MAST CELLS- THE MASTER BLASTER: AN OVERVIEW

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ABSTRACT

Mast cells are multi-tasking cells. They have both pro-inflammatory and anti-inflammatory effects. In the recent times their actions in various diseases have been investigated and have divulged many new facts owing to the plethora of cytokines secreted at different times under different conditions. Related aspects of the mast cells with their actions in some common oral lesions have been succinctly put together for exploring the possibility of treatment modality options involving mast cells. This overview is a collection of observations based on review of publications on the subject matter.

KEY WORDS: Mast cells, Mediators, Degranulation, Cytokines

INTRODUCTION

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, sub mucosa 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 IgEFC 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).

Functions

Mast cells together with blood basophils cause type 1 hypersensitivity reaction. As these cells are often associated with small blood vessels, it has been suggested that they play a role in maintaining normal tissue stability and vascular homeostasis.

Mast cells contribute to a broad spectrum of physiologic, immunologic, and pathologic processes. The degranulation of mast cells result in the release of primary and secondary mediators.

Primary mediators are those which are preformed and are stored in the granules. They are responsible for immediate reactions.

Secondary mediators are either synthesized after target cell activation, or are released by the breakdown of membrane phospholipids during degranulation process.

Intracellular events leading to mast cell degranulation.

The cytoplasmic domains of the mast cells are FcRI(cell surface receptors). Cross linkage of FcRI results in the formation of Ca2+ channels. The Ca2+ increase leads to the formation of Arachidonic acid, which is converted to prostaglandins and leukotrienes. The increased Ca2+ promotes the assembly of microtubules and the contraction of the microfilaments, resulting in the movement of granules to the plasma membrane. Concomitantly, with Ca2+ increase, there is a transient increase in cAMP initially. A later drop in cAMP is required for
degranulation to proceed. cAMP dependent protein kinase are thought to phosphorylate the granule, thereby changing the permeability of the granules to water and Ca2+. The consequent swelling of granules facilitate fusion with plasma membrane releasing the mediators. 1

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. 1

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. 1

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. 1

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. 2

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. 4

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. 5

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. 6 (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 were found to be present in substantial numbers in odontogenic keratocyst walls as well as in the walls of dentigerous and radicular cysts.

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 resorption.7.

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 cysts.7

The leukotriens and cytokines have a role in chemoattracting the neutrophils, eosinophils and lymphocytes thereby maintaining the inflammatory condition of the lesion.3

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 neurofibroma.8 Mast cells secrete proteins that can remodel ECM and initiate angiogenesis.9,10

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.5

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.11

Squamous Cell Carcinoma

Squamous cell carcinoma of head and neck is a common disease with a high degree of mortality and morbidity. How exactly mast cells (host local immunity) contribute to the behaviour of the disease is unclear, but in-vivo studies have shown sequential infiltration of mast cells and degranulation in squamous cell carcinoma. Angiogenic factors including VEGF, bFGF and platelet derived growth factors have been reported to stimulate mast cell migration. Hypoxia might induce tumor cells to release angiogenic factors which in turn could chemoattract the mast cells to migrate into the hypoxic areas of the tumor and then the mast cells release angiogenic products that stimulate the infiltration of more mast cells. Both heparin and tryptase are potent angiogenic factors. Tryptase activates latent metalloproteinases and plasminogen activator which degrade the extracellular matrix which is important for the initial stages of angiogenesis.12

Fibroblastic growth factor is a potent angiogenic substance which promotes angiogenesis and facilitates local tumour invasion. S Ch'ng in his studies has concluded that mast cells have a direct inhibitory effect on the proliferation of cells by dysregulating key genes in apoptosis and cell cycle control.12 Due to these conflicting reports Tomita et al have hypothesized that the cytotoxic effect of mast cells suppress tumor activities initially when the mast cell infiltrate the tumor tissue. However after infiltration the tumor cells might promote the angiogenic properties of the mast cells while suppressing their cytotoxic effects when mast cell: tumor ratio is greater than 20:1.12

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.  

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. 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. Mast cells are increased in known auto-immune diseases like pemphigus vulgaris, developing subdermal bullous diseases and also in pemphigoid.

CONCLUSION

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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