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Assessment the role of Interferon Lambda in Regulating Immune Response in SLE Disorder

Mohammed A. Kamil[1], Hazima M. Alabassi[2]

[1,2]Department of Biology, University of Baghdad, Iraq.

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Abstract:

The role of interferons in modulating immune responses following infections or various danger signals is a crucial one, as they belong to a class of powerful antiviral cytokines. The first description of Type III interferons, known as IFNλs, was that they are a distinct mechanism that prevents viral replication at epithelial barrier sites and reduces inflammation. type III interferons have a complicated impact on both the innate and adjustive immune systems and may also have a detrimental impact on systemic autoimmune disorders. Respective autoimmune conditions such as arsenic general lupus erythematosus bear been associated with elevated levels of IFNλs in the blood and tissues of individuals and those levels are connected to particular clinical manifestations and lab findings. This review aims to difficultly assess the existing literature on the biology of IFNλs and explore their potential contribution to immune dysregulation and tissue injury in SLE diseases. This article review the new advances of the literature along the orderly look of interferons lambda and their receptor in association SLE.

Keywords: Systemic lupus erythematosus ,SLE , IFNλ , IFNL3

Corresponding author: (Email**:** mohammed.amer1202a@ihcoedu.uobaghdad.edu.iq).

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition marked by the production of autoantibodies and widespread inflammation affecting multiple organ systems (1). This disease is classified as a systemic immune disorder, implicating more than one organ when it manifests (2). The pathogenesis of SLE is influenced by the complicated interplay between genetic predispositions and environmental influences as revealed by research involving human subjects and experimental animal model. These interactions get run to immune dysregulation and breakdown in immunological tolerance, after consequent in the generation of autoantibodies and multi-organ inflammation (3,4).

The SLE encompasses a range of autoimmune disorders with diverse clinical presentations one of which is serositis characterized by inflammation of serosal membranes and including conditions such as pericarditis pleuritis and peritonitis (5). This disease is renowned for its relapsing nature with symptoms that get change significantly inc severity, ranging from mild and transient to potentially life-threatening. SLE onset typically occurs during adolescence and early adulthood predominantly affecting females aged 15 to 44 (6). The check gets affect

aggregate variety organs with important manifestations much determined in the kidneys and central nervous system (7). Also complications arising from treatment and ongoing disease activity frequently add to organ damage in patients with SLE (8). Alternatively, interferon plays an important role in SLE. These cytokines which are produced in response to infections or different inflammatory triggers are class of cytokines that have strong antiviral properties and play important role in modulating immune cell activity. (9, 10). type III interferons may also have a role in the pathogenesis of autoimmune and chronic inflammatory diseases. New findings suggest that the biology of IFNλ is more complex than previously believed. The host may be harmed by the prolonged and excessive activation of the IFN pathway.

This review aimed to highlight the potential impact of IFN lambda in regulating of immune response in autoimmune diseases, particularly in (SLE).

Pathogenesity of SLE

Systemic lupus erythematosus (SLE) has a difficult pathophysiology that is difficult to pinpoint due to a highly complex and multifactorial interaction between various genetic and environmental factors. Additionally, multiple genes contribute to disease susceptibility (11, 12). Additionally, the hypothalamo-pituitary-adrenal axis, sex, and hormonal milieu interact to alter this vulnerability and the disease's clinical manifestation. Remarkably, the development of SLE is significantly influenced by immune regulatory systems that are malfunctioning, such as the removal of immune complexes and apoptotic cells. B cell hyperactivity and the generation of harmful autoantibodies are caused by the loss of immunological tolerance, increased antigenic load, excess T helper cells (Th), impaired B cell suppression, and the switching of T helper 1 (Th1) to Th2 during immune responses. Finally, Inflammatory cells and particles produce changes in the number, shape, and size of bone marrow cells and peripheral blood cells during the inflammatory phase in SLE. In contrast, these cytokines are produced by neutrophils and platelets and contribute to neutrophils and platelets activation. Neutrophils are the most common type of leukocyte, and they play an important role in inflammatory processes; platelet activation also is detected in SLE patients. Additionally, pathways that produce interferon (IFN) are linked to tissue damage and a reduction in tolerance (12).

Interferon-lambda and receptors

In order to create a comprehensive antiviral response, interferons (IFNs) are essential cytokines. Based on their structural characteristics, receptor use, and biological activity, IFNs are classified into three different types: type I, type II, and type III (13). An intriguing new era in IFN research began in early 2003 with the identification and preliminary characterisation of the interferon lambda (IFN-λ) family. There are three IFN-λ genes that encode three closely related proteins known as IFN-λ1, IFN-λ2, and IFN-λ3, which correspond to interleukin-29 (IL-29), IL-28A, and IL-28B, respectively (14). Collectively, these three cytokines comprise the type III subset of IFNs. They differ from type I and type II IFNs in a number of ways, one of which is that they employ

a different heterodimeric receptor complex to signal than do type I or type II IFNs. Both type I IFNs (like IFN-α and IFN-β) and type III IFNs (IFN-λ) activate the same intracellular signaling pathways and many of the same biological functions, including antiviral activity, across a wide range of target cells, despite the variations in receptor complexes (15). The expression of IFN-λ genes and their related proteins is triggered by infections with different viruses, which is consistent with their antiviral effects. Therefore, type III IFNs (IFN-λs) have extremely comparable expression and main biological action to type I IFNs (16). its IFN-λ receptors are mostly located on epithelial cells, in contrast to IFN-α receptors, which are widely expressed on most cell types, including leukocytes. As a new antiviral therapeutic drug, IFN-λ potential clinical importance is becoming more and clearer. Additionally, preclinical research indicates that IFN-λ could be helpful as a therapeutic agent for additional clinical uses, such as treating certain cancers (17).

Furthermore, it is observed that the IFN-λ genes are grouped together on both the murine chromosome 7 (in the 7A3 area) and human chromosome 19 (more precisely, in the 19q13.13 region). Interestingly, the transcription of the IFN-λ3 gene (IL28B) is reversed from that of the IFN-λ1 (IL29) and IFN-λ2 (IL28A) genes. The coding region of each of these genes is separated into five exons. The conserved architecture of genes encoding cytokines linked to IL-10 is strongly correlated with the intron-exon arrangement of the genes encoding IFN-λs (18, 19). The exon sizes and locations, together with the frames of the intron/exon junctions, are substantially consistent among type III IFN genes and cytokines linked to IL-10, despite the fact that the intron sizes vary greatly. However, as seen in Figure (1), type I IFN genes lack introns(20).

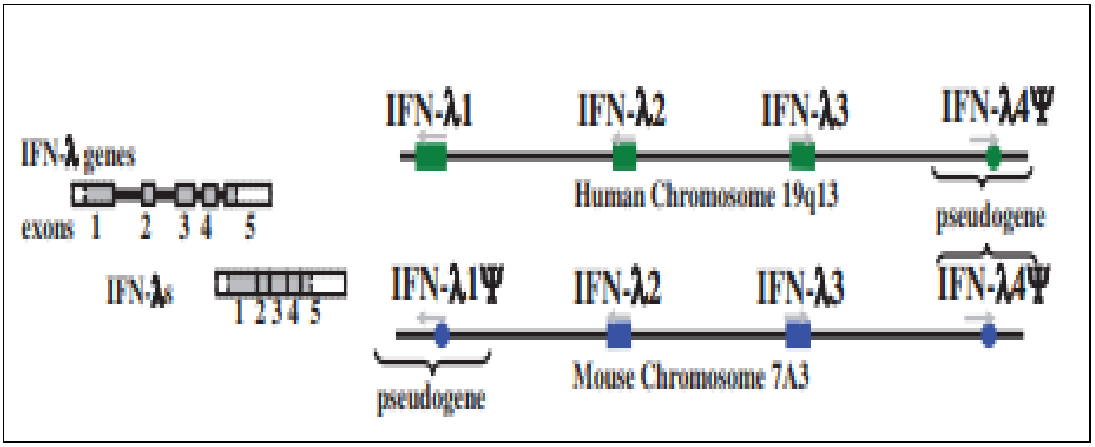

Figure (1): Organization of the genes encoding the IFN- λ s and their receptors. Schematic representations of the chromosomal regions of the human and mouse genomes that encode the IFN- λ)

IFNλs and Autoimmune disease

This section will specifically concentrate on the elements of the IFNλ response that are pertinent to autoimmunity and Autoimmune deasese.on the other hand, Interferon lambda (IFNλ) cytokines exert direct influences on various populations of innate immune cells (21, 22). In vivo investigations have shown that mice with a neutrophil-specific deletion of Ifnlr1 are more susceptible to Aspergillus infections, and IFNλs can also boost the generation of reactive oxygen species (ROS) in mouse neutrophils 23) suggesting that IFNλs play a crucial role in regulating antifungal immunity through specific modulation of neutrophil functionality. On the other hand, IFNλs seem to prevent ROS generation and degranulation in mouse neutrophils during intestinal inflammation through a non-translational, STAT1-independent mechanism (24, 25). Furthermore, it has been demonstrated that IFNλs prevent human neutrophils from producing ROS in response to TNF and prevent neutrophil extracellular traps (NETs) from forming in response to activated platelets or platelet-derived inorganic polyphosphate (26). There is uncertainty about how human peripheral bloods neutrophils react to IFNλs in various situations, nevertheless, as contradictory data suggest that IFNλs do not increase ISG expression in these cells. Subsets of dendritic cells (DCs) are also important components of the IFNλ response network. It has been demonstrated that IFNλs increase the production of chemokines and type I interferon in human plasmacytoid DCs (pDCs) (23, 27). Additionally, they have the ability to increase the production of co-stimulatory molecules and class I and II major histocompatibility complex (MHC) molecules on pDCs, which may aid in T cell activation (28). On the other hand, whereas NK cells do not seem to react directly to IFNλs, these cytokines can indirectly alter NK cell activity by influencing macrophages (29). Conversely, certain adaptive immune cells are directly impacted by interferon lambda (IFNλ) proteins. There is proof that human lymphocytes are capable of reacting to IFNλ. Additionally, IFNλ stimulates the development of plasmablasts inside human B cells and increases antibody production mediated by Toll-like receptors (TLR7 and TLR8) (26). Notably, pre-treatment with IFNλ can inhibit influenza-induced IgG production in human peripheral blood mononuclear cells (PBMCs) (30). But rather than directly affecting B cell function, this inhibitory effect was shown in a mixed cell population and could be due to a reduction in T helper 2 cell cytokine output. This is consistent with research indicating that IFNλs promote a bias in T helper 1 cell responses. Compared to B cells the effects of IFNλs on human T cells are less obvious. Furthermore, through indirect pathways, IFNλs can contribute to the coordination of adaptive immunity (31).

IFNλ Pathogenesity in SLE

A crucial factor in the evolution of SLE is the interest of type I interferons which have been connected to the

disease pathogenesis. A characteristic type I interferon signature found in the blood and afflicted tissue of many SLE patients (32, 33). Functionally, these interferons trigger the abnormal activating of immune cells by enhancing the product of autoantibodies and immune complicated, leading to tissue damage. Also, type I interferons have the ability to modify T cell activities, change antigen-presenting cell (APC) activity and sensitize neutrophils, all of which add to the autoimmune damage that characterizes SLE (34). Studies have indicated that SLE is associated with a dysregulation of type III interferons as well as type I interferons. Serum IFNλ1 and IFNλ3 levels were higher in SLE patients than in healthy people, according to several investigations (35). Also, it has been demonstrated that in comparison to healthy controls IFNL1 transcript expression rises in peripheral blood mononuclear cells (PBMCs) but IFNL2 and IFNL3 transcripts rise in activated CD4+ T cells of SLE patients (36). Crucially, higher serum IFNλ concentrations are linked to more severe illness and particular laboratory results; increasing IFNλ levels are correlated with higher anti-double-stranded DNA (dsDNA) autoantibody levels and higher SLE illness Activity Index scores (37), and diminished C3 and C4 complement proteins. Moreover, raised IFNλ levels correspond with various disease manifestations including arthritis, nephritis, serositis, and skin symptoms (35). Genetic studies have also identified links between genetic variations and SLE risk. Specific variants of IFNL3 and IFNL4 are associated with lupus nephritis in Taiwanese patients, while the rs4649203 single nucleotide polymorphism in IFNLR1 is implicated in a heightened risk of SLE among individuals in a Chinese Han population (38). The presence of IFNλs has been confirmed in affected tissues of SLE patients. Compared to healthy subjects or those with other inflammatory skin conditions like psoriasis and atopic dermatitis, immunohistochemistry studies of skin tissues showed significantly higher levels of IFNλs and IFNLR1 in people with chronic discoid lupus erythematosus or subacute cutaneous lupus erythematosus (39). The epidermis is where IFNλs is most noticeable, while mononuclear cells in the dermis also exhibit some staining. It is noteworthy that individuals with chronic lupus erythematosus, especially those with extensive lesions, exhibit higher blood levels of IFNλ1. A case study showed that following glucocorticoid and hydroxychloroquine therapy, serum IFNλ1 levels decreased during clinical remission (40). Apart from skin tissue, lupus nephritis patients' kidney tissues also contain IFNλs and IFNLR1, especially in glomerular crescents and regions with inflammatory infiltrates. Interestingly, follow-up biopsies showed that patients who reacted well to therapy had lower levels of IFNλ staining in their glomeruli (41). It is important to remember that kidney tissue from disease-matched and healthy control groups was not compared in these investigations. Generally, evidence suggests that IFNλs may play a significant role in the skin and kidney complications associated with SLE and illustrate the complex dysregulation of the immune system that characterizes the disease, possibly reflecting differences in B cell responsiveness between species. These findings indicate that IFNλs may contribute to SLE-associated skin disease by

enhancing the production of pro-inflammatory chemokines in keratinocytes (See Figure 2). Importantly, keratinocytes treated with both IFNα and IFNλ1 showed higher chemokine production than those treated with either cytokine alone, suggesting that type I and type III interferons work together to promote skin inflammation. Additionally, IFNλs encourage keratinocytes to express MHC class I molecules, which may help pathogenic CD8+ T cell responses (42). Mice missing IFNLR1 showed decreased kidney ISG expression, decreased glomerulosclerosis, and decreased immune complex deposition in a TLR7-induced lupus model. Also it was demonstrated that IFNλs might affect kidney structural cells by inducing the synthesis of chemokines and ISGs in mice mesangial cells. IFNλs may also affect different kidney cells specifically epithelial ones (43). Nucleic acids immunological complicated and the activation of intracellular sensors are some of the Methodes that start the production of interferons in SLE (see Figure 2).

Type I interferons are mostly produced by plasmacytoid dendritic cells (pDCs) in SLE (44) and are also involved in producing IFNλs. In Human RNA-containing immune Complicates get trigger type III interferon product through subset of pDCs that also produce type I interferons (45). The addition of hydroxychloroquine or an IRAK4 inhibitor very importantly decreased the *in vitro* generation of IFNλs by pDCs indicating that RNA-containing immune Complicates trigger IFNλ synthesis via the endosomal TLR–Myd88 pathway.A further investigation showed that cathelicidin LL-37 and endogenous nucleic acids from keratinocytes can stimulate the synthesis of IFNλ(46). These results are agreeing with the find that inflammation in SLE skin lesions is exacerbated by keratinocyte cell death and increased nuclear debris (47) (see Figure 2). Furthermore, subsequently existence stimulated by IFNα, keratinocytes can increase IFNL transcripts, indication a feed-forward loop that intensifies the type III interferon pathway in skin inflammation. Finally, recent evidence highlights the potentially harmful role of IFNλs in SLE emphasizing their varied and tissue-specific effects.

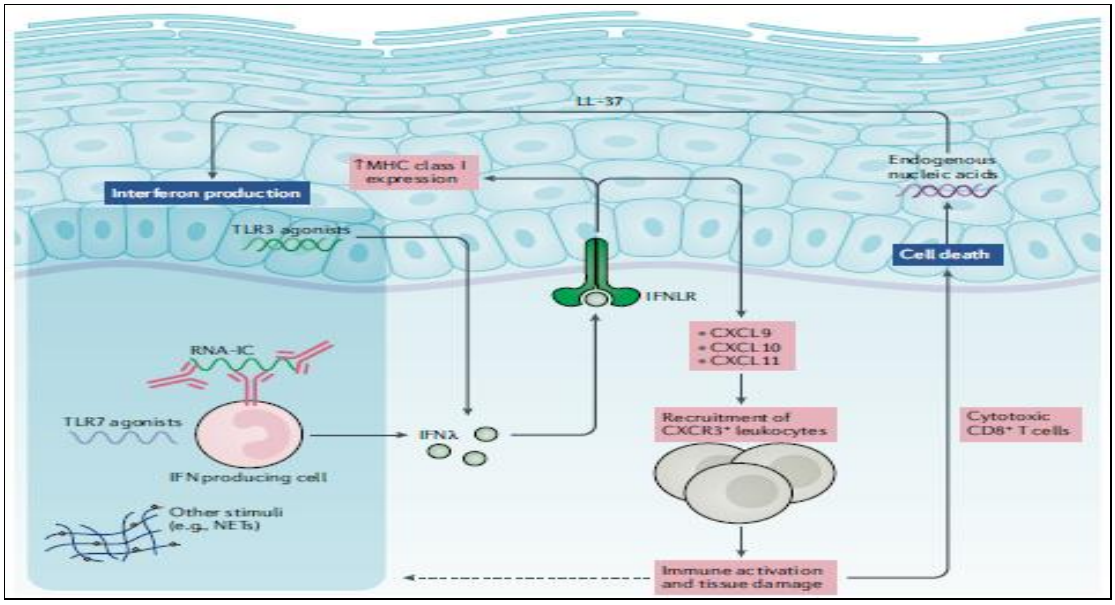

Figure (2): IFNλs in SLE conditioin .produced IFNλ by blasmacytoid dendritic cells & keratinocyte and stimulate MHC classI with some chemokines.

Conclusions

The review cites several sources highlighting the role of interferon lambda in regulating immune responses. It reduces inflammation and minimizes damage to the body. However, in autoimmune conditions like SLE, where levels of interferon lambda are abnormally high, this signaling pathway is continuously activated.

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