Editorial

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Mast Cells in Oral Pathologies: Opportunities, Problems, and Prospects

Gargi S Sarode[1], Sachin C Sarode[2], Shankargouda Patil[3]

Contributors:

[1]Associate Professor, Department of Oral Pathology and Microbiology, Dr. D.Y. Patil Dental College and Hospital, Pimpri, Pune, Maharashtra, India; [2]Professor, Department of Oral Pathology and Microbiology, Dr. D.Y. Patil Dental College and Hospital, Pimpri, Pune, Maharashtra, India; [3]Associate Professor, Department of Diagnostic Sciences, Division of Oral Pathology, College of Dentistry, Jazan University, Jazan, Kingdom of Saudi Arabia. Email: drsachinsarode@gmail.com

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Mast cells (MC) are granulocytes derived from myeloid stem cells and considered as potent effector cells of immune system. They are arguably the most productive chemical factory in the body and influence other cells through both soluble mediators and cell-to-cell interaction. These cells are known for their role in allergies and anaphylaxis. Moreover, phenomena such as angiogenesis, immune intolerance, and defense against pathogens have been found to be associated with MCs.

Literature search indicates extensive research work on MC in different pathologies including malignancies.[1] In malignancies, they have been attributed to tumor rejection as well as tumor promotion. MC can directly influence tumor cell proliferation and invasion and help the cells indirectly by organizing the microenvironment and modulating the immune responses to tumor cells.[1]

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity. Its constant association with a myriad of oral potentially malignant disorders (OPMDs) makes it exceptionally unique from other malignancies of the body.[2] Recently proposed classification of OPMDs depicts the array of disorders associated with oral cancer, some of which may not show clinical and histomorphological alterations.[2-4] Among all OPMDs, oral lichen planus (OLP), oral submucous fibrosis (OSMF), and oral leukoplakia have been reported to be associated with alterations in the MC number.[5]

In OLP, MCs through their interaction with T-cells are responsible for initiation, vaso-induction, and effector phases of OLP. Moreover, MCs are considered as the offender in destructing epithelial basement membrane. They release tumor necrosis factor-alpha (TNF-a) causing increased synthesis of collagenase-like matrix metalloproteinases (MMPs). These MMPs are responsible for epithelial basement membrane destruction and increased expression of adhesion molecules (E-select in and ICAM). Histamine is responsible for vasopermeability resulting into edema at the submucosal level and causes proliferation of antigen-induced T-cells.[6]

OLP has been found to be associated with *Candida* infection in 37-50% of cases.[7] The candidiasis in OLP could be attributed to: (1) Altered systemic and/or local immunity (2) changes in the oral epithelium (3) prosthesis (4) concomitant systemic conditions.[8] Thus, one cannot ignore candidiasis in the presence of OLP. In this regard, the most intriguing situation is the role of MCs in tackling the fungal infection. MC possesses many surface receptors among which Toll-like receptor and C-type lectin receptors are known for antifungal response. Toll-like receptor-4 signals are important for the recognition of fungal pathogens, and their absence may allow for the persistence of infection.[9] Thus, an association of MCs with OLP with superimposed candidiasis further complicates the pathogenesis.

OSMF is an OPMD characterized by fibrosis in the connective tissue stroma of oral mucosa attributed to areca nut chewing.[10] Malignant transformation of OSMF is usually associated with better grade of tumor differentiation.[11] Similar to OLP, few of the signs and symptoms of OSMF like formation of vesicles, burning sensation are attributed to histamine released from the MCs. Recently burning sensation has been proposed to be associated with lack of mucin secreted by the minor salivary glands.[12] Hence, future studies are needed to investigate the exact cause of burning sensation in OSMF. Moreover, association of OSMF with primary burning mouth syndrome (BMS) possesses diagnostic challenge for the clinicians.[13] Histamine is probably responsible for edema occurring at the submucosal level, which occurs in the early stages of OSMF. There is increase in the vasopermeability resulting in the release of eosinophilic chemotactic factor by MCs. MC-derived interleukin-1 and tryptase increase fibroblastic response and synthesis of type-1 collagen and fibronectin, respectively, resulting in severe fibrosis. MC-derived tryptase should be given due consideration for being a vital mediator in activation and proliferation of fibroblasts in malignant transformation of OSF.[14]

Studies have concluded that active agents in MCs might be responsible for the inflammatory reaction in oral leukoplakia. Stimulation of MCs releases interleukin-1 causing increased proliferation of epithelium in oral leukoplakia. Histamine alters mucosal permeability and facilitates penetration of the antigen into connective tissue.[15]

Recently, MCs have been associated with BMS. It is proposed that activation of MC degranulation could be induced by nerve growth factor, whose role in BMS is well established,[16] and that MCs could be a further source of this neurotrophin. Moreover, tryptase secreted by MCs could be involved in the initiation of neuropathic pain.[17] Although it is an interesting hypothesis, needs extensive research for its validation. Criteria for establishing a diagnosis of "true" BMS are presence of burning sensation on clinically healthy oral mucosa in the absence of all known local and systemic etiological factors. When burning is associated with a known pathological condition, it becomes secondary BMS.[18] In MC related studies in BMS, it is of paramount importance to rule out secondary BMS, thus eliminating any biased results.

Angiogenesis is an integral part of tumerogenesis. Many cells, including MCs, are responsible for secretion of pro-angiogenic and angiogenic factors important for progressive angiogenesis. There are certain mechanisms involving MCs which stimulate malignancy transformation. These include involvement in immunosuppression, synthesis of pro-angiogenic and mitogenic factors and participation in the extracellular matrix degradation. MCs can release numerous cytokines such as histamine, heparin, tryptase, chymase, TNF-a, transforming growth factor-beta (TGF-b), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), interleukin-6 (IL-6), and vascular endothelial growth factor along with various angiogenic factors.[19] Recently, we have reported a phenomenon of cellular cannibalism in oral cancer cells and proposed lack of nutrition as one of the causes.[20,21] The nutrition to cancer cells is derived from adjacent blood vessels, which are formed in response to pro-angiogenic and angiogenic factors released by MC like cells. Thus, it would be interesting to see the correlation between MC density in OSCC and number of cannibalistic cells in tumor mass. One step further, the study of secretory products of MCs (histamine, heparin, tryptase, chymase, TNF-a, TGF-b, PDGF, bFGF, IL-6 and vascular endothelial growth factor) with respect to cellular cannibalism would be an interesting research proposal. We also recommend future studies on benign lesions,[22,23] which show cellular cannibalism like central and peripheral giant cell granulomas and their association with MCs.

Targeted therapy is gaining popularity in various oral pathologies mainly in oral cancer and OPMDs.[24] Looking at the fore mentioned aspects, the therapeutic approach toward MC modulation can bring revolution in the management of MC-related oral pathologies. MCs are inflammatory cells and targeted therapy toward inflammation-mediated carcinogenesis process has already showing promising results.[25,26] Similarly, numerous therapeutic approaches like the use of MC stabilizer blockade of stem cell factor/inhibitors of TGF-b, tryptase and chymase have already validated some clinical benefits in tissue fibrosis and various inflammatory diseases by constraining MC stimulation. It would be really interesting to see how MC related oral pathologies discussed in the present paper respond to these kinds of therapeutic approaches.

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