REVIEW ARTICLE

Interferon Lambda: An Anonymous Warrior of Host-Microbial Fray in The Pathogenesis of Periodontal Diseases

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ABSTRACT

The current body of research focuses primarily on three fundamental groups of interferons: alpha, beta, and gamma interferons. However, little attention is paid to another important group of interferons called lambda interferons (IFN-λs), which have demonstrated activity against periodontal pathogens, particularly viruses. These recently discovered interferon-lambdas provide a striking contrast to the periodontal pathogens, exerting impact both at the capacity of the immune system and the cell, thereby affecting a variety of inflammatory and response pathways. Thus, this review sheds light on role of interferon lambda in the development of periodontal disease and associated activities. In order to collect the information necessary for this review, an exhaustive search of the relevant literature was conducted. The review focused on the structure, regulatory mechanisms, and role of interferon lambda in medical and periodontal infections and diseases. The findings of our review indicated that IFN-λs have an effect on the immunological regulatory mechanisms of the host in relation to viruses, bacteria, fungi, and parasites; nevertheless, their primary role is antiviral, and they have little to no effect on the immune system's ability to fight bacteria.

Keywords

Immunity, Interferons, Interferon-lambda, Periodontal diseases, cytokines

INTRODUCTION

The periodontium is the supporting machinery of the tooth with potential mechanisms to defend against the mechanical and microbial challenges constantly posed to it. An exquisite balance exists between the symbiotic bacteria and the pathogenic bacteria that surround it. This balance is disrupted by immunoregulatory dysfunction leading to dysbacteriosis with a transition to gram-negative, anaerobic, and virulent periodontal pathogens. Much literature emphasizes the deleterious role of viruses, fungi, and protozoa other than bacteria in the etiopathogenesis of periodontal disease. Local, systemic, immunological, environmental and genetic risk factors govern the process of periodontal defence against the microbial threat. The consequence of combined partake of periodontal dysbiosis, risk factors, and host response is periodontal inflammation that manifests clinically as gingivitis and periodontitis. Both innate and adaptive immunity contribute to inflammatory immune regulation against periodontal pathogens through the participation of immune cells and the release of cytokines, complement cascade, neuropeptides, chemokines and other immunomodulators. Interferons, which are produced by a variety of

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cells, are one such powerful defence mechanism that influences both humoral and acquired responses against periodontal pathogens.

Interferons lambdas (IFN-λs), the type III interferons are a more modern subtype of interferons that are produced and preferentially expressed by epithelial cells through interferon lambda receptor-1. IFN-λs were once thought to be active on the surfaces of epithelial barrier membranes, but more recent studies have shown that they also affect innate and adaptive immunity and are effective against autoimmune and viral illnesses. The importance of IFN-λs in the defence against periodontal pathogens has increased with the increasing evidence for involvement of viruses in the periodontal diseases etiopathogenesis.

IFN-λs Structure:

IFN-λs are divided into four subclasses: interferon lmbda-1 (IFN-λ1), interferon lmbda-2 (IFN-λ2), interferon lmbda-3 (IFN-λ3) and interferon lmbda-4 (IFN-λ4). IFN-λs and interleukin-10-related cytokines shares extracellular six α-helices motifs and exhibits receptor-mediated signalling that is included as a class II cytokine receptor family, thus joining the class II cytokine family.[1] IFN-λR1, a specific high affinity R1 receptor, and IL-10R2, a low affinity R2 receptor that is shared by IL-10 family members, make up the IFNs receptor system.[2,3] On chromosome 19, IFN-λ genes are encoded, and they are surrounded by single nucleotide polymorphisms.[4] The phylogenetic alignment of IFN-λ genes reveals their alignment between the genes of cytokines linked to IL-10 and interferon type I with amino acid sequence similarity ranging from 5% to 18%.[5] The homologous IFN-λ subgroups share amino acid similarity, with IFN-λ2 and IFN-λ3 sharing the most and IFN-λ3 and IFN-λ4 having the least.[6,7] Formerly the IFN-λ4 was thought to be a not a true gene, the IFN-λ4 gene has since been identified.[8]

IFN-λs Regulatory Mechanisms:

IFN-λs and type I group of interferons function similarly in response to viral invasion via JAK-STAT with the difference in receptors triggering the interferon stimulated genes that render against viral infection, despite structural differences.[9-11] Once the virus gained host access, pattern recognition receptors detect the pathogen-associated molecular pattern with the activation of transcription factors, namely interferon regulatory factors-1, 3, 7 and nuclear factor kappa B (NFκB) secrete IFN-λs which in turn activate the JAK-STAT pathway in stimulation of interferon-stimulating genes (ISGs) to establish antiviral disposition.[12,13] Furthermore, IFN-λs has an impact on immune cells in response to viral infection by limiting viral replication, lowering viral load, and delaying the development of viral drug resistance, resulting in the development of antiviral immunity.[14-21]

Due to the scarcity of researches, the precise involvement of IFN-λs in non-viral inflammatory conditions is yet be precisely investigated. IFN-λs are primarily expressed by epithelial cells, but myeloid cells, neutrophils, B lymphocytes, and dendritic cells have also been found to express IFN-λs.[22-24] IFN-λs alter the function of cells involved in humoral and acquired immunity, including polymorphonuclear leukocytes, B lymphocytes, T lymphocytes, CD4 cells, CD8 cells, macrophages and dendritic cells.[25] According to some researches, inhibitory effects of IFN-λs on dendritic cells and natural killer cells result in anti-inflammatory actions.[26-28]

IFN-λs Influence on Medical Diseases and Disorders:

As a potent antiviral molecule, IFN-λs are capable of a variety of functions against: Hepatitis C virus,[29] Hepatitis B virus,[30] Herpes viruses,[31-34] Human immunodeficiency virus,[35] Dengue virus,[36] Zika virus,[37] SARS corona virus,[38,39] Influenza virus,[40] human metapneumovirus,[41] Lymphocytic choriomeningitis virus,[42] Norovirus,[43] Rhinovirus,[44] and many others. In addition to viral diseases, IFN-λs have a wide variety of actions in reduction and control of bacterial, fungal, and parasitic infections.[45-48] IFN-λs potential for managing and controlling human cancers has been hinted at in a few papers.[49,50] IFN-λs have been proven to have positive benefits on asthma,[51] but there is strong evidence that they have deleterious effects on autoimmune diseases such systemic and cutaneous lupus erythematosus, Crohn's disease and rheumatoid arthritis.[52-54] The auditory function depends on IFN-λs as well, and hereditary sensorineural hearing loss is linked to its mutation.[55]

IFN-λs Influence on Periodontal Diseases:

The principal etiological agent for the onset and progression of periodontal diseases is dental plaque, a microbial complex entrenched in an organic matrix adhering to the teeth and other oral surfaces. Although bacteria are thought to be the main biofilm pathogens

responsible for periodontal diseases, there is a wealth of information about the role of viruses in these diseases that has been available for one to two decades. Periodontal viruses are harmonious inhabitants of the periodontium in compatibility with periodontal bacteria. In response to periodontal pathogens, a wide range of host defence mechanisms are activated including release of cytokines and chemokines, activation of receptor complexes and involvement of immune system. IFN-λs induction is one such mechanism. As discussed in previous sections, the broad biological roles of IFN-λs have paved the way to emphasize their importance in understanding the aetiopathogenesis of periodontal disease.

A genomic investigation by Zahra et al., found a connection between periodontal infection and two single nucleotide polymorphisms of IFN-λ2, rs8099917 and rs12979860.[56] As reported by Shivaprasad et al., patients with periodontitis have more IFN-λs levels than periodontally healthy people do.[57] Additional researches by Shivaprasad et al., show that IFN-λ1 is highly expressed in the aggressive form of periodontitis, whereas IFN-λ2 in chronic form.[58,59] Immunohistochemical analysis by Tabari et al., has revealed that chronic and aggressive periodontitis both have elevated levels of IFN-λ1.[60] IFN-λs levels rise as periodontal measures such as gingival index, periodontal probing depths, and clinical attachment loss increase and additionally, periodontal therapy results in higher expression of IFN-λs than baseline levels as reported by Shivaprasad et al.[57] A PCR investigation by Muzammil et al. revealed that virus-positive individuals had higher concentrations of IFN-λ1 than virus-negative persons, indicating that its antiviral activity in the periodontal tissue.[61] However, all of these investigations hypothesize about the protective defensive function of IFN-λs in periodontal diseases without taking into account their inflammatory effects and bacterial interactions, as evidenced in the medical literature.

It is well known that bacteria and viruses exhibit synergistic relationship to invade the host immune mechanisms.[62] IFN-λs released in response to viral presence can alter the course of bacterial infections. In response to IFN-λs signalling, Paul et al., have identified the alterations in the microbiota with increased bacterial replication rate.[62] The reduced chemotaxis of neutrophils caused by virally produced IFN-λs may enhance the likelihood of bacterial superinfection.[63,64] Not simply in reaction to viral infection, but also in response to bacterial infection, IFN-λs are increasingly secreted.[45,65] The bacterial microbiome affects the regional expression of the receptor profile and thus regulates the IFN-λs response.[66] IFN-λs generated in response to the viral load has not been found by Jeremy et al., to have any antibacterial properties.[65] According to Fang et al., the IFN-λs exerts proinflammatory effects through inducing proinflammatory mediators.[67] In the presence of IFN-λs, keratinocytes and mesenchymal cells release chemokines that attract immune cells that contribute to tissue inflammation.[68] The published research by Amol et al., has shown that IFN-λs mediated anti-inflammatory action is insufficient.[69]

Moreover, there have been a very small number of IFN-λs related periodontal studies, and the most of them have focused on IFN-λ1 with limited information on IFN-λs2 and 3 and totally lacking data on IFN-λ4.

CONCLUSION

IFN-λs have an impact on the immune regulatory mechanisms of the host in terms of viruses, bacteria, fungi, and parasites, with their main function being antiviral and having little to no antibacterial impact. Despite having a different structural makeup, the IFN-λs performs similarly to α and β interferons and yet it is still unclear what part they play in periodontal disease. With very few research studies to draw any conclusions on their beneficial or detrimental impact, we have only just begun to comprehend the precise role of IFN-λs in the etiopathogenesis of periodontal disease. Periodontal researchers need to pay more attention to IFN-λs are as important as IFN-α and IFN-β which have received a great deal of attention for decades.

Conflict of Interest

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

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Authors' Contribution

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper's drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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