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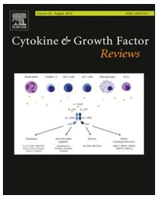

The role of the IL-33/ST2 axis in autoimmune disorders: Friend or foe?

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ABSTRACT

Autoimmune diseases (ADs), which are common immune-mediated inflammatory syndromes, are characterized by an imbalance between T effector (Th)1/Th17 cells and T regulatory cells. Interleukin (IL)-33, a member of the IL-1 family, induces inflammatory disease development by mediating type 2 immune responses. Recently, IL-33/ST2 axis was reported to induce autoimmunity involving Th1 and Th17 cells. In this review, we focus on the expression, regulation and function of IL-33/ST2 pathway in the context of autoimmune disorders. We discuss the clinical potential of this signaling pathway in predicting disease activity and severity and offer possible future therapeutic alternatives.

1. Introduction

Interleukin (IL)-33 is encoded by the *IL-33* gene and belongs to the IL-1 cytokine family. IL-33 is also called IL-1F11, following IL-1 family nomenclature [1]. In 2003, IL-33 was named nuclear factor from high endothelial venules (HEV-NF), as it is highly expressed in the high endothelial venule (HEV) endothelial cell (EC) nucleus [2]. It is well recognized that HEVs are involved in the activation and mobilization of lesional lymphocytes infiltration [3,4], indicating that HEV-NF might induce chronic inflammation. In 2005, Schmitz et al. rediscovered IL-33 through computational sequence scanning research, and identified IL-33 as a member of the IL-1 family [5]. IL-33 is primarily secreted by ECs, fibroblasts, epithelial cells, and various immune cells, such as dendritic cells (DCs) and macrophages [5–9]. Its cytokine function involves combining with its receptor, suppression of tumorigenicity 2 (ST2, which is also named as growth STimulation expressed gene 2), which is commonly expressed on CD4^{+} T cells, CD8^{+} T cells, mast cells (MCs), macrophages, DCs, basophils, eosinophils, natural killer T cells, and group 2 innate lymphoid cells (ILC2s) [10–12]. The IL-33/ST2 axis has been implicated in various diseases, such as asthma, food allergies, central nervous system (CNS) inflammation, inflammatory bowel diseases (IBDs), atopic dermatitis, cancer, and various fibrotic diseases [13–15].

Autoimmune diseases (ADs) are self-reactive, pathologic immune disorders that act against autologous tissues. Rheumatoid arthritis (RA), IBDs, multiple sclerosis (MS), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), psoriasis, type 1 diabetes (T1D), uveitis and autoimmune thyroid diseases are the most common ADs [16,17]. As a

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Abbreviations: ADs, autoimmune diseases; Th, T effector; IL-33, interleukin-33; HEV, high endothelial venules; ECs, endothelial cells; DCs, dendritic cells; ST2, suppression of tumorigenicity 2; MCs, mast cells; ILC2s, group 2 innate lymphoid cells; CNS, central nervous system; IBDs, inflammatory bowel diseases; RA, rheumatoid arthritis; MS, multiple sclerosis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; IFIL-33, full-length IL-33; TF, transcription factor; NF-κB, nuclear factor kappaB; TNF, tumor necrosis factor; HC, healthy control; TLRs, toll-like receptors; TGF-β, transforming growth factor-β; IFN, interferon; TIR, toll-like receptor/IL-1 receptor; IL-1RAcP, IL-1 receptor accessory protein; MyD88, myeloid differentiation factor 88; IRAK, IL-1R-associated kinase; TRAF6, TNF receptor-associated factor 6; AP-1, activator protein-1; ERK, extracellular signal-regulated kinase; p38MAPK, p38 mitogen-associated protein kinase; JNK, c-Jun N-terminal kinase; TIR, toll/IL-1 receptor; SIGIRR, single Ig IL-1R-related molecule; ECM, extracellular matrix; M2 macrophage, the alternatively activated macrophage; Tregs, regulatory T cells; SF, synovial fluid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CIA, collagen-induced arthritis; WT, wild-type; AIA, autoantibody-induced arthritis; HIF-1α, hypoxia-inducible factor-1α; UC, ulcerative colitis; CD, Crohn's disease; DSS, dextran sodium sulfate; CSF, cerebrospinal fluid; OPCs, oligodendrocyte precursor cells; EAE, experimental autoimmune encephalomyelitis; MDSCs, myeloid-derived suppressor cells; PKC, protein kinase C; I/R, ischemia/reperfusion; DKZ, diacylglycerol kinase zeta; PBMC, peripheral blood mononuclear cell; lcSSc, limited cutaneous SSc; PI3K, phosphatidylinositide 3-kinases; AKT, protein kinase B; eNOS, endothelial nitric oxide synthase; BD, Behcet's disease; RPE, retinal pigment epithelial; EAU, experimental autoimmune uveitis; AIHA, autoimmune hemolytic anemia; PBC, primary biliary cirrhosis

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public health problem, these diseases are chronic and incurable, leading to both significant individual suffering and societal costs. Immune abnormalities are characterized by imbalanced immune tolerance and are driven by self-reactive T effector (Th) 1/Th17 cells and B cells [18]. Previous evidence has suggested that IL-33/ST2 signaling contributes to allergic disorders by inducing Th2 cell activation, Th2 cytokine production and predominantly type 2 immune responses [15]. IL-33/ST2 axis also exacerbates Th17 cell-mediated airway inflammation [19]. Increasing evidence suggests that IL-33 is a key component of autoimmunity. In this review, we summarize the current knowledge concerning the roles of IL-33/ST2 signaling in several ADs. We conclude that IL-33 has both proautoimmune effects and antiautoimmune functions; thus, the therapeutic effects of targeting IL-33 and ST2 seem promising.

2. The location and function of intracellular IL-33

Intracellular IL-33 is expressed in the nucleus of epithelial cells involved in mechanical barriers, which consist of keratinocytes, epithelial cells, fibrocytes, fibroblasts, and smooth muscle cells. Moreover, IL-33 is highly expressed in the nucleus of human HEV ECs and called HEV-NF, indicating the role of IL-33 in EC homeostasis. An IL-33-LacZ genetrap reporter mouse exhibits nuclear IL-33 expression in the embryonic tissues during embryonic development, and in the secondary lymphoid tissues and brain of adults mice [6]. In contrast, constitutive IL-33 expression in the nucleus is not detected in mouse blood vessels, but the induction of IL-33 expression under inflammatory conditions can be measured [6], suggesting different expression of nuclear and induced IL-33 in mice and humans [8,9].

In previous studies, nuclear IL-33 was regarded as a heterochromatin-related nuclear factor possessing transcriptional regulatory properties. Human intracellular full-length IL-33 (IFIL-33) and mouse IFIL-33 consist of 270 and 266 amino acids, respectively [10]. There is a specific structure in the N terminus and the typical IL-1 fold in the C terminus of human IFIL-33. The domain mentioned above is necessary for nuclear localization, heterochromatin interactions and transcriptional suppression [2,20]. The IL-33 peptide docks in the acidic pocket formed by the H2A-H2B dimer in heterochromatin, promotes nucleosome-nucleosome interactions and regulates gene expression [21]. Moreover, the interaction between IL-33 and the transcription factor (TF) nuclear factor kappa B (NF-κB) regulates the release of NF-κB-associated proinflammatory signals. Through recognition involving the N-terminal domain, IFIL-33 can bind to the NF-κB p65 subunit, reducing the association of TFs with DNA-response elements. These changes decrease the transactivation of target genes, including IkBα, tumor necrosis factor (TNF)-α and C-REL [22]. Choi YS et al. [23] have found that IL-33 combines with the p65 promoter region and upregulates nuclear p65 expression. IL-33 then induces EC activation by mediating the expression of vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1. In addition, IL-33-deficient human ECs show altered NF-κB-dependent IL-6 expression, downregulated expression of the chemokines RANTES and Fractalkine, and increased release of the soluble form of ST2 (sST2) [24]. Further studies have indicated that IL-33 binds to the transcriptional repressor histone methyltransferase SUV39H1 and to multiple putative homeodomain protein binding motifs in the proximal and distal promoters of the *ST2* gene. Bessa J et al. [25] reported that the expression of an IL-33 mutant protein lacking the N-terminal domain led to high circulating IL-33 levels, and heterozygous mice carrying this mutant protein had high mortality attributes to eosinophilic infiltration into multiple organs. Taken together, these findings show that the IFIL-33 located in the nucleus exerts regulatory effects on immune homeostasis.

3. The release and processing of extracellular IL-33

Although IL-33 constitutively localizes to the nucleus in several local barrier cells and immune cells, cellular necrosis leading to the extracellular release of IFIL-33 [26] raises questions concerning how effectively active IL-33 is processed and released. In the absence of cellular necrosis, mechanical strain induces IL-33 secretion in murine fibroblasts in vitro and in vivo [27]. Additionally, the increased myocardial pressure in hypertension affects cardiac ECs, causing them to release IL-33. Thus, myocardial pressure overload can become systemic inflammation [28]. Fluorescent pulse-chase fate tracking experiments have indicated that the dynamic IL-33 flux between the nucleus and cytoplasm is mediated by nuclear pore complex functions [27]. Notably, the upregulation of IL-33 protein levels in extracellular fluids was shown to be related to reduced staining for IL-33 in the cell nucleus of nasal ECs, indicating the release of prepared IL-33 from the nucleus to the extracellular space [29]. Because of its ability to sense damage, IL-33 functions as an “alarmin” or a damage-associated molecular pattern molecule. IL-33, which is primarily expressed by structural and barrier cells, is released from injured and stressed cells to send out warning signals to the innate and adaptive immune systems following cellular necrosis or tissue injury [26,30,31].

Initially, full-length IL-33, a 30-kDa form, is biologically active [32,33]. Like the other IL-1 family members IL-1β and IL-18, IL-33 is produced and subsequently cleaved by caspase-1 into a mature 18-kDa form (hIL-$33_{112\text{-}270}$) [5]. In contrast, Cayrol C et al. have found that caspase-1 processing leads to IL-33 inactivation [26]. In consistent with this finding, increased IL-33 mRNA and bioactive protein levels are detected in caspase-1 knockout mice [34]. Moreover, caspase-1, which is activated by the NLRP3/ASC inflammasome complex, downregulates IL-33 expression and dampens IL-33-mediated allergic lung inflammation [34]. These findings collectively indicate that the roles of caspase-1 in the process of IL-33 production and the molecular mechanism of IL-33 remain to be elucidated. Interestingly, caspase-1 fails to affect IL-33 cleavage in the absence of other proteases [35], suggesting that caspase-1 can activate other proteases, and caspase-1 may affect the activation of IL-33 [36]. In addition, during apoptosis, IL-33 can be cleaved by caspase-3 and caspase-7 at a cleavage site located within the IL-1-like domain, causing the release of biologically inactive 20-22-kDa forms (hIL-$33_{1\text{-}178}$ and hIL-$33_{179\text{-}270}$) [9,26,35,37]. The cleavage and inactivation of IL-33 by caspases might be important to sustain bioactive IL-33-induced tissue damage during programmed cell death.

In contrast, released proteases during inflammatory conditions seem to increase the biological activity of IL-33. Serine proteases produced by activated MCs (chymase and tryptase) [38] and neutrophils (cathepsin G and elastase) [39] process full-length IL-33 into functional forms containing the IL-1-like cytokine domain (IL-$33_{95\text{-}270}$, IL-$33_{99\text{-}270}$ and IL-$33_{109\text{-}270}$) with 30-fold higher biological activity than the full-length protein. Notably, the cleavage site of these proteases is situated outside of the IL-1-like domain in the C terminus. In summary, in the presence of inflammatory stimuli or under inflammatory conditions, the bioactivity of IL-33 can be enhanced by limited N-terminal domain proteolysis in the inflamed tissue. The mature form is released extracellularly and regulates inflammatory processes via ST2 signaling. The nuclear IL-33 expressed in ECs, fibroblasts and epithelial cells can maintain barrier functions and initiate immune responses following stimuli or damage in multiple diseases such as asthma [40,41] and cardiovascular disease [42,43].

4. Stimulated IL-33 expression

Notably, IL-33 can be expressed in various cell types (mainly ECs) and localizes to the nucleus under healthy conditions [24]. Compared to healthy controls (HCs), bronchial asthma patients [44] and COPD patients [45] exhibit increased IL-33 expression in the nucleus of airway epithelial cells. In mouse vascular ECs, endogenous IL-33 is not expressed constitutively. Interestingly, IL-33 can be stimulated by the lipopolysaccharide (LPS)-induced systemic inflammatory response [6]. Following nematode infection or the intranasal administration of chitin, the nuclear level of IL-33 in alveolar epithelial type II cells is increased, and lung eosinophilic inflammation is induced in mice [46]. In addition, the inducible extracellular release of IL-33 is also observed in a set of diseases associated with infection and inflammation [42,47–49]. More importantly, IL-33 acts as a disease-associated biomarker for the high level of IL-33 that is generally associated with the activity and severity of diseases, especially asthma, atopic allergy, cancer, etc. [12,13].

IL-33 is confirmed to have a role as an alarmin by the discovery that IL-33 expression is positively mediated by pattern-recognition receptors, especially toll-like receptors (TLRs). In human corneal epithelium studied ex vivo and in vitro, the mRNA and protein levels of IL-33 are increased and mainly induced by the TLR3 ligand poly(I:C) and the TLR5 ligand flagellin, and these increases can be blocked by an anti-TLR3 antibody and an anti-TLR5 antibody, respectively [50]. IL-33 mRNA expression has been observed to increase in the lungs, spleen, liver and stomach in a mouse model 4 h after the systemic administration of the TLR4 agonist LPS (2 mg/kg) [51]. Moreover, the TLR3 agonist poly(I:C), TLR4 agonist LPS, TLR7/8 agonist R848 and TLR9 ligand CpG oligodeoxynucleotides have been indicated to induce IL-33 expression in immune cells activating DCs and macrophages [49,51–53]. Interestingly, poly(I:C)-stimulated IL-33 induction is boosted by the addition of transforming growth factor (TGF)-β [54], which indicates that the interaction among poly(I:C), TGF-β and IL-33 promotes myofibroblast differentiation and mucosal homeostasis. In addition, in mouse embryonic fibroblasts, following Newcastle disease virus infection, IL-33 mRNA is induced depending RIG-I, a non-TLR ligand [52]. These findings support the conclusion that IL-33, a proallergic cytokine derived from the epithelium, is regulated by microbial ligands through the TLR- and non-TLR-mediated signaling pathways of innate immunity.

Notably, under inflammatory conditions, the effects of proinflammatory cytokines on IL-33 induction cannot be discarded. In human epidermal keratinocytes, interferon (IFN)-γ and TNF-α treatment stimulated the release of a mature form of IL-33 (20-kDa) [55]. In cultured nasal and synovial fibroblasts, adipocytes, preadipocytes, bone marrow stromal cells, and osteoclasts, IL-33 expression was strongly mediated by TNF-α and IL-1β [5,48,56–58]. In addition, constitutive IL-33 expression is increased in CNS glial cells by IL-1β treatment [59]. In cardiac tissue and the vasculature, TNF-α, IL-1β and IFN-γ obviously elevated both IL-33 protein and mRNA levels in cardiac fibroblasts and myocytes as well as smooth muscle cells in the human coronary artery [42,60]. Additionally, IL-33 production by immune cells through an autoregulatory mechanism is essential for the activation of immune cells, including DCs, macrophages and MCs. It has been reported that IL-33 stimulates its own production and release via a positive feed-forward loop in DCs, skin macrophages and mouse bone marrow-derived macrophages [61,62]. Moreover, the expression and release of IL-33 then elevates the production of DC maturation markers, such as CD40 and CD80, and induces macrophages to release microbicidal NO, increasing immune cell activity. Taken together, these studies have shown that inflammatory environment or inflammatory factors can induce the expression or secretion of IL-33, a process that can maintain immune homeostasis but also promote the persistence of inflammation via ST2 signalling, which is consistent with IL-33 inducing skin chronic inflammation via a regulatory loop with IFN-γ [63]. However, numerous studies have detected only IL-33, and little is certain about the forms of full-length IL-33 or how IL-33 is processed. Further studies are needed to determine the mechanisms about IL-33 induction and release, and the consequences under inflammatory environment.

5. ST2

The receptor ST2 (also known as IL-1R4, DER4, Fit-1, or T1 [5,8]) is a type-1 transmembrane protein encoded by the *IL-1RL1* gene. In human tissues, it has been identified in three isoforms created by alternative splicing [64–66] — a transmembrane receptor (ST2L or ST2), a released soluble form (sST2, acts as a decoy receptor) and a variant of ST2 (ST2V). Xu D et al. [67] reported that ST2 was expressed stably and constitutively on the Th2 cell surface but not on the surface of Th1 cells, suggesting ST2 functions as a significant effector molecule in Th2 responses. Notably, T-bet and STAT4 induce increased production of ST2 in Th1 cells, promoting antiviral Th1 responses [68]. ST2 is primarily expressed on the surface of fibroblasts, MCs, and Th2 cells. In addition, GATA3 and STAT5, which are important transcription factors involved in Th2 cell and ILC2 differentiation [69,70], can regulate ST2 expression in several immune cells [71,72]. Although ST2 belongs to the toll-like receptor/IL-1R (TIR) superfamily, it was considered an "orphan" receptor for a long time because conventional biochemical methods failed to determine a specific ligand [73,74]. In 2005, a computational database search of the IL-1R family demonstrated the association between IL-33 and ST2 [5]. In MCs, ST2 and the receptor tyrosine kinase c-Kit interact constitutively, resulting in cross-activation. The activation of c-Kit by its ligand stem cell factor strongly synergizes with the IL-33-stimulated production of proinflammatory cytokines, including IL-6 [75]. It has been reported that the transmembrane protein TMED1 promotes IL-33/ST2-stimulated IL-8 and IL-6 production by coprecipitating with ST2, and this promotion is dependent on an interaction with the TIR domain [76]. In addition, Sugita S et al. have reported that Hes1 and its cofactor calcium/calmodulin-dependent protein kinase-2δ, both of which are important targets of Notch signaling, regulate ST2 expression in cultured chondrocytes [77]. The roles of ST2 and IL-33/ST2 signaling in inflammatory diseases are further researched in subsequent studies.

6. IL-33/ST2 signaling

IL-33 is extracellularly secreted and induces various inflammatory responses. IL-33 interacts with ST2 and IL-1 Receptor Accessory Protein (IL-1RAcP) [78] (Fig. 1). The complex created by IL-33 binding to the ST2 receptor functions as a docking site for the adapter protein Myeloid Differentiation Factor 88 (MyD88), which recruits IL-1R-associated kinase 1 (IRAK1) and 4 (IRAK4) as well as TNF receptor-associated factor 6 (TRAF6) [79]. These signaling molecules activate different types of transcription factors, such as NF-κB, activator protein-1 (AP-1), extracellular signal-regulated kinase (ERK)1/2, p38 mitogen-associated protein kinase (p38MAPK) and c-Jun N-terminal kinase (JNK), through TRAF6-dependent and TRAF6-independent pathways [13,15], thereby triggering inflammatory cytokine production (Fig. 1). Despite the extracellular region of ST2 containing immunoglobulin domains, the signaling function of ST2 is mediated by its intracellular TIR domain [80]. Furthermore, IL-33/ST2 signaling is regulated by several mechanisms (Fig. 1). Rapid oxidation leads to the inhibition of IL-33 and ST2 binding through the formation of two disulfide bridges, which is confirmed to limit the range and duration of IL-33 actions [81]. The ST2 receptor has a transmembrane form (ST2 or ST2L) and a soluble secreted form (sST2, which lacks the transmembrane domain). During inflammatory processes, ST2 mediates the effects of IL-33, whereas sST2 acts as a decoy receptor that inhibits IL-33-induced immune responses by competitively binding to IL-33 [79]. In addition, a soluble form of IL-1RAcP modulates the biological activity of IL-33 by decreasing IL-33-stimulated IL-6 secretion in MCs [78]. Moreover, single Ig IL-1R-related molecule (SIGIRR), a member of the IL-1R family that participates in the regulation of IL-18 and IL-1 [82], interacts with ST2, MyD88, IRAK or TRAF6, interfering with downstream signaling [13].

7. The cellular targets of the IL-33/ST2 axis in various inflammatory diseases

IL-33 affects the activation and functions of various cell types through membrane-bound ST2 signaling. IL-33/ST2 signaling plays an important role in several inflammatory diseases by inducing

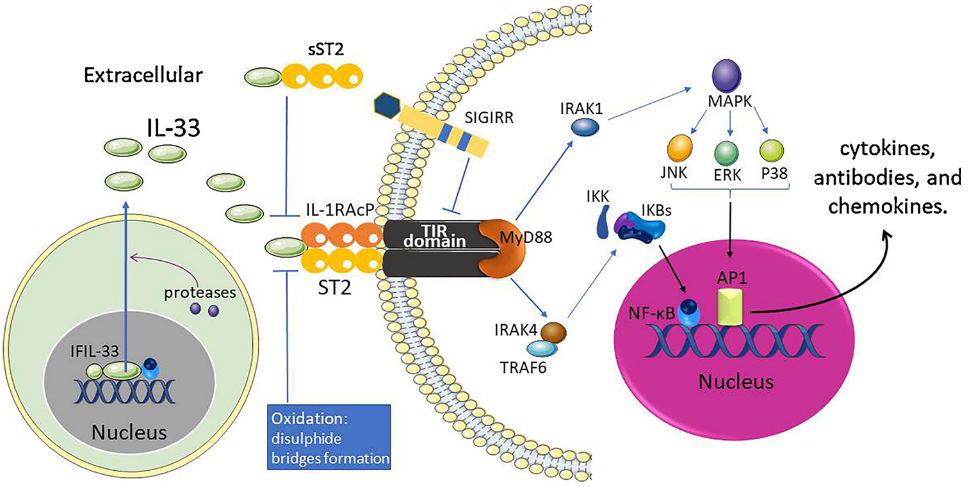

Fig. 1. IL-33/ST2 signaling pathways. After IL-33 activation, the heterodimeric receptor complex consisting of ST2 and IL-1RAcP recruits MyD88 through the intracellular TIR domain. The downstream events include: (A) The activation of TRAF6 and IRAK4 promotes inhibitor of NF-κB kinase (IKK) degradation, resulting in NF-κB liberation and activation. (B) The downstream activators of IRAK1 are MAPKs, which stimulate AP-1. NF-κB and AP-1 then bind to DNA and stimulate the production of proinflammatory cytokines, antibodies and chemokines. The sST2 variant binds to IL-33 through the extracellular domain and negatively regulates IL-33/ST2 signaling. Additionally, SIGIRR interferes with the TIR domain and represses the IL-33/ST2 signaling pathway.

proinflammatory cytokine and chemokine expression. The expression of IL-33 and ST2 in the epithelium, ECs and fibroblasts suggests that this pathway might be involved in the local cellular response. IL-33/ST2 promotes fibroblast proliferation and increases the expression of collagen III by asthmatic fibroblasts, inducing airway deposition of extracellular matrix (ECM) components [83,84]. IL-33 stimulates dermal fibroblasts to release chemokines, such as CXCL8, through processes dependent on the activation of the ERK, JNK, and p38 MAPK pathways, inducing eosinophil infiltration [85]. Following stimulation with IL-33, bronchial epithelial cells exhibit surface expression of ST2 and release IL-17 F. Further studies have indicated that this process is mediated by ERK1/2 and mitogen- and stress-activated protein kinase1 activation [86].

IL-33/ST2 exerts bioeffects on several types of immune cells, including MCs, eosinophils, basophils, DCs, macrophages and B cells, and primarily mediates type 2 immune responses. IL-33 promotes the survival and maturation of MCs [87]. It induces the IgE-mediated degranulation of MCs [88] and leads to the synthesis, storage and release of serotonin [89]. In addition, IL-33 activates MCs to produce various cytokines and chemokines, such as IL-8, IL-9, IL-13, CCL2 and CCL3 [12,87,90,91]. IL-33/ST2 signaling promotes the migration of basophils and facilitates the production of IL-4, IL-5, IL-13 and chemokines by basophils [29,92]. Notably, IL-33/ST2-induced eosinophilia plays an important role in airway or skin allergic disorders [93]. IL-33 has the ability to induce the migration and activation of eosinophils by promoting chemokine production in eosinophils [85], MCs or other immune cells [29]. Furthermore, the IL-33/ST2 axis induces the expression of IL-4, IL-5, IL-6, and IL-8 in eosinophils [29,94,95]. IL-33 has been found to stimulate its own production and secretion via a positive feed-forward loop in macrophages and DCs [61,62]. Alveolar macrophages respond to IL-33, express ST2, and produce high levels of CCL24 and CCL17. IL-33-treated macrophages polarize toward the alternatively activated (M2) macrophage phenotype in an IL-13-dependent manner [96]. DCs are another type of myeloid lineage cell. In vivo and in vitro, IL-33/ST2 induces DC recruitment and activates DCs to produce IL-6, IL-1β, and CCL17. Importantly, IL-33-activated DCs prime naive lymphocytes to produce the Th2 cytokines IL-5 and IL-13 [97], suggesting an additional indirect role for IL-33 in the induction of adaptive immune responses. In addition, it has been reported that the IL-33/ST2 pathway induces neutrophil polarization and activates neutrophils to produce IL-4, IL-5, IL-9 and IL-13 via JNK or NF-κB signaling [98]. For B cells, IL-33 promotes B cell proliferation and CD40 L expression on T cells, leading to B cell activation and the synthesis and release of IgE and antigen-specific IgG1 antibodies [95,99].

Given the early discovery of the selective expression of ST2 by Th2 cells but not Th1 cells, further studies have been carried out to explore and expand the role of IL-33/ST2 signaling in T cells. The IL-33/ST2 axis induces IL-4, IL-5 and IL-13 production in Th2 cells [5]. Further studies have indicated that IL-33 is a selective chemoattractant for Th2 cells [100] and that IL-33 polarizes naive T cells to produce cytokines such as IL-5 and IL-13 [101]. Moreover, IL-33/ST2/p38 signaling has been proven to drive pathogenic memory Th2 cells to produce IL-5 in the context of airway inflammation [102]. ILC2s are lineage-negative, CD127^{+} cells, and ILC2s are recognized as novel stimulators of type 2 innate immune responses. IL-33 is also an inducer of ILC2 expansion and IL-5 and IL-13 production by ILC2s [103,104]. The IL-33/ST2 axis suppresses regulatory T cell (Treg) differentiation and makes Tregs lose their ability to suppress effector T cells [105,106]. Although IL-33 primarily targets Th2 cells, it has also been shown to be associated with Th1 and Th17 cells. Dermal CD4^{+} T cells respond to IL-33 and produce high levels of IFN-γ, suggesting a potential role for IL-33 in Th1 cell activation and chronic dermatitis [63]. Baumann C et al. reported that IL-33/ST2 might act as a critical and direct cofactor to drive antiviral Th1 effector cell activation [68]. In addition, IL-33/ST2 induces IL-17A production and provokes a Th17 immune response [107]. Notably, Cho KA et al. have found that IL-33-induced MCs trigger Th17 polarization accompanied by IL-17 production [19]. Because of its ability to activate cells of both the innate and adaptive immune system, IL-33 may be an important cytokine in the initiation and perpetuation of inflammation development through ST2 signalling.

8. The role of IL-33/ST2 in ADs

8.1. The role of IL-33/ST2 in RA

RA is a chronic autoimmune disease that includes the typical symptoms joint malfunction, cartilage destruction, and debilitating pain. The balance of lymphocyte differentiation in RA is skewed toward the Th1 subtype, with decreases in the numbers of cells with the Th2 or Treg phenotype [108]. IL-33 expression is increased in the serum and synovial fluid (SF) of RA patients [48,109]. Notably, the SF levels of IL-33 are higher than the serum IL-33 levels [110]. Further study demonstrated IL-33 expression in synovial fibroblasts [111]. Moreover, the IL-33 level is related to the phenotype, severity and activity of RA. The serum IL-33 levels are associated with the levels of IgM, rheumatoid factor, anticitrullinated protein antibodies [112], IL-1β, IL-6 [109], MMP-3 [113], and C-reactive protein (CRP) as well as the WBC count [114], erythrocyte sedimentation rate (ESR) and the glucose phosphate isomerase level [115]. Moreover, the IL-33 and sST2 levels are connected to plaque development and disruption as well as the onset and severity of cardiovascular disease in RA patients [116,117]. Similarly, increased serum IL-33 levels are associated with RA complications, such as interstitial lung disease and bone erosion [113]. Overall, the relationship between high-level IL-33 expression and RA severity indicates a potential role for IL-33 in RA pathology. In addition, IL-33 gene polymorphisms influence RA susceptibility. RA patients carrying the CC genotype of IL-33 rs7044343 have lower serum levels of IL-33. Moreover, this genotype has been shown to be resistant to RA [118]. Similarly, the IL-33 rs3939286 allele T was demonstrated to be a potential protective factor that reduced the risk of subclinical atherosclerosis in RA patients [119].

Because IL-33 and ST2 expression is upregulated in RA, studies aiming to explore the possible association between the levels of IL-33 and ST2 and drug responsiveness have been conducted. In 10 treatment-naive RA patients, conventional drug treatment suppressed IL-33 and sST2 expression and inflammation [109]. In addition, the serum IL-33 level might predict clinical responsiveness to rituximab, a chimeric monoclonal antibody against the CD20 protein [120]. In cultured synovial fibroblasts, TNF-α stimulates IL-33 mRNA transcription and protein translation [48,121]. Furthermore, the levels of IL-33 in patient serum decrease after anti-TNF-α treatment [112,114]. Although TNF inhibitors have improved patient outcomes, 30–40% of patients exhibit negative effects after TNF inhibitor therapy. In nonresponders, the IL-33 levels are consistently elevated in the serum and SF. Continuous IL-33 expression in the serum and SF may be responsible for the decreased responsiveness to TNF inhibitors [122]. In a mouse model, an anti-arthritic herb [123] and budlein A [124] inhibited IL-33 production, ameliorating arthritis-induced inflammation.

In a mouse model, the IL-33 mRNA level was increased during the early phase of collagen-induced arthritis (CIA) [48]. Similarly, compared with wild-type(WT) or untreated mice, mice lacking ST2 expression [111] or administered an anti-ST2 antibody during disease onset [48], respectively, developed milder CIA and exhibited decreased collagen-specific antibody induction and reduced production of proinflammatory cytokines, including TNF-α, IL-17, and IFN-γ. In contrast, IL-33 treatment exacerbates CIA [111] and autoantibody-induced arthritis (AIA) [125], increasing the production of both proinflammatory mediators and antibodies. A histological analysis indicated that IL-33 treatment notably increases mononuclear and polymorphonuclear cell infiltration into the joints, with obvious synovial hyperplasia, adjacent cartilage damage, and eventual bone erosion. However, this change is not found in MC-deficient mice [125], suggesting that MCs might be involved in IL-33-induced experimental arthritis. $ST2^{-/-}$ mice engrafted with MCs from WT but not those engrafted with MCs from $ST2^{-/-}$ mice show exacerbated CIA and AIA after IL-33 treatment. Further in vitro study found that MCs express high ST2 levels and respond to IL-33 by producing various proinflammatory cytokines, such as GM-CSF, IL-1β, IL-6 and IL-13, as well as chemokines, including MCP-1 and MIP-1α [111]. IL-33/ST2 also synergistically increases immune complex-induced IL-8 and TNF-α production in human synovium-derived MCs [126]. In inflamed synovial tissue in vivo, Xu D et al. found that IL-33 promoted MC degranulation, but IL-33 did not promote MC degranulation in naive mice without an autoantibody injection [125]. In addition, IL-33 administration also induces higher concentrations of serum IgG1 and IgG2a. These results indicate that the IL-33/ST2 axis exacerbates experimental autoimmune arthritis by inducing IgG-mediated MC activation and degranulation. In mice challenged with methylated bovine serum albumin, Verri WA et al. [127] found that IL-33 induced AIA inflammation and cartilage destruction by mediating neutrophil migration, and these negative outcomes were absent in $IL\text{-}33R^{-/-}$ mice or mice whose IL-33 signaling was inhibited by sST2. Further studies in vivo and vitro have indicated that IL-33 induces neutrophil recruitment directly and notably by stimulating macrophages and synoviocytes to release chemokines and cytokines, including CXCL1, CCL3, TNFα and IL-1β [127]. Thus, targeting IL-33 may represent a potential new strategy against a range of inflammatory diseases involving persistent neutrophil accumulation. Moreover, in RA synovial fibroblasts, IL-33 acts on hypoxia-inducible factor-1α (HIF-1α) to form a HIF-1α/IL-33 regulatory circuit that perpetuates the inflammatory state in RA [128]. In addition, IL-33 stimulates RA fibroblast-like synoviocytes to form multinucleated osteoclasts with increased NF-κB ligand and IP-10 mRNA expression, a process that is blocked by anti-ST2 treatment [129]. Therefore, elevated plasma IL-33 levels in RA patients seem to increase the likelihood of bone erosion. Because IL-33 is derived predominantly from synovial fibroblasts, this research proposes a new mechanism whereby the host tissue-derived IL-33 produced by fibroblasts can improve the activation of innate immune cells and then play a regulatory role as an effector in the adaptive immune response in inflammatory arthritis. These studies suggest that IL-33 plays its pathogenic role in RA development primarily via an ST2-dependent pathway.

Despite these findings, the effects of IL-33/ST2 axis remain controversial. In a mouse model, the repetitive administration of IL-33 during both the early and late stages of CIA attenuated clinical and histological signs of arthritis [130]. Notably, the protective mechanism was related to an enhanced type 2 immune response involving ILC2s, Th2 cells, and eosinophils in the response to IL-33 treatment. Serum IgE and Th2 cytokine (IL-4, IL-5, IL-10, IL-13) levels are increased in IL-33-treated mice. A further in vitro study revealed that IL-33/ST2 favors Treg expansion and improves the immunosuppressive effects of Tregs on effector T cells, decreasing IFN-γ production [130].

The current evidence clearly shows that the expression of IL-33 and ST2 is a potential indicator of RA severity. Although most studies have demonstrated that the IL-33/ST2 axis has a disease-causing effect, the true contribution of this axis remains controversial, and more experimental data are needed to explore the specific effects and molecular mechanisms of the axis in RA.

8.2. *The role of IL-33/ST2 in IBDs*

IBDs, a series of refractory or relapsing diseases, impart significant morbidity in Western society. IBDs are characterized by recurrent dysfunction in the epithelial barrier restricted to the colon and/or rectum in ulcerative colitis (UC) or any possible part of the gastrointestinal tract in Crohn’s disease (CD) [131]. IL-33 and ST2 are dysregulated in patients with UC or CD. Moreover, intestinal epithelial cells and ulceration-associated myofibroblasts are the main sources of mucosal IL-33 production [54,132]. Notably, increased expression of the IFIL-33 protein is found in the epithelium, and IBD serum contains high levels of the cleaved 20–22 kDa forms rather than IFIL-33 [132]. Moreover, the IL-33 level is related to IBD severity and activity. The serum IL-33 level correlates with both the circulating high-sensitivity CRP levels and disease activity [133]. In patients with pediatric Crohn's ileitis, Masterson et al. have found that increased intestinal epithelial IL-33 expression is related to increased disease activity, eosinophilia in the ileum, and complex fibrostenotic disease [134]. In addition, the A allele of IL-33 rs3939286 is strongly related to disease severity. UC patients carrying risk genotypes (AG + AA) have an increased incidence of extensive colitis [135].

The serum ST2 level is increased in UC and CD patients. Moreover, it correlates with disease activity and severity [136]. In addition, the sST2 level is elevated in the serum [132] and colonic mucosa of UC patients compared with those of HCs [137]. The serum sST2 level is associated with the Mayo clinic endoscopic subscore and the mucosal ST2 and fecal calprotectin levels and may represent a potential biomarker for evaluating clinical severity in UC patients [138]. Notably, in studies of mouse models, following the administration of quercetin-loaded microcapsules [139], baicalin [140] or the anti-TNF agent infliximab [132], which are all antioxidant and anti-inflammatory drugs, IL-33 expression was inhibited, and the severity of experimental colitis in the mice was suppressed (measured by morphological and histological tests). Moreover, the IL-33 level in the colonic crypts is decreased, and disease severity is controlled after anti-TNF therapy in patients [141]. Given these findings, IL-33 and its receptor may represent potential biomarkers for predicting disease activity and remission.

To clarify the role and underlying mechanisms of IL-33/ST2 in IBDs, several studies investigated the function of IL-33/ST2 in disease development using IBD mouse models. In relapsing IBD patients and an experimental model, immunohistochemical analysis showed conspicuous subepithelial infiltration by ST2-positive cells [142]. After exposure to trinitrobenzene sulfonic acid or dextran sodium sulfate (DSS), two well-established methods of inducing acute colitis in mice, ST2-deficient or IL-33-deficient mice showed decreased morbidity, signs of inflammation and epithelial ulceration. In addition, an anti-ST2 antibody protected mice from DSS-induced colitis. DSS-treated ST2$^{-/-}$ mice showed persistent expression of connexin 43, which is important for enterocyte migration and wound healing, indicating that the IL-33/ST2 axis might alter epithelial barrier permeability [142]. Moreover, the absence of ST2 improved coalescence after acute mechanical injury of the colon, suggesting that the IL-33/ST2 axis might negatively affect the process of re-epithelialization and wound healing [142]. Notably, IL-33/ST2-mediatated regulation of wound healing involves suppressed Notch-mediated signalling pathway [143]. Pushparaj PN et al. reported that ST2$^{-/-}$ BALB/c mice exhibit alleviated diarrhea and impaired acute colonic inflammation, including reduced expression of CXCL9, CXCL10, IL-4, IL-6 and IL-13 [144]. Further study found that recombinant IL-33 exacerbates the acute colitis induced by DSS in WT mice, and this exacerbation was not seen in IL-4$^{-/-}$ and IL-4R$^{-/-}$ mice [144]. IL-33/ST2 may contribute to UC development through an IL-4 signaling-dependent mechanism. Furthermore, in colonic lamina propria lymphocytes, IL-33-induced colitis exacerbation is associated with decreased levels of IL-17A and IFN-γ and elevated levels of Th2 cytokines, such as IL-5 and IL-13 [145]. In summary, IL-33 promotes the development of acute colitis by inducing the Th2 cell response and suppressing Th17 and Th1 cell responses (Fig. 2). Independent of colonic inflammation, IL-33 also induces epithelial barrier dysfunction.

Despite these findings, the role of IL-33/ST2 in chronic intestinal inflammation during the IBD process is still controversial. Ileal remodeling and fibrosis are considered sequelae in chronic IBDs. Increasing studies support the role of eosinophil activation in these changes. In vitro, IL-33 induces eosinophils to secrete peroxidase and produce IL-13. Moreover, coculturing fibroblasts with IL-33-treated eosinophils primed the fibroblasts to promote IL-6, TNF-α, IL-1β, CCL24 and CCL26 production [134]. Therefore, IL-33-induced eosinophil activation may play an important pathogenic role in perpetuating chronic inflammation in IBDs. This conclusion was further supported by a study of chronic experimental Crohn's-like ileitis using SAMP1/YitFc mice, a well-characterized, spontaneous model of IBDs [146]. In this study, De Salvo C et al. have found that exogenous IL-33 treatment increases disease severity and promotes eosinophil infiltration into the gut mucosa and the production of elevated levels of eotaxins and Th2 cytokines, and these effects were reversed by blocking IL-33 signaling or depleting eosinophils. Collectively, these findings suggest that IL-33 contributes to chronic intestinal inflammation by inducing eosinophilia. In contrast, other studies have indicated that IL-33 plays a protective role in chronic IBDs. In a study of DSS-induced chronic colitis in C57BL/6 mice, IL-33 treatment resulted in significant alleviations of colonic tissue injury and clinical symptoms via the inhibition of the Th17 response and the shift from a Th1 response to a Th2 response, which resulted in lower levels of IFN-γ and IL-17A [147,148]; in contrast, IL-33 treatment of acute colitis resulted in aggravated inflammation [147]. In addition, the level of IL-33, a cytokine constitutively expressed in the intestinal epithelium, is increased after tissue damage or inflammatory responses to stimuli. IL-33 functions as an alarmin that regulates Tregs, a role that has also attracted wide attention. In Tregs obtained from the colonic tissue of mice with chronic colitis, Schiering et al. [72] found ST2 expression. Moreover, IL-33/ST2 signaling in T cells promotes Treg accumulation and functions by enhancing TGF-β1-mediated Treg generation, differentiation and maintenance [72]. In the presence of TGF-β1, the IL-33/ST2 axis induces GATA3 and RNA polymerase II recruitment to the *Foxp3* promoter to regulate *Foxp3* expression. In addition, IL-33 also promotes ST2 mRNA expression in Tregs by favoring the expression of GATA3, which is known to regulate ST2 expression in Th2 cells. In summary, after tissue injury, IL-33 is able to amplify regulatory functions by providing an amplification loop for further enhnacing Treg differentiation, demonstrating a more general mechanism whereby alarmins limit autoimmune damage in barrier tissues.

Most data indicate that the IL-33/ST2 axis plays detrimental roles in IBDs, especially during the acute phases of these diseases (Fig. 2).

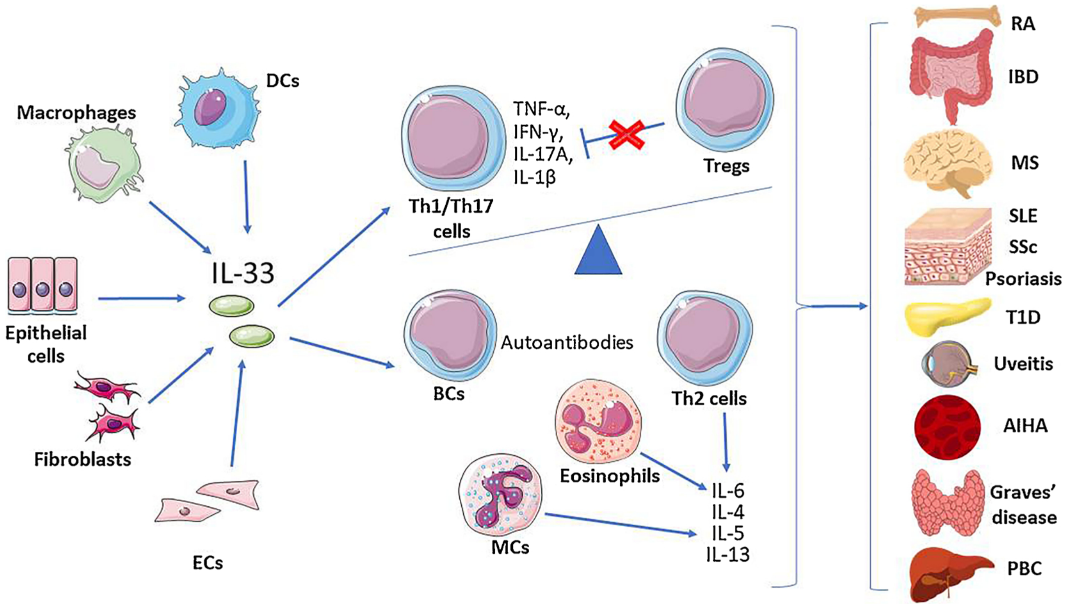

Fig. 2. The detrimental roles of IL-33-mediated immune responses in ADs. After tissue damage caused by several stimuli, IL-33 is released by epithelial cells, fibroblasts, ECs, DCs and macrophages. Then, IL-33 promotes the differentiation of Th1 and Th17 cells to increase the expression of TNF-α, IFN-γ, IL-17A and IL-1β. IL-33 contributes to Treg differentiation and dysfunction. Under autoimmune conditions, IL-33 might promote autoantibody production by BCs. Additionally, IL-33 exerts its bioeffects on Th2 cells, eosinophils and MCs to drive the production of Th2 cytokines (IL-4, IL-5, IL-6, IL-13). Consequently, IL-33 induces the occurrence or progression of several ADs by benefiting Th1/Th17 cells, the type 2 immune response and Treg dysfunction.

Significant improvements in the symptoms of experimental IBDs mediated by the administration of a specific anti-ST2 agent [142] provide strong evidence for targeted therapy. The modulation of IL-33/ST2 signaling may be a novel biological therapeutic target for IBDs. However, both positive and negative roles for IL-33 have been demonstrated in mouse models of chronic colitis. We postulate that there is a more complex immune network involved in chronic processes and that there are differences in pathogenesis between different mouse models. The role of IL-33 in IBDs, especially in the chronic phases of these diseases, merits further study.

8.3. *The role of IL-33/ST2 in MS*

MS is a common autoimmune and demyelinating disease that occurs in the CNS. IL-33 and ST2 expression is increased in the CNS and crucial to the pathogenesis of CNS diseases. However, the role of IL-33 in MS remains unclear. Increased levels of IL-33 have been found in the serum, cerebrospinal fluid (CSF) and brain tissue of MS patients compared with those from HCs [149,150]. Furthermore, immunohistochemical analysis of MS patient brain tissue revealed that IL-33 is expressed by neurons, microglia, astrocytes and oligodendrocytes, whereas ST2 is expressed in brain lesions by oligodendrocytes [151]. This suggests that the IL-33/ST2 pathway is involved in MS. The serum levels of IL-33 are associated with disease severity measured by the expanded disability status scale [152]. In addition, an anti-MS drug was shown to affect plasma IL-33 levels. In comparison to control subjects, IFN-β-treated MS patients were shown to exhibit decreased IL-33 levels [149,153]. Furthermore, IL-33 induction is necessary for the disease protection mediated by anti-inflammatory IgG Fc antibody fragments [154] and antiautoimmune *Fasciola hepatica* excretory-secretory products [155] in MS mouse models. In summary, the IL-33 level is a potential indicator of MS severity and clinical therapeutic responses.

In vitro studies have been conducted to investigate the effect of IL-33/ST2 on various cells. Upon inflammatory stimulation, astrocytes actively secrete IL-33 in vitro [156]. In rat myelinating coculture studies, ST2 was expressed by oligodendrocytes, and IL-33 treatment significantly elevated oligodendrocyte numbers and reduced the proportion of myelinated axons in the culture, suggesting that the IL-33/ST2 axis inhibited CNS myelination [151]. In contrast, in cultured oligodendrocyte precursor cells (OPCs), IL-33 treatment benefits myelin repair by promoting p38MAPK-related myelin gene transcription and inducing OPC diff ;erentiation to form myelin-producing cells, demonstrating the neuroprotective function of IL-33 in MS [157]. In addition, Tregs play a crucial role in the development of MS. In the MS patient brain, ST2-expressing Tregs exhibit highly potent regulatory functions and produce IL-10, illustrating the stable suppressive functions of Tregs in the inflamed brain [158].

Experimental autoimmune encephalomyelitis (EAE) is a commonly used animal model of MS [159]. IL-33 and ST2 levels are markedly increased in the spinal cord of EAE mice. Notably, polyclonal anti-IL-33 antibody treatment during the induction phase dramatically suppresses the onset and severity of EAE; reduces IFN-γ, IL-17, T-bet and RORγt production; and increases the levels of IL-10 and TGF-β in the spinal cord. In contrast, recombinant IL-33 treatment accelerates EAE disease development and is associated with elevated IFN-γ and IL-17 expression [160]. IL-33/ST2 might play harmful roles in the pathogenesis of EAE via Th1/Th17 immune activation. However, recent studies have indicated that the IL-33/ST2 axis exerts protective effects in the context of EAE autoimmunity that are associated with the suppression of Th1/Th17 immune phenotypes. During the onset and peak stages of EAE, extracellular IL-33 expression is elevated in the spinal cord [156]. Activated astrocytes and damaged neurons release IL-33 during EAE. Further studies have indicated that the release of IL-33 regulates the immune response and suppresses EAE development. Using both in vitro and in vivo methods, Milovanovic et al. [161] have illustrated that knocking out ST2 expression reduces the inherent resistance of mice to EAE induction. The deletion of ST2 may result in enhanced numbers of proinflammatory antigen presenting cells and continuous encephalitogenic T cell differentiation in the draining lymph nodes, along with elevated expression of IFN-γ, IL-17, TNF-α, GM-CSF and T-bet. Additionally, Jiang et al. [162] isolated macrophages from the lymph nodes and spleen of mice after IL-33 treatment. They found that macrophages polarized into the M2 phenotype. Moreover, subsequent adoptive transfer of these macrophages attenuated EAE development. In contrast, compared to WT mice, $ST2^{-/-}$ mice exhibited enhanced EAE development. In addition, IL-33-treated mice exhibited decreased expression of IL-17 and IFN-γ and elevated levels of IL-5 and IL-13 [162]. Finlay CM et al. found that IL-33 promoted eosinophil expansion and exerted protective effects against EAE autoimmunity that were dependent on IL-5 [155]. These studies indicate that the IL-33/ST2 axis converts Th17/Th1 responses to Th2 responses and proinflammatory M1 macrophages to anti-inflammatory M2 macrophages.

IL-33/ST2 exerts protective effects against MS and EAE that are dependent on the Th2 response and M2 macrophage phenotype polarization. Targeting IL-33 or ST2 may be a potential solution in future treatments for MS. Further studies are needed to test this hypothesis and to explore additional mechanisms involving IL-33/ST2 in the immune complex of MS.

8.4. *The role of IL-33/ST2 in SLE*

SLE is a severe systematic autoimmune disorder and the major cause of death from chronic inflammatory diseases in young women. The immune complex deposits in the kidneys and high-level serum anti-dsDNA antibody indicate disease activity. IL-33 levels are reported to be significantly increased in the serum of SLE patients compared to that of HCs [163]. Moreover, serum IL-33 levels are closely correlated with the ESR, CRP level, IgA level, and anti-SSB antibody level as well as thrombocytopenia and erythrocytopenia [163]. In addition, serum sST2 levels have been shown to be much higher in active SLE patients than in HCs and related to anti-dsDNA antibody levels, the SLE Disease Activity Index, and the prednisolone dosage, while these levels are reported to be negatively correlated with C3 [164]. Periodontitis, which is caused by abnormal interactions between a subgingival bacterial community and host immune response [165], occurs more frequently in SLE patients than HCs. Corrêa found that increased IL-33 levels in the saliva were positively associated with the presence of pathogenic bacteria in SLE patients with periodontitis [166]. The positive correlation between the serum IL-33 and sST2 levels and disease activity indicates that these levels may act as markers of disease activity. In addition, IL-33 gene polymorphisms can be used to predict SLE susceptibility. Allele G for IL-33 rs1929992 correlates with susceptibility to SLE [167]. In contrast, the IL-33 rs7044343 polymorphism is not associated with SLE susceptibility. In addition, the IL-33 rs1891385 polymorphism may alter the expression of IL-33. Compared to the rs1891385 A allele, the C allele is related to a significantly increased SLE disease risk [168].

To clarify the role of IL-33/ST2 in SLE development, Li P et al. [169] reported that anti-IL-33 antibody administration reduced the mortality of lupus-prone MRL/lpr mice. Moreover, proteinuria, serum anti-dsDNA antibody levels and immune complex deposits were obviously reduced in anti-IL-33-treated mice compared with control-treated mice [169]. Further study illustrated that the anti-IL-33 antibody significantly increased the numbers of Tregs and myeloid-derived suppressor cells (MDSCs), while decreasing the Th17 cell numbers and downregulating the IL-1β, IL-17, and IL-6 levels [169]. Targeting IL-33 may attenuate SLE via the expansion of MDSCs and Tregs and the suppression of Th17 cells and proinflammatory responses. The pharmacological inhibition of IL-33/ST2 signaling may be an alternative strategy for SLE therapy.

IL-33 and its receptor are strong surrogate markers for SLE activity. Although a limited number of studies have shown that IL-33/ST2 might play a detrimental role in SLE (Fig. 2), more studies are needed to confirm this hypothesis and to explore the underlying molecular mechanisms.

8.5. The role of IL-33/ST2 in T1D

T1D, a chronic autoimmune disease, exhibits vascular complications during its late stages. Interestingly, the serum IL-33 levels are decreased in diabetic patients with or without nephropathy and are negatively correlated with the severity of microalbuminuria and insulin resistance [170]. The authors explained that T1D is characterized by enhanced Th1 responses and suppressed Th2 responses. In contrast, IL-33 and ST2 levels are higher in the serum of T1D patients than that of HCs [171,172]. Accumulating studies indicate that the IL-33 and ST2 levels are novel markers for T1D clinical features and drug responsiveness. Serum sST2 levels are increased and strongly associated with markers of diabetes, such as triglycerides, glucose, soluble ICAM-1 and liver function, in patients with diabetes, especially those without vascular disease [173]. In diabetic rats following the induction of contrast-induced nephropathy, Onk D et al. found that the IL-33 levels were elevated in the kidney tissue but suppressed after melatonin treatment [174]. In addition, the release of IL-33 may be responsible for the beneficial effects of oral treatment with some probiotics in T1D mice [175]. The dysregulated expression of IL-33 and ST2 in T1D supports their potential roles in diabetes.

To illuminate the role of IL-33/ST2 in T1D, several studies have been conducted both in vitro and in mouse models. In a murine T1D model, ST2 gene deficiency enhanced diabetes susceptibility and was associated with increased glycemic levels, glycosuria levels, numbers of infiltrating cells, β cell loss and mRNA expression of IL-17, TNF-α and IFN-γ in the pancreatic lymph nodes [176]. ST2-mediated signaling may modulate Th1/Th17-mediated pathological autoimmune processes in a diabetes-resistant strain of mice. In a diabetic mouse model, the IL-33 levels in the myocardial tissue were decreased and correlated with enhanced protein kinase C βII (PKCβII) activation [177]. The downregulation of IL-33 might be contributed to the activation of miR-375 and miR-380-5p, which are directly targeting the 3′-UTR of the IL-33 [177]. Moreover, IL-33 administration attenuated high glucose-induced ischemia/reperfusion (I/R) injuries (measured as myocardial infarction size and rate of apoptosis). An additional in vitro study found that IL-33 prevents PKCβII activation and increases diacylglycerol kinase zeta (DKZ) expression in cardiomyocytes [177]. It has been reported that in diabetes mellitus chronic PKC activation leads to higher vascular permeability and myocardial dysfunction through c-Jun NH_2-terminal MAPK activation [178]. Thus, IL-33 promotes DKZ expression and downregulates PKCβII activation, decreasing myocardial injury induced by hyperglycemia. In a hypoxia-induced I/R model in vitro and in vivo, the IL-33/ST2 axis induces the expression of the antiapoptotic factors survivin, XIAP, and cIAP1 and suppresses caspase-3 activity, reducing cardiomyocyte injury and fibrosis [179]. Moreover, IL-33/ST2-mediated myocardial-protective effects (measured as reduced cardiac hypertrophy and fibrosis) in the context of I/R injury are ascribed to the attenuated angiotensin II-induced activation of JNK, p38 MAPKs and NF-κB in cardiomyocytes [42]. In addition, recent studies have suggested that the IL-33/ST2 axis also exerts regulatory functions on other immune cells, including Tregs and macrophages. As T1D is an autoimmune disease with Treg defects, studies on the effect of IL-33 on Tregs were conducted. In a study comparing peripheral blood mononuclear cells (PBMCs) from T1D patients with those from HCs, IL-33 treatment induced significant upregulation of $CD4^{+}CD25^{high}FOXP3^{+}$ Treg frequencies as well as increased surface expression of ST2 in the PBMCs from T1D patients [172]. Further research with an in vitro coculture system has indicated that IL-33 treatment enhances the ability of Tregs to affect effector T lymphocytes by suppressing IFN-γ production [180]. Recently, a study in streptozotocin-induced diabetic mice found that IL-33 delivery promoted diabetic wound healing with elevated re-epithelialization through the promotion of angiogenesis and ECM deposition [181]. IL-33 enhances the development of M2 macrophages in wound sites in vivo. Furthermore, in vitro, these changes are ascribed to the IL-33-stimulated polarization of macrophages (derived from bone marrow) into M2 macrophages, which augments fibroblast proliferation and ECM deposition [181]. Collectively, the IL-33/ST2 pathway exerts a protective effect on T1D.

In summary, IL-33 and ST2 expression is dysregulated in T1D, and IL-33 can regulate the imbalanced immune activation in T1D by balancing Th1/Th17 and Th2 immune responses. In vitro studies have deepened our knowledge of the role of IL-33 in the regulation of T1D involving Treg functions, and relevant animal experiments are needed to confirm this hypothesis. Further studies are also needed to confirm and improve our understanding of the specific effects and molecular mechanisms of IL-33/ST2 in T1D.

8.6. The role of IL-33/ST2 in SSc

SSc is an autoimmune connective tissue disease with manifestations such as fibrosis of the skin and/or viscera. Even in skin biopsies from healthy subjects, nuclear IL-33 protein is constitutively expressed in keratinocytes and dermal ECs, while ST2 exhibits only slight expression in fibroblasts and ECs [182]. In the early stage of SSc, the ST2 receptor is overexpressed on the surface of ECs, perivascular-infiltrating MCs, macrophages, T cells, B cells and myofibroblasts in all affected organs. In addition, the draining of endothelial IL-33 protein involves all affected organs, while IL-33 expression is upregulated in skin biopsies from patients with late-stage SSc [182]. In contrast, the serum IL-33 levels were markedly higher in early-stage SSc patients than in both HCs and patients with progressive SSc [183]. These studies suggest that in patients with early-stage SSc, IL-33 is released into the serum following EC activation and exerts profibrotic effects through ST2 on immune cells and myofibroblasts. The increased circulating IL-33 level suggests that IL-33 potentially plays a role in SSc development. Notably, the levels of IL-33 and its receptor differ in different types of SSc. Compared to patients with limited cutaneous SSc (lcSSc), those with diffuse cutaneous SSc exhibit higher IL-33 levels [184]. Increased serum sST2 levels are found in patients suffering from lcSSc for 9 years or more compared with HCs or SSc patients with early-stage pathological skin changes or a disease duration less than 9 years. Additionally, the levels of sST2 can be controlled with iloprost treatment [185]. Moreover, elevated serum IL-33 levels in SSc patients are positively correlated with the degree of skin lesion sclerosis and pulmonary fibrosis and negatively related to the percent predicted forced vital capacity [184]. In addition, IL-33 elevation is correlated with the capillaroscopic activities characterized by frequent expanded capillaries and capillary hemorrhages [186]. In SSc, IL-33 might further affect the active abnormalities in the microcirculation. Terras et al. found that in a large cohort of SSc patients, the circulating levels of IL-33 correlate with the presence of digital ulcers [187]. Furthermore, the IL-33 rs7044343 polymorphism interacts with SSc susceptibility in the Turkish population [188] and influences dyspnea severity in the Chinese population [189].

The demonstrated positive relationship between the IL-33 levels and the clinical manifestation of SSc suggests that IL-33 may play important roles in SSc progression. Further studies support the role of the IL-33/ST2 axis in the pathogenic mechanisms of SSc, such as inflammation, fibrosis, immune abnormalities and abnormal angiogenesis. Choi YS et al. [190] have reported that IL-33 positively affects the expansion, infiltration, and morphologic differentiation of human ECs and subsequently enhances angiogenesis in vivo. IL-33 also promotes endothelial permeability in vitro and induces vascular leakage in C57BL/6 mouse skin. These changes are ascribed to the IL-33-induced endothelial NO production mediated by the IL-33/ST2/phosphatidylinositide 3-kinases (PI3K)/protein kinase B (PKB, also known as AKT)/endothelial nitric oxide synthase (eNOS) axis. In addition, mice treated with IL-33 show an ST2-dependent accumulation of eosinophils and extensive cutaneous fibrosis with high levels of tissue inhibitors of metalloproteases-1, collagen VI, collagen III, and IL-13 [191]. In vitro, bone marrow-derived eosinophils produce IL-13 in response to IL-33 treatment [191].

In summary, the IL-33/ST2/eosinophil/IL-13 axis induces local tissue fibrosis during SSc pathogenesis (Fig. 2). In addition, MacDonald KG et al. [192] have reported that Tregs from SSc lesions produce considerable amounts of IL-4 and IL-13. In vitro, IL-33 induces Tregs to differentiate into Th2-like cells, promoting IL-4 and IL-13 expression in Tregs [192]. IL-33 seems to be a significant mediator of local Treg dysfunction (Fig. 2); however, additional mouse model studies are needed to confirm this hypothesis.

Collectively, these findings suggest that the IL-33/ST2 axis may play detrimental roles in SSc pathological changes by modulating the activation and functions of several cell types, including ECs, eosinophils, and Tregs. Further studies are urgently needed to clarify the functions of the IL-33/ST2 pathway in other SSc effector cells and the potential therapeutic effects of targeting this pathway.

8.7. *The role of IL-33/ST2 in psoriasis*

Psoriasis is a prevalent autoimmune disorder of the skin featuring epidermal keratinocyte hyperplasia and high-level proinflammatory cytokine expression. The IL-33 and ST2 levels are elevated in the affected skin lesions and serum of psoriasis patients compared with those of HCs [193–195]. Interestingly, IL-33 expression is also increased in the unaffected psoriatic skin of patients [196]. Furthermore, epidermal IL-33 expression is correlated with a positive Köbner response in psoriasis [197] and psoriasis-relevant pain [198]. In addition, TNF-α inhibitor treatment, which effectively treats psoriatic plaques, significantly downregulates both the IL-33 mRNA levels and psoriasis area severity index scores in patients with psoriatic plaques [199]. Recently, Meephansan J et al. reported that methotrexate reduces the IL-33 mRNA concentrations in psoriatic plaques and the IL-33 protein levels in the serum of psoriasis patients [200]. The observed relationships between IL-33 production and disease activity or pharmacological reaction indicate that the IL-33/ST2 axis may be involved in psoriatic development.

An additional study illustrated that keratinocytes and MCs are the main sources of IL-33 and that IL-33 expression is enhanced by TNF-α [193], explaining why TNF-α inhibition reduces the IL-33 concentration in psoriatic patients. Further studies have found that IL-33 stimulates IL-6, IL-8 [194], MCP-1 and VEGF [193] secretion in psoriatic keratinocytes and HaCaT cells. Additionally, IL-33 augments peptide substance P-mediated gene expression and VEGF secretion in human LAD2 MCs and umbilical cord blood-derived cultured MCs, inducing angiogenesis during psoriasis pathogenesis [196]. The underlying mechanism includes the activation of ERK and JNK MAPKs and the increase in cytosolic calcium. To investigate the interaction between IL-33 and MCs, Suttle MM et al. activated the Köbner reaction in the unaffected skin of psoriatic patients and found that IL-33 seems to promote IL-6 and CD126 expression by MCs in skin biopsies from Köbner-positive patients [201]. In a mouse model induced by phorbol ester, compared with WT mice, ST2$^{-/-}$ mice exhibited decreased skin inflammatory responses. In contrast, the injection of IL-33 into the ear induced psoriatic skin lesions with high levels of IL-5, IL-13, CXCL1 and MCP-1 [202]. Compared with WT mice, MC-deficient mice showed a significant delay in the initial phase of the response to the injection of IL-33 into the ear and decreased clinical scores. Furthermore, in the early stage, IL-33 treatment mediated neutrophil migration into the ear lesions via the upregulation of CXCL1 expression. IL-33/ST2-mediated psoriatic skin inflammation is dependent on the neutrophil recruitment mediated by CXCL1 and MC activation [202]. These results imply a potential role for the interactions among IL-33, keratinocytes, and MCs in the inflammatory milieu of psoriasis.

These studies demonstrate that the IL-33/ST2 axis may play harmful roles in this hyperproliferative autoimmune skin disorder (Fig. 2). More physiologically relevant cellular and animal studies are needed to study the activation and molecular mechanism of IL-33/ST2 in psoriasis.

8.8. *The role of IL-33/ST2 in uveitis*

Uveitis is a blinding intraocular inflammatory disease primarily mediated by autoantigen-specific CD4$^+$ T cells, and the activation of these T cells occurs along with the migration of tissue-damaging neutrophils and macrophages into the retina and choroid. Uveitis can occur independently or in conjunction with other systemic immune diseases, including Vogt-Koyanagi-Harada disease and Behcet's disease (BD). IL-33 expression is reported to be upregulated in the serum and aqueous humor of patients with idiopathic anterior uveitis or HLA-B27-associated anterior uveitis [203]. The levels of IL-33 and sST2 are higher in the skin tissue and serum of BD patients compared to those of HCs. Moreover, the sST2 levels correlate with the ESR and CRP concentrations in the serum of patients with BD and are significantly related to the BD current activity form and Iranian BD dynamic activity measure [204]. Hamzaoui K et al. have found that high IL-33 serum levels are possibly associated with the active presence of retinal vasculitis [205]. In addition, the IL-33 CSF levels are positively correlated with the inflammatory chemokines monocyte chemotactic protein-1 and IP-10 [206]. The local IL-33 levels are higher than the serum levels in BD patients. For single nucleotide polymorphisms, IL-33 rs7044343 and rs11792633 are correlated with a reduced risk of BD [207]. The rare TT variants might be protective against BD susceptibility. In conclusion, the serum IL-33 levels are increased in active uveitis patients and correlate with disease incidence and activity.

Despite these findings, the role of IL-33/ST2 in uveitis remains unknown. IL-33 and ST2 are expressed in murine retinal pigment epithelial (RPE) cells [208], and possibly Muller glial cells collected from inner nuclear layer of retina [6]. To investigate this finding further, Barbour M et al. established a mouse model of experimental autoimmune uveitis (EAU) [208]. Compared with WT mice, ST2-deficient mice exhibited exacerbated EAU, and the injection of IL-33 into WT mice attenuated EAU severity. The attenuated EAU in the IL-33-treated mice was associated with decreased numbers of IFN-γ$^+$/IL-17$^+$ T cells and decreased production of IFN-γ and IL-17, while the amount of IL-5$^+$/IL-4$^+$ T cells and the production of IL-5 were increased in the spleen and draining lymph nodes. In addition, compared to untreated WT mice, the IL-33-injected mice showed remarkably higher macrophage polarization toward the M2 macrophage phenotype. These results indicate that IL-33 represents a latent protective agent in uveitis. Notably, the expression of IL-33 is increased under inflammatory conditions in vitro; following culture with respective stimulant, the IL-33 level is enhanced in PBMCs and macrophages from active BD patients compared to those from HCs [205]. Under uveitis conditions, RPE-derived IL-33 release might function as an alarmin to regulate the immune system and control tissue damage. Hence, further studies are required to understand the mechanism of the IL-33/ST2 signaling pathway in uveitis pathogenesis and progression.

8.9. *The role of IL-33/ST2 in other ADs*

Since the dual nature of IL-33/ST2 in mainstream ADs has been well demonstrated, IL-33 and its receptor have been suggested as potential biomarkers for the development of other ADs. In patients with Graves' disease, the serum IL-33 concentrations are significantly elevated and positively associated with the free triiodothyronine and thyroxine levels and negatively correlated with the thyroid-stimulating hormone level [209]. IL-33 and sST2 expression is increased in the salivary glands and serum from Sjogren's syndrome patients and is associated with thrombocytopenia and disease duration [210].

The correlation between the IL-33 levels and disease severity is also relevant in ADs affecting the blood. Plasma IL-33 levels are decreased, and the sST2 levels are increased in patients with active immune

Table 1
IL-33 and its receptors expression and function in ADs.

ADs	IL-33 and its receptors levels	Function
RA	Increased IL-33 and sST2 in sera and SF [48,109,110]. Serum IL-33 expression has a tight relationship with RA activity and severity [112,113,114,115,116,117]. IL-33 level is decreased after treatment [109,120,121,122,123,124].	IL-33 administration exacerbates CIA and AIA [111,125] ST2 neutralizing attenuates CIA and AIA [48,111,125] IL-33 activates MCs to produce inflammatory cytokines and chemokines [111,126] IL-33 promotes the function of neutrophil, macrophage and fibroblast-like synoviocytes [127,129]. IL-33 administration suppresses CIA [130]
IBD	Increased IL-33, sST2 and ST2 in intestinal epithelium and serum [54,132,133,136,137] IL-33, sST2 and ST2 correlate with disease activity and severity [133,134,136,138] IL-33 concentration is decreased after treatment [139,140,141].	IL-33 administration exacerbates DSS-induced colitis [142,144] ST2 neutralizing attenuates DSS-induced colitis [144] Harmful role dependent on eosinophilia and Th2 immune activation [134,144,145,146] Protective role dependent on Th2 immune activation [147,148] IL-33/ST2 induces Treg accumulation and function [72]
MS	Increased IL-33 in serum, cerebrospinal fluid and brain tissues of MS patients [149,150,151]. Serum IL-33 correlates disease severity [152] IL-33 concentration is decreased after treatment with IFN-β [149,153]	neuroprotective role via inducing oligodendrocytes myelin repair function and regulating Treg [156,157,158] IL-33 administration exacerbates EAE [160] IL-33 or ST2 neutralizing exacerbates EAE [161,162] IL-33 protects mice from EAE via inducing Th2 activity and M2 macrophages polarization [155,162].
SLE	IL-33 and sST2 are increased in serum and correlate with disease activity [163,164,166]	IL-33 neutralizing attenuates disease severity and results in the expansion of Tregs and MDSCs, and the reduction of Th17 cells [169].
T1D	Increased IL-33, ST2, sST2 in serum or kidney tissue [171,172,173,174] IL-33 concentration is decreased after treatment with melatonin [174]	ST2 neutralizing exacerbates T1D [176] IL-33/ST2 mediates myocardial-protective effects [177,179] IL-33 favors Treg cells function and stimulates M2 macrophage polarization [172,180,181]
SSc	Increased IL-33 and ST2 in serum and skin tissue [182,183] Serum IL-33 or sST2 level relates to disease activity and severity [184,185,186,187]	IL-33/ST2-IL-13 axis induces angiogenesis and cutaneous fibrosis [190,191] IL-33 induces Treg cells differentiation and promotes IL-4 and IL-13 expression in Treg cells [192]
Psoriasis	Increased IL-33 and ST2 in skin lesions and serum [193,194,195,196] Epidermal IL-33 correlates with disease severity [197,198] IL-33 level is decreased after treatment [199,200]	IL-33 stimulates IL-6, IL-8, MCP-1 and VEGF secretion in keratinocytes [193,194] IL-33 induces VEGF and IL-6 expression in MCs [196,201] IL-33/ST2 axis promotes skin inflammation in mice [202]
Uveitis	IL-33 level is increased in aqueous humor, serum and skin tissue [203,204]. Increased IL-33 and sST2 levels correlate with disease activity [204,205,206]	Exacerbated EAU in ST2-deficient mice and reduced EAU severity in IL-33-treated mice [208]
Other ADs	IL-33 and ST2 levels are positively associated the activity and severity of several ADs, such as Graves' disease, Sjogren's syndrome, active immune thrombocytopenia, AIHA, PBC [209,210,211,212].	AIHA incidence and disease activity were ameliorated by IL-33 blockade and promoted by recombinant IL-33 protein [212]. IL-33 enhances the infiltration and function of neutrophils and ILC2s in immune-mediated hepatitis [213,215]

thrombocytopenia [211]. In patients with autoimmune hemolytic anemia (AIHA) caused by autoantibodies targeting red blood cells (RBCs), the serum IL-33 level is positively correlated with disease severity [212]. Moreover, IL-33 induces the release of Th2 cytokines (IL-4, IL-6 and IL-13) and IgG and anti-RBC autoantibody production in PBMCs isolated from active AIHA patients (Fig. 2). Further studies involving the immunization of B6 mice with rat RBCs demonstrate that AIHA frequency and disease severity are ameliorated by IL-33 blockade and promoted by treatment with a recombinant IL-33 protein [212]. In summary, IL-33 might play a critical role in AIHA development by inducing autoantibody production.

Increasing studies indicate that IL-33 is a novel biomarker for the progression of autoimmune liver diseases. In primary biliary cirrhosis (PBC) patients, serum IL-33 production is elevated and positively correlated with the alkaline phosphatase levels and Child-Pugh scores. In vitro chemotaxis assays show that IL-33 promotes neutrophil migration [213]. These data collectively demonstrate that IL-33 might affect PBC development via the recruitment of neutrophils into the liver. After immunosuppressive therapy, the serum levels of both IL-33 and sST2 are markedly reduced in autoimmune hepatitis patients. In addition, serum IL-33 production is positively associated with the levels of IgA, IgG, IgM, and the cytokines IL-4 and IL-17A [214]. Utilizing the immune-mediated murine model of hepatitis induced by Con A, Neumann et al. [215] found that hepatic IL-33 expression correlated with ILC2 expansion in the liver. The expansive number of ILC2s was correlated with severe hepatitis, which was characterized by strongly elevated plasma ALT activity, IFN-γ expression and hepatocyte death by necrosis, which subsequently caused the formation of necrotic lesions. IL-33-treated mice exhibited highly increased numbers of hepatic ILC2s. Further in vitro study found that IL-33 induces hepatic ILC2s to produce GATA3, IL-5 and IL-13 [215]. Moreover, the adoptive transfer of hepatic ILC2s led to the aggravation of the immune-mediated hepatitis and higher expression of IFN-γ. Collectively, the results show that the subsequent hepatic IL-33 production causes the liver ILC2 activation that produces IL-5 and IL-13 during the development of immune-mediated hepatitis. Notably, in a recent study, an anti-IL-33 antibody treatment resulted in significantly decreased serum ALT/AST levels associated with reduced IL-4 and IL-17 production in mice [214]. The above findings demonstrate a potential protective role for IL-33/ST2 in the development of several ADs. However, the limited data concerning this field necessitate establishing better animal models to explore the actual functions and underlying immune mechanisms of IL-33 and its receptor in this context.

9. Conclusions

This review summarizes the current studies on the emerging role of IL-33/ST2 in various ADs (Table 1). The IL-33/ST2 levels are associated with disease severity and treatment, suggesting that IL-33 and/or ST2 might represent potential targets for predicting AD development and the subsequent clinical efficacy of therapeutics. Data from several studies reveal that IL-33 plays pivotal roles in ADs dependent on ST2-mediated pathways. Although IL-33/ST2 has dichotomous effects on ADs, we can still identify patterns and form conclusions (Table 1). In summary, the IL-33/ST2 pathway exerts more detrimental effects on RA, SSc, SLE and psoriasis, while in MS, T1D and uveitis, studies have primarily shown protective effects. For IBDs, we present the novel hypothesis that the IL-33/ST2 axis exerts detrimental effects on IBDs, especially during the acute phase. In contrast, both protective and detrimental effects of this pathway on chronic colitis have been demonstrated. Thus, IL-33/ST2 has a clear dual role in various types of diseases, and the effect of IL-33/ST2 depends on the underlying immune mechanism of pathogenesis in each disease condition.

The IL-33/ST2 axis has been shown in multiple reported studies to influence many of the immune cell types involved in autoimmunity. The IL-33/ST2 axis exerts bioeffects on Th2 cells to drive the production of Th2 cytokines (IL-4, IL-5, and IL-13). In this review, we summarize that in the autoimmune environment, the IL-33/ST2 pathway promotes the activation and functions of Th1 and Th17 cells as well as the upregulation of the expression of TNF-α, IFN-γ, IL-17A and IL-1β. Tregs are another important regulator of autoimmunity. IL-33 contributes to Treg differentiation and dysfunction. Although IL-33 is reportedly associated with autoantibody production, its direct effects on B cells need to be investigated under autoimmune conditions. In addition, IL-33 drives M2 macrophage phenotype polarization and neutrophil activation. IL-33 induces IL-13 and IL-4 expression by MCs and ILC2s by binding to membrane-associated ST2. Furthermore, IL-33/ST2 induces eosinophilia and the release of peroxidase, IL-6 and chemokines, such as CXCL8 and CCL20, by eosinophils. Additionally, IL-33 affects the functions of local tissue cells, including oligodendrocytes, cardiomyocytes, and ECs, and the underlying mechanism involves the stimulation of endothelial NO production by IL-33 through the IL-33/ST2/PI3K/AKT/eNOS signaling pathway. IL-33 can act on other proinflammatory molecules, such as HIF-1α, to perpetuate inflammatory states. Collectively, the data indicate that the IL-33/ST2 pathway plays key roles in perpetuating autoimmunity by acting on a variety of cells.

Most studies conclude that IL-33/ST2 exerts detrimental effects in several autoimmune disorders, including RA, SSc, SLE, psoriasis and acute IBDs. Potential mechanisms include the IL-33/ST2-mediated dysfunction of Tregs, benefiting Th1/Th17 cells. In addition, IL-33-induced type 2 immune responses are responsible for the exacerbation of acute colitis. These results demonstrate that the effects of IL-33 is elusive in ADs. In summary, IL-33 and its receptor ST2 are molecules of focus in AD studies. We conclude that the IL-33/ST2 axis primarily plays a detrimental role in the initiation and progression of ADs. Nevertheless, it remains unclear whether IL-33 and its receptor may serve as biomarkers to predict disease severity and activity. The role of IL-33 differs across diverse diseases and/or disease phases. Given the limited current data, these problems should be prioritized in future AD studies. We propose additional studies to demonstrate the precise function and detailed mechanisms of IL-33/ST2 in ADs.

Author contributions

Conception and design: W.S., S.Z.; Drafting and revising of the article: W.S., X.L., Y.X., Y.P. and H.L.; Final approval: W.S., S.Z.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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References

[1] J.E. Sims, M.J. Nicklin, J.F. Bazan, J.L. Barton, S.J. Busfield, J.E. Ford, et al., A new nomenclature for IL-1-family genes, Trends Immunol. 22 (2001) 536–537.

[2] E.S. Baekkevold, M. Roussigné, T. Yamanaka, F.E. Johansen, F.L. Jahnsen, F. Amalric, et al., Molecular characterization of NF-HEV, a nuclear factor preferentially expressed in human high endothelial venules, Am. J. Pathol. 163 (2003) 69–79.

[3] D.E. Cavender, Lymphocyte adhesion to endothelial cells in vitro: models for the study of normal lymphocyte recirculation and lymphocyte emigration into chronic inflammatory lesions, J. Invest. Dermatol. 93 (1989) 88S-95S..

[4] M. Miyasaka, T. Tanaka, Lymphocyte trafficking across high endothelial venules: dogmas and enigmas, Nat. Rev. Immunol. 4 (2004) 360–370.

[5] J. Schmitz, A. Owyang, E. Oldham, Y. Song, E. Murphy, T.K. McClanahan, et al., IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines, Immunity 23 (2005) 479–490.

[6] M. Pichery, E. Mirey, P. Mercier, E. Lefrancais, A. Dujardin, N. Ortega, et al., Endogenous IL-33 is highly expressed in mouse epithelial barrier tissues, lymphoid organs, brain, embryos, and inflamed tissues: in situ analysis using a novel Il-33-LacZ gene trap reporter strain, J. Immunol. 188 (2012) 3488–3495.

[7] A. Yagami, K. Orihara, H. Morita, K. Futamura, N. Hashimoto, K. Matsumoto, et al., IL-33 mediates inflammatory responses in human lung tissue cells, J. Immunol. 185 (2010) 5743–5750.

[8] N.T. Martin, M.U. Martin, Interleukin 33 is a guardian of barriers and a local alarmin, Nat. Immunol. 17 (2016) 122–131.

[9] C. Cayrol, J.P. Girard, IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy, Curr. Opin. Immunol. 31 (2014) 31–37.

[10] A. Lingel, T.M. Weiss, M. Niebuhr, B. Pan, B.A. Appleton, C. Wiesmann, et al., Structure of IL-33 and its interaction with the ST2 and IL-1RAcP receptors–insight into heterotrimeric IL-1 signaling complexes, Structure 17 (2009) 1398–1410.

[11] W.V. Bonilla, A. Fröhlich, K. Senn, S. Kallert, M. Fernandez, S. Johnson, et al., The alarmin interleukin-33 drives protective antiviral $CD8^+$ T cell responses, Science 335 (2012) 984–989.

[12] F.Y. Liew, N.I. Pitman, I.B. McInnes, Disease-associated functions of IL-33: the new kid in the IL-1 family, Nat. Rev. Immunol. 10 (2010) 103–110.

[13] M. De la Fuente, T.T. MacDonald, M.A. Hermoso, The IL-33/ST2 axis: role in health and disease, Cytokine Growth Factor Rev. 26 (2015) 615–623.

[14] Q. Gao, Y. Li, M. Li, The potential role of IL-33/ST2 signaling in fibrotic diseases, J. Leukoc. Biol. 98 (2015) 15–22.

[15] R.K. Gupta, K. Gupta, P.D. Dwivedi, Pathophysiology of IL-33 and IL-17 in allergic disorders, Cytokine Growth Factor Rev. 38 (2017) 22–36.

[16] G.S. Cooper, M.L. Bynum, E.C. Somers, Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases, J. Autoimmun. 33 (2009) 197–207.

[17] C.G. Parks, F.W. Miller, K.M. Pollard, C. Selmi, D. Germolec, K. Joyce, et al., Expert panel workshop consensus statement on the role of the environment in the development of autoimmune disease, Int. J. Mol. Sci. 15 (2014) 14269–14297.

[18] S. Leung, X. Liu, L. Fang, X. Chen, T. Guo, J. Zhang, The cytokine milieu in the interplay of pathogenic Th1/Th17 cells and regulatory T cells in autoimmune disease, Cell. Mol. Immunol. 7 (2010) 182–189.

[19] K.A. Cho, J.W. Suh, J.H. Sohn, J.W. Park, H. Lee, J.L. Kang, et al., IL-33 induces Th17-mediated airway inflammation via mast cells in ovalbumin-challenged mice, Am. J. Physiol. Lung Cell Mol. Physiol. 302 (2012) L429–40.

[20] V. Carriere, L. Roussel, N. Ortega, D.A. Lacorre, L. Americh, L. Aguilar, et al., IL-33, the IL-1-like cytokine ligand for ST2 receptor, is a chromatin-associated nuclear factor in vivo, Proc Natl Acad Sci U S A 104 (2007) 282–287.

[21] L. Roussel, M. Erard, C. Cayrol, J.P. Girard, Molecular mimicry between IL-33 and KSHV for attachment to chromatin through the H2A-H2B acidic pocket, EMBO Rep. 9 (2008) 1006–1012.

[22] S. Ali, A. Mohs, M. Thomas, J. Klare, R. Ross, M.L. Schmitz, et al., The dual function cytokine IL-33 interacts with the transcription factor NF-κB to dampen NF-κB-stimulated gene transcription, J. Immunol. 187 (2011) 1609–1616.

[23] Y.S. Choi, J.A. Park, J. Kim, S.S. Rho, H. Park, Y.M. Kim, et al., Nuclear IL-33 is a transcriptional regulator of NF-κB p65 and induces endothelial cell activation, Biochem. Biophys. Res. Commun. 421 (2012) 305–311.

[24] D. Shao, F. Perros, G. Caramori, C. Meng, P. Dormuller, P.C. Chou, et al., Nuclear IL-33 regulates soluble ST2 receptor and IL-6 expression in primary human arterial endothelial cells and is decreased in idiopathic pulmonary arterial hypertension, Biochem. Biophys. Res. Commun. 451 (2014) 8–14.

[25] J. Bessa, C.A. Meyer, M.C. de Vera Mudry, S. Schlicht, S.H. Smith, A. Iglesias, et al., Altered subcellular localization of IL-33 leads to non-resolving lethal inflammation, J. Autoimmun. 55 (2014) 33–41.

[26] C. Cayrol, J.P. Girard, The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 9021–9026.

[27] R. Kakkar, H. Hei, S. Dobner, R.T. Lee, Interleukin 33 as a mechanically responsive cytokine secreted by living cells, J. Biol. Chem. 287 (2012) 6941–6948.

[28] W.Y. Chen, J. Hong, J. Gannon, R. Kakkar, R.T. Lee, Myocardial pressure overload induces systemic inflammation through endothelial cell IL-33, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 7249–7254.

[29] Y. Haenuki, K. Matsushita, S. Futatsugi-Yumikura, K.J. Ishii, T. Kawagoe, Y. Imoto, et al., A critical role of IL-33 in experimental allergic rhinitis, J. Allergy Clin. Immunol. 130 (2012) 184-94.e11.

[30] J.J. Oppenheim, D. Yang, Alarmins: chemotactic activators of immune responses, Curr. Opin. Immunol. 17 (2005) 359–365.

[31] G. Haraldsen, J. Balogh, J. Pollheimer, J. Sponheim, A.M. Küchler, Interleukin-33 - cytokine of dual function or novel alarmin, Trends Immunol. 30 (2009) 227–233.

[32] J. Hong, S. Bae, H. Jhun, S. Lee, J. Choi, T. Kang, et al., Identification of constitutively active interleukin 33 (IL-33) splice variant, J. Biol. Chem. 286 (2011) 20078–20086.

[33] S. Ali, D.Q. Nguyen, W. Falk, M.U. Martin, Caspase 3 inactivates biologically active full length interleukin-33 as a classical cytokine but does not prohibit nuclear translocation, Biochem. Biophys. Res. Commun. 391 (2010) 1512–1516.

[34] F. Madouri, N. Guillou, L. Fauconnier, T. Marchiol, N. Rouxel, P. Chenuet, et al., Caspase-1 activation by NLRP3 inflammasome dampens IL-33-dependent house dust mite-induced allergic lung inflammation, J. Mol. Cell Biol. 7 (2015) 351–365.

[35] D. Talabot-Ayer, C. Lamacchia, C. Gabay, G. Palmer, Interleukin-33 is biologically active independently of caspase-1 cleavage, J. Biol. Chem. 284 (2009) 19420–19426.

[36] M. Lamkanfi, T.D. Kanneganti, P. Van Damme, T. Vanden Berghe, I. Vanoverberghe, J. Vandekerckhove, et al., Targeted peptidecentric proteomics reveals caspase-7 as a substrate of the caspase-1 inflammasomes, Mol. Cell Proteomics 7 (2008) 2350–2363.

[37] A.U. Lüthi, S.P. Cullen, E.A. McNeela, P.J. Duriez, I.S. Afonina, C. Sheridan, et al., Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases, Immunity 31 (2009) 84–98.

[38] E. Lefrançais, A. Duval, E. Mirey, S. Roga, E. Espinosa, C. Cayrol, et al., Central domain of IL-33 is cleaved by mast cell proteases for potent activation of group-2 innate lymphoid cells, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 15502–15507.

[39] E. Lefrançais, S. Roga, V. Gautier, A. Gonzalez-de-Peredo, B. Monsarrat, J.P. Girard, et al., IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 1673–1678.

[40] M.Y. Tjota, J.W. Williams, T. Lu, B.S. Clay, T. Byrd, C.L. Hrusch, et al., IL-33-dependent induction of allergic lung inflammation by FcγRIII signaling, J. Clin. Invest. 123 (2013) 2287–2297.

[41] H.Y. Kim, Y.J. Chang, S. Subramanian, H.H. Lee, L.A. Albacker, P. Matangkasombut, et al., Innate lymphoid cells responding to IL-33 mediate airway hyperreactivity independently of adaptive immunity, J. Allergy Clin. Immunol. 129 (2012) 216-27.e1-6.

[42] S. Sanada, D. Hakuno, L.J. Higgins, E.R. Schreiter, A.N. McKenzie, R.T. Lee, IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system, J. Clin. Invest. 117 (2007) 1538–1549.

[43] A.M. Miller, D. Xu, D.L. Asquith, L. Denby, Y. Li, N. Sattar, et al., IL-33 reduces the development of atherosclerosis, J. Exp. Med. 205 (2008) 339–346.

[44] D. Préfontaine, J. Nadigel, F. Chouiali, S. Audusseau, A. Semlali, J. Chakir, et al., Increased IL-33 expression by epithelial cells in bronchial asthma, J. Allergy Clin. Immunol. 125 (2010) 752–754.

[45] D.E. Byers, J. Alexander-Brett, A.C. Patel, E. Agapov, G. Dang-Vu, X. Jin, et al., Long-term IL-33-producing epithelial progenitor cells in chronic obstructive lung disease, J. Clin. Invest. 123 (2013) 3967–3982.

[46] K. Yasuda, T. Muto, T. Kawagoe, M. Matsumoto, Y. Sasaki, K. Matsushita, et al., Contribution of IL-33-activated type II innate lymphoid cells to pulmonary eosinophilia in intestinal nematode-infected mice, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 3451–3456.

[47] D.J. Jackson, H. Makrinioti, B.M. Rana, B.W. Shamji, M.B. Trujillo-Torralbo, J. Footitt, et al., IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo, Am. J. Respir. Crit. Care Med. 190 (2014) 1373–1382.

[48] G. Palmer, D. Talabot-Ayer, C. Lamacchia, D. Toy, C.A. Seemayer, S. Viatte, et al., Inhibition of interleukin-33 signaling attenuates the severity of experimental arthritis, Arthritis Rheum. 60 (2009) 738–749.

[49] Y.J. Chang, H.Y. Kim, L.A. Albacker, N. Baumgarth, A.N. McKenzie, D.E. Smith, et al., Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity, Nat. Immunol. 12 (2011) 631–638.

[50] L. Zhang, R. Lu, G. Zhao, S.C. Pflugfelder, D.Q. Li, TLR-mediated induction of proallergic cytokine IL-33 in ocular mucosal epithelium, Int. J. Biochem. Cell Biol. 43 (2011) 1383–1391.

[51] D. Talabot-Ayer, N. Calo, S. Vigne, C. Lamacchia, C. Gabay, G. Palmer, The mouse interleukin (Il)33 gene is expressed in a cell type- and stimulus-dependent manner from two alternative promoters, J. Leukoc. Biol. 91 (2012) 119–125.

[52] S.K. Polumuri, G.G. Jayakar, K.A. Shirey, Z.J. Roberts, D.J. Perkins, P.M. Pitha, et al., Transcriptional regulation of murine IL-33 by TLR and non-TLR agonists, J. Immunol. 189 (2012) 50–60.

[53] T. Shimosato, M. Fujimoto, M. Tohno, T. Sato, M. Tateo, H. Otani, et al., CpG oligodeoxynucleotides induce strong up-regulation of interleukin 33 via Toll-like receptor 9, Biochem. Biophys. Res. Commun. 394 (2010) 81–86.

[54] J. Sponheim, J. Pollheimer, T. Olsen, J. Balogh, C. Hammarström, T. Loos, et al., Inflammatory bowel disease-associated interleukin-33 is preferentially expressed in ulceration-associated myofibroblasts, Am. J. Pathol. 177 (2010) 2804–2815.

[55] J. Meephansan, H. Tsuda, M. Komine, S. Tominaga, M. Ohtsuki, Regulation of IL-33 expression by IFN-γ and tumor necrosis factor-α in normal human epidermal keratinocytes, J. Invest. Dermatol. 132 (2012) 2593–2600.

[56] S. Saidi, F. Bouri, P. Lencel, L. Duplomb, M. Baud'huin, S. Delplace, et al., IL-33 is expressed in human osteoblasts, but has no direct effect on bone remodeling, Cytokine 53 (2011) 347–354.

[57] Wood IS, Wang B, Trayhurn P. IL-33, a recently identified interleukin-1 gene family member, is expressed in human adipocytes, Biochem. Biophys. Res. Commun. 384 (2009) 105–109.

[58] K. Nomura, T. Kojima, J. Fuchimoto, K. Obata, T. Keira, T. Himi, et al., Regulation of interleukin-33 and thymic stromal lymphopoietin in human nasal fibroblasts by proinflammatory cytokines, Laryngoscope 122 (2012) 1185–1192.

[59] C.A. Hudson, G.P. Christophi, R.C. Gruber, J.R. Wilmore, D.A. Lawrence, P.T. Massa, Induction of IL-33 expression and activity in central nervous system glia, J. Leukoc. Biol. 84 (2008) 631–643.

[60] S. Demyanets, C. Kaun, R. Pentz, K.A. Krychtiuk, S. Rauscher, S. Pfaffenberger, et al., Components of the interleukin-33/ST2 system are differentially expressed and regulated in human cardiac cells and in cells of the cardiac vasculature, J. Mol. Cell. Cardiol. 60 (2013) 16–26.

[61] C. Li, H. Li, Z. Jiang, T. Zhang, Y. Wang, Z. Li, et al., Interleukin-33 increases antibacterial defense by activation of inducible nitric oxide synthase in skin, PLoS Pathog. 10 (2014) e1003918.

[62] Z. Su, J. Lin, F. Lu, X. Zhang, L. Zhang, N.B. Gandhi, et al., Potential autocrine regulation of interleukin-33/ST2 signaling of dendritic cells in allergic inflammation, Mucosal Immunol. 6 (2013) 921–930.

[63] J. Seltmann, T. Werfel, M. Wittmann, Evidence for a regulatory loop between IFN-γ and IL-33 in skin inflammation, Exp. Dermatol. 22 (2013) 102–107.

[64] S. Kumar, M.N. Tzimas, D.E. Griswold, P.R. Young, Expression of ST2, an interleukin-1 receptor homologue, is induced by proinflammatory stimuli, Biochem. Biophys. Res. Commun. 235 (1997) 474–478.

[65] K. Yanagisawa, T. Takagi, T. Tsukamoto, T. Tetsuka, S. Tominaga, Presence of a novel primary response gene ST2L, encoding a product highly similar to the interleukin 1 receptor type 1, FEBS Lett. 318 (1993) 83–87.

[66] T. Si, K. Kuroiwa, K. Tago, H. Iwahana, K. Yanagisawa, N. Komatsu, Presence and expression of a novel variant form of ST2 gene product in human leukemic cell line UT-7/GM, Biochem. Biophys. Res. Commun. 264 (1999) 14–18.

[67] D. Xu, W.L. Chan, B.P. Leung, H. Fp, R. Wheeler, D. Piedrafita, et al., Selective expression of a stable cell surface molecule on type 2 but not type 1 helper T cells, J. Exp. Med. 187 (1998) 787–794.

[68] C. Baumann, W.V. Bonilla, A. Fröhlich, C. Helmstetter, M. Peine, A.N. Hegazy, et al., T-bet- and STAT4-dependent IL-33 receptor expression directly promotes antiviral Th1 cell responses, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 4056–4061.

[69] J. Mjösberg, J. Bernink, K. Golebski, J.J. Karrich, C.P. Peters, B. Blom, et al., The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells, Immunity 37 (2012) 649–659.

[70] J. Zhu, H. Yamane, J. Cote-Sierra, L. Guo, W.E. Paul, GATA-3 promotes Th2 responses through three different mechanisms: induction of Th2 cytokine production, selective growth of Th2 cells and inhibition of Th1 cell-specific factors, Cell Res. 16 (2006) 3–10.

[71] L. Guo, G. Wei, J. Zhu, W. Liao, W.J. Leonard, K. Zhao, et al., IL-1 family members and STAT activators induce cytokine production by Th2, Th17, and Th1 cells, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 13463–13468.

[72] C. Schiering, T. Krausgruber, A. Chomka, A. Fröhlich, K. Adelmann, E.A. Wohlfert, et al., The alarmin IL-33 promotes regulatory T-cell function in the intestine, Nature 513 (2014) 564–568.

[73] S. Kumar, M.D. Minnich, P.R. Young, ST2/T1 protein functionally binds to two secreted proteins from Balb/c 3T3 and human umbilical vein endothelial cells but does not bind interleukin 1, J. Biol. Chem. 270 (1995) 27905–27913.

[74] M.A. Gayle, J.L. Slack, T.P. Bonnert, B.R. Renshaw, G. Sonoda, T. Taguchi, et al., Cloning of a putative ligand for the T1/ST2 receptor, J. Biol. Chem. 271 (1996) 5784–5789.

[75] S. Drube, S. Heink, S. Walter, T. Löhn, M. Grusser, A. Gerbaulet, et al., The receptor tyrosine kinase c-Kit controls IL-33 receptor signaling in mast cells, Blood 115 (2010) 3899–3906.

[76] D.J. Connolly, L.A. O'Neill, A.F. McGettrick, The GOLD domain-containing protein TMED1 is involved in interleukin-33 signaling, J. Biol. Chem. 288 (2013) 5616–5623.

[77] S. Sugita, Y. Hosaka, K. Okada, D. Mori, F. Yano, H. Kobayashi, et al., Transcription factor Hes1 modulates osteoarthritis development in cooperation with calcium/calmodulin-dependent protein kinase 2, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 3080–3085.

[78] G. Palmer, B.P. Lipsky, M.D. Smithgall, D. Meininger, S. Siu, D. Talabot-Ayer, et al., The IL-1 receptor accessory protein (AcP) is required for IL-33 signaling and soluble AcP enhances the ability of soluble ST2 to inhibit IL-33, Cytokine 42 (2008) 358–364.

[79] R. Kakkar, R.T. Lee, The IL-33/ST2 pathway: therapeutic target and novel biomarker, Nat. Rev. Drug Discov. 7 (2008) 827–840.

[80] E.K. Brint, D. Xu, H. Liu, A. Dunne, A.N. McKenzie, L.A. O'Neill, et al., ST2 is an inhibitor of interleukin 1 receptor and Toll-like receptor 4 signaling and maintains endotoxin tolerance, Nat. Immunol. 5 (2004) 373–379.

[81] E.S. Cohen, I.C. Scott, J.B. Majithiya, L. Rapley, B.P. Kemp, E. England, et al., Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation, Nat. Commun. 6 (2015) 8327.

[82] C. Garlanda, H.J. Anders, A. Mantovani, TIR8/SIGIRR: an IL-1R/TLR family member with regulatory functions in inflammation and T cell polarization, Trends Immunol. 30 (2009) 439–446.

[83] G. An, X. Zhang, W. Wang, Q. Huang, Y. Li, S. Shan, et al., The effects of interleukin-33 on airways collagen deposition and matrix metalloproteinase expression in a murine surrogate of asthma, Immunology (2018).

[84] S. Saglani, S. Lui, N. Ullmann, G.A. Campbell, R.T. Sherburn, S.A. Mathie, et al., IL-33 promotes airway remodeling in pediatric patients with severe steroid-resistant asthma, J. Allergy Clin. Immunol. 132 (2013) 676-85.e13.

[85] C.K. Wong, K.M. Leung, H.N. Qiu, J.Y. Chow, A.O. Choi, C.W. Lam, Activation of eosinophils interacting with dermal fibroblasts by pruritogenic cytokine IL-31 and alarmin IL-33: implications in atopic dermatitis, PLoS One 7 (2012) e29815.

[86] J. Fujita, M. Kawaguchi, F. Kokubu, G. Ohara, K. Ota, S.K. Huang, et al.,

Interleukin-33 induces interleukin-17F in bronchial epithelial cells, Allergy 67 (2012) 744–750.

[87] M. Iikura, H. Suto, N. Kajiwara, K. Oboki, T. Ohno, Y. Okayama, et al., IL-33 can promote survival, adhesion and cytokine production in human mast cells, Lab. Invest. 87 (2007) 971–978.

[88] P.N. Pushparaj, H.K. Tay, S.C. H'ng, N. Pitman, D. Xu, A. McKenzie, et al., The cytokine interleukin-33 mediates anaphylactic shock, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 9773–9778.

[89] L.C. Sjöberg, J.A. Gregory, S.E. Dahlén, G.P. Nilsson, M. Adner, Interleukin-33 exacerbates allergic bronchoconstriction in the mice via activation of mast cells, Allergy 70 (2015) 514–521.

[90] A. Matsuda, Y. Okayama, N. Terai, N. Yokoi, N. Ebihara, H. Tanioka, et al., The role of interleukin-33 in chronic allergic conjunctivitis, Invest. Ophthalmol. Vis. Sci. 50 (2009) 4646–4652.

[91] C.Y. Chen, J.B. Lee, B. Liu, S. Ohta, P.Y. Wang, A.V. Kartashov, et al., Induction of Interleukin-9-Producing mucosal mast cells promotes susceptibility to IgE-Mediated experimental food allergy, Immunity 43 (2015) 788–802.

[92] E.D. Gordon, L.J. Simpson, C.L. Rios, L. Ringel, M.E. Lachowicz-Scroggins, M.C. Peters, et al., Alternative splicing of interleukin-33 and type 2 inflammation in asthma, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 8765–8770.

[93] W. Ding, G.L. Zou, W. Zhang, X.N. Lai, H.W. Chen, L.X. Xiong, Interleukin-33: its emerging role in allergic diseases, Molecules (2018) 23.

[94] W.B. Cherry, J. Yoon, K.R. Bartemes, K. Iijima, H. Kita, A novel IL-1 family cytokine, IL-33, potently activates human eosinophils, J. Allergy Clin. Immunol. 121 (2008) 1484–1490.

[95] M. Komai-Koma, F. Brombacher, P.N. Pushparaj, B. Arendse, C. McSharry, J. Alexander, et al., Interleukin-33 amplifies IgE synthesis and triggers mast cell degranulation via interleukin-4 in naïve mice, Allergy 67 (2012) 1118-26.

[96] M. Kurowska-Stolarska, B. Stolarski, P. Kewin, G. Murphy, C.J. Corrigan, S. Ying, et al., IL-33 amplifies the polarization of alternatively activated macrophages that contribute to airway inflammation, J. Immunol. 183 (2009) 6469-77.

[97] A.G. Besnard, D. Togbe, N. Guillou, F. Erard, V. Quesniaux, B. Ryffel, IL-33-activated dendritic cells are critical for allergic airway inflammation, Eur. J. Immunol. 41 (2011) 1675–1686.

[98] B. Sun, L. Zhu, Y. Tao, H.X. Sun, Y. Li, P. Wang, et al., Characterization and allergic role of IL-33-induced neutrophil polarization, Cell. Mol. Immunol. (2018).

[99] D. Canbaz, L. Utsch, A. Logiantara, R. van Ree, L.S. van Rijt, IL-33 promotes the induction of immunoglobulin production after inhalation of house dust mite extract in mice, Allergy 70 (2015) 522–532.

[100] M. Komai-Koma, D. Xu, Y. Li, A.N. McKenzie, I.B. McInnes, F.Y. Liew, IL-33 is a chemoattractant for human Th2 cells, Eur. J. Immunol. 37 (2007) 2779–2786.

[101] M. Kurowska-Stolarska, P. Kewin, G. Murphy, R.C. Russo, B. Stolarski, C.C. Garcia, et al., IL-33 induces antigen-specific IL-5+ T cells and promotes allergic-induced airway inflammation independent of IL-4, J. Immunol. 181 (2008) 4780–4790.

[102] Y. Endo, K. Hirahara, T. Iinuma, K. Shinoda, D.J. Tumes, H.K. Asou, et al., The interleukin-33-p38 kinase axis confers memory T helper 2 cell pathogenicity in the airway, Immunity 42 (2015) 294–308.

[103] D.K. Chu, A. Llop-Guevara, T.D. Walker, K. Flader, S. Goncharova, J.E. Boudreau, et al., IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization, J. Allergy Clin. Immunol. 131 (2013) 187-200.e1-8.

[104] Y. Imai, K. Yasuda, Y. Sakaguchi, T. Haneda, H. Mizutani, T. Yoshimoto, et al., Skin-specific expression of IL-33 activates group 2 innate lymphoid cells and elicits atopic dermatitis-like inflammation in mice, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 13921–13926.

[105] L.M. Judd, R.G. Heine, T.R. Menheniott, J. Buzzelli, N. O'Brien-Simpson, D. Pavlic, et al., Elevated IL-33 expression is associated with pediatric eosinophilic esophagitis, and exogenous IL-33 promotes eosinophilic esophagitis development in mice, Am. J. Physiol. Gastrointest. Liver Physiol. 310 (2016) G13–25.

[106] C.C. Chen, T. Kobayashi, K. Iijima, F.C. Hsu, H. Kita, IL-33 dysregulates regulatory T cells and impairs established immunologic tolerance in the lungs, J. Allergy Clin. Immunol. 140 (2017) 1351-63.e7.

[107] L. Vocca, C. Di Sano, C.G. Uasuf, A. Sala, L. Riccobono, S. Gangemi, et al., IL-33/ST2 axis controls Th2/IL-31 and Th17 immune response in allergic airway diseases, Immunobiology 220 (2015) 954–963.

[108] M.C. Boissier, Cell and cytokine imbalances in rheumatoid synovitis, Joint Bone Spine 78 (2011) 230–234.

[109] Y.S. Hong, S.J. Moon, Y.B. Joo, C.H. Jeon, M.L. Cho, J.H. Ju, et al., Measurement of interleukin-33 (IL-33) and IL-33 receptors (sST2 and ST2L) in patients with rheumatoid arthritis, J. Korean Med. Sci. 26 (2011) 1132–1139.

[110] Y. Matsuyama, H. Okazaki, H. Tamemoto, H. Kimura, Y. Kamata, K. Nagatani, et al., Increased levels of interleukin 33 in sera and synovial fluid from patients with active rheumatoid arthritis, J. Rheumatol. 37 (2010) 18–25.

[111] D. Xu, H.R. Jiang, P. Kewin, Y. Li, R. Mu, A.R. Fraser, et al., IL-33 exacerbates antigen-induced arthritis by activating mast cells, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 10913–10918.

[112] R. Mu, H.Q. Huang, Y.H. Li, C. Li, H. Ye, Z.G. Li, Elevated serum interleukin 33 is associated with autoantibody production in patients with rheumatoid arthritis, J. Rheumatol. 37 (2010) 2006–2013.

[113] Z. Xiangyang, Y. Lutian, Z. Lin, X. Liping, S. Hui, L. Jing, Increased levels of interleukin-33 associated with bone erosion and interstitial lung diseases in patients with rheumatoid arthritis, Cytokine 58 (2012) 6–9.

[114] Y. Kageyama, E. Torikai, K. Tsujimura, M. Kobayashi, Involvement of IL-33 in the pathogenesis of rheumatoid arthritis: the effect of etanercept on the serum levels of IL-33, Mod. Rheumatol. 22 (2012) 89–93.

[115] S. Tang, H. Huang, F. Hu, W. Zhou, J. Guo, H. Jiang, et al., Increased IL-33 in synovial fluid and paired serum is associated with disease activity and autoantibodies in rheumatoid arthritis, Clin. Dev. Immunol. 2013 (2013) 985301.

[116] A. Ahmed, I. Hollan, S.A. Curran, S.M. Kitson, M.P. Riggio, K. Mikkelsen, et al., Brief report: proatherogenic cytokine microenvironment in the aortic adventitia of patients with rheumatoid arthritis, Arthritis Rheumatol. 68 (2016) 1361–1366.

[117] J. Shen, Q. Shang, C.K. Wong, E.K. Li, S. Wang, R.J. Li, et al., IL-33 and soluble ST2 levels as novel predictors for remission and progression of carotid plaque in early rheumatoid arthritis: a prospective study, Semin. Arthritis Rheum. 45 (2015) 18–27.

[118] C. Li, R. Mu, J. Guo, X. Wu, X. Tu, X. Liu, et al., Genetic variant in IL33 is associated with susceptibility to rheumatoid arthritis, Arthritis Res. Ther. 16 (2014) R105.

[119] R. López-Mejías, F. Genre, S. Remuzgo-Martínez, M. Robustillo-Villarino, M. García-Bermúdez, J. Llorca, et al., Protective role of the interleukin 33 rs3939286 gene polymorphism in the development of subclinical atherosclerosis in rheumatoid arthritis patients, PLoS One 10 (2015) e0143153.

[120] J. Sellam, E. Rivière, A. Courties, P.O. Rouzaire, B. Tolusso, E.M. Vital, et al., Serum IL-33, a new marker predicting response to rituximab in rheumatoid arthritis, Arthritis Res. Ther. 18 (2016) 294.

[121] E. Kunisch, S. Chakilam, M. Gandesiri, R.W. Kinne, IL-33 regulates TNF-α dependent effects in synovial fibroblasts, Int. J. Mol. Med. 29 (2012) 530–540.

[122] Y. Matsuyama, H. Okazaki, M. Hoshino, S. Onishi, Y. Kamata, K. Nagatani, et al., Sustained elevation of interleukin-33 in sera and synovial fluids from patients with rheumatoid arthritis non-responsive to anti-tumor necrosis factor: possible association with persistent IL-1β signaling and a poor clinical response, Rheumatol. Int. 32 (2012) 1397–1401.

[123] C. Chunxia, Z. Peng, P. Huifang, R. Hanli, H. Zehua, W. Jizhou, Extracts of Arisaema rhizomatum C.E.C. Fischer attenuate inflammatory response on collagen-induced arthritis in BALB/c mice, J. Ethnopharmacol. 133 (2011) 573–582.

[124] A.C. Zarpelon, V. Fattori, F.O. Souto, L.G. Pinto, F.A. Pinho-Ribeiro, K.W. Ruiz-Miyazawa, et al., The sesquiterpene lactone, Budlein A, inhibits antigen-induced arthritis in mice: role of NF-κB and cytokines, Inflammation 40 (2017) 2020–2032.

[125] D. Xu, H.R. Jiang, Y. Li, P.N. Pushparaj, M. Kurowska-Stolarska, B.P. Leung, et al., IL-33 exacerbates autoantibody-induced arthritis, J. Immunol. 184 (2010) 2620–2626.

[126] J. Kashiwakura, M. Yanagisawa, H. Lee, Y. Okamura, T. Sasaki-Sakamoto, S. Saito, et al., Interleukin-33 synergistically enhances immune complex-induced tumor necrosis factor alpha and interleukin-8 production in cultured human synovium-derived mast cells, Int. Arch. Allergy Immunol. 161 (Suppl 2) (2013) 32–36.

[127] W.A. Verri, F.O. Souto, S.M. Vieira, S.C. Almeida, S.Y. Fukada, D. Xu, et al., IL-33 induces neutrophil migration in rheumatoid arthritis and is a target of anti-TNF therapy, Ann. Rheum. Dis. 69 (2010) 1697–1703.

[128] F. Hu, L. Shi, R. Mu, J. Zhu, Y. Li, X. Ma, et al., Hypoxia-inducible factor-1α and interleukin 33 form a regulatory circuit to perpetuate the inflammation in rheumatoid arthritis, PLoS One 8 (2013) e72650.

[129] E.J. Lee, M.W. So, S. Hong, Y.G. Kim, B. Yoo, C.K. Lee, Interleukin-33 acts as a transcriptional repressor and extracellular cytokine in fibroblast-like synoviocytes in patients with rheumatoid arthritis, Cytokine 77 (2016) 35–43.

[130] J. Biton, S. Khaleghparast Athari, A. Thiolat, F. Santinon, D. Lemeiter, R. Hervé, et al., In vivo expansion of activated Foxp3+ regulatory t cells and establishment of a type 2 immune response upon IL-33 treatment protect against experimental arthritis, J. Immunol. 197 (2016) 1708–1719.

[131] A. Kaser, R.S. Blumberg, Autophagy, microbial sensing, endoplasmic reticulum stress, and epithelial function in inflammatory bowel disease, Gastroenterology 140 (2011) 1738–1747.

[132] L. Pastorelli, R.R. Garg, S.B. Hoang, L. Spina, B. Mattioli, M. Scarpa, et al., Epithelial-derived IL-33 and its receptor ST2 are dysregulated in ulcerative colitis and in experimental Th1/Th2 driven enteritis, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 8017–8022.

[133] O.I. Saadah, S.E. Al-Harthi, J.A. Al-Mughales, Y.Y. Bin-Taleb, R.S. Baeshen, Serum Interleukin-33 level in Saudi children with inflammatory bowel disease, Int. J. Clin. Exp. Pathol. 8 (2015) 16000–16006.

[134] J.C. Masterson, K.E. Capocelli, L. Hosford, K. Biette, E.N. McNamee, E.F. de Zoeten, et al., Eosinophils and IL-33 perpetuate chronic inflammation and fibrosis in a pediatric population with Stricturing Crohn's ileitis, Inflamm. Bowel Dis. 21 (2015) 2429–2440.

[135] A. Latiano, O. Palmieri, L. Pastorelli, M. Vecchi, T.T. Pizarro, F. Bossa, et al., Associations between genetic polymorphisms in IL-33, IL1R1 and risk for inflammatory bowel disease, PLoS One 8 (2013) e62144.

[136] S. Boga, H. Alkim, A.R. Koksal, A.A. Ozagari, M. Bayram, S. Tekin Neijmann, et al., Serum ST2 in inflammatory bowel disease: a potential biomarker for disease activity, J. Investig. Med. 64 (2016) 1016–1024.

[137] C.J. Beltrán, L.E. Núñez, D. Díaz-Jiménez, N. Farfan, E. Candia, C. Heine, et al., Characterization of the novel ST2/IL-33 system in patients with inflammatory bowel disease, Inflamm. Bowel Dis. 16 (2010) 1097–1107.

[138] D. Díaz-Jiménez, M. De la Fuente, K. Dubois-Camacho, G. Landskron, J. Fuentes, T. Pérez, et al., Soluble ST2 is a sensitive clinical marker of ulcerative colitis evolution, BMC Gastroenterol. 16 (2016) 103.

[139] C.F. Guazelli, V. Fattori, B.B. Colombo, S.R. Georgetti, F.T. Vicentini, R. Casagrande, et al., Quercetin-loaded microcapsules ameliorate experimental colitis in mice by anti-inflammatory and antioxidant mechanisms, J. Nat. Prod. 76 (2013) 200–208.

[140] C.L. Zhang, S. Zhang, W.X. He, J.L. Lu, Y.J. Xu, J.Y. Yang, et al., Baicalin may alleviate inflammatory infiltration in dextran sodium sulfate-induced chronic ulcerative colitis via inhibiting IL-33 expression, Life Sci. 186 (2017) 125–132.

[141] M.D. Gundersen, R. Goll, J. Hol, T. Olsen, R. Rismo, S.W. Sørbye, et al., Loss of interleukin 33 expression in colonic crypts - a potential marker for disease

remission in ulcerative colitis, Sci. Rep. 6 (2016) 35403.

[142] M.A. Sedhom, M. Pichery, J.R. Murdoch, B. Foligné, N. Ortega, S. Normand, et al., Neutralisation of the interleukin-33/ST2 pathway ameliorates experimental colitis through enhancement of mucosal healing in mice, Gut 62 (2013) 1714–1723.

[143] H. Imaeda, A. Andoh, T. Aomatsu, K. Uchiyama, S. Bamba, T. Tsujikawa, et al., Interleukin-33 suppresses Notch ligand expression and prevents goblet cell depletion in dextran sulfate sodium-induced colitis, Int. J. Mol. Med. 28 (2011) 573–578.

[144] P.N. Pushparaj, D. Li, M. Komai-Koma, R. Guabiraba, J. Alexander, C. McSharry, et al., Interleukin-33 exacerbates acute colitis via interleukin-4 in mice, Immunology 140 (2013) 70–77.

[145] J. Zhu, F. Yang, L. Sang, J. Zhai, X. Zhang, D. Yue, et al., IL-33 aggravates DSS-Induced acute colitis in Mouse Colon Lamina propria by enhancing Th2 cell responses, Mediators Inflamm. 2015 (2015) 913041.

[146] C. De Salvo, X.M. Wang, L. Pastorelli, B. Mattioli, S. Omenetti, K.A. Buela, et al., IL-33 drives eosinophil infiltration and pathogenic type 2 helper T-Cell immune responses leading to chronic experimental ileitis, Am. J. Pathol. 186 (2016) 885–898.

[147] P. Groβ, K. Doser, W. Falk, F. Obermeier, C. Hofmann, IL-33 attenuates development and perpetuation of chronic intestinal inflammation, Inflamm. Bowel Dis. 18 (2012) 1900–1909.

[148] J. Zhu, Y. Wang, F. Yang, L. Sang, J. Zhai, S. Li, et al., IL-33 alleviates DSS-induced chronic colitis in C57BL/6 mice colon lamina propria by suppressing Th17 cell response as well as Th1 cell response, Int. Immunopharmacol. 29 (2015) 846–853.

[149] G.P. Christophi, R.C. Gruber, M. Panos, R.L. Christophi, B. Jubelt, P.T. Massa, Interleukin-33 upregulation in peripheral leukocytes and CNS of multiple sclerosis patients, Clin. Immunol. 142 (2012) 308–319.

[150] L. Sosvorova, R. Kanceva, J. Vcelak, L. Kancheva, M. Mohapl, L. Starka, et al., The comparison of selected cerebrospinal fluid and serum cytokine levels in patients with multiple sclerosis and normal pressure hydrocephalus, Neuro Endocrinol. Lett. 36 (2015) 564–571.

[151] D. Allan, K.J. Fairlie-Clarke, C. Elliott, C. Schuh, S.C. Barnett, H. Lassmann, et al., Role of IL-33 and ST2 signalling pathway in multiple sclerosis: expression by oligodendrocytes and inhibition of myelination in central nervous system, Acta Neuropathol. Commun. 4 (2016) 75.

[152] E. Kouchaki, O.R. Tamtaji, E. Dadgostar, M. Karami, H. Nikoueinejad, H. Akbari, Correlation of serum levels of IL-33, IL-37, soluble form of vascular endothelial growth factor receptor 2 (VEGFR2), and circulatory frequency of VEGFR2-expressing cells with multiple sclerosis severity, Iran. J. Allergy Asthma Immunol. 16 (2017) 329–337.

[153] F. Alsahebfosoul, I. Rahimmanesh, M. Shajarian, M. Etemadifar, N. Sedaghat, Z. Hejazi, et al., Interleukin-33 plasma levels in patients with relapsing-remitting multiple sclerosis, Biomol. Concepts 8 (2017) 55–60.

[154] B.M. Fiebiger, J. Maamary, A. Pincetic, J.V. Ravetch, Protection in antibody- and T cell-mediated autoimmune diseases by antiinflammatory IgG Fcs requires type II FcRs, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) E2385–94.

[155] C.M. Finlay, A.M. Stefanska, K.P. Walsh, P.J. Kelly, L. Boon, E.C. Lavelle, et al., Helminth products protect against autoimmunity via innate type 2 cytokines IL-5 and IL-33, which promote eosinophilia, J. Immunol. 196 (2016) 703–714.

[156] H. Chen, Y. Sun, L. Lai, H. Wu, Y. Xiao, B. Ming, et al., Interleukin-33 is released in spinal cord and suppresses experimental autoimmune encephalomyelitis in mice, Neuroscience 308 (2015) 157–168.

[157] C. Natarajan, S.Y. Yao, S. Sriram, TLR3 agonist Poly-IC induces IL-33 and promotes myelin repair, PLoS One 11 (2016) e0152163.

[158] S. Zandee, R.A. O'Connor, I. Mair, M.D. Leech, A. Williams, Anderton SM. IL-10-producing, ST2-expressing Foxp3+ t cells in multiple sclerosis brain lesions, Immunol. Cell Biol. 95 (2017) 484–490.

[159] L.X. Du, Y.Q. Wang, G.Q. Hua, W.L. Mi, IL-33/ST2 pathway as a rational therapeutic target for CNS diseases, Neuroscience 369 (2017) 222–230.

[160] M. Li, Y. Li, X. Liu, X. Gao, Y. Wang, IL-33 blockade suppresses the development of experimental autoimmune encephalomyelitis in C57BL/6 mice, J. Neuroimmunol. 247 (2012) 25–31.

[161] M. Milovanovic, V. Volarevic, B. Ljujic, G. Radosavljevic, I. Jovanovic, N. Arsenijevic, et al., Deletion of IL-33R (ST2) abrogates resistance to EAE in BALB/C mice by enhancing polarization of APC to inflammatory phenotype, PLoS One 7 (2012) e45225.

[162] H.R. Jiang, M. Milovanović, D. Allan, W. Niedbala, A.G. Besnard, S.Y. Fukada, et al., IL-33 attenuates EAE by suppressing IL-17 and IFN-γ production and inducing alternatively activated macrophages, Eur. J. Immunol. 42 (2012) 1804–1814.

[163] Z. Yang, Y. Liang, W. Xi, C. Li, R. Zhong, Association of increased serum IL-33 levels with clinical and laboratory characteristics of systemic lupus erythematosus in Chinese population, Clin. Exp. Med. 11 (2011) 75–80.

[164] M.Y. Mok, F.P. Huang, W.K. Ip, Y. Lo, F.Y. Wong, E.Y. Chan, et al., Serum levels of IL-33 and soluble ST2 and their association with disease activity in systemic lupus erythematosus, Rheumatology (Oxford) 49 (2010) 520–527.

[165] G. Hajishengallis, Periodontitis: from microbial immune subversion to systemic inflammation, Nat. Rev. Immunol. 15 (2015) 30–44.

[166] J.D. Corrêa, D.C. Calderaro, G.A. Ferreira, S.M. Mendonça, G.R. Fernandes, E. Xiao, et al., Subgingival microbiota dysbiosis in systemic lupus erythematosus: association with periodontal status, Microbiome 5 (2017) 34.

[167] W. Xu, Y. Liu, D. Ye, Association between IL-33 gene polymorphisms (rs1929992, rs7044343) and systemic lupus erythematosus in a chinese han population, Immunol. Invest. 45 (2016) 575–583.

[168] J. Guo, Y. Xiang, Y.F. Peng, H.T. Huang, Y. Lan, Y.S. Wei, The association of novel IL-33 polymorphisms with sIL-33 and risk of systemic lupus erythematosus, Mol. Immunol. 77 (2016) 1–7.

[169] P. Li, W. Lin, X. Zheng, IL-33 neutralization suppresses lupus disease in lupus-prone mice, Inflammation 37 (2014) 824–832.

[170] G. Anand, R. Vasanthakumar, V. Mohan, S. Babu, V. Aravindhan, Increased IL-12 and decreased IL-33 serum levels are associated with increased Th1 and suppressed Th2 cytokine profile in patients with diabetic nephropathy (CURES-134), Int. J. Clin. Exp. Pathol. 7 (2014) 8008–8015.

[171] S. Shruthi, V. Mohan, A. Amutha, V. Aravindhan, Increased serum levels of novel T cell cytokines IL-33, IL-9 and IL-17 in subjects with type-1 diabetes, Cytokine 86 (2016) 6–9.

[172] M. Ryba-Stanisławowska, P. Werner, M. Skrzypkowska, A. Brandt, J. Myśliwska, IL-33 effect on quantitative changes of CD4+CD25highFOXP3+ regulatory t cells in children with type 1 diabetes, Mediators Inflamm. 2016 (2016) 9429760.

[173] A.M. Miller, D. Purves, A. McConnachie, D.L. Asquith, G.D. Batty, H. Burns, et al., Soluble ST2 associates with diabetes but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes, PLoS One 7 (2012) e47830.

[174] D. Onk, O.A. Onk, K. Turkmen, H.S. Erol, T.A. Ayazoglu, O.N. Keles, et al., Melatonin attenuates contrast-induced nephropathy in diabetic rats: the role of Interleukin-33 and oxidative stress, Mediators Inflamm. 2016 (2016) 9050828.

[175] J. Dolpady, C. Sorini, C. Di Pietro, I. Cosorich, R. Ferrarese, D. Saita, et al., Oral probiotic VSL#3 prevents autoimmune diabetes by modulating microbiota and promoting indoleamine 2,3-Dioxygenase-Enriched tolerogenic intestinal environment, J. Diabetes Res. 2016 (2016) 7569431.

[176] N. Zdravkovic, A. Shahin, N. Arsenijevic, M.L. Lukic, E.P. Mensah-Brown, Regulatory T cells and ST2 signaling control diabetes induction with multiple low doses of streptozotocin, Mol. Immunol. 47 (2009) 28–36.

[177] T. Rui, J. Zhang, X. Xu, Y. Yao, R. Kao, C.M. Martin, Reduction in IL-33 expression exaggerates ischaemia/reperfusion-induced myocardial injury in mice with diabetes mellitus, Cardiovasc. Res. 94 (2012) 370–378.

[178] L. Kong, M. Andrassy, J.S. Chang, C. Huang, T. Asai, M.J. Szabolcs, et al., PKCbeta modulates ischemia-reperfusion injury in the heart, Am. J. Physiol. Heart Circ. Physiol. 294 (2008) H1862–70.

[179] K. Seki, S. Sanada, A.Y. Kudinova, M.L. Steinhauser, V. Handa, J. Gannon, et al., Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling, Circ. Heart Fail. 2 (2009) 684–691.

[180] M. Ryba-Stanisławowska, L. Buksa, A. Brandt, U. Juhas, M. Myśliwiec, IL-33 improves the suppressive potential of regulatory T cells in patients with type 1 diabetes, Diabetes Res. Clin. Pract. 128 (2017) 67–73.

[181] R. He, H. Yin, B. Yuan, T. Liu, L. Luo, P. Huang, et al., IL-33 improves wound healing through enhanced M2 macrophage polarization in diabetic mice, Mol. Immunol. 90 (2017) 42–49.

[182] M. Manetti, L. Ibba-Manneschi, V. Liakouli, S. Guiducci, A.F. Milia, G. Benelli, et al., The IL1-like cytokine IL33 and its receptor ST2 are abnormally expressed in the affected skin and visceral organs of patients with systemic sclerosis, Ann. Rheum. Dis. 69 (2010) 598–605.

[183] S. Vettori, G. Cuomo, M. Iudici, V. D'Abrosca, V. Giacco, G. Barra, et al., Early systemic sclerosis: serum profiling of factors involved in endothelial, T-cell, and fibroblast interplay is marked by elevated interleukin-33 levels, J. Clin. Immunol. 34 (2014) 663–668.

[184] K. Yanaba, A. Yoshizaki, Y. Asano, T. Kadono, S. Sato, Serum IL-33 levels are raised in patients with systemic sclerosis: association with extent of skin sclerosis and severity of pulmonary fibrosis, Clin. Rheumatol. 30 (2011) 825–830.

[185] A. Wagner, M. Köhm, A. Nordin, E. Svenungsson, J.M. Pfeilschifter, H.H. Radeke, Increased serum levels of the IL-33 neutralizing sST2 in limited cutaneous systemic sclerosis, Scand. J. Immunol. 82 (2015) 269–274.

[186] M. Manetti, S. Guiducci, C. Ceccarelli, E. Romano, S. Bellando-Randone, M.L. Conforti, et al., Increased circulating levels of interleukin 33 in systemic sclerosis correlate with early disease stage and microvascular involvement, Ann. Rheum. Dis. 70 (2011) 1876–1878.

[187] S. Terras, E. Opitz, R.K. Moritz, S. Höxtermann, T. Gambichler, A. Kreuter, Increased serum IL-33 levels may indicate vascular involvement in systemic sclerosis, Ann. Rheum. Dis. 72 (2013) 144–145.

[188] S.S. Koca, Y. Pehlivan, M. Kara, F. Alibaz-Oner, S. Oztuzcu, N. Yilmaz, et al., The IL-33 gene is related to increased susceptibility to systemic sclerosis, Rheumatol. Int. 36 (2016) 579–584.

[189] X.L. Huang, G.C. Wu, Y.J. Wang, X.K. Yang, G.J. Yang, J.H. Tao, et al., Association of interleukin-1 family cytokines single nucleotide polymorphisms with susceptibility to systemic sclerosis: an independent case-control study and a meta-analysis, Immunol. Res. 64 (2016) 1041–1052.

[190] Y.S. Choi, H.J. Choi, J.K. Min, B.J. Pyun, Y.S. Maeng, H. Park, et al., Interleukin-33 induces angiogenesis and vascular permeability through ST2/TRAF6-mediated endothelial nitric oxide production, Blood 114 (2009) 3117–3126.

[191] A.L. Rankin, J.B. Mumm, E. Murphy, S. Turner, N. Yu, T.K. McClanahan, et al., IL-33 induces IL-13-dependent cutaneous fibrosis, J. Immunol. 184 (2010) 1526–1535.

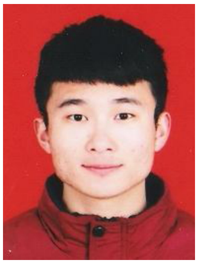
[192] K.G. MacDonald, N.A. Dawson, Q. Huang, J.V. Dunne, M.K. Levings, R. Broady, Regulatory T cells produce profibrotic cytokines in the skin of patients with systemic sclerosis, J. Allergy Clin. Immunol. 135 (2015) 946-946.e9.

[193] A. Balato, S. Lembo, M. Mattii, M. Schiattarella, R. Marino, A. De Paulis, et al., IL-33 is secreted by psoriatic keratinocytes and induces pro-inflammatory cytokines via keratinocyte and mast cell activation, Exp. Dermatol. 21 (2012) 892–894.

[194] A. Mitsui, Y. Tada, T. Takahashi, S. Shibata, M. Kamata, T. Miyagaki, et al., Serum IL-33 levels are increased in patients with psoriasis, Clin. Exp. Dermatol. 41 (2016) 183–189.

[195] J. Meephansan, M. Komine, H. Tsuda, M. Karakawa, S. Tominaga, M. Ohtsuki,

Expression of IL-33 in the epidermis: the mechanism of induction by IL-17, J. Dermatol. Sci. 71 (2013) 107–114.
[196] T.C. Theoharides, B. Zhang, D. Kempuraj, M. Tagen, M. Vasiadi, A. Angelidou, et al., IL-33 augments substance P-induced VEGF secretion from human mast cells and is increased in psoriatic skin, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 4448–4453.
[197] M.M. Suttle, M. Enoksson, A. Zoltowska, M. Chatterjee, G. Nilsson, I.T. Harvima, Experimentally induced psoriatic lesions associate with rapid but transient decrease in interleukin-33 immunostaining in epidermis, Acta Derm. Venereol. 95 (2015) 536–541.
[198] C. Patruno, M. Napolitano, N. Balato, F. Ayala, M. Megna, A. Patrì, et al., Psoriasis and skin pain: instrumental and biological evaluations, Acta Derm. Venereol. 95 (2015) 432–438.
[199] D.P. Vageli, A. Exarchou, E. Zafiriou, P.G. Doukas, S. Doukas, A. Roussaki-Schulze, Effect of TNF-α inhibitors on transcriptional levels of pro-inflammatory interleukin-33 and Toll-like receptors-2 and -9 in psoriatic plaques, Exp. Ther. Med. 10 (2015) 1573–1577.
[200] J. Meephansan, U. Subpayasarn, S. Ponnikorn, P. Chakkavittumrong, P. Juntongjin, M. Komine, et al., Methotrexate, but not narrowband ultraviolet B radiation, suppresses interleukin-33 mRNA levels in psoriatic plaques and protein levels in serum of patients with psoriasis, J. Dermatol. (2017).
[201] M.M. Suttle, G. Nilsson, E. Snellman, I.T. Harvima, Experimentally induced psoriatic lesion associates with interleukin (IL)-6 in mast cells and appearance of dermal cells expressing IL-33 and IL-6 receptor, Clin. Exp. Immunol. 169 (2012) 311–319.
[202] A.J. Hueber, J.C. Alves-Filho, D.L. Asquith, C. Michels, N.L. Millar, J.H. Reilly, et al., IL-33 induces skin inflammation with mast cell and neutrophil activation, Eur. J. Immunol. 41 (2011) 2229–2237.
[203] B. Zhao, W. Chen, R. Jiang, R. Zhang, Y. Wang, L. Wang, et al., Expression profile of IL-1 family cytokines in aqueous humor and sera of patients with HLA-B27 associated anterior uveitis and idiopathic anterior uveitis, Exp. Eye Res. 138 (2015) 80–86.
[204] D.J. Kim, S.Y. Baek, M.K. Park, K.S. Park, J.H. Lee, S.H. Park, et al., Serum level of interleukin-33 and soluble ST2 and their association with disease activity in patients with Behcet's disease, J. Korean Med. Sci. 28 (2013) 1145–1153.
[205] K. Hamzaoui, W. Kaabachi, B. Fazaa, L. Zakraoui, I. Mili-Boussen, F. Haj-Sassi, Serum IL-33 levels and skin mRNA expression in Behçet's disease, Clin. Exp. Rheumatol. 31 (2013) 6–14.
[206] K. Hamzaoui, A. Borhani-Haghighi, W. Kaabachi, A. Hamzaoui, Increased interleukin 33 in patients with neuro-Behcet's disease: correlation with MCP-1 and IP-10 chemokines, Cell. Mol. Immunol. 11 (2014) 613–616.
[207] S.S. Koca, M. Kara, F. Deniz, M. Ozgen, C.F. Demir, N. Ilhan, et al., Serum IL-33 level and IL-33 gene polymorphisms in Behçet's disease, Rheumatol. Int. 35 (2015) 471–477.
[208] M. Barbour, D. Allan, H. Xu, C. Pei, M. Chen, W. Niedbala, et al., IL-33 attenuates the development of experimental autoimmune uveitis, Eur. J. Immunol. 44 (2014) 3320–3329.
[209] H.T. Celik, S. Abusoglu, S.F. Burnik, S. Sezer, M.A. Serdar, M. Ercan, et al., Increased serum interleukin-33 levels in patients with Graves' disease, Endocr. Regul. 47 (2013) 57–64.
[210] A. Awada, C. Nicaise, S. Ena, L. Schandéné, J. Rasschaert, I. Popescu, et al., Potential involvement of the IL-33-ST2 axis in the pathogenesis of primary Sjogren's syndrome, Ann. Rheum. Dis. 73 (2014) 1259–1263.
[211] P.P. Li, X.M. Zhang, D. Yuan, X. Liu, Y. Li, N.N. Shan, Decreased expression of IL-33 in immune thrombocytopenia, Int. Immunopharmacol. 28 (2015) 420–424.
[212] X. Bu, T. Zhang, C. Wang, T. Ren, Z. Wen, IL-33 reflects dynamics of disease activity in patients with autoimmune hemolytic anemia by regulating autoantibody production, J. Transl. Med. 13 (2015) 381.
[213] Y. Sun, J.Y. Zhang, S. Lv, H. Wang, M. Gong, N. Du, et al., Interleukin-33 promotes disease progression in patients with primary biliary cirrhosis, Tohoku J. Exp. Med. 234 (2014) 255–261.
[214] M. Liang, Z. Liwen, Z. Yun, D. Yanbo, C. Jianping, Serum levels of IL-33 and correlation with IL-4, IL-17A, and hypergammaglobulinemia in patients with autoimmune hepatitis, Mediators Inflamm. 2018 (2018) 7964654.
[215] K. Neumann, K. Karimi, J. Meiners, R. Voetlause, S. Steinmann, W. Dammermann, et al., A proinflammatory role of type 2 innate lymphoid cells in murine immune-mediated hepatitis, J. Immunol. 198 (2017) 128–137.



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