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Review

Therapeutic Strategies for Targeting IL-33/ST2 Signalling for the Treatment of Inflammatory Diseases

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Key Words
Interleukin-33 • Inflammatory diseases • Immunotherapeutics

Abstract
Interleukin (IL)-33, a member of the IL-1 family of cytokines, is involved in innate and adaptive immune responses via interaction with its receptor, ST2. Activation of ST2 signalling by IL-33 triggers pleiotropic immune functions in multiple ST2-expressing immune cells, including macrophages, neutrophils, eosinophils, basophils, mast cells, type 2 helper T cells, regulatory T cells, and group 2 innate lymphoid cells. IL-33-mediated effector functions contribute to the tissue inflammatory and reparative responses in various organs including lung, skin, kidney, central nerve system, cardiovascular system, and gastrointestinal system. Endogenous IL-33/ST2 signaling exhibits diverse immune regulatory functions during progression of different diseases. IL-33 likely functions as a disease sensitizer and plays pathological roles in inflamed tissues in allergic disorders that involve hyperreactive immune responses in the context of skin and pulmonary allergy. However, IL-33 also mediates tissue-protective functions during the recovery phase following tissue injury in the central nerve system and gastrointestinal system. Modulation of the IL-33/ST2 axis, therefore, represents a promising strategy for treating immune disorders that involve dysregulation of the cytokine signalling. In the past two decades, therapeutic strategies blocking IL-33/ST2 have been extensively studied for the treatment of diseases in animal models. In this review, the current progress on the development of therapeutic biologics for targeting IL-33/ST2 signalling in inflammatory diseases is summarized.

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Introduction

Cytokines are major mediators of inflammation and contribute to autoimmune diseases. Therapeutic targeting of cytokines and their receptors has revolutionized the treatment of immune-mediated disorders. More than 90 cytokines and cytokine receptors have been identified, some of which are the basis for the current therapeutics on the market [1]. Selecting the cytokines to target and, in particular, identifying the cytokines that regulate the rate-limiting steps of disease pathways are crucial to the success of such strategies.

Recent studies indicated that interleukin (IL)-33, a member of the IL-1 cytokine family, participates in the pathogenesis of various inflammatory diseases, including allergic diseases [2, 3], autoimmune diseases [4, 5], infectious diseases [6, 7], and neuropathic pain [8]. Targeting IL-33 and its receptor, therefore, has great potential as a new therapeutic strategy [9]. In this review, we focus on the pathological roles of IL-33 in inflammatory diseases and highlight potential strategies to target IL-33/ST2 signalling.

IL-33 and ST2 signalling

IL-33 is constitutively expressed in epithelial barrier tissues and endothelial cell barriers and that the nucleus IL-33 has recently been identified as an alarmin or the damage-associated molecular patterns (DAMP) [10-12]. The receptor complex for IL-33 consists of the specific subunit ST2, which is encoded by the *IL1RL1* gene [11, 13]. At least 2 major transcription variants of ST2, the full-length transmembrane form (ST2L) and the soluble form (sST2), have been identified [14]. sST2 lacks the transmembrane domain and binds to IL-33 as a natural decoy receptor [15]. IL-33 activity is negatively regulated by sST2, which binds to IL-33 and prevent its activity (Fig. 1a). IL-33 signals through ST2L, which associates with IL-1RAcP to induce MyD88-dependent signalling [3]. Stimulation of ST2L elicits the recruitment of MyD88, IRAK1, IRAK4, and TRAF6, then activates the downstream NF-κB, JNK, p38, and ERK signalling pathways (Fig. 1a). In addition to ST2, the GOLD domain-containing protein TMED1 and c-kit have also been reported to be involved in IL-33 signalling [16, 17]. TIR8 (SIGIRR) also reportedly negatively regulates IL-33-driven allergic responses via interaction with ST2 [18].

Activation of ST2 signalling via IL-33 triggers pleiotropic immune functions in ST2-expressing immune cells, which include macrophages, neutrophils, eosinophils, basophils, mast cells, type 2 T helper cells (Th2), group 2 innate lymphoid cells (ILC2s), and regulatory T cells (Tregs) [19]. IL-33 preferentially activates type 2 immune responses; it promotes M2 macrophage polarization, activates ILC2s and Th2 cells [20, 21], and functions as a disease-sensitizing mediator in the pathogenesis of allergic disorders, including respiratory allergies (asthma and allergic rhinitis) and skin allergies (atopic dermatitis) [2].

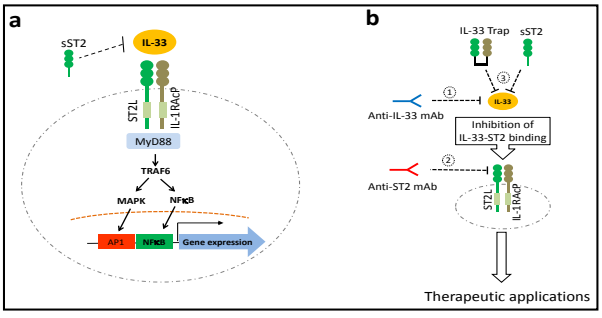

Fig. 1. Current therapeutic strategies targeting IL-33/ST2 signalling and their putative mechanisms of action. (a) IL-33 binds to the receptor complex comprised of ST2L and IL-1RAcP on the cell membrane and induces the recruitment of MyD88 and TRAF6, thereby activating the downstream NFκB and MAPK pathways. sST2, binding IL-33 as a decoy receptor, has been postulated as a biomarker for various inflammatory diseases. (b) Three major therapeutic biologics for targeting IL-33/ST2 signalling: 1) Anti-IL-33 monoclonal antibodies, 2) soluble IL-33 receptors, and 3) anti-ST2 monoclonal antibodies, all of which interfere with the binding of IL-33 to ST2. mAbs, monoclonal antibodies; IL-33 Trap, fusion protein of sST2 with the accessory protein IL-1RAcP.

Therapeutic strategies targeting IL-33/ST2 signalling

In the past 2 decades, scientists have made remarkable progress in the development of IL-33/ST2 blocking tools (Fig. 1b). IL-33 and ST2 have been drug targets in preclinical studies and pharmaceutical pipelines. There are 3 major therapeutic strategies for directly blocking the binding of IL-33 to ST2: (1) IL-33 neutralizing antibodies; (2) soluble decoy receptors; and (3) anti-ST2 receptor antibodies (Fig. 1b).

Monoclonal antibodies against extracellular cytokines and their receptors have been translated from scientific tools to powerful clinical therapeutics with dramatic effects [22]. Multiple neutralizing antibodies against IL-33 have been developed by several groups in the past 2 decades, which were used in clinical trials for the treatment of allergic diseases. Soluble receptor antagonists for IL-33 have also been developed to block the function of free IL-33 [23]. At least two IL-33 decoy receptors have been developed, including a form of sST2 and the IL-33 Trap, a fusion protein formed by sST2 and the accessory protein IL-1RAcP [23]. IL-33 Trap, generated using a knob-in-hole technology, is comprised of the extracellular cellular domains of mouse IL-1RAcP and mouse ST2; it ameliorates the pathology of a mouse model of macular disease [23]. Both decoy receptors inhibit IL-33-mediated biological functions *in vitro* and *in vivo*. Anti-ST2 antibodies are also currently in phase I–II clinical trials for the treatment of chronic obstructive pulmonary disease. In addition to the therapeutic benefit of blocking IL-33/ST2 signalling, the activation of IL-33 signalling by recombinant IL-33 is beneficial in certain disease models [24]. Therefore, the administration of exogenous IL-33 recombinant protein may be beneficial in patients with these diseases. Below, we summarized the beneficial and pathological effects of IL-33/ST2 signalling in inflammatory diseases of different organs (Table 1).

Table 1. Role of the IL-33/ST2 axis in inflammatory diseases

Disease model	Role of IL-33	Effects of IL-33/ST2 blockade	Strategies	Refs
Pulmonary system				
House dust mite asthma	Pathogenic	Protective	IL-33 vaccination	[25]
Ovalbumin-induced airway inflammation	Pathogenic	Protective	Anti-IL-33, sST2	[26]
Ovalbumin-induced airway inflammation	Pathogenic	Protective	Adenovirus-sST2	[27]
Bleomycin-induced pulmonary fibrosis	Pathogenic	Protective	Anti-IL-33	[28]
Allergic rhinitis	Pathogenic	Protective	Anti-IL-33	[29-31]
Cigarette smoke-induced lung inflammation	Pathogenic	Protective	Anti-IL-33	[32]
Fungal-induced asthma	Pathogenic	Protective	Anti-ST2	[33]
Skin				
Food anaphylaxis	Pathogenic	Protective	Anti-ST2, anti-IL-33	[34]
AD	Pathogenic	–	IL-33 overexpression	[37]
AD	Pathogenic	Protective	Anti-IL-33	[38, 39]
Wound healing	Protective	–	IL-33	[41]
Cardiovascular system				
TAC	Protective	Exacerbated in IL1RL1 KO	IL-33	[43, 44]
TAC	Protective	Exacerbated in IL1RL1 KO	IL33 knockout	[44, 45]
Atherosclerosis	Protective	–	IL-33	[46]
Myocardial infarction	Protective	Exacerbated in IL1RL1 KO	IL-33	[47]
Myocardial infarction	Protective	–	IL-33	[48]
CBV3-induced viral myocarditis	Protective	–	IL33 plasmid	[49]
CBV3-induced viral myocarditis	Pathogenic	Protective	sST2	[50]
Kidney				
IRI	Pathogenic	Protective	sST2	[51]
IRI	Protective	–	IL-2–IL-33 hybrid	[54]
Cisplatin-induced AKI	Pathogenic	–	IL-33	[52]
Ovalbumin-induced nephrotoxicity	Pathogenic	–	Anti-IL-33	[53]
Adriamycin-induced glomerulosclerosis	Protective	–	IL-33	[55]
Gastrointestinal system				
DSS- or TNBS-induced colitis	Pathogenic	Protective	Anti-ST2	[58]
TNBS-induced IBD	Protective	–	IL-33	[59]
DSS-induced colitis	Protective (early phase) Pathogenic (recovery phase)	–	IL-33	[59, 60]
TNBS-induced colitis	Protective	–	IL-33	[20]
DSS-induced colitis	Protective	–	IL-33	[61]
Central nervous system				
Ischaemic stroke	Protective	–	IL-33	[63]
Ischaemic stroke	Protective	–	IL-33	[62]
Ischaemic stroke	Protective	–	IL-33	[64]
Spinal cord injury	Protective	–	IL-33	[65]
Spinal cord injury	Protective	–	IL-33	[66]
Alzheimer's disease model	Protective	–	IL-33	[66]
A. cantonensis-induced meningitis	Pathogenic	Protective	Anti-IL-33	[67]
A. cantonensis-induced meningitis	Pathogenic	Protective	Anti-ST2	[68]
EAE	Protective	–	IL-33	[69]
EAE	Protective	–	IL-33	[70]
EAE	Pathogenic	Protective	Anti-IL-33	[71]

Pulmonary diseases

Blockade of IL-33 or ST2 is protective in allergic diseases, especially in the respiratory system. In the house dust mite asthma model, vaccination against IL-33 elicits high titres of specific anti-IL-33 antibodies and decreases airway hyperresponsiveness, eosinophilia, and pulmonary inflammation [25]. Blockade of IL-33 or administration of sST2 before the initiation of ovalbumin-induced allergic airway inflammation reduces total cell counts and eosinophil counts, as well as the levels of IL-4, IL-5, and IL-13, in the bronchoalveolar lavage fluid [26]. Additionally, adenovirus-mediated delivery of sST2 attenuates ovalbumin-induced allergic asthma in mice [27].

In the bleomycin-induced pulmonary fibrosis model, *IL1RL1* deficiency, anti-IL-33 antibody treatment, and alveolar macrophage depletion are protective, whereas exogenous IL-33 and adoptive transfer of ILC2s exacerbate lung inflammation and fibrosis [28]. Blocking IL-33 also has protective effects in experimental allergic rhinitis [29-31]. In a cigarette smoke-induced lung inflammation model, anti-IL-33 treatment reduces the infiltration of neutrophils and macrophages, as well as lung inflammation [32]. An anti-ST2 antibody potentiates CpG-mediated therapeutic effects in a fungal-induced asthma model [33]. In a mouse model of food anaphylaxis, *IL1RL1* deficiency and ST2 blockade reduce the severity of anaphylaxis [34].

In comparison to blockade of only the IL-33/ST2 pathway, the combined inhibition of IL-13 and IL-33 results in greater inhibition of type 2 immune responses, as indicated by decreased eosinophilia and pulmonary inflammation in a mouse helminth infection model [35]. Therapeutic biologics that target the key mediators of type 2 immune responses, IL-4 and IL-13, are in clinical development [36]. The combined targeting of the IL-13 and IL-33 pathways, therefore, represents a promising strategy for treating type 2 inflammation-associated immune disorders. Taken together, these findings indicate that IL-33-mediated type 2 inflammation can be successfully ameliorated in animal models of allergic disorders, and that the utility of IL-33 blocking agents merits further investigation in clinical allergy studies.

Skin diseases

The overexpression of IL-33 in the epidermis leads to a spontaneous atopic dermatitis (AD)-like phenotype [37]. IL-33 blockade and deficiencies in *IL33* or *IL1RL1* have been shown to reduce the severity of AD in mouse models [38, 39]. Reduction of the secretion of IL-33 is associated with attenuated disruption of epithelial tight junctions [40]. Although IL-33 is pathogenic in AD models, a tissue-reparative function of IL-33 was demonstrated in wound-healing models. IL-33 treatment improves wound healing in diabetic mice by enhancing M2 macrophage polarization [41] or the expansion of ILC2s [42].

Cardiovascular system

In the cardiovascular system, IL-33 likely functions as a cardioprotective cytokine. In myocardial pressure overload-induced cardiac fibrosis and hypertrophy models, deficiency of *IL1RL1* exacerbates transaortic constriction (TAC)-induced cardiac fibrosis, whereas exogenous IL-33 attenuates pressure overload-induced cardiac injuries [43-45]. In addition, administration of IL-33 reduces the development of atherosclerosis via IL-5 [46]. IL-33 is also protective in a mouse model of ischaemic cardiac injury by reducing cell death of cardiomyocytes [47, 48]. In coxsackiesvirus group B3 virus (CBV3)-induced viral myocarditis, the delivery of an IL-33-expressing plasmid reduces myocarditis via expansion of M2 macrophages [49]. IL-4 neutralization abolishes IL-33-mediated cardiac functional improvement in mice with myocarditis [49].

Interestingly, another study showed that IL-33 promotes eosinophilic pericarditis in CBV3-induced myocarditis, and that sST2 treatment improves systolic functions [50]. The potential use of exogenous IL-33 as a therapeutic for the treatment of cardiovascular disease

without triggering unwanted immune activation remains a challenging issue; it awaits further comprehensive pharmacological kinetic studies to define the optimal route, timing, and dosages in different disease models.

Kidney diseases

Several studies have revealed the pathological roles of IL-33 in renal ischaemia-reperfusion injury (IRI) [51], cisplatin-induced acute kidney injury (AKI) [52], and ovalbumin-induced nephrotoxicity models [53]. Intriguingly, a beneficial function of IL-33 has also recently been reported in a study that developed a hybrid IL-2–IL-33 fusion; researchers observed a protective role for the fusion protein in kidney IRI models, mediated via the expansion of renal ILC2s [54]. Short-term treatment with IL-33 also leads to the sustained expansion of renal ILC2s and protects against adriamycin-induced glomerulosclerosis [55]. IL-33/ST2 signalling likely functions as a double-edged sword, and participates in both the pathological and tissue-reparative processes in different kidney diseases, by affecting various cell types at different phases of disease progression [56].

Gastrointestinal diseases

The IL-33/ST2 axis is important for the maintenance of the epithelial integrity of the gastrointestinal tract [57]. Similar to its roles in the cardiovascular and central nervous system, IL-33 plays both beneficial and pathological roles in gastrointestinal diseases [57]. In mouse models of experimental colitis induced by dextran sulphate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS), deficiency of the *IL33* or *IL1RL1* genes leads to amelioration of the disease, compared to its outcome in wild-type control mice, and treatment with an ST2 blocking antibody ameliorates experimental colitis by enhancing mucosal healing in mice [58]. However, other studies have shown that administration of recombinant IL-33 ameliorates TNBS-induced inflammatory bowel disease (IBD) in mice [20, 59]. Intriguingly, treatment with IL-33 at the onset of DSS-induced colitis exacerbates the disease severity, whereas treatment with IL-33 during the recovery phases ameliorates DSS-induced colitis. These findings indicate that IL-33-mediated protection may be time-dependent and act via the regulation of Tregs during disease onset [59, 60]. Another report demonstrated that IL-33-mediated ILC2–amphiregulin–EGFR signalling protects against DSS-induced intestinal inflammation [61]. The balance between IL-33-mediated tissue inflammation and repair must be further addressed in these models to evaluate the potential therapeutic applications of IL-33.

Central nervous system

In the setting of experimental ischaemic stroke, exogenous IL-33 is protective; it reduces brain inflammation and the development of lesions [62-64]. In spinal cord injury models, IL-33 mediates neuronal protection via type 2 immune responses [65, 66]. Although IL-33 is likely to be neuroprotective in stroke and spinal cord injury models, the development of an effective strategy for the delivery of recombinant protein to the injured brain tissue remains a challenging issue that awaits further study.

In a mouse model of Alzheimer's disease, the administration of IL-33 ameliorates disease progression and prevents cognitive decline [66]. Conversely, IL-33 mediates pathogenic eosinophilic responses in *Angiostrongylus cantonensis* infection-induced meningitis, and antibodies against ST2 or IL-33 blockade reduce disease severity [66-68]. In the model of experimental autoimmune encephalomyelitis (EAE), IL-33 blockade mediates both pathogenic and protective roles [69-71]. Collectively, the data indicate that IL-33 likely mediates neuroprotective functions in various brain injury models. However, IL-33-sensitized type 2 inflammation may be pathogenic in the context of infection or autoimmune disorders [72].

Conclusion

IL-33 exhibits diverse immune regulatory functions during the various phases of different diseases. IL-33 likely functions as a disease sensitizer and plays pathological roles in inflamed tissues in allergic disorders that involve hyperreactive immune responses. In contrast, IL-33 also mediates tissue-protective functions during the recovery phase following tissue injury, which involves activation of tissue-reparative M2 macrophages [41], ILC2s [42], and Tregs [73]. Therefore, determining how to fine-tune and appropriate time to manipulate IL-33/ST2 signalling is crucial for treating inflammatory diseases characterized by immune imbalance.

Given their central roles in the regulation of immune responses, cytokines are appealing targets for therapeutic intervention. IL-33/ST2 signalling has diverse cellular targets and functions. Neither the pathological functions nor the physiological functions of this cytokine in human diseases are fully understood, and await additional exploration. Pinpointing the specific roles of IL-33 in genetically modified mice will allow us to better understand its roles in the pathogenesis of inflammatory diseases. A better understanding of the molecular mechanism by which IL-33/ST2 signalling is involved in pathological immune disorders will facilitate the development of novel therapeutic strategies that target IL-33 and ST2 signalling. Monoclonal antibodies against IL-33 or ST2 are under development by pharmaceutical companies and in phase I–II clinical trials for the treatment of allergic diseases. The combination of IL-33 blockade with other therapeutics could be an option for the efficacious treatment of inflammatory diseases. However, the key to best therapy is to determine the various components of combination. It is currently too early to answer this question because the scientific evidence is insufficient. Further studies comparing the efficacies of different therapeutic combinations will help answer these questions.

Abbreviations

IL (interleukin); ST2L (full-length transmembrane ST2); sST2 (soluble ST2); ILC2 (group 2 innate lymphoid cell); AD (atopic dermatitis); IL-33 (Trap, fusion of sST2 with the accessory protein IL-1RAcP); CBV3 (coxsackiesvirus group B3 virus); IRI (ischaemia–reperfusion injury); AKI (acute kidney injury); DSS (dextran sulphate sodium); TNBS (trinitrobenzene sulfonic acid); EAE (experimental autoimmune encephalomyelitis).

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Disclosure Statement

The authors declare no conflicts of interest.

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