Mast cell disorders in periodontal disease

G. Cathrine1, Priya Lochana Gajendran2*

ABSTRACT

The aim of the review is to give an insight into the role of mast cells (MCs) and its disorders in periodontal health and disease. MCs are mobile, bone marrow-derived, granule-containing immune cells that are found in all connective tissue and mucosal environments and the peripheral and central nervous systems. MCs are able to phagocytose, process and present antigens as effectively as macrophages. MC disorders are conditions in which MCs are either increased in number, hyper-reactive, or both. These conditions range in severity from relatively benign disorders that do not impact life span to malignant clonal diseases that progress rapidly. Recently, MCs were found in high numbers in chronically inflamed gingival tissue taken from patients with chronic marginal periodontitis. This topic will review the classification of MC disorders, provide a brief clinical description of each disorder and highlights the role of MCs in periodontal health and disease.

KEY WORDS: Connective tissue, Inflammation, Innate immunity, Mast cell, Oral mucosa; periodontitis

INTRODUCTION

Mast cells (MCs) were depicted sometime prior in the mucosa of the oral cavity and especially in human gingiva and experimental gingivitis. In periodontal disease and especially gingivitis, the MC thickness fundamentally increases without a clarification in regard to their involvement in maintaining or progression of inflammation.

A current report has demonstrated a relationship between MC degranulation and the seriousness of periodontitis. It was discovered that the thickness of de-granulated tryptase positive MCs is essentially higher in serious periodontitis contrasted with direct periodontitis and normal tissue. Be that as it may, it was unrealistic to finish up if degranulation was inflammatory infiltrate or a degranulation induced accumulation of inflammatory cells. In addition, numerous creators in periodontal disease announced expanded MC thickness comes about are most likely to a limited extent due to various checking strategies and the moderately low number of cases.[1]

MCs are of 20–30 μm in the distance across having different shapes, for example, polyhedral, fusiform, ovoid, and rectangular and have a halfway put and circular core. Cytoplasm contains granules extend in estimate from 0.3 μm to 0.8 μm up to 40% of the volume of MC is possessed by layer – encased secretory granules.

There are 50–500 secretory granules introduce in develop human MC. Since these granules contain heparin (or chondroitin sulfate), a sulfated glycosaminoglycan, they recolor meta-chromatically with toluidine blue. Electron microscope investigations of the granules uncover that there were contrasts in size and type of granules and showed varieties in ultrastructure even they were available within similar cells.[2]

MCs are practically various cells that have a constitutive nearness at mucosal surfaces and expound noteworthy exhibit of arbiters, making them an attractive therapeutic target.

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MCs

MCs are seemingly perpetual tissue-occupant cells with an essential part in numerous inflammatory settings including host resistance to parasitic contamination and unfavorably susceptible responses. MCs are found at the limits among tissues and the outside condition, for instance, at mucosal surfaces of the gut and lungs, in the skin, and around veins.[3] MCs are players in the inflammatory reaction as they can be actuated to discharge a wide assortment of provocative mediators, by a wide range of antigens including allergens, pathogens, and physiological arbiters.

MCs get from the bone marrow yet not at all like other white platelets, MCs are discharged into the blood as MC begetters and do not completely develop until the point when they are enlisted into the tissue where they experience their terminal separation. Undifferentiated organism factor (stem cell factor) is a cytokine fundamental for MC improvement, multiplication, and survival.

DISTRIBUTION

MCs are situated all through the body in the connective tissue legitimate, where they are thought along little veins. They likewise are available in the subepithelial connective tissue of the respiratory and stomach related frameworks. MCs are conveyed generally all through various organs.[4]

- Skin (around veins, lymphatic, nerves, and glandular tissues).
- Upper and lower respiratory tract.
- GIT payer’s patch.
- Bone marrow.
- Liver.
- Spleen.
- Oral mucosa.
- Gingiva.

ORIGIN AND FUNCTION

MC mediator impact numerous destinations engaged with

- All phase of wound healing
  - Acute inflammatory
    - Promote the inundation of inflammatory cells to damage the site.
  - Proliferative phase
    - Re-epithelialization and angiogenesis.
    - Release numerous angiogenic elements to initiate re-vascularization of harm tissue.
    - Heparin from MC fortifies endothelial cell relocation to frame fresh recruits vessel.
    - MC trypase: Stimulates vessel tube arrangement and enhances the development of microvascular endothelial cells.
- MC chymase: Promotes angiogenesis through impacts of angiotensin II.
- Generate development factors: Fibroblast growth factor, vascular endothelial growth factor, platelet determined growth factor, and nerve growth factor.
- Remodeling phase
  - As fibroblast extends in past stage, they store collagen and other extracellular matrix proteins, shaped, and rebuilt into scar tissue.[3]
- Hair follicle recycling
  - MC histamine, tumor necrosis factor (TNF), and substance P included are thought to contribute in hair follicle reusing (where hair development and relapse persistently happen).
- Bone remodeling
  - MC-insufficient mice have femurs that are lighter and more slender than wild-type mice be approved with MC reconstituted mice.
  - MCs are a wellspring of osteopontin, glycoprotein part of the bone grid that add to bone resorption and calcification (instrument of bone redesigning).
  - In human fundamental mastocytosis, bone turnover is quickened which brings about bone misfortune.[6]

MC – ROLE IN IMMUNITY

(DIRECT INTERFACE BETWEEN INNATE AND ACQUIRED IMMUNITY)

Different pathogen and their items enacts MCs through Toll-like receptors (TLRs), supplement Rc, Fc Rc.[7]

- In the early stage, MCs discharge performed go between that enlist effector cells (e.g., Neutrophil) to freedom of pathogen.
- Activate dendritic cells (DCs) and T cells and their movement to lymph nodes.
- Increasing proof that capacity as antigen-presenting cells (express major histocompatibility complex [MHC] Class I and up-manage articulation of MHC Class II when animated with interferon, TNF, and lipopolysaccharides [LPS]).

INNATE IMMUNITY

- Resistance to a disease that an individual has by the prudence of hereditary and established makeup.
- Prior contact with microorganisms or their items is not essential.
- Refers to the components of the safe reaction that is dictated by acquired elements (inborn).
- Limited specificity.
- “Fixed” (they do not change or enhance amid an insusceptible response or due to past introduction to the pathogen).
- They are enacted when the essential safeguards are broken.
• If inborn reactions neglect to dispense with contamination, at that point the effector cells versatile insusceptibility (lymphocytes) is actuated.

MCs are known to be the primary effector cells in the elicitation of the IgE-mediated allergic response. The ability of mast cells to perform phagocytosis and to deliver and emit a wide range of arbiters have driven to propose a potential part of mast cells in innate immune responses. Certain microorganisms have been found to interface either straightforwardly or in a roundabout way with MCs. This communication brings about MC initiation and mediator release, which evoke an inflammatory reaction. The in vivo significance of these in vitro perceptions has been exhibited by the utilization of complement-deficient and/or MC-deficient and MC-reconstituted mice. Regulation of MC numbers in vivo was, additionally, found to influence the host reaction against bacterial disease. Regardless of whether MCs take an interest in innate immune responses in the protection of human host against microbes remain to be resolved.

SALIVA

• Saliva discharged from three noteworthy salivary organs and additionally from various minor organs has a vital part in keeping up oral wellbeing.
• It contains sub-atomic segments that add to have safeguards against bacterial colonization and periodontal ligament (PDL) sickness.

MCs have been involved in numerous immune-inflammatory disorders. Deranged MC dispersion and function may add to the nearby pathomechanisms in the labial salivary organs in Sjogren’s syndrome. Proof for MC presence, localization, recurrence, subtype, and level of actuation were looked for utilizing reverse transcriptase-polymerase chain reaction, immunohistochemistry, transmission electron microscopy, Western blotting, spectrophotometric activity assay, and radioimmunoassay.

EPITHELIAL TISSUES

These are the fundamental beginning site of association between plaque microorganisms and host. The keratinized epithelium of sulcular and gingival epithelial gives insurance to hidden PDL tissues, in addition, goes about as hindrance against microorganisms and their items. Epithelial cells fortified with bacterial segments and cytokines create matrix metalloproteinases (MMP’s) that add to the loss of connective tissue. Epithelial cells express antimicrobial peptides and the combination and emission of these atoms is up managed in light of periodontal microscopic organisms. These antimicrobial peptides have a more extensive part in managing intrinsic and versatile invulnerable reactions to contamination. These have chemokine-like action, animating the chemotaxis of scope of leukocytes associated with intrinsic and obtained invulnerability.

GINGIVAL CREVICAL FLUID

It has a flushing activity in gingival fissure yet in addition likely groups to bring the blood segments of host safeguards in the sulcus. Stream of greatest common factor (GCF) increments in aggravation and neutrophils is a particularly vital component of GCF in health and disease.

There has been a relentless developing pattern amid the most recent couple of decades to create tools to screen periodontitis, in the field of oral disease finding. Since GCF has the possibility of being intently approximated to the periodontal tissues where periodontal disease starts, it appears to give more data than markers in saliva. Existing ideal models in the science of periodontitis have upheld the discovery of increased levels of these mediators in GCF.

INITIATION OF IMMUNE RESPONSE

Sentinel cells perceive their essence and flag defensive invulnerable reactions. DCs express scope of example acknowledgment receptors pattern recognition receptors that cooperate with particular sub-atomic structures on organisms – MAMP’s activation of resistant reaction to give prompt assurance.

ADAPTIVE IMMUNITY

• It is slower and dependent on complex cooperation between antigen exhibiting cells, T- and B-lymphocytes.
• Key components: Antigen specificity of the reactions that encourage particular focusing of a separated scope of effector components (cytotoxic T cells and antibodies).
• It has the capacity to enhance during the introduction to antigen.
• T cells are dominating in gingivitis and stable periodontal injuries.
• In contrast, in dynamic periodontitis, B cells prevail and are related with stash arrangement and movement of infection.

ANTIGEN PROCESSING AND PRESENTATION

MHC is a locus on the short arm of chromosome 6 (6p21.3) that encodes MHC Classes I, II, and III, which are associated with antigen take-up, handling, and introduction.
• MHC Class I particles: Exhibit intracellular antigens to CD8+ T cells and NK cells.
• MHC Class II particles: Introduce extracellular antigens to CD4+ T cells.
• MHC Class III atoms incorporate supplement factors B, C2, and C4.

ANTIGEN PRESENTING CELLS
This includes B cells, macrophages, dermal DCs and Langerhans cells. These cells normally express MHC-II atoms to initiate particular effector T cells. Produce antigen particular resistant reaction to periodontal pathogens.

MC IN INFECTION
• Helminth contamination
  • MC degranulation impact DC enactment of T cells from Th1, toward Th2 reaction (system of this capacity due to histamine which can stifle Interleukin [IL]-12 discharges by DC).
  • MCs are actuated by helminth and MC hyperplasia is seen in helminth disease.
  • However, basic contribution in pathogenesis has appeared in few kinds of this contamination, for example, Trichinella spiralis is expelled by MC-determined MMCP-1, TNF, and IL-4. Nippostrongylus brasiliensis additionally instigates MC hyperplasia.¹³
• Bacterial infection
  • MC - determined TNF, together with LTC4 and LTB4 added to enrollment neutrophils to clearance Klebsiella pneumoniae, Listeria monocytogenes, and Pseudomonas aeruginosa.
  • MC can deliver antimicrobial nets containing proteases and LL37 (Cathelicidin antimicrobial peptide, polypeptides found in lysosomes in macrophages and polymorphonuclear leukocytes).
• Fungal infection
  • Animal MCs react to yeast cell divider zymosan and peptidoglycan by discharging cys-teiny LT and by the creation of reactive oxygen species.
  • Human MCs react to zymosan, however not peptidoglycan, through dectin-1, Beta-glucan Rc for C-type lectin family.
  • Trichoderma viride, indoor parasite, instigate MC degranulation (high dosage), however, low measurement improves histamine emission from MCs.
  • Aspergillus fumigatus incite Ig E-autonomous MC degranulation.¹⁴
• Viral infection
  • This viewpoint is a rising field.
  • Report from HIV-contaminated patients.
  • Increased serum Ig-E and more elevated amounts anticipate awful visualization.
• Fewer MCT in intestinal mucosa of patients with AIDS and it shows a part for utilitarian T lymphocytes in the advancement of the T MC compose in people.¹⁵
• Dengue infection can initiate MCs to discharge IL-1, IL-6.
• RANTES, MIP-1 Alpha, and MIP-1
  • Dengue infection, additionally, incites caspase-subordinate MC apoptosis, yet not apoptosis of other Fc - communicating cell writes.
  • Respiratory syncytial infection (a significant reason for LRT in baby and connected with the improvement of asthma sometime down the road).
  • Airway MC numbers increment in Para flu contamination.

PERIODONTAL DISEASE PATHOGENESIS
Histopathology of Periodontal Disease
Periodontal pathogenesis is comprehensively sub-isolated into clinically solid and kindled periodontal and gingival tissue. Indeed, even in the gingival that show up clinically typical, there is a constant poor quality test exhibited by sub-gingival plaque microbes. In any case, deregulated, the susceptible inflammatory reaction for a given bacterial challenge prompting expanded tissue breakdown.

Clinically Healthy Gingival Tissues
Clinically sound gingival tissue is not aroused, pink in appearance, not swollen and immovably appended to the basic tooth/bone, with insignificant seeping on testing. The dentogingival intersection is a remarkable anatomic component whose capacity is the connection of the gingiva to the tooth.

HISTOPATHOLOGY OF GINGIVITIS AND PERIODONTITIS
Invasion of tissues by various defense cells especially neutrophils, macrophages, plasma cells, and lymphocytes.¹⁶ There is an interruption of the life systems of the connective tissues bringing about collagen consumption and consequent multiplication of junctional epithelium. Vasodilatation and expanded vascular permeability prompts expanded spillage of liquid out of the vessels and encourages the entry of resistance cells from the vasculature into the tissues, which seem erythematous and edematous.

INFLAMMATORY RESPONSES IN THE PERIODONTIUM
During the inflammatory response, there are particular atoms which signal tissue harm as the
provocative reaction forms into sub-gingival microflora and host immune-inflammatory response. The microscopic organisms are vital in light of the fact that they drive and propagate the aggravation; however, they are in charge of a moderately little extent of tissue damage.

- Microbial virulence factors
- Host-derived inflammatory mediators
- Role of specific inflammatory mediators

**MICROBIAL VIRULENCE FACTORS**

**Lipopolysaccharide**

Lipid segment polysaccharide part (Lipid A)
- Found in the external film of Gram-negative microscopic organisms.
- Act as endotoxins.
- Elicit a solid, resistant reaction.
- Has a critical part of keeping up the structural integrity of bacterial cells.

Resistant framework perceives LPS through TLRs. TLRs are cell surface receptors that perceive microorganism related atomic examples (MAMPs), which are monitored sub-atomic structure situated in various pathogens.

**Bacterial Enzymes and Noxious Products**

Plaque microorganisms deliver various metabolic waste items, which contribute specifically to tissue harm. These toxic specialists incorporate smelling salts, hydrogen sulfide, and short chain unsaturated fats.

These substances have a professional discovered impact on have cells which are as per the following
- The short chain unsaturated fat guide *Porphyromonas gingivalis* disease through tissue obliteration and furthermore make a supplement supply for the life form the seeping into the periodontal pocket.[17]
- Plaque microbes produce proteases which are equipped for break bringing down the basic parts of the periodontium, for example, collagen, elastin. These process proteins and give nourishment to microscopic organisms.
- *P. gingivalis* produces two classes of cysteine proteases known as gingipains isolated into lysine-particular gingipain and arginine-particular gingipain (Rgp A Rgp B).

Conceivably prompting expanded tissue harm. These can decrease the centralization of cytokines and process and inactivate TNF-α. Fortify cytokine discharge by means of initiation of protease-enacted receptors in this manner invigorating cytokine emission.[18]

**HOST DERIVED INFLAMMATORY MEDIATORS**

The incendiary and safe procedures that create in the periodontal tissues in light of the long haul nearness of sub-gingival bio-film are defensive by aim yet result in significant tissue harm. The dominant part of the tissue harm in periodontitis gets from the inordinate and deregulated creation of an assortment of incendiary middle people and chemicals that are comprehensively named takes after.

- Cytokines.
- Prostaglandins.
- MMPS.

**ROLE OF SPECIFIC INFLAMMATORY MEDIATORS**

IL-1β invigorates the combination of PG2, PAF, and NO that causes vascular changes related to irritation. It expands the declaration of intercellular adhesion molecule-1 on endothelial cells and animates the discharge of chemokines. It synergizes with other ace provocative cytokines and prostaglandin E2 (PGE2) to initiate bone resorption. It has a part in versatile invulnerability and manages the improvement of antigen-exhibiting cells, for example, DCs. An “alarmin” to flag the resistant framework amid cell harm. IL-1Ra - ties to IL-1 receptor (IL-R1). Be that as it may, authoritative of IL-Ra does not bring about flag transduction, in this way IL-1Ra alienates the activity of IL-1β. It is imperative in controlling fiery and thought to be a mitigating cytokine. IL-18 - cooperates with IL-1β. It is delivered by invigorated macrophages and monocytes. It brings about inflammatory reactions including initiation of neutrophils. It is a chemoattractant for T-cells, and it communicates with IL-12 and IL-15 to prompt Th1 cells cell-intervened invulnerability. TNF-α, it is emitted by initiated macrophages, especially in light of bacterial LPS.[19]

**PRO-INFLAMMATORY EFFECTS**

- Stimulation of endothelial cells to express selectins that encourage leukocyte enrollment.
- Activation of IL-1b generation.
- Induction of PGE2 by macrophages and fibroblasts.
- GCF levels of TNF-α increment as gingival aggravation creates.
- Role of MCs in periodontal pathogenesis.

**PERIODONTAL INFLAMMATION**

There are two distinctive MC populaces exhibit in human solid gingival tissue, for example, McT and McTC. Gingival irritation and periodontal infections are activated 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 danger. The invade comprises basically of leukocytes including plasma cells, lymphocytes, macrophages, and neutrophils that serve a few capacities in the barrier against periodontal disease. Imperative elements of neutrophils are phagocytosis and executing of microorganisms – basic factors in limiting the ruinous impacts of the periodontopathogenic microscopic organisms. While macrophages likewise work as phagocytes, the cells should introduce antigens to T-cells and open up particular safe reactions.[20]

A few properties of the inflammatory cell invade in chronic periodontitis and strangely, well-discovered high quantities of MCs equivalent to and regularly surfacing the quantities of macrophages in the excited periodontal lesion. Numerous reports have, amid the most recent 15 years, shed new light on the MC as a pivotal cell in both natural and obtained invulnerability. As of late, we found that MCs firmly express network MMP-1, ~2, and -8, which are enter compounds in the debasement of periodontal delicate tissue. It is recommended that MCs as key players in gingival homeostasis that might be critical in the movement of periodontitis.

GIN GIVAL INFLAMMATION

MCs are the unremarkable parts of the connective tissues. They are found in various densities and diverse locales of the aggravated and sound gingival tissues. Quantities of MCs were discovered increased on aroused tissues contrasting with solid tissues. This incrementation is proximately related to the level of aggravation. MC densities were fundamentally augmented in constant periodontal illness/gingival provocative injuries contrasted and clinically salubrious gingival tissues (Health) interestingly by the resistant histochemical method. Strikingly, MCs were immersed particularly in close relation to mononuclear cells.[21] Connections between MCs and aggressive periodontitis were examined, there was no factually considerable relationship between MC tallies, clinical connection misfortune, and pathologic irritation and inferred that MC numbers are not distinctive in aggressive periodontitis and gingivitis.

PHENYTOIN-INDUCED GINGIVAL ENLARGEMENT

Angelopolous in 1975 examined the part of MC in the pathogenesis of phenytoin gingival expansion and found that phenytoin has coordinate impact on the gingival MC bringing about degranulation and freedom and all the more particularly heparin, taken up and used by the encompassing fibroblasts, which thus are fortified to create there claim new and particular mucopolysaccharides of the ground substances and collagen fibrils.

REFERENCES


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