

## Pathogenetic mechanism of oral granulomatous diseases: An update

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### ABSTRACT

Oral granulomatous diseases are an intriguing group of lesions characterized by granuloma formation. Mechanisms of granuloma formation differ from disease-to-disease. This article provides an insight into common granulomatous pathogenic mechanisms involving these lesions including immunodeficient states. Understanding various pathogenic mechanisms underlying various granulomatous conditions affecting oral tissues which mainly revolve around inflammatory cells such as macrophages, T lymphocytes, and genetic mutations might aid in devising treatment modalities without having significant side-effects or morbidity in affected subjects.

**Keywords:** Chronic, granuloma, oral, pathogenesis

### Introduction

Granulomatous reaction represents tissue reaction pattern to immunogenic substances which are insoluble.<sup>[1]</sup> Oral granulomatous disease represent a form of chronic inflammation.<sup>[2]</sup> Chronic granulomatous disease represents a heterogenous disease complex characterized by granuloma formation. A granuloma can be defined as “a collection of inflammatory cells, mainly macrophages forming an aggregate in response to antigen.” On initiation of granuloma formation, antigen-presenting cells release numerous pro-inflammatory cytokines and chemoattractants which recruit neutrophils and activate monocytes. The infectious agent is resistant to neutrophil activity, antigen is engulfed by macrophages. On internalization, these cells secrete pro-inflammatory mediators which digest the foreign body. The antigen-derived peptides and lipids via MHC class II and CD1 molecules present these to T antigen. The naïve T cells

differentiate into th1 cells, which secrete IL-2, thereby promoting survival. The activated Th1 cells are attracted into the granuloma via the endothelial cells wherein they freely move around. Any antigen persistence further leads to chronicity and development of a mature granuloma.<sup>[3]</sup> Histopathologically, granulomas are composed of epithelioid macrophages, multinucleated giant cells, fibroblasts, and lymphocytes. It has multifactorial etiology. Differential diagnosis of granulomatous diseases include orofacial granulomatosis, Crohn’s disease, foreign body reaction, sarcoidosis, and infections.<sup>[4]</sup>

The ethical clearance to proceed with the review was obtained from the Institutional Review Board (IRB). The IRB approval number is “FRP/2019/186/35/38.”

This article describes various pathogenetic mechanisms involved in granulomatous disease affecting oral cavity.

### Orofacial granulomatosis

The term “Orofacial granulomatosis” was first introduced by Wiesenfeld (1985). It encompasses Melkerson-Rosenthal

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syndrome and Miescher's cheilitis granulomatosa.<sup>[5]</sup> Orofacial granulomatosis is characterized by chronic, non-caseating granulomas which are primarily found affecting the oral cavity. A specific oligo-type of *S. salivarius* was found to be in higher prevalence in these subjects.<sup>[6]</sup> Its mechanism of formation is related to cell-mediated hypersensitivity reaction which is evidenced by activated helper T lymphocytes which express interleukin-2 receptors found in these granulomas.<sup>[5]</sup> Higher CD3 + T cells and dendritic cells' counts have been reported in orofacial granulomatosis when compared to oral Crohn's disease suggestive of variations in composition of inflammatory cell infiltrate.<sup>[7]</sup> T lymphocytes show minor production of reactive oxygen species (ROS) which demonstrates an increased risk of autoimmune diseases.<sup>[8]</sup>

Numerous treatment modalities some of which are recently used in treatment of orofacial granulomatosis include topical agents like corticosteroids and calcineurin inhibitors; intralesional corticosteroids and systemic agents like azathioprine, thalidomide, metronidazole, and corticosteroidal drug therapy.<sup>[9]</sup>

### Chronic granulomatous disease

Chronic granulomatous disease is a rare disorder with an incidence of one in every 2,50,000 subjects. It usually manifests at an early age, mostly during first 2 years of life. Individuals suffering from chronic granulomatous disease report with recurring infections of bacterial and fungal origins. Infection spreads both by contact as well as hematogenous route, therefore involving liver, kidneys, brain, and bones.<sup>[10]</sup>

Chronic granulomatous disease represents heterogenous disease complex which is characterized by defect in respiratory burst generation from phagocytic cells. Thus, there is an inability in superoxide generation, thereby an inability to evade pathogenic organisms.<sup>[11]</sup> Also, a defect in NADPH oxidase production has been demonstrated by Hohn and Lehrer.<sup>[12]</sup>

Neutrophils act by production of ROS to destroy phagocytosed microbes. These cells in X-linked chronic granulomatous disease (CGD) have defective ability for ROS production due to absence or abnormality of gp91<sup>phox</sup> which is a transmembrane protein encoded by CYBB. X-linked CGD occurs due to mutations in gp91<sup>phox</sup>. It is also termed as "CYBB" spanning a 30 kb region in chromosome X921.1.<sup>[13]</sup>

Due to this defect, individuals with X-linked CGD develop life-endangering bacterial and fungal infections. ROS produce a molecular signal that acts by initiating or accelerating apoptosis within neutrophilic leukocytes. Thus, an altered neutrophil and unresolved inflammatory process contributes to granuloma formation in X-linked chronic granulomatous disease.<sup>[14]</sup>

NADPH gene components CYBB (X chromosome) encodes gp91<sup>phox</sup>, CYBA encodes p22<sup>phox</sup>, NCF1 encodes p47<sup>phox</sup>, NCF2 encodes p67<sup>phox</sup> while NCF4 encodes p40<sup>phox</sup>.<sup>11</sup> p22<sup>phox</sup>, p47<sup>phox</sup>

and p67<sup>phox</sup> defects have an autosomal recessive inheritance.<sup>[14,15]</sup> However, the X-linked form has more severity and is associated with an earlier presentation and higher mortality rate. The CYBB gene is composed of 13 exons which span 30 kb length of genomic DNA and is localized on chromosome Xp21.1. This gene is responsible for encoding the gp91-phox subunit which is a transmembrane protein within the NADPH oxidase complex. The gp91-phox contains four domains which include N-terminal domain and a loop over the NADPH-binding domain. Also, these along with p22<sup>phox</sup> form heterodimers which are responsible for phagocytic maturation and expression.<sup>[9]</sup> Common mutations involved in X-linked chronic granulomatous disease are single nucleotide substitutions such as nonsense, missense, and splice-site mutations. Other mutations include insertions and deletions.<sup>[15]</sup>

A loss or reduction-in-function in these genes can result in chronic granulomatous disease. In absence of mutations in these genes, mRNA mis-splicing due to mutations in introns are responsible for disease pathogenesis.<sup>[14]</sup>

Inherited immunodeficient disorders can be manifested during adult age. The chronic granulomatous disease should be considered as diagnosis in any individual reporting with recurrent fungal and bacterial infections and granulomatous colitis.<sup>[16,17]</sup>

Recent treatment strategies involve anti-inflammatory therapy like Anakuira, a recombinant IL-1 Receptor antagonist. Adjunctive therapy using interferon- $\gamma$  and hematopoietic stem cell transplantation have been used.<sup>[17]</sup>

### Sarcoidosis

Sarcoidosis is a multifactorial disease characterized by discrete non-caseating granulomas.<sup>[18]</sup> Over 90% of subjects demonstrate pulmonary involvement.<sup>[19]</sup> It shows a positive correlation with HLA-A1, -B8, and -DR3, few infectious microorganisms like pollen, silica, and occupational exposures. Th1 lymphocytes play an important role in granuloma formation due to deposition of poorly soluble antigenic material.<sup>[18]</sup>

In absence of spontaneous resolution of a granuloma, it gets converted into an avascular and acellular connective tissue. With chronicity, hyalinization and fibrosis takes place. PGE2 plays an important role in fibroblastic proliferation along with neutrophils which act by production of superoxide anions or immune complexes.<sup>[19]</sup>

Sarcoidosis is a reduced delayed-type hypersensitivity response wherein there is a balance between regulatory T cells (Treg). These cells accumulate at periphery of a granuloma while exerting an anti-proliferative effect on naïve T cells along with suppression of TNF- $\alpha$ , therefore promoting granuloma formation.<sup>[20]</sup> The non-caseating granuloma of sarcoidosis is characterized by surrounding macrophage which differentiate to epithelioid cells that fuse to form multinucleated giant cells. The CD4 + T helper

cells are distributed throughout while the CD8 + T cells, T cells, Treg cells, B lymphocytes, and fibroblasts form the periphery. The Treg cells in sarcoid granulomas secrete IL-4, a pro-inflammatory cytokine that promotes macrophage formation.<sup>[19]</sup>

Corticosteroid therapy is the treatment of choice for treating sarcoidosis. Also in recent years, tumor necrosis factor- $\alpha$  (TNF-  $\alpha$ ) and Infliximab have shown good response in sarcoidosis therapy.<sup>[20]</sup>

## Tuberculosis

Granulomas are central for immunopathogenesis of tuberculosis. Cytokine production is required for recruitment of inflammatory cell infiltrate. For early macrophage recruitment, chemokine binding to CCR2 receptor is mandatory. The TNF production by macrophages along with T lymphocytes plays an important role in granuloma maintenance. The CD4 + T lymphocytes secrete IL-2, IFN- $\gamma$  and lymphotoxin A. Also, a shift toward M2 polarization in macrophages aid in their mycobactericidal capability.<sup>[21]</sup>

The TB granuloma plays a significant role in expansion of mycobacterial infection. This takes place by engulfment of apoptotic debris of infected macrophages, thus re-infecting themselves. This process of infected cell apoptosis and rephagocytosis results in granuloma expansion.<sup>[22]</sup>

Current laboratory assays employed for tuberculosis diagnosis are as follows:<sup>[23,24]</sup>

- a. Smear examination: It is used for identifying acid fast bacilli after staining with Ziehl-Neelson or Auramin stain under microscope.<sup>[23,24]</sup>
- b. Xpert MTB/RIF assay: It is a real-time quantitative polymerase chain reaction assay for detection of tuberculosis by amplification of *rpoB* gene. It is a WHO-approved test for detection of pulmonary, extra-pulmonary, and pediatric tuberculosis.<sup>[23,24]</sup>
- c. Xpert MTB/RIF Ultra assay: It is a successor technology to Xpert using similar hardware for testing.<sup>[23,24]</sup>
- d. GeneXpert OMNI: GeneXpert OMNI is more capable than Ultra due to its handling characteristics in extreme conditions of temperature and humidity with up to 4 h of battery back-up.<sup>[23,24]</sup>
- e. Lateral flow lipoarabinomannan commercial test: This test is used for detecting the Lipoarabinomannan component in cell wall of mycobacteria.<sup>[23,24]</sup>

## Granuloma formation in immunodeficiency states

A complicated process between microbial contents, epithelial and immunologic components is involved in granuloma formation in these conditions. Genoma Wide Association Studies have identified nearly 70 genetic polymorphisms associated with Crohn's disease of which prominent ones are those associated with autophagy (e.g. NOD2, ATG16L1, IRGM, LRRK2, ULK1).<sup>[2]</sup>

NOD2 is responsible for pro-inflammatory cytokine release and induction of autophagy. ATG16L1 is recruited to cell membrane by NOD2 and acts as a receptor for n-acetylmuramyl-L-alanyl-D-isoglutamine, which is a subunit of bacterial peptidoglycans. ATG16L1 is expressed on intestinal epithelial cells, leukocytes, and spleen. Mutation in this gene is associated with formation of ileal Crohn's disease.<sup>[3]</sup> Poor formation of granuloma occurs by deficiencies in IFN- $\gamma$ , IL-12 or TNF $\alpha$ .<sup>[25,26]</sup>

Recent tests for diagnosing various primary immunodeficiency's include flow cytometry, chemotaxis and phagocytosis assay, Enzyme assays for myeloperoxidase and G6PD dehydrogenase, bone marrow biopsy, targeted gene and whole genome sequencing.<sup>[27]</sup>

In depth understanding of the pathogenetic mechanism of different diseases have beneficial impact on the oral cavity. It helps in better treatment planning and prevents antibiotic misuse. This can help in correct medications for the specific disease, thereby preventing the disease to attain the untreatable condition and helps patient satisfaction and adherence to the medication for better prognosis.

## Conclusion

There are numerous pathogenetic mechanisms involved in development of chronic granulomatous diseases. An understanding of each can help in planning the management, thereby reducing the morbidity in affected subjects in entire spectrum of granulomatous disease.

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## Conflicts of interest

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