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# Interleukin-13: A promising therapeutic target for autoimmune disease

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ABSTRACT

Interleukin-13 (IL-13) was previously thought to be a redundant presence of IL-4, but in recent years its role in immunity, inflammation, fibrosis, and allergic diseases has become increasingly prominent. IL-13 can regulate several subtypes of T helper (Th) cells and affect their transformation, including Th1, Th2, T17, *etc.*, thus it may play an important role in immune system. Previous studies have revealed that IL-13 is implicated in the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), ulcerative colitis (UC), type 1 diabetes (T1D), sjogren's syndrome (SS), *etc*. In this review, we will briefly discuss the biological features of IL-13 and summarize recent advances in the role of IL-13 in the development and pathogenesis of autoimmune diseases. This information may provide new perspectives and suggestions for the selection of therapeutic targets for autoimmune diseases.

## 1. Introduction

Autoimmune diseases are a common category of diseases because of the breakdown in self-tolerance which include a series of diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), ulcerative colitis (UC), type 1 diabetes (T1D), sjogren's syndrome (SS), *etc*. Although rapid progress has been made in the treatment of autoimmune diseases in the past few decades, the exact pathogenesis of autoimmune diseases remains to be clarified as the causes of autoimmune diseases may involve many factors, including genetic factors, environmental factors, hormones [1], *etc.*

Naive CD4+ 'helper' T cells can differentiate into multiple effector subsets, such as T helper (Th)1, Th2, Th17 and regulatory T cells (Tregs), and the unbalance between these cells is the common

*Abbreviations:* IL-13, interleukin-13; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSc, systemic sclerosis; UC, ulcerative colitis; T1D, type 1 diabetes; SS, Sjogren's syndrome; Tregs, regulatory T cells; ILC2s, group 2 innate lymphoid cells; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-17, interleukin-17; TNF-α, tumor necrosis factor-alpha; IL-21, interleukin-21; IL-25, interleukin-25; CIA, collagen-induced arthritis; FOXP3, fork-head box protein P3; Jak/STAT, the Janus kinase/signal transducers and activators of transcription; NKT, natural killer T; PI-3K, phosphatidylinositol-3-kinase; MAPK, mitogen-activated protein kinase; IRS, insulin receptor substrate; AKT/PKB, protein kinase B; TGF-β, transforming growth factor-β; AP-1, activator protein 1; Ig, Immunoglobulin; VEGF, vascular endothelial growth factor; IL-10, interleukin-10; LSG, labial salivary glands; SLEDAI, the activity index of SLE; ESR, erythrocyte sedimentation rate; LN, lupusnephritis; 5-azaC, demethylating agent 5-azacytidine; pDCs, plasmacytoid dendritic cells; RF, rheumatoid factor; CRP, C-reactive protein; anti-CCP, anti-cyclic peptide containing citrulline; AIA, adjuvant-induced arthritis; PGE2, prostaglandin E2; FcγRI, Fcγ receptor I; RANKL, receptor activator of NF-kappa B ligand; VCAM-1, vascular adhesion molecule-1; IL-1α, interleukin-1α; IL-1β, interleukin-1β; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; MIP-1α, macrophage inflammatory protein-1α; MIP-1β, macrophage inflammatory protein-1β; MIP-3α, macrophage inflammatory protein-3α; VDIPEN, MMP-mediated cartilage damage, measured as neoepitope; 5-LOX, 5-lipoxygenase; LXA4, lipoxin A4; sclGVHD, sclerodermatous graft-versus-host disease; ECM, extracellular matrix; IGF-1, insulin-like growth factor-1; TN-C, tenascin-C; ILD, interstitial lung disease; OC, oxazolone colitis; LPT, lamina propria T; Tric, tricellulin; ENaC, epithelial sodium channel; CFTR, cystic fibrosis transmembrane conductance regulator; GAD, glutamic acid decarboxylase; NOD, diabetes-prone nonobese diabetic; MCL-1, myeloid leukaemia-1; BCLXL, B cell lymphoma-extra large; LG, lacrimal gland; PSS, primary Sjogren's syndrome; SSS, secondary Sjogren's syndrome; PBMCs, peripheral blood mononuclear cells; GATA-3, transcription factor GATA binding protein 3; ERK, extracellular-signal-regulated kinases; JNK, c-Jun N-terminal kinase; IECs, intestinal epithelial cells

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characteristic of autoimmune diseases [2–7]. Th1 and Th17 cells are the pro-inflammatory subsets of Th cells responsible for inducing autoimmunity whereas Tregs exert an antagonistic effect [8,9]. Th2 response is predominant in SLE, fibrosis and allergic diseases, and Th2 cytokines including Interleukin-13 (IL-13), IL-4, IL-5, *etc*. Group 2 innate lymphoid cells (ILC2s) have the capacity to secrete copious amounts of IL-13 and IL-5, potentially in the absence of adaptive immunity, which suggests that Th2-type immunity is coming to us in a more important way [10]. Nowadays, IL-13 has been widely used as a therapeutic target for Th2 disease because it can drive inflammation and fibrosis independently in many diseases, such as fibrosis diseases [11,12]. Moreover, IL-13 interferes with the apoptosis pathway in CD4 + T cells to enhance tissue damage in immune response by repressing the expression of p53, caspase 3 and tumor necrosis factor-alpha (TNF-α) [13]. IL-25 inhibited the activation and differentiation of CD4 + T cells into Th17 cells in human RA and collagen-induced arthritis (CIA) models and this process dependent on IL-13 rather than IL-4 and IL-5 [14]. A series of studies have shown that IL-13 could directly or indirectly inhibit the development of Th17 cells and Th17 cytokines secretion [15,16]. Barik *et al.* [17] found that IL-13 probably influences Th17 cells to convert to Th1 cells and to acquire increased sensitivity to the suppression of Tregs through IL-4Rα/IL-13Rα1 receptor complex. Th1- and Th17- effector T cells often produce IL-13 in response to both self and foreign antigens [18], considering the plasticity of CD4 + T cell populations [2], IL-13 production probably represents a general feature of acute T-cell responses, no matter what role Th1, Th2 or Th17 cells play. IL-13 receptors are widely expressed on almost every cell in the body and change during disease, and IL-13 has been shown to regulate multiple immune and non-immune cells primarily through Jak/STAT6 pathway, including B cells, T cells, mast cells, natural killer T (NKT) cells, macrophage, eosinophil, fibroblast [19,20], *etc*. STAT6 is necessary for the differentiation and development of Treg cells since it is required for complete induction of fork-head box protein P3 (FOXP3) expression, the major transcription factor of Tregs [21]. At the same time, STAT6 also inhibits the immunosuppressive activity of Tregs [22] so that IL-13 may inhibit the immunosuppressive activity of Tregs by activating STAT6. There is solid evidence that the pathogenesis of autoimmune disease is related to Th17 and Treg balance and Th17-type inflammation [23]. Therefore, due to the regulatory effect of IL-13 on Th1, Th17 and Treg cells, targeting this cytokine may have therapeutic benefits in clinical settings where classical Th2-type response cells are not clear, such as during Th1- and Th17-type inflammation. Moreover, IL-13 can regulate cellular inflammation driven by Th1 and Th17 cells, but it cannot be regarded as an anti-inflammatory cytokine only since it can also drive the inflammatory response of Th2 cells [11,24].

In this review, we will briefly discuss the biological functions of IL-13 and summarize recent advances in the role of IL-13 in the development and pathogenesis of autoimmune diseases. The discoveries gained from these findings might translate into future therapies for these diseases.

## 2. IL-13 and its signal channel

IL-13 is a pleiotropic Th2 cell-derived cytokine which plays a key role in asthma, allergy, fibrosis and other eosinophilic disorders [11,24–26]. Its molecular weight is about 10KD and gene is located in the human chromosome 5q23-31 closely linked to the *IL-14* gene [27]. Besides, IL-13 and IL-4 use the same IL-4Rα and signal through STAT6 [28], which may explain the similarities in some of their functions. IL-13 is mainly derived from Th2 cells, but a variety of other cells can also produce it, including Th1 cells and Th17 cells [18], ILC2 [29], NKT cells [30], mast cells [31], eosinophils [32], basophils [19], macrophages [33], *etc*.

IL-13 performs multiple functions through its complex receptors, including IL-4Rα, IL-13Rα1 and IL-13Rα2. IL-4Rα and IL-13Rα1 exist in the form of homologous dimmers. Three intracellular signaling pathways activated by IL-13 bind with IL-4Rα/IL-13Rα1, following the Jak/STAT pathway, PI-3K pathway and MAPK pathway activation [34]. One of the most classic pathways is the Jak/STAT6. IL-13 binds to IL-13Rα1 with low affinity and then recruits IL-4Rα on the opposite side to form a signal transducer and activator of transcription 6 signaling complex, a stable complex activating STAT6 signal [35,36]. Then STAT6 is phosphorylated and pSTAT6 translocates to the nucleus where it binds DNA promoter elements to regulate gene transcription. Additionally, after IL-13 or IL-4 binds to IL-4Rα/IL-13Rα1, IRS1/2 is convened and phosphorylated, and IRS then activates PI-3K, resulting in activation of the PI-3K-AKT/PKB pathway, eventually regulates gene expression in the nucleus and promotes cell survival and proliferation [37]. IL-13Rα2 exists in the transmembrane, intracellular and soluble forms, and sIL-13Rα2 binds to IL-13 to form a stable complex that blocks the binding of IL-13 to IL-4Rα/IL-13Rα1 [38,39]. IL-13Rα2 has been found to combine with IL-13 in a more stable form with high affinity *in vitro* and less expression *in vivo*, and it is usually considered a decoy receptor due to no intracellular part [40–42]. However, one study found that IL-13 signaling through the IL-13Rα2 receptor is involved in induction of transforming growth factor-β (TGF-β) 1 production and fibrosis by activating activator protein 1 (AP-1) [43]. In some diseases, IL-13 has been found to play a role in activating the extracellular-signal-regulated kinases (ERK)/AP-1, MAPK or JNK/AP-1 pathway by binding to IL-13Rα2 receptors [44–47]. The role of IL-13Rα2 in IL-13 biology has been somewhat elusive, and different forms of IL-13Rα2 may have different functions. The receptor for IL-4 is IL-4Rα, upon IL-4 binding to IL-4Rα, the IL-4/IL-4Rα-complex will bind a secondary receptor chain, either IL-2Rγc (γc) or IL-13Rα1 [35]. Binding of IL-4 to IL-4Rα/γc receptor activates STAT6 and IRS-2 pathways [20]. The receptors and signaling pathways for IL-13 and IL-4 described above are shown in Fig. 1. The function of IL-13 is partly overlapped with IL-4, but also unique, such as its role in fibrosis and mucus secretion. This may be explained by differential expression of the receptor configuration of the effector cells and differential spatiotemporal secretion of IL-4 and IL-13 [11,48]. In a word, the signal pathways and functions of IL-13 are diverse and wide and the special role of IL-13 in autoimmune diseases deserves further study.

## 3. Immunological functions of IL-13

IL-13 and IL-4 induce the expression of surface antigens in B lymphocytes including MHC class II and CD23, synthesis of immune proteins especially Immunoglobulin (Ig) E, and promote the proliferation and differentiation of B lymphocytes, leading to the formation of a large number of antibodies [19]. IL-13 activates macrophages, promotes their anti-inflammatory properties and induces the expression alternately activated macrophages through the activation of STAT6 in an IL-13Rα1 dependent pathway [49], These activated macrophages produce anti-inflammatory cytokines, such as IL-10, that inhibit the inflammatory activity of natural killer cells, T cells, and growth factors that promote tissue repair, such as vascular endothelial growth factor (VEGF) and TGF-β, these growth factors contribute to angiogenesis and the deposition of extracellular matrix proteins [50–53]. IL-13 also induces eosinophil aggregation and promotes its activation and survival [54]. IL-13 was previously considered to be a redundant function of IL-4, later, it was demonstrated that IL-13 has many important features that draw a distinction between IL-4 [55]. As an example, IL-13 is the most important cytokine that promotes fibrosis rather than IL-4 [56]. Previous studies have shown that IL-13 receptors are expressed on human B cells, basophils, eosinophils, mast cells, endothelial cells, fibroblasts, monocytes, and macrophages; however, functional IL-13 receptors have not been demonstrated on human or mouse T cells [42]. Afterwards, Newcomb *et al.* [57,58] found that functional IL-13 receptors were expressed on Th17 cells in humans and mice and IL-13 also decreased Th17 cytokines production, as an example IL-17 A, a typical member of a family of IL-17 cytokines. This finding suggests that IL-13 may

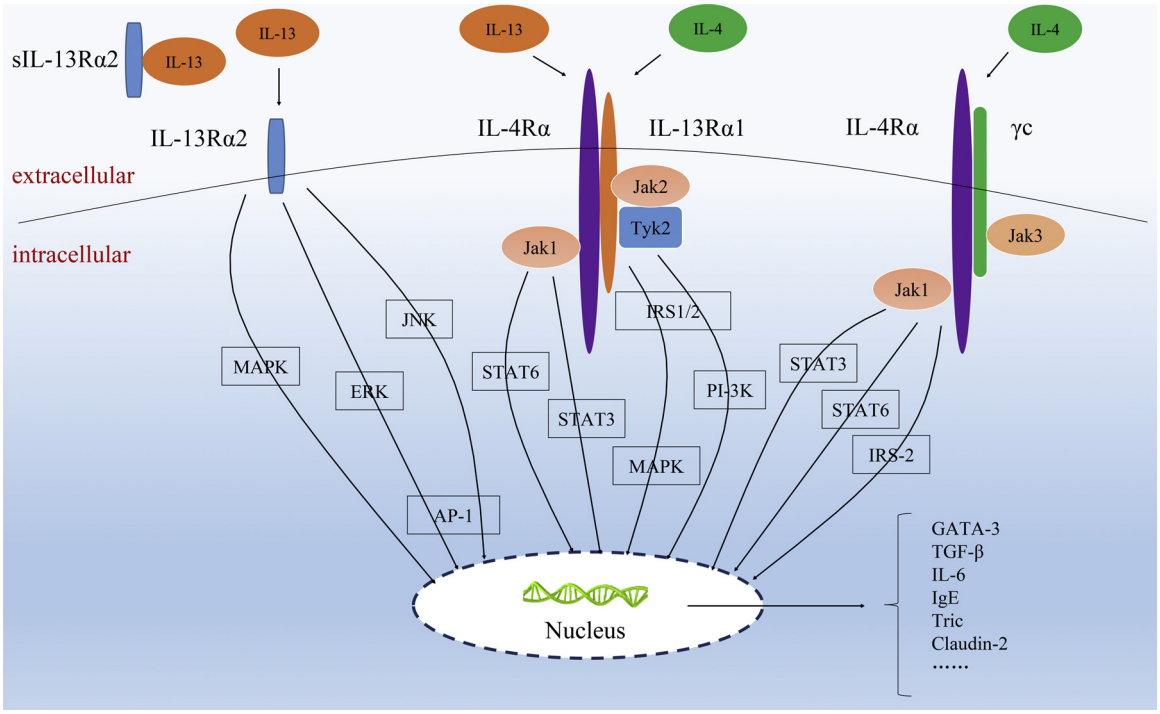


**Fig. 1.** Receptors and signal transduction pathways of IL-13 and IL-4.
The type 1 IL-13Rα1/IL-4Rα receptor binds both IL-13 and IL-4 (although IL-4 can also signal through the IL-4Rα/common γ chain receptor). Three intracellular signaling pathways activated by IL-13 or IL-4 bind with IL-4Rα/IL-13Rα1, following Jak/STAT pathway, PI-3 K pathway and MAPK pathway activation. IL-13Rα2 exists in the transmembrane, intracellular and soluble forms and the role of IL-13Rα2 in IL-13 biology has been somewhat elusive. IL-13Rα2 on cell membrane binds only IL-13 and it's usually considered a decoy receptor in the past. However, IL-13 has been found to play a role in activating the ERK/AP-1, MAPK or JNK/AP-1 pathway by binding to IL-13Rα2 receptors. sIL-13Rα2 can play a negative role in regulating IL-13 by binding to extracellular IL-13. IL-13 activates multiple pathways by binding to two receptors to regulate transcription and expression of multiple genes in the nucleus, such as GATA-3,TGF-β, *etc*.

provide a potential therapy for Th17-mediated diseases and blocking the treatment of IL-13 may exacerbate Th17-driven disease. This deduction is also confirmed by the following experimental results. IL-13 negatively regulated differentiation of Th17 cells and secretion of cytokines *in vitro* and significantly inhibited Th1 and Th17 responses without the presence of IL-13Rα2 in *IL10-/-* mice [15]. A recent study also found IL-17 A could improve the capacity of IL-13 to activate intracellular signaling pathway, STAT6, an IL-13 antagonizes IL-17 A dependent pathway [59]. There is a negative feedback regulation between IL-13 and IL-17 A. The biological effects of IL-13 can also affect a variety of non-immune cells and tissue including fibroblasts [60–62], intestinal epithelial cells [47,63–65] and pancreatic islet β cells [66], vessels [67] and labial salivary glands (LSG) [68]. The specific functions are presented in Fig. 2.

## 4. IL-13 in autoimmune diseases

Autoimmune diseases are characterized by abnormal immune responses, which produce a large number of abnormal antibodies that crack down on the body's own cells and tissues and thus cause damage to tissues and organs. A series of autoimmune diseases include SLE, RA, SSc, UC, T1D and SS, *etc.* Although there are lots of symptomatic treatments for autoimmune diseases so far, most of the precise causes are not clear. Cytokines are crucial in the pathogenesis of autoimmune diseases, such as IL-17 and IL-23 [69–72]. Recent findings have revealed that abnormal expression of IL-13 in multiple autoimmune diseases may be involved in the development of these diseases, including SLE [73,74], RA [74–78], SSc [24,79–83], UC [30,84–86], T1D [87,88] and SS [68,74] (Table 1).

### 4.1. Systemic lupus erythematosus

SLE is a chronic autoimmune disease which can involve various organs and tissues including cardiovascular, kidney, skin and brain, occurring more frequently in women of childbearing age [89]. Its cause remains unclear and the pathogenesis can be summarized into two parts: (1) loss of autoimmune tolerance resulting in the formation of auto-antibodies and (2) inflammation and other adverse reactions caused by pathogenic auto-antibodies and immune complexes [90]. Multifactorial interactions, among genetic, environmental, hormone may be involved together. Various cytokines and pathways are involved which provide a basis for the existence of multiple possible therapeutic targets in SLE. SLE is so for the autoimmune disease with the largest number of detectable auto-antibodies, however most current treatments rely on immunosuppressants with limits of efficacy and side effects [91–93]. Therefore, it is necessary to further explore novel therapeutic targets of SLE and to promote the progress of SLE treatment.

#### 4.1.1. Circulating IL-13 expression in SLE

The plasma and serum levels of IL-13 in SLE patients were significantly elevated than healthy controls [73,74]. Furthermore, active SLE patients had a higher serum IL-13 concentration than inactive patients, a positive correlation was found between IL-13 and the activity index of SLE (SLEDAI) or erythrocyte sedimentation rate (ESR) [94]. The concentration of serum IL-13 in lupus nephritis (LN) patients was higher compared to SLE patients without kidney involvement [95]. In the lupus model, IL-13 was also highly expressed in glomeruli and around renal vessels [96]. IL-13 mRNA levels in renal tissues of patients with active LN were elevated and positively correlated with serum creatinine and disease activity [97].

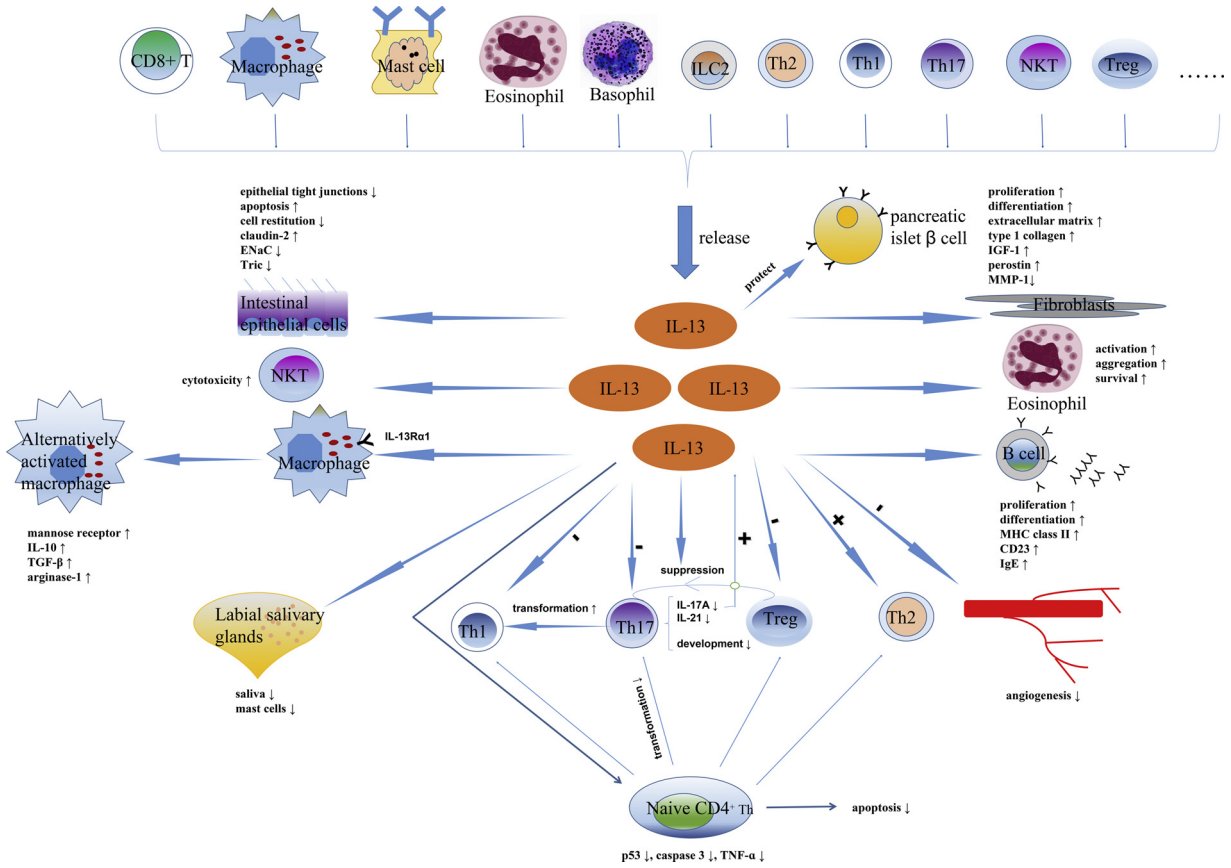


**Fig. 2.** Source of IL-13 and its function in immune cells and non-immune cells.
The sources of IL-13 are extremely abundant, including Th1, Th2, Th17, ILC2 cells, etc. IL-13 interferes with the apoptosis pathway in CD4 + T cells to enhance tissue damage in immune response and inhibits the transformation of CD4 + T cells to Th17 cells. In addition, IL-13 negatively regulates differentiation and development of Th17 cells and secretion of IL-17 A and IL-21. In turn, IL-17 A enhances the role of IL-13. IL-13 is required for the transformation of Th17 cells to Th1 cells and also affects the sensitivity of Treg cells to Th17 inhibition. Furthermore, IL-13 inhibits Th1 immune response and the immunosuppressive activity of Treg cells and enhances Th2 immune response. IL-13 promotes the proliferation and differentiation of B cells, induces MHC class II, CD23, and IgE, enhances activation, aggregation and survival of eosinophils. In inflammation, IL-13 activates macrophages, promotes their anti-inflammatory properties and induces alternately activated macrophages and inhibits angiogenesis. In UC, IL-13 decreases epithelial tight junctions, cell restitution, Tric production, and ENaC-dependent sodium transport, increases cell apoptosis, claudin-2 production, and NKT cells' cytotoxicity leading to the destruction of the intestinal epithelial barrier. In SSc, IL-13 promotes the proliferation and differentiation of fibroblasts, the production of extracellular matrix, type 1 collagen, IGF-1, and periostin, decreases MMP-1 production. In SS, IL-13 decreases saliva production and the number of mast cells. In T1D, IL-13 protects the activity of pancreatic islet β cells.

**Table 1**
Expression of IL-13 in autoimmune diseases.

| Disease name | Expression of IL-13 | Increase/decrease/NSD compared with controls | Reference |
|---|---|---|---|
| SLE | Plasma | Increase | [73] |
| | Serum | Increase | [74] |
| RA | Serum | Increase | [73,75,78] |
| SSc | Serum | Increase | [81] |
| | Peripheral blood effector CD8 + T cells | Increase | [80] |
| | Treg cells in skin lesions | Increase | [83] |
| UC | Serum | Increase | [84,85] |
| | Serum | NSD | [86] |
| | Lamina propria T cells | Increase | [30] |
| T1D | Invariant natural killer T cells | Decrease | [88] |
| SS | Serum | Increase | [74] |

IL-13: Interleukin-13; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; UC: ulcerative colitis; T1D: type 1 diabetes; SS: sjogren's syndrome; NSD: no significant differences.

#### 4.1.2. Genetic and epigenetic association of IL-13 gene with SLE

*IL-13* gene polymorphisms are associated with SLE in a Chinese population and *IL-13 rs20541* may be a susceptibility gene to SLE, furthermore, CT and TT genotypes in rs20541 are related to increased risk of renal disorder [73]. Epigenetic dysregulation plays an important role in pathogenesis of autoimmune diseases and DNA demethylation is a hallmark of epigenetic deregulation in SLE CD4 + T cells and closely associated with the pathogenesis of SLE [98]. Additionally, DNA methylation levels within *IL-10* and *IL-13* gene regulatory domains are reduced in SLE CD4 + T cells relative to healthy controls and negatively correlate with IL-10 and IL-13 mRNA expression. What's more, treating healthy CD4 + T cells with the demethylating agent 5-azacytidine (5-azaC) increased IL-10 and IL-13 mRNA transcription. The above evidence suggested DNA hypomethylation may be the reason of IL-13 over expression in SLE patients [99].

#### 4.1.3. Pathogenic role of IL-13 and its potential as therapeutic target in SLE

IL-13 induces the production of IgE, IL-6 and surface antigens [19,100,101], which contributes to the development of SLE disease. Autoreactive IgE favor accumulation of DNA-containing immune complexes in phagosome, it could increase the disease activity of SLE and IgE antibodies specific for double-stranded DNA greatly potentiated plasmacytoid dendritic cells (pDCs) functions by triggering phagocytosis via FcεRI followed by Toll-like receptor 9-mediated DNA sensing in phagosomes [102,103]. B cells drive autoimmunity via local IL-6 production required for T follicular helper cell differentiation and

autoimmune germinal centers formation in mouse SLE [104]. Furthermore, IL-13 may be associated with the pathogenesis of SLE by inducing antibody production based on the its induction of B cell proliferation and differentiation. Zhou *et al.* [105] also reported the beneficial effects of melatonin on the pristane-induced lupus mice accompanied with decreased IL-13 levels. Therefore, over-expression of IL-13 is related to the pathogenesis of SLE, but more animal and human studies are needed to demonstrate its feasibility as a target for the treatment of SLE.

### 4.2. Rheumatoid arthritis

RA is a chronic, systemic autoimmune disease which is characterized by synovial hyperplasia with inflammatory cell infiltration, angiogenesis, as well as bone and cartilage erosion with high disability rate [106]. Disturbance of Th1/ Th1/Th17 cytokines is an important factor in the pathogenesis of RA and the lymphocytes of RA patients are significantly inclined to Th1 and Th17 phenotype, which was characterized by excessive production of IFN-γ, IL-17, and proinflammatory response and inadequate production of Th2 cytokines [107,108]. The imbalance of cytokine network induces chronic inflammation, the destruction of bone and cartilage, and the loss of self tolerance so that cytokines are attractive therapeutic targets in RA [106]. IL-25 attenuates CIA development by suppressing the Th17 immune response, a process that relies on IL-13 [14]. The activation of IL-13 pathway in some RA patients also suggests targeted IL-13 pathway therapy may be useful [109].

#### 4.2.1. Circulating IL-13 expression in RA

Significantly higher IL-13 level was observed in rheumatoid synovium and recombinant IL-13 can reduce the production of inflammatory factors [76], however, Th cells expressing IL-13 was higher in early RA synovial fluid while with low expression of IL-13 in established RA synovial fluid [107]. Serum levels of IL-13 were increased in RA patients and positively correlated with rheumatoid factor (RF) level [74,75,78], but naturally rising levels could not sufficient to counteract the inflammatory response [110]. Cytokine expression analysis of subcutaneous nodules in 10 patients with RA by reverse transcription–polymerase chain reaction of extracted RNA showed that transcripts for TNF-α, IL-1β, and IL-10 were present in all 10 nodules, transcripts for IL-13 was observed in only five nodule [111]. Furthermore, the serum concentrations of IL-13 in early RA patients was positively correlated with disease activity and the diagnostic efficacy was higher than that of existing biomarkers such as the C-reactive protein (CRP), ESR, and anti-cyclic peptide containing citrulline (anti-CCP) [112].

#### 4.2.2. Genetic association of IL-13 gene with RA

The relationship between IL-13 gene polymorphism and RA is controversial. The polymorphism of IL-4/IL-13/IL-4Rα loci did not contribute significantly to the genetic background of RA either individually or in combination [113]. Similarly, no association was observed between IL-13 gene polymorphisms and RA in the Chinese population, however, stratification analyses suggested that the IL-13 rs1800925 C/T genotype increased the risk of RA in ESR < 25.00 patients [114]. The frequency of the T allele of the IL-13 polymorphism -1112C/T was higher in the subgroup with faster progression of the disease [115]. The reasons for these differences may be geographical and ethnic differences, and the relationship between RA and IL-13 gene polymorphisms requires a larger sample size study.

#### 4.2.3. Pathogenic role of IL-13 and its potential as therapeutic target in RA

IL-13 could significantly inhibit the production of pro-inflammatory cytokines (such as IL-1α, IL-1β, TNF-α, and IL-6) and chemokines (such as IL-8, MIP-1α, MIP-1β and MIP-3α) by freshly isolated RA synovial tissue cells, activated monocytes, and synovial macrophages *in vitro* experiments [52,116,117], which may reduce the recruitment of inflammatory cells and weakens the inflammatory response in the joints. Besides, activation of IL-13/STAT6 signaling pathway induces the transformation of pro-inflammatory macrophages into anti-inflammatory macrophages and enter inflamed joints, anti-inflammatory macrophages could secrete some anti-inflammatory cytokines to inhibit inflammatory response, such as IL-10 and TGF-β [118,119]. Woods *et al.* [120] found that mice treated with adenovirus producing rat IL-13 (AxCArIL-13) reduce the symptoms of rat adjuvant-induced arthritis (AIA) compared with the control group, including reducing inflammation, vascularization and bone destruction. They also found that IL-13 produced by adenoviral vectors encoding the genes for human IL-13 (AxCAIL-13) reduced the release of inflammatory cytokines and prostaglandin $E_2$ ($PGE_2$) in RA synovium [121]. $PGE_2$ is an effective lipid medium for immune inflammation, which exerts its important proinflammatory effect in RA [122]. An adenovirus vector containing AxCAIL-13, a control vector with no insert (AxCANI), or phosphate buffered saline (PBS) were respectively injected into the ankle joint of RA model by a rat adjuvant in each rats [67]. Results of this experiment suggested that IL-13 may exert its antiangiogenic function *in vivo* via activation of PKC*α/β*II and ERK-1/2, with concomitant down-regulation of the NF-κBp65 pathway and down-regulation of matrix metalloproteinase-2 (MMP-2) and MMP-9 expression and activity in RA model. IL-13 can reduce the death of chondrocytes and MMP-mediated VDIPEN expression to protect the cartilage from destruction probably because the expression of Fcγ receptor I (FcγRI) is reduced by IL-13, which is important in inducing cartilage damage [123,124]. Radstake *et al.* [125] also found that DCs form RA patients lack the IL-13 mediated increase of inhibitory FcyRII expression compared with normal controls. IL-13 regulates the expression of vascular adhesion molecule-1 (VCAM-1) not only in vascular endothelial cells but also in human osteoblasts since these cells express RANKL, the major osteoclastogenic factor and osteoclast precursors are found adjacent to osteoblasts [126]. 5-lipoxygenase (5-LOX) induced by IL-13 might regulate the production of lipoxin A4 (LXA4) to have an anti-inflammatory effect against proinflammatory lipid mediators in inflamed joints [127]. IL-13 can protect human synovial cells from apoptosis through IL-4R signal transduction pathways, contributing to synovial proliferation [128,129]. The relationship between IL-13 and the pathogenesis of RA is presented in Fig. 3. In general, IL-13 can be invoked as a serum biomarker and therapeutic target for RA to diagnose and predict disease progression and to reduce joint inflammation in order to delay the course of disease.

### 4.3. Systemic sclerosis

SSc, a multisystem connective tissue disease with unknown etiology and high mortality, is characterized by the autoimmunity, vascular disease and fibrosis, including diffuse cutaneous and limited cutaneous types [130]. The pathogenesis of SSc remains incompletely clear and no effective treatment to reverse the disease process. As an autoimmune disease, the most important feature of the disease is fibrosis of skin and visceral organs, and it is generally believed that the disproportionate increase in Th2 cytokines more than Th1 cytokines is considered to be the basis of the pathogenesis of SSc [131]. Stimulating Th1 immune response prevented the development of scleroderma-like syndrome in tight-skin mice, which suggested restoring the balance between Th1 and Th2 cytokines can be an effective treatment strategy for SSc [132,133]. IL-13, a Th2 cytokine, the main profibrotic mediator, is paramount for tissue fibrosis and has been recognized as a potential therapeutic target for fibrous diseases [134].

#### 4.3.1. Circulating IL-13 expression in SSc

Previous work consistently found that circulating IL-13 levels were increased in SSc patients and peripheral blood and skin effect CD8 + T cells from patients with SSc produced a host of IL-13 compared with healthy controls [24,79–81]. IL-13 may be a serological marker of

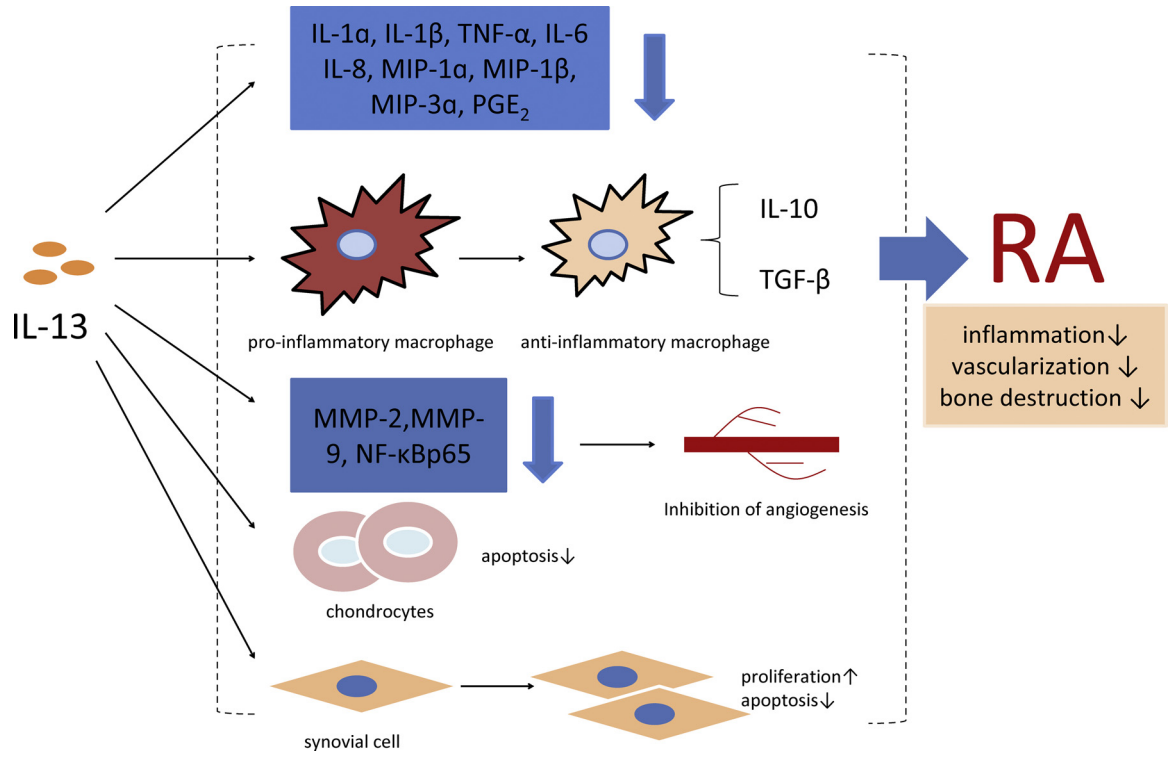


**Fig. 3.** The relationship between IL-13 and the pathogenesis of RA.
IL-13 reduces the expression of a series of proinflammatory cytokines and chemokines in RA synovial tissue cells, activated monocytes, and synovial macrophages, including IL-1, IL-6, and IL-8, *etc.* Besides, IL-13 induces pro-inflammatory macrophages to transform into anti-inflammatory macrophages and secrete anti-inflammatory cytokines such as IL-10 and TGF-β. IL-13 can also inhibit angiogenesis and protects synoviocytes and chondroblasts from apoptosis. All of these processes can reduce inflammation, vascularization and bone destruction in RA.

systemic inflammation in patients with SSc because it is associated with ESR and CRP [135]. Besides, IL-13 and its receptor were raised in skin lesions in parallel with dermal sclerosis progression in the murine model of bleomycin-induced scleroderma [82]. Treg cells in the affected skin of SSc patients could produce a multitude of IL-13, and the proportion of Treg cells producing IL-13 in the skin of patients with SSc increased significantly which suggested tissue-localized differentiation of Treg cells into Th2-like cells might contribute to fibrosis [83].

#### 4.3.2. Genetic association of IL-13 gene with SSc

No significant associations were observed between gene polymorphism of IL-4, IL-13 and its receptors and SSc, and their polymorphisms did not influence the expression of their corresponding transcript in peripheral blood cells [136]. However, Granel *et al.* [137,138] observed that the gene polymorphisms of *IL-13* (rs1800925, rs2243204) and *IL13Rα2* gene were associated with SSc and skin fibrosis manifestation in the Caucasian population. Comparison of gene expression profiles of scleroderma between human and mouse suggested that IL-13 drives the inflammatory response of scleroderma. Mice deficient in IL-13 or IL-4Rα were protected from murine sclerodermatous graft-versus-host disease (sclGVHD) [139]. The global gene expression profiling also indicated that IL-13 pathways were deregulated in subsets of systemic sclerosis patients and IL-13 gene was potential therapeutic targets [140].

#### 4.3.3. Pathogenic role of IL-13 and its potential as therapeutic target in SSc

IL-13 induced and activated TGF-β1 in the lungs of mice which suggested fibrosis mediated by IL-13, at least in part through the induction and activation of TGF-β [141], however, Kaviratne *et al.* [142] have shown that the process of stimulating tissue fibrosis by IL-13 was not related to TGF-β in liver fibrosis caused by schistosoma mansoni infection. Whether IL-13 mediated fibrosis partly through TGF-β pathway is not clear, but the role of IL-13 in promoting fibrosis can't be ignored.IL-13 directly activates fibroblasts to increase extracellular matrix (ECM) production and induces type 1 collagen synthesis [60]. More, IL-13 mediates collagen deposition in fibroblasts via STAT6 signaling pathway independent on TGF-β1, and microRNA-135b, a small RNA targeting STAT6 to reduce collagen induction, is significantly reduced in SSc fibroblasts [143]. Prolonged application of recombinant IL-13 on dermal fibroblasts in SSc patients could well reduce the expression of MMP-1, which contributed to the accumulation of collagen [61]. And these inhibition processes may be mediated by PKB/Akt pathway [144]. IL-13 could promote the expression of insulin-like growth factor-1 (IGF-1) in a STAT6-dependent manner, which is beneficial to the proliferation and survival of fibroblasts and myofibroblasts [145]. IL-13 up-regulates Tenascin-C (TN-C) expression in human skin fibroblasts via the PI3 K/Akt and the protein kinase C (PKC) signaling pathways, and TN-C is an early response ECM molecule implicated in pulmonary fibrotic disorders [146,147]. Moreover, IL-13 can stimulate the expression of periostin, which is a marker of fibrosis in some allergic diseases, and can accelerate pathologic fibrosis in a mouse model of scleroderma [62,148]. IL-13 induced CCL-2 expression through IL-4Rα dependent pathway and higher CCL-2 levels in the circulation were predictive of interstitial lung disease (ILD) progression and poorer survival in SSc [149,150]. CCL-2 contributes to the transformation of macrophages into fibrotic phenotypes. Riccieri *et al.* [81] firstly found that IL-13 is associated with nailfold capillaroscopy abnormalities in patients with SSc, suggesting that it is involved not only in fibrosis and immune process, but also in the microangiopathy of SSc. The frequency of CD8 + CD28- T cell with direct cellular cytotoxicity and pro-fibrotic function was increased in the blood and affected skin of SSc patients which produced high levels of IL-13, and correlated with the extent of skin fibrosis, especially in early stages of disease [79,80,151]. This provides evidence of pathological mechanism for extensive skin fibrosis

in patients with SSc and suggests that we should develop therapeutic methods targeting specific cells. An increase in CD226 receptor expression on CD8 + T cells contributes to the production of IL-13 and is associated with skin and lung involvement, according to a study [152]. Similarly, transcription factor GATA-3 positively regulates the level of IL-13, silencing of GATA-3 with small interfering RNA significantly reduced IL-13 production by CD8 + T cells [153,154]. On the other hand, transcription factor T-box expressed in T cells (T-bet) may inhibit the process of fibrosis mediated by IL-13 by reducing the level of IL-13 at the transcriptional level in mice [131,155]. The adaptor protein 14-3-3z binds to T-bet in CD8 + T cells from patients with SSc and prevents its translocation to the nucleus leading to reduction in the amount of GATA-3 combined with T-bet and more GATA-3 in nucleus can be used to bind IL-13 promoter and induce IL-13 expression [156]. The results of the above studies provided a novel molecular mechanism for the overexpression of IL-13 on CD8 + T cells in patients with SSc. TGF-β up-regulates IL-13 synthesis via GATA-3 transcription factor regulation through Smad3 and p38-MAPK signaling pathways in T lymphocytes of patients with SSc, but the reverse occurs in healthy patients [157]. The relationship between IL-13 and the pathogenesis of SSc is presented in Fig. 4. Pregnane X receptor (PXR) reduced fibrosis symptoms in experimental dermal fibrosisby attenuating the release of IL-13 [158]. Niclosamide improved the symptoms of hypochlorous acid (HOCl)-induced SSc in mice due to the inhibition of STAT3, AKT, and Wnt/b-catenin pathways as well as IL-13 production in the skin [159]. Erlotinib could reduce IL-13 secretion in skin of GVHD mice which helped to improve skin fibrosis [160]. All of these evidence demonstrated that IL-13 was the causative agent of SSc, strategies focusing on IL-13 and its intracellular signal transduction has achieved some preliminary results.

### 4.4. Ulcerative colitis

UC is a chronic nonspecific inflammatory disease with unclear etiology and limited lesion location, which is closely related to Th2 response [30]. A large amount of IL-13 secreted by NKT cells is toxic to intestinal mucosal epithelial cells and in turn increases the cytotoxicity of NKT, thus destroying the mucosal barrier [30,161]. IL-13Rα2-Fc, a soluble receptor of IL-13, can effectively prevent the deterioration of oxazolone colitis (OC) that has a histologic resemblance to human UC [162]. IFN-β relieves the inflammation of UCby inhibiting the production and activity of IL-13 [163], which suggests IL-13 closely related to the pathogenesis of UC.

#### 4.4.1. Circulating IL-13 expression in UC

Serum IL-13 levels in UC patients were significantly higher than those patients with other digestive diseases and healthy controls [84,85]. In UC mucosal specimens, IL-13 mRNA levels were markedly higher compared to CD and control specimens [164]. Lamina propria T (LPT) cells from UC patients produce significantly greater amounts of

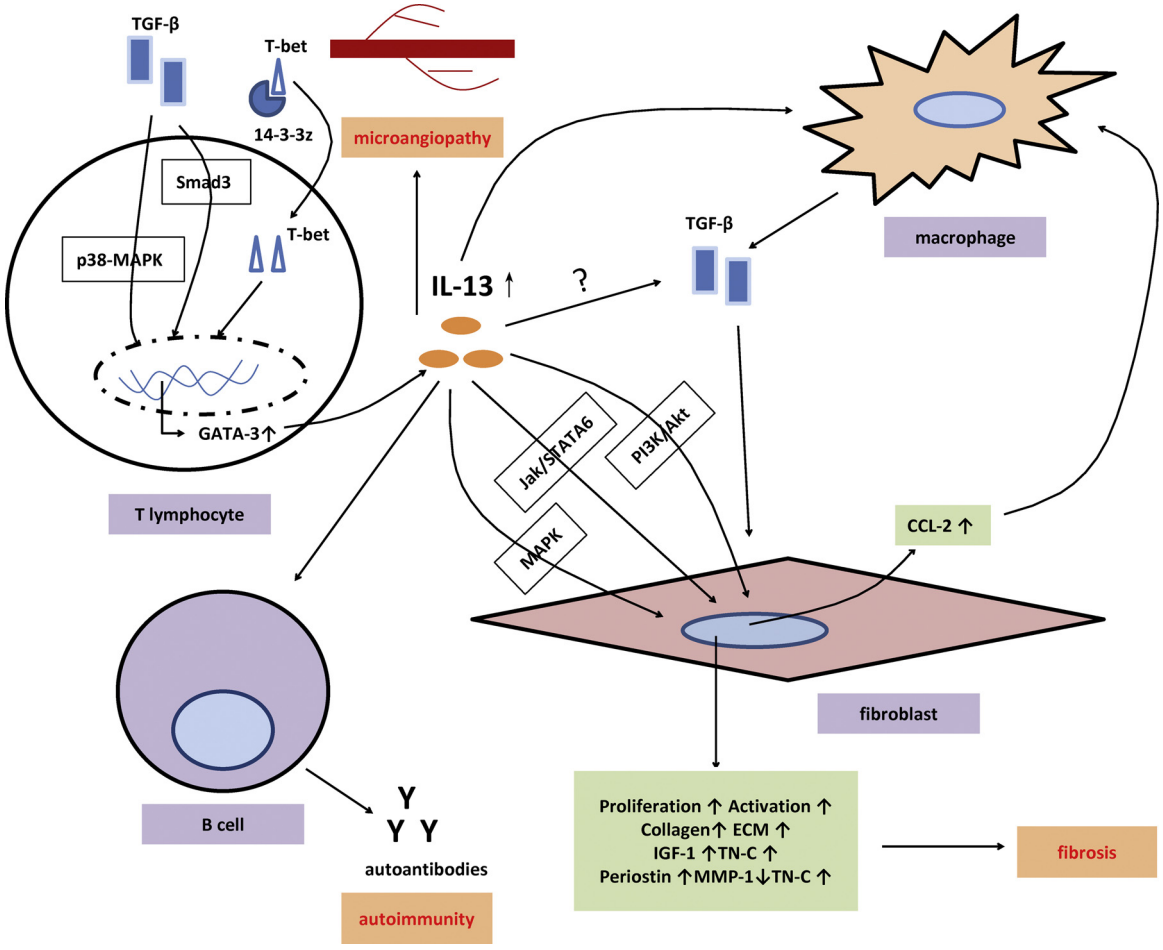


**Fig. 4.** The relationship between IL-13 and the pathogenesis of SSc.
The level of IL-13 is positively regulated by GATA-3, and TGF-β induces IL-13 expression by up-regulating GATA-3 transcription. In autoimmunity, IL-13 activated B cells produced a large number of autoantibodies. In fibrosis, IL-13 induced fibroblast differentiation and activation, and up-regulated the expression of various fibroblast cytokines. On the other hand, IL-13 could induce macrophages to transform into fibrotic phenotypes, producing TGF-β, a fibrogenic cytokine. IL-13 probably acts not only on fibroblasts alone, but also on fibroblasts through TGF-β.

IL-13 than control patients and CD patients [30]. On the contrary, IL-13 is not produced in excess by both mucosal explants and LPMCs collected from inflamed areas of UC patients in comparison to inflamed areas of CD patients and healthy mucosa [165]. No significant difference was found in serum IL-13 concentration between 67 UC patients and 21 healthy controls [86]. One study found mRNAs associated with a type 2 immune responses including *IL13,* and *IL13Rα2* genes in mucosal samples from patients with UC have significantly higher than patients with colon-only CD [166]. The amount of *IL-13* mRNA in the inflammatory tissue of intestinal mucosa in UC patients was 20 times higher than that in the non-inflammatory tissue [167]. However, the expression of IL-13 mRNA was substantially lower in UC patients compared with control samples when measured using quantitative reverse transcription-PCR (qRT-PCR) [168]. The expression of IL-13 in the intestine is controversial [169], different expression of IL-13 in different colon sites of same UC patients or at different stages. MicroRNA-31 and microRNA-155 are overexpressed in inflammatory colonic tissue of UC patients and attenuate IL-13 signaling by decreasing IL13Rα1's expression [170]. This suggests that there is a negative feedback mechanism in UC, which may explain the different levels of IL-13 in UC patients.

#### 4.4.2. Genetic association of IL-13 gene with UC

IL-13 deficient (IL-13$^{-/-}$) mice administered dextran sulfate sodium (DSS) exhibited significantly reduced severity of colitis compared to wild-type (WT) mice and IL-13$^{-/-}$ mice also exhibited reduced severity of DNBS-induced colitis [171]. Przybylowska *et al.* [172] found that people with genotype *IL-13* −1112 CT genotypes have a higher risk of UC in Poland. However, the *IL-13* gene +2044 G/A allele frequency was similar in CD, UC and healthy controls thus its mutation has no significant role in susceptibility to and phenotype of UC [173]. There is not much research on the relationship between polymorphism of *IL-13* gene and susceptibility to UC, so it is necessary to further study the relationship between polymorphism of *IL-13* gene and susceptibility to UC.

#### 4.4.3. Pathogenic role of IL-13 and its potential as therapeutic target in UC

Adequate studies have shown that IL-13 was associated with the pathogenesis of UC, and it affected epithelial tight junctions, apoptosis, and cell restitution leading to the destruction of intestinal epithelial barrier [63,174,175]. Previous mouse tests found that IL-13 activated caspase-3 via TWEAK/Fn14 pathway to induce apoptosis and dissociation of IEC intercellular junctions [176]. IL-13 may also increase flux across ion-selective pores by stimulating the production of claudin-2 in a STAT6-dependent manner, thus promoting ion flux across the barrier and increasing the permeability of colon epithelium [47,64,177]. Besides, IL-13 down-regulates matriptase and prostasin through phosphorylation of STAT6 leading to the loss of this barrier-protective protease pathway [178]. The STAT6 site in the targeted IL-13 signaling pathway is also an option for disease treatment. IL-13 downregulated tricellulin (Tric) by IL-13Rα2 in UC patients, therefore increased the passage of macromolecules [47], which may provide a biological mechanism for the abnormal uptake of macromolecular antigen by mucosal barrier. IL-13 impairs epithelial sodium channel (ENaC)-dependent sodium transport by activating the JAK1/2–STAT6–p38 MAPK signalling pathway modulation in distal colon epithelium in an intestinal cell model as well as in mouse distal colon [65,179]. Furthermore, IL-13/IL-13Rα1 up-regulates $Cl^-$ secretion mediated by cystic fibrosis transmembrane conductance regulator (CFTR) [180]. Thus, the electrolyte transport system at the end of the colon is damaged, leading to diarrhea, a main clinical symptoms of UC patients (Fig. 5). Colitis was more severe in GATA-3 Tg mice than in T-bet and retinoic acid-related orphan receptor gamma-t (RORγt) Tg mice, mainly due to a significant increase in IL-13 levels [181]. Clinical trials on IL-13 in UC patients in recent years are as follows. Anrukinzumab, an antibody blocking the attachment of IL-13 to IL-4Rα by binding to IL-13, showed no significant therapeutic effect in active UC [167]. However, IL-13 could induce colitis in the absence of IL-4Rα signalling which may explain the failure of anrukinzumab therapy [182]. Furthermore, UC patients were identified to have a faster clearance (CL) of anrukinzumab than healthy volunteers and asthma patients which suggested a higher dose level may be required for this population [183]. Tralokinumab, an IL-13-specific human monoclonal antibody, which binds and neutralizes IL-13, induced no significantly clinical improvement in UC but at least led to the improvements in clinical remission rates and mean partial Mayo score in some patients [184]. Although the above clinical trials have failed to block ulcerative colitis, the dual antagonists of IL-4 and IL-13 have been shown to be effective in the treatment of colitis in mice, suggesting therapeutic potential of double antagonism between IL-4 and IL-13 [185].

### 4.5. Type 1 diabetes

T1D is a chronic disease characterized by the destruction of insulin-producing pancreatic β cells due to the imbalance between proinflammatory and inflammatory suppression caused by lymphocytes in the immune system. Anti-inflammatory cytokines have a protective effect on islet β cells, and IL-13 can reduce the onset of spontaneous diabetes in NOD mice [186,187]. Moreover, the function of islet β cells is positively correlated with the cytokine reactivity of IL-13 [188]. Previous studies have shown that glutamic acid decarboxylase (GAD) can achieve therapeutic results by inducing Th2 immune response, especially the secretion of IL-13, to promote the rebalancing of Th1/Th2 in T1D patients [189]. All above evidence suggests IL-13 plays an important role in the pathogenesis of T1D as an anti-inflammatory factor and a Th2 immunomodulator.

#### 4.5.1. Circulating IL-13 expression in T1D

The expression of IL-13 in pancreatic tissue of T1D patients was significantly lower than that in healthy control group [88]. Spontaneous secretion of IL-13 in T1D high-risk population and newly diagnosed children decreased significantly [87,190]. The production of IL-13 by peripheral blood mononuclear cells (PBMCs) was significantly lower in high risk of insulin-dependent diabetes mellitus (IDDM), compared to subjects with low genetic risk of T1D, and adding insulin to the peripheral blood culture significantly increased the production of IL-13 in the diabetic precursor group [191]. The above evidence suggests that the change of IL-13 level in T1D patients is related to the pathogenesis of T1D.

#### 4.5.2. Genetic association of IL-13 gene with T1D

A case-control study from the Philippines showed that genotype combinations of IL-4, IL-13 and IL-4R had some effect on susceptibility to T1D [192]. However, a large sample size European population study failed to find the association of T1D with the three and their interaction [193]. There was also a lack of association between these three factors and T1D in diabetic pedigree studies or a large sample study from a queue, including *IL-13* gene [194,195]. So far, the association of *IL-4R* gene polymorphism with T1D is more common than that of IL-13, but the results are also contradictory [196,197]. Regional and ethnic differences may lead to inconsistencies in these results, and the association between *IL-13* gene and T1D susceptibility requires a larger sample size study.

#### 4.5.3. Pathogenic role of IL-13 and its potential as therapeutic target in T1D

Human invariant natural killer T (iNKT) cells have protective effect in diabetes-prone nonobese diabetic (NOD) mice model of T1D, although the specific mechanism is unclear. Usero *et al.* [88] have observed that iNKT cells inhibited T effector cells (Teffs) proliferation in an IL-13 dependent manner and the decrease of IL-13 secretion in T1D patients may lead to the deterioration of autoimmune process. Furthermore, RT-PCR and flow cytometry have showed that Teffs from

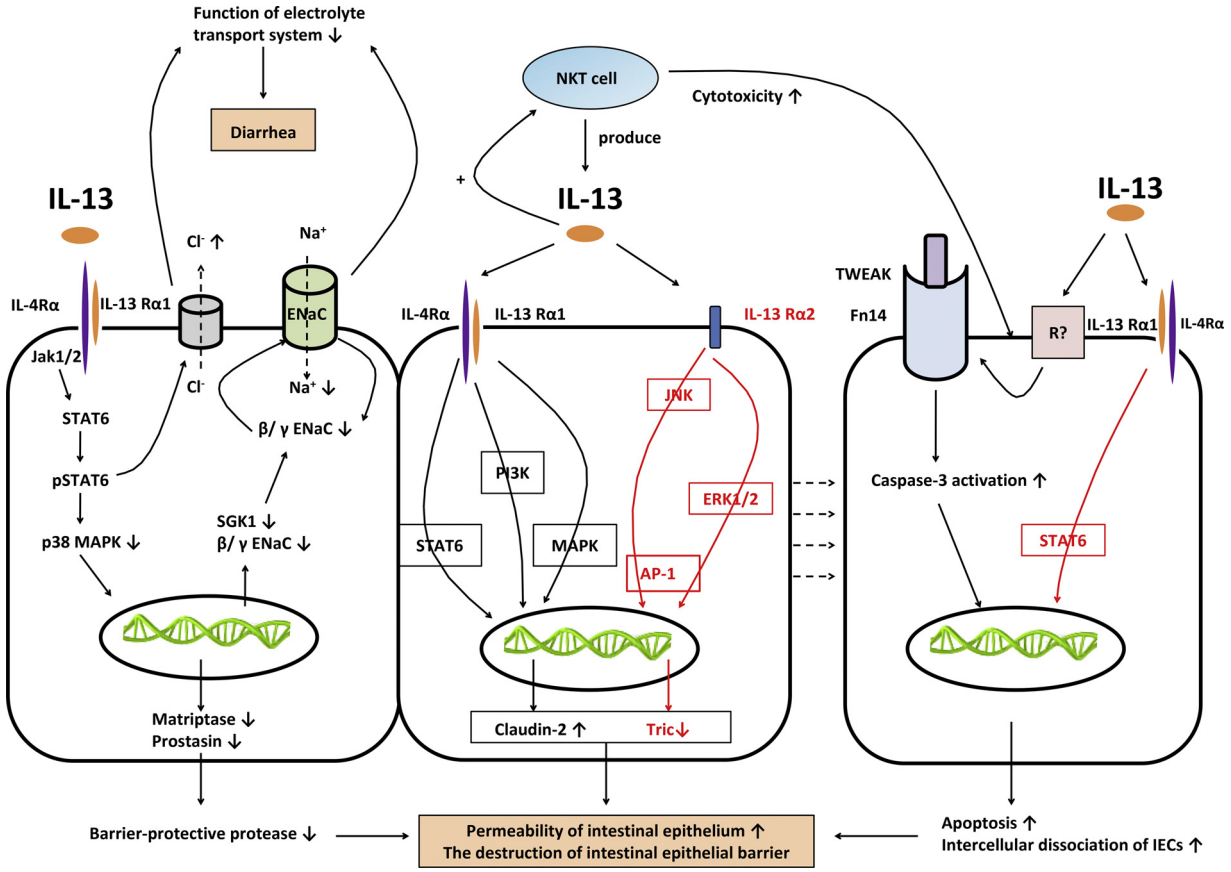


**Fig. 5.** The relationship between IL-13 and the pathogenesis of UC.
IL-13 acts on IECs through multiple signal pathways to induce apoptosis and abnormal expression of cytokines and proteases, including matriptase, prostasin, claudin-2,and tricellulin. Moreover, IL-13 can also enhance the toxicity of NKT cells to IECs. The above process leads to the destruction of the intestinal epithelial barrier. Besides, IL-13 also impairs epithelial sodium channel (ENaC)-dependent sodium transport and $Cl^-$ secretion, resulting in the disruption of electrolyte transport system, leading to diarrhea eventually. These processes lead to a vicious cycle of intestinal inflammation in patients with UC.

patients with T1D with a higher expression of IL13Rα1 and a significantly lower level of IL13Rα2 than controls, which suggested defects related to the IL-13 pathway may be responsible for the impaired Teff regulation by T1D-derived iNKT cells [88]. Rutti *et al.* [198] firstly observed that IL-13 could protect human islet β cells from IL-1β-induced apoptosis probably through PI-3 K/Akt signaling pathway. However, one study found that IL-13 activated IAK/STAT6 signaling pathway by binding to IL-13Rα1/IL-4Rα receptor to protect the activity of rodent β-cell line (INS-1E) cells and the PI-3K inhibitor wortmannin did not influence this cytoprotective response [66] A recent study also found that IL-13 significantly up-regulated the expression of anti-apoptotic genes in pancreatic β cells through STAT6, including myeloid leukaemia-1 (MCL-1) and B cell lymphoma-extra large (BCLXL), moreover, the expression of STAT6 in pancreatic β cells decreased significantly in T1D patients [199]. The silencing of STAT6 eliminates the protective effect of IL-13, and SIRPα, a novel regulator of β cell viability whose expression is dependent on the activation of STAT6 [199]. Prolonged treatment with recombinant human IL-13 (rhIL-13) markedly diminished the incidence of spontaneous T1D in the mice by downregulating immunoinflammatory diabetogenic pathways in NOD mice [187]. But it's worth noting that the incidence and development rate of T1D in IL-13Rα1–deficient ($13R^{-/-}$) or IL-4Rα-deficient mice decreased significantly, probably due to the IL-4Rα/IL-13Rα1 receptor supported the development of suppressive $Foxp3^{int}$ Tregs and sustaining the persistence of $CD206^+$ macrophages in the pancreas [200,201]. From the above evidence, it can be concluded that increasing the level of IL-13 may be a promising treatment for TID.

### 4.6. Sjogren's syndrome

SS is an autoimmune disease characterized by the destruction of salivary and lacrimal gland (LG) due to abnormal activation of the immune system, which is divided into two types: primary Sjogren's syndrome (PSS) and secondary Sjogren's syndrome (SSS). The frequent complaints of SS patients are dry eye and dry mouth, and the cause is unknown. The imbalance of Th1 and Th2 reactions is considered to be an important cause of SS, most studies suggest that SS is dominated by Th1 reactions, but others disagree, and no consistent conclusions have been reached so far [202,203].

#### 4.6.1. Circulating IL-13 expression in SS

Serum IL-13 level was significantly increased in SS patients and Id3 knockout ($Id3^{-/-}$) mice, which representing a model for T cell mediated SS [68,74,204]. In SS patients, IL-13 and IFN-γ are expressed both at the mRNA and protein level in the majority of LSG, and Th2cytokines such as IL-13 probably prevails in low-grade infiltration, while Th1e-specially IFN-γ increases in patients with definite SS and patients with advanced lymphocytic infiltration [205]. The balance of Th1/Th2 changes with the progress of immunopathology of SS, and IL-13 plays a potentially important role in the regulation of glands and pathological mechanisms of disease.

#### 4.6.2. Genetic association of IL-13 gene with SS

*IL-13* gene expression was not observed in PBMCs from either PSS patients or healthy controls, and was limited to PSS salivary glands [206]. There were no significant differences in the genotype or allele

frequencies of *IL4 2590*, *IL13 + 2044*, or *IFNG + 874* between pSS patients and controls, and Th2 cytokine genotypes are associated with a milder form of PSS [203].

*4.6.3. Pathogenic role of IL-13 and its potential as therapeutic target in SS*

The elevated levels of IL-13 in $Id3^{-/-}$ mouse are due to aberrant production of IL-13 by T cells, notably both CD4 αβ T cells and Vγ1.1/Vδ6.3 expressing γδ T cells and removal of γδ T cells prevented gland function impairment, but not lymphocytic infiltration [204]. The removal of αβ T cells in $Id3^{-/-}$ mice also eliminated disease symptoms, including lymphocytic infiltration in the gland tissues, and impaired saliva production [68]. Id3/IL-13 double knockout mice did not prevent lymphocytes from infiltrating into the glands, but avoided gland impairment [204]. The number of mast cells in the salivary glands of $Id3^{-/-}$ mice is significantly increased, and negatively correlated with saliva production [68]. Treatment of young $Id3^{-/-}$ mice with neutralizing anti-IL-13 monoclonal antibody over a two month period resulted in a significant reduction in serum IL-13 levels, increased saliva production and the reduction of mast cells present in the mandibular gland tissue [68]. IFN-γ aggravates LG destruction and secretory dysfunction and the deletion of IFN-γ in the CD25KO mice strain delays glandular destruction and preserves glandular function, the decreased ratio of IL-13/IFN-γ increased glandular apoptosis and facilitated apoptosis through increasing expression of IFN-γR by glandular epithelium and activation of caspases [207,208]. IL-13 can regulate the production of IFN-γ *in vitro* and *in vivo*, thus it may be an important role in SS. The above evidence suggests that IL-13 can regulate the function of glandular tissue and the recruitment of mast cells to the gland.

## 5. IL-13 serves as a promising therapeutic target for autoimmune diseases

Due to its role in the inflammatory response, fibrosis and immune regulation function, IL-13 is crucial to the pathogenesis of autoimmune diseases. Understanding the specific mechanisms of IL-13 in autoimmune diseases, and together with the knowledge of the capacity of current treatment strategy to target this process, may open avenues for the development of novel therapeutic strategies for autoimmune diseases.

The signal transduction pathway of IL-13 is shown in Fig. 1, and the function of IL-13 can be regulated by neutralizing cytokine antibodies, blocking receptor chains, inhibiting soluble inhibitors of receptors and targeting intracellular signal transduction. Some of these methods have been tried or are being applied to Th2 disease. There are several kinds of conventional IL-13 antibodies, lebrikizumab, tralokinumab and anrukinzumab, and RPC4046, novel anti-IL-13 antibody blocks IL-13 binding to IL-13α1 and α2 receptors [209,210]. Monoclonal antibodies against IL-13 have entered various clinical trials or animal experiment in succession and have been shown to be effective in the treatment of asthma, including lebrikizumab [211,212], tralokinumab [213], and RPC4046 [209]. Dupilumab, a fully human anti-interleukin-4 receptor α monoclonal antibody that blocks both IL-13 and IL-4, has been proven to be effective in controlling asthma symptoms and improving lung function signaling [214]. Tofacitinib, an small-molecule Janus kinase inhibitor especially targeting for JAK1 and JAK3, has shown a higher rate of mucosal healing and remission in the treatment of UC [215], SLE and RA [216], *etc.* which suggested targeting intracellular signal transduction of IL-13 is effective for treatment.

In addition to these human clinical drug trials for some diseases, animal experiments targeting IL-13 and its signaling pathways have produced favorable results for several autoimmune diseases. Many experiments have shown that IL-13 gene therapy could significantly reduce inflammation, bone destruction and angiogenesis in rat models of RA [67,120]. Mice lacking IL-13 or IL-4Rα showed a decrease in the incidence and severity of sclGVHD [139]. When the signal transduction of IL-13 is inhibited, the degree of fibrosis of the mouse is reduced, and this process is not dependent on increased IFN-γ activity [217]. Long-term use of recombinant human IL-13 (hIL-13) can significantly reduce the incidence of spontaneous T1D in mice [187]. Treatment of young $Id3^{-/-}$ mice with anti-IL-13 antibodies resulted in a decrease in serum IL-13 levels, the number of mast cells in salivary glands and improved saliva production [68]. Growing studies suggested that IL-13 was pivotal in autoimmune diseases and IL-13 may act as a therapeutic target for these diseases in clinical application. However, further studies are needed to make sure the validity and feasibility of clinical application for the following reasons. First, most work is based on animal experiments and may not be suitable for humans. Second, population-based drug trials have drawn inconsistent results and need further replication. Third, the exact mechanism of IL-13 in autoimmune diseases is not fully elucidated.

## 6. Conclusion

IL-13 is produced by multiple innate and non-innate immune cells and it has been shown abnormal expression in various autoimmune diseases, including SLE, RA, SSc, UC, T1D and SS. In addition, drug therapy targeting IL-13 has achieved some advances in UC, fibrosis and allergic diseases. Nonetheless, studies on most autoimmune diseases have been mostly remained in animal experiments. Despite the repeated function of IL-13 in humoral immunity, especially in B cells, the unique efficacy of IL-13 should make us recognize its importance on its powerful therapeutic potential for autoimmune diseases. IL-13 is not a pure Th2 cytokine since it is also produced by Th1 and Th17 cells. It is important to understand the role of IL-13 in autoimmune and non-Th2 inflammatory diseases in which the source might not be the Th2 cells. The beneficial and harmful effects of IL-13 on Th1 / Th2 /Th17 cells-mediated diseases may be different and the specific role of IL-13 in its therapeutic target deserves a further study. IL-13 acts on a variety of immune and non-immune cells by activating the Jak/STAT pathway, especially STAT6, to promote fibrosis, inhibit Th1 inflammation and the differentiation and development of Th17 cells and Th17 cytokines, and enhance Th2 immune response, as well as to regulate Treg cells somewhat. Therefore, the study of IL-13 as a therapeutic target may provide new ideas and insight into the treatment of autoimmune diseases. However, the signal transduction pathway of IL-13 is still unclear, especially the role of IL-13Rα2 receptors in autoimmune diseases. Further in-depth studies, especially in humans, are awaited to reveal the exact role of IL-13 in autoimmune diseases.

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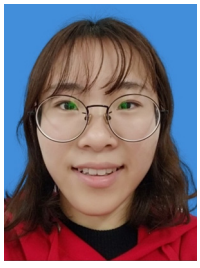

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