in their number and distribution could contribute to the pathogenesis of odontogenic cysts⁸.

Along with other cells like plasma cells, histiocytes, endothelial cells and fibroblasts, mast cells also produce prostaglandins. The prostaglandins are known to activate osteoclasts resulting in bone resorption⁸.

TNF-alfa, a cytokine produced by mast cells also activates osteoclast activating factor leading to bone resorption. Many researchers have compared the presence of mast cells between periapical granuloma and periapical cysts and have concluded that although mast cells are present in the granulomas, but they are less in number. The bone loss in the granuloma can be inferred to be similar to that of the periapical cysts⁴.

**NEUROFIBROMA**

The basic component of neurofibroma are: Nf1-/- Schwann cells which act as tumorigenic instigators, mast cells which act as inducers and Nf+/- fibroblasts, Schwann cells, perineural cells and endothelial cells act as responders. There is abundant kit ligand secreted by Nf1-/- schwann cells which act as inciting factor for mast cell to migrate due to their c-kit receptors. Given the breadth of cytokine expression found in degranulating mast cell, it is tempting to speculate that these cells could play a central role in the initiation of neurofibroma⁸. Mast cells secrete proteins that can remodel ECM and initiate angiogenesis.¹¹,¹²

**LICHEN PLANUS (LP)**

It has been suggested that mast cell degranulation in response to release of neuropeptides is a key event in the pathogenesis of oral LP. The most superficial region of lamina propria is the highest number of interactions of nerves with mast cells. Although mast cells are not professional antigen presenting cells, the antigen presentation and co-stimulatory signals delivered by mast cells may contribute to the development of a specific T-lymphocyte response in the induction phase of inflammation in conditions like LP. In the connective tissue they share a strategic perivascular location with dendritic antigen presenting cells, and their production of cytokines in this location may be equally important as the expression of accessory molecules on their cell surface.⁶

TNF-alfa released from mast cell causes increased synthesis of matrix metalloproteases like collagenase which causes basement membrane destruction. The TNF also causes increased expression of adhesion molecules like E-Selectin, ICAM. This may cause increased leukocytic migration. Histamine causes vasopermeability leading to submucosal oedema, Ag induced T-cell proliferation thereby leading to the characteristic trafficking of lymphocytes.¹³

**SQUAMOUS CELL CARCINOMA**

Squamous cell carcinoma of head and neck is a common disease with a high degree of mortality and morbidity. Conti, Castellani, and colleagues point out that many tumors are surrounded by mast cell infiltrates. They present evidence that these mast cells secrete inflammatory cytokines that in some cases benefit the cancer. Once mast cells are attracted to tumors by chemo-attractants like SCF, they are then triggered to secrete molecules that act as growth factors aiding tumor growth, angiogenesis, and metastasis.¹⁴ The mast cells ‘remodel’ the tumor microenvironment so as to promote tumor growth. This increases secretion of inflammatory chemicals, increasing activity of NF-kappaB and increasing the tumor’s ability to suppress T cell and natural killer cell attacks against it.¹⁵

Ribatti and Crivelatto in 2009 suggested that mast cells could be a target for cancer treatment¹⁶. They suggested by tumor models, that mast cells play a decisive role in inducing the angiogenic switch which precedes malignant transformation. There is, moreover, strong evidence that mast cells significantly influence angiogenesis and thus growth and progression in human cancers.¹⁷ It would appear that if we could decrease mast cells we might inhibit both tumor angiogenesis and tumor growth.¹⁸

In some cancers, mast cells clearly act to support tumor growth. Ribatti demonstrated a direct correlation between mast cells and disease progression in multiple myeloma in 1999.¹⁹

Nakayama was able to show this effect was mediated at least in part by mast cell production of angiopoietin-1.²⁰ Mast cells aid the development of squamous cell carcinoma. Coussens et al reported in 1999 that mast cells, “infiltrate hyperplasias, dysplasias, and invasive fronts of carcinomas,” and then release the mast cell–specific proteases chymase and tryptase—the former acting as a mitogen and the latter being angiogenic to skin fibroblasts. In experiments, tumor
angiogenesis was stopped when implanted in mice genetically devoid of mast cells. Cancer progression in their experiment required an inflammatory response to tissue abnormality. In hyperplasias, dysplasias, and invading cancer fronts, inflammatory mast cells are drafted to reorganize stromal architecture and hyperactivate angiogenesis. Without mast cells, progression halted. 21

**LEUKOPLAKIA, ORAL SUBMUCOUS FIBROSIS**
In common oral lesions associated with chronic inflammation such as leukoplakia, oral submucous fibrosis, oral lichen planus and squamous cell carcinoma mast cells are shown to be increased in number when compared with normal oral mucosa as shown by Ankle et al suggesting a role for mast cells. 15

**AUTOIMMUNITY**
Mast cells are known to produce strong response to minute allergens. Recent observations reveal that they may have a key role in co-ordinating the early phases of autoimmunity particularly involving auto-antibodies 211. Given their both pro-inflammatory as well as anti-inflammatory functions with a good ability to multitask, Some studies have clearly implicated mast cells in the initiation and/or progression of autoimmune disease. 21 Mast cells are increased in known auto-immune diseases like pemphigus vulgaris, developing subdermal bullous diseases and also in pemphigoid. 22

**THERAPEUTIC IMPLICATIONS**
Based on the concept that mast cells play a critical role in the induction of inflammation, it is logical to use therapeutic agents to alter mast cell function and secretion, to thwart inflammation at its earliest phases 21. For cutaneous inflammation, this has been accomplished in vitro and in vivo with the mast cell stabilizing agent disodium cromoglycate and a related compound, proxicromilin. Blockade of dental pulp mast cell responses in vitro has been achieved with neutralizing antibodies to TNF, and with substance P receptor antagonists 24–25.

An additional stratagem is the use of soluble receptors to inactivate the TNF released from mast cells. 27 Corticosteroids have been utilized for decades in the treatment of inflammatory conditions of the dental pulp and oral mucosa 28–30. An important property of corticosteroids that may contribute to their therapeutic efficacy is their ability to deplete mast cells locally at sites of prolonged or occlusive application 31–33.

**CONCLUSION**
these enigmatic, multifaceted protagonists of natural immunity are functionally relevant to many more aspects of tissue physiology than just to the generation of inflammatory and vasodilatory responses to IgE-dependent environmental antigens. Mast cells have gained a lot of importance in the recent years owing to vast number of chemical mediators they release with wide range of actions in many of the disease processes.

The anti mast cell therapy may offer an adjunct to the existing treatment modalities in the coming years.

**References**
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