ROLE OF MAST CELL IN ORAL PATHOLOGY

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Abstract

Mast cells in oral tissues releases various pro-inflammatory cytokine tumor necrosis factor alpha (TNF-ά) which promotes leukocyte infiltration in various inflammatory condition of oral cavity such as oral lichen planus (OLP), periapical lesions, gingivitis & periodontitis. T lymphocyte derived cytokines influences mast cell migration & mediator release. Mast cell secreted proteases, activates matrix-metalloprotinases-9 (MMP-9) which may contribute to alteration in basement membrane in inflammatory condition such as Lichen Planus. Hence by understanding the role of mast cells in the pathogenesis of various diseases; therapies should be targeted to enhance the prognosis of the diseases.

Key Words: Mast cells, Degranulation, Cytokines, Tryptase, Chymase.

Introduction

Mast cells (MC) are large spherical or elliptical mononuclear cells found in a variety of tissues including skin, submucosa or connective tissue of various organs & mucosal epithelial tissues [(1)] & also in dental pulp. They are mobile, bone marrow derived, and typically containing 80-300 granules. [(2)] These metachromatic granules are easily detected by stains such as toluidine blue. They are typically distributed in perivascular & perineural regions. The granules are rich in heparin, chondroitin sulphate, proteoglycan & numerous enzymes including collagenase. These cells believed to play role in remodelling of extracellular matrix (ECM) during wound healing, progresion of rheumatoid arthritis & the progression of a fibrotic diseases such as interstitial pulmonary fibrosis, progressive systemic sclerosis, retroperitoneal fibrosis.[(3)] Mast cells also produces a variety of lipid & protein alpha mediators with pro-inflammatory activities including chemotactins, cell activating & cell growth factor. Tissue mast cells are not homogenous for eg. enzymes within granules of mucosal & connective tissue mast cells are different from each other. The ranges of mast cell activity is specialized for their anatomic location, as the granules are different for mucosal and connective tissue mast cells.[(3)] Under light microscope mast cells gives a characteristic metachromatic staining pattern with toluidine blue.

Ultrastructure of Mast Cell:-

In oral mucosa & skin the granules in mast cell have complex form with the amorphous region located next to crystalline region. The crystalline region ranges in configuration & three types of mast cell population is identified.[(4)]

1. Cells deeper in connective tissue (except that in close vicinity to blood vessels) are round /oval in shape & dark purple in colour. The cell borders are well defined &

nucleus is not visible due to granules making the nucleus & is called as intact cells. [4]

2. In the superficial connective tissue. Immediately below infiltrate in OLP & near the blood vessels the mast cells appear flattened / irregular & cytoplasm appears granular. The cell borders are not defined & the nucleus is only partially appreciable; these cells are called spreading cells. [5]

3. The third type called degranulated cells found within the infiltrate & appeared paler as the staining has changed from metachromatic violet to light pink, the nucleus blue in color & well defined. [2]

Masts cells are classified according to protease content in:-

a) MC_T phenotype contain tryptase only

b) MC_{TC} contain both tryptase & chymase [5]

Mast Cell Degranulation:-

Degranulation of mast cell releases pro-inflammatory mediators such as: - TNF-alpha (TNF-ά), chymase, tryptase, MMPs, bFGF, heparin, histamine, various interleukins (IL3, IL4, IL5, IL6, IL8, IL10, IL13, IL16 and cytokine RANTES.[6,7] Tryptase is the most abundant serine proteinase stored in MC granules. It promotes inflammation, ECM degranulation and tissue remodeling & is considerd an important angiogenic factor. Mast cell degranulation is induced by various stimulus such as IgE receptors, neuropeptides (substance P), chemokines & other physical stimulus.[2] RANTES (regulated on activation, normal T cells expressed & secreted), TNF-ά may up regulates endothelial cells adhesion molecule (CD62E, CD54 & CD106) expression in OLP that is required for lymphocyte adhesion to the luminal surface of blood vessels & subsequent extravasation. RANTES are a member of chemokine family produced by various cells; such as activated T-lymphocyte, bronchial epithelial cell, oral keratinocytes & mast cell. RANTES secreted by activated T-cells attract mast cell & stimulates degranulation.[8]

Mediators of Mast Cells:-

The degranulation mediators can be grouped into 2 categories [2]
a) Mediators that are preformed in their granules are:- serine proteases:- Tryptase, chymase & cathepsin G, histamine, heparin, serotonin, acid hydrolases &cytokine, TNF-α, IL-16.

b) Mediators following activation of mast cell are[2,3,5,9] :- IL-1, IL-3 ,IL-4,IL-5,IL-6,IL-8,IL-10IL-13 &IL-16, platelet activating factor (PAF) RANTES, macrophage inflammatory protein (MIF -1alpha) & arachidonic acid metabolites, prostaglandin & leukotriene C4 (LTC4). [2,5].

Role of mast cell released cytokines: -

IL-3 – induce basophil recruitment & activation
IL-5-eosinophil recruitment & activation
IL-13 – induction of IgE synthesis

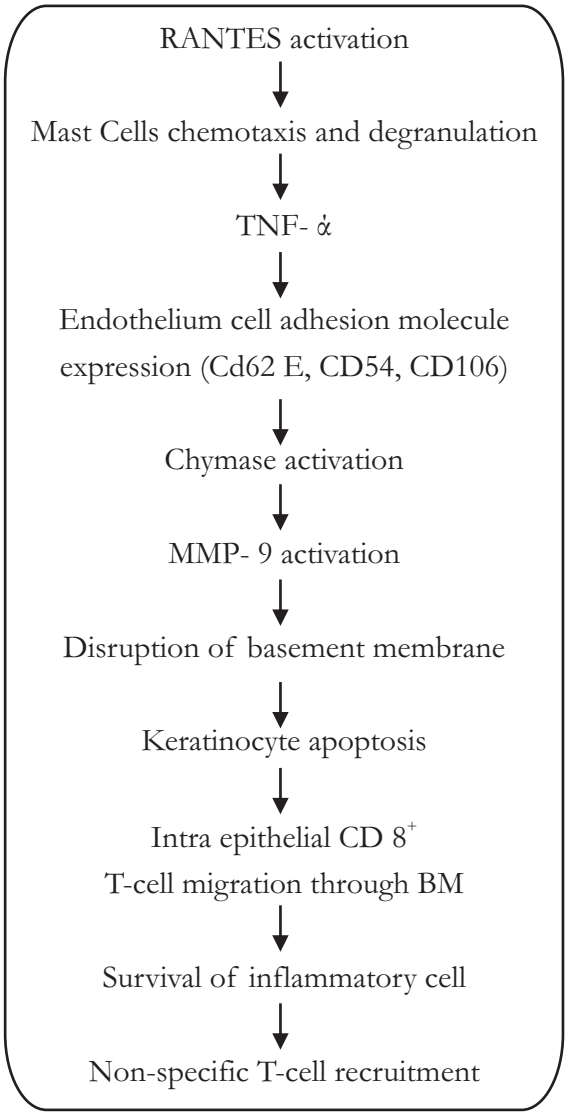
Mast cell bears receptors for IgE & degranulates when this cytophilic antibody is cross-linked by antigen. But other factors such as mechanical trauma, complement C5a, eosinophil –derived cationic protein, and bacterial products can cause mast cell RANTES degranulation. Thus mast cell can promote inflammation in the absence of IgE mediated activation & likely infiltrate inflammatory events under many circumstances. [9]

Thus, mast cells release proinflammatory mediators, promotes inflammation and angiogenesis, extracellular matrix degeneration and tissue remodeling. The main role of mast cells are in the following oral diseases:-

Role of MC in Oral Pathologies:

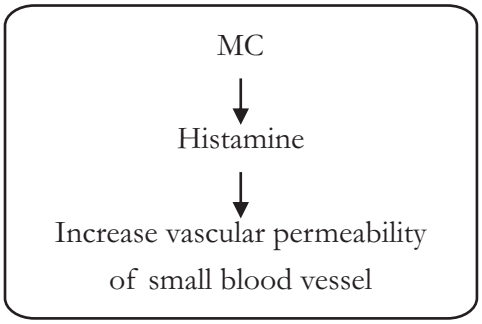
1) Role of MC in OLP

MC play major role in non-specific mechanism of the OLP. [6,10]



2) Role of MC in Periapical lesions

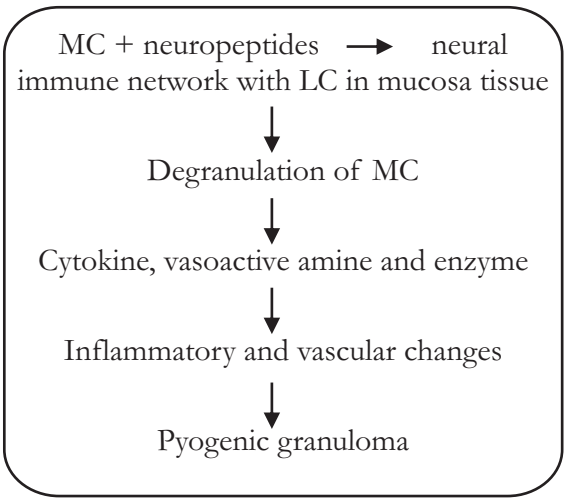
Mast cell express KIT (CD117) which is a Trans membrane tyrosine kinase receptor protein encoded by the protooncogene c-kit that maps to chromosome 4 (4q11-12).[9,11] According to Drazic et al 2012, MC can be analyzed qualitatively and semi quantitatively in periapical lesions based on immunohistochemistry expression of CD117. There is strong membrane reactivity of CD117 for MC and can be helpful in diagnosis of MC disorder. MC can also be demonstrated in periapical granuloma and periapical cyst.[11] Its pathogenesis is connected with hypersensitivity reactions.[9]



MCs are present in both inflammatory infiltrate and fibrous area of periapical lesions. MC contributes to fibrous tissue formation by production of hyaluronic acid.

3) Role of MC in Pyogenic Granuloma

MC on stimulation undergoes degranulation and causes inflammatory and vascular changes leading to formation of pyogenic granuloma as follows-[12]



MC related pyogenic granuloma represents a reactive lesion resulting from local etiological factors like gingival inflammation, calculus or trauma which activates MC resulting in release of mediators which leads subsequent changes in tissue leading to formation of pyogenic granuloma.

4) Role of MC in wound healing

Wound healing is a dynamic process consisting of four continuous overlapping phases.[13]

1. Homeostasis
2. Inflammation

3. Proliferation
4. Tissue remodeling and resolution

MC can activate fibroblast via tryptase synthesize collagens. As well as due to hyaluronic acid MC contributes to fibrous tissue formation.MC along with fibroblast adheres to fibronectin integrin receptor and helps in wound healing. [13] MC derived MMP-9 also facilitate wound healing.[13] Wound healing involves degradation, cell migration, synthesis of matrix consisting of fibronectin, fibrin and high amount of collagen type II and matrix remodeling to return the tissue to normality. MMP-9 is linked with remodeling of granulation tissue matrix.[14]

5) Role of MC in angiogenesis in oral squamous cell carcinoma

Angiogenesis/Neovascularization helps in progression and metastasis of malignant tumor. Mast cells cause neovascularization by producing angiogenic factors, such as VEGF, or substances with angiogenic properties, such as tryptase, FGF, TNF, interleukin (IL)-8, histamine and heparin. The accumulation of mast cells is a harbinger of the growth and invasion of several kinds of malignancy. The heparin from the mast cells cause vasoproliferation and increases the half-life of basic fibroblastic growth factor (FGF), which is a potent angiogenic substance, thereby promoting tumour angiogenesis and facilitating local tumour invasion. Interleukin-1 leads to epithelial proliferation.[15]

Tryptase is thought to be potent angiogenic factor for tumor angiogenesis in oral squamous cell carcinoma as it directly induce cell proliferation of human dermal microvasculature and endothelial cell. Tryptase and chymase act as a powerful MMP activator. Among MMP's, gelatinase B (MMP-9), plays vital role in angiogenesis, tumor invasion and metastasis because of its ability to cleave type IV collagen in basement membrane.[7]

6) Role of MC in Actinic cheilitis

Actinic cheilitis is a chronic inflammatory condition which occurs mainly in the lower lip in adulthood, which is caused by chronic in excessive exposure of the lips to solar U.V radiation.[7] This lesion is potentially malignant and may transform to squamous cell carcinoma. Product of MC degranulation like histamine and TNF- ά are key mediators of U.V induced immune separation, which can increase the susceptibility for skin cancer and actinic cheilitis.[2,7]

Also it is found that enzymes which are linked to elastosis formation such as cathepsin G, carboxypeptidase and gelatinases A & B are found in MC_{TC}.

7) Role of MC in Orofacial granulomatosis

Orofacial granulomatosis is a descriptive term used for a group of chronic granulomatous disorders which share similar clinical and histological characteristics. It is characterized clinically by labial and facial swelling and histologically by the presence of lymphoedema and non-caseating epithelial granulomatous lesions.[16]The term orofacial granulomatosis is restricted to otherwise healthy patients in whom systemic granulomatous diseases have been excluded.

Degradation of MC mediators is deposited in extra cellular compartment and affects endothelial cells. Histamine binds to specific cell surface receptors H_1 and H_2, seen on endothelial cell surface. When bound contraction of endothelial cell occurs, leading to the widening of the gaps between these cells which promotes inflammation by aiding the extravasations of fluid, proteins and circulating inflammatory cells into the tissue.[16]
TNF- ά also contributes to the inflammatory process by -

1. Endothelial expression of E selective CD62E (ELAM-1) which is a adhesion molecule.
2. Chemotaxis of macrophages and neutrophils.
3. Activation of langerhans cells (LC)
4. Autocrine stimulation of MC to release histamine and tryptase.

It is found that there is direct relationship between MC degranulating and development of inflammatory leading to orofacial granulomatosis.

8) Role of MC in Oral submucous fibrosis (OSMF)

Oral submucous fibrosis (OSMF) is associated with chronic inflammation in adjacent connective tissue. Mast cells are the local residents of the connective tissue, and are said to be pro-inflammatory, immunoamplifying in action and producing mitogenic cytokines. These functions of mast cells may play a significant role in the pathogenesis of OSMF.[17] Histamine could probably attribute to submucosal edema seen in early stages of oral submucous fibrosis. Due to increased vasopermeability, eosinophilic chemotactic factor (ECF) is released from the mast cells. This could probably attribute to the eosinophils that are sometimes a part of inflammatory cell infiltrate seen in the early stages of oral submucous fibrosis. Interleukin-5 causes increased proliferation and differentiation of eosinophils. Interleukin-1 from the mast cells could cause increased fibroblastic response and mast cell derived tryptase causes increased production of type-I collagen and fibronectin thereby attributing to the increased fibrosis.[17]

Conclusion

Mast cells are multifunctional cells that play an important role in inflammation in oral mucosa and the dental pulp. They are associated with both resistance and greater susceptibility to tumor development. Because of the unique properties of the mast cells, these cells are ideally poised to serve as 'gatekeepers' of the microvasculature in the oral cavity. An appreciation of the multiple interactions among mast cells, endothelial cells, nerves, and other immune system provides a basis for therapies for targeting mast cell responses. Hence, this overview aims to understanding of role of mast cells in the pathogenesis of various diseases; could target to enhance the prognosis of the diseases. It makes it easier for us to direct therapeutic modalities against mast cell and its granules to alter the course of the disease.

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