

# Role of IL-33/ST2 signalling pathway in systemic sclerosis and other fibrotic diseases

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## ABSTRACT

*Systemic sclerosis (SSc) is a complex autoimmune disease characterised by fibrosis of the skin and multiple internal organs. Interleukin 33 (IL-33) has recently been investigated as a potential key player in the pathogenesis of SSc and other fibrotic diseases, owing to its effects on tissue fibrosis. Understanding how IL-33 is regulated and how it contributes to the development of fibrosis will be important to elucidate disease pathogenesis and may shed light on new areas for therapeutic development for patients. Here we discuss the recent research progress in our understanding of the role and the underlying mechanisms of IL-33/ST2 signalling pathway in SSc and other fibrotic diseases.*

## Introduction

Systemic sclerosis (SSc), or scleroderma, is a heterogeneous autoimmune disease characterised by vascular injury, immune dysfunction and multiple organ fibrosis. Raynaud's phenomenon is usually the first clinical symptom of the disease, and skin thickening and fibrosis are the most typical features of SSc. Pathological changes in the lung, gastrointestinal tract, kidney, and heart, especially pulmonary fibrosis and pulmonary hypertension are the major causes of premature death in patients with SSc (1).

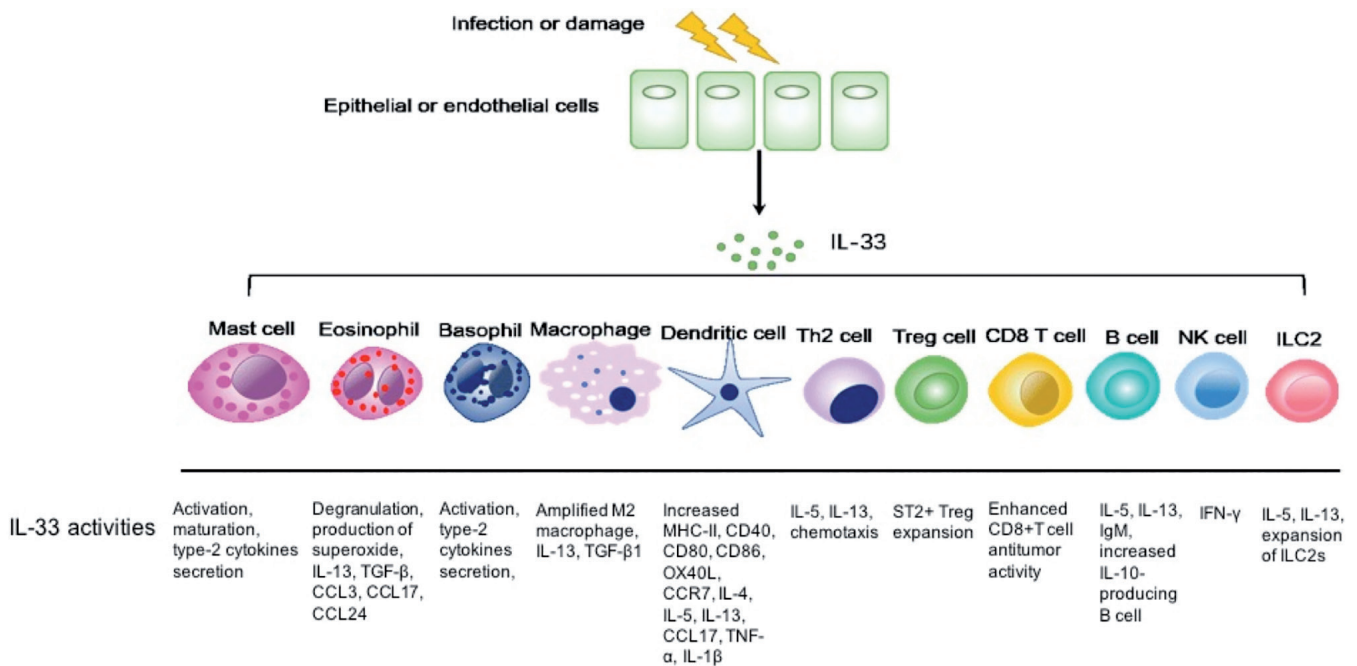
The aetiology and pathogenesis of SSc are complex. The activation of microvascular endothelial cells (ECs) and fibroblasts, and the dysfunction of the acquired immune system are the main pathogenic processes of SSc (2-3). Fibroblast dysfunction results in over-expression and accumulation of collagen and other matrix components, which leads to the occurrence and development of SSc (4). Despite intense research efforts, the pathogenesis of SSc

remains poorly understood and currently only symptomatic treatment is available for patients (5).

Interleukin-33 (IL-33), a member of the IL-1 family, plays a key role in innate and adaptive immunity. Full-length IL-33 (fl-IL-33) is mainly produced by ECs, fibroblasts, smooth muscle cells and epithelial cells, such as, lung and gut epithelial cells (6). It is stored in the nucleus and released by necrotic cells in damaged tissues to modulate inflammatory responses (7). The IL-33 receptor, also known as ST2, is selectively expressed by a variety of immune cells, including mast cells, macrophages, basophils, eosinophils, dendritic cells, B cells, T helper 2 (Th2) cells, type 2 innate-like lymphoid cells (ILC2s), natural killer (NK) cells, CD8<sup>+</sup>T cells and regulatory T (Treg) cells (8-12). IL-33 has pleiotropic biological functions that facilitate the proliferation, survival and cytokine secretion of ST2<sup>+</sup> cells (figure 1) and several studies suggest that IL-33 could be involved in the pathogenesis of tissue fibrosis. Accordingly, in this article, we summarise the evidence for pathogenic roles of IL-33 in SSc and other fibrotic diseases and discuss its potential value as a therapeutic target.

## IL-33 and its receptor ST2

The human *IL-33* gene is found on the short arm of chromosome 9 and spans about 42 kb of genomic DNA (13). Human *IL33* mRNA encodes a peptide of 270aa residues which constitutes a three-dimensional structure (14). Fl-IL-33 is constitutively expressed at high levels in the nucleus and acts as an intracellular gene regulator in the steady state (15). During inflammation or undergoing necrosis, the induced expression level of IL-33 can be markedly elevated and fl-IL-33 is released in the extracellular space. Fl-IL-33 protein



**Fig. 1.** The effects of IL-33 on ST2<sup>+</sup> immune cells. Infection or other cause of damage activates epithelial or endothelial cells to release IL-33 molecule, which in turn binds to ST2 on a variety of immune cells and then enhances their functions.

can be cleaved by neutrophil elastase and cathepsin G, as well as mast cell chymase and trypsin, generating shorter mature forms of IL-33 with between 10-30-fold higher biological activity than fl-IL-33 (16-17).

IL-33 receptor ST2 is a member of the Toll-like receptor (TLR)/IL-1 superfamily. It has at least three isoforms and two of them are the most important: a membrane-bound receptor (ST2L) and a soluble form (sST2). The structure of ST2L contains an extracellular domain, a single transmembrane domain, and an intracellular TIR cytoplasmic domain (18, 21). IL-33 binding to ST2L leads to interaction between ST2 and IL-1 receptor accessory protein (IL-1RAcP), which clusters their toll/interleukin-1 receptor (TIR) domains and in turn recruits myeloid differentiation primary response protein 88 (MYD88), the IL-1R associated kinase 4 (IRAK4), IRAK1, and TNF receptor-associated factor 6 (TRAF6) proteins (19). Subsequently, several downstream signalling cascades including nuclear factor- $\kappa$ B (NF- $\kappa$ B), p38, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) are activated to increase the production of Th2-associated cytokines, such as IL-4, IL-5, and IL-13, and support the pro-

liferation and survival of ST2<sup>+</sup> cells including Th2 cells, Treg cells and ILC2s (20-21).

In addition, the biological activity of IL-33 is closely regulated by sST2, which avidly binds to free IL-33 as a decoy receptor, thus disrupting functional IL-33/signalling via cell surface-bound ST2 (14). The IL-33/ST2 signalling pathway is also negatively regulated by single immunoglobulin domain IL-1R-related molecule (SIGIRR), which likely inhibits IL-33-mediated signalling through interaction with the ST2 receptor complex (22).

#### Pathological roles of IL-33

IL-33 released through cell death or damage can induce excessive inflammatory responses, causing damage to local and systemic tissues. It has been well documented that IL-33/ST2 has pleiotropic roles in many immune mediated diseases and its specific function is disease and model dependent. Numerous studies have shown an important role for IL-33 in a variety of inflammatory diseases such as asthma (23-25), allergic lung diseases (26-28), cardiovascular diseases (29-31), musculoskeletal diseases (32-34), inflammatory bowel disease (35-36), atopic dermatitis (37-38) and some neurologi-

cal degenerative disease (39-40) (Table I). In addition, IL-33 may be a major effector molecule in the initiation and progression of a number of fibrotic diseases through both direct effects on ECs and fibroblast activation and indirect mechanisms such as stimulation of IL-13 and TGF- $\beta$  production (41-42). The purpose of this review is to highlight the pathological roles of IL-33/ST2 signalling in fibrotic diseases, especially in SSc.

#### Role of IL-33/ST2 in fibrotic disorders

IL-33 is a proinflammatory and profibrotic mediator in many fibrotic disorders, including fibrosis of lung, liver and heart tissues. IL-33 levels were elevated in the bronchoalveolar lavage fluids of patients with idiopathic pulmonary fibrosis (IPF) and lung homogenates from bleomycin-injury mice (43-44). Luzina *et al.* (44) also showed that the fl-IL-33 may enhance bleomycin-induced lung inflammation and fibrosis through stimulating expression of TGF- $\beta$  and some non-Th2 cytokines like IL-6 and MCP-1. Interestingly, mature IL-33 was able to participate in the polarisation of alternatively activated M2 macrophages and induce the expansion of ILC2s to increase IL-13

**Table I.** Roles of IL-33/ST2 signalling in inflammatory and fibrotic diseases.

Disease	Role of IL-33/ST2 signalling	Reference
Asthma	IL-33 levels were correlated with clinical asthma severity. <i>IL-33</i> variants have been implicated in the risk of asthma. IL-33 induced airway hyperresponsiveness.	23, 24, 25
Allergic lung diseases	IL-33 was significantly increased in OVA-induced acute allergic lung inflammation. Blockade of either IL-33 or ST2 reduced airway inflammation.	26, 27, 28
Cardiovascular diseases	Patients suffering myocardial infarction had elevated serum sST2 levels. Recombinant IL-33 reduced aortic atherosclerotic plaque development. ST2 <sup>-/-</sup> mice showed more cardiac fibrosis, and decreased survival recombinant IL-33 significantly reduced cardiac hypertrophy and fibrosis.	29, 30, 31, 52
Musculoskeletal diseases	IL-33 levels were correlated with disease activity in RA patient. In mice, blocking of IL-33 led to decreased disease severity, and treatment with IL-33 at disease onset exacerbated disease development.	32, 33, 34
Inflammatory bowel disease	IL-33 KO mice and ST2 KO mice had attenuated IBD. Recombinant IL-33 treatment at the onset of DSS-induced colitis exacerbated disease severity, treatment during recovery or chronic phases ameliorated colitis.	35, 36
Atopic dermatitis	Patients with atopic dermatitis have higher IL-33 expression levels in their skin lesions. Transgenic mice expressing IL-33 had spontaneous atopic dermatitis-like inflammation.	37, 38
Alzheimer disease	IL-33 expression was decreased in the brain of patients, and levels of serum IL-33 and sST2 are elevated.	39, 40
Lung fibrosis	Level of IL-33 was elevated in the bronchoalveolar lavage fluids of patients with IPF. IL-33 may enhance bleomycin-induced lung inflammation and fibrosis in mice. Treatment with anti-IL-33 antibody markedly reduced airway inflammation and lung fibrosis.	43, 44
Liver fibrosis	IL-33 <sup>-/-</sup> mice showed decreased hepatic collagen deposition and ECM-associated gene expression. IL-33 aggravated hepatic fibrosis in mice.	49, 50
IgG4-RD	In mice, IL-33 expression was markedly enhanced in the pancreas. Neutralising Ab against ST2 protected mice from the development of chronic pancreatitis. In patients, IL-33 concentrations were correlated with disease activity.	56, 57, 58
SSc	Polymorphism of <i>IL-33</i> gene was related to increased susceptibility to SSc. In early SSc, the expression of IL-33 protein in ECs and epidermis of skin was down-regulated, while the levels remained the same in late stage SSc. Serum levels of IL-33 were elevated in SSc patients and associated with the severity of skin and pulmonary fibrosis. Recombinant IL-33 treatment aggravated bleomycin-induced fibrosis in mice.	60, 63, 64, 71

and TGF- $\beta$  production in the lung (45). Collectively, these data suggest that IL-33 plays important roles in the fibrotic process via a variety of mechanisms. The expressions of MMP-9, TIMP-1, TRAF-6, and NF- $\kappa$ B are increased in human embryonic lung fibroblasts when stimulated with IL-33, and in turn promoted an inflammatory reaction, injured the alveolar epithelial cells, stimulated fibroblast collagen synthesis and accelerated the process of pulmonary fibrosis (46). In bleomycin-induced lung fibrosis in WT mice, treatment with anti-IL-33 antibody markedly reduced airway inflammation and lung fibrosis (45). Therefore, neutralising IL-33 may become a potential therapeutic strategy in lung fibrosis.

Normal hepatocytes constitutively express IL-33 mRNA, whereas the expression levels of IL-33 and ST2 mRNA

can be further elevated in the process of hepatic fibrosis (47). Extracellular IL-33 led to activation and expansion of ILC2s in the liver via an ST2-dependent signalling pathway. Activated hepatic ILC2s could produce IL-13, which mediated activation hepatic stellate cells by phosphorylation of STAT6 (48, 49). *IL-33*<sup>-/-</sup> mice showed decreased hepatic collagen deposition and a reduction in extracellular matrix (ECM)-associated gene expression of *COL1A1* and *COL3A1* in their hepatocytes (49). When fed with high-fat diet, IL-33 aggravated hepatic fibrosis in WT mice, but not in *ST2*<sup>-/-</sup> (50). These results also indicated that IL-33 drives ECM deposition in liver fibrosis in an ST2-dependent manner.

Myocardial production of IL-33 and sST2 changes over time in the development of cardiac fibrosis (51). IL-33/

ST2 signalling may have beneficial therapeutic potential for regulating the response of cardiomyocytes and cardiac fibroblasts to overload. In a murine model of transverse aortic constriction (TAC), *ST2*<sup>-/-</sup> mice showed more cardiac fibrosis, and decreased survival compared with WT mice (52). Treatment with recombinant IL-33 significantly reduced cardiac hypertrophy and fibrosis, and also improved survival after TAC in WT mice. This phenomenon was not observed in *ST2*<sup>-/-</sup> littermates, which confirmed that the therapeutic effect is ST2 dependent (52). In brief, IL-33/ST2 pathway might play a protective role in the fibrosis and remodeling of myocardial cells, and stifle the progression of heart failure. Conversely, after inducing myocardial infarction by coronary artery ligation in a rat model, the expression of ST2 mRNA was

found in cardiac myocytes and sST2 was transiently increased (53). The myocardial level of sST2 was shown to be positively correlated with the processes of inflammation and fibrosis (54).

IgG4-related disease (IgG4-RD) is a rare inflammatory disorder, characterised by elevated serum IgG4, infiltration of IgG4-positive cells in multiple organs, sclerosing and severe fibrosis (55). Watanabe *et al.* reported that IL-33 expression was markedly enhanced in the pancreas of mice with experimental IgG4-RD compared with those without IgG4-RD (57). Mice treated with neutralising Ab against ST2 were protected from the development of chronic pancreatitis (58). In patients with IgG4-RD, IL-33 expression has been noted in plasmacytoid dendritic cells and M2 macrophages within the salivary glands (56). Furukawa *et al.* also showed that the serum concentration of IL-33 is reduced upon corticosteroid treatment in patients with IgG4-RD, suggesting that IL-33 concentration is correlated to the disease activity (56). The potential of IL-33/ST2 pathway in the treatment of IgG4-RD is worth exploring.

In summary, IL-33 plays different but important roles in the development of fibrosis in various tissues and organs. While IL-33 is a pro-fibrogenetic mediator in the fibrosis of lung and liver in ST2- and ILC2-dependent fashions, it demonstrates cardioprotective and anti-fibrotic effects on cardiac tissues through currently unknown mechanisms.

### IL-33/ST2 in the pathogenesis of SSc

It is well documented that the family history of SSc represents increased risk for developing the disease (59). Since susceptibility genes can provide hints for pathological mechanisms, several studies focused on the association of genetic polymorphism of *IL-33* in SSc patients (60). A multicentric preliminary study in 300 Turkish patients with SSc and 280 healthy controls showed that rs7044343 polymorphism of *IL-33* gene was related to increased susceptibility to SSc (61). However, a study in a Chinese population involving 58 patients with SSc and 113 healthy

control individuals failed to find any association between *IL-33* rs7044343 polymorphism and SSc susceptibility (62). Different ethnic backgrounds and the small number of patients may partly explain this discrepancy. More studies are warranted to uncover the possible active role of *IL-33* gene polymorphism in SSc.

Recently, there has been accumulating evidence for an involvement of IL-33 in the development of SSc. Manetti *et al.* (63) investigated IL-33/ST2 expression in the skin biopsies from patients with early SSc and showed that the expression of IL-33 protein was down-regulated in ECs and epidermis, while IL-33 mRNA levels remained unchanged or even up-regulated. ST2 expression was elevated significantly in cell membranes of ECs, activated fibroblasts and perivascular infiltrating mast cells, macrophages, T cells and B cells. By contrast, in patients with late stage SSc, IL-33 protein was constitutively found in most ECs while ST2 expression was weaker. This study suggested that IL-33 might be mobilised from ECs upon its activation to signal through ST2 in fibroblasts and immune cells.

Subsequently, Yanaba *et al.* found that serum levels of IL-33 were elevated in patients with SSc compared with healthy controls (64). The result was further confirmed by Terras *et al.* in a German SSc cohort, Manetti *et al.* in an Italian cohort, and our group in a Chinese cohort (65-67). Studies also found that the high serum levels of IL-33 were associated with peripheral vascular involvement, such as digital ulcers (68-69) and the severity of skin sclerosis and pulmonary fibrosis (64). A Swedish group found that serum sST2 was elevated in late phase limited cutaneous SSc (lcSSc) compared with shorter disease duration, or with the diffused subtype of SSc. After iloprost (prostacyclin) treatment, serum sST2 levels were lowered (70). These findings potentially warrant further research on the role of sST2 in pathological processes of SSc. Thus serum IL-33 and/or sST2 may act as a progression biomarker for vascular involvement or fibrosis in lcSSc.

To explore the consequences of dysregulated IL-33 signalling pathway

in skin, Rankin *et al.* injected recombinant IL-33 to IL-1RAcP<sup>-/-</sup>, ST2<sup>-/-</sup>, IL-13<sup>-/-</sup> and WT mice subcutaneously, and found the development of cutaneous fibrosis was followed by ST2 and IL-1RAcP-dependent accumulation of CD3<sup>+</sup> lymphocytes and eosinophils. Then, IL-33 stimulated bone marrow-derived eosinophils to secrete IL-13, which might be a key mechanism of IL-33 induced fibrosis (71). Besides, IL-33 also induced elevated expressions of some ECM-associated genes, such as *COL6A1*, *COL3A1*, *TIMP-1* and *MMP-12*, while significantly reducing the expression levels of other ECM-associated genes, such as *COL2A* and *COL4A1*. The altered expression of ECM-associated genes may contribute to IL-33 induced cutaneous fibrosis (71).

A recent work by MacDonald *et al.* showed the high tissue-localised expression of IL-33 caused the differentiation of Treg cells into Th2-like cells in SSc lesion skin. They also found that a significantly higher percentage of skin FOXP3<sup>+</sup>Treg cells co-expressed ST2 compared with FOXP3<sup>+</sup>Tconv cells (72). Furthermore, in bleomycin-treated *Fli1<sup>+/-</sup>* mice model for SSc, dermal fibroblast-produced IL-33 contributed to Th2-like Treg trans-differentiation (73). These data suggests that the presence and accumulating of Th2-like Treg cells in localised skin might aggravate fibrosis in patients with SSc and therefore provides new insight into the role of IL-33 in SSc.

### Conclusions and future perspectives

In conclusion, aberrant expression of IL-33 and ST2 in tissues is associated with a variety of fibrotic diseases, and the critical role of IL-33 in SSc pathogenesis has begun to be elucidated. However, present studies are not enough to sufficiently understand the precise function of IL-33 in the process of fibrosis. Therefore, to comprehensively explore the therapeutic potential of IL-33/ST2 signalling pathway in SSc and other fibrotic diseases, further studies on the function and the underlying molecular mechanisms of IL-33/ST2 signalling pathway are required, especially in human systems.

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