ACADEMIA International Journal for Social Sciences
Volume 4, Issue 4, 2025 ISSN-L (Online): 3006-6638

Interferon-gamma (IFN-γ) A Perspective Biomarker for Diagnosis of Oral Diseases

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Received: 12-07-2025 **Revised:** 22-08-2025 **Accepted:** 17-09-2025 **Published:** 31-10-2025

IFN-γ (Interferon gamma) a proinflammatory cytokine, initially considered as a crucial biological molecule as a potent anti-tumor cytokine, macrophage activator, antigen precentor, regulating mucosal homeostasis and cell-mediated immunity and repairing tissue within the oral cavity(1, 2). An innovative transformation has been established in the field of diagnosis due to an advancement of Interferon-gamma (IFN-γ) from its simple pro-inflammatory function to a more sophisticated model of immune regulation. IFN-γ serves dual function such as bone resorption through osteoclastogenesis, besides the unexpected and protective effects mediated by T regulatory cells, has demonstrated its specific and spatiotemporal expressing patterns(3). Based on these innovations the current therapeutic strategies have shifted from broad IFN-γ suppression toward targeted and phase-specificized interventions. Research have focused on how lymphocyte-derived IFN-γ is directly influencing keratinocyte apoptosis and sustaining chronic inflammation via specific chemokine pathways facilitating the development of highly selective therapies and blocking this cytokine axis without causing broad immunosuppression. Additionally, the dual role of IFN-γ in oral diseases, predominantly its complex function in oral squamous cell carcinoma, has emerged as a critical area of investigation(4, 5).

In chronic periodontitis, Dutzan et al. report that active sites exhibit higher IFN-γ in gingival crevicular fluid (approximately 99.9 pg/mL) compared with inactive sites (around 68.9 pg/mL; P values between 0.03 and 0.04)(6). For oral lichen planus (OLP), Malekzadeh et al. document a significantly altered IFN-γ/IL-4 ratio in reticular OLP (7.74 ± 0.09; P = 0.042). In studies of oral squamous cell carcinoma (OSCC), Abbas et al. measured median salivary IFN-γ levels of 120.2 pg/mL in patients versus 244.5 pg/mL in controls. Ghallab et al., demonstrated that a significant decline has been observed in the levels of IFN-γ after the prednisone therapy in the management of erosive OLP (Oral lichen Planus), whereas an increase in the levels has been reported after the surgery of OSCC(7). Additionally, the increasing salivary levels in the oral Graft-versus-Host Disease (oGVHD) is serving as an early and preclinical indicating marker for T-cell mediated immune response(8).

Based on these investigations recent prognostic models have highly integrated the IFN-γ marker to predict the responses of immune therapy and progression of disease utilizing saliva as a noninvasive monitoring source for oral diseases diagnosis(9). Multiplexed biomarkers approaches have been utilized for the diagnostic potential of IFN- γ, such as high IFN-γ, IL-17, and IL-23 levels suggesting a mixed Th1/Th17 response in the progression of periodontitis whereas the high levels of IFN-γ, CXCL9, and CXCL10 is characteristic of the chief Th1-axis in OLP(10, 11).

Advanced techniques have demonstrated that by Proteomic Activation Fingerprinting evaluating the functional outcomes of IFN-γ signaling through the analysis of JAK-STAT pathway phosphorylation, such as STAT1, in exfoliated mucosal cells, therefore providing a direct "IFN-γ activation levels. The techniques utilized for the detection of IFN-γ levels have significantly emerged and addresses a more sophisticated diagnostic requirements, surpassing conventional methods(12, 13). The Enzyme-Linked Immunosorbent Assay (ELISA) is essential for evaluating baseline values of IFN- γ in saliva and gingival crevicular fluid (GCF) other Molecular techniques such as RNA isolation, cDNA synthesis, and quantitative real-time PCR, are utilized for gene expression analysis and IGRA-based assays like

QuantiFERON-TB Gold and T-SPOT.TB a highly sensitive and specific method for detection of systemic IFN- γ, has also been approved by FDA and CDC(14-16). However, the limitations of these diagnostic technologies, such as the need for specialized laboratories, lack of real-time analysis, skilled technicians and high costs, have motivated the implementation of novel approaches including Aptasensors. These modified Biosensors have shifted the field of diagnostics increasingly towards a portable, sensitive, capability of detection ultralow limits of biomarkers and real-time diagnostic platforms(17).

The emerging technologies have presented integrated biosensors, which might be embedded in oral devices, enabling continuous, offers a rapid, quantitative "cytokine profile" and real-time monitoring of IFN-γ levels. The clinical efficacy of topical cytokine balancing mediators in management of symptomatic OLP, OSCC, and periodontitis is the focus of emerging clinical trials and the translational potential of targeting IFN- γ pathway is making significant progress.

Hence IFN- γ is no longer considered as a mere inflammatory cytokine, however the paradigm has been shifted revealing its clinical ability relating its levels in the diagnosis of oral diseases and suggesting an era of diagnostic precision and targeted immunotherapy.

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