

## REVIEW ARTICLE

**Mast Cells In Periodontal Health And Disease - A Review**Sidharth Shrikant Joshi<sup>1</sup>, Atul A. Pandharbale<sup>2</sup>**ABSTRACT**

Albeit mast cells were discovered more than a century ago, their functions beyond their role in allergic replications remained elusive until recently. However, there is a growing appreciation that a consequential physiological function of these cells is the apperception of pathogens and modulation of felicitous immune replications. Mast cells are tissue-denizen immune cells that participate in a variety of allergic and inflammatory conditions. Circumscribed attention has been given to the role of mast cells in periodontal diseases, and the effects of mast cell degranulation on the chronic stages of non-allergic inflammation, particularly in periodontitis, are not kened, hence present review was made to understand the role of mast cells in periodontal health and disease.

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**INTRODUCTION**

A Histaminocyte is a denizen cell of connective tissue that contains many granules affluent in histamine and heparin. Albeit best kened for their role in allergy and anaphylaxis, mast cells

play a consequential protective role as well, being intimately involved in wound rejuvenating and bulwark against pathogens.<sup>1</sup>

Mast cells were first described by Paul Ehrlich in 1878 on the substratum of their unique staining characteristics and astronomically immense granules. These granules withal led him to the misconstrue notion that they subsisted to victual the circumventing tissue, and he designated them "mastzellen", denoting "alimenting-cells". Nowadays, they are considered part of the immune system. Mast cells are very homogeneous to basophil granulocytes (a class of white blood cells) in blood; the homogeneous attributes between mast cells and basophils have led many to notionally theorize that mast cells are basophils that have "homed in" on tissues.<sup>2</sup>

Mast cells originate from pluripotential hematopoietic cells in the bone marrow, undergo part of their differentiation in this site, then enter the circulation and complete their differentiation in peripheral mucosal or connective tissue (CT) microenvironments rich in fibroblasts and other mesenchymal elements. One hall mark in mast cell development is that c-kit (CD13), the receptor of stem cell factor (SCF), is expressed by mast cells and their progenitors, including the pluripotential progenitors of mast cells, committed mast cell progenitors, immature mast cells and mature tissue mast cells.<sup>3</sup>

**MAST CELLS MORPHOLOGY**

Mast cells are of 20 to 30  $\mu\text{m}$  in diameter having various shapes such as polyhedral, fusiform, ovoid, and rectangular, and possess a centrally placed, spherical nucleus. Cytoplasm contains granules range in size from 0.3 to 0.8  $\mu\text{m}$  upto 40% of the volume of mast cell is occupied by membrane – enclosed secretory granules. There are 50 to 500 secretory granules present in mature human mast cell. Because these granules contain heparin (or chondrolin sulfate), a sulfated glycosaminoglycan, they stain metachromatically

with toluidine blue. Electron microscopic studies of the granules reveal that there were differences in size and form of granules and displayed variations in ultrastructure even they were present with in the same cells.<sup>9</sup>

**MAST CELL HETEROGENITY AND OCCURRENCE**

On the basis of their proteinase content, mast cells are divided into CT and mucosal phenotypes. The CT phenotypes contain both tryptase and chymase (MC<sup>TC</sup>), while the mucosal phenotype contains only tryptase (MC<sup>T</sup>). Recently researchers have found third mast cell population which contains only chymase (MCc). Seen in axillary lymph nodes and lungs and bowel mucosa and submucosa.<sup>5</sup>

Because basophils and mast cells share some characteristics, it was once believed that mast cells were basophils that had left the blood stream to perform their tasks in the connective tissues.<sup>5</sup>

Characteristic Features	Mast Cells	Basophils
Origin	Homopoietic stem cell	Homopoietic stem cell
Site of differentiation	Connective tissue	Bone marrow
Cell divisions	Yes	No
Life span	Weeks to months	Days
Shape of nucleus	Round	Segmented
Granules	Many, large	Few, small
Surface Fc receptors for IgE antibodies	Present	Present

Table-1: Difference between mast cell and basophils

**DISTRIBUTION**

Mast cells are located throughout the body in the connective tissue proper, where they are concentrated along small blood vessels. They also are present in the subepithelial connective tissue of the respiratory and digestive systems.<sup>5, 6</sup>

Mast Cells are distributed widely throughout different organ:

- Skin (around blood vessels, lymphatics, nerves and glandular tissues)
- Upper and lower respiratory tract
- GIT payer's patch
- Bone marrow

- Liver
- Spleen
- Oral mucosa, gingiva

**MAST CELL FUNCTIONS**

Mast cells functions in tissues are not clearly known, but mast cells perform homeostatic regulation of nerves and blood vessels as well as host bulwark.

There appears to be a functional and anatomic connection between mast cells and the peripheral nervous system, as skin and intestinal mast cells are often in close approximation with nerves.

In addition, mast cell derived histamine causes neuropeptide release from afferent neurons, and nerves appear capable of stimulating mast cells, thus indicating the presence of bidirectional communication between these two cell populations.

Mast cell mediators also are known to affect endothelial cells by inducing vasodilation and are capable of initiating the recruitment of inflammatory cells.<sup>5</sup>

**MEDIATORS**

The pharmacological agents present in the granules are referred to as the primary mediators (also known as preformed mediators). Mast cells synthesize a number of mediators from membrane arachidonic acid precursors and these newly synthesized mediators are formed at the time of their release and are collectively referred to as secondary (or newly synthesized) mediators.<sup>10</sup>

<b>PGD<sub>2</sub></b>	Vasodilation, increase vasopermeability, contracts smooth muscle, bronchoconstriction, increase neutrophil chemotaxis, decrease platelet aggregation.
<b>LTC<sub>4</sub>, LTD<sub>4</sub></b>	Vasodilatation, contracts smooth muscle, increase vasopermeability, promotes prostaglandin and Leukotriene-4 generation.
<b>Platelet activating factor</b>	Vasoconstriction, increase vasopermeability, increase PMN and monocyte chemotaxis.

Table-3: Newly formed mast cell mediators<sup>12</sup>

**MAST CELL ACTIVATION AND DEGRANULATION**

Mast cells possess high affinity cell surface Fc receptors (FceRI) for immunoglobulin E (IgE). They function in the immune system by initiating an inflammatory response known as the immediate hypersensitivity reaction.<sup>12</sup>

This response commonly induced by foreign proteins (antigens) such as bee venom, pollen, and certain drugs, as follows:<sup>5, 13</sup>

1. The first exposure to any of these antigens elicits formation of IgE antibodies, which bind to the FceRI receptors of the plasma lemma of mast cells, thereby sensitizing these cells.
2. On subsequent exposure to the same anti-

gen, the antigen binds to the IgE on the mast cell surface, causing cross-linking of the bound IgE antibodies and clustering of receptors.

3. Cross-linking and clustering activate membrane bound receptor coupling factors, which in turn initiate at least two independent processes, the release of primary mediators from the granules and synthesis and release of the secondary mediators from arachidonic acid precursors as well as from other cytoplasm or membrane lipid sources.

**MAST CELLS INFLAMMATORY RESPONSE IN PERIODONTAL DISEASE SEQUENCE OF THE EVENTS<sup>14</sup>**

Mast cell degranulation is usually a localized phenomenon and they show typical inflammatory response which is mild and site specific. At the periodontal inflammatory site, Histamine and Bradykinin which are power visodialator cause increase in the vascular permeability and vasodilation of microvasculature in the vicinity of the periodontal tissues. Complement components leak out of blood vessels and are cleaved by neutral proteases to form additional agents of inflammation. Neutrophil chemotactic factor attracts neutrophils to the site of inflammation. These cells phagocytose and kill microorganisms. Eosinophil chemotactic factors attract eosinophils to the site of inflammation. These cells phagocytose antigen-antibody complexes, destroy microorganisms, and limit the inflammatory response.<sup>13, 14</sup>

<b>TNF- alpha</b>	Increase fibroblast growth and chemotaxis, increase production of PGE <sub>2</sub> and collageanse, increase PMN cell chemotaxis, phagocytosis, and superoxide production,
<b>IL-4</b>	Increase fibroblast proliferation, chemotaxis and matrix protein production, increase IgE production, increase B cell proliferation, increase B cell IL-6 production, increase T cell proliferation, decrease macrophage killing activity and cytokine production.
<b>IL-5</b>	Increase eosinophil chemotaxis, growth and survival.
<b>IL-6</b>	Increase IgE production, T cell growth and differentiation, increase airway mucous production.
<b>IL-8</b>	Increase PMN cell chemotaxis
<b>Chondroitin sulfate</b>	Binds to and inactivates histamine.
<b>Aryl sulfalase</b>	Inactivates leukotrieneC <sub>4</sub> , thus limiting the inflammatory response.
<b>Neutral proteases</b>	Protein cleavage to activate complement (especially C3a); increases inflammatory response.
<b>Neutral proteases</b>	Attracts eosinophils to site of inflammation
<b>Eosinophil chemotactic factor</b>	Attracts eosinophil to site of inflammation

Table-4: Mast cell cytokines<sup>13</sup>

**ROLE OF MAST CELLS Periodontal innate immunity**

These include activation by : (a) sensory neurons that secrete several neuropeptides, such as corticotrophin-releasing factor (CRF), nerve growth factor (NGF), neurotensin (NT), pituitary adenylate cyclase activating polypeptide (PaCAP) and substance P (SP), that could activate mast cells alone or in association with each other and keratinocytes activated by UV radiation to secrete CRF, SP and interleukin 1 (IL-1), which could all trigger mast cell

activation and deregulation in the periodontal tissues integration, activated keratinocytes relinquished IL-4 could stimulate maturation and upregulation of CRF receptors and tachykinin NK1 receptors on mast cells. Periodontal bacteria through Toll-like receptor 2 (TLR-2) and TLR-4 activate mast cells, which all lead to the secretion of concrete cytokines, chemokines and tumor necrosis factor a (TNF-a). Induction of Bcl-xL by bacteria obviates mast cell apoptosis. Trypsin derived from mast cells can stimulate protease activated receptor 2 (PAR2) on endothelial cells, leading to microvascular leakage, and could lead to further mast cell activation by a direct action on PAR2 on mast cells, which cause the engenderment of chemokines (IL-8) and cytokines (IL-6 and TNF-a) from mast cells and an inflammatory replication in periodontal tissues.<sup>15,16</sup>

### **In collagen synthesis of fibroblast**

Non inflammatory gingival enlargement is regulated by a special type of gene naming Hereditary gingival fibromatosis (GF). Microscopy of connective tissue reveals the presence of collagen bundles and fibroblast. In ultrastructural examination of gingival hyperplasia noticed that fibroblasts phagocytes the mast cells granules and mast cells stimulate collagen synthesis which results in hyperplasia.

In the connective tissues, there was well defined bundles of collagen fibres were found together with fibroblasts and capillaries when gingival tissues of 5 patients with GF were examined ultrastructurally. These capillaries with collapsed lumen were surrounded by mast cells. Mast cells proximity with fibroblast shows that mast cells play some role on collagen synthesis of fibroblasts.<sup>23</sup>

### **Periodontal inflammation**

There are two different mast cell populations present in human healthy gingival tissue. Such as McT and McTC.<sup>8</sup>

Gingival inflammation and periodontal diseases are triggered by accumulation of bacterial at the dentogingival margin. The host generates an inflammatory cell infiltrate in the tissue subjacent to the periodontal pocket as a defense against the

microbial threat. The infiltrate consists primarily of leukocytes including plasma cells, lymphocytes, macrophages and neutrophils that serve several functions in the defense against periodontal infection.<sup>17</sup> Important functions of neutrophils are phagocytosis and killing of microorganisms – critical factors in minimizing the destructive effects of the periodontopathogenic bacteria. While macrophages also operate as phagocytes, the cells may as well present antigens to T cells and amplify specific immune responses.<sup>19</sup>

Several properties of the inflammatory cell infiltrate in chronic periodontitis and interestingly, well found high numbers of mast cells equal to and often surmounting the numbers of macrophages in the inflamed periodontal lesion. Many reports have, during the last 15 years, shed new light on the mast cell as pivotal cell in both innate and acquired immunity). Recently, we found that mast cells strongly express matrix metalloproteinase (MMP)-1, ~2 and -8, which are key enzymes in degradation of periodontal soft tissue. It is suggested that mast cells as key players in gingival homeostasis that may be important in the progression of periodontitis.<sup>20</sup>

### **Gingival inflammation**

Mast cells are the mundane components of the connective tissues. They are found in different densities and different regions of the inflamed and healthy gingival tissues. Numbers of mast cells were found incremented on inflamed tissues comparing to healthy tissues. This incrementation is proximately cognate with the degree of inflammation.<sup>21</sup>

Mast cell densities were significantly incremented in chronic periodontal disease/gingival inflammatory lesions compared with clinically salubrious gingival tissues (Health) uniquely by immunohistochemical technique. Interestingly, mast cells were satuated specially in close apposition to mononuclear cells.

Relationships between Mast Cells and aggressive Periodontitis was studied There were no statistically consequential cognation between mast cell counts, clinical attachment loss and pathologic inflammation & concluded that Mast cell numbers aren't different in aggressive periodontitis and gingivitis.<sup>22</sup>

### Phenytoin induced gingival enlargement

Angelopoulos AP 1975 investigated the role of mast cell in the pathogenesis of phenytoin gingival enlargement and found that phenytoin has direct effect upon the gingival mast cell resulting in degranulation and liberation and more specifically heparin, taken up and metabolized by the surrounding fibroblasts, which in turn are stimulated to produce their own fresh and specific mucopolysaccharide of the ground substances as well as collagen fibrils, these building up connective tissue, some of these mucopolysaccharides are then broken down, rebuilt and stored in their sulphated form within the granules of regenerating mast cell. The local irritating factors in the oral cavity being capable of inducing inflammation in the gingival tissues have some what similar effects on the gingival mast cells.<sup>24</sup>

These factors play an important role in pathogenesis of the gingival overgrowth because they direct, exaggerate and modify the effect of phenytoin on the gingival mast cell.<sup>24</sup>

### DISCUSSION

Mast cells were described some time ago in the mucosa of the oral cavity and particularly in human gingiva and experimental gingivitis.<sup>25, 26</sup> Incremented mast cell counts have been reported in the gingiva as compared to other salubrious tissues.<sup>27</sup> Mast cells of the gingiva are sensitive not only to chemical substances, but also to physical agents, like metal ions or low-intensity laser irradiation that induces massive degranulation.<sup>28</sup> Alternatively, in 1955 and 1963 studies observed that mast cell population reduced in inflamed gingival tissue.<sup>9,29</sup> A Gemmell et al compared chronic periodontitis lesions with salubrious/gingivitis ones and denoted decreased mast cell counts in periodontal disease.<sup>30</sup> These cells had a different of shapes, and were often in close sodality with remaining collagen fibers, as well as with more minuscule fibrils and other collagen fragments. Plenarily disrupted, necrotic mast cells were withal observed which had morphologically intact granules in continuity with the extracellular space.<sup>31</sup>

Shiguang Huang et al analyzed the relationship between the mast cell degranulation and human periodontal disease progression and he indicated that mast cell degranulation appears to be associated with human periodontal disease.<sup>32</sup> Naesse et al examined the expression by gingival mast cells of matrix metalloproteinases and he concluded that the chronically inflamed periodontal lesions appeared with little evidence of mast cell degranulation, however, that mast cells in inflamed gingiva have the potential to degrade extracellular matrix if appropriately triggered.<sup>33</sup> Günhan et al examined the number of mast cells in gingival tissues of healthy controls and patients with chronic periodontal disease before and three weeks after surgical treatment, he noticed the numbers of mast cells were found to be increased on postoperative healed tissues and inflamed. This increase is closely related to fibrosis in connective tissues.<sup>34</sup> Silveira LB et al investigate the effect of low-intensity laser irradiation on the total count of mast cells as well as the percentage of degranulation in human gingiva and proposed that red and infrared wavelengths enhanced mast cell degranulation in human gingival tissue.<sup>35</sup>

### CONCLUSION

Mast cells are considered to be multifunctional immune cells implicated in several physiological and disease states including periodontal disease. . Because of the paramountcy of periodontal diseases, inadequate research and possible relationships between mast cells and pathogenesis of periodontal diseases, further research is needed so that the pathogenesis of periodontitis might be elucidated more pellucidly and efficacious treatment approaches can be suggested.. The therapeutic implicative insinuations strategies directed toward the possible utilization of drugs to influence mast cell secretion and thereby avert inflammation and maintenance of chronicity, or even with the aim of amending periodontal regeneration.

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