REVIEW

Diverse Roles of Macrophages in Oral Inflammatory and Benign Lesions - A Narrative Review

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Abstract

Background: Macrophages are immune cells with diverse profiles and functions. Macrophages play significant roles in the repair and resolution of inflammatory and reactive lesions. They secrete cytokines and modulate the tissue microenvironment and surrounding cellular responses.

Objectives: The present article reviews the histological presentation and role of macrophages in the pathogenesis of oral inflammatory and benign lesion.

Materials and Methods: Data was collected by electronic search of databases including PubMed and Google Scholar for Macrophages, Periapical Granuloma, Mucocele, and Verruciform Xanthoma.

Result: Distinct profiles of macrophages participate in regulation of pathogenesis, lesion size, and resolution of periapical lesions. In trauma-associated reactive or benign lesions, macrophages show phagocytosis and exhibit characteristic foamy histological appearance. The immunohistochemical profiles of macrophages aid in identifying the surface receptors and profiles of macrophages in oral lesions.

Conclusion: Identifying and understanding macrophage-mediated pathogenesis can help diagnose and develop targeted therapies against various oral lesions.

Key words: Macrophages, Mucinophages, Periapical Granuloma, Periapical Cyst, Verruciform Xanthoma.

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Introduction

Macrophages are adaptive cells of the immune system that recognize and respond to various stimuli from the microenvironment and aid in maintaining tissue homeostasis. Macrophages differ according to their function, morphology, origin, and location. However, the primary function is to eliminate pathogens and participate in tissue repair.[1,2] With the evolving knowledge of macrophages and their cross talks with other immune cells, their roles in various reactive lesions, infectious diseases, and other pathologies like verruciform xanthoma,[3] multiple sclerosis,[4] tuberculosis,[5] lichen planus,[6] amongst many others are brought to focus.[7] Hetergeneous populations of macrophages and their distinct roles are studied in atherosclerosis,[8] fibrosis,[9] lung carcinoma,[10] ovarian carcinoma and metastasis,[11] breast carcinoma - bone metastasis,[12] and other carcinomas.[13]

Though initially thought to be of monocyte origin, macrophages are now addressed as long-living, self-renewing, "tissue-resident macrophages" with multiple origins. These macrophages are environment specific and play a central role in regulating homeostasis and health.[2] Research has highlighted the role of epigenetics in mediating macrophage differentiation in various tissues.[1,2] Epigenetic comprising of post-translational histone modifications, DNA methylation and competing RNAs including microRNAs and long noncoding RNAs are being explored in regulating macrophage function. Histone modifications and remodeling of chromatin have been observed during activation of pro inflammatory phenotype of macrophages.[2]

DNA demethylation causes changes in genes that regulate phagocytosis and actin, and hence, are critical in maintaining macrophage cytoskeleton and function.[14,15] In terms of miRNA, three miRNAS: miRNA-34, miRNA-146 and miRNA-221 have been studied in monocyte-macrophage differentiation and macrophage phenotype regulation.[14] Increased miRNA-155 causes polarization of the pro inflammatory macrophages while miRNA-99a

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inhibits this change.[16] Many other modifications alone or together have been studied for modulating macrophage plasticity in health and disease. The elaboration and application of these epigenetic modification hosts opportunities for changing the macrophage phenotype and thereby disease status.[2]

Broadly, macrophages have been broadly classified into two phenotypes - pro-inflammatory, i.e., M1, and anti-inflammatory or pro-resolving, i.e., M2 profiles. However, intermediate phenotypes with characteristics of both M1 and M2 have also been observed.[17] These macrophages use different pathways for function and for regulation of the lipid and amino acid metabolism. Hence, different conditions present with diverse macrophage phenotypes based on the function in focus. It is known that defective clearance of apoptotic material or cells is associated with the pathogenesis of both inflammatory and autoimmune diseases. Thus, identifying macrophages in various pathologies is essential for accurate diagnosis and management of refractory lesions.[17,18] In the present narrative review, we focus on the role of macrophages in the pathogenesis of various inflammatory oral lesions.

Macrophages in Periapical lesions:

Periapical granulomas and radicular cysts are commonly observed chronic lesions that develop in response to dental pulp infections. Macrophages are abundant in these lesions and play complex roles by regulating phagocytosis, producing inflammatory cytokines, and by acting as antigen-presenting cells.[18,19] Researchers observed different phenotypes of macrophages in periapical granulomas and cysts. Periapical granulomas are rich in inflammatory cells and comprise of granulation tissue surrounded by dense collagen capsule. It has been found that M2 macrophages and their associated cytokines like Interleukin - 4 are present in abundance in periapical granulomas. M2 macrophages in periapical granulomas present show immunomodulatory characteristics with functions of phagocytosis and possible healing. The exact mechanism for the different polarization of macrophages is not fully understood, however, factors like bacterial lipopolysaccharides and genetic predisposition have been proposed to play a role.[20,21,22]

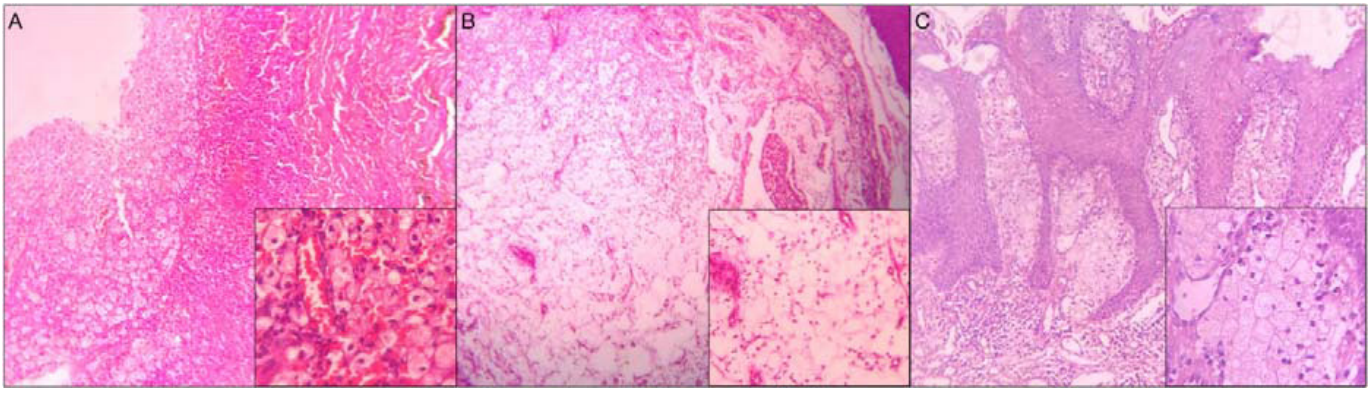
Immunohistochemical analysis for macrophage involves use of two key macrophage markers, namely CD68 and CD 163. CD68 is an intracellular glycoprotein that recognizes both M1 and M2 macrophages, considering its occurrence in the granules of macrophage lysosomes. CD163 is a glycoprotein that belongs to the scavenger receptor group and is found abundantly in the M2 macrophages.

Weber et al[20] used macrophage markers like CD163 and Macrophage mannose receptor C- type 1 (MRC1) to study the distribution of M2 macrophages; while CD68 and CD11c along with the respective ratios were used to study M1 phenotype distribution in periapical granulomas and other odontogenic cysts. They found increased M1 polarization in radicular cyst in contrast to the M2 predominance in periapical granulomas.[20] Similar observations of M1-M2 macrophage distributions in periapical lesions were put forth by Franca et al.[19]

Furthermore, macrophage subtypes have also been associated with T-helper 1 cell response and symptomatic pain.[19] M1 macrophage release cytokines like Interleukins-1 and -6 along with prostaglandin E2 and mediate T-helper 1 response thereby clinically presenting with symptomatic pain. Franca et al[19] hypothesized in their study that periapical cysts were more symptomatic than granulomas due to the predominance of M1 macrophages.

In terms of the pathogenesis of radicular cysts, M1 macrophages show interactions with the cystic epithelium by the production of cytokines like Tumor necrosis factor-alpha (TNFα) that regulate bone remodeling. Bacterial lipopolysaccharides and interferons bring about TNFα related complement system activation, thereby mediating the origin of M1 macrophages. These M1 macrophages further via TNFα play a role in regulating inflammation, cystic epithelium proliferation, and apoptosis. Active M1 macrophages show an increase in cell size and lysosomal enzyme content, and they exhibit an active metabolism to destroy the pathogenic organisms. M2 macrophages, on the other hand, require interleukins for their activation. These macrophages function to curtail the pro-inflammatory functions of M1 macrophages and are associated with angiogenesis, anti-inflammatory effects, tissue repair and remodeling, and fibrosis.

Researchers have identified that CD68 positive macrophages were found more commonly in larger cysts and were associated with lesion size and bone destruction. Location-wise, a high incidence of CD68 positive cells were found in the active sites of in-



Figs 1A to C: A. Macrophages in a case of periapical cyst [H&E;10x]. Inset shows macrophages around blood vessels and inflammatory cells [40x]. **B.** Mucinophages in a case of mucocele with extravasated mucin beneath the epithelium [H&E;10x]. Inset shows mucinophages with clear cytoplasm due to mucin engulfment [40x]. **C.** Macrophages in a case of verruciform xanthoma. Epithelium shows keratin plugging and neutrophils in superficial layers. Connective tissue between epithelial ridges shows foamy xanthoma cells. [H&E;10x]. Inset shows foamy macrophages (xanthoma cells) with clear cytoplasm indicative of lipid phagocytosis.

flammation, i.e., in the center of granulomas and juxta-epithelially in cysts. They suggested that the periapical microenvironment defines the nature of the lesion being developed and the origin of the macrophage subtype within that lesion.[23]

Macrophages in Mucocele:

Besides infection, macrophages play dual roles in trauma-associated lesions due to their phagocytic and reparative functions. In contrast to periapical cysts, pseudocysts like mucous extravasation cyst or mucocele may occur due to trauma, leading to a series of chronic inflammatory changes. In mucous extravasation cyst, the spillage of mucin from the salivary duct occurs in the tissue containing leucocytes and histiocytes. This spillage causes granuloma formation filled with foamy macrophages to multinucleate giant cells. In mucoceles, the term mucinophages was used for the "foamy" macrophages containing the phagocytized mucin.[24] Mucoceles heal within a few days but may recur and appear to persist for a year or more. Suzuki Y et al[25] studied the immunohistochemical profile of macrophages and have shown that they are CD68 positive with phagocytic and antigen-presenting function. Rarely mucoceles with macrophages showing clear cytoplasm with signet ring cell changes have also been reported. These changes are proposed due to fixation artifacts, storage of mucin, lipid, or glycogen within the cell, or due to lack of cellular organelles.[26]

Macrophages in Verruciform Xanthoma:

The macrophages in the case of verruciform xanthoma are known as foam cells or xanthoma cells, due to their role in the ingestion of lipids produced from the degenerating keratinocytes.[27] These macrophages are thus limited to the connective tissue papillae extending till the epithelium. Rawal et al.[28] found that these macrophages are present in the backdrop of immune cells of chronic inflammatory origin, primarily T-cells. The T-cell accumulation in the subepithelial area also triggers chemoattraction of neutrophils (via IL-8) and macrophages. T-cells activate Monocyte Chemotactic Protein-1, which causes migration of macrophages (expressing CCR2) towards the basal layer of epithelium.[29] This upregulated the macrophage scavenger receptor, which causes recognition and ingestion of lipids released by degenerating keratinocytes. The lipid is eventually autolyzed, resulting in the self-necrosis of the macrophages in Verruciform Xanthoma.[29,30] The inflammatory response to necrosis attracts more macrophages, thereby perpetuating the process. Furthermore, Mostafa et al[31] have found that the foamy macrophages in xanthoma are of monocyte lineage and are CD68 positive.

On histological evaluation of macrophages in the above conditions [Figures 1a-c], we can find that the periapical lesion shows macrophages near the blood vessels component surrounded by chronic inflammatory cells [Figure 1a]. While the cytoplasm of macrophages that have phagocytosed either mucin or lipid appears foamy with clear vacuoles and are located near the site of injury as in mucocele and verruciform xanthoma [Figure 1b-c].

Recently, the role of macrophages has also been studied in the pathogenesis of autoimmune dis-orders, potentially malignant disorders, and oral squamous cell carcinomas.[18,32,33] Targeting macrophages in these inflammatory and malignant disorders has gained interest and directed therapies are being proposed. CD163 positive macrophages have been targeted for cancer therapy.[18] Thus, the study of role of these cells with diverse phenotypes and origins is critical for both identification and possible development of treatment modalities.

Conclusion

Oral lesions containing macrophages associated with or without trauma can exhibit variable macrophage subpopulations. As these macrophages are known to modulate the tissue microenvironment via cytokines, there is a need to determine their roles in the pathogenesis, progression and resolution of various oral lesions.

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