Introduction

The newly discovered cytokine interleukin-29 (IL-29) belongs to type III interferon (IFN), which has another two subfamilies IL-28A and IL-28B. They are also known as IFN-λ1, IFN-λ2 and IFN-λ3, respectively. The gene encoding IL-29 owns 5 exons and locates on the long arm of human chromosome 19. These mediators are members of a large family called IL-10 family, composed of nine cytokines: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28A, IL-28B and IL-29. All type III IFNs bind to the same receptor complex consisting of IFN-LR1 (also named IL-28R1, CRF2-12 or LICR) and IL-10R2 (IL-10R2 and CRF2-4). Recently, IL-29 has been focused much attention. Production of IL-29 was found specific to some tissues, and there was a tissue specificity responding to IL-29. IL-29 receptor is expressed in dendritic cells, T cells, intestinal epithelial cells and leukaemia cells. The important role of IL-29 in tumours and its potential use for clinical therapy has been widely discussed. Due to antiviral and immunoregulatory characteristics of IL-29, studies also showed that IL-29 performed significantly in the pathogenesis of inflammatory autoimmune diseases, for instance, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriasis and systemic sclerosis. Furthermore, functional analysis revealed that IL-29 may involve in the pathogenesis of the inflammatory autoimmune disorders. In this review, we will systematically review the current knowledge about IL-29. The information collected revealed the regulatory role of IL-29 and may give important implications for its potential in clinical treatment.
a new field of IFN research in which IL-29 is considered to be a core member. On account of the strong association between this molecule and inflammatory autoimmune diseases, we systematically review recently published articles on this significant relationship. The regulatory capacity of IL-29 in inflammatory autoimmune diseases has drawn increased attention to these studies. It is hoped that the information collected will contribute to future research on IL-29, and may provide some clues for its role in inflammatory autoimmune diseases. Furthermore, our review may give important implications for its potential in clinical treatment.

2 | IL-29 SIGNALLING

Studies suggested that IL-29 is able to activate downstream signalling pathways, and therefore induces the generation of inflammatory components. Activation of Janus kinase/signal transduction and activator of transcription (JAK-STAT) signalling pathway might be induced by IL-29 through STAT1 and STAT2. Similarly, activation of STAT3 and STAT5 by IL-29 also proved to affect the JAK-STAT signalling. Consistently, IL-29 induced signal transduction through activation of protein kinase B (Akt) and mitogen-activated protein kinase (MAPK). It is notable that the ability of IL-29 to affect signalling pathways may depend on specific cells. Osteoarthritis (OA) fibroblast-like synovial cells (FLS) stimulated with IL-29 activated JAK-STAT, MAPK and Akt signalling pathways, resulted in phosphorylation of the proteins. Mast cell line P815 treated with IL-29 promoted the production of IL-4 and IL-13 through phosphatidylinositol 3-kinase (PI3K)/Akt and JAK-STAT3 signalling pathways. Monocyte-derived macrophage responded to IL-29 treatment via STAT1 phosphorylation. In RAW266.7 cells, an elevation of lipopolysaccharide (LPS)-induced nuclear factor-kappa B (NF-κB) signalling activation was observed following IL-29 stimulation. In addition, IL-29 down-regulated expression of nuclear factor of activated T cell 1 (NFATc1)-mediated osteoclastogenic genes such as tartrate-resistant acid phosphatase (TRAP), cathepsin K (CTSK) and matrix metalloprotein 9 (MMP-9) through activation of c-Jun N-terminal kinase (JNK), and inhibition of c-Fos, and NFATc1 in receptor activator of nuclear factor-κB ligand (RANKL)-stimulated RAW266.7 cells. Moreover, IL-29 regulated toll-like receptor 3 (TLR3) expression in keratinocytes, but it was hindered following adding JAK inhibitor 1, suggesting that IL-29–induced TLR3 generation may depend on the activation of JAK-STAT pathway. It is recognized that bone erosion in RA correlated with increased production of pro-inflammatory cytokines and accelerated osteoclastogenesis in affected joints. IL-29 suppressed osteoclastogenesis by activation of STAT signalling pathway and inhibition of NF-κB activation, and NFATc1 translocation. When tyrosine residues on STATs were phosphorylated, some homodimers and heterodimers were formed and translocated into nucleus, and then combined with IFN-stimulated response elements (ISREs) in regulatory regions of the IFN-stimulated genes (ISGs). For example, ISG factor 3 (ISGF3), a transcription complex, consisted of phosphorylated STAT1, STAT2 and IFN regulatory factor (IRF) 9, initiated the transcription of ISGs. Subsequently, IL-29 presented the ability of antiviral protection, anti-proliferative response, antitumour activities and immune regulation. All these revealed that IL-29 may

![FIGURE 1](image-url)
Involve in cytokine secretion and regulation of cellular function through modulating the activation and signalling transduction of signalling pathways (Figure 1).

3 | BIOLOGIC FUNCTIONS OF IL-29

3.1 | Effect of IL-29 on non-immune cells

Human keratinocytes (KCs) were reported to induce expression of antiviral proteins and TLR3. Treatment of KCs with IL-29 up-regulated 2',5'-oligoadenylate synthetase (2',5'-OAS) and myxovirus resistance A (MxA) expression. Administration of IL-29 in KCs also promoted TLR3 expression. IL-29 treatment significantly enhanced the expression of IFN-γ induced by herpes simplex virus type 1 (HSV-1) and protected KCs from HSV-1 attack. Therefore, IL-29 could regulate TLR3 and IFN-γ expression in KCs and then play a part in antiviral activity.

3.2 | Significant role of IL-29 in innate immunity

Monocytes respond well to IL-29 and produce several cytokines. Human monocytes stimulated with IL-29 significantly up-regulated levels of IL-6, IL-8 and IL-10. IL-19 is a member of IL-10 family cytokine. IL-29 treatment on monocytes had an ability to enhance levels of IL-19. Monocytes morphology changed quickly and became motile with IL-29 treatment. These data suggested the potential role of IL-29 in function of monocytes. IL-29-stimulated monocyte-derived macrophage in combination with LPS or TLR7/8 agonist resiquimod (R848) treatment enhanced tumour necrosis factor (TNF) production. Similarly, IL-29 could enhance IL-12p40 expression in human monocyte-derived macrophage. IL-29 treatment also up-regulated TLR8 expression. IL-29 stimulation on human monocyte-derived macrophages led to increased IL-10–induced pSTAT3 and IL-10R1 expression, indicating an ability of IL-29 to augment IL-10 signalling events in macrophages. IL-29 improved cell surface expression of interferon gamma receptor 1 (IFNGR1) on monocyte-derived macrophage. In addition, macrophage reacted to IL-29 promoted the generation of inflammatory cytokines IL-6, IL-8 and IL-10. Natural killer (NK) cell does not express IFN-γ R1 chain. It is impossible for IL-29 to affect the cell directly. However, IL-29 showed an indirect role in cytokine-dependent manner through the interaction between macrophage and NK cell, where IL-29 combined with IFN-γ indirectly influenced NK cell through macrophage-mediated IL-12 production, and subsequently elicited IFN-γ production. Therefore, IL-29 indirectly affected NK cells, mediated through the stimulation of macrophages, suggesting that IL-29 modulates the function of macrophages.

Interleukin-29–treated plasmacytoid dendritic cells (pDCs) showed reduced expression of IFN-γ, IL-13 and IL-10, and negatively regulated the maturation and activation of pDCs. Stimulation of pDCs with IL-29 could up-regulate the expression of CD80 and inducible costimulatory molecule-L (ICOS-L), C-C chemokine receptor type 7 (CCR7) and L-selectin (CD62L). IL-29 in combination with IFN-α significantly enhanced the expression of the costimulatory molecules CD80, CD83 and ICOS-L. pDCs are the main secretor of IFN-α. IL-29 combined with cytosine-phosphate-guanosine oligodeoxynucleotides (CpG-ODN) or GPG2216 stimulation on pDCs promoted INF-α secretion. These data reflected that IL-29 is able to regulate costimulatory molecules expression and may play a role in activation and immunostimulatory potential of pDCs.

Neutrophils and neutrophil-released meshwork structures are called extraneutrophil traps (NETs), which are the main mediators and emerging therapeutic targets of thrombosis. Treatment of IL-29 inhibited NET formation in neutrophils. Amount of cytoplasmic tissue factors in neutrophil was also hindered after IL-29 stimulation. In addition, IL-29 suppressed the neutrophil migratory capacity in prothrombotic and proNETotic functions of neutrophils, indicating the function of IL-29 in neutrophils, for instance, inhibiting thrombo-inflammation.

Mast cells expressing IL-29 are located in some human tissues such as colon, tonsil and lung. Mast cells release IL-29 under proteolytic allergen stimulation. After stimulating mast cells with IL-29, levels of IL-4 and IL-13 were enhanced. In addition, exposure of mast cells to IL-29 up-regulated the secretion of IL-6. However, the effect of IL-29 on inflammatory cytokine generation can be inhibited following adding IL-29 antibody. Action of tryptic proteases in mast cells is influenced by IL-29, where IL-29 down-regulated expression of protease-activated receptor (PAR)1, and up-regulated expression of PAR2, PAR3 and PAR4. Injection of IL-29 in mouse peritoneum induced mast cell accumulation, whereas the accumulation of IL-29–induced mast cells was abolished after adding Scinna-2 (SC2) antibody. These findings suggested that IL-29 had an ability to regulate cytokine release and induce mast cell infiltration.

3.3 | IL-29 plays important roles in adaptive immunity

Human CD27− naïve and CD27+ B cells stimulated by IL-29 alone or in combination with the TLR7/8 ligand R848 significantly up-regulated the marker CD69, indicating that both naïve and memory B cell populations were responsive to IL-29 stimulation. CD19+ cells stimulated with IL-29 could significantly up-regulate IFN-stimulated genes myxovirus resistance-1 (Mx1) and OAS1 expression. IL-29 stimulation on CD19+ B cells could significantly up-regulate INF-stimulated genes myxovirus resistance-1 (Mx1) and OAS1 expression. IL-29 stimulation on CD19+ B cells also up-regulated TLR7 expression. Intriguingly, the combination of IL-29 with R848 enhanced TLR7/8-mediated IgG and IgM production, and the production of R848-mediated IL-6 on treated CD19+ B cells, implying the role of IL-29 to regulate TLR7/8-triggered cytokine secretion. Addition of IL-29 enhanced R848-induced proliferation of CD19+ B cell. Collectively, these findings suggested IL-29 to regulate the function of B cells, especially binding to TLR7/8 ligation.

Interleukin-29 directly inhibited Th2 polarization by regulating Th2 restrictive transcription factor GATA3. IL-4, IL-5 and IL-13 are three Th2 cytokines. IL-29 treatment on CD4+ T cells inhibited the production of IL-13 and enhanced IFN-γ (representative of Th1 responses). IL-4 strongly increased IL-13 production in naïve CD4+ T
cells, showing that IL-29 is possible to antagonize the activity of IL-4 in Th2 response. IL-29 receptor IL-28Rα was expressed on naive and memory CD4+ T cells. Naive or memory CD4+ T cells under the Th2-polarizing condition in the presence of IL-29 significantly reduced the secretion of a Th2 cytokine IL-5. Furthermore, stimulation of CD3+ CD4+ T cells with IL-29 down-regulated the levels of IL-13 and the amount of IL-13+ CD3+ CD4+ T cells. IL-29 treatment on CD3+ CD4+ T cells also noted reduction in IL-4 and IL-5 production. Collectively, IL-29 may affect release of inflammatory cytokines in T cells and regulation of T cell differentiation (Figure 2).

4 | IL-29 AND INFLAMMATORY AUTOIMMUNE DISEASES

4.1 | IL-29 expression in inflammatory autoimmune disorders

Rheumatoid arthritis is a type of chronic systemic autoimmune disease. IL-29 was expressed in CD68+ macrophage and FGF-2+ fibroblast in the lining layers of RA synovium. Expression of IL-29 was significantly higher in serum, peripheral blood mononuclear cells (PBMCs) and synovial tissue in RA patients compared with that in healthy controls. Levels of IL-29 in synovial fluid (SF) were higher in RA patients compared with that in OA patients. Serum levels of IL-29 positively correlated with rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody and disease activity score of 28. Interestingly, anti-CCP-positive RA patients had higher serum IL-29 levels than that in healthy controls and anti-CCP-negative RA patients. In RA synovial fluid, increased level of granzyme M (GrM) could induce the release of IL-29. In SLE patients, IL-29 expression was increased in SLE patients as compared to healthy controls. SLE patients with active disease showed elevated IL-29 serum levels as compared to that in healthy controls. Serion patients with intermediate minor salivary gland tissue (MSG) infiltrates when compared to the controls. Psoriasis and atopic dermatitis (AD) are two common chronic inflammatory skin diseases. IL-29 can be derived from Th17 cells, and IL-29 expression was enhanced in lesion skin of psoriasis patients. Levels of IL-29 in psoriatic lesions positively correlated with antiviral protein expression. Similarly, serum levels of IL-29 were elevated in psoriasis patients as compared to healthy controls. IL-29 levels were significantly higher in the skin of AD patients when compared to healthy controls. Hashimoto’s thyroiditis (HT) is a typical autoimmune thyroid disease. Serum levels of IL-29 were higher in HT patients as compared to healthy controls. Furthermore, systemic sclerosis (SSc) patients showed increased IL-29 serum levels as compared to those with idiopathic uveitis. Taken together, IL-29 levels were abnormal in some other inflammatory autoimmune diseases including SS, psoriasis, AD, HT, SSc and uveitis (Table 1).

4.2 | IL-29 regulates the production of autoimmune-related components

TLR4 plays an important role in synovial inflammation and contributes to the pathogenesis of RA. Expression of TLR4 in RAW264.7 cells was increased when exposed to IL-29. IL-6, IL-8 and MMP-3 protein levels were significantly enhanced in RA fibroblast cell line M174 by IL-29 stimulation, whereas IL-29 exposure down-regulated IL-10 expression. Administration of IL-29 further promoted...
the TLR4-mediated IL-6 and IL-8 expression in RA arthritis synovial fibroblasts. Similarly, IL-29 up-regulated TLR2, TLR3 and TLR4 expression in RA FLS. Chronic inflammation is an important factor of ongoing cartilage damage and joint degeneration in OA pathogenesis. IL-29 was reported to induce the up-regulation of MMP-1/TIMP-1, MMP-2/TIMP-1, MMP-3/TIMP-1 and MMP-13/TIMP-1 ratio in OA FLS. Levels of IL-1β, IL-6, IL-8 and MMP-3 in OA FLS were up-regulated by IL-29 incubation. On the contrary, the effect of IL-29 on these cytokines was disrupted by usage of IL-29 blocking antibody. IL-29 treatment on psoriatic mouse skin showed increased expression of C-X-C motif chemokine 10 (CXCL10) and CXCL11, provoked T cell infiltration and skin swelling. Biopsies obtained from the lesion of psoriasis patients under the condition of anti-IL-29 antibody treatment down-regulated the expression of antiviral proteins. Overall, above findings provided clues that IL-29 may involve in the pathogenesis of inflammatory autoimmune diseases by regulating expression of the inflammatory components.

### 4.3 Therapeutic potential of IL-29

Previous investigations have confirmed that IL-29 plays a vital role in several therapeutic fields, including hepatitis C and B, and melanoma, due to its ability of antiviral and antitumour. In recent years, attention has been paid to the role of this cytokine in immune regulation. IL-29 is abnormally expressed in some inflammatory autoimmune diseases. Moreover, numerous researches have shown that IL-29-mediated inflammation plays an important role in the pathogenesis of these diseases. Given the biological role of IL-29 in many immune and non-immune cells, including KCs, monocytes, pDC, B cells, mast cells and its regulatory ability in many autoimmune components, this cytokine may be considered as a therapeutic target for the complex inflammatory diseases such as OA and RA. However, more information about the application of IL-29 in the treatment of inflammatory autoimmune disorders needs to be further clarified.

### 5 | Regulation of IL-29 expression

Above findings showed that IL-29 regulates the production of inflammatory cytokines and chemokines, and therefore may play a potential role in inflammatory autoimmune disease. In turn, regulation of IL-29 expression may reverse the abnormal expression and function of IL-29, giving the possibility to inhibit the generation of inflammatory components and suppress the development of the disorders. In normal conditions, pDCs treated with HSV or imiquimod produced high levels of IL-29. IL-29 is known to induce IL-12p40 production in macrophages. However, the effect can be inhibited in the presence of IFN-α. Exposure of P815 cells to SC2 antibody hindered the capacity of IL-29 to induce IL-4, IL-13 and IL-6 release. After adding rPer, a common allergen, the levels of IL-29 in HMC-1 cell were increased. Interestingly, the effect of rPer on IL-29 expression in HMC-1 cell was suppressed by adding PAI blocking antibody. Poly(I:C) induced significant up-regulation of IL-29 expression. Studies have shown that IL-29 makes a significant effect on the Th2 response via antagonizing the effect of CD4+ T cells and Th2-related cytokine production. Nevertheless, production of IFN-α in turn was controlled by Th2 cytokines. IL-29 was able to regulate IL-13 release, but was abolished following adding proteinase-K in naive CD3+ T cells. When stimulated PBMCs from volunteers with IL-4, transcription and secretion of IL-29 were increased. IL-29 is recognized to regulate IL-19 expression. However, the capacity of IL-29 to induce IL-19 was hindered by IL-10 in PBMCs. When stimulated human fibroblasts with purified granzymes, expression of IL-29 was increased. These data indicated that IL-29 can be regulated by different stimulation in normal conditions, such as IFN-α and Th2-related cytokines. In autoimmunity, it was accepted that IL-29 secretion was inhibited by IL-4 stimulation on Th17 cells from psoriasis patients. In arthritis, the role of IL-29 to enhance the expression of TLR4 in macrophage cell line RAW264.7 cells could be strengthened after adding LPS stimulation. Activation of NF-κB signalling became more significant when RAW264.7 cells stimulated with both IL-29 and LPS than IL-29 stimulation alone, suggesting that LPS may regulate the effect of IL-29 and the role of IL-29. In RA patients, serum IL-29 levels were reduced after the treatment with DMARDs. Collectively, these data suggested that IL-29 is also controlled in autoimmunity.

### 6 | Conclusion

Interleukin-29 is a newly discovered cytokine and belongs to the IL-10 family. This cytokine has become a research hotspot recently.
Compared to IL-28A and IL-28B, IL-29 is more structurally unique. Furthermore, IL-29 is considered to be an effective IFN molecule in human and seems to be the most abundant IFN molecule in serum.\textsuperscript{31,32,34,35,43,44} For example, TLR7/8-mediated B cell proliferation and IgG production are enhanced via IL-29 stimulation. IL-29 is able to inhibit T cell differentiation. Moreover, IL-29 can enhance the IL-10 signalling events in macrophage and plays a vital role in modulating the function of monocyte-derived macrophage. IL-29 signals via binding to receptors, including IL-28Rα and IL-10R2. Inflammatory autoimmune diseases are a group of diseases, such as SLE, RA and OA. These kinds of diseases are characterized by damage and dysfunction of specific or multiple organs and tissues.\textsuperscript{48,49} The present study reviewed much findings that discussed the role of IL-29 in inflammatory autoimmune disorders, suggesting the therapeutic potential of IL-29 in inflammatory diseases. However, the pathogenesis of inflammatory autoimmune diseases is complex. Therefore, further studies regarding the clear role and therapeutic effects of IL-29 are required.

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**CONFLICT OF INTEREST**

All the authors who have taken part in this study declared that they have no conflicts of interest to this manuscript.

**AUTHOR CONTRIBUTIONS**

J. M. W contributed to the literature search and manuscript editing. A. F. H drew pictures and edited tables. W. D. X and L. C. S contributed to the reviewing of the manuscript.

**DATA AVAILABILITY STATEMENT**

Data are available.

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