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Interleukin-29 in Autoimmune Diseases: Review Article

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ABSTRACT

Background: A number of cytokines are produced when interleukin-29 (IL-29) is introduced to monocytes. High creation of IL-6, IL-8, and IL-10 was seen after stimulating human monocytes with IL-29. The cytokine Interlukin-19 belongs to the interleukin-10 family. When interleukin-29 was added to monocytes, IL-19 production was increased. In response to IL-29, monocytes exhibited rapid morphological changes.

Objective: To study and focus on role of Interleukin-29 in autoimmune diseases.

Methods: We scoured medical papers and databases including PubMed, Google Scholar, and Science Direct for information on IL-29 and autoimmune illnesses. Only the most recent or comprehensive study conducted between April 2002 and December 2020 was included in the analysis. The authors also assessed the usefulness of references drawn from similar books. Documents written in languages other than English have been neglected because of a lack of funding to translate them. Unpublished articles, oral talks, conference abstracts, and dissertations were all generally agreed upon not to constitute valid scientific investigation.

Conclusion: As a newly found type III interferon, interleukin-29 (IL-29) is an exciting discovery. It mediates signal transmission and results in the generation of inflammatory components via interactions with its receptor complex that initiate further signal transduction. Recent studies have linked dysregulated IL-29 expression to a wide variety of inflammatory autoimmune diseases, involving osteoarthritis, systemic sclerosis, rheumatoid arthritis, psoriasis, systemic lupus erythematosus as well as Sjögren's syndrome. Furthermore, functional investigation suggested that IL-29 may contribute to the onset of autoimmune inflammatory disorders.

Keywords: Autoimmune diseases, Interleukin-29.

INTRODUCTION

The interleukin-29 receptor is expressed on some cell types such as dendritic cells, T cells, leukaemia cells, and intestinal epithelial cells. There has been a lot of talk about how interleukin-29 plays a crucial function in tumours and how it could be used in clinical therapy. In addition to its role as an antiviral and immunoregulatory cytokine, research has shown that interleukin-29 plays a crucial role in inflammatory autoimmune illnesses [(1)].

In the recently identified type III IFN family, interleukin-29 plays a pivotal role. Due of the considerable link between it among inflammatory autoimmune disorders, we thoroughly examined the most recent literature on this topic. More people are paying attention to these researches because of the potential role of IL-29 as a regulator in inflammatory autoimmune disorders. The data gathered are expected to aid in the study of interleukin-29 in the future, and may yield insights into the role of this cytokine in inflammatory autoimmune disorders. Important implications for its potential in clinical therapy may also be gleaned from our review [(2)].

There has been a lot of interest in interleukin-29 as of late. Some tissues were found to be the only ones that produced interleukin-29. There has been a lot of talk about how interleukin-29 plays a crucial function in tumours and how it could be used in clinical therapy. In addition to its role as an antiviral and immunoregulatory cytokine, research has shown that interleukin-29 (interleukin-29) plays a crucial role in inflammatory autoimmune illnesses like osteoarthritis, rheumatoid arthritis (RA), Sjögren's syndrome, systemic sclerosis, psoriasis, as well as systemic lupus erythematosus [(1)].

Structure:

In spite of its structural similarities to other members of the IFN- family, interleukin-29's core amino acid sequence (and, by extension, its activity) is more like to that of type I interferons. It interacts with a heterodimeric receptor consisting of the IFN-specific IFNL1R subunit and the IL-10 family-wide IL10RB subunit [(3)].

Signaling and mechanism of action of IL-29:

Interleukin-29 is the most abundant type III interferon (IFN) protein subtype, and it acts as a signal transducer through stimulation of the Akt/protein kinase B (PKB) and mitogen-activated protein kinase (MAPK) signaling pathways in response to cytokines. Mediating interleukin-29 signaling are the IL-28R alpha and IL-10R beta 2 receptor complexes [(4)].

It's worth noting that interleukin-29 may have a limited effect on signaling pathways outside of certain cells. After being stimulated with interleukin-29, fibroblast-like synovial cells (FLS) from people with osteoarthritis (OA) phosphorylated proteins in the mitogen-activated protein kinase (MAPK) and Akt signaling pathways. The IL29-treated mast cell line P815 increased its production of IL-4 and IL-13 via the phosphatidylinositol 3kinase (PI3K)/Akt and JAKSTAT3 signaling pathways. Macrophages generated from monocytes react to interleukin-29 treatment by being phosphorylated at the signal transducer and activator of transcription [(5)].

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Increased nuclear factor kappa B signaling activity in rheumatoid arthritis W264.7 cells in response to lipopolysaccharide was seen after interleukin-29 stimulation (LPS). Furthermore, interleukin-29 inhibited c-Fos and c-Jun N-terminal kinase in rankl-stimulated RAW cells, resulting in a reduction in the expression of NFATc1-mediated osteoclastogenic genes including tartrate-resistant acid phosphatase [(4)].

The capacity of interleukin-29 to create TLR3 may depend on the activation of the JAK-STAT system, since its effects on keratinocytes' Toll-like receptor 3 (TLR3) synthesis were inhibited by the addition of JAK inhibitor 1. Bone deterioration is a well-known feature of RA, and it has been linked to both the increased production of pro-inflammatory cytokines and the increased rate of osteoclastogenesis in affected joints. Reducing osteoclast generation was one of interleukin-29's effects because it blocked NF-B activation and NFATc1 translocation [(1)].

Tyrosine phosphorylation of STATs causes the formation of certain homodimers and heterodimers, which are then translocated into the nucleus, where they act on IFN-stimulated response elements (ISREs) in the regulatory regions of IFN-stimulated genes (ISGs). For instance, the transcription complex ISG factor 3 (ISGF3), which included phosphorylated forms of STAT1, STAT2, and IFN regulatory factor (IRF) 9, was critical for kicking off ISG production [(6)].

Consequently, interleukin-29 shown its capacity to inhibit viral replication, suppress cell proliferation, fight tumours, and control the immune system. These results suggest that interleukin-29 plays a role in controlling cellular activity and cytokine production by influencing the activation and transduction of signaling pathways [(4)].

Interleukin-29's impact on immune-nonimmune cells:

Antiviral protein and Toll-like receptor 3 (TLR3) expression has been shown to be induced in human keratinocytes (KCs). TLR3 expression was likewise upregulated in KCs when IL-29 was administered to the cells. Treatment with interleukin-29 shielded KCs from herpes simplex virus type 1 (HSV-1) infection and dramatically upregulated the production of IFN- elicited by HSV-1. This suggests that interleukin-29 may play a role in KCs' antiviral activity via modulating their production of TLR3 [(7)].

Essential function of interleukin-29 in innate immunity:

Several cytokines are produced as a result of IL-29 stimulation of monocytes. Increased production of IL-6, IL-8, and IL-10 was seen after stimulating human monocytes with interleukin-29. The cytokine IL-19 belongs to the interleukin-10 family. When interleukin-29 was added to monocytes, IL-19 production is increased. The treatment with IL-29 caused rapid morphological changes and increased motility in monocytes. Based on these findings, it appears that interleukin-29 may play a role in monocyte function. In conjunction with lipopolysaccharide (LPS) or the TLR7/8 agonist resiquimod (R848), interleukin-29 - stimulated monocyte-derived macrophages produce more tumour necrosis factor (TNF) [(8)].

The expression of IL-12p40 in human monocyte-derived macrophages was also induced by interleukin-29. TLR8 expression was likewise reduced by treatment with interleukin-29. The upregulation of IL-10-induced pSTAT3 and IL-10R1 expression in human monocyte-derived macrophages in response to interleukin-29 stimulation demonstrates that interleukin-29 can boost IL-10 signaling events in macrophages. It has been found that monocyte-derived macrophages exhibit higher levels of interferon gamma receptor 1 (IFNGR1) after being exposed to interleukin-29 [(5)].

The inflammatory cytokines IL-6, IL-8, and IL-10 were also secreted by macrophages in response to interleukin-29. The IFN-R1 chain is not only not made by NK cells, but it is also not expressed by them. Interleukin-29, a kind of cytokine, is ineffective at directly affecting cells. However, interleukin-29 demonstrated an indirect cytokine-dependent action via macrophage-NK cell contact, where interleukin-29 plus IFN- boosted IFN- production via macrophage-mediated IL-12 synthesis. This indicates that interleukin-29 controls macrophage activity, and it is through stimulation of macrophages that interleukin-29 has its indirect influence on NK cells (Figure 1) [(9)].

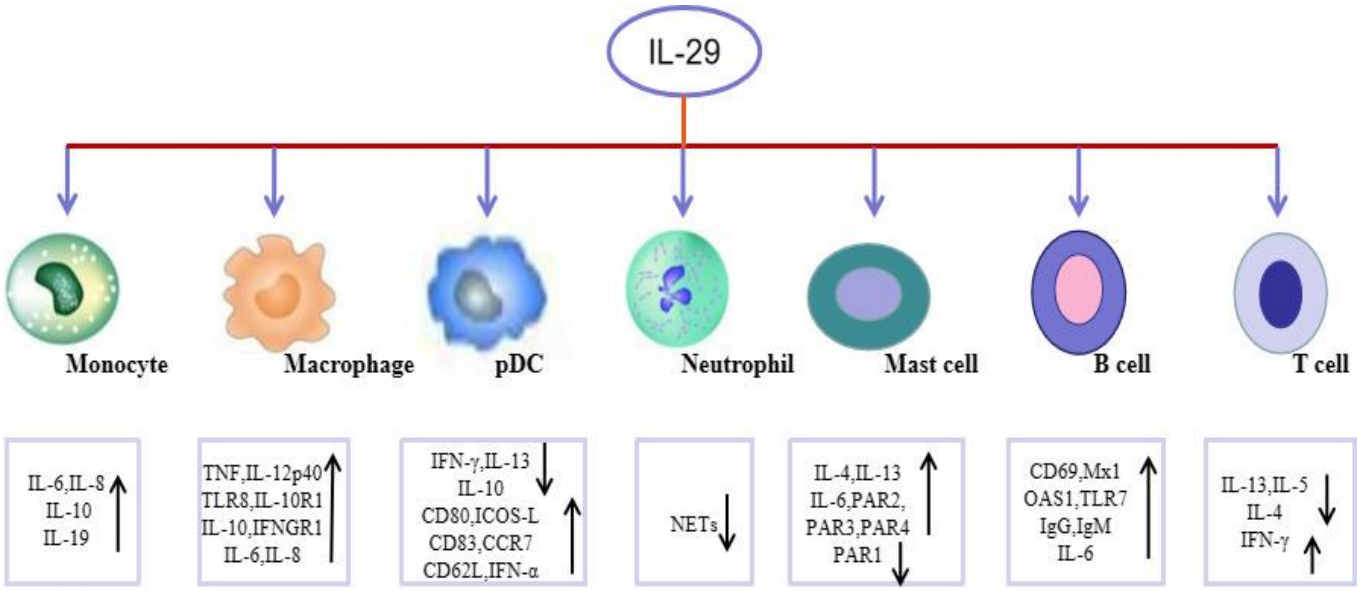

Figure (1): Inflammatory autoimmunity and the role of IL-29[9].

Inhibition of maturation and activation of plasmacytoid dendritic cells (pDCs) was observed after treatment with IL-29. CD80, inducible costimulatory molecule L (ICOSL), CC chemokine receptor 7 (CCR7), and L selectin expression could be up-regulated in pDCs after IL-29 stimulation (CD62L). Co-stimulation with interleukin-29 and IFN- resulted in a dramatic upregulation of CD80, CD83, and ICOS-L expression in pDCs, the primary source of IFN-. As shown by these results, IL-29 has the potential to control the activation and immunostimulatory capacity of pDCs via modulating the expression of costimulatory molecules [10].

Thrombosis' major mediators and promising therapeutic targets are neutrophils and extraneutrophil traps (NETs), which are neutrophil-released meshwork structures. Neutrophil extracellular trap (NET) production was reduced after IL-29 treatment. IL-29 stimulation also reduced the quantity of neutrophil cytoplasmic tissue components. The purpose of IL-29 in neutrophils, for example, is to reduce thromboinflammation by lowering neutrophil migratory potential in prothrombotic and proNETotic processes [11].

The human intestine, tonsil, and lung all include mast cells that express interleukin-29. When activated by proteolytic allergens, mast cells secrete interleukin-29. High quantities of IL-4 and IL-13 were produced after mast cells were activated with interleukin-29. In addition, interleukin-29 treatment of mast cells induced IL-6 production. However, interleukin-29 antibody can block interleukin-29's effect on inflammatory cytokine production [8].

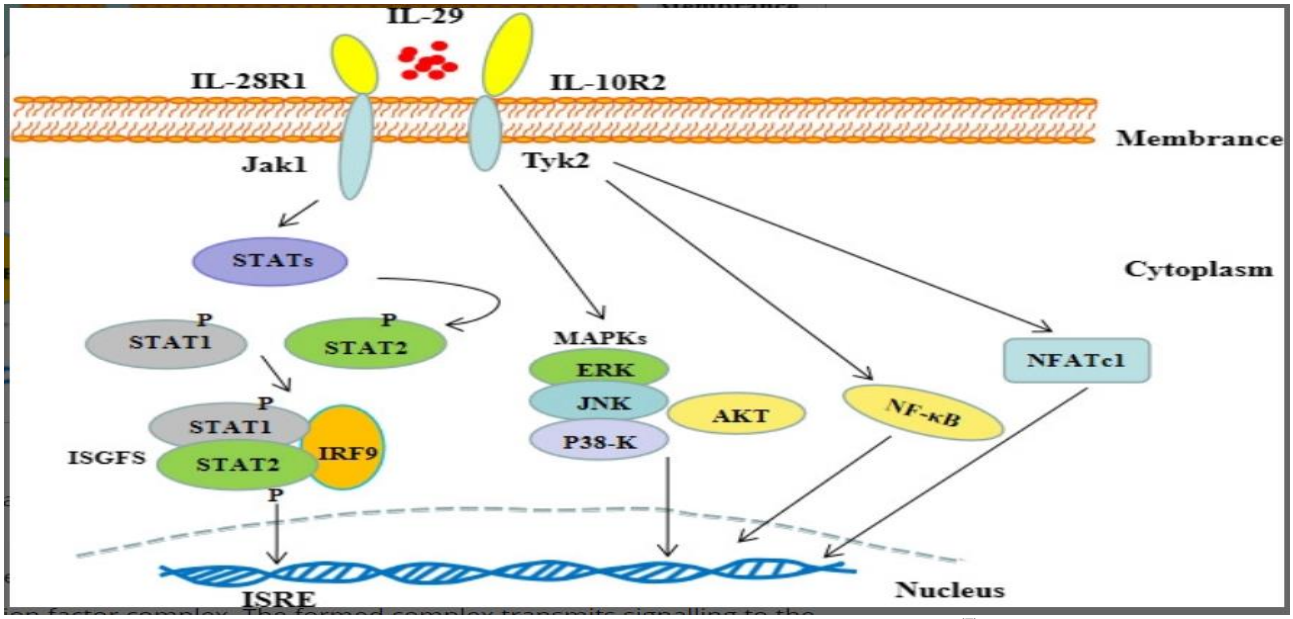

Figure (2): Interleukin-29 and inflammatory processes [7].

Mast cell tryptic proteases are controlled by IL-29, this upregulates the expression of PAR2, PAR3, and PAR4 while downregulating PAR 1. When IL-29 was injected into the peritoneum of mice, a buildup of mast cells was seen. However, the addition of the Scianna 2 (SC2) antibody prevented this. These findings demonstrated that IL-29 might regulate cytokine secretion and initiate mast cell invasion (Figure 2) [7].

Essential functions of IL-29 in adaptive immunity:

Both naive and memory human CD27+ B cells showed strong up-regulation of the marker CD69 after being exposed to IL-29, regardless of whether or not the cells had already been activated with the TLR7/8 ligand R848. Increased expression of myxovirus resistance-1 (Mx1) and oxidative stress-associated gene 1 (Osa1) was seen in CD19+ B cells after stimulation with interleukin-29. Stimulating CD19+ B cells results in an increase in TLR7 expression in addition to the increase in interleukin-29 [9].

By controlling the expression of the Th2-restrictive transcription factor GATA3, IL-29 has a direct inhibitory effect on Th2 polarisation. Th2 cytokines include IL-4, IL-5, and IL-13. Treating CD4+ T cells with IL-29 reduced IL-13 production and increased IFN (representative of Th1 responses). Naive CD4+ T cell IL-13 production was significantly upregulated by IL-4, demonstrating that IL-29 can inhibit the activity of IL-4 in Th2 response [12].

IL-29 and RA:

Rheumatoid arthritis is a debilitating autoimmune disorder that can affect any part of the body. The lining layers of RA synovium contained CD68(+) macrophages and FGF2(+) fibroblasts, both of which expressed IL-29. Patients with RA had significantly increased IL-29 expression in their serum, PBMCs, and synovial tissue than did healthy controls. There detected a high concentration of interleukin-29 in the synovial fluid (SF) of rheumatoid arthritis (RA) patients. Synovial fluid from people with RA often contains elevated levels of granzyme M (GrM), which may stimulate the release of IL-29 [13].

Rheumatoid arthritis has been linked to the toll-like receptor 4 (TLR4), which plays a role in synovial inflammation and the disease's aetiology. Increased expression of the TLR4 gene was seen in RAW264.7 cells after treatment with IL-29. Treatment with IL-29 further increased TLR4-mediated IL-6 and IL-8 expression in RA arthritic synovial cells. In RA, interleukin-29 similarly upregulated TLR2, TLR3, and TLR4 expression [14].

In vitro investigations have revealed a novel role for IL-29 in boosting synovial inflammation throughout the development of RA. Recombinant IL-29 stimulates a human synovial fibroblast cell line termed MH7A to generate more proinflammatory cytokines [15].

IL-29 and SLE:

Recent studies show that IL-29 suppresses IL-13 release in vitro, which changes the Th1/Th2 response and decreases human Th2 responses. After being exposed to IL-29, dendritic cells increase IL-2 dependent CD4+CD25+Foxp3+ T cell proliferation, while monocytes secrete more IL-6, IL-8, and IL-10. Recent studies have linked IL-29 to the pathophysiology of systemic lupus erythematosus by activating peripheral blood mononuclear cells to produce the chemokines IP-10, MIG, and IL-8 [16, 17].

Chemokines are a class of tiny chemicals that regulate the differentiation and proliferation of dendritic cells, T cells, and bone marrow progenitors, as well as guide cell migrations necessary for the start of a T cell immune response. They can also regulate the production of adhesion molecules while encouraging the migration of monocytes, NK cells, and T cells. SLE is characterised by an inflammatory response and organ dysfunction, both of which are influenced by these factors [18, 19].

In response to interferon (IFN), PBMC, fibroblasts, and endothelial cells release a CXC chemokine called IFN-inducible protein-10 (IP-10), which recruits monocytes, T cells, and NK cells to the site of inflammation. When renal tissue has been injured by an immune response, another CXC chemokine, IL-8, can attract immune cells to the glomerulus. IL-8 is strongly neutrophil-chemotactic [20, 21].

Patients with active SLE have been found to have elevated amounts of IL-8, IP-10, and IFN-g-generated monokine in their plasma (MIG). Higher levels of IL-8 in the urine have been observed in people with SLE who also had active renal disease [22, 23].

CONCLUSION

Interleukin-29 is a fascinating new find because it is a type III interferon. By attaching to its receptor complex and activating downstream signaling pathways, it mediates signal transmission and leads to the production of inflammatory components. Multiple inflammatory autoimmune illnesses, including as osteoarthritis, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, psoriasis, and systemic lupus erythematosus, have been associated to IL-29 expression dysregulation in recent studies. Furthermore, functional investigation suggested that IL-29 may contribute to the onset of autoimmune inflammatory disorders.

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