# IL-12 family cytokines and autoimmune diseases: A potential therapeutic target?

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## ARTICLE INFO

## ABSTRACT

In recent years, the discovery of IL-12 family cytokines, which includes IL-12, IL-23, IL-27, IL-35, and IL-39, whose biological functions directly or indirectly affect various autoimmune diseases. In autoimmune diseases, IL-12 family cytokines are aberrantly expressed to varying degrees. These cytokines utilize shared subunits to influence T-cell activation and differentiation, thereby regulating the balance of T-cell subsets, which profoundly impacts the onset and progression of autoimmune diseases. In such conditions, IL-12 family members are aberrantly expressed to varying degrees. By exploring their immunomodulatory functions, researchers have identified varying therapeutic potentials for each member. This review examines the physiological functions of the major IL-12 family members and their interactions, discusses their roles in several autoimmune diseases, and summarizes the progress of clinical studies involving monoclonal antibodies targeting IL-12 and IL-23 subunits currently available for treatment.

## 1. Introduction

The IL-12 family of cytokines is a distinctive group, characterized by their heterodimeric structure, which consists of an α-chain (p19, p28, or p35) and a β-chain (p40 or EBI3). This family primarily includes IL-12, IL-23, IL-27, IL-35, and IL-39 [1]. A notable characteristic of these cytokines is the sharing of subunits, which facilitates unique pairings with five receptor chains to mediate signaling [2]. Except for IL-35, these cytokines are predominantly secreted by monocytes, macrophages, and dendritic cells (DCs) in response to microbial or host immune stimuli, such as Toll-like receptors and interferon. They all activate the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, a process that stems from the homologous receptor components [3]. Despite the structural similarities among these cytokines, their receptors, and downstream signaling components, they exhibit markedly diverse biological functions (Table 1).

The imbalance in the ratio of T-cell subset has been identified as one of major mechanisms in autoimmune diseases [4,5]. This imbalance is modulated by the IL-12 family of cytokines, which influence the activation and differentiation of T cells into specific subsets, thereby regulating immune homeostasis. The IL-12 family of cytokines is considered one of the key factors in immunological research [1]. These cytokines have been the focus of extensive research in various autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriasis. Studies on these cytokines have led to the development and approval of monoclonal antibodies such as Ustekinumab, Guselkumab, and Tildrakizumab, which have demonstrated significant efficacy in treatment. In this review, we provide an overview of the structure and function of each member of the IL-12 cytokine family and explore the evidence from preclinical and clinical studies regarding their potential roles in the pathogenesis of several autoimmune diseases.

## 2. Overview of IL-12 family cytokines

The IL-12 family of cytokines achieved diverse and specific functions through unique combinations of subunits and their corresponding

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receptor pairings. For instance, IL-12 is composed of the p40 and p35 subunits, where p40 can also pair with p19 to form IL-23. This structural configuration enables both IL-12 and IL-23 to interact with the IL-12Rβ1 receptor. Their downstream affects the differentiation of Th1 and Th17 cells, respectively, with IL-12 driving T cells toward the Th1 lineage, while the differentiation of the CD 4⁺ T cell subset into Th17 is IL-23-dependent [6]. The subunits of IL-27 are p28 and EBI3 (Epstein-Barr virus-induced gene 3), and the EBI3 can in turn combine with p35, to form IL-35. The receptors for these cytokines also reflect this complexity: the IL-27 receptor is comprised of IL-27R and gp130, while the IL-35 receptor includes gp130 and IL-12Rβ2 [7,8]. In this context, IL-27 acts as a dual-function immunomodulator with both pro-inflammatory and anti-inflammatory properties [7]. Contrasting with IL-27, functions of IL-35 as an inhibitory cytokine predominantly produced by naturally occurring thymus-derived regulatory T cells(nTreg) [8]. Moreover, the recent identification of IL-39, formed by the binding of p19 subunit with EBI3, suggests its potential proinflammatory role in immunomodulation [9]. The following figure shows the specific structures and downstream signals (Fig. 1).

### 2.1. IL-12

IL-12, as the main pro-inflammatory factor mediating Th1 response, was first isolated and purified in 1989 by Kobayashi M et al., who also clarified its heterodimeric structure [10]. Initially, it was found that IL-12 is produced by B cells and stimulates human peripheral blood mononuclear cells (PBMCs) produce IFN-γ, while enhancing the cytotoxicity of natural killer (NK) cells and the responsiveness of T cells. Subsequent research revealed that IL-12 is also produced by macrophages and other antigen-presenting cells (APCs). When secreted by macrophages, IL-12 elicits an inflammatory response to infection. However, when secreted by APCs, it primarily promotes the production of Th1 cells and the differentiation of cytotoxic T lymphocytes (CTLs) [11]. Further studies clarified that the IL-12 family is composed of a light chain of approximately 35 kDa (p35 or IL-12α) and a heavy chain of about 40 kDa (p40 or IL-12β), encoded by two unrelated genes located on different chromosomes. Gearing et al. highlighted the relationship between p40 and IL-6 R, as well as the similarity between p35 residues and the IL-6 and granulocyte colony-stimulating factor (G-CSF) families, suggesting homology between the subunits of IL-12 and those of IL-6 and its receptor alpha chain [12]. The IL-12 receptor comprises two chains, IL-12Rβ1 and IL-12Rβ2, expressed predominantly by activated T cells and NK cells, as well as by dendritic cells and B cell lines. Activation of the T-cell receptor (TCR) enhances IL-12R transcription and expression in T cells, with IL-12 itself further upregulating its receptor expression, elucidating the rapid responsiveness of certain NK and T cells subset to IL-12 [13]. The binding of IL-12 to its receptor triggers the downstream

JAK-STAT1, STAT4, and STAT5 signaling pathways. The activation of STAT4 is the core link in the Th1 cell differentiation and functioning, considered to play a pivotal role in the signaling cascade of IL-12. IL-12 promotes Th1 cell differentiation by inducing high expression of the transcription factors T-bet and STAT4 in naïve CD4⁺ T cells and opposes Th2 differentiation and the production of IL-4, IL-5, and IL-13. Furthermore, there exists a positive feedback loop between T-bet transcription and increased IFN-γ, enhancing IL-12R expression and thereby augmenting IFN-γ secretion [14]. Deficiencies in IL-12 subunits p35, p40, or receptors IL-12Rβ1, IL-12Rβ2 in mice result in markedly reduced IFN-γ secretion and Th1 differentiation, with an increase in Th2 development and IL-4 production [15,16]. This indicates IL-12's critical role in cell-mediated immune responses through the STAT4 pathway, although excessive STAT4 activation may contribute to autoimmune diseases such as SLE and RA [17,18]. Thus, modulating IL-12 and STAT4 signaling could offer new treatment avenues for these conditions. Moreover, IL-12 and STAT4 signaling play a dual role in inflammatory response: on the one hand, they resist infection by enhancing Th1 response; on the other hand, excessive Th1 response may lead to pathological inflammation and tissue damage [19]. The phenotype of Loss-of-Function (LOF) mutation contains impaired Th1 responses, reduced IFN-γ production, increased susceptibility to intracellular pathogens like Mycobacterium and Salmonella. Altare et al. identified for the first time a human disease caused by a defective cytokine gene due to a deletion of a gene in IL12B with specificity [20]. And mutations in IL12B or IL12RB1 cause Mendelian susceptible mycobacterial disease (MSMD). The phenotype of Gain-of-Function (GOF) mutation contains excessive Th1 activation and IFN-γ production, potential autoimmune and inflammatory diseases due to hyperactive immune responses. Overall, IL-12 is a potent inducer of Th1 responses and mediates inflammation and cytotoxic T lymphocyte (CTL) function.

### 2.2. IL-23

In 2000, p19 was discovered as a new protein related to IL-6 and IL-12p35, binding with p40 to form the novel cytokine IL-23 [21]. IL-23 is a pro-inflammatory cytokine, like IL-12, produced by activated DCs, Macrophages in response to microbial pathogens. It is enhanced by the interaction between the costimulatory molecule CD40 and its ligand. Additionally, B cells and endothelial cells also secrete IL-23. IL-12 share subunit p40 and receptor chain IL-12Rβ1 with IL-23. The other chain that makes up the receptor for IL-23 is a unique subunit, IL-23R. IL-12Rβ1 is mainly expressed on T cells, NK cells, and DCs, while IL-23R is found at lower levels on activated and memory T cells, as well as on NK cells, monocytes/macrophages, and DCs [22]. The structural commonality of cytokine and receptor allows IL-23 to share some functions with IL-12, yet it also possesses distinct biological properties.

**Table 1**
Members of IL-12 family cytokine.

| Members | Time of identification | Subunits | Receptors | Cytokine-producing cells | Loss of function | Gain of function |
|---|---|---|---|---|---|---|
| **IL-12** | 1989 | p40, p35 | IL-12Rβ1, IL-12Rβ2 | Phagocytic cells, B cells, APC | Th1 responses impairment; susceptibility to intracellular pathogens; MSMD | Th1 hyperactivation; autoimmune and inflammatory |
| **IL-23** | 2000 | p40, p19 | IL-12Rβ1, IL-23R | DCs, Macrophages, B cells, Endothelial cells | Developmental impairment of Th17; susceptibility to fungal infections; protection against chemically induced carcinogenesis; | Enhanced Th17 responses and related autoimmune diseases |
| **IL-27** | 2002 | p28, EBI3 | WSX-1, gp130 | Macrophages, Monocytes, Microglias, DCs | Excessive inflammatory damage; autoimmune diseases | Excessive suppression of Th17 responses; expression of pro-inflammatory cytokines |
| **IL-35** | 2007 | p35, EBI3 | IL-12Rβ2, gp130 | Tregs, Bregs, Macrophages, DCs | Inflammatory; autoimmune | Overactive immunosuppression |
| **IL-39** | 2016 | p19, EBI3 | IL-23R, gp130 | B cells | | |

Abbreviation: DCs, dendritic cells; APC, Antigen-presenting cells; Tregs, Regulatory T cells; Bregs, regulatory B cells; MSMD, Mendelian susceptible mycobacterial disease.
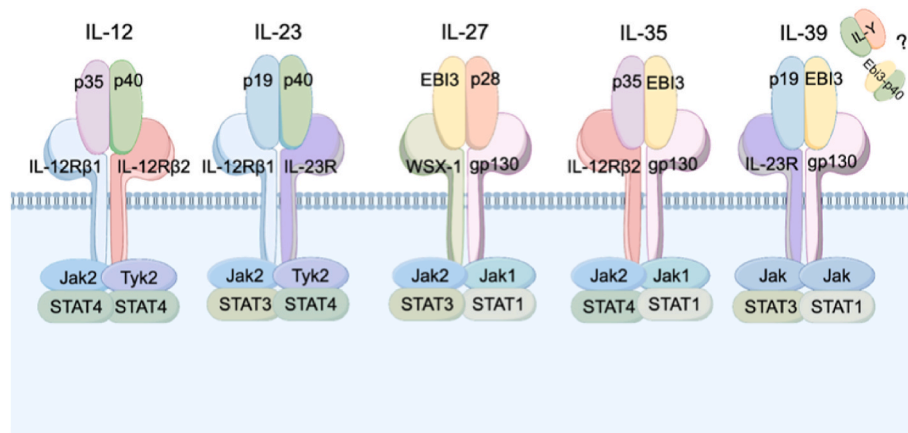
**Fig. 1. Structure of the IL-12 cytokine family members, corresponding receptors, and regulation of downstream signaling pathways.** Members of the IL-12 family of cytokines are presented together with their receptors and Jak-STAT signaling partners. EBI3-p40,IL-Y,newly family members; Tyk2, kinase of the Jak family.

Both can activate downstream Tyk2/STAT signaling through p40-IL-12R β 1, promoting Th cell differentiation. Otherwise, the activation of JAK2 and tyrosine kinase 2(Tyk2) by IL-23 triggers the phosphorylation of STAT transcription factors, including STAT1, 3, 4, and 5 [23]. IL-23 drives the secretion of cytokines such as IL-17A and IL-22 from CD4$^+$ Th17 cells mainly via the STAT3 signaling pathway. Unlike IL-12, this may be related to the association of IL-12 p40 with another subunit. This characteristic provides clues for the functional overlap and divergence within the IL-12 family. While Th17 differentiation is largely regulated by IL-6, TGF-β, IL-1β, it is sustained by IL-21 and IL-23, establishing a robust link of IL-23/Th17 related autoimmune disease [24]. Experimentally, IL-23 has been shown to stimulate the differentiation of Th17 cells from mice splenic CD4$^+$ T cells in vitro [25]. In vivo, p19-deficient mice in a collagen-induced arthritis (CIA) model failed to develop bone and joint pathology, linked to the absence of IL-17 production by CD4$^+$ T cells [26]. The recognition of the IL-23/Th17 axis has spurred further research into other diseases, causing the development and clinical success of monoclonal antibodies targeting this pathway. However, the function of IL-23 in these diseases may not be homogeneous. For example, in psoriasis, IL-23 stimulates IL-22 production by skin-infiltrating Th17 cells in conjunction with IL-6, contributing to epidermal hyperplasia [27]. Conversely, IL-23 can maintain the homeostasis of the gut microbiota and the integrity of the intestinal barrier [28]. The phenotype of LOF mutation contains impaired Th17 cell development and reduced IL-17 production, increased susceptibility to fungal infections, protection against chemically induced carcinogenesis, and possible protection against Th17-mediated autoimmune diseases like psoriasis and inflammatory bowel disease (IBD). The phenotype of GOF mutation contains enhanced Th17 responses and related autoimmune diseases. While this discussion focuses on the regulation of T cells by IL-23, its impact on innate immunity and its role in various diseases continue to be active areas of research.

### 2.3. IL-27

Two years after the identification of IL-23, IL-27 was discovered [29]. IL-27 is a heterodimer consisting of the non-covalently linked subunits EBI3 and p28, primarily produced by macrophages, inflammatory monocytes, microglias, and DCs. Its receptor, IL-27R, includes the unique subunit WSX-1 (TCCR or IL-27Rα) and gp130. Initial studies highlighted the essential role of WSX-1 in Th1 polarization [30]. Over time, IL-27 was recognized for its dual pro-inflammatory and anti-inflammatory effects. It activates naïve CD4$^+$ T cells and NK cells to produce IFN-γ and induces T-bet and IL-12Rb2 expression to promote

Th1 effector function, primarily through the STAT1 and STAT3 pathways. Further research revealed an exaggerated Th2 response to parasitic infections in IL-27Rα knockout (KO) mice [31], partially because IL-27 suppresses Th2 differentiation via the GATA binding protein-3 (GATA-3), a key regulator that mediates STAT1's inhibition of Th2 cell differentiation [32]. Additionally, IL-27R-deficient mice exhibited severe IL-17-related neuritis [33], underscoring the inhibitory of IL-27 effects on IL-17 production in both mice and human T cells [34]. In vitro studies showed that IL-27 suppresses retinoid orphan nuclear receptor α(RORα) and retinoid orphan nuclear receptor γ (RORγ), transcription factors essential for Th17 development, and also inhibits IL-22 production, crucial for Th17 effector functions [35,36]. The influence of IL-27 on regulatory T cells (Tregs) is complex. IL-27 promotes human Treg differentiation and function, evidenced by up-regulation of Foxp3$^+$ T cells when naïve CD4$^+$ T cells from healthy controls (HCs) are stimulated with IL-27 under induced regulatory T cell (iTreg) polarizing conditions, alongside induced STAT1 phosphorylation [37]. In contrast, in mice models, IL-27 downregulated CD25 and cytotoxic T lymphocyte associate protein-4(CTLA-4) expression in naïve CD4$^+$ T cells, upregulated TNF-α expression, and induced STAT3 phosphorylation [38]. Moreover, IL-27 enhances lipopolysaccharide (LPS)-induced pro-inflammatory cytokine production in monocytes through the JAK/STAT and Nuclear factor-κB (NF-kB) signaling pathways [39]. The pro-inflammatory properties of IL-27 are also demonstrated in models of bacterial, parasitic, and other infections, where loss of IL-27 leads to enhanced neutrophil function and bacterial clearance [40,41]. The phenotype of LOF mutation contains increased susceptibility to excessive inflammatory damage during infections, possible increased susceptibility to certain autoimmune diseases. The phenotype of GOF mutation contains excessive suppression of Th17 responses, as well as acting on the innate immune system to promote the expression of pro-inflammatory cytokines by mast cells. Thus, the complexity of IL-27's role in immunomodulation also means that IL-27 is less likely to serve as a good therapeutic target, and the significance of IL-27 for various autoimmune diseases needs to be further explored.

### 2.4. IL-35

While exploring the functions of IL-12 and IL-27, researchers hypothesized the potential combination of the p35 and EBI3 subunits, and in 2007, scientists confirmed IL-35 as a distinct cytokine, initiating further research into its role within the immune response [8,42]. The receptor for IL-35 shares the structural characteristics with the receptors for both IL-12 and IL-23. Initially, IL-35 was reported to be produced primarily by Treg, essential for their maximal inhibitory activity [8].

Subsequent studies expanded the known sources of IL-35 to include regulatory B cells (Breg) as well as macrophages and DCs [43,44]. IL-35, like other family members, primarily activates the JAK/STAT signaling pathway upon binding to its receptor in T cells. However, IL-35 secreted by T cells can consist of an IL-12Rβ2 homodimer, a gp130 homodimer, or an IL-12Rβ2/gp130 heterodimer. Previous studies have shown that IL-12R β 2 mainly induces STAT4 phosphorylation, while gp130 mainly induces STAT1 phosphorylation. In B cells, IL-35 signaling through the IL-12Rβ2 heterodimer activates STAT1 and STAT3 [45]. The receptor variants of IL-35 have different effects on T cells and B cells. T cells expressing a single receptor chain exhibit partial resistance to inhibition of iTr35 cells, indicating that signal transduction can occur when only one receptor chain is expressed. When the receptor is expressed as a heterodimer, downstream induction of STAT 1-STAT 4 heterodimer formation promotes different modes of binding to the IL-12 α and Ebi 3 promoters and activation of these genes, inducing iTr35 cells [46]. In addition, B cells secreting IL-35, i35-Breg, inducing infectious tolerance that and reprogram conventional B and T lymphocytes into IL-10 and/or IL-35-producing cells [47]. One of the key immunosuppressive effects of IL-35 is its ability to block the proliferation of Th1 and Th17 cells by keeping early T cells in the G1 phase of cytokinesis [48]. Furthermore, IL-35 enhances the differentiation and function of Treg cells, which are critical in suppressing inflammatory responses and maintaining immune tolerance. This cytokine promotes the production of IL-10, IL-35, and TGF-β in Treg cells. Notably, IL-35 has been shown to convert human and mice naïve T cells into inducible Treg cells (iTr35) that are functionally stable, do not express Foxp3, but secrete IL-35 [49]. Additionally, IL-35 inhibits the development of Th2 cells by suppressing the expression of GATA3 and IL-4 and can mediate the conversion of Th2 cells into Treg cells, although this process can be blocked by IFN-γ [1]. The phenotype of LOF mutation contains reduced Treg-mediated suppression, leading to heightened inflammatory and autoimmune, and increased severity of autoimmune diseases. The phenotype of GOF mutation contains overactive immunosuppression, which could impair anti-infectious or anti-tumor immunity responses. In the context of autoimmune diseases, IL-35 has been identified as a potent immunosuppressive factor that can attenuate several disease symptoms and pathological changes. Due to its significant role in regulating immune responses and maintaining tolerance, IL-35 is considered a promising therapeutic target for treating autoimmune diseases.

### 2.5. IL-39

In 2016, researchers identified a new cytokine in mice, IL-39, formed by the heterodimerization of IL-23 p19 and EBI3. Primarily secreted by activated B cells, murine IL-39 has been shown to activate neutrophils and mediate inflammation in models of lupus-like disease [9,50]. It was suggested that IL-39 signals through the IL-23R and gp130 on target cells, activating downstream STAT1 and STAT3 signaling pathways [51]. Wang et al. conducted studies demonstrating that GL7+ B cells, when injected into lupus-like mice, induced increased levels of proteinuria, enlarged spleens, and heightened spleen weight. Conversely, mice receiving GL7+ B cells deficient in either p19 or EBI3 showed significant reductions in these symptoms, pointing to their potential role in the pathogenesis of systemic lupus erythematosus (SLE) and highlighting them as possible targets for therapeutic intervention [50]. Further research also revealed that interferon regulatory factor 6 (IRF6) regulates certain responses of toll-like receptor 3 (TLR3) in human keratinocytes, including the production of novel IL-12 family heterodimers like p19/EBI3 [52]. This suggests a regulatory axis involving TLR3, IRF6, and p39 that may influence keratinocyte and immune cell functions, particularly in the context of skin cell injury and wound healing. Despite these advancements, the study of IL-39 is still relatively nascent. The full scope of its physiological roles remains underexplored, and many questions about its specific mechanisms of action in autoimmune diseases are unresolved, making further research necessary

(Table 1).

## 3. Interaction between IL-12 family cytokine members

The IL-12 family of cytokines is distinguished by a common feature of subunit sharing, which facilitates significant crosstalk between its members. The α subunits of these cytokines share structural similarities with the IL-6 family cytokines such as IL-6, IL-11, LIF, OSM, and CNTF, all of which are characterized by a four-helix bundle long-chain cytokine structure. The β subunits, specifically p40 and EBI3, are homologous to the non-signaling receptors of the IL-6 family, including IL-6R, IL-11R, and CNTFR [53]. These β-subunits or receptors are composed of two tandem fibronectin type III structural domains, which form a characteristic cytokine receptor homology region (CHR). Additionally, they feature an N-terminal immunoglobulin (Ig) domain, a structural motif that is absent in EBI3 [54,55].

### 3.1. Subunits exist as monomers and perform physiological functions

Some members of the IL-12 family exhibit functional autonomy as monomers, contributing uniquely to cytokine signaling. Notably, subunit p40 of IL-12 and IL-23 can be released as both a monomer and a homodimer [56], binding receptor IL-12Rβ1, serving to enhance immune, but antagonize IL-12 and IL-23 signaling [57]. Similarly, mice IL-27 p28 can be secreted independently of EBI3 and acts to counteract cytokine signaling through the gp130 receptor and IL-6-mediated production of IL-17 and IL-10. Studies suggest that IL-27 p28 can independently block IL-27 activity both in vitro and in vivo [58]. Additionally, it has been reported that the interaction of p28 with the gp130/Wsx-1 heterodimer or gp130 homodimer is regulated by a novel molecular switch, which is induced by EBI3 or IL-6R [59]. The subunits of IL-35, namely p35 and EBI3, are also capable of being secreted as monomers, which then inhibit the secretion of pro-inflammatory cytokines and foster the development of regulatory T-cells [60]. Both p35 monomers and homodimers have demonstrated inhibitory effects on naïve CD4+ T cells and CD19+ B cells, with p35 monomers specifically blocking downstream STAT activation mediated by IL-6 and IL-12 [61]. EBI3 as a monomer has been shown to time-dependent induce STAT3 activation in both CD4+ T cells and B cells [62], enhancing IL-6 function through STAT3 signal [63]. In cancer research contexts, EBI3 has been noted to regulate tumor growth and anti-tumor CTLs responses through bidirectional modulation of the STAT3 signaling pathway [64]. Structural studies have further indicated a stabilizing charge effect from the pairing of subunits in IL-12 family members [65–67], and the α- and β-chains of the IL-12 family can pair with other relatives from the IL-6 superfamily. A novel inhibitory cytokine, identified as IL-Y, is composed of the p28/p40 heterodimer [68]. Moreover, the p40-EBI3 heterodimer has been confirmed to exist and is recognized as a novel anti-inflammatory cytokine, though the specifics of a stabilizing interaction for its heterodimer binding remain to be established [69]. In summary, these findings imply that the monomeric or homodimeric forms of IL-12 family subunits may significantly influence the function of IL-12 family cytokines and potentially broader immune effects, but these findings need to be confirmed by further studies.

### 3.2. Subunit sharing exists between receptors

Subunit sharing is not only characteristic of the cytokines within the IL-12 family but extends to their corresponding receptors, which utilize shared receptor chains. Specifically, IL-12Rβ1 is a common component of both the IL-12 and IL-23 receptors, IL-12Rβ2 is shared between the IL-12 and IL-35 receptors, and gp130 is a component of the receptors for IL-27 and IL-35 [55,70]. P28 has been shown to be able to bind gp130 as a monomer, and IL-12 p40 monomer ameliorates symptoms in EAE mice by binding IL-12Rβ1, but not IL-12Rβ2, suggesting that the subunits compete for binding to the corresponding receptor as a monomer [71]. It

is illustrated that when subunits bind to each other and form hetero-dimeric forms, there may also be competition for binding receptor sites, which can mutually affect the exertion of their anti-inflammatory or pro-inflammatory effects.

### 3.3. Similarities and differences in the physiological functions of IL-12 family members

The IL-12 family of cytokines demonstrates significant functional diversity through the binding of distinct subunits and recruitment of specific receptors, despite some level of subunit sharing among them. The variability in the physiological functions of these cytokines is influenced by several factors. Firstly, the structural stability and secretion capacity of these cytokines differ due to their distinct modes of linkage. IL-12 and IL-23, which are linked by disulfide bonds, can be efficiently secreted. In contrast, IL-27 and IL-35 lack such bonds, resulting in poorer subunit pairing and consequently lower secretion levels [72,73]. This difference in structural stability may also lead to competitive interactions within the family, where the more stable IL-12 and IL-23 could potentially antagonize the binding and the secretion of the less stable IL-27 and IL-35 [1]. More importantly, different signaling pathways are activated downstream of each family member, leading to their different regulatory effects for the corresponding cellular subsets. In addition, IL-12 family cytokines are regulated by local microenvironmental influences, post-translational modifications and gene expression.

On the other hand, T-cell exhaustion, a concern in the treatment of autoimmune diseases and oncology, is also thought to be regulated by IL-12 family cytokines. In autoimmune diseases, T-cell exhaustion has been analyzed to be associated with better clinical outcomes. In the tumor microenvironment, exhausted tumor-infiltrating lymphocytes (TILs) failed to control tumor progression, which was associated with tumor immune escape. Immune checkpoint therapy targeting exhaustion-associated T-cell inhibitory receptors restores effective anti-tumor T-cell responses. In chronic infections, the memory response of CD8$^+$ T cells is dependent on the co-stimulation of CD4$^+$ T cells, which allows chronic infections to subside, but exhaustion of CD8$^+$ T cells occurs when antigen persists in the absence of co-stimulation [74]. The effect of IL-12 on T cell exhaustion is currently viewed differently. It has

been suggested that engineered IL-7 synergizes with IL-12 immunotherapy in the treatment of tumors by resisting T-cell depletion [75], and in vitro IL-12 together with IL-2 induces the generation of strong effector CD8$^+$ T-cells resistant to depletion, which may be related to the fact that IL-12 upregulates the expression of T-bet to inhibit the transcription and translation of PD-1 [76]. Moreover, IL-12-pretreated CD8$^+$ T cells adoptive cell therapy for tumor treatment are expected to enhance the activation and function of CD8$^+$ T cells in vivo [77]. In contrast, it has been shown that IL-12 induces the expression of TIM-3 on CD4$^+$ T cells from patients with follicular B cell non-Hodgkin lymphoma in vitro, causing dysfunction and leading to CD4$^+$ T-cell exhaustion [78]. Study has also targeted CD8$^+$ tumor-infiltrating lymphocytes (TILs), suggesting that their exhaustion state is differentially promoted by IL-12 and IL-27 [79]. Blocking IL-27 signaling reduces the number of exhausted T cells in the tumor and slows down tumor growth [80]. IL-35 secreted by Tregs is thought to limit effective anti-tumor immunity, which is associated with the promotion of BLIMP 1-dependent exhaustion of TILs [81, 82].

In conclusion, while IL-12 family cytokines share subunits, the significant differences in their subunit combinations, receptor bindings, and downstream signaling pathways lead to distinct physiological functions. This diversity and complexity enable the cytokines of the IL-12 family to create a regulatory network, fine-tuning immune responses through intricate interplays that control their secretion and function. Particularly noteworthy is their role in the immune homeostasis of T cells, where IL-12 family members regulate various T cell subsets through their nuanced interactions and functions (Fig. 2).

## 4. Role of IL-12 family members in autoimmune diseases

### 4.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex inflammatory autoimmune disease characterized by multiple organ and system damage during recurrence and remission periods. One of the central pathological features is the dysregulation of the immune system. The immune response characteristics of SLE are the autoantibodies production and complement activation, which leads to the formation and deposition of immune complexes, causing tissue damage and affecting
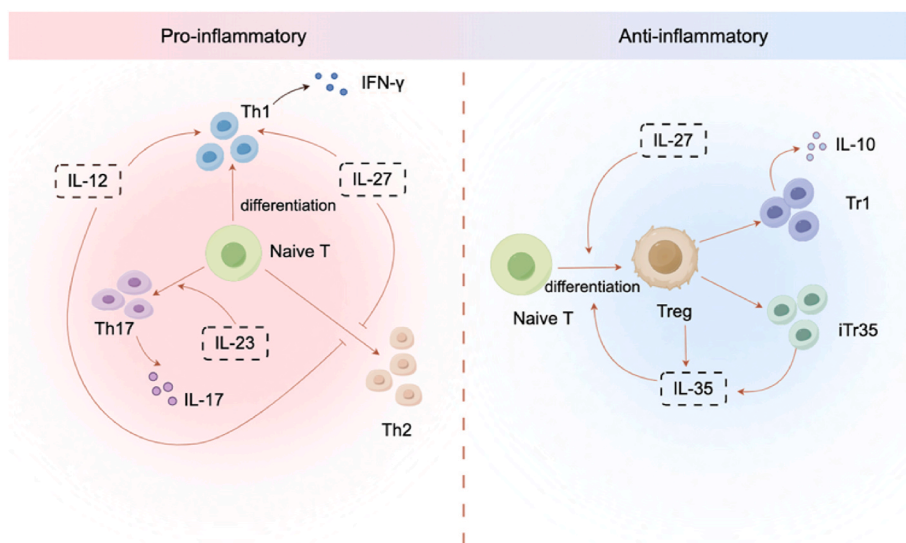


**Fig. 2. The regulatory effect of IL-12 family cytokines on T cell subsets.** IL-12 and IL-27 stimulate the differentiation of naïve T cells into Th1 cells, acting on the main transcription factor T-bet of Th1 and promoting the secretion of pro-inflammatory cytokine IFN - γ. IL-23 maintains the Th17 cell phenotype and promotes the secretion of pro-inflammatory cytokine IL-17. IL-12 and IL-27 inhibit the polarization of naïve T cells towards Th2 and Th17. IL-27 induces Treg differentiation into Tr1, thereby promoting the secretion of IL-10. IL-35 inhibit Th17 differentiation, and stimulate the differentiation of iTr35 cells, which in turn further promotes the secretion of IL-35 and IL-10. Abbreviation: iTr35, IL-35 dependent induction of regulatory T cells; Tr1, type 1 regulatory T cells.

multiple organs. The differentiation and development of CD4$^+$ T cell subsets and the secretion of corresponding cytokines are dysregulated to varying degrees, which plays a key role in the pathological process [83]. Research indicates that PBMCs from SLE patients show significantly elevated levels of T-bet, a transcription factor specific to Th1 cells. This elevation is associated with higher serum levels of IFN-γ and IL-18, as well as increased disease activity [84]. In CD4$^+$ T cells, the absence of T-bet reduces IFN-γ expression, thereby inhibiting Th1 cell differentiation while enhancing Th2 cell activity [85]. Moreover, elevated T-bet expression in T cells from a mice model of lupus nephritis correlates with increased proteinuria and glomerular inflammation, suggesting that

heightened T-bet expression may exacerbate the progression of lupus [86]. On the other hand, under the stimulation of IL-12, Treg is induced to express T-bet, named Th1-like Treg. Research has shown that it exhibits defects in immunosuppressive function and has been found to be significantly upregulated in many autoimmune diseases [87], which may be one of the mechanisms underlying the dysregulation of T cell subsets in SLE. Further studies have also revealed that T-bet may suppress Th17 cell differentiation and the production of related transcription factors and cytokines [88,89]. Clinically, patients with a higher proportion of T-bet$^+$ B cells have been found to exhibit significantly higher SLE Disease Activity Index (SLEDAI) scores. These patients also
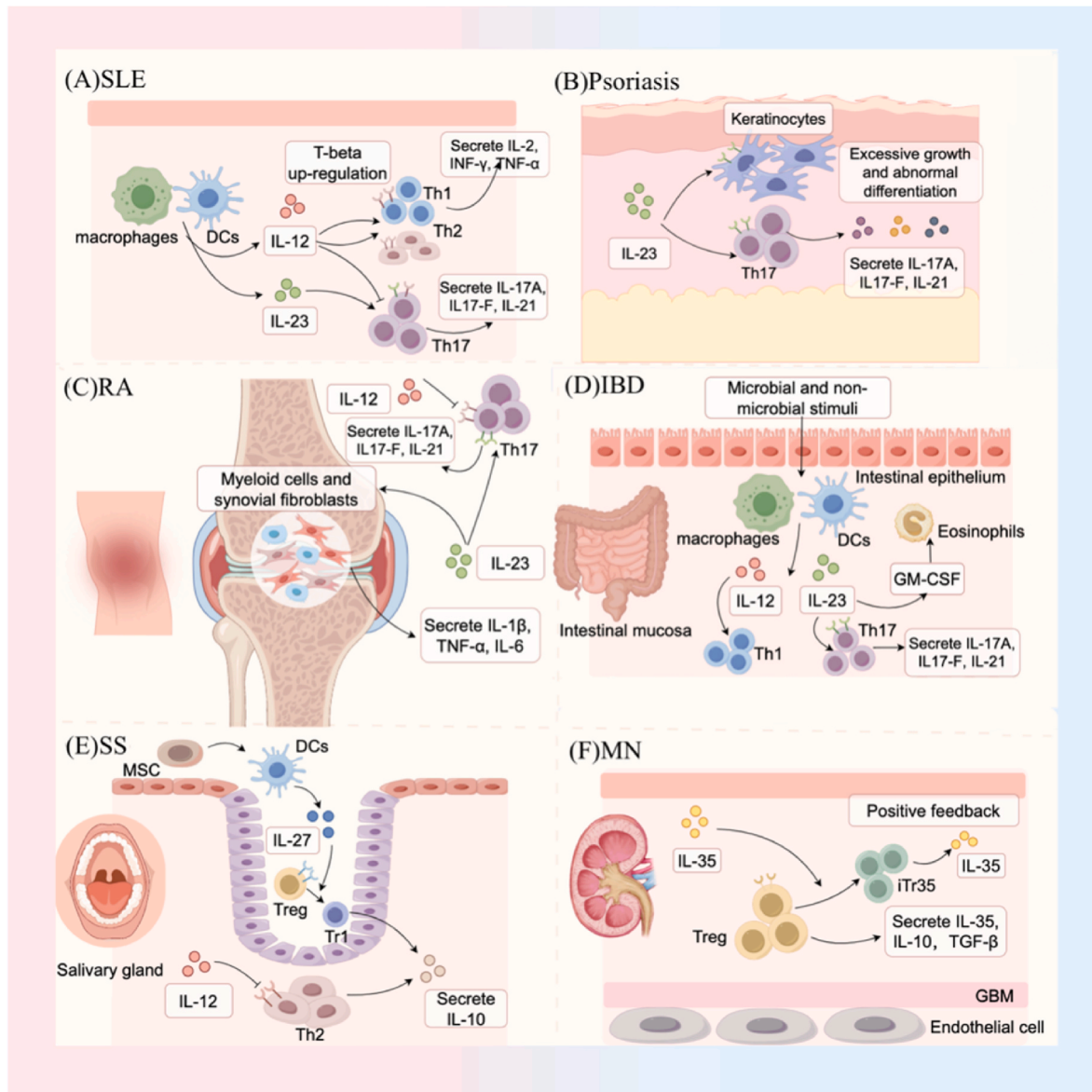


**Fig. 3. Possible intervenable mechanisms of IL-12 family members in autoimmune diseases.** (A) SLE: Macrophages and dendritic cells secrete IL-12 and IL-23. IL-12 upregulates T-bet expression, promotes Th1 cell response, while IL-23 promotes Th17 cell response and secretes IL-17A, IL17-F, IL-21. (B) Psoriasis:In the local area of the skin lesion, IL-23 maintains Th17 cells function, secreting pro-inflammatory cytokines. Additionally, IL-23 promotes excessive growth and abnormal differentiation of keratinocytes. (C)RA: In the serum and synovial fluid, IL-12 possibly inhibiting Th17 cell responses. IL-23 not only enhances the survival of Th17 cells, but activates myeloid cells and synovial fibroblasts, promoting the secretion of IL-1β, TNF-α, IL-6. (D) IBD: Stimulated by microbial and non-microbial, macrophages and DCs secrete IL-23 and IL-12. IL-12 promotes Th1 cells response. IL-23 enhances the survival of Th17 cells, releasing the IL-17, IFN-γ, IL-22 and granulocyte-macrophage colony stimulating factor (GM-CSF) cytokines, the last of these promoting accumulation of granulocyte-monocyte progenitor cells (GMPs) and activated eosinophils in the intestine. (E) SS: In salivary glands, IL-12 inhibits Th2 cell responses and secretion of IL-10. Mesenchymal stem cell (MSC) transplantation promotes the production of IL-27 by DCs, induces differentiation of Tregs into Tr1 cells, and promotes the secretion of IL-10. (F) MN: IL-35 promotes Treg function, secreting anti-inflammatory cytokines, and improves the inflammatory microenvironment. In addition, IL-35 induces Tregs to differentiate into iTr35 cells, secreting IL-35, and form positive feedback.

show increased levels of antinuclear antibody (ANA) and anti-dsDNA antibodies, alongside a shorter disease duration [90].

All these evidences suggest that the regulation of T-bet for Th cells exerts a greater influence in SLE disease onset and progression, in which the IL-12 family of cytokines exerts a regulatory role. The following evidence underscores the varied roles of specific cytokines within this family: a. IL-12 may promote Th1 cell response to exacerbate the development of SLE disease by upregulating T-bet expression (Fig. 3A). Moreover, studies have shown that IL-12 can induce differentiation of nTregs into Th1-like Tregs. Serum IL-12 levels are significantly higher in SLE patients compared to healthy controls (Hc), with even higher levels observed in patients with active SLE [91]. In studies focusing on Th1 cells, an increase in Th1 cells, along with elevated levels of dsDNA antibodies, was noted in treated lupus nephritis (LN) patients. These Th1 cells predominantly expressed the IL-12 receptor (IL-12R$^+$), which demonstrated the prominence of IL-12R$^+$ T cells in the immune response of such patients [92]. Moreover, experimental using MRL/lpr mice model demonstrated that IL-12 injections accelerated lupus nephritis pathology, while administration of anti-IL-12 antibodies inhibited the disease's development [91]. b. The IL-23/Th-17 axis has a potential role in promoting the onset of SLE and LN(31). Previous studies have reported that circulating IL-23, IL-17 serum levels and renal tissue expression in LN patients are higher than those in the control group, and positively correlated with disease activity scores [32]. In addition, high IL-23 serum levels were shown to correlate with other manifestations of SLE in humans, including skin involvement and plasma membrane inflammation [93]. In addition, high IL-23 and IL-17 receptors are expressed in Lupus-susceptible mice [93,94]. c. The role of IL-27 in SLE remains ambiguous. Different studies report varying findings: a Polish study found no association between serum IL-27 levels and SLE Disease Activity Index (SLEDAI), nor with markers such as anti-dsDNA, C3, and C4[95]. Contrastingly, a Chinese study reported reduced IL-27 levels in SLE patients, particularly lower in those with lupus nephritis compared to non-LN patients [96]. However, another study showed significantly higher serum and urinary IL-27 and IL-23 levels in SLE patients with and without LN compared to HCs, with urinary levels correlating with renal SLE Disease Activity Index scores and proteinuria. Urinary IL-27 expression was significantly higher in patients with SLE combined with LN after 6 months of immunosuppressive therapy [97]. These findings suggest that IL-27 may have a dual regulatory role, modulating autoimmunity and tissue inflammation. d. The IL-35 levels differ markedly in SLE patients. Research indicates that patients experiencing persistent SLE flares have lower IL-35 concentrations in their blood compared to HCs and patients with latent SLE[98], [99]. Treatment with glucocorticoids alone has been shown to elevate serum IL-35 levels. Furthermore, studies in MRL/lpr mice, a model for lupus, revealed that deficiency in EBI3, a subunit of IL-35, leads to autoimmune glomerulonephritis [100].

### 4.2. Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune disorder characterized by the presence of autoantibodies and progressive fibrosis affecting the skin, viscera, and small vessels [101]. Recent studies have highlighted an imbalance in the immune system, particularly an increased Th17/Treg ratio and elevated serum levels of IL-17A, which are thought to play crucial roles in the pathogenesis of SSc [102], Moreover, proliferation of fibroblasts and collagen synthesis are important causes of pathological changes.

a. Currently, IL-12 levels are considered serve as serological markers for disease activity and prognosis. Early research has identified significantly higher serum IL-12 levels in patients with systemic sclerosis (SSc) compared to HCs [103]. However, findings from another study suggest a dynamic association where IL-12 levels initially lower than HCs increased with the improvement of dermatofibrosis, reflecting a shift from a Th2 to a Th1 response [104]. Further studies highlighting the

correlation between IL-12 receptor and downstream TYK2, STAT4 genes, implicating IL-12 in SSc pathogenesis [105]. b. The IL-23/Th17 axis is crucial in regulating the Th17/Treg balance and has been implicated in the progression of SSc. Elevated serum levels of IL-23 in SSc patients correlate with disease duration and the presence of pulmonary fibrosis [106]. Although some studies found no correlation between IL-23R gene variants and SSc [107], recent research focuses on IL-17's role, linking increased peripheral blood Th17 cells and IL-17 levels with disease severity and collagen overproduction [108]. c. Serum IL-27 levels are significantly elevated in SSc patients compared to controls and are positively associated with the extent of skin and lung fibrosis and immune dysregulation. Further comparison shows that compared with the group with higher IL-27 levels, the normal level group has a longer disease course, milder clinical manifestations, and lower levels of pulmonary fibrosis [109]. IL-27 stimulation in SSc patients leads to increased IgG production by B cells, enhanced IL-17 production by CD4$^+$ T cells, and stimulated fibroblast proliferation and collagen synthesis. In fibroblasts, IL-17 stimulation can upregulate the expression of IL-27R α, revealing that IL-27 may interact with IL-17 and then upregulate the production of inflammatory components [110]. Post-hematopoietic stem cell transplantation (HSCT), IL-27 levels rise, prompting investigations into its potential as a biomarker to predict HSCT outcomes [111]. The above shows that the impact of IL-27 on diseases is complex, and further research is needed to determine whether it can be used as an intervention target. d. IL-35 is not only a biomarker, but also a potential target for improving fibrosis. Serum IL-35 levels are higher in SSc patients than in HCs, and these levels decrease with the progression of the disease, inversely correlating with disease duration [112,113]. IL-35 also enhances in a TGF-β-dependent manner in SSc skin and dermal fibroblasts. In vitro studies show that IL-35 can induce the differentiation of resting fibroblasts into myofibroblasts, leading to increased collagen release [112]. The significant variation in IL-35 levels before and after treatment suggests its potential as a therapeutic target, although the specific mechanisms require further elucidation.

### 4.3. Psoriasis

Psoriasis is a chronic, immune-mediated skin disease, with plaque psoriasis being its most prevalent form. Research indicates that a hyperactive adaptive immune system plays a central role in the pathogenesis of psoriasis [114]. Initially, the disease process is triggered by the release of antimicrobial peptides (AMPs) from keratinized cells were damaged, and then acted on myeloid dendritic cells. Once activated, these dendritic cells enhance the maturation and differentiation of Th1 and Th17 cells. Th1 cells contribute to the disease mechanism by producing IFN-γ and TNF-α, while Th17 cells secrete IL-17, IL-22, and TNF-α. Furthermore, activated myeloid dendritic cells migrate to the lymph nodes, where they directly release various inflammatory cytokines such as TNF-α, IL-12, and IL-23. These cytokines are crucial in exacerbating psoriasis as they stimulate keratinocyte proliferation. This cascade of events leads to increased cell proliferation, enhanced expression of angiogenic mediators and endothelial adhesion molecules, and the subsequent infiltration of immune cells into the affected skin areas [115].

a. The difference of IL-12 expression in psoriasis is not significant. While cell isolation experiments from psoriatic tissues have shown upregulation in the mRNA expression of p40 and p19, there is no significant increase in the IL-12 p35 subunit [116]. Serum levels of IL-12/23 p40 are significantly higher in psoriasis patients compared to controls and correlate with Psoriasis Area and Severity Index (PASI) [117]. However, contrasting results from Aikaterini et al. indicate that while TNF-α levels are elevated in psoriasis patients, levels of IL-12/23 p40 and IL-17 do not differ significantly from healthy controls and do not correlate with PASI [118]. These findings suggest that serum IL-12 levels may not accurately reflect localized disease activity. The

efficacy of targeted anti-IL-12/23 p40 and anti-IL-23 p19 monoclonal antibodies in treatment suggests their action might be more pronounced locally within skin lesions, pointing towards IL-23, rather than IL-12, as the principal regulator of pathogenic Th17 cells in psoriatic lesions. b. IL-23 plays a key role in maintaining Th17 cell secretion of IL-17 in the progression of psoriasis (Fig. 3B). The activation of the Th17 pathway by IL-23 is a critical source of IL-17 in psoriasis patients. Additionally, IL-23 promotes excessive growth and abnormal differentiation of keratinocytes [119]. In psoriatic arthritis (PsA), IL-23 promotes the production of IL-17, IL-22, and TNF-α, leading to osteomalacia, bone erosion, and inflammation. This mechanism has been corroborated in animal models [120]. c. In patients with psoriasis, there are completely opposite research results regarding IL-27. In addition, serum IL-27 levels are significantly elevated compared to controls and correlate with both disease severity and serum IFN-γ levels. In vitro studies have demonstrated that IL-27 induces the production of Th1-type chemokines through STAT1 activation [121]. Experimental interventions using subcutaneous IL-27 injections in the imiquimod (IMQ) mice model of psoriasis resulted in exacerbated psoriasis-like skin inflammation and an upregulation of mRNA levels for Th1 cytokines/chemokines and TNF-α, with no significant changes in Th17 cytokine/chemokine levels [122]. In contrast, a study from China reported significantly lower IL-27 and IL-27Ra expression in the skin lesions of patients with moderate-to-severe psoriasis, alongside reduced serum IL-27 levels. Treatment with recombinant IL-27 protein lessened the severity of IMQ-induced psoriasis-like lesions and decreased serum IL-17A levels; in vitro, IL-27 also significantly inhibited IL-17 secretion from CD4$^+$ T lymphocytes [123]. Increasing evidence now supports the anti-inflammatory effects of IL-27 in psoriasis, primarily through inhibiting Th17 cell differentiation [34,124].

### 4.4. Rheumatoid arthritis

Rheumatoid arthritis (RA) is characterized by chronic inflammation that primarily affects the joints, though patients often exhibit extra-articular manifestations as well. The inflammatory environment within the RA synovium is sustained by key cytokines such as TNF and IL-6. These cytokines, along with various chemokines, activate endothelial cells and attract immune cells, exacerbating the inflammatory response [125]. In RA pathogenesis, heterogeneous autoantibodies found in patients' serum led to significant complement activation. The pathomechanism involves complex immunoregulatory abnormalities, including dysregulated secretion of the IL-12 family of cytokines, suggesting their potential impact on both the progression and treatment of RA [126].

a. Elevated levels of IL-12 were observed in both the serum and synovial fluid of RA patients, correlating strongly with the decrease of disease activity scores, which is possibly by inhibiting Th17 cell responses [127] (Fig. 3C). The ratio of Th17/Th1 cell is significantly higher in both the local and peripheral blood of RA patients, indicating a more prominent role for Th17 cells and IL-17 in disease development compared to Th1 [128]. Early studies using a collagen-induced arthritis (CIA) mice model showed that co-administration of type II collagen and IL-12 prevented CIA [129]. Conversely, knockdown of IFN-γ or its receptor increased Th17 cells activation and IL-17 secretion, while reducing Th1 cell numbers, exacerbating CIA [130]. b. IL-23 supports Th17 cells survival in RA and stimulates myeloid cells and RA synovial fibroblasts to produce IL-1β, TNF, and IL-6, mediating chronic inflammation (Fig. 3C). Mice lacking IL-23 are highly resistant to CIA, underscoring its direct role in disease progression [131]. c. Serum IL-27 levels can serve as a biomarker. It is significantly elevated in RA serum and positively correlates with the disease activity score 28 (DAS-28), reducing somewhat post-treatment, which suggests reflect to inflammatory states [132,133]. Locally, IL-27 levels are higher in RA synovium and synovial fluid compared to healthy tissues [134,135]. In vivo, IL-27 treatment induced remission in Th17-dominant CIA mice but

exacerbated symptoms in Th1-dominant proteoglycan-induced arthritis (PGIA) mice [136,137]. These contrasting outcomes IL-27 is not only a biomarker but a factor involved in disease progression, except that its mechanism of action is multifaceted, with unresolved questions regarding the therapeutic potential of targeting this pathway. d. The anti-inflammatory effect of IL-35 seems to be more significant locally. Some studies report elevated serum levels of IL-35 in RA patients [138], while others find them significantly lower compared to HCs [139]. Furthermore, serum IL-35 levels were higher at the onset of treatment and decreased post-treatment [140], making it difficult to use peripheral blood IL-35 levels to assess disease activity. Locally, IL-35 appears to play a clearer role; it reduces antigen-specific inflammation and impairs disease progression in CIA mice by upregulating IL-35 secretion [141]. In vitro, IL-35 doses-dependently inhibits proliferation and promotes apoptosis in fibroblast-like synoviocytes derived from CIA mice, suggesting a local anti-inflammatory effect in the synovium [142].

### 4.5. Inflammatory bowel disease

Inflammatory bowel disease (IBD) encompasses complex gastrointestinal disorders such as ulcerative colitis (UC) and Crohn's disease (CD), both characterized by similar pathogenetic mechanisms. These diseases arise from inappropriate immune responses in genetically predisposed individuals to environmental triggers, including interactions with the intestinal microbiota [143]. This response is compounded by the infiltration of inflammatory cells into the gut mucosa, impaired autophagy, and a breakdown in barrier function. Managing these conditions often requires long-term pharmacological therapy aimed at modulating the dysregulated immune system. In the current understanding of IBD, CD is predominantly associated with a Th1 immune response, which involves the production of pro-inflammatory cytokines like IFN-γ and TNF-α. On the other hand, UC is thought to be mediated by a Th2 pathway, characterized by the production of cytokines such as IL-4 and IL-13, which influence tissue repair and fibrosis [144,145].

a. Clinical therapies targeting IL-12 and IL-23 have been approved and are now widely used for treating inflammatory bowel disease (IBD), underscoring the significant roles these cytokines play in IBD pathogenesis [146]. Research indicates that both the IL-12/IL-23 p40 promoter activity and IL-23 p19 protein are constitutively present in the terminal ileum of healthy mice, highlighting the small intestine as a critical site for these cytokines under normal conditions [147]. In the non-inflamed mucosa, IL-23 is notably expressed in the terminal ileum. In lamina propria CD11c$^+$ DCs, where it shows constitutive expression of the shared p40 subunit, influenced by gut microflora [147]. Besides, in UC and CD, IL-23 p19 expression is elevated, primarily in macrophages and DCs, which promote IL-23 production in response to microbial and non-microbial stimuli [148,149]. IL-23 enhances the survival of Th17 cells releasing the IL-17, IFN-γ, IL-22 and granulocyte-macrophage colony stimulating factor (GM-CSF) cytokines, the last of these promoting accumulation of granulocyte-monocyte progenitor cells (GMPs) and activated eosinophils in the intestine (Fig. 3D). In CD, higher IL-23 p19 mRNA levels correlate with the severity of visible endoscopic lesions [150]. Experimental models further support IL-23's predominant role in chronic inflammation over IL-12, as IL-23p19-and IL-12p40-deficient mice are protected from autoimmune conditions like encephalomyelitis and colitis, whereas IL-12 p35-deficient mice are not [151, 152]. Genome-wide association studies (GWAS) have identified variants in the IL-23R gene that alter susceptibility to CD and UC, reinforcing the critical roles of IL-23 and IL-17 in IBD pathogenesis [153]. IL-23 also supports gut barrier function. Activated by IL-23, Th17 cells in the small intestine secreted IL-17, directly affects intestinal epithelial cells by regulating tight junction proteins and molecules essential for maintaining barrier integrity [154]. Conversely, mice with the IL-17R adaptor protein ACT1 deleted show compromised intestinal protective effects of IL-17A [155]. b. IL-27 exhibits dual regulatory effects in IBD due to its combined pro-inflammatory and anti-inflammatory

properties. Studies have shown that IL-27 can both ameliorate colitis in mice, with reductions in disease activity, histopathology scores, and pro-inflammatory gene expression, or increased severity of colitis through antibody-mediated neutralization or genetic knockout in IL-27-deficient mice [156,157]. Besides modulating immune responses, IL-27 also influences intestinal flora and promotes epithelial barrier integrity, suggesting multiple protective roles in the gut [158]. However, some reports highlight the harmful effects of IL-27 in intestinal inflammation, where blocking IL-27 signaling has improved outcomes [159]. Most of the literature supports IL-27 as an inhibitor of intestinal inflammation induced by a variety of injuries, but IL-27 signaling may trigger different responses based on cell type and timing during disease development.

### 4.6. Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by lymphocyte infiltration into exocrine glands, particularly the salivary and lacrimal glands. Approximately 25 % of SS patients develop ectopic germinal centers, which facilitate the local proliferation of antigen-specific B cells. The interaction between CD4$^+$ T cells and B cells appears to be a crucial factor in driving disease progression [160]. Research has found that Th1 and Th2 cytokines coexist in SS and are in a dynamic state of change. In the early stages of the disease, type 2 response may be predominant, while in high infiltration, the response tends to tilt towards Th1 cells. This indicates that as the disease progresses, type 1 response may become more pronounced [161]. In addition, the development of SS involves other T cell subsets, including follicular T helper cells (Tfh), Th17 cells, and Tregs.

a. IL-12 is considered to exacerbate SS by affecting the balance of Th1/Th2 cells (Fig. 3E). Earlier studies have indicated that IL-12p40 exhibits high expression levels in autoimmune salivary gland inflammation in MRL/lpr mice [162]. This indicates that IL-12p40 promotes the secretion of IFN-γ locally by activating Th1 response, suggesting that IL-12 or IL-23 may be related to the development of SS. In serum from SS patients, IL-12 levels were significantly higher than in HCs and correlated with disease activity [163]. A number of conditions associated with SS are exhibited by IL-12-transgenic mice, which suggests a correlation with SS pathogenesis [164]. Elevated levels of IL-12 were also observed in the plasma of SS-like non-obese diabetic (NOD) model mice. Anti-IL-12 treatment reduced the proportion of myeloid-derived suppressor cells (MDSCs) in the bone marrow and spleen, improving symptoms in these mice. MDSCs are believed to exacerbate SS by inhibiting Th2 cells, although the exact mechanism requires further investigation [165]. b. IL-23 has not been considered a good intervention target. Recent studies have found increased expression of IL-23 and IL-22 in the inflamed salivary glands of SS patients, with the presence of IL-17 protein and mRNA in minor salivary glands (MSGs) [166]. The infiltration of Th17 cells in SS is thought to be crucial for B-cell activation and the formation of germinal centers in the glands, suggesting the importance of the IL-23/IL-17 pathway in disease progression [167]. In a spontaneous SS model mice, genetic ablation of IL-17 reduced lymphocyte infiltration and restored glandular function [168]. However, clinical treatment with rituximab showed a significant reduction in IL-17 expression in the salivary glands of SS patients, with no significant difference in IL-23 levels [169]. Furthermore, inhibition of IL-23 using the p40 monoclonal antibody ustekinumab did not significantly improve symptoms [170]. At present, it is believed that the pathogenesis of SS is a complex process involving multiple factors and stages. This process not only involves the imbalance of T cell subsets and related cytokines, but also the infiltration of B and T cells in the glandular area, forming lymphoid follicles and germinal centers, and secreting antibodies. The infiltration of lymphocytes also leads to the destruction of parenchymal structures, ultimately affecting the function of glands. Thus, the therapeutic potential of targeting the IL-12p40 or IL-23/Th17 pathway in SS requires further study. c. Targeting IL-27 may be a new direction for SS

therapy. IL-27 has an inhibitory role in autoimmune diseases by stimulating IL-10 producing Type 1 regulatory T cells (Tr1) [171]. A study detected significantly reduced serum IL-27 levels in SS patients. IL-27$^{-/-}$ NOD mice exhibited more severe SS-like symptoms and fewer splenic CD4$^+$IL-10$^+$ T cells compared to wild-type NOD mice. Injection of exogenous IL-27 increased splenic CD4$^+$IL-10$^+$ T cells and ameliorated symptoms in mice [172]. Additionally, mesenchymal stem cell (MSC) transplantation, an effective treatment for experimental SS, alleviates symptoms by promoting IL-27 production by dendritic cells [173] (Fig. 3E). d. Further research is needed to determine whether IL-35 can be considered as a biomarker for SS. Peripheral blood levels of IL-35 in SS patients were significantly lower than in HCs. The percentage of CD19$^+$EBI3$^+$ B cells in peripheral blood was significantly higher in SS patients compared to normal controls. Levels of IL-35, EBI3 gene expression, and the percentage of CD4$^+$EBI3$^+$ T cells were negatively correlated with disease activity scores [174]. Elevated serum IL-35 levels have also been reported to positively correlate with disease activity in SS patients [175]. Further research is needed to elucidate the pathogenesis of IL-35 in SS, as current studies are limited.

### 4.7. Autoimmune nephropathy

Autoimmune nephropathies encompass a range of disorders where kidney injury results from autoimmune mechanisms, including the action of autoantibodies targeting intrinsic glomerular antigens, as seen in membranous nephropathies, or the trapping and accumulation of nonspecific antibodies in glomerulus, as observed in IgA nephropathies, C3 glomerulopathies, and ANCA-associated glomerulonephritis [176]. In these conditions, autoantibodies initiate the recruitment and activation of the complement system, leading to inflammation and cellular damage. This complement activation not only produces chemokines attracting neutrophils and macrophages but also forms membrane attack complexes (MACs) that disrupt the glomerular filtration barrier [177]. Further complicating the pathology, autoantibodies in the kidneys attract inflammatory cells expressing Fc receptors, such as NK cells, γδ T cells, activated T cells, neutrophils, and macrophages. These cells release cytokines, creating a local inflammatory milieu that contributes to tissue damage and the progression of nephropathy [178].

A specific example of these processes is seen in Membranous Nephropathy (MN), where there is thickening of the glomerular capillary walls and deposition of immune complexes in the outer basement membrane [179]. The pathogenesis of MN involves circulating autoantibodies binding to antigens on podocytes, forming immune complexes deposited beneath the glomerular epithelium. This leads to podocyte damage and dysfunction, disrupting the filtration barrier and causing significant proteinuria [180,181]. The immune response in MN is characterized by a dominant Th2 cell-mediated response, with heightened activity of B cells and production of IgG. Alongside, there is an up-regulation of Th17 cells and increased levels of IL-17, with a concomitant decrease in Th1 and Treg cell subsets, including a reduction in Foxp3 expression. This shift results in diminished Treg cell activity and their suppressive capacity, suggesting potential therapeutic targets. Studies focusing on the regulation of the Th1/Th2 or the Th17/Treg cell ratio could offer new directions for intervention in treating autoimmune nephropathies [182,183]. IL-27 receptor knockout MRL/lpr mice demonstrated impaired Th1 differentiation and marked Th2 skewing, mirroring the pathological features of human membranous nephropathy, including IgG deposition in the glomeruli and elevated serum levels of IgG1 and IgE [184]. Further research on EBI3, a subunit of IL-27, showed that EBI3$^{-/-}$ MRL/lpr mice had increased IFN-γ and IL-4 expression, alongside elevated IgG1 and IgE serum levels, indicating IL-27 shifted in immune response [100]. IL-35 may serve as a new intervention target for Primary Membranous Nephropathy (PMN) (Fig. 3F). In terms of IL-35 and its relationship with PMN, a study on rituximab treatment for PMN revealed that Treg numbers significantly increased post-B-cell depletion, alongside a notable rise in serum IL-35

levels [185]. Further analysis by our team confirmed an increase in IL-35 levels following remission in PMN patients, establishing baseline IL-35 levels as an independent risk factor for predicting time to remission [186]. Currently, clinical treatments for PMN primarily focus on reducing antibody levels and suppressing immune cell activation, utilizing cytokine levels mainly to assess the status of the immune response. IL-27 and IL-35, as effective regulatory factors of T cell subsets, may become potential intervention targets for MN in the future. By regulating their levels, it affects the balance of T cell homeostasis and cytokine networks, thereby improving the inflammatory environment of the disease. IgA nephropathy (IgAN) is the most prevalent form of glomerulonephritis globally. It is characterized by the presence of circulating and glomerular immune complexes, composed of IgA1 lacking galactose residues from its hinge region O-glycan side chains — commonly termed galactose deficient-IgA1 (Gd-IgA1), specific IgA and IgG antibodies, and C3 [187]. Typical pathological features include mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis [188]. Although early studies did not find significant differences in IL-12 serum levels [189],in vitro culture of peripheral blood mononuclear cells (PBMCs) from IgAN patients showed that both spontaneous and lipopolysaccharide (LPS)-induced IL-12 levels were significantly higher in patients with nephrotic syndrome (NS) compared to those without NS, underscoring the enhanced immune activity in IgAN [190]. Subsequent research involved administering recombinant murine IL-12 intraperitoneally in an established IgA nephropathy (IgAN) mice model, HIGA mice, to assess its effects on serum IgA levels and renal lesions. The results indicated that daily intraperitoneal injections of IL-12 for one week significantly increased crescent formation, glomerular macrophage aggregation, and interstitial cell infiltration, while decreasing serum IgA levels. This suggests that IL-12 can exacerbate the progression of IgAN, and its mechanism may be related to promoting Th1 cell response [191]. While these findings provide insights into the role of IL-12 in autoimmune nephropathies, comprehensive studies on other members of the IL-12 family have not been as thoroughly conducted. It is hypothesized that T cell-regulated immune homeostasis is crucial in autoimmune glomerulonephritis [192]. This observation underscores the complexity of the IL-12 family in immune regulation and highlights the necessity for further in-depth exploration of its roles and mechanisms in such diseases. The research results related to IL-12 family cytokines in autoimmune diseases are in Table 2.

## 5. Progress in the study of drugs related to IL-12 family members

The IL-12 family cytokines play a central role in immune regulation, showing great potential as targets for the treatment of autoimmune diseases. These cytokines regulate the strength and direction of immune responses by activating immune cells such as T cells and NK cells. Modulating the levels and activity of IL-12 family cytokines may help alleviate autoimmune conditions. This can be achieved through injections of monoclonal antibodies, cell therapy, gene therapy, and other methods (Table 3).

### 5.1. Ustekinumab

Ustekinumab, a monoclonal IgG1 κ antibody targeting the p40 subunit shared by IL-12 and IL-23, has emerged as a significant biologic agent in the treatment of inflammatory diseases. Originally utilized for its impact on IL-12 in inflammatory bowel disease (IBD), the identification of IL-23's role, sharing the p40 subunit with IL-12, has shifted the focus towards the importance of IL-23 in these conditions. A phase 3, randomized, double-blind, placebo-controlled trial assessed the safety and efficacy of ustekinumab in treating moderately to severely active ulcerative colitis. The trial involved 8 weeks of induction therapy followed by 44 weeks of maintenance therapy. The outcomes were promising, with a significantly higher percentage of patients receiving intravenous ustekinumab achieving clinical remission at week 8 compared to those on placebo. This trend continued through week 44 of maintenance treatment, where clinical remission rates were significantly higher among ustekinumab-treated patients than those receiving placebo [193]. Beyond IBD, ustekinumab has also made significant strides in dermatology. It was the first biologic approved by the U.S. Food and Drug Administration (FDA) to directly inhibit IL-23 for the treatment of psoriasis. In a phase 3, double-blind, multicenter, placebo-controlled trial for moderate-to-severe psoriasis, patients treated with ustekinumab showed significant regression of skin lesions

**Table 2**
Changes in IL-12 family cytokines in autoimmune diseases.

| | IL-12 | IL-23 | IL-27 | IL-35 |
|---|---|---|---|---|
| **SLE** | Increase in serum; Promote disease by promote Th1 cell response. | Increase in serum; Promote disease progression by IL-23/Th17 axis. | Unclear | Decrease in serum; Up regulation following hormone therapy. |
| **SSc** | Increase in serum; Considered to be a biomarker. | Increase in serum; May have a potential promoting effect on diseases. | Increase in serum; As a biomarker for predicting the success of HSCT. | Increase in serum; As a biomarker and potential target that can improve fibrosis. |
| **Psoriasis** | No significant difference, and not the main regulatory factor. | Promote psoriasis and PsA disease by maintain circulating Th17 cell phenotype; As the main intervention target of therapy. | Unclear | Unclear |
| **RA** | Increase in serum and synovial fluid Promote disease by inhibiting Th17 cell response. | Promote disease by maintain circulating Th17 cell phenotype, and promote inflammation locally. | Increase in serum and synovial fluid; Currently considered to be a biomarker. | Plays anti-inflammatory effects locally in the joints. |
| **IBD** | Unclear | Increase of local expression in the intestine; As the main intervention target of therapy. | Unclear | Unclear |
| **SS** | Increase in serum; Be likely to exacerbate SS by inhibiting Th2 cell responses. | Increased expression in the inflamed salivary glands; Not used as an intervention target. | Decrease in serum; Exert immunosuppressive effects by acting on Tr1 cells. | Unclear |
| **PMN** | Unclear | Unclear | Unclear | Increase in serum; As a independent risk factor; Exerts immunosuppressive effects in diseases through Treg. |
| **IgAN** | Increase in PBMCs; Exacerbating the disease by promoting Th1 response. | Unclear | Unclear | Unclear |

Abbreviation: SLE, systemic lupus erythematosus; SSc, systemic sclerosis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; SS, sjögren's syndrome; PMN, primary membranous nephropathy; IgAN, IgA nephropathy; Tr1, type 1 regulatory T cells; PBMC, peripheral blood mononuclear cell.

**Table 3**

Clinical trials related to IL-12 family cytokines and autoimmune diseases.

| Drug | Conditions | INTERVENTIONS | Main Results | NCT Number | Ref |
|---|---|---|---|---|---|
| Ustekinumab | UC/IBD | Placebo IV/Placebo SC/Ustekinumab IV/ Ustekinumab SC | During 200 weeks of maintenance therapy, 55.2 % of 348 patients receiving ustekinumab achieved symptomatic remission, with a particularly high rate of remission in biologic-primed patients. | NCT02407236 | [193] |
| | Crohn's Disease/IBD/ Colitis/Inflammatory Bowel Disease(UNITI-1) | Placebo/Ustekinumab 130 mg/Ustekinumab approximately 6 mg/kg | The rates of response at week 6 among patients receiving intravenous ustekinumab at a dose of either 130 mg or approximately 6 mg per kilogram were significantly higher than the rates among patients receiving placebo (in UNITI-1, 34.3 %, 33.7 %, and 21.5 %, respectively, with P ≤ 0.003 for both comparisons with placebo). | NCT01369329 | [194] |
| | Crohn's Disease/ Inflammatory Bowel Disease/IBD/Colitis (UNITI-2) | Placebo/Ustekinumab 130 mg/Ustekinumab approximately 6 mg/kg | The rates of response at week 6 among patients receiving intravenous ustekinumab at a dose of either 130 mg or approximately 6 mg per kilogram were significantly higher than the rates among patients receiving placebo(in UNITI-2, 51.7 %, 55.5 %, and 28.7 %, respectively, with P < 0.001 for both doses). | NCT01369342 | [194] |
| | Crohn's Disease/Colitis/ IBD/Inflammatory Bowel Disease | Placebo SC/Placebo IV/Ustekinumab 90 mg SC q8w/Ustekinumab 130 mg IV/Ustekinumab 90 mg SC q12w | In the groups receiving maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53.1 % and 48.8 %, respectively, were in remission at week 44, as compared with 35.9 % of those receiving placebo (P = 0.005 and P = 0.04, respectively). | NCT01369355 | [194, 195] |
| | Crohn's Disease | Ustekinumab | IUS showed that ustekinumab-treated CD patients achieved progressive IUS response (46.3 %) and transmural remission (24.1 %) through week 48, with a more robust response in the colon and biologic-naïve patients. | NCT03107793 | [196] |
| | Crohn's Disease | Placebo for Ustekinumab/Placebo or Adalimumab/Ustekinumab (6 mg/kg)/ Ustekinumab (90 mg)/Adalimumab (40 mg) | There was no significant difference between the ustekinumab and adalimumab groups in the occurrence of the primary endpoint; at week 52, 124 (65 %) of 191 patients in the ustekinumab group versus 119 (61 %) of 195 in the adalimumab group were in clinical remission (between-group difference 4 %, 95 % CI -6 to 14; p = 0·42). | NCT03464136 | [197] |
| | Crohn's Disease | Placebo (IP)/Ustekinumab 1 mg/kg (IP)/ Ustekinumab 3 mg/kg (IP)/Ustekinumab 6 mg/kg (IP) Placebo IV - Responder - Placebo SC/Placebo IV - Nonresponder - Ustekinumab 270/90 mg SC/ Ustekinumab IV - Responder - Placebo SC/ Ustekinumab IV - Responder - Ustekinumab 90 mg SC/Ustekinumab IV - Nonresponder - Placebo SC/ Ustekinumab IV - Nonresponder - Ustekinumab 90 mg SC | The proportions of patients who reached the primary end point were 36.6 %, 34.1 %, and 39.7 % for 1, 3, and 6 mg of ustekinumab per kilogram, respectively, as compared with 23.5 % for placebo (P = 0.005 for the comparison with the 6-mg group). The rate of clinical remission with the 6-mg dose did not differ significantly from the rate with placebo at 6 weeks. | NCT00771667 | [198] |
| | Severe plaque-type psoriasis | Ustekinumab/Placebo | 171 (67.1 %) patients receiving ustekinumab 45 mg, 170 (66.4 %) receiving ustekinumab 90 mg, and eight (3.1 %) receiving placebo achieved PASI 75 at week 12 (difference in response rate vs placebo 63.9 %, 95 % CI 57.8–70.1, p < 0.0001 for 45 mg and 63.3 %, 57.1–69.4, p < 0.0001 for 90 mg). | NCT00267969 | [199] |
| | Psoriasis | Ustekinumab/Guselkumab/Placebo for ustekinumab/Placebo for guselkumab | Guselkumab is effective in the treatment of patients with moderate-to-severe plaque psoriasis (scaly rash) who do not respond well to Ustekinumab. | NCT02203032 | [200] |
| | Psoriasis | Placebo/Ustekinumab (CNTO 1275) 45 or 90 mg/ Ustekinumab (CNTO 1275) 45mg/Ustekinumab (CNTO 1275) 90 mg | 273 (66.7 %) patients receiving ustekinumab 45 mg, 311 (75.7 %) receiving ustekinumab 90 mg, and 15 (3.7 %) receiving placebo achieved the primary endpoint (difference in response rate 63.1 %, 95 % CI 58.2–68.0, p < 0.0001 for the 45 mg group vs placebo and 72.0 %, 67.5–76.5, p < 0.0001 for the 90 mg group vs placebo). | NCT00307437 | [201] |
| | Psoriasis | Ustekinumab 45 mg/Ustekinumab 90 mg/Placebo | Divergence of microbial communities within lesional and non-lesional skin after ustekinumab treatment. | NCT01550744 | [202] |
| | Psoriatic Arthritis | Placebo/Ustekinumab 45 mg/Ustekinumab 90 mg | More ustekinumab-treated (87 of 205 [42·4 %] in the 45 mg group and 101 of 204 [49·5 %] in the 90 mg group) than placebo-treated (47 of 206 [22·8 %]) patients achieved ACR20 at week 24 | NCT01009086 | [203, 204] |

*(continued on next page)*

**Table 3** (*continued*)

| Drug | Conditions | INTERVENTIONS | Main Results | NCT Number | Ref |
|---|---|---|---|---|---|
| | Psoriatic Arthritis | Placebo/Ustekinumab 45 mg/Ustekinumab 90 mg | (p < 0.0001 for both comparisons); responses were maintained at week 52. 256/927 (27.6 %) PSUMMIT-1/PSUMMIT-2 patients (placebo/ustekinumab, n = 92/164) comprised the evaluable spondylitis subset. At week 24, in this analysis subset, significantly more patients achieved BASDAI20/50/70 responses (54.8 %/29.3 %/15.3 % vs 32.9 %/11.4 %/0 %; p ≤ 0.002), improvement in BASDAI question 2 concerning axial pain (1.85 vs 0.24; p < 0.001) and mean per cent ASDAS-CRP improvements (27.8 % vs 3.9 %; p < 0.001) for ustekinumab versus placebo recipients, respectively. | NCT01077362 | [204] |
| | Systemic Lupus Erythematosus | Ustekinumab IV/Placebo Infusion/Placebo SC 2 more | At week 112, 79 % and 92 %, respectively, had an SRI-4 response; 92 % in both groups had ≥ 4-point improvement from baseline in SLEDAI-2K score; 79 % and 93 %, respectively, had ≥30 % improvement from baseline in PGA; | NCT02349061 | [205] |
| Guselkumab | Systemic Lupus Erythematosus | Placebo/Ustekinumab (approximately 6 mg/kg)/Ustekinumab 90 mg | Status:Terminated | NCT03517722 | NO |
| | Psoriasis (VOYAGE 1) | Guselkumab 100mg/Placebo for guselkumab/Adalimumab/Placebo for adalimumab | The proportions of patients in the guselkumab group who achieved clinical responses at week 252 in VOYAGE 1, respectively, were 84·1 % [≥90 % improvement in Psoriasis Area and Severity Index (PASI)]; 82·4 % [Investigator's Global Assessment (IGA) 0 or 1] | NCT02207231 | [206] |
| | Psoriasis (VOYAGE 2) | Guselkumab 100mg/Placebo for Guselkumab/Adalimumab/Placebo for Adalimumab | The proportions of patients in the guselkumab group who achieved clinical responses at week 252 in VOYAGE 2, respectively, were 82·0 % [≥90 % improvement in Psoriasis Area and Severity Index (PASI)]; 85·0 % [Investigator's Global Assessment (IGA) 0 or 1] | NCT02207244 | [206] |
| | Psoriasis | Guselkumab/Placebo | At Week 16, significantly higher proportions of guselkumab-treated (N = 62) than placebo-treated (N = 16) patients achieved IGA 0/1 (80.6 % vs. 0.0 %, p < 0.001) and PASI90 (75.8 % vs. 0.0 %, p < 0.001) responses. | NCT02905331 | [207] |
| | Psoriasis | Guselkumab/Placebo/Secukinumab | The proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group (451 [84 %]) than in the secukinumab group (360 [70 %]; p < 0·0001). Although non-inferiority (margin of 10 percentage points) was established for the first major secondary endpoint (452 [85 %] of patients in the guselkumab group vs 412 [80 %] of patients in the secukinumab group achieving a PASI 75 response at both weeks 12 and 48), superiority was not established (p = 0·0616). | NCT03090100 | [208] |
| | Psoriatic Arthritis | Guselkumab/Ustekinumab/Placebo | Guselkumab significantly improved signs and symptoms of active psoriatic arthritis and was well tolerated during 44 weeks of treatment. | NCT02319759 | [209] |
| | Psoriatic Arthritis | Guselkumab/Placebo | Significantly greater proportions of patients in the guselkumab every 4 weeks group (156 [64 %] of 245 [95 % CI 57–70]) and every 8 weeks group (159 [64 %] of 248 [58–70]) than in the placebo group (81 [33 %] of 246 [27–39]) achieved an ACR20 response at week 24 (percentage differences vs placebo 31 % [95 % CI 22–39] for the every 4 weeks group and 31 % [23–40] for the every 8 weeks group; both p < 0·0001). | NCT03158285 | [210] |
| | Ulcerative Colitis | Placebo/Guselkumab | Week-12 clinical response percentage was greater with guselkumab 200 mg (61.4 %) and 400 mg (60.7 %) vs placebo (27.6 %; both P < 0.001). | NCT04033445 | [211] |
| | Colitis, Ulcerative | Guselkumab Dose 1/Guselkumab Dose 2/Golimumab Dose 1/Golimumab Dose 2/Placebo | At week 12, 59 (83 %) of 71 patients in the combination therapy group had achieved clinical response compared with 44 (61 %) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 22·1 % [80 % CI 12·9 to 31·3]; nominal p = 0·0032) and 53 (75 %) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference 8·5 % [-0·2 to 17·1]; nominal p = 0·2155). | NCT03662542 | [212] |
| | Crohn's Disease | Guselkumab Dose 1/Guselkumab Dose 2/Guselkumab Dose 3/Guselkumab Dose 4/ | At week 12, all 3 dose regimens of guselkumab induced greater clinical and endoscopic | NCT03466411 | [213] |

**Table 3** (*continued*)

| Drug | Conditions | INTERVENTIONS | Main Results | NCT Number | Ref |
|------|-----------|---------------|--------------|------------|-----|
| Tildrakizumab | | Guselkumab Dose 5/Guselkumab/Ustekinumab/Placebo | improvements vs placebo, with a favorable safety profile. | | |
| | Crohn's Disease | Guselkumab | Status:Active, not recruiting | NCT04397263 | NO |
| | Crohn's Disease | Guselkumab/Golimumab/JNJ-78934804/Placebo | Status:Recruiting | NCT05242471 | NO |
| | Psoriasis | Tildrakizumab/Placebo | At week 16, PASI 75 responses were 33·3 % (n = 14), 64·4 % (n = 58), 66·3 % (n = 59), 74·4 % (n = 64) and 4·4 % (n = 2) in the 5-, 25-, 100- and 200-mg tildrakizumab and placebo groups, respectively (P ≤ 0·001 for each tildrakizumab dose vs. placebo). | NCT01225731 | [214] |
| | Plaque Psoriasis (reSURFACE 1) | Tildrakizumab 200mg/Tildrakizumab 100 mg/Matching Placebo | At week 12, 192 patients (62 %) in the 200 mg group and 197 patients (64 %) in the 100 mg group achieved PASI 75, compared with 9 patients (6 %) in the placebo group (p < 0·0001 for comparisons of both tildrakizumab groups vs placebo). | NCT01722331 | [215] |
| | Plaque Psoriasis (reSURFACE 2) | Tildrakizumab 200mg/Tildrakizumab 100mg/Tildrakizumab Placebo/Etanercept Placebo/Etanercept 50 mg | At week 12, 206 patients (66 %) in the 200 mg group, and 188 patients (61 %) in the 100 mg group achieved PASI 75, compared with 9 patients (6 %) in the placebo group and 151 patients (48 %) in the etanercept group (p < 0·0001 for comparisons of both tildrakizumab groups vs placebo; p < 0·0001 for 200 mg vs etanercept and p = 0·0010 for 100 mg vs etanercept). | NCT01729754 | [215] |
| | Psoriasis | Injections of tildrakizumab | Of 55 patients enrolled, 53 were assessed at W28. Mean (standard deviation [21]) total PGWBI score improved from baseline to W28 (change, 3.7 [12.4]; p = 0.033), as did the positive well-being (1.0 [2.9]; p = 0.018) and general health (1.5 [2.2]; p < 0.001) domain scores. | NCT03718299 | [216] |
| | Plaque Psoriasis | Tildrakizumab 100mg/Placebo | At week 12, tildrakizumab demonstrated significantly higher PASI 75 response rates (66.4 % [73/110] vs. 12.7 % [14/110]; difference, 51.4 % [95 % confidence interval (CI), 40.72, 62.13]; P < 0.001) and Physician's Global Assessment (60.9 % [67/110] vs. 10.0 % [11/110]; | NCT05108766 | [217] |
| | Active Psoriatic Arthritis | SUNPG1623 I/SUNPG1623 II/SUNPG1623 III/SUNPG1623 IV/Placebo | At W24, 71.4%–79.5 % of tildrakizumab-treated versus 50.6 % of placebo-treated patients achieved ACR20 (all p < 0.01). Patients receiving tildrakizumab versus placebo generally achieved higher rates of ACR50, Disease Activity Score in 28 joints with C reactive protein <3.2, minimal disease activity and 75 %/90 %/100 % improvement from baseline Psoriasis Area and Severity Index responses at W24 and through W52. | NCT02980692 | [218] |

Abbreviation: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's Disease; IV, intravenous; sc, subcutaneous; IP, intraperitoneal.

after just 12 weeks compared to those in the placebo group [199]. Furthermore, ustekinumab has been investigated in SLE through a multicenter, randomized, double-blind, placebo-controlled study. After 24 weeks of treatment, a significantly higher proportion of patients in the ustekinumab group reached the clinical endpoint compared to those in the placebo group, indicating encouraging results [219]. However, despite these promising findings, the phase III trial in SLE has been terminated, highlighting the need for further research to fully establish the therapeutic role of ustekinumab in this complex autoimmune disease. Based on the analysis of safety data in adult patients with Ustekinumab, the most common adverse reactions (>5 %) in the controlled phase of clinical studies using Ustekinumab for all indications were nasopharyngeal pain and headache, most of which were mild. Other common adverse reactions included injection site erythema, injection site pain, fatigue, back pain, myalgia, arthralgia, dizziness, headache, oropharyngeal pain, diarrhoea, nausea, vomiting and immunogenicity. The most serious adverse reaction is severe hypersensitivity.

### 5.2. Guselkumab

In July 2017, the FDA approved guselkumab, the first specific IL-23

inhibitor for treating moderate to severe psoriasis [220]. This drug selectively targets the p19 subunit of IL-23, blocking its intracellular and downstream signaling pathways effectively. The efficacy of guselkumab was highlighted in two Phase 3 multicenter, randomized, double-blind trials—VOYAGE 1 and VOYAGE 2. In VOYAGE 1, patients receiving guselkumab experienced significantly greater regression of skin lesions by week 16 compared to those in the placebo group. VOYAGE 2 further confirmed these results, showing even more pronounced effects at the same timeframe [221,222]. Guselkumab also demonstrated superior efficacy compared to other targeted therapies [223]. Expanding beyond dermatological applications, guselkumab was also assessed for treating inflammatory bowel disease (IBD). A phase 2b double-blind, placebo-controlled, dose-ranging induction study focused on its potential in treating moderate to severe active ulcerative colitis (UC). This study involved patients who had shown inadequate responses or intolerance to prior treatments, including corticosteroids and immunosuppressants [211]. The results were promising, with a significantly higher percentage of patients in the guselkumab group achieving clinical response at week 12 compared to the placebo group. Additionally, guselkumab-treated patients reached all major secondary endpoints, including clinical remission, highlighting its effectiveness for UC. To

further validate these findings, a phase 3 trial (NCT05528510) is underway. This randomized, double-blind, placebo-controlled, parallel-group, multicenter study aims to evaluate the efficacy and safety of subcutaneous induction therapy with guselkumab in participants with moderately to severely active UC. The primary hypothesis is that guselkumab will be superior to placebo in achieving clinical remission by week 12, potentially offering a new therapeutic avenue for UC patients. Common adverse reactions to Guselkumab injection include injection site reactions, diarrhoea, headache, and in some patients, immunogenicity, which is the development of anti-drug antibodies in the body after treatment.

### 5.3. Tildrakizumab

Tildrakizumab, a fully humanized IgG1-κ antibody, selectively targets the p19 subunit of IL-23 with high affinity, representing a targeted approach to treating plaque psoriasis [224]. In a phase 2b clinical trial, 355 patients received subcutaneous injections of tildrakizumab or placebo at Weeks 0 and 4, followed by rerandomization based on response. By week 16, a dose-dependent increase in the proportion of patients meeting the primary endpoint was observed, indicating a clear therapeutic benefit over placebo [214]. Further evaluation in two phase 3 trials demonstrated the superior efficacy of tildrakizumab in doses of 100 mg and 200 mg compared to placebo and etanercept in patients with moderate-to-severe plaque psoriasis. By week 12, a higher percentage of patients treated with tildrakizumab achieved the primary endpoint, showcasing its effectiveness against this chronic condition [215,225]. Real-world data further support the clinical utility of tildrakizumab. Dredleman et al. conducted the largest real-world study to date, assessing the efficacy and safety of tildrakizumab in 150 psoriasis patients through week 28. The findings revealed rapid and significant reductions in mean skin lesion assessments, confirming its high efficacy and rapid action in routine clinical practice [226]. Additionally, a multicenter retrospective study echoed these results, reporting significantly higher response rates in psoriasis patients treated with tildrakizumab [227]. Notably, tildrakizumab also demonstrated significant efficacy in difficult-to-treat areas, highlighting its potential as a comprehensive treatment option for psoriasis [228]. In addition, there are some monoclonal antibodies against IL-23 p19, such as Risankizumab, Mirikizumab, and Brazikumab. The current efficacy research focuses on the treatment of psoriasis and IBD. With the deepening of research in this field and the improvement of researchers' understanding of cytokines, therapies targeting IL-12 family cytokines will gradually be applied to more autoimmune diseases. Adverse reactions occurring with Tildrakizumab injection were predominantly injection site reactions, upper respiratory tract infections, and diarrhoea, and like other therapeutic proteins, the drug caused hypersensitivity reactions or immunogenicity in some patients.

### 6. Conclusions and prospects

The IL-12 family of cytokines plays a crucial role in immune regulation, particularly impacting T cell activation and differentiation. Composed of various subunits that form heterodimeric or monomeric structures, these cytokines bind specific receptors to activate downstream signaling pathways, influencing immunity. Their role in autoimmune diseases has garnered increasing interest due to their variable expression and significant clinical efficacy in conditions like psoriasis and IBD.

However, several challenges persist that necessitate further research. Firstly, more sensitive and precise methods are required for detecting these cytokines, which remains a limitation in ongoing studies. Secondly, the dynamics of these cytokines in their monomeric and heterodimeric forms, including the conditions under which they bind or act, and their secretion as monomers, need detailed investigation. Thirdly, it is crucial to understand the potential competition among subunits

binding and the subsequent activation of signaling pathways. Fourthly, the interactions produced by subunits in different combinations can lead to divergent effects, the mechanisms of which are yet to be fully understood. Fifthly, despite showing more significant clinical efficacy, monoclonal antibodies usually suffer from safety issues, including immune reactions such as allergy and immunogenicity, as well as infections, cancers, autoimmune diseases, and organ-specific events, which is a common problem in monoclonal antibody research [229]. In theory, due to the role of IL-12 in promoting the infiltration of cytotoxic T cells in tumor immunity, while the impact of IL-23 on tumors is more complex, IL-12 p40 monoclonal antibodies have potential carcinogenicity issues. Therefore, mitigation of side effects and development of more specific antibodies are issues that need to be further addressed. The complexity of the IL-12 family means that these cytokines may have varied, sometimes opposing, roles across different diseases. Thus, gaining a deeper understanding of their specific mechanisms is vital for developing more targeted therapeutic strategies. Future research should focus on elucidating the functional differences of these cytokines in various immune microenvironments and their interactions with other immunomodulatory factors. This approach could lead to more precise targets for personalized treatment of autoimmune diseases. In summary, while the therapeutic targeting of IL-12 family cytokines has shown promise in clinical settings, many aspects of their biology remain underexplored. Addressing these gaps could unlock more effective and specific therapies, potentially enhancing patient outcomes and quality of life as research progresses.

**Glossary**

| | |
|---|---|
| AMP | antimicrobial peptide |
| ANA | antinuclear antibody |
| APC | antigen-presenting cell |
| Breg | regulatory B cell |
| CD | crohn's disease |
| CHR | cytokine receptor homology region |
| CIA | collagen-induced arthritis |

| | |
|---|---|
| CTL | cytotoxic T lymphocyte |
| CTLA-4 | cytotoxic T lymphocyte associate protein-4 |
| DC | dendritic cell |
| EBI3 | epstein-barrvirus-induced gene 3 |
| FDA | food and drug administration |
| GM-CSF | granulocyte-macrophage colony stimulating factor |
| GMP | granulocyte-monocyte progenitor cell |
| GWAS | genome-wide association study |
| HC | healthy control |
| HSCT | hematopoietic stem cell transplantation |
| IBD | inflammatory bowel disease |
| IgAN | IgA nephropathy |
| IMQ | imiquimod |
| IRF6 | interferon regulatory factor 6 |
| iTreg | induced regulatory T cell |
| iTr35 | IL-35 dependent induction of regulatory T cells |
| JAK-STAT | Janus kinase-signal transducer and activator of transcription |
| KO | knockout |
| LN | lupus nephritis |
| MAC | membrane attack complex |
| MDSC | myeloid-derived suppressor cell |
| MN | membranous nephropathy |
| MSG | minor salivary gland |
| NF-kB | nuclear factor-k-gene binding |
| NK | natural killer |
| NOD | non-obese diabetic |
| nTreg | natural regulatory T cell |
| PASI | psoriasis area and severity index |
| PBMC | peripheral blood mononuclear cell |
| PGIA | proteoglycan-induced arthritis |
| PMN | primary membranous nephropathy |
| PsA | psoriatic arthritis |
| RA | rheumatoid arthritis |
| RORα | retinoid orphan nuclear receptor α |
| RORγ | retinoid orphan nuclear receptor γ |
| SLE | systemic lupus erythematosus |
| SLEDAI | SLE disease activity index |
| SSc | Systemic sclerosis |
| SS | Sjögren's syndrome |
| TCR | T-cell receptor |
| Th cell | helper T cell |
| TLR3 | toll-like receptor 3 |
| Treg | regulatory T cell |
| Tr1 | type 1 regulatory T cell |
| TYK2 | Tyrosine Kinase 2 |
| UC | ulcerative colitis |

## Data availability

No data was used for the research described in the article.

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