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10.5005/jp-journals-10037-1094

REVIEW ARTICLE

Mast Cells in Health and Oral Disease

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ABSTRACT

Introduction: Mast cells (MC) are multifunctional secretory cells characterized by numerous large metachromatic staining protease-rich intracellular granules. They are derived from hematopoietic progenitor cells in bone marrow and do not mature into terminally differentiated cells until they reach the tissue or organ in which they become resident. They play a vital role in a number of defense and repair mechanisms due to their strategic location in the connective tissue at the interface with the microvasculature.

Objectives: This review attempts to help improve our understanding on the types of MC, their morphology, staining characteristics, distribution, biological function, and their pathogenesis in inflammation, oral potentially malignant disorders, and oral squamous cell carcinoma. We hope this review recognizes the integral role of MC in oral pathological disorders and facilitates the opening of novel approaches to better therapies for improving the quality of life.

Conclusion: Mast cells has shown to remodel extracellular matrix during wound healing. The entire ambit of allergic and hypersensitivity reactions are the adverse effects produced by the degranulation of MC. They participate in many inflammatory oral diseases as they possess diverse roles ranging from pro-inflammatory to immuno-modulatory. They accumulate at the boundary between healthy tissues and malignancies and are found in close association with blood vessels within the tumor microenvironment as they play an early role in angiogenesis.

Keywords: Allergy, Biological, Function, Immunity, Inflammatory, Intracellular granules, Leukoplakia, Lichen planus, Mast cell, Morphology, Pathological, Response, Squamous cell carcinoma, Submucous fibrosis.

How to cite this article: Pynadath MK, George A, Jayapalan CS, Noufal A. Mast Cells in Health and Oral Disease. Oral Maxillofac Pathol J 2017;8(1):23-27.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Mast cells (MC) have fascinated the medical community over decades because of their metachromatic staining protease-rich large cytoplasmic granules and due to the general lack of true understanding of their biological function.[1] von Recklinghausen (1863), Kuhne (1864), Friedlander (1867), and Flemming (1867) among others together may be considered as the earliest researchers who first identified and described MC.[2] Many later researchers noted their perivascular habitat, but it was the German biologist Paul Ehrlich (1877) who coined the term "mastzellen," which meant "sleek, fat, and well fed."[2] He was of the opinion that they had a role in nutrition as the MC were found in tissues where nutrition was enhanced and he believed that the intracellular granules were phagocytosed nutrients.[2] Some experts refer to MC as "unicellular endocrine glands," because of their ability to release a wide variety of chemical mediators that have potent biological actions, such as recruitment of inflammatory cells, phagocytosis, stimulation of fibroblasts, neoangiogenesis, and release of few vasoactive substances.[3] They exhibit an array of surface molecules and immune response receptors, which give them the capacity to react against specific and nonspecific stimuli, hence playing an important role in host defense mechanism, innate immunity, homeostasis, remodeling, and fibrosis.[4,5] Many theories have been proposed toward the origin of these cells, including from the pericytes located along the capillaries.[5] They are now considered to be of hematopoietic origin and are derived from the bone marrow cells.[5] They circulate as committed progenitors and on an inflammatory stimuli traverse from the vascular space and mature in the peripheral tissues.[2]

In this review we provide an overview of the types of MC, their morphology, staining characteristics, distribution, biological function, and their potential role in pathological conditions of the oral cavity. Through the understanding of MC, we hope to help researchers in the development of novel interventions to alter MC response in the pathological environment to help inhibit the developing pathology.

CLASSIFICATION

- Based on age of MC
  - Young MC (type I): Stains metachromatically blue and homogeneously with toluidine blue (TB) and stains negative for periodic acid Schiff (PAS) reaction[6]
  - Mature MC (type II): Stains metachromatically violet and with granularity on TB and stains positive for PAS[6]

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- Based on differences in neutral protease composition, ultrastructure, and dependency on T-lymphocyte function
  - MC_T cell: Containing tryptase[7]
  - MC_{TC} cell: Containing tryptase and chymase[7]
  - Immature forms have been described which have indistinct ultrastructural features but have the same protease compositions as of their mature counterparts.[7]
- Based on tissue distribution, staining characteristics, and presence of proteases
  - Mucosal MC: Positive for chymase[8,9]
  - Connective tissue MC: Positive for both tryptase and chymase[8,9]
- MC in human gingiva
  - Typical MC (TMC): Having distinct metachromatic cytoplasmic granules with definite cytoplasmic boundaries.[8]
  - Atypical MC (AMC): Having indistinct or faint metachromatic material of granular, linear, vacuolated, or homogeneous appearance partially or totally surrounding the nucleus, and with indefinite cytoplasmic boundaries.[8]

Morphology

Light microscopic study of MC revealed four basic cell morphologies: round, ovoid, spindle or elongated, and pseudopodia.[10] Tissue MC have small nucleus with a mean diameter of 4 µ and have a round-oval shape, which may sometimes be longitudinally stretched, indented, kidney, or fusiform shaped.[2] The cells have polymorphous cytoplasmic contour and appear as oval, pyriform, spindle, or star shaped due to the aggregation of the intracytoplasmic granules.[2] The granules are often so numerous that they may obliterate the view of the cell nucleus. Oval and oblong MC vary in diameter from 3.5 to 14 µ and in some instances may attain 28 µ.[8] The intracytoplasmic granules are spherical-oval membrane-bounded organelles with a mean diameter of 0.2 to 0.4 µ.[8] Often empty vacuoles representing discharged granules are present.[8] Changes in the morphology may occur due to the intrinsic (genetic origin, ameboid movement, physiological conditions) and/or extrinsic factors (environmental factors, such as the medium of fixation, embedding, staining).[2] Under the electron microscope, the nucleus appeared to lie more or less centrally with clumped chromatin.[10] The cells had an irregular outline with numerous characteristic cytoplasmic processes in the form of pseudopodia and microvilli.[10] The cytoplasm contained numerous mitochondria, fibrillar structures, sparse smooth endoplasmic reticulum, diffusely distributed ribosomes, well-developed golgi complex, and scattered secretory granules.[10]

Staining Characteristics

Under hematoxylin and eosin (H&E), MC are not prominent and can be easily overlooked.[4] Basic aniline dyes, such as ethylene blue or crystal violet are classically used to demonstrate their presence.[4] MC granules have a strong affinity for basic dyes and they stain the granules metachromatically, with the blue dyes giving a red stain and the red dyes giving a yellow stain.[2] The metachromasia is due to the presence of large amount of sulfated glycosaminoglycan heparin in the granules.[4] The other basic dyes that stain MC are thionine, TB, methylene blue, methylene violet, cresyl violet, brilliant cresyl blue, amethyst, acridine red, neutral red, pyronine, safranine, azure, and acridine orange.[2,11] Positivity for PAS, alcian blue, astral blue, and colloidal iron suggests the presence of acid mucopolysaccharides.[4] The different staining characteristics of MC within the same tissue and between tissues suggests the heterogeneity of their chemical constituents or the difference in cell maturation.[2] MC have shown immunopositivity toward bcl-x(L), CD68R, CD45, CD117 (c-kit), and HLA-DR.[29] CD2 may be a novel useful marker in mastocytosis, since in other pathologic conditions MC are CD2 negative.[12]

Distribution

MC are granular secretory cells seen in the underlying connective tissue of the oral mucosa.[13] MC are abundant in the bone marrow, serous membranes, around superficial small vessels or capillaries of all organs, microvascular endothelium of the oral mucosa, and in the extremities including face, hands, and feet.[2,5] They are seen in close proximity to the basement membranes of blood vascular channels and nerves as a result of their interaction with the laminin-specific receptor CD49f (a6/pi) integrin.[14] Large numbers of MC are found around the blood vessels in the gingiva and in the middle layers of lamina propria of the buccal mucosa.[15] MC have been identified within the bilaminar tissues and vasculature of temperomandibular joints.[16] MC_T are almost exclusively found in the alveolar walls of the lungs and intestinal mucosa, while MC_{TC} were seen more predominant around the blood vessels and the skin appendagial structures in the superficial dermis.[7] MC_T and MC_{TC} demonstrated almost equal distribution in the connective tissue.[7] Scars, cartilage, and bone are devoid of MC.[2]

Biological Function

MC arise from multipotent CD34+ precursors in the bone marrow and circulate in the peripheral blood as a granular monocytes.[3] The progenitors differentiate from primitive cells under the influence of interleukin (IL)-3

and migrate to other parts of the body.[12] On migrating into the connective tissues, these immature cells assume their typical granular morphology.[5] MC has surface adhesion molecules integrins and c-kit that mediate binding to other cells and extracellular matrix (ECM) glycoproteins.[17] MC activation results in the expression of adhesion molecules and their ligands, which help in their localization and migration. Extracellular matrix proteins, such as laminin of vascular and neural basement membrane, are important in the localization of MC.[17] Two principal cytokines IL-3 and stem cell factor (SCF) promotes MC proliferation and differentiation.[1] IL-3 is important for its early proliferation, whereas SCF acts to maintain cell viability by suppressing apoptosis and by promoting maturation.[1] MC along with the neutrophils, macrophages, and platelets play an important role in immunity. It contains chemical mediators, such as histamine, tryptase, tumor necrosis factor (TNF), and IL that can increase fibroblast proliferation and act as chemotactic factor for neutrophils.[1] Heparin, fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) induce endothelial cell migration and angiogenesis.[1] MC induce and enhance angiogenesis via multiple interacting pathways including: (i) Release of potent proangiogenic factors, such as VEGF, bFGF, TGF-α, -β, and IL-8; (ii) proteinases and heparin that release heparin-binding proangiogenic factors; (iii) histamine, VEGF, and certain lipid-derived mediators that induce microvascular hyperpermeability; (iv) chemotactic recruitment of monocytes/macrophages and lymphocytes; (v) activation of platelets; (vi) activation of neighboring non-MC, which release ECM degrading proteinases and SCF; (vii) auto- and paracrine stimulation of MC by SCF.[17] As a result of ECM degradation and changes in the microenvironment, the MC populations may change in number, phenotype, and function. Chemical mediators in MC can be grouped into: (1) Preformed secretory granule mediators: Histamine, proteoglycans, serine proteases, carboxypeptidases; (2) lipid-derived mediators: Leukotriene – C4, D4, E4 (SRS-A), prostaglandin, platelet activating factor; (3) MC-derived cytokines: (a) Proinflammatory cytokines – TNFα, IL-1α, -1β, (b) mitogenic cytokines/growth factors: IL-3, -4, -5, -10, GM-csf, (c) immunomodulator cytokines: IL-1α, -1β, IL-4, -10, IFNγ.[18]

Mast Cells in Disease

Adverse effects of anaphylaxis and drug allergy are produced by the activation of MC and basophils.[5] MC are activated to release inflammatory mediators during expressions of cell-mediated delayed hypersensitivity.[5] Their proliferation in cellular immune response is regulated by the products of T lymphocytes.[5] When immunoglobulin (Ig)-E antibodies are raised against a certain allergen, they bind to MC surface Fc-receptors and cause the MC to undergo characteristic biochemical and morphological changes and release their contents by degranulation.[3,5] They release histamines, leukotriens, and prostaglandin in response to the antigen challenge.[5] Subsequent exposure leads to immediate degranulation and release of the chemical mediators.[3] MC and their proteases increase in inflammatory conditions and bring about alterations in the basement membrane that allows cytotoxic lymphocytes to enter the epithelium.[2]

MC in periodontitis: The exact role of MC in inflammation is not yet known but their presence has been interpreted as a sign of healing. MC count is decreased in acute gingivitis but increased in chronic gingivitis, chronic generalized periodontitis, and in proliferative fibrotic lesions like phenytoin enlargement.[19] The increase in MC count suggests the possible participation of these cells in the defensive and the destructive events of chronic inflammation. MC express matrix metalloproteinase (MMP) which are enzymes that degrade the gingival ECM, and they are known to release preformed cytokines which initiate immune response.[20]

MC in periapical lesion: MC are now recognized for its immunoregulatory properties, but little is known about the complex interactions between the cells, cytokines, and other inflammatory elements in periapical lesions. They tend to be more in the peripheral regions of periapical lesions and are found in close proximity to lymphocytes in both periapical granulomas and cysts.[21] A functional relationship exists between these two cell populations and may facilitate elicitation of an immune response i.e., contributory to the pathogenesis of the periapical lesions.[21]

MC in oral lichen planus (OLP): A specific pattern of MC distribution in mucous membrane diseases like OLP, pemphigoid, and desquamative gingivitis has been described by various researchers.[10] They are increased significantly in OLP.[10,22] They contain proinflammatory TNF-α in their granules, the release of which promotes leukocyte infiltration through the induction of endothelial leukocyte adhesion molecules. TNF induces lesional T-cells to secrete chemokine RANTES, which stimulates MC degranulation.[22] The expression of RANTES and its receptors on MC and T-cells prolong the survival of these cells and thus induce inflammation.[22] The association of MC with laminin was an important determinant of MC density in the immediate perivascular region, thus providing an ideal situation for MC-derived mediators to influence the circular endothelium and cause the progression of OLP.[22]

MC in oral submucous fibrosis (OSMF): MC was observed in all the grades of OSMF. In grade I and II, they were

identified predominantly near the blood vessels where the reaction of the tissues to the irritants were strong.[23] MC were low in advanced stages where the connective tissue was hyalinized.[23] The MC and vascular response in OSMF was similar to those identified in autoimmune diseases.[24] Researchers claim that MC histamine chain causes changes in the submucosa and basement membrane that lead to cancerous change in OSMF. The MC response in OSMF is consistent with the overall sequential tissue response in the disease. The smooth muscle hypertrophy in OSMF could be due to the degranulating MC products.[24]

MC in leukoplakia: Researchers found an increase in MC in epithelial dysplasia, suggesting a probable role in its pathogenesis.[25] The biological and pharmacological active agents in MC may contribute to the inflammatory reaction seen in leukoplakia. The stimulated MC release IL-1 causes increased keratinocyte proliferation.[26] Histamine increases mucosal permeability that facilitate increased access for the antigen to the connective tissue. MC mediators IL-1, TNF, histamine, and heparin could lead to the various histopathological and clinical features identified in leukoplakia.[25] MC response was significantly greater in precancerous epithelial dysplasia than in overt carcinoma.[27]

MC in Oral Squamous Cell Carcinoma (OSCC): MC are said to play a defensive role in tumor growth. Studies suggest that MC exert an inhibitory effect on tumor growth and that the inhibitory factor could be serotonin.[27] Tissue MC are usually absent or extremely sparse in deeper regions of carcinoma but tend to accumulate in the adjoining normal tissue and in the regional lymph nodes.[2] The density of MC consistently decreased with increasing dedifferentiation and with increasing numbers of mitotic figures. In high MC group the overall survival rate was double that for the group with few MC.[28] In tumor models MC have shown to play a decisive role in inducing the angiogenic switch which precedes malignant transformation.[17] The number of MC and microvasculature were found to be higher in OSCC, suggesting that MC may upregulate tumor angiogenesis by expressing tryptase. MC_{TC} were significantly increased at tumor invasion zone where both ECM degradation and angiogenesis are required. MC_T were found at the intratumoral stroma where angiogenesis was required.[7,29]

CONCLUSION

MC serve as the gate keepers of microvasculature due to their unique distribution and properties in health and disease. They exhibit an array of adhesion molecules, immune response receptors, and other surface molecules that give them the capability to react to multiple nonspecific and specific stimuli. There is no disease, biological condition, or animal model till date that exhibits an absolute lack of MC from which or in which their exact biological role could be studied in detail. MC and its mediators have a definite role to play in the pathogenesis of many pathological conditions. They have been regarded as being important in the initiation and amplification of acute inflammatory responses. In tumor models, MC have been shown to play a decisive role in inducing angiogenesis which precedes malignant transformation. We hope that this review recognizes the integral role of MC in oral pathological disorders and help researchers in the development of novel interventions to help improve the quality of life in these patients.

AUTHOR CONTRIBUTION

All the authors contributed actively in the conception, design, drafting, and critical revision of the manuscript. All the authors read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors acknowledge the supporting and auxiliary staff of the Department of Oral Pathology and Microbiology.

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