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The Role of the IL-33/ST2 Immune Pathway in Autoimmunity: New Insights and Perspectives

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ABSTRACT

Interleukin (IL)-33, a member of IL-1 cytokine family, is produced by various immune cells and acts as an alarm to alert the immune system after epithelial or endothelial cell damage during cell necrosis, infection, stress, and trauma. The biological functions of IL-33 largely depend on its ligation to the corresponding receptor, suppression of tumorigenicity 2 (ST2). The pathogenic roles of this cytokine have been implicated in several disorders, including allergic disease, cardiovascular disease, autoimmune disease, infectious disease, and cancers. However, alerted levels of IL-33 may result in either disease amelioration or progression. Genetic variations of *IL33* gene may confer protective or susceptibility risk in the onset of autoimmune diseases. The purpose of this review is to discuss the involvement of IL-33 and ST2 in the pathogenesis of a variety of autoimmune disorders, such as autoimmune rheumatic, neurodegenerative, and endocrine diseases.

KEYWORDS

IL-33; autoimmune disorders; ST2; pathogenic; protective

Introduction

Interleukin (IL)-33 (also called IL-1F11) is one of the members of IL-1 cytokine family that play a wide range of roles in the immune system. In response to various pathologic stimuli, different cells, such as endothelial cells, epithelial cells, myofibroblasts, adipocytes, macrophages, stromal fibroblasts, and dendritic cells (DCs) produce IL-33, primarily as a proinflammatory cytokine (Sims et al. 2001; Zhou et al. 2020). IL-33 acts as an alarm to alert the immune system after epithelial or endothelial cell damage during cellular necrosis,

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viral infection, stress, trauma (Cayrol and Girard 2009; Haraldsen et al. 2009). Other than a role as an extracellular cytokine through binding to suppression of tumorigenicity 2 (ST2), IL-33 has also an intracellular function and acts as a chromatin-binding transcriptional regulator. The IL-33/ST2 signaling has major role in maintenance of entire epithelial barrier and inflammation (Michaudel et al. 2018). IL-33 is highly expressed in the nucleus of endothelial cells present in the high endothelial venule (HEV), hence IL-33 is also called nuclear factor of HEV (HEV-NF) (Baekkevold et al. 2003). HEV has been implicated in the mobilization and activation of lymphocytic traffic, suggesting that IL-33 might activate chronic inflammatory responses (Miyasaka and Tanaka 2004). Proteases and caspases cleave IL-33, leading to generation of mature and inactivated form of this cytokine (Ali et al. 2010; Cayrol and Girard 2009; Lefrançais et al. 2012; Lüthi et al. 2009).

The IL-33/ST2 pathway primarily intensifies the T helper (Th) 17-mediated inflammatory responses (Cho et al. 2012). This pathway has been reported to be involved in various diseases (Table 1), such as neurodegenerative disorders, including Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Multiple sclerosis (MS), Autism spectrum disorder (ASD) (De la Fuente et al. 2015; Gao et al. 2015), autoimmune rheumatic diseases, including Ankylosing spondylitis (AS), Systemic lupus erythematosus (SLE), Systemic sclerosis (SSc), Rheumatoid arthritis (RA), psoriasis, as well as other autoimmune disorders, like Myasthenia gravis (MG), autoimmune thyroid diseases, Inflammatory bowel disease (IBD), and uveitis (Jeppesen and Benros 2019; Parks et al. 2014). In this review, we attempted to clarify the current understandings regarding the roles of IL-33/ST2 pathway in multiple autoimmune diseases. In addition, disease-associated *IL-33/ST2* genetic polymorphisms in association with altered risk of susceptibility to autoimmune diseases were discussed.

IL-33/ST2 expression pattern, signaling, and function

The discovery of IL-33 in 2005 as a ST2 ligand provided novel perspectives into ST2 signaling. The *ST2* gene is located in the human IL-1 gene cluster and is harbored in human chromosome 2q12. ST2, which is also known as Interleukin 1 receptor-like 1 (IL-1 RL1), T1, FIT-1, or IL-33 receptor, is a member of the Toll-like/IL-1-receptor superfamily with a common intracellular domain named Toll/Interleukin-1 receptor (TIR) domain (Xu et al. 1998). ST2 has two more known isoforms; ST2 ligand (ST2L, also known as IL1RL1-b) and soluble ST2 (sST2, also known as IL1RL1-a) (Yanagisawa et al. 1993). ST2L is the membrane form and is involved in signaling transduction and sST2 acts as a decoy. ST2 is highly expressed on helper T (Th) 2 cells, $CD8^+$ T cells, basophils, eosinophils, macrophages, DCs, group 2 innate lymphoid cells (ILC2), and natural killer T (NKT) cells (Hosseini et al. 2020; Mohammadi et al. 2018c). IL-33/ST2 signaling induces inflammation by modulating the expression of Th2 cytokines, particularly IL-5 and IL-13 (Smith 2010).

There are 2 types of IL-33, intracellular form and extracellular one. The intracellular IL-33 functions as chromatin-binding transcriptional regulator (Kakkar et al. 2012). Moreover, IL-33 can be released from different cells after mechanical injury or cell damage (Lingel et al. 2009; Moussion et al. 2008), then bind to ST2L, that subsequently leads to recruitment of IL-1 receptor accessory protein (IL-1RAcP) and development of a trimeric complex (Liu et al. 2013).

Table 1. The protective and pathogenic roles of IL-33/ST2 axis in various autoimmune and neurodegenerative diseases.

Disease	Sample	Method	IL-33, ST2 and sST2 Level or expression alterations	Proposed Role of IL-33/ST2	Reference
AD	Brain	Direct mRNA quantification	IL-33 ↓	Protective	(Chapuis et al. 2009)
	Entorhinal cortex sections	Immunohistochemistry	IL-33 and ST2 ↑	Pathogenic	(Xiong et al. 2014)
ALS	Serum	ELISA	IL-33 ↓, sST2 ↑	Protective	(Lin et al. 2012)
AS	Serum	ELISA	IL-33 ↑	Pathogenic	(Li et al. 2013)
	Serum, and PBMC	RT-PCR	IL-33 and ST2 mRNA expression ↑		
ASD	PBMC	RT-PCR	IL-33 mRNA levels ↓	Protective	(Saresella et al. 2016)
	Serum	ELISA	Same IL-33 levels in ASD and HC	No specific role	(Tsilioni et al. 2015)
AIH1	Serum	Luminex bead array	IL-33 ↑	Pathogenic	(Abe et al. 2019)
	Serum	ELISA	sST2 ↑		
	Liver section	Immunohistochemistry	Strong expression of IL-33		
AIP	Pancreas section	Immunofluorescence	IL-33 ↑	Pathogenic	(Watanabe et al. 2017b)
AITD	Plasma	ELISA	IL-33 and sST2 ↑ in Hashimoto's Thyroiditis	Pathogenic	(Wang et al. 2019a)
	Thyroid tissues	RT-PCR	mRNA expressions of IL-33 and ST2 ↑ in Hashimoto's Thyroiditis		
	Serum	ELISA	IL-33 ↑ in Graves' disease	Pathogenic	(Celik et al. 2013)
BD	Serum	ELISA	IL-33 ↓ in active BD	Protective	(Koca et al. 2015)
	Serum	ELISA	IL-33 ↑ in active BD	Pathogenic	(Hamzaoui et al. 2015)
	Serum	ELISA	Il-33 and sST2 ↑	Pathogenic	(Kim et al. 2013)
COPD	Serum	ELISA	IL-33 and ST2 ↑	Pathogenic	(Xia et al. 2015)
IBD	Colonic mucosa	Western blot, and RT-PCR	IL-33 and sST2 ↑ in active UC and CD	Pathogenic	(Pastorelli et al. 2010)
	Serum	Western blot, and ELISA	IL-33 and ST2 ↑		
	Intestinal epithelial cells	Western blot, and RT-PCR	IL-33 expression ↑ and ST2L expression ↓ in UC		
MS	Plasma	ELISA	IL-33 ↑	Pathogenic	(Christophi et al. 2012)
	Brain section	ELISA, and RT-PCR	Protein and mRNA level of IL-33 ↑		
	CSF and serum	ELISA	IL-33 ↑	Pathogenic	(Jafarzadeh et al. 2016)
MG	Serum	ELISA	IL-33and ST2 ↑	Pathogenic	(Wang, Wang et al. 2019b)
	PBMCs	RT-qPCR	IL-33 and ST2 mRNA expression ↑		
NOSD	Serum	ELISA	IL-33 ↑	Pathogenic	(Zhang et al. 2018a)
PSS	Serum	ELISA	IL-33 and sST2 ↑	Pathogenic	(Awada et al. 2014)
	Salivary glands	Immunohistochemistry	ST2L ↓		
	Serum	ELISA	Same levels of IL-33 in PSS and HCs.	No specific role	(Pasoto et al. 2019)

(*Continued*)

Table 1. (Continued).

Disease	Sample	Method	IL-33, ST2 and sST2 Level or expression alterations	Proposed Role of IL-33/ST2	Reference
Psoriasis (vulgaris)	Skin biopsies	Immunohistochemistry, and immunofluorescence	IL-33 and ST2 expression in psoriatic lesions ↑	Pathogenic	(Duan et al. 2019)
	Serum	ELISA	IL-33 ↑		
Psoriasis	Serum	ELISA	Same level of IL-33 in psoriasis and HC	No specific role	(Tamagawa-Mineoka et al. 2014)
RA	Serum	ELISA	IL-33 and sST2 ↑	Pathogenic	(Wang et al. 2018)
	Serum and synovial fluid	ELISA	IL-33 ↑	Pathogenic	(Tang et al. 2013)
SLE	Serum	Multi-array ELISA	IL-33 ↓ and sST2 ↑	Pathogenic	(Italiani et al. 2018a)
	Serum	ELISA	IL-33 ↑	Pathogenic	(Guo et al. 2019)
	Serum	ELISA	Same levels of IL-33 in SLE patients and HCs, sST2 ↑	No specific role	(Mok et al. 2010)
SSc	Serum	ELISA	IL-33 ↑	Pathogenic	(Zhang et al. 2018b)
	Skin biopsy	Immunohistochemistry, Immunofluorescence, Western blot, and RT-PCR.	Early SSc: IL-33 expression is normal or increased, IL-33 protein ↓ and ST2 expression ↑ Late SSc: IL-33 ↑ and ST2 expression ↓	Pathogenic	(Manetti et al. 2010)
Vitiligo	Serum	ELISA	IL-33 protein levels ↑	Pathogenic	(Vaccaro et al. 2016)

IL-33; Interleukin-33, ***ST2;*** Suppression of tumorigenicity 2, ***AD***; Alzheimer disease, ***ALS;*** Amyotrophic lateral sclerosis, ***AS;*** Ankylosing spondylitis, ***ASD;*** Autism spectrum disorder, ***HC;*** Healthy control, ***PBMC;*** Peripheral blood mononuclear cells, ***AIH;*** Autoimmune hepatitis, ***AIP;*** Autoimmune pancreatitis, ***AITD;*** Autoimmune thyroid disease, ***BD;*** Bechet's disease, ***COPD;*** Chronic pulmonary obstructive disease, ***IBD;*** Inflammatory bowel disease, ***UC;*** Ulcerative colitis, ***CD;*** Crohn's disease, ***MS;*** Multiple sclerosis, ***CSF;*** Cerebrospinal fluid, ***MG;*** Myasthenia gravis, ***NMOSD;*** Neuromyelitis optica spectrum disorder, ***PSS;*** Primary sjogren syndrome, ***RA;*** Rheumatoid arthritis, ***SLE;*** Systemic lupus erythematosus, ***SSc;*** Systemic sclerosis.

IL-33 is generated as a full length 32 kDa protein, which is the active form of IL-33.Various biological processes may restrict full-length IL-33 activity following its release and can interfere with detection of IL-33 in the serum or plasma samples. ST2 and IL-1RAcP function as decoy receptors to neutralize IL-33 in serum or plasma. Additionally, IL-33 is quickly inactivated in the extracellular biological fluids by oxidation of cysteine residues by inflammatory proteases. IL-33 may be cleaved by caspases-1, caspases-3, and caspases-7 at D178, leading to inactive IL-33 form (Cohen et al. 2015; Liew et al. 2016; Sanada et al. 2007). Detection of the actual levels of IL-33 is difficult by the currently available commercial ELISA kits in human serum samples, as such assays lack sensitivity and specificity. IL-1RL1-a (soluble ST2) also interferes with accurate quantification of IL-33 (Ketelaar et al. 2016). These issues might explain in part the contradictory results observed during different studies.

IL-33/ST2 signaling transduction activates intracellular signaling pathways through MyD88, IL-1R-associated kinase 4 (IRAK4), and Tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6) (Funakoshi-Tago et al. 2008; Schmitz et al. 2005), ultimately resulting in activation of mitogen-activated protein kinases (MAPKs) such as P38, ERK, JNK, and Nuclear factor (NF)-κB (Mohammadi et al. 2018b).

IL-33/ST2 axis and autoimmune diseases

A bulk of studies have testified the clinical value of IL-33/ST2 axis in the development or exacerbation of autoimmune disorders. Although IL-33/ST2 axis has been implicated with a double-edge sword function in autoimmunity, a wide range of evidence attribute the modulated IL-33/ST2 signaling to an exacerbated manifestation of such disorders. Reports suggest that IL-33/ST2 signaling may modulate the balance between inflammatory Th1/Th17 cells and regulatory T (Treg) cells, therefore promote the development of autoimmunity. In addition, type 2 immune responses are also under the regulatory mechanisms of IL-33/ST2 signaling, suggesting an anti-inflammatory implication during autoimmune disorders. In the rest of this article, involvement of dysregulated IL-33/ST2 axis, with respect to cellular as well as molecular levels, in the context of a variety of autoimmune diseases is discussed.

Ankylosing spondylitis

Ankylosing spondylitis (AS) is an autoimmune disease that is characterized by back pain and spinal complications (Mohammadi et al. 2018b).This disease involves joints, particularly spinal and sacroiliac ones (Babaie et al. 2020). Serum levels of IL-33 is increased in AS patients and is correlated with the disease severity (Mohammadi et al. 2018a). IL-33 can participate in AS pathogenesis by contributing to the higher production of IL-17, TNF-α, and IL-6 and also migration of neutrophils (Babaie et al. 2018; Hemmatzadeh et al. 2019). In addition, Li *et al.* indicated that IL-33 induced the production of Th2 cytokines, including IL-13, and IL-4, that was associated with active form of AS (Li et al. 2013). AS pathogenesis has been attributed to increased number of osteoclasts and a promoted activity of the osteoblasts, resulting in excessive bone apposition (Baum and Gravallese 2016). It was observed that IL-33 promoted multi-nuclear osteoclast formation from monocytes and stimulated increased expression of osteoclasts differentiating factors (Mun et al. 2010). Paradoxically, other studies reported that IL-33 had no direct role in multinucleated osteoclasts formation (Saidi et al. 2011; Saleh et al. 2011; Schulze et al. 2011).As a result,

IL-33/ST2 signaling might be involved in the AS pathogenesis through the dysregulation of osteoclasts and osteoblasts.

A number of polymorphisms of *IL33* gene, such as rs1891385, rs10118795, rs2210463, rs1929992, rs10975519, and rs1048274 has been associated with AS pathogenesis. Fan *et al.* reported that theses SNPs and the TTCG (rs10118795, rs1929992, rs10975519, and rs1048274) haplotype of the *IL-33* gene were associated with an increased risk of AS susceptibility in a Chinese Han population (Fan et al. 2014). A summary of disease-associated *IL33/ST2* polymorphisms is listed in Table 2.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoinflammatory disease that is characterized by joint inflammation and destruction (Wasserman 2011). Presence of inflammatory cells in the joints lined by a synovial membrane results in swelling and pain (Azizi et al. 2017). High levels of IL-33 have been reported in the serum as well as synovial fluid of RA patients (Tang et al. 2013). Furthermore, Wang and co-workers reported elevated levels of sST2 in serum of these patients (Wang et al. 2018). It has been reported that several cytokines (such as TNF-α and IL-6) can affect IL-33 levels in RA (Choi et al. 2018). For instance, TNF-α-stimulated synovial fibroblasts produce IL-33 (Kunisch et al. 2012). Wu *et al.* recently reported that IL-33 suppressed apoptosis via increased Bcl-2 protein expression and boosted proliferation of fibroblast-like synoviocytes through elevated expression levels of inflammatory cytokines and activation of NF-κβ pathway (Wu et al. 2020). IL-33 is involved in the pathogenesis of RA through recruiting neutrophils to inflamed joints that directly express ST2L on their surface (Verri et al. 2010). Furthermore, IL-33 can unbalance IL-10 and IL-17, thus contributes to pathogenesis of RA (Wang et al. 2018). Notably, IL-33 was correlated with rheumatoid factor (RF) titer as well as levels of anti-cyclic citrullinated protein (anti-CCP) antibodies in RA patients (Mu et al. 2010). *In vitro* experiments demonstrated that IL-33 upregulated TNF-α induced production of matrix metalloproteinase (MMP)-3, IL-8, and IL-6 from RA synovial fibroblasts (RASFs) (Kunisch et al. 2012). On the other hand, evidence shows the anti-inflammatory roles of IL-33 in RA through shifting immune responses toward Th2 responses (Chan et al. 2019; Miller 2011). Although the pro-inflammatory activities of IL-33 are more highlighted, it might also confer immunomodulatory properties, depending on the disease phase and severity, as well as probable contribution of genetics.

Mejías *et al.* reported a role of the *IL33* gene rs3939286 SNP in increased risk of subclinical atherosclerosis in RA patients (López-Mejías et al. 2015). In addition, Li *et al.* reported that rs7044343 polymorphism of the *IL33* gene was associated with RA risk through downregulating the IL-33 expression (Li et al. 2014). Little data are available with respect to involvement of genetic polymorphisms of the IL33 gene in the RA etiopathogenesis.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic, systemic, autoimmune disorder that is characterized by widespread production of antinuclear antibodies, leading to formation of

Table 2. A summary of disease-associated *IL33* and *ST2* genetic polymorphisms in different populations.

Gene	SNP	Population	Amino acid change	Protective/Risk	Reference
Ankylosing spondylitis					
IL33	rs1891385	Han Chinese	Intronic	Risk	(Fan et al. 2014)
	rs2210463	Han Chinese	Intronic	Risk	
	rs10118795	Han Chinese	Intronic	Risk	
	rs1929992	Han Chinese	Intronic	Risk	
	rs10975519	Han Chinese	Intronic	Risk	
	rs1048274	Han Chinese	3' UTR Variant	Risk	
	rs16924144	Han Chinese	Intronic	None	
	rs16924159	Han Chinese	Intronic	None	
Rheumatoid arthritis					
IL33	rs3939286	Spanish	Intronic	Protective	(López-Mejías et al. 2015, Li et al. 2014)
	rs7044343	Han Chinese	Intronic	Protective	
		Spanish		None	
	rs10975514	Spanish	Intronic	None	
	rs7025417	Han Chinese	Intronic	None	
Systemic lupus erythematosus					
IL33	rs1929992	Han Chinese	Intronic	Risk	(Zhu et al. 2019, Guo et al. 2016, Xu et al. 2016)
	rs1891385	Han Chinese	Intronic	Risk	
	rs7044343	Han Chinese	Intronic	None	
	rs10975498	Han Chinese	Intronic	None	
	rs10975519	Chinese	Intronic	None	
Systemic sclerosis					
IL33	rs7044343	Turkish	Intronic	Risk	(Koca et al. 2016, Huang et al. 2016)
		Chinese		None	
	rs1157505	Turkish	Intronic	None	
	rs11792633	Turkish	Intronic	None	
	rs1929992	Turkish	Intronic	None	
Bechet's disease					
IL33	rs1342326	Azari population of Iran	Intronic	Risk?	(Talei et al. 2019)
	rs7044343	Turkish	Intronic	Protective	(Koca et al. 2015)
	rs11792633	Turkish	Intronic	Protective	
	rs1157505	Turkish	Intronic	None	
	rs1929992	Turkish	Intronic	None	
Alzheimer disease					
IL33	rs11792633	Han Chinese, Caucasian	Intronic	Protective	(Chapuis et al. 2009, Yu et al. 2012, Tian et al. 2015, Zhong et al. 2017)
	rs7044343	Han Chinese, Caucasian	Intronic	Protective	
	rs1157505	Han Chinese, Caucasian	Intronic	Protective	

(*Continued*)

Table 2. (Continued).

Gene	SNP	Population	Amino acid change	Protective/Risk	Reference
Multiple sclerosis					
IL33	rs1342326	Iranian	Intronic	None	(Ahmadi et al. 2019)
	rs10204137	Iranian	Intronic	Risk	
Autoimmune thyroid disease					
IL33	rs1929992	Chinese	Intronic	None	(Wang et al. 2016)
	rs10975519	Chinese	Intronic	None	
ST2	rs6543116	Chinese	Intronic	Risk	
Chronic pulmonary obstructive disease					
IL33	rs1891385	Chinese	Intronic	Risk	(Sun et al. 2019)
Inflammatory bowel disease					
IL33	rs3939286	Italian	Intronic	Risk	(Latiano et al. 2013)
	rs7025417	Italian	Intronic	None	
	rs7044343	Italian	Intronic	None	

immune complexes and deposition in various organs of the body (Kenny et al. 2019). In patients with SLE, enhanced levels of sST2 but decreased serum levels of IL-33 have been reported (Italiani et al. 2018a). In contrast, studies showed elevated serum levels of IL-33 in SLE patients (Guo et al. 2019). Paradoxically, Mok *et al*. observed no different IL-33 serum levels between SLE patients and healthy subjects (Mok et al. 2010). IL-33 might dysregulate ILCs and contribute to SLE progression. IL-33 was attributed to enhanced frequency of ILC1 that caused activation of type 1 immune responses in the SLE patients (Guo et al. 2019). Although there is little evidence about the role of IL-33 in SLE, it seems that clinical presentations exacerbate due to the abnormal levels of this cytokine.

Two polymorphisms (rs1929992-G and rs1891385A/C) of *IL33* gene were seen to affect the risk of SLE susceptibility. *IL33* gene rs1929992 polymorphism might be a potential risk biomarker for SLE predisposition (Guo et al. 2016; Xu et al. 2016; Zhu et al. 2019). In addition, rs1929992 polymorphism was detected to impress the effect of current smoking status in the SLE risk (Zhu et al. 2019). Hence, genetic polymorphisms of *IL33* gene might interact with environmental risk factors to influence on the development of SLE.

Systemic sclerosis

Systemic sclerosis (SSc) is characterized by fibrotic changes, primarily in the skin (Burbelo et al. 2019). SSc has two subtypes, including limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (Chan et al. 2019). The complex biology of IL-33 in the context of dermatological conditions has been discussed (Balato et al. 2016).

One study reported elevated serum levels of IL-33 in SSc patients (Wagner et al. 2015). Furthermore, patients with early SSc had decreased levels of IL-33 in their skin, while enhanced levels of IL-33 were detected in the skin of patients with late SSc (Zhang et al. 2018b). As a result, IL-33 might behave differently during the early or late phases of SSc. A study indicated that IL-33 was dependent on its receptors (ST2 and IL-1RAcP) to induce skin fibrosis through type 2 immunity (Rankin et al. 2010). In fact, IL-33 can participate in SSc pathogenesis by stimulating IL-13 and transforming growth factor (TGF)-β1 production by M2 macrophages through polarization of these cells (Manetti et al. 2010). Moreover, IL-33 enhances IL-13 levels by inducing ILC2 proliferation (Kurowska-Stolarska et al. 2009). Notably, IL-13 and TGF-β1 are two cytokines that participate in pathological fibrosis (Manetti et al. 2010). Hence, IL-33 contributes to skin fibrosis in SSc through upregulating the cytokines (like IL-13 and TGF-β1) involved in this process.

There is paucity of data regarding the involvement of polymorphisms of *IL33* gene in SSc risk. Koca *et al*. reported that rs7044343 polymorphism of *IL33* gene was associated with the risk of SSc susceptibility in Turkish population (Koca et al. 2016). A meta-analysis indicated that *IL33* gene rs7044343 allele frequency was associated with dyspnea in the SSc patients (Huang et al. 2016).

Bechet's disease

Bechet's disease (BD) is an autoimmune disorder that is characterized by complications in vessels, particularly veins (Seyahi 2016), skin, genital and aphthous lesions, and uveitis (Çerçi et al. 2017). Controversial data have been reported about IL-33 levels in BD. One study indicated that serum levels of IL-33 in active BD patients was almost lower compared to

healthy individuals and inactive patients (Koca et al. 2015). In contrast, Hamzaoui *et al.* reported that inactive BD patients have decreased level of IL-33 compared to active ones (Hamzaoui et al. 2013). Furthermore, another study reported higher serum levels of IL-33 and sST2 in BD patients compared to healthy controls (Kim et al. 2013). Moreover, enhanced expressions of IL-33 and sST2 in skin lesion of BD patients were reported (Kim et al. 2013). Hence, more experiments are required to clear the status of IL-33 levels and roles in BD. However, according to IL-33 roles, it seems that elevated levels of IL-33 may lead to BD exacerbation during inflammation, while result in tissue repair in recovery phase (Hamzaoui et al. 2015). Notably, unlike sST2, elevated levels of IL-33 are not considered as a marker of disease activity (Çerçi et al. 2017; Kim et al. 2013). Increased expression of IL-33 and thymic stromal lymphopoietin (TSLP) in lesions of BD patients led to upregulation of Th2 responses, and ultimately resulted in skin inflammation (Kacem et al. 2018). Furthermore, elevated secretion of IL-18 and IL-1 cytokines, induction of Th1 responses, and regulation of IL-17 and IL-6 levels were also related to IL-33 in BD (Hamzaoui et al. 2013).

With respect to the genetic variations, some polymorphisms of *IL33* gene are related to BD pathogenesis, including rs1342326, rs7044343, and rs11792633 (Koca et al. 2015; Talei et al. 2019). For example, Talei *et al.* (Talei et al. 2019) reported that rs1342326 polymorphism may increase the risk of susceptibility to BD in part via immunoregulation of the IL-33 expression. On the contrary, Koca *et al.* reported that *IL33* gene rs7044343 and rs11792633 polymorphisms were associated with a decreased risk of BD susceptibility (Koca et al. 2015).

Psoriasis

Psoriasis is an autoimmune disease that consists of three types, namely pustular psoriasis (PP), psoriasis vulgaris (PV), and psoriatic arthritis (PsA) (Balato et al. 2016; Mitsui et al. 2016). Expression of IL-33 is elevated in serum and lesions of patients with PV (Duan et al. 2019). In contrast, one study reported similar serum levels of IL-33 in psoriatic patients and healthy individuals (Tamagawa-Mineoka et al. 2014). IL-33 can participate in psoriasis pathogenesis through activation of mast cells, neutrophils, and keratinocytes and also stimulation of the IL-6 and IL-8 secretion by keratinocytes (Balato et al. 2014, 2012; Mitsui et al. 2016). Moreover, some studies have shown that IL-33 may develop psoriasis through maturation and degranulation of mast cells and also secretion of Vascular endothelial growth factor (VEGF), IL-1, IL-6, IL-13, TNF-α, CCL2 and CCL3 from these cells (Allakhverdi et al. 2007; Iikura et al. 2007; Theoharides et al. 2010). In another study, Raimondo *et al.* reported that IL-33 induced the secretion of a wide range of pro-osteoclastogenic triggers (such as receptor activator of nuclear factor kappa-B ligand [RANKL]) from the skin that induced monocyte differentiation in osteoclasts and promotes to bone damage (Raimondo et al. 2017). Subsequently, increased levels of IL-6 and IL-1 result in Th17 cell differentiation and secretion of IL-22 and IL-17 cytokines from these cells (Acosta-Rodriguez et al. 2007; Ortega et al. 2009), resulting in Th17-mediated inflammation in the psoriasis patients (Figure 2).

Vitiligo

Vitiligo causes melanocyte destruction and is manifested by white macules that becomes larger over the years (Hayakawa et al. 2016; Hertz et al. 1977). Compared to healthy

individuals, Patients with vitiligo had higher serum levels of IL-33, which correlated with the disease activity (Hayakawa et al. 2016; Vaccaro et al. 2016). IL-33 contributes to vitiligo progression through activation of neutrophils, mast cells, and keratinocytes (Hayakawa et al. 2016). Moreover, Li *et al.* demonstrated that IL-33 may cause upregulation of IL-6 and TNF-α and also downregulation of stem cell factor (SCF) and basic fibroblast growth factor (bFGF) in keratinocytes, which are important stimulators of proliferation and migration of melanocytes (Li et al. 2015). Although little is known about the role of IL-33 in vitiligo, it appears that this cytokine might modulate the melanocytes in a pathogenic way.

Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease that occurs due to neurofibrillary tangles (NFTs) formation inside neurons and extracellular deposition of β amyloid (βA) plaques (Italiani et al. 2018b; Nishizaki 2018). IL-33 can inhibit formation of NFTs and paired helical filaments (PHFs) through inactivating the glycogen synthase kinase-3b (GSK-3b) (Hernandez et al. 2013; Nishizaki 2018). Xiong *et al.* indicated that expressions of ST2 and IL-33 in entorhinal cortex lesions are elevated in AD patients (Xiong et al. 2014). They also stated that IL-33 resulted in AD progression through stimulating astrocytes and microglia to produce proinflammatory cytokines (Xiong et al. 2014). In contrast, Chapuis *et al.* reported downregulated expression of IL-33 in brain of AD patients (Chapuis et al. 2009). They also demonstrated that upregulation of IL-33 expression *in vitro* can downregulate βA peptide secretion (Fu et al. 2016). Other protective roles of IL-33 in AD patients are reported as well. For instance, administration of IL-33 in the APP/PS1 mouse model decreases the deposition of amyloid plaques and also soluble βA levels through activation of p38 signaling and increased phagocytosis of βA by microglia cells (Fu et al. 2016). Moreover, they reported that IL-33 could downregulate the expression of pro-inflammatory cytokines and also polarize the macrophages and microglia cells to an anti-inflammatory phenotype, resulting in modulation of the innate immunity responses (Fu et al. 2016). Furthermore, one study indicated that administration of IL-33 may increase production of chemokines (like CCL2, CCL3, CCL5, CXCL10), anti-inflammatory cytokine (like IL-10), pro-inflammatory cytokines (like TNF-α, IL-1β), and nitric oxide (NO) through induction of microglia proliferation (Yasuoka et al. 2011). In addition, IL-33 can affect microglia cells to increase their phagocytosis of NO and chemokines (Yasuoka et al. 2011). Interestingly, Italiani *et al.* reported that IL-33 caused significant upregulation of nearly all anti-inflammatory effectors and slight increase of inflammatory cytokines (IL-1α and IL-1β) in AD patients (Italiani et al. 2018b).

The minor alleles of three polymorphisms in the *IL33* gene, including rs1157505, rs11792633, and rs7044343 have been shown to be protective in AD risk (Chapuis et al. 2009). Additionally, Yu *et al.* reported that the minor alleles of rs11792633 SNP was significantly associated with a reduced risk of late onset AD.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects alpha motor neurons (Briones et al. 2018; Lalancette-Hebert et al. 2016). Serum levels of sST2 are increased in ALS patients. However, due to caspases and high levels of sST2, IL-33 serum levels are lower in ALS patients compared to healthy individuals (Lin et al. 2012). It seems that inflammation in

ALS disease is induced by high serum levels of sST2 (Lin et al. 2012). Some studies suggest that in neurological disease, IL-33 can result in brain protection, and generally it is an important factor in functions of brain (Jiang et al. 2012; Korhonen et al. 2015; Milovanovic et al. 2012; Pomeshchik et al. 2015). *In vitro* studies demonstrated that IL-33 indirectly affected neurons and astrocytes through altering the responses of peripheral T cells, which ultimately resulted in ALS improvement by decreasing harmful activation of astrocytes (Korhonen et al. 2019).

Autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodegenerative disorder that involves impaired development of the neurons and is characterized by difficulties with social communication (Leung et al. 2016). Various factors, such as genetics and environment can affect neurons and lead to complications in brain connectivity in children (Babinská et al. 2014). Although a number of studies has shown same levels of IL-33 in ASD patients and healthy individuals (Supekar et al. 2013; Tsilioni et al. 2015), Saresella *et al.* reported lower levels of IL-33 in ASD and demonstrated that IL-33 caused increased levels of Absent in melanoma 2 (AIM2) and Nod-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasomes and also enhanced production of IL-1 and IL-18, which ultimately promoted inflammation (Saresella et al. 2016). When stimulated by IL-33 and TSLP, ILC2s produce IL-4, IL-5, IL-9, and IL-13 (Mjösberg et al. 2012). Interestingly, high serum levels of IL-4 and IL-5 in pregnant women have been associated with the birth of autistic children (Goines et al. 2011). Thus, IL-33 might be involved in giving autistic child birth through stimulating production of these cytokines from ILC2s.

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune neurodegenerative disorder that occurs due to degeneration of myelin sheath of neurons (Afshar et al. 2019; Esmaeil Amini et al. 2020; Ghaderian et al. 2020). IL-33 levels are elevated in cerebrospinal fluid (CSF) (Jafarzadeh et al. 2016), plasma, and white matter of nervous system in MS patients (Christophi et al. 2012). Researchers have reported that DCs and macrophages may contribute to degeneration of myelin in response to enhanced IL-33 levels (Christophi et al. 2012). Moreover, IL-33 results in MS progression through promoting Th17 and Th1 cells responses (Jafarzadeh et al. 2016). Paradoxically, various protective roles of IL-33 have also been reported in MS patients. For instance, it was observed that IL-33 stimulated Forkhead box P3 $(Foxp3)^{+}$ regulatory T (Treg) cells to produce IL-10, which ultimately led to suppressive effects of Treg cells in brain (Zandee et al. 2017). Furthermore, Natarajan *et al.* revealed that administration of IL-33 might induce transcription of genes involved in myelin production and maturation of cells that generate myelin (Natarajan et al. 2016). Additionally, it was reported that IL-33 might ameliorate MS through promoting Th2 responses, repressing Th1 and Th17 cells activity, and triggering the polarization of anti-inflammatory M2 macrophages in lymph nodes and spleen (Jiang et al. 2012). Ahmadi *et al.* reported that MS patients had a higher serum level of IL-33 in compared to the control group and also rs10204137 polymorphism was associated with the increased risk of MS in Iranian population (Ahmadi et al. 2019). Hence, IL-33 might act paradoxically in the MS disease both through promoting adverse responses as well as ameliorative reactions in the immune cells.

Neuromyelitis optica spectrum disorder

Neuromyelitis optica spectrum disorder (NMOSD) involves central nervous system (CNS) and is manifested by optic neuritis and transverse myelitis (Lennon et al. 2004; Wingerchuk et al. 2006). Serum level of IL-33 was reported to be enhanced in NMOSD. Additionally, NMOSD patients with brain lesions had elevated levels of IL-33 compared to those lacking brain lesions (Zhang et al. 2018a). Zhang *et al*. found that IL-33 might participate in the disease pathogenesis through regulation of Th2 responses in NMOSD (Zhang et al. 2018a). More studies are still required to clarify the IL-33 roles in NMOSD patients.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a chronic autoimmune and inflammatory disorder of the liver that is classified into 3 types (AIH-1, AIH-2, and AIH-3) based on the profile of autoantibodies. The AIH-1 is more common that is characterized by increased levels of antinuclear antibody (ANA) and anti-smooth muscle antibody (SMA) in the serum of patients (Liang et al. 2018). AIH is associated with failure of liver and cirrhosis (Manns et al. 2010). Abe *et al.* demonstrated increased serum level of IL-33 and sST2 in AIH-1 patients in comparison to healthy group (Abe et al. 2019). They also stated that patients who were in acute phase had higher levels of IL-33 and sST2 compared to those who were in a chronic phase (Abe et al. 2019). In addition, sST2 levels correlated with disease severity in the AIH-1 patients (Abe et al. 2019). IL-33 can participate in AIH pathogenesis through regulating Th2 and Th17 responses or stimulating ILC2s to produce type 2 cytokines (Neumann et al. 2017). Furthermore, elevated serum levels of IL-33 in acute-onset AIH patients resulted in increased levels of pro-inflammatory cytokines (like IL-17A and IL-4), and also higher levels of liver injury markers (like gamma-glutamyl transferase [γ-GT] and alkaline phosphatase [ALP]) and gamma globulins (such as IgA, IgM, and IgG) in blood (Liang et al. 2018). Even though IL-33 can stimulate the production of Th2 and ILC2 cytokines, its harmful effects have been more highlighted in the AIH subjects.

Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is characterized by fibrosis of pancreas, lymphoplasmacytic lymphoma, and also obstructive jaundice (Shimosegawa et al. 2011). Type 1 AIP is an IgG4-related disease, while type 2 is less severe (Umehara et al. 2012). Serum level of IL-33 is elevated in pancreas of AIP patients (Watanabe et al. 2017b). It is reported that type I interferon (IFN)-induced IL-33 secretion from pancreatic acinar cells causes IL-13 and TGF-β1 secretion, and subsequently leads to fibrosis of pancreas (Watanabe et al. 2017a). Thus, IL-33 signaling pathway blockage can lead to improvement of AIP (Watanabe et al. 2017b).

Autoimmune thyroid disease

Autoimmune thyroid disease (AITD) is a chronic autoimmune disorder that causes either hyperthyroidism or hypothyroidism. Hashimoto's thyroiditis (HT) and Graves' disease (GD) is two types of AITD (Wang et al. 2016). Reports show that serum level of IL-33 is elevated in GD (Celik et al. 2013). In addition, patients with HT demonstrated increased mRNA

expression of IL-33 and sST2/ST2L in plasma and thyroid tissue compared to controls (Wang et al. 2019a). T cells expressing ST2 were observed to be expanded in HT patients compared to healthy individuals (Wang et al. 2019a). Studies show that HT and GD are related to Th1 and Th2 cytokine responses, respectively (Savenije et al. 2011; Wang et al. 2016). IL-33 plays a crucial role in HT pathogenesis through stimulating the production of inflammatory cytokines (Celik et al. 2013). Therefore, the pathogenic role of IL-33 has been more highlighted in the pathogenesis of AITD.

A number of the *IL33* and *ST2* genes polymorphism has been associated with AITD predisposition (Wang et al. 2016). The rs1929992, rs10975519, and rs6543116 polymorphisms were associated with increased risk of susceptibility to HT and GD in Han Chinese population (Wang et al. 2016).

Primary Sjogren syndrome

Primary Sjogren syndrome (pSS) is characterized by headache and mood disorders like depression [127], as well as dryness of eyes and mouth due to lymphocyte infiltration to the lacrimal and salivary glands and related autoimmune injuries [128]. Serum levels of IL-33 and sST2 are elevated in pSS, whereas expression of ST2L is decreased in salivary gland [129]. In contrast, one study reported that serum level of IL-33 was not different between pSS patients and healthy controls [127]. IL-33 plays roles in pSS pathogenesis through acting as a synergist of IL-12 and IL-23 to induce IFN-γ secretion by NK and NKT cells [129]. As a consequence, IL-33 is primarily involved in the exacerbation of inflammatory autoimmune responses in the pSS disease.

Chronic pulmonary obstructive disease

Chronic pulmonary obstructive disease (COPD) is an autoimmune inflammatory disease of lung and airways. COPD is characterized by emphysema with obstruction of airflow and/or chronic bronchitis (Zou et al. 2018). Upregulated serum levels of IL-33 and ST2 were reported in this disease (Xia et al. 2015). IL-33 can result in COPD progression through different pathways, such as IL-1RacP/ST2 and MAPKs, so that it induces expression of IL-8 and IL-6 in peripheral blood mononuclear cells (PBMCs) and bronchial epithelial cells (Shang et al. 2015). Furthermore, Celli *et al.* indicated that IL-33 induced proliferation and differentiation of ILC2s and promoted secretion of IL-4, IL-5, and IL-6 from PBMCs of COPD patients (Celli and MacNee 2004). In addition, IL-33 induced the apoptosis of epithelial cells in the COPD patients due to downregulation of cortactin (Zhao et al. 2012), leading to upregulation of autoantibody levels against airway epithelial cells (Li et al. 2019), increased permeability of vascular endothelium (Choi et al. 2009), progression of eosinophilic inflammation in the airways (Tworek et al. 2018), and decreased respiration capacity (Byers et al. 2013). Interestingly, it was reported that IL-33 signaling could be more continuous in damaged lung (Lee et al. 2019). Increased IL-33 in the COPD patients may increase the inflammation in the airways, leading to exacerbation of the complications (Figure 1).

IL33 gene rs1891385 polymorphism was associated with the onset of COPD and genotype AA was linked to a higher level of IL-33 (Sun et al. 2019). Hence, different genotypes of the rs1891385 SNP might affect the plasma levels of IL-33, which in turn influence on the inflammatory state in the COPD patients.

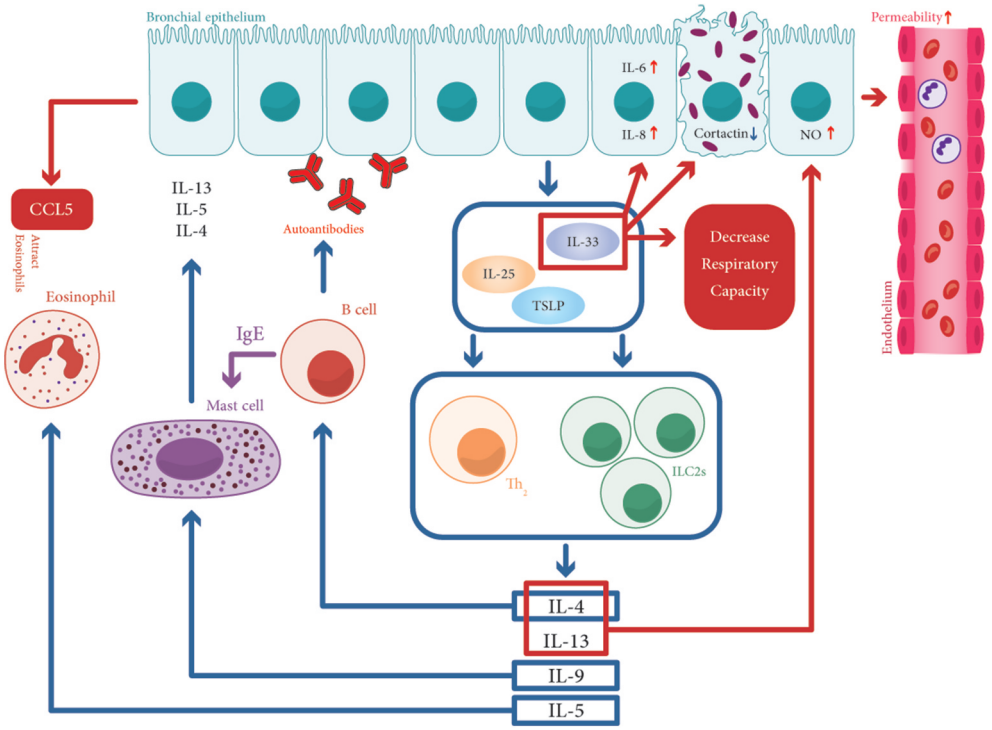

Figure 1. Roles of IL-33 in COPD. IL-33, IL-25 and TSLP are released from airway epithelium upon infection or cell damage and stimulate Th2 cells and ILC2s to produce IL-4, IL-5, IL-9 and IL-13. On the other hand, IL-13 and IL-4 increase the endothelium permeability through inducing the production of NO in bronchial epithelial cells. Additionally, IL-4 stimulates B cells to secret autoantibodies against bronchial epithelium. Moreover, IL-9 stimulates mast cells to produce cytokines, including IL-4, IL-5 and IL-13. IL-5 is involved in the development of eosinophilic inflammation in the airways. Furthermore, IL-33 induces the apoptosis of bronchial cells through decreasing the level of cortactin protein in these cells. It can also induce IL-6 and IL-8 expressions in these cells. CCL5; CC-chemokine ligand 5, COPD; Chronic obstructive pulmonary disease, IgE; Immunoglobulin E; IL; Interleukin, ILC2s; Type 2 innate lymphoid cells, NO; nitric oxide, Th2; T helper-2, TSLP; Thymic stromal lymphopoietin.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) consists of two major subtypes, including Crohn's disease (CD) and ulcerative colitis (UC), which are manifested by diverse signs and symptoms related to gastrointestinal system (Imhann et al. 2018). Colon and intestine can be involved in UC and CD patients, respectively (de Vries et al. 2019). Pastorelli *et al.* reported higher levels of IL-33 and sST2 in serum and mucosa of IBD patients (Pastorelli et al. 2010). The high level of IL-33 led to inhibition of NF-κB signals, which resulted in inflammation suppression. Subsequently, in response to this inhibition, stronger activation of NF-κB signaling pathway led to inflammation (Buckley et al. 2019). Furthermore, IL-33 participates in IBD progression through regulating the function of immune cells, including neutrophils, eosinophils, macrophages, DCs, ILC2s, Th2 cells, and Treg cells (De Salvo et al. 2016; Pastorelli et al. 2010; Seidelin et al. 2015). Interestingly, Groβ *et al.* observed that administration of IL-33 led to inflammatory and protective effects in acute and recovery phases of IBD, respectively (Groβ

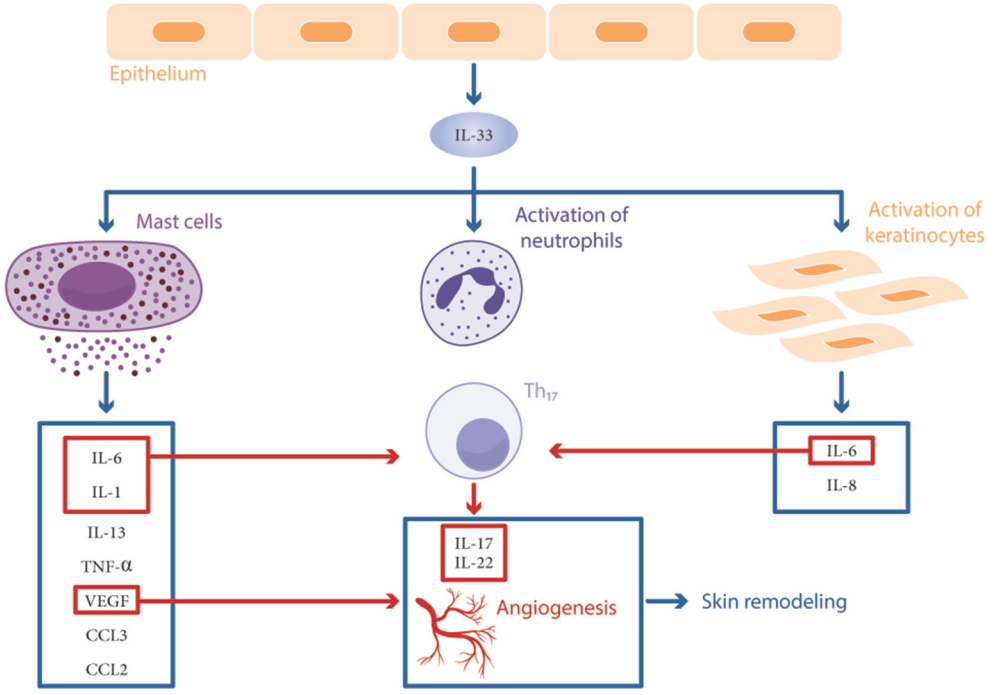

Figure 2. Roles of IL-33 in psoriasis. IL-33 released from epithelial cells causes activation of neutrophils, keratinocytes, and mast cells. Activated keratinocytes secret IL-6 and IL-8. Additionally, IL-33 promotes the maturation and degranulation of mast cells and also stimulates these cells to produce IL-1, IL-6, IL-13, TNF-?, VEGF, CCL3, and CCL2. In turn, IL-6 and IL-1 together induce the Th17 cells differentiation and secretion of IL-17 and IL-22 from these cells. Furthermore, VEGF stimulates the angiogenesis. Ultimately, IL-22, IL-17, and angiogenesis result in skin remodeling in the psoriasis disease. CCL; CC-chemokine ligand, IL; interleukin, Th17; T helper-17, TNF-?; Tumor necrosis factor ?, VEGF; vascular endothelial growth factor.

et al. 2012). In fact, IL-33 causes protective effects during the recovery phase because of Th2 cytokine induction (Groβ et al. 2012). IL-33 can also play protective roles in IBD through promoting the Treg cell proliferation, Th2 cell differentiation (Duan et al. 2012; Matta et al. 2014), and M2 macrophages polarization (Duan et al. 2012; Seo et al. 2017; Tu et al. 2017), leading to production of IL-13 and IL-22 by a mast cell-dependent pathway (He et al. 2018). IL-33 also contributed to gut epithelial cells repair by induction of epithelial-derived microRNA-320 (Lopetuso et al. 2018), which was detected to be reversed in the early stages of disease (Lopetuso et al. 2018). Notably, IL-33 can be used as a marker to monitor UC improvement, when it is expressed in crypts of colons (Gundersen et al. 2016). Generally, IL-33 leads to protection and repair of intestine in both the endogenous and exogenous forms (Lopetuso et al. 2018). Nonetheless the role of this cytokine is mostly dependent on the disease phase.

In genetic association studies, Latiano *et al.* indicated that *IL33* gene rs3939286 polymorphism was associated with the increased risk of IBD in Italian population (Latiano et al. 2013).

Myasthenia gravis

Myasthenia gravis (MG) occurs due to destruction of nicotinic acetylcholine receptor (AChR) in muscles by autoantibodies and is characterized by fatigue and weakness of muscles (Okumura et al. 1994; Patrick and Lindstrom 1973). Notably, MG is more common in women than men (Rozmilowska and Adamczyk-Sowa 2018). Serum levels of IL-33 and ST2 were shown to be elevated in the MG patients (Wang, Wang et al. 2019b). It has been reported that Th17 cells play crucial roles in MG progression (Wang et al. 2012). Wang and co-workers reported that generation of Th17 cells might be inhibited by TSLP in the MG patients (Wang, Wang et al. 2019b). Accordingly, IL-33 appears to participate in MG pathogenesis by downregulation of TSLP, which in turn leads to development of Th17 cells and subsequent inflammatory responses (Wang, Wang et al. 2019b).

Conclusion

Dysregulated IL-33 levels have been observed in various types of neurodegenerative and autoimmune disease. In this article, we discussed altered levels of IL-33/ST2 and related implications in autoimmune diseases. In fact, protective roles of this cytokine in some autoimmune diseases (e.g., ALS and ASD) as well as pathogenic roles in some other ones, including AS, AIH, AIP, AITD, COPD, MG, NMOSD, pSS, RA, SLE, SSc, psoriasis, and vitiligo have been indicated. IL-33/ST2 axis might exhibit the potential molecular targets as biomarker for predicting disease severity and activity as well as the probable efficacy of the future clinical therapeutic. Serum sST2 levels in nonsurviving severe cases of coronavirus disease 2019 (COVID-19), as a current crisis world wide, are persistently high during disease progression, which might be contributing factor in identification of inflammatory status and illness severity in COVID-19 patients (Zeng et al. 2020). Additionally, a bulk of contradictory data has been reported about the roles of IL-33 in autoimmune disorders, in which some studies consider pathogenic roles and some others highlight the protective functions. Thus, the IL-33/ST2 pathway acts as a double-edged sword in various types of autoimmune disorders, and the impact of IL-33/ST2 axis depends on the underlying mechanisms of pathogenesis in each disease state. Additionally, a number of genetic polymorphisms my affect on the levels of either IL-33 or ST2 in the patients, and hence ameliorate or exacerbate the disease manifestations. Therefore, further studies are still required to clarify the exact roles of IL-33/ST2 axis in the autoimmune and neurodegenerative diseases.

Disclosure of potential conflicts of interest

Faezeh Ramezani, Farhad Babaie, Saeed Aslani, Maryam Hemmatzadeh, Fatemeh Sadat Mohammadi, Arezoo Gowhari Shabgah, Farhad Jadidi-Niaragh, Fatemeh Ezzatifar, and Hamed Mohammadi declare that they have no conflict of interest.

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Author Contributions

Faezeh Ramezani; Performed literature search, prepared the draft of the paper, and read the manuscript critically.
Farhad Babaie; Performed literature search, prepared the draft of the paper, and read the manuscript critically.
Saeed Aslani; Participated in manuscript drafting and read the manuscript critically.
Maryam Hemmatzadeh; Participated in manuscript drafting and read the manuscript critically.
Fatemeh Sadat Mohammadi; Draw the figures and read the manuscript critically.
Arezoo Gowhari Shabgah; Participated in manuscript drafting and read the manuscript critically.
Farhad Jadidi-Niaragh; Participated in manuscript drafting and read the manuscript critically.
Fatemeh Ezzatifar; Developed the main idea, designed the work, and read the manuscript critically.
Hamed Mohammadi; Developed the main idea, designed the work, and read the manuscript critically.

References

Abe K, Takahashi A, Fujita M, Hayashi M, Okai K, Nozawa Y, Ohira H. 2019. Interleukin-33/ST2-Mediated Inflammation Plays a Critical Role in the Pathogenesis and Severity of Type I Autoimmune Hepatitis. Hepatol Commun. 3(5):670–84.

Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F. 2007. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol. 8(9):942–49.

Afshar B, Khalifehzadeh-Esfahani Z, Seyfizadeh N, Rezaei Danbaran G, Hemmatzadeh M, Mohammadi H. 2019. The role of immune regulatory molecules in multiple sclerosis. J Neuroimmunol. 337:577061.

Ahmadi M, Fathi F, Fouladi S, Alsahebfosul F, Manian M, Eskandari N. 2019. Serum IL-33 Level and IL-33, IL1RL1 Gene Polymorphisms in Asthma and Multiple Sclerosis Patients. Curr Mol Med. 19 (5):357–63.

Ali S, Nguyen DQ, Falk W, Martin MU. 2010. Caspase 3 inactivates biologically active full length interleukin-33 as a classical cytokine but does not prohibit nuclear translocation. Biochem Biophys Res Commun. 391(3):1512–16.

Allakhverdi Z, Smith DE, Comeau MR, Delespesse G. 2007. Cutting edge: the ST2 ligand IL-33 potently activates and drives maturation of human mast cells. J Immunol. 179(4):2051–54.

Awada A, Nicaise C, Ena S, Schandéné L, Rasschaert J, Popescu I, Gangji V, Soyfoo MS. 2014. Potential involvement of the IL-33-ST2 axis in the pathogenesis of primary Sjogren's syndrome. Ann Rheum Dis. 73(6):1259–63.

Azizi G, Tavakol M, Rafiemanesh H, Kiaee F, Yazdani R, Heydari A, Abouhamzeh K, Anvari P, Mohammadikhajehdehi S, Sharifia L, et al. 2017. Autoimmunity in a cohort of 471 patients with primary antibody deficiencies. Expert Rev Clin Immunol. 13(11):1099–106.

Babaie F, Hosseinzadeh R, Ebrazeh M, Seyfizadeh N, Aslani S, Salimi S, Hemmatzadeh M, Azizi G, Jadidi-Niaragh F, Mohammadi H. 2020. The roles of ERAP1 and ERAP2 in autoimmunity and cancer immunity: new insights and perspective. Mol Immunol. 121:7–19.

Babaie F, Ebrazeh M, Hemmatzadeh M, Mohammadi FS, Shabgah AG, Hajaliloo M, Ebrahimi AA, Shirafkan N, Azizi G, Mohammadi H, et al. 2018. Association analysis of ERAP1 gene single nucleotide polymorphism in susceptibility to ankylosing spondylitis in Iranian population. Immunol Lett. 201:52–58.

Babinská K, Bucová M, Ďurmanová V, Lakatošová S, Jánošíková D, Bakoš J, Hlavatá A, Ostatníková D. 2014. Increased plasma levels of the high mobility group box 1 protein (HMGB1) are associated with a higher score of gastrointestinal dysfunction in individuals with autism. Physiol Res. 63(Suppl 4): S613–8.

Baekkevold ES, Roussigné M, Yamanaka T, Johansen FE, Jahnsen FL, Amalric F, Brandtzaeg P, Erard M, Haraldsen G, Girard JP. 2003. Molecular characterization of NF-HEV, a nuclear factor preferentially expressed in human high endothelial venules. Am J Pathol. 163(1):69–79.

Balato A, Di Caprio R, Canta L, Mattii M, Lembo S, Raimondo A, Schiattarella M, Balato N, Ayala F. 2014. IL-33 is regulated by TNF-α in normal and psoriatic skin. Arch Dermatol Res. 306(3):299–304.

Balato A, Lembo S, Mattii M, Schiattarella M, Marino R, De Paulis A, Balato N, Ayala F. 2012. IL-33 is secreted by psoriatic keratinocytes and induces pro-inflammatory cytokines via keratinocyte and mast cell activation. Exp Dermatol. 21(11):892–94.

Balato A, Raimondo A, Balato N, Ayala F, Lembo S. 2016. Interleukin-33: increasing role in dermatological conditions. Arch Dermatol Res. 308(5):287–96.

Baum R, Gravallese EM. 2016. Bone as a target organ in rheumatic disease: impact on osteoclasts and osteoblasts. Clin Rev Allergy Immunol. 51(1):1–15.

Briones MRS, Snyder AM, Ferreira RC, Neely EB, Connor JR, Broach JR. 2018. A possible role for platelet-activating factor receptor in amyotrophic lateral sclerosis treatment. Front Neurol. 9:39.

Buckley ML, Williams JO, Chan Y-H, Laubertová L, Hayley Gallagher JW, Moss E, Ramji DP. 2019. The interleukin-33-mediated inhibition of expression of two key genes implicated in atherosclerosis in human macrophages requires MAP kinase, phosphoinositide 3-kinase and nuclear factor-κB signaling pathways. Sci Rep. 9(1):11317.

Burbelo PD, Gordon SM, Waldman M, Edison JD, Little DJ, Stitt RS, Bailey WT, Hughes JB, Olson SW. 2019. Autoantibodies are present before the clinical diagnosis of systemic sclerosis. PLoS One. 14(3):e0214202.

Byers DE, Alexander-Brett J, Patel AC, Agapov E, Dang-Vu G, Jin X, Wu K, You Y, Alevy Y, Girard JP, et al. 2013. Long-term IL-33-producing epithelial progenitor cells in chronic obstructive lung disease. J Clin Invest. 123(9):3967–82.

Cayrol C, Girard JP. 2009. The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1. Proc Natl Acad Sci U S A. 106(22):9021–26.

Celik HT, Abusoglu S, Burnik SF, Sezer S, Serdar MA, Ercan M, Uguz N, Avcikucuk M, Ceylan B, Yildirimkaya M. 2013. Increased serum interleukin-33 levels in patients with Graves' disease. Endocr Regul. 47(2):57–64.

Celli BR, MacNee W. 2004. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 23(6):932–46.

Çerçi P, Altıner S, İnal A, Köse K, Keskin G, Ölmez Ü. 2017. Investigating the role of IL-33 in the pathogenesis of Behçet's Disease. Acta Clin Belg. 72(6):434–38.

Chan BCL, Lam CWK, Tam LS, Wong CK. 2019. IL33: roles in Allergic Inflammation and Therapeutic Perspectives. Front Immunol. 10:364.

Chapuis J, Hot D, Hansmannel F, Kerdraon O, Ferreira S, Hubans C, Maurage CA, Huot L, Bensemain F, Laumet G, et al. 2009. Transcriptomic and genetic studies identify IL-33 as a candidate gene for Alzheimer's disease. Mol Psychiatry. 14(11):1004–16.

Cho KA, Suh JW, Sohn JH, Park JW, Lee H, Kang JL, Woo SY, Cho YJ. 2012. IL-33 induces Th17-mediated airway inflammation via mast cells in ovalbumin-challenged mice. Am J Physiol Lung Cell Mol Physiol. 302(4):L429–40.

Choi IA, Lee SJ, Park W, Park SH, Shim SC, Baek HJ, Yoo DH, Kim HA, Lee SK, Lee YJ, et al. 2018. Effects of Tocilizumab Therapy on Serum Interleukin-33 and Interleukin-6 Levels in Patients With Rheumatoid Arthritis. Arch Rheumatol. 33(4):389–94.

Choi Y-S, Choi H-J, Min J-K, Pyun B-J, Maeng Y-S, Park H, Kim J, Kim Y-M, Kwon Y-G. 2009. Interleukin-33 induces angiogenesis and vascular permeability through ST2/TRAF6-mediated endothelial nitric oxide production. Blood. 114(14):3117–26.

Christophi GP, Gruber RC, Panos M, Christophi RL, Jubelt B, Massa PT. 2012. Interleukin-33 upregulation in peripheral leukocytes and CNS of multiple sclerosis patients. Clin Immunol. 142 (3):308–19.

Cohen ES, Scott IC, Majithiya JB, Rapley L, Kemp BP, England E, Rees DG, Overed-Sayer CL, Woods J, Bond NJ, et al. 2015. Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation. Nat Commun. 6(1):8327.

De la Fuente M, MacDonald TT, Hermoso MA. 2015. The IL-33/ST2 axis: role in health and disease. Cytokine Growth Factor Rev. 26(6):615–23.
De Salvo C, Wang XM, Pastorelli L, Mattioli B, Omenetti S, Buela KA, Chowdhry S, Garg RR, Goodman WA, Rodriguez-Palacios A, et al. 2016. IL-33 drives eosinophil infiltration and pathogenic type 2 Helper T-cell immune responses leading to chronic experimental ileitis. Am J Pathol. 186(4):885–98.
de Vries JHM, Dijkhuizen M, Tap P, Witteman BJM. 2019. Patient's dietary beliefs and behaviours in inflammatory bowel disease. Dig Dis. 37(2):131–39.
Duan L, Chen J, Zhang H, Yang H, Zhu P, Xiong A, Xia Q, Zheng F, Tan Z, Gong F, et al. 2012. Interleukin-33 ameliorates experimental colitis through promoting Th2/Foxp3□ regulatory T-cell responses in mice. Mol Med. 18(1):753–61.
Duan Y, Dong Y, Hu H, Wang Q, Guo S, Fu D, Song X, Kalvakolanu DV, Tian Z. 2019. IL-33 contributes to disease severity in Psoriasis-like models of mouse. Cytokine. 119:159–67.
Esmaeil Amini M, Shomali N, Bakhshi A, Rezaei S, Hemmatzadeh M, Hosseinzadeh R, Eslami S, Babaie F, Aslani S, Torkamandi S, et al. 2020. Gut microbiome and multiple sclerosis: new insights and perspective. Int Immunopharmacol. 88:107024.
Fan D, Ding N, Yang T, Wu S, Liu S, Liu L, Hu Y, Duan Z, Xia G, Xu S, et al. 2014. Single nucleotide polymorphisms of the interleukin-33 (IL-33) gene are associated with ankylosing spondylitis in Chinese individuals: a case-control pilot study. Scand J Rheumatol. 43(5):374–79.
Fu AK, Hung KW, Yuen MY, Zhou X, Mak DS, Chan IC, Cheung TH, Zhang B, Fu WY, Liew FY, et al. 2016. IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. Proc Natl Acad Sci U S A. 113(19):E2705–13.
Funakoshi-Tago M, Tago K, Hayakawa M, Tominaga S, Ohshio T, Sonoda Y, Kasahara T. 2008. TRAF6 is a critical signal transducer in IL-33 signaling pathway. Cell Signal. 20 (9):1679–86.
Gao Q, Li Y, Li M. 2015. The potential role of IL-33/ST2 signaling in fibrotic diseases. J Leukoc Biol. 98(1):15–22.
Ghaderian S, Shomali N, Behravesh S, Danbaran GR, Hemmatzadeh M, Aslani S, Jadidi-Niaragh F, Hosseinzadeh R, Torkamandi S, Mohammadi H. 2020. The emerging role of lncRNAs in multiple sclerosis. J Neuroimmunol. 347:577347.
Goines PE, Croen LA, Braunschweig D, Yoshida CK, Grether J, Hansen R, Kharrazi M, Ashwood P, Van de Water J. 2011. Increased midgestational IFN-γ, IL-4 and IL-5 in women bearing a child with autism: a case-control study. Mol Autism. 2:13.
Groβ P, Doser K, Falk W, Obermeier F, Hofmann C. 2012. IL-33 attenuates development and perpetuation of chronic intestinal inflammation. Inflamm Bowel Dis. 18(10):1900–09.
Gundersen MD, Goll R, Hol J, Olsen T, Rismo R, Sørbye SW, Sundnes O, Haraldsen G, Florholmen J. 2016. Loss of interleukin 33 expression in colonic crypts - a potential marker for disease remission in ulcerative colitis. Sci Rep. 6:35403.
Guo C, Zhou M, Zhao S, Huang Y, Wang S, Fu R, Li M, Zhang T, Gaskin F, Yang N, et al. 2019. Innate lymphoid cell disturbance with increase in ILC1 in systemic lupus erythematosus. Clin Immunol. 202:49–58.
Guo J, Xiang Y, Peng YF, Huang HT, Lan Y, Wei YS. 2016. The association of novel IL-33 polymorphisms with sIL-33 and risk of systemic lupus erythematosus. Mol Immunol. 77:1–7.
Hamzaoui K, Bouali E, Hamzaoui A. 2015. Interleukin-33 and Behçet disease: another cytokine among others. Hum Immunol. 76(5):301–06.
Hamzaoui K, Kaabachi W, Fazaa B, Zakraoui L, Mili-Boussen I, Haj-Sassi F. 2013. Serum IL-33 levels and skin mRNA expression in Behçet's disease. Clin Exp Rheumatol. 31(3 Suppl 77):6–14.
Haraldsen G, Balogh J, Pollheimer J, Sponheim J, Küchler AM. 2009. Interleukin-33 - cytokine of dual function or novel alarmin? Trends Immunol. 30(5):227–33.
Hayakawa H, Hayakawa M, Tominaga SI. 2016. Soluble ST2 suppresses the effect of interleukin-33 on lung type 2 innate lymphoid cells. Biochem Biophys Rep. 5:401–07.
He Z, Song J, Hua J, Yang M, Ma Y, Yu T, Feng J, Liu B, Wang X, Li Y, et al. 2018. Mast cells are essential intermediaries in regulating IL-33/ST2 signaling for an immune network favorable to mucosal healing in experimentally inflamed colons. Cell Death Dis. 9(12):1173.

Hemmatzadeh M, Babaie F, Ezzatifar F, Mohammadi FS, Ebrazeh M, Golabi Aghdam S, Hajaliloo M, Azizi G, Gowhari Shabgah A, Shekari N, et al. 2019. Susceptibility to ERAP1 gene single nucleotide polymorphism modulates the inflammatory cytokine setting in ankylosing spondylitis. Int J Rheum Dis. 22(4):715–24.

Hernandez F, Lucas JJ, Avila J. 2013. GSK3 and tau: two convergence points in Alzheimer's disease. J Alzheimers Dis. 33(Suppl 1):S141–4.

Hertz KC, Gazze LA, Kirkpatrick CH, Katz SI. 1977. Autoimmune vitiligo: detection of antibodies to melanin-producing cells. N Engl J Med. 297(12):634–37.

Hosseini SH, Sharafkandi N, Seyfizadeh N, Hemmatzadeh M, Marofi F, Shomali N, Karimi M, Mohammadi H. 2020. Progression or suppression: two sides of the innate lymphoid cells in cancer. J Cell Biochem. 121(4):2739–55.

Huang XL, Wu GC, Wang YJ, Yang XK, Yang GJ, Tao JH, Duan Y, Yan JW, Li XP, Ye DQ, et al. 2016. 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 (4):1041–52.

Iikura M, Suto H, Kajiwara N, Oboki K, Ohno T, Okayama Y, Saito H, Galli SJ, Nakae S. 2007. IL-33 can promote survival, adhesion and cytokine production in human mast cells. Lab Invest. 87 (10):971–78.

Imhann F, Vich Vila A, Bonder MJ, Fu J, Gevers D, Visschedijk MC, Spekhorst LM, Alberts R, Franke L, van Dullemen HM, et al. 2018. Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. Gut. 67(1):108–19.

Italiani P, Manca ML, Angelotti F, Melillo D, Pratesi F, Puxeddu I, Boraschi D, Migliorini P. 2018a. IL-1 family cytokines and soluble receptors in systemic lupus erythematosus. Arthritis Res Ther. 20 (1):27.

Italiani P, Puxeddu I, Napoletano S, Scala E, Melillo D, Manocchio S, Angiolillo A, Migliorini P, Boraschi D, Vitale E, et al. 2018b. Circulating levels of IL-1 family cytokines and receptors in Alzheimer's disease: new markers of disease progression? J Neuroinflammation. 15(1):342.

Jafarzadeh A, Mahdavi R, Jamali M, Hajghani H, Nemati M, Ebrahimi HA. 2016. Increased concentrations of interleukin-33 in the serum and cerebrospinal fluid of patients with multiple sclerosis. Oman Med J. 31(1):40–45.

Jeppesen R, Benros ME. 2019. Autoimmune diseases and psychotic disorders. Front Psychiatry. 10:131.

Jiang HR, Milovanović M, Allan D, Niedbala W, Besnard AG, Fukada SY, Alves-Filho JC, Togbe D, Goodyear CS, Linington C, et al. 2012. IL-33 attenuates EAE by suppressing IL-17 and IFN-γ production and inducing alternatively activated macrophages. Eur J Immunol. 42(7):1804–14.

Kacem O, Kaabachi W, Dhifallah IB, Hamzaoui A, Hamzaoui K. 2018. Elevated expression of TSLP and IL-33 in Behçet's disease skin lesions: IL-37 alleviate inflammatory effect of TSLP. Clin Immunol. 192:14–19.

Kakkar R, Hei H, Dobner S, Lee RT. 2012. Interleukin 33 as a mechanically responsive cytokine secreted by living cells. J Biol Chem. 287(9):6941–48.

Kenny EF, Raupach B, Abu Abed U, Brinkmann V, Zychlinsky A. 2019. Dnase1-deficient mice spontaneously develop a systemic lupus erythematosus-like disease. Eur J Immunol. 49 (4):590–99.

Ketelaar ME, Nawijn MC, Shaw DE, Koppelman GH, Sayers I. 2016. The challenge of measuring IL-33 in serum using commercial ELISA: lessons from asthma. Clin Exp Allergy. 46(6):884–87.

Kim DJ, Baek SY, Park MK, Park KS, Lee JH, Park SH, Kim HY, Kwok SK. 2013. 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(8):1145–53.

Koca SS, Kara M, Deniz F, Ozgen M, Demir CF, Ilhan N, Isik A. 2015. Serum IL-33 level and IL-33 gene polymorphisms in Behçet's disease. Rheumatol Int. 35(3):471–77.

Koca SS, Pehlivan Y, Kara M, Alibaz-Oner F, Oztuzcu S, Yilmaz N, Cetin GY, Kisacik B, Ozgen M, Pamuk ON, et al. 2016. The IL-33 gene is related to increased susceptibility to systemic sclerosis. Rheumatol Int. 36(4):579–84.

Korhonen P, Kanninen KM, Lehtonen Š, Lemarchant S, Puttonen KA, Oksanen M, Dhungana H, Loppi S, Pollari E, Wojciechowski S, et al. 2015. Immunomodulation by interleukin-33 is protective in stroke through modulation of inflammation. Brain Behav Immun. 49:322–36.

Korhonen P, Pollari E, Kanninen KM, Savchenko E, Lehtonen Š, Wojciechowski S, Pomeshchik Y, Van Den Bosch L, Goldsteins G, Koistinaho J, et al. 2019. Long-term interleukin-33 treatment delays disease onset and alleviates astrocytic activation in a transgenic mouse model of amyotrophic lateral sclerosis. IBRO Rep. 6:74–86.

Kunisch E, Chakilam S, Gandesiri M, Kinne RW. 2012. IL-33 regulates TNF-α dependent effects in synovial fibroblasts. Int J Mol Med. 29(4):530–40.

Kurowska-Stolarska M, Stolarski B, Kewin P, Murphy G, Corrigan CJ, Ying S, Pitman N, Mirchandani A, Rana B, van Rooijen N, et al. 2009. IL-33 amplifies the polarization of alternatively activated macrophages that contribute to airway inflammation. J Immunol. 183(10):6469–77.

Lalancette-Hebert M, Sharma A, Lyashchenko AK, Shneider NA. 2016. Gamma motor neurons survive and exacerbate alpha motor neuron degeneration in ALS. Proc Natl Acad Sci U S A. 113 (51):E8316–e8325.

Latiano A, Palmieri O, Pastorelli L, Vecchi M, Pizarro TT, Bossa F, Merla G, Augello B, Latiano T, Corritore G, et al. 2013. Associations between genetic polymorphisms in IL-33, IL1R1 and risk for inflammatory bowel disease. PLoS One. 8(4):e62144.

Lee JH, Hailey KL, Vitorino SA, Jennings PA, Bigby TD, Breen EC. 2019. Cigarette smoke triggers IL-33-associated inflammation in a model of late-stage chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 61(5):567–74.

Lefrançais E, Roga S, Gautier V, Gonzalez-de-Peredo A, Monsarrat B, Girard JP, Cayrol C. 2012. IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G. Proc Natl Acad Sci U S A. 109(5):1673–78.

Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG. 2004. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 364(9451):2106–12.

Leung RC, Vogan VM, Powell TL, Anagnostou E, Taylor MJ. 2016. The role of executive functions in social impairment in Autism Spectrum Disorder. Child Neuropsychol. 22(3):336–44.

Li C, Mu R, Guo J, Wu X, Tu X, Liu X, Hu F, Guo S, Zhu J, Xu H, et al. 2014. Genetic variant in IL33 is associated with susceptibility to rheumatoid arthritis. Arthritis Res Ther. 16(2):R105.

Li GX, Wang S, Duan ZH, Zeng Z, Pan FM. 2013. Serum levels of IL-33 and its receptor ST2 are elevated in patients with ankylosing spondylitis. Scand J Rheumatol. 42(3):226–31.

Li P, Ma H, Han D, Mou K. 2015. Interleukin-33 affects cytokine production by keratinocytes in vitiligo. Clin Exp Dermatol. 40(2):163–70.

Li Q, Hu Y, Chen Y, Lv Z, Wang J, An G, Du X, Wang H, Corrigan CJ, Wang W, et al. 2019. IL-33 induces production of autoantibody against autologous respiratory epithelial cells: a potential mechanism for the pathogenesis of COPD. Immunology. 157(2):137–50.

Liang M, Liwen Z, Yun Z, Yanbo D, Jianping C. 2018. Serum Levels of IL-33 and Correlation with IL-4, IL-17A, and Hypergammaglobulinemia in Patients with Autoimmune Hepatitis. Mediators Inflamm. 2018:7964654.

Liew FY, Girard J-P, Turnquist HR. 2016. Interleukin-33 in health and disease. Nat Rev Immunol. 16 (11):676–89.

Lin CY, Pfluger CM, Henderson RD, McCombe PA. 2012. Reduced levels of interleukin 33 and increased levels of soluble ST2 in subjects with amyotrophic lateral sclerosis. J Neuroimmunol. 249 (1–2):93–95.

Lingel A, Weiss TM, Niebuhr M, Pan B, Appleton BA, Wiesmann C, Bazan JF, Fairbrother WJ. 2009. Structure of IL-33 and its interaction with the ST2 and IL-1RAcP receptors–insight into heterotrimeric IL-1 signaling complexes. Structure. 17(10):1398–410.

Liu X, Hammel M, He Y, Tainer JA, Jeng US, Zhang L, Wang S, Wang X. 2013. Structural insights into the interaction of IL-33 with its receptors. Proc Natl Acad Sci U S A. 110 (37):14918–23.

Lopetuso LR, De Salvo C, Pastorelli L, Rana N, Senkfor HN, Petito V, Di Martino L, Scaldaferri F, Gasbarrini A, Cominelli F, et al. 2018. IL-33 promotes recovery from acute colitis by inducing

miR-320 to stimulate epithelial restitution and repair. Proc Natl Acad Sci U S A. 115(40):E9362–e9370.
López-Mejías R, Genre F, Remuzgo-Martínez S, Robustillo-Villarino M, García-Bermúdez M, Llorca J, Corrales A, González-Juanatey C, Ubilla B, Miranda-Filloy JA, et al. 2015. Protective role of the interleukin 33 rs3939286 gene polymorphism in the development of subclinical atherosclerosis in rheumatoid arthritis patients. PLoS One. 10(11):e0143153.
Lüthi AU, Cullen SP, McNeela EA, Duriez PJ, Afonina IS, Sheridan C, Brumatti G, Taylor RC, Kersse K, Vandenabeele P, et al. 2009. Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases. Immunity. 31(1):84–98.
Manetti M, Ibba-Manneschi L, Liakouli V, Guiducci S, Milia AF, Benelli G, Marrelli A, Conforti ML, Romano E, Giacomelli R, et al. 2010. 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(3):598–605.
Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, Bahr MJ, Günther R, Hultcrantz RW, Spengler U, et al. 2010. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 139 (4):1198–206.
Matta BM, Lott JM, Mathews LR, Liu Q, Rosborough BR, Blazar BR, Turnquist HR. 2014. IL-33 is an unconventional Alarmin that stimulates IL-2 secretion by dendritic cells to selectively expand IL-33R/ST2+ regulatory T cells. J Immunol. 193(8):4010–20.
Michaudel C, Mackowiak C, Maillet I, Louis Fauconnier CA, Akdis MS, Dreher A, Tan H-TT, Quesniaux VF, Ryffel B, Togbe D. 2018. Ozone exposure induces respiratory barrier biphasic injury and inflammation controlled by IL-33. J Allergy Clin Immunol. 142(3):942–58.
Miller AM. 2011. Role of IL-33 in inflammation and disease. J Inflamm (Lond). 8(1):22.
Milovanovic M, Volarevic V, Ljujic B, Radosavljevic G, Jovanovic I, Arsenijevic N, Lukic ML. 2012. Deletion of IL-33R (ST2) abrogates resistance to EAE in BALB/C mice by enhancing polarization of APC to inflammatory phenotype. PLoS One. 7(9):e45225.
Mitsui A, Tada Y, Takahashi T, Shibata S, Kamata M, Miyagaki T, Fujita H, Sugaya M, Kadono T, Sato S, et al. 2016. Serum IL-33 levels are increased in patients with psoriasis. Clin Exp Dermatol. 41(2):183–89.
Miyasaka M, Tanaka T. 2004. Lymphocyte trafficking across high endothelial venules: dogmas and enigmas. Nat Rev Immunol. 4(5):360–70.
Mjösberg J, Bernink J, Golebski K, Karrich JJ, Peters CP, Blom B, Fokkens WJ, van Drunen CM, Spits H. 2012. The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. Immunity. 37(4):649–59.
Mohammadi H, Babaie F, Hemmatzadeh M, Azizi G, Hajaliloo M, Ebrahimi AA, Kazemi T, Yousefi M, Rezaiemanesh A, Safarzadeh E, et al. 2018a. Evaluation of ERAP1 gene single nucleotide polymorphism in impressing the inflammatory cytokine profile of ankylosing spondylitis patients. Iran J Allergy Asthma Immunol. 17(5):464–74.
Mohammadi H, Hemmatzadeh M, Babaie F, Gowhari Shabgah A, Azizi G, Hosseini F, Majidi J, Baradaran B. 2018b. MicroRNA implications in the etiopathogenesis of ankylosing spondylitis. J Cell Physiol. 233(8):5564–73.
Mohammadi H, Sharafkandi N, Hemmatzadeh M, Azizi G, Karimi M, Jadidi-Niaragh F, Baradaran B, Babaloo Z. 2018c. The role of innate lymphoid cells in health and disease. J Cell Physiol. 233 (6):4512–29.
Mok MY, Huang FP, Ip WK, Lo Y, Wong FY, Chan EY, Lam KF, Xu D. 2010. Serum levels of IL-33 and soluble ST2 and their association with disease activity in systemic lupus erythematosus. Rheumatology (Oxford). 49(3):520–27.
Moussion C, Ortega N, Girard JP. 2008. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel 'alarmin'? PLoS One. 3(10): e3331.
Mu R, Huang HQ, Li YH, Li C, Ye H, Li ZG. 2010. Elevated serum interleukin 33 is associated with autoantibody production in patients with rheumatoid arthritis. J Rheumatol. 37(10):2006–13.

Mun SH, Ko NY, Kim HS, Kim JW, Kim DK, Kim AR, Lee SH, Kim YG, Lee CK, Lee SH, et al. 2010. Interleukin-33 stimulates formation of functional osteoclasts from human CD14(+) monocytes. Cell Mol Life Sci. 67(22):3883–92.
Natarajan C, Yao SY, Sriram S. 2016. TLR3 Agonist Poly-IC Induces IL-33 and Promotes Myelin Repair. PLoS One. 11(3):e0152163.
Neumann K, Karimi K, Meiners J, Voetlause R, Steinmann S, Dammermann W, Lüth S, Asghari F, Wegscheid C, Horst AK, et al. 2017. A proinflammatory role of type 2 innate lymphoid cells in murine immune-mediated hepatitis. J Immunol. 198(1):128–37.
Nishizaki T. 2018. IL-33 suppresses GSK-3β activation through an ST2-independent MyD88/TRAF6/RIP/PI3K/Akt pathway. Heliyon. 4(11):e00971.
Okumura S, McIntosh K, Drachman DB. 1994. Oral administration of acetylcholine receptor: effects on experimental myasthenia gravis. Ann Neurol. 36(5):704–13.
Ortega C, Fernández AS, Carrillo JM, Romero P, Molina IJ, Moreno JC, Santamaría M. 2009. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. J Leukoc Biol. 86(2):435–43.
Parks CG, Miller FW, Pollard KM, Selmi C, Germolec D, Joyce K, Rose NR, Humble MC. 2014. Expert panel workshop consensus statement on the role of the environment in the development of autoimmune disease. Int J Mol Sci. 15(8):14269–97.
Pasoto SG, de Oliveira Martins VA, Bonfa E. 2019. Sjögren's syndrome and systemic lupus erythematosus: links and risks. Open Access Rheumatol. 11:33–45.
Pastorelli L, Garg RR, Hoang SB, Spina L, Mattioli B, Scarpa M, Fiocchi C, Vecchi M, Pizarro TT. 2010. 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(17):8017–22.
Patrick J, Lindstrom J. 1973. Autoimmune response to acetylcholine receptor. Science. 180 (4088):871–72.
Pomeshchik Y, Kidin I, Korhonen P, Savchenko E, Jaronen M, Lehtonen S, Wojciechowski S, Kanninen K, Koistinaho J, Malm T. 2015. Interleukin-33 treatment reduces secondary injury and improves functional recovery after contusion spinal cord injury. Brain Behav Immun. 44:68–81.
Raimondo A, Lembo S, Di Caprio R, Donnarumma G, Monfrecola G, Balato N, Ayala F, Balato A. 2017. Psoriatic cutaneous inflammation promotes human monocyte differentiation into active osteoclasts, facilitating bone damage. Eur J Immunol. 47(6):1062–74.
Rankin AL, Mumm JB, Murphy E, Turner S, Yu N, McClanahan TK, Bourne PA, Pierce RH, Kastelein R, Pflanz S. 2010. IL-33 induces IL-13-dependent cutaneous fibrosis. J Immunol. 184 (3):1526–35.
Rozmilowska IM, Adamczyk-Sowa MH. 2018. What is the role of interleukin 33 and ST2 receptor in myasthenia gravis? J Neuroimmunol. 315:50–57.
Saidi S, Bouri F, Lencel P, Duplomb L, Baud'huin M, Delplace S, Leterme D, Miellot F, Heymann D, Hardouin P, et al. 2011. IL-33 is expressed in human osteoblasts, but has no direct effect on bone remodeling. Cytokine. 53(3):347–54.
Saleh H, Eeles D, Hodge JM, Nicholson GC, Gu R, Pompolo S, Gillespie MT, Quinn JM. 2011. Interleukin-33, a target of parathyroid hormone and oncostatin m, increases osteoblastic matrix mineral deposition and inhibits osteoclast formation in vitro. Endocrinology. 152 (5):1911–22.
Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. 2007. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest. 117 (6):1538–49.
Saresella M, Piancone F, Marventano I, Zoppis M, Hernis A, Zanette M, Trabattoni D, Chiappedi M, Ghezzo A, Canevini MP, et al. 2016. Multiple inflammasome complexes are activated in autistic spectrum disorders. Brain Behav Immun. 57:125–33.
Savenije OE, Kerkhof M, Reijmerink NE, Brunekreef B, de Jongste JC, Smit HA, Wijga AH, Postma DS, Koppelman GH. 2011. Interleukin-1 receptor-like 1 polymorphisms are associated with serum IL1RL1-a, eosinophils, and asthma in childhood. J Allergy Clin Immunol. 127 (3):750–6.e1-5.

Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zurawski G, Moshrefi M, Qin J, Li X, et al. 2005. 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 (5):479–90.

Schulze J, Bickert T, Beil FT, Zaiss MM, Albers J, Wintges K, Streichert T, Klaetschke K, Keller J, Hauer TN, et al. 2011. Interleukin-33 is expressed in differentiated osteoblasts and blocks osteoclast formation from bone marrow precursor cells. J Bone Miner Res. 26(4):704–17.

Seidelin JB, Coskun M, Kvist PH, Holm TL, Holgersen K, Nielsen OH. 2015. IL-33 promotes GATA-3 polarization of gut-derived T cells in experimental and ulcerative colitis. J Gastroenterol. 50(2):180–90.

Seo DH, Che X, Kwak MS, Kim S, Kim JH, Ma HW, Kim DH, Kim TI, Kim WH, Kim SW, et al. 2017. Interleukin-33 regulates intestinal inflammation by modulating macrophages in inflammatory bowel disease. Sci Rep. 7(1):851.

Seyahi E. 2016. Behçet's disease: how to diagnose and treat vascular involvement. Best Pract Res Clin Rheumatol. 30(2):279–95.

Shang J, Zhao J, Xiaojie W, Yongjian X, Xie J, Zhao J. 2015. Interleukin-33 promotes inflammatory cytokine production in chronic airway inflammation. Biochem Cell Biol. 93(4):359–66.

Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Klöppel G, Lerch MM, Löhr M, et al. 2011. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 40(3):352–58.

Sims JE, Nicklin MJ, Bazan JF, Barton JL, Busfield SJ, Ford JE, Kastelein RA, Kumar S, Lin H, Mulero JJ, et al. 2001. A new nomenclature for IL-1-family genes. Trends Immunol. 22(10):536–37.

Smith DE. 2010. IL-33: a tissue derived cytokine pathway involved in allergic inflammation and asthma. Clin Exp Allergy. 40(2):200–08.

Sun BB, Ma LJ, Qi Y, Zhang GJ. 2019. Correlation of IL-33 gene polymorphism with chronic obstructive pulmonary disease. Eur Rev Med Pharmacol Sci. 23(14):6277–82.

Supekar K, Uddin LQ, Khouzam A, Phillips J, Gaillard WD, Kenworthy LE, Yerys BE, Vaidya CJ, Menon V. 2013. Brain hyperconnectivity in children with autism and its links to social deficits. Cell Rep. 5(3):738–47.

Talei M, Abdi A, Shanebandi D, Jadidi-Niaragh F, Khabazi A, Babaie F, Alipour S, Afkari B, Sakhinia E, Babaloo Z. 2019. Interleukin-33 gene expression and rs1342326 polymorphism in Behçet's disease. Immunol Lett. 212:120–24.

Tamagawa-Mineoka R, Okuzawa Y, Masuda K, Katoh N. 2014. Increased serum levels of interleukin 33 in patients with atopic dermatitis. J Am Acad Dermatol. 70(5):882–88.

Tang S, Huang H, Hu F, Zhou W, Guo J, Jiang H, Mu R, Li Z. 2013. Increased IL-33 in synovial fluid and paired serum is associated with disease activity and autoantibodies in rheumatoid arthritis. Clin Dev Immunol. 2013:985301.

Theoharides TC, Zhang B, Kempuraj D, Tagen M, Vasiadi M, Angelidou A, Alysandratos KD, Kalogeromitros D, Asadi S, Stavrianeas N, et al. 2010. 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(9):4448–53.

Tian M, Deng YY, Hou DR, Li W, Feng XL, Yu ZL. 2015. Association of IL-1, IL-18, and IL-33 gene polymorphisms with late-onset Alzheimer's disease in a Hunan Han Chinese population. Brain Res. 1596:136–45.

Tsilioni I, Taliou A, Francis K, Theoharides TC. 2015. Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6. Transl Psychiatry. 5(9):e647.

Tu L, Chen J, Xu D, Xie Z, Yu B, Tao Y, Shi G, Duan L. 2017. IL-33-induced alternatively activated macrophage attenuates the development of TNBS-induced colitis. Oncotarget. 8(17):27704–14.

Tworek D, Majewski S, Szewczyk K, Kiszałkiewicz J, Kurmanowska Z, Górski P, Brzeziańska-Lasota E, Kuna P, Antczak A. 2018. The association between airway eosinophilic inflammation and IL-33 in stable non-atopic COPD. Respir Res. 19(1):108.

Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, et al. 2012. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 22(1):21–30.

Vaccaro M, Cicero F, Mannucci C, Calapai G, Spatari G, Barbuzza O, Cannavò SP, Gangemi S. 2016. IL-33 circulating serum levels are increased in patients with non-segmental generalized vitiligo. Arch Dermatol Res. 308(7):527–30.

Verri WA Jr., Souto FO, Vieira SM, Almeida SC, Fukada SY, Xu D, Alves-Filho JC, Cunha TM, Guerrero AT, Mattos-Guimaraes RB, et al. 2010. IL-33 induces neutrophil migration in rheumatoid arthritis and is a target of anti-TNF therapy. Ann Rheum Dis. 69(9):1697–703.

Wagner A, Köhm M, Nordin A, Svenungsson E, Pfeilschifter JM, Radeke HH. 2015. Increased Serum Levels of the IL-33 Neutralizing sST2 in Limited Cutaneous Systemic Sclerosis. Scand J Immunol. 82(3):269–74.

Wang X, Shao X, Liu X, Qin Q, Xu J, Zhang JA. 2019a. Dysregulated Interleukin −33/ST2 pathway perpetuates chronic inflammation in hashimoto's thyroiditis. Endocr Metab Immune Disord Drug Targets. 19(7):1012–21.

Wang X, Zhu YF, Li DM, Qin Q, Wang Q, Muhali FS, Jiang WJ, Zhang JA. 2016. Polymorphisms of ST2-IL18R1-IL18RAP gene cluster: a new risk for autoimmune thyroid diseases. Int J Immunogenet. 43(1):18–24.

Wang Y, Chen Z, Huang Y, Yafei L, Tu S. 2018. Prognostic significance of serum interleukins and soluble ST2 in traditional chinese medicine (TCM) syndrome-differentiated rheumatoid arthritis. Med Sci Monit. 24:3472–78.

Wang Z, Wang W, Chen Y, Wei D. 2012. T helper type 17 cells expand in patients with myasthenia-associated thymoma. Scand J Immunol. 76(1):54–61.

Wang Z, Wang W, Chen Y, Shengjie X, Wei D, Huang X. 2019b. Elevated expression of interleukin-33 in myasthenia gravis patients. Journal of Clinical Neuroscience. 63:32–36.

Wasserman AM. 2011. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 84 (11):1245–52.

Watanabe T, Asano N, Kudo M, Strober W. 2017a. Nucleotide-binding oligomerization domain 1 and gastrointestinal disorders. Proc Jpn Acad Ser B Phys Biol Sci. 93(8):578–99.

Watanabe T, Yamashita K, Arai Y, Minaga K, Kamata K, Nagai T, Komeda Y, Takenaka M, Hagiwara S, Ida H, et al. 2017b. Chronic fibro-inflammatory responses in autoimmune pancreatitis depend on IFN-α and IL-33 produced by plasmacytoid dendritic cells. J Immunol. 198 (10):3886–96.

Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology. 66(10):1485–89.

Wu S, Jiang Y, Teng Y, Liu X, Zhou L, Li W. 2020. Interleukin-33 promotes proliferation and inhibits apoptosis of fibroblast-like synoviocytes in rheumatoid arthritis. Clin Exp Rheumatol.

Xia J, Zhao J, Shang J, Li M, Zeng Z, Zhao J, Wang J, Xu Y, Xie J. 2015. Increased IL-33 expression in chronic obstructive pulmonary disease. Am J Physiol Lung Cell Mol Physiol. 308(7):L619–27.

Xiong Z, Thangavel R, Kempuraj D, Yang E, Zaheer S, Zaheer A. 2014. Alzheimer's disease: evidence for the expression of interleukin-33 and its receptor ST2 in the brain. J Alzheimers Dis. 40 (2):297–308.

Xu D, Chan WL, Leung BP, Fp Huang R, Piedrafita WD, Robinson JH, Liew FY. 1998. Selective expression of a stable cell surface molecule on type 2 but not type 1 helper T cells. J Exp Med. 187 (5):787–94.

Xu W, Liu Y, Ye D. 2016. Association between IL-33 Gene Polymorphisms (rs1929992, rs7044343) and systemic lupus erythematosus in a Chinese Han Population. Immunol Invest. 45(7):575–83.

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

Yasuoka S, Kawanokuchi J, Parajuli B, Jin S, Doi Y, Noda M, Sonobe Y, Takeuchi H, Mizuno T, Suzumura A. 2011. Production and functions of IL-33 in the central nervous system. Brain Res. 1385:8–17.

Yu J-T, Song J-H, Wang N-D, Wu Z-C, Zhang Q, Zhang N, Zhang W, Xuan S-Y, Tan L. 2012. Implication of IL-33 gene polymorphism in Chinese patients with Alzheimer's disease. Neurobiol Aging. 33(5):1014.e11-1014.e14.

Zandee SEJ, O'Connor RA, Mair I, Leech MD, Williams A, Anderton SM. 2017. IL-10-producing, ST2-expressing Foxp3(+) T cells in multiple sclerosis brain lesions. Immunol Cell Biol. 95 (5):484–90.

Zeng Z, Hong X-Y, Zhou H, Liao F-L, Guo S, Yunhui L, Chen W, Yang G, Guangming Y, Yirong L 2020. Serum soluble ST2 as a novel biomarker reflecting inflammatory status and disease severity in patients with COVID-19. *Available at SSRN 3594550*.

Zhang Y, Yao XY, Gao MC, Ding J, Hong RH, Huang H, Zhuang L, Wang YG, Hao Y, Guan YT. 2018a. Th2 axis-related cytokines in patients with neuromyelitis optica spectrum disorders. CNS Neurosci Ther. 24(1):64–69.

Zhang YJ, Zhang Q, Yang GJ, Tao JH, Wu GC, Huang XL, Duan Y, Li XP, Ye DQ, Wang J. 2018b. Elevated serum levels of interleukin-1β and interleukin-33 in patients with systemic sclerosis in Chinese population. Z Rheumatol. 77(2):151–59.

Zhao J, Wei J, Mialki RK, Mallampalli DF, Chen BB, Coon T, Zou C, Mallampalli RK, Zhao Y. 2012. F-box protein FBXL19-mediated ubiquitination and degradation of the receptor for IL-33 limits pulmonary inflammation. Nat Immunol. 13(7):651–58.

Zhong X, Liu M-Y, Miao H, Du K, Wei M-J. 2017. Association of interleukin-33 gene polymorphisms with susceptibility to late onset Alzheimer's disease: a meta-analysis. Neuropsychiatr Dis Treat. 13:2275–84.

Zhou Q, Xiongyan W, Wang X, Zhenjia Y, Pan T, Zhen L, Chang X, Jin Z, Jianfang L, Zhu Z, et al. 2020. The reciprocal interaction between tumor cells and activated fibroblasts mediated by TNF-α/IL-33/ST2L signaling promotes gastric cancer metastasis. Oncogene. 39(7):1414–28.

Zhu X, Xie L, Qin H, Liang J, Yang Y, Xu J, Zhang T. 2019. Interaction between IL-33 gene polymorphisms and current smoking with susceptibility to systemic lupus erythematosus. J Immunol Res. 2019:1547578.

Zou SC, Jiang J, Song J. 2018. IL-33 induced inflammation exacerbated the development of chronic obstructive pulmonary disease through oxidative stress. Eur Rev Med Pharmacol Sci. 22 (6):1758–64.