

# Crucial and Diverse Role of the Interleukin-33/ST2 Axis in Infectious Diseases

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**Interleukin-33 (IL-33) has now emerged as a cytokine with diverse and pleiotropic functions in various infectious and inflammatory diseases. IL-33 is expressed by epithelial cells, endothelial cells, fibroblasts, and hepatocytes. The target cells of IL-33 are Th2 cells, basophils, dendritic cells, mast cells, macrophages, NKT cells, and nuocytes, newly discovered natural helper cells/innate lymphoid cells bearing the ST2 receptor. IL-33 has dual functions, both as a traditional cytokine and as a nuclear factor that regulates gene transcription. IL-33 functions as an “alarmin” released following cell death, as a biomarker, and as a vaccine adjuvant, with proinflammatory and protective effects during various infections. The exacerbated or protective role of the IL-33/ST2 axis during different infections is dependent upon the organ involved, type of infectious agent, whether the infection is acute or chronic, the invasiveness of the infectious agent, the host immune compartment, and cellular and cytokine microenvironments. In this review, we focus on recent advances in the understanding of the role of the IL-33/ST2 axis in various viral, bacterial, fungal, helminth, and protozoal infectious diseases gained from animal models and studies in human patients. The functional role of IL-33 and ST2 during experimentally induced infections has been summarized by accumulating the data for IL-33- and ST2-deficient mice or for mice exogenously administered IL-33. In summary, exploring the crucial and diverse roles of the IL-33/ST2 axis during infections may help in the development of therapeutic interventions for a wide range of infectious diseases.**

The interplay between pathogens and the host immune responses is crucial and determines the outcome of a disease process. The host-pathogen interaction at the cellular and molecular levels is very important for the elimination of the pathogen and mechanism of development of disease. Among them, the cytokine immune response plays a vital role in the orientation of the immune response during the course of disease or infection. The cytokine interleukin-33 (IL-33) is a member of the IL-1 family and was discovered in 2005 (1). First described as an alarmin, IL-33 has been shown to induce multivalent functions, resulting in pro- or anti-inflammatory effects in various pathologies (2). During infection, protective or deleterious functions of IL-33 highly depend on the organ involved, the cytokine microenvironment, and the type or stage of infectious disease (Fig. 1). Recent data have shown that IL-33 may serve as a biomarker associated with the severity of some infectious diseases.

In contrast to other IL-1 family cytokines, the full-length bioactive form of IL-33 is released by necrotic cells following cell damage or tissue injury and acts as an endogenous danger signal, or alarmin (3–6). On the contrary, apoptotic caspases cleave IL-33 and destroy its bioactivity (3, 7). Despite this paradigm, IL-33 can also be released by living cells in its full-length bioactive form (8). IL-33 is constitutively expressed by tissue barrier cells, such as the epithelial and endothelial cells of many organs (1, 2), and it is also expressed in other cell types, including innate immune cells (1, 9), fibroblasts (5, 9, 10), and hepatocytes (11). Once secreted, IL-33 binds to its specific receptor, ST2. Membrane-bound ST2 recruits the IL-1 receptor accessory protein (IL-IRAcP), leading to the activation of MyD88 and the NF- $\kappa$ B signaling pathway (2), whereas soluble ST2 (sST2) is a decoy receptor of IL-33 (12). The target cells of IL-33 include B cells, T helper 2 (Th2) cells, T CD8<sup>+</sup> cells, macrophages, dendritic cells, basophils, and a recently identified

population of innate lymphoid cells called nuocytes in different tissues, including lungs, gut, liver, spleen, and skin (1, 13–16). IL-33 is mainly associated with the initiation or progression of specific Th2 responses through secretion of IL-5 and IL-13. IL-33 contributes to macrophage alternative polarization, dendritic cell regulation, and direct effects on T cells (1, 17–20). These pleiotropic effects explain how IL-33 plays contrasting roles in human diseases. It is deleterious in autoimmune diseases, such as rheumatoid arthritis (21, 22) or inflammatory bowel disease (23), and in asthma/allergic diseases (24, 25). However, IL-33 is cardio-protective and plays a beneficial role in metabolic diseases (26) and in many diseases associated with an exacerbated Th1 response, such as atherosclerosis (27). Although IL-33 has been extensively studied in the setting of various inflammatory diseases, a comprehensive overview on the role of this cytokine during infectious diseases is actually lacking. Therefore, based upon our findings and other published data, we have reviewed the role of the IL-33/ST2 axis during viral, bacterial, fungal, and parasitic infections in animal models and human patients.

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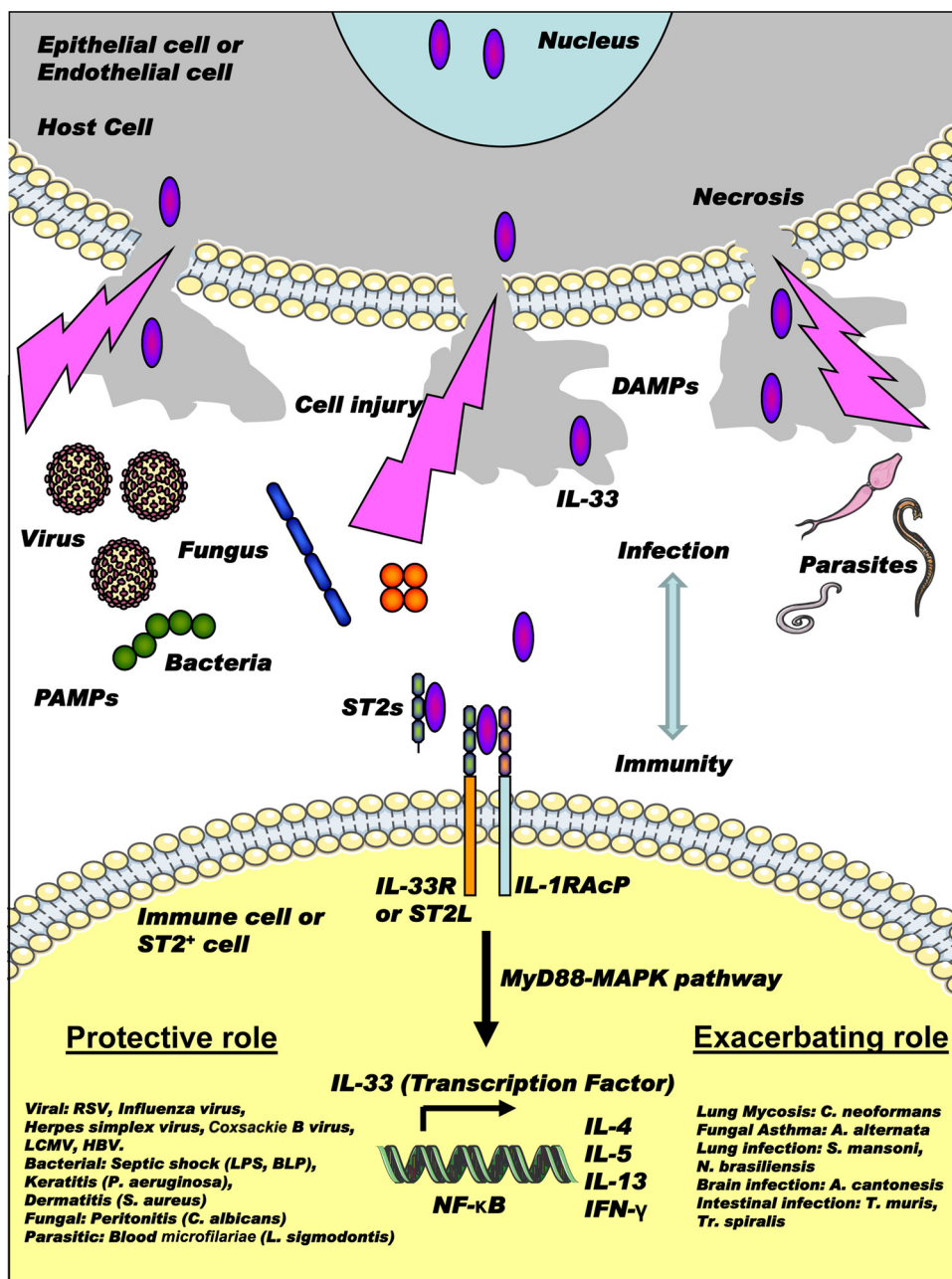
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**FIG 1** Diverse role of the IL-33/ST2 axis during microbial infections. The alarmin cytokine IL-33 is released during viral, bacterial, fungal, and parasitic infections of host cells or during cellular demise. IL-33 interacts with ST2-bearing immune cells to induce secretion of various cytokines. IL-33/ST2 signaling is mediated by the MyD88/mitogen-activated protein kinase/NF- $\kappa$ B pathway. The IL-33/ST2 axis plays a dual-edge function, as it either is protective, for example, in RSV, influenza virus, herpes simplex virus, coxsackie B virus, LCMV, HBV, septic shock (LPS, BLP), keratitis (*P. aeruginosa*), dermatitis (*S. aureus*), peritonitis (*C. albicans*), or blood microfilaria (*L. sigmodontis*) infections, or has an exacerbating role in Th2-biased lung mycosis (*C. neoformans*), fungal asthma (*A. alternata*), lung infection (*S. mansoni*, *N. brasiliensis*), brain infection (*A. cantonesis*), or intestinal infections (*T. muris*, *T. spiralis*). At the nucleus level, IL-33 acts also as a transcription repressor. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns.

### THE IL-33/ST2 PATHWAY AND VIRAL INFECTIONS

The control of viral infection is mainly dependent on a Th1-polarized immune response. Since IL-33 is classically described as a Th2 cytokine, it plays a deleterious role during several viral infections, as summarized in Table 1.

IL-33 and ST2 are mainly associated with a Th2 inflammatory response in experimental viral infection models. In the

mouse model of respiratory syncytial virus (RSV) infection, ST2 was shown to be expressed by a subpopulation of CD4<sup>+</sup> T cells infiltrating the lungs during a Th2-driven eosinophilic illness following attachment of RSV proteins (28). The blockade of ST2 via use of a monoclonal antibody reduced lung inflammation and disease severity in mice following RSV infection. Such a strategy could be a promising therapeutic perspective against Th2-driven

TABLE 1 Role of the IL-33/ST2 axis during viral diseases

Disease or pathogen	Species involved	Principal findings	Reference(s)
Bronchiolitis	Mouse	Reduction of inflammation and severity of RSV-induced lung infection by blockage of ST2 receptor	28
Influenza	Mouse	Induction of IL-33 in pulmonary endothelial cells and alveolar epithelial cells after influenza virus infection	29
	Human	Overexpression of IL-33 in human epithelial cell line MLE-15 in response to different strains of influenza virus	29
	Mouse	Production of IL-13 by ST2 <sup>+</sup> auxiliary lymphoid cells in response to IL-33 induced by alveolar macrophages following virus infection	30
	Mouse	Blockage of IL-33 results in repression of pulmonary functions and remodeling/repair of tracheal passage due to suppression of innate lymphoid ST2 <sup>+</sup> cells	31
	Mouse	As a vaccine adjuvant with viral hemagglutinin protein, IL-33 enhanced the production of IgG and IgA protective antibodies and Th1/Th2 cytokines in mice	33
Herpes simplex virus	Mouse	IL-33 from keratinocytes induces TNF- $\alpha$ and IL-6 expression in mast cells, leading to a protective immune response	34
Coxsackie B virus	Mouse	IL-33 enhances production of IFN- $\gamma$ and TNF- $\alpha$ by CD8 <sup>+</sup> T and NK cells and triggers production of IL-4 from mast cells, leading to attenuation of inflammatory pancreatitis	35
Lymphocytic choriomeningitis virus	Mouse	Endogenously secreted alarmin IL-33 from necrotic cells favors activation, clonal expansion, and cytotoxic activity of CD8 <sup>+</sup> ST2 <sup>+</sup> T lymphocytes	36
Dengue fever	Human	Elevated sST2 levels in serum of patients infected with dengue virus	37, 38
	Human	sST2 levels are associated with disease severity and proinflammatory cytokines	38
	Human	IL-33 levels are inversely correlated with platelet counts and positively correlated with serum transaminases	37
AIDS	Human	Increased serum level of sST2 and decreased IL-33 observed in HIV patients vs healthy controls	39
Viral hepatitis	Human	Elevated serum levels of IL-33 in chronically infected HBV patients; IL-33 decrease after IFN treatment	41
	Human	Elevated serum levels of IL-33 and AST/ALT <sup>a</sup> are correlated in chronically infected HCV patients, and IL-33 levels were decreased following IFN treatment	42
	Human	Overexpression of IL-33 in vascular endothelial cells, sinusoidal endothelial cells, and fibroblasts during liver fibrosis in humans infected with HBV/HCV	10
	Mouse	IL-33 is overexpressed in hepatocytes during acute hepatitis in mice experimentally infected with MHV3	43

<sup>a</sup> AST, aspartate transaminase; ALT, alanine aminotransferase.

lung injuries due to viruses (28). During influenza virus infection, IL-33 is highly overexpressed in mouse lungs, both in endothelial and alveolar epithelial cells (29). This overexpression is correlated with proinflammatory cytokine expression (tumor necrosis factor alpha [TNF- $\alpha$ ], gamma interferon [IFN- $\gamma$ ], IL-1 $\beta$ , and IL-6), as well as IFN- $\beta$  expression. *In vitro*, infection of human epithelial MLE-15 cells with different influenza virus strains also induced IL-33 overexpression, suggesting a role for IL-33 in the lung immune response against influenza virus in both humans and mice (29). In addition to endothelial and epithelial cells, alveolar macrophages are able to express IL-33 in response to influenza virus infection, leading to IL-13 production by resident non-B non-T ST2<sup>+</sup> innate lymphoid cells in mice (30). Such a mechanism contributes to airway reactivity and could partially explain severe forms of flu-associated asthma in humans (30). Another study confirmed the existence of these new resident innate cells in lungs of both humans and mice (31, 32). However, the suppression of these cells or treatment with recombinant IL-33 (rIL-33) both impaired lung function and airway modeling in mice. This result suggests a critical role for IL-33-dependent innate lymphoid cells in airway epithelium repair after influenza virus infection, through amphiregulin production and epithelial growth factor receptor (EGFR) activation (31, 32). Regarding these results,

IL-33 could be protective in this special case with differential functions, depending on the experimental model and the induced pathology. Thus, the targeting of IL-33 synthesis and of its responding cells as a therapeutic strategy against flu and other airway infections needs to be considered with caution (31, 32).

In addition, some authors have hypothesized that IL-33 could serve as an adjuvant for vaccine development against viruses. A mucosal vaccine containing recombinant influenza virus hemagglutinin and IL-33 as an adjuvant was intranasally administered in a mouse model (33). Mice showed significantly higher levels of specific IgG in the plasma and IgA in mucous secretions, with higher levels of both Th1 and Th2 cytokines leading to significant protection against a lethal influenza virus infection compared to control mice without adjuvant IL-33. The efficacy of adjuvant IL-33 was significantly reduced in mast cell-deficient mice, showing the important role of this cell population in the induction of specific mucosal immunity (33). Another study pointed out the link between IL-33 and mast cells. IL-33 expressed by keratinocytes infected with herpes simplex virus induces the expression of TNF- $\alpha$  and IL-6 in mast cells, leading to a protective immune response (34). Similar to other intracellular infections, the control of coxsackie B virus infection is associated with Th1 cells producing IFN- $\gamma$  and TNF- $\alpha$ , but an exacerbated Th1 response may lead

to injurious inflammatory lesions (35). In a model of mice treated with recombinant IL-33, IL-33 was shown to enhance the production of IFN- $\gamma$  and TNF- $\alpha$  by CD8<sup>+</sup> T and NK cells, which is associated with viral clearance (35). IL-33 also triggers the production of IL-4 by mast cells, leading to attenuation of inflammatory pancreatitis through alternative macrophage and T regulatory cell differentiation. These data further suggest a novel approach in treating virus-induced pancreatitis (35).

Finally, in a model of lymphocytic choriomeningitis virus (LCMV) infection, the IL-33 released by necrotic cells enhanced activation and clonal expansion of ST2<sup>+</sup> CD8<sup>+</sup> T lymphocytes for cytotoxic responses against viral infection in mice (36). Moreover, injection of recombinant IL-33 increased the cytotoxic T cell response induced by a nonreplicative adenovirus vaccine, showing its protective role in that model (36).

**Circulating soluble ST2 in humans: a potential biomarker in viral infections.** Clinical studies have been performed to determine circulating levels of IL-33 and soluble ST2 (sST2) during the course of viral diseases. Elevated serum sST2 levels have been found in patients with dengue fever, especially in patients with secondary infection, compared with other febrile patients (37). This high sST2 level was negatively correlated with platelet and other blood cell counts and positively correlated with thrombin time and transaminase activity. The sST2 level significantly decreases with defervescence and could thus be a potential marker of severity of dengue virus infection (37). Another recent study reported high levels of sST2 and IL-33 during dengue fever in infants with severe myocarditis (38). Whereas IL-33 levels were similar between patients and healthy subjects, high sST2 levels have been observed and correlated with (i) the severity of the disease, (ii) the level of creatine kinase isoenzyme MB, and (iii) the level of circulating proinflammatory cytokines, such as IL-6 and IL-8. Conversely, sST2 levels were inversely correlated with blood cell counts. These results suggest once more that ST2 could be a predictive marker of dengue fever severity that could be used in combination with clinical algorithms (38). More studies with larger patient cohorts are needed to confirm these results and to determine the cellular sources of sST2.

The IL-33/ST2 axis has also been studied for AIDS infection. High levels of sST2 have been detected in the serum of patients infected with human immunodeficiency virus (HIV) compared to levels in atopic dermatitis patients and healthy people (39). In contrast, IL-33 levels were lower in HIV-infected patients than in controls, with a decreasing tendency correlated with disease severity. Therefore, a decrease of CD4<sup>+</sup> T cells due to virus infection, high sST2 levels, and low IL-33 levels could represent surrogate markers of immunodeficiency during opportunistic HIV infections in humans (39).

**The IL-33/ST2 axis during hepatotropic viral infections.** In a mouse model of viral hepatitis induced by adenovirus, IL-33 and ST2 were expressed in the liver during the first week of infection and were associated with attenuated liver injury due to an increase in T regulatory cells but a decrease in macrophages, dendritic cells, and NK cells in the liver (40). If IL-33 enhances both Th1 and Th2 cytokines, it repressed TNF- $\alpha$  expression in the liver through direct effects and nuocyte activation. Thus, IL-33 acts as a potent immune stimulator and a hepato-protective cytokine in acute viral hepatitis and could be a potentially promising therapeutic candidate for the management of viral hepatitis (40).

Finally, the role of the IL-33/ST2 axis has been studied during

hepatitis B and C virus (HBV and HCV) infections in humans. In patients with chronic hepatitis B, the serum level of IL-33 was significantly higher than in healthy people. The level of cytokine decreased in serum in response to a 12-week treatment with adefovir dipivoxil (41). During hepatitis C, the serum level of IL-33 correlated with transaminase levels and was higher in patients with chronic hepatitis than in patients who spontaneously recovered or in healthy people (42). Similar to hepatitis B, the IL-33 level decreased after a 12-week interferon treatment (42). Thus, IL-33 is associated with hepatic damage in hepatitis B and C. These results are supported by previous work by our team. We found an association between IL-33 and ST2 overexpression in the liver and hepatic fibrosis during chronic HBV, HCV, and alcoholic hepatitis (10), while hepatic stellate cells and liver sinusoidal endothelial cells have been shown to be the main sources of IL-33 during liver fibrosis in both mice and humans (10). The cellular sources of IL-33 are sinusoidal endothelial cells, vascular endothelial cells, and hepatocytes in murine models of acute viral hepatitis induced by the toll-like receptor 3 (TLR3) activator viral mimetic poly(I·C) or by the pathogenic mouse hepatitis virus 3 (MHV3) (43).

### THE IL-33/ST2 AXIS AND BACTERIAL INFECTIONS

IL-33 signaling via ST2 is described as a downregulating mechanism of the TLR pathway (44, 45) and has been associated with different diseases involving specific recognition of bacterial pathogens by these receptors. The involvement of the IL-33/ST2 axis in bacterial infections is summarized in Table 2.

**The IL-33/ST2 axis promotes neutrophil influx and bactericidal activity during sepsis.** Since different TLRs induce similar signaling pathways, their concomitant activation by a large number of pathogens could have a synergistic, deleterious effect during sepsis, inducing important tissue damage. However, moderate activation of TLRs in response to bacterial infections could reduce the immune activation threshold, allowing better tolerance to endotoxins and more efficient bacterial clearance in subsequent infections (46). This theory was supported by a study in which pretreatment with TLR agonists promoted the control of further infection in a model of murine septic peritonitis (44, 47, 48). This protecting mechanism was associated with the recruitment of neutrophils in the peritoneal cavity and with cytokine repression partially due to a default in MyD88 activity. ST2 has been described as a repressor of the TLR2 and TLR4 pathways because it is able to sequester MyD88 in this model. Therefore, ST2 contributes to lipopolysaccharide (LPS) tolerance; however, it is dispensable for the tolerance induced by bacterial lipoprotein (BLP), as ST2-deficient mice showed improved survival against a lethal dose of BLP (44, 47, 48). The plausible reason may be due to differences in reprogramming of the intracellular transduction signaling and mechanism of antimicrobial activity between TLR2-mediated tolerance (BLP tolerance) and TLR4-mediated tolerance (LPS tolerance). Mice treated with recombinant IL-33 showed an important neutrophil influx compared with nontreated mice, and this led to more efficient bacterial clearance (49). CXCL2 and IL-8/KC are key chemokines for neutrophil recruitment during bacterial infections. The activation of the TLR4/MyD88 pathway inhibited CXCR2 expression in neutrophils; however, IL-33 reversed this inhibition pathway and promoted neutrophil influx to allow efficient sepsis control (49). Alternatively, the IL-33/ST2 pathway has protective functions against sepsis through other mechanisms. IL-33 was shown to repress GRK2, a serine-threonine kinase re-



TABLE 2 Associations of the IL-33/ST2 axis with bacterial diseases

Disease or pathogen	Species involved	Principal findings	Reference
Septic shock	Mouse	Tolerance to bacterial LPS is induced by inhibiting the TLR4 pathway via blockade of IL-1R and MyD88 by ST2	44
	Mouse	Overexpression of ST2 occurs in response to pretreatment with a TLR2 agonist in a model of septic peritonitis	47
	Mouse	ST2 represses the TLR2 pathway in a dose-dependent manner in BLP-stimulated macrophages; ST2-deficient mice primed with a sublethal dose of BLP showed improved survival against lethal BLP challenge	48
	Mouse	IL-33 prevents TLR4-mediated downregulation of CXCR2 expression in neutrophils and their chemotaxis; IL-33 treatment facilitates influx of neutrophils and prevents sepsis induced by cecal ligation and puncture	49
	Mouse	ST2-deficient mice are more susceptible to septic shock due to inefficient phagosome maturation, decreased NOX2, and free radical production	18
	Human	Elevated plasma concentration of sST2 in sepsis patients vs healthy controls following trauma or abdominal surgery	54
	Human	Increased sST2 correlates with severity of disease and mortality after sepsis in humans	55
Keratitis	Mouse	Blocking ST2 in mice leads to increased corneal bacterial ( <i>P. aeruginosa</i> ) changes associated with overexpression of proinflammatory and Th1 cytokines	53
	Mouse	Decrease in bacterium-induced changes ( <i>P. aeruginosa</i> ) in response to rIL-33 treatment in mice is associated with polarization of M2 macrophages and Th2-mediated immune response	17
Leptospirosis	Human	Circulating sST2 in patients is correlated with hemorrhage and mortality during severe leptospirosis	56
Tuberculosis	Mouse	No evident difference in bacterium-induced pulmonary changes found between wild-type and ST2 <sup>-/-</sup> mice despite modest induction of Th1 polarization in ST2 <sup>-/-</sup> mice	58
Skin infection	Mouse	Upregulation of IL-33 mRNA and protein during cutaneous infection with methicillin-resistant <i>S. aureus</i> ; injection of rIL-33 prevents <i>S. aureus</i> colonization and accelerates cutaneous wound healing	52
	Human	Expression of IL-33 was increased in skin of <i>S. aureus</i> -infected patients compared to healthy controls	51

responsible for the internalization of chemokine receptors, including CXCR2, in neutrophils in response to TLR4 activation. This mechanism promotes neutrophil recruitment during experimental cecal ligation and puncture-induced sepsis (49). Moreover, ST2-deficient mice show an increased susceptibility to sepsis due to a default in bactericidal activity. Indeed, an inefficient maturation of phagosomes and a strong repression of NOX2 led to limited production of reactive oxygen species and a default in bactericidal activity (50).

**IL-33 has antimicrobial and wound-healing effects during skin infections.** In the skin, IL-33 is abundantly expressed in *Staphylococcus aureus*-infected patients compared to healthy subjects. In a mouse model of *S. aureus* skin infection, staphylococcal peptidoglycan (PGN) and lipoteichoic acid (LTA) activated the TLR2 signaling pathway, leading to IL-33 overexpression in dermal macrophages (51). In this model, IL-33 improved the antimicrobial capacity of dermal macrophages with increased nitric oxide (NO) production via inducible NO synthase (iNOS). The inhibition of iNOS with aminoguanidine significantly blocked the capacity of IL-33 to inhibit the growth of *S. aureus*, whereas IL-33 silencing in macrophages significantly increased survival of *S. aureus* in macrophages (51). In another study, recombinant IL-33 administration on *S. aureus*-infected skin promoted the proliferation of neutrophils and CXCR2 expression and consequent neutrophil influx into infectious sites for wound healing (52). Wound healing has also been found associated with collagen and fibronectin synthesis in response to recombinant IL-33 (52). Thus, IL-33 has protective antimicrobial and wound-healing effects during skin bacterial infections.

**IL-33 and ST2 contribute to corneal resistance against *Pseudomonas aeruginosa*.** IL-33 and ST2 are both expressed in the normal cornea in resistant BALB/c mice and susceptible C57BL/6 mice. In a model of corneal infection, the IL-33/ST2 expression

levels were significantly higher in infected BALB/c mice than in C57BL/6 mice and decreased after 5 days (17, 53). In BALB/c mice, the use of a blocking fusion protein, ST2-Fc, led to impaired control of the bacterial load, improved neutrophil influx, increased levels of proinflammatory and Th1 cytokines in the cornea, and decreased levels of Th2 cytokines (53). On the contrary, the injection of recombinant IL-33 into C57BL/6 mice led to better control of the bacterial load, decreased neutrophil influx, decreased levels of proinflammatory and Th1 cytokines in the cornea, and overexpression of Th2 cytokines (IL-4, IL-5, and IL-10) (17). This improved Th2 response led to a preferential M2 polarization of macrophages in response to IL-33 both *in vitro* and *in vivo*. The macrophage phenotype was notably characterized by the expression of arginase, IL-5, and IL-10 rather than iNOS, IL-12, and IFN- $\gamma$  (17). In this model, the neutrophil recruitment by IL-33 has a deleterious effect on the outcome of infection compared with some viral infections.

**Circulating soluble ST2: a biomarker of severity of bacterial infection.** During sepsis, it was shown in clinical studies that an increased sST2 plasma concentration was significantly correlated with the severity of disease and with patient mortality (54, 55). Another study showed that people who recovered from sepsis displayed significantly lower sST2 plasma levels than did patients who died from sepsis (49). These results reinforced the idea of measuring sST2 as a marker of disease severity. sST2 levels correlate with hemorrhages and mortality in patients with severe forms of leptospirosis (56). *In vitro*, peripheral blood mononuclear cells infected with leptospires did not secrete sST2, suggesting that sST2 was released following tissue damage in severe cases (56).

In pregnant women, preterm premature rupture of membranes is mostly induced by subclinical intrauterine bacterial infections, which increase mortality and morbidity (57). In a group of women with preterm premature membrane rupture associated

TABLE 3 Involvement of the IL-33/ST2 axis during fungal diseases

Disease or pathogen	Species involved	Principal findings	Reference
Fungal peritonitis	Mouse	Pretreatment with IL-33 ameliorated clearance of <i>Candida albicans</i> and survival of mice that was associated with increased infiltration of neutrophils and phagocytes	59
Bronchopulmonary mycosis	Mouse	Th2 cytokines produced by ST2 <sup>+</sup> T lymphocytes resulted in defective pulmonary <i>Cryptococcus neoformans</i> fungal control	60
	Mouse	BALB/c mice infected with <i>C. neoformans</i> revealed induction of IL-33 with accumulation of type 2 pulmonary innate lymphoid cells and activated macrophages in lungs; ST2-deficient mice infected with <i>C. neoformans</i> showed improved survival rate and decreased fungal burdens in lungs, spleen, and brain compared to wild-type control	61
Fungal asthma	Mouse	IL-33 was secreted during <i>Alternaria alternata</i> infection, with production of IL-5 and IL-13 by innate lymphoid cells and eosinophilic infiltration	63
	Mouse	<i>A. alternata</i> induced abrupt increase in airway levels of IL-33 accompanied by ST2 <sup>+</sup> natural helper cell (NHC) production of IL-5 and IL-13; STAT6 found to regulate <i>Alternaria</i> -induced lung NHC proliferation and expression of amphiregulin	90
	Mouse	<i>Aspergillus fumigatus</i> -induced asthma in mice was significantly attenuated by treatment with anti-ST2L monoclonal antibody plus CpG	65

with histological chorioamnionitis, the levels of IL-33 and sST2 were significantly higher than in the control group. This study proposed IL-33 and ST2 as reliable predictive biomarkers to determine subclinical infection (57). Overall, the IL-33/ST2 axis seems to play an important regulatory function, repressing the TLR response and promoting a Th2 tolerogenic response. Such a pro-Th2 response could be harmful in the setting of infections due to intracellular pathogens, such as *Mycobacterium tuberculosis*, where the Th1 response is necessary for infection control (58). In a mouse model of tuberculosis, IL-33 was indeed shown to impair the protective Th1 response, but this effect seemed to have limited consequences, since ST2-deficient mice did not have better outcomes than wild-type mice (58).

### THE IL-33/ST2 AXIS AND FUNGAL DISEASES

The IL-33/ST2 pathway plays a crucial role during fungal diseases as well; a comprehensive summary is presented in Table 3.

**IL-33 improves neutrophil influx and microbicidal mechanisms in response to candidiasis.** The intraperitoneal injection of recombinant IL-33 before infection with *Candida albicans* in mice leads to fungal clearance and decreases mortality caused by fungal peritonitis (47, 49, 59). These observations can be explained by the increased production of both CXCL1 and CXCL2 by peritoneal macrophages and by the concomitant inhibition of CXCR2 repression induced by TLR in neutrophils, leading to an early and sustained neutrophil influx (47, 49, 59). In addition, the induction of TLRs and the Dectin-1 pathway following IL-33 treatment leads to overexpression of the complement receptor CR3 and an increase in production of reactive oxygen species, which promote yeast phagocytosis and destruction (59).

**The IL-33/ST2 pathway contributes to Th2-biased mycosis and fungal asthma.** A deleterious function during lung mycosis has been attributed to the pro-Th2 function of IL-33. In a mouse model of intranasal infection with *Cryptococcus neoformans*, ST2 overexpression was correlated with Th2 response activation (60). T helper ST2<sup>+</sup> lymphocytes significantly overexpressed IL-4, IL-5, and IL-13 compared to ST2<sup>+</sup> T helper cells and were associated with an inefficient control of fungal infection (60). In another study, ST2-deficient mice had improved survival and lower *C.*

*neoformans* burdens in the lungs, spleen, and brain (61). The ST2 deficiency led to a decrease in production of IL-5 and IL-13 by innate type 2 lymphoid cells and impaired Th2 mucosal immunity (61). These data suggest that the IL-33/ST2 pathway contributes to *C. neoformans* growth and its dissemination through a Th2-biased immune response.

IL-33 is classically described as a pro-Th2 factor that is associated with asthma (62). During fungal asthma, airway exposure to *Alternaria alternata* spores leads to an increase in IL-33 levels in fluid from bronchoalveolar washes in mice, leading to resident innate lymphoid cell activation, proliferation with subsequent IL-5 and IL-13 production, and eosinophil recruitment (63, 64). As observed during the course of the flu, these innate lymphoid cells induce amphiregulin expression in response to *Alternaria* and improve the EGFR pathways in the airway epithelium, a mechanism associated with the pathogenesis of asthma (64). These immune cells were also observed in bronchoalveolar lavage fluid from human patients and appeared to be a main actor in a novel mechanism associated with Th2 allergic diseases, including fungal asthma (64). Targeting the IL-33/ST2 pathway could thus offer new therapeutic opportunities in this setting. Recently, in an asthma model with C57BL/6 mice sensitized with *Aspergillus fumigatus*, the blockade of the ST2 receptor with a specific monoclonal antibody improved the effect of treatment with CpG oligodeoxynucleotides, leading to a switch from a Th2 response to protective Th1 immunity through TLR9 activation (65).

### ROLE OF IL-33/ST2 IN HELMINTH DISEASES

The efficient immune response against helminth parasites requires a Th2-biased response involving an interaction between IL-33 and its receptor, ST2. The role of the IL-33/ST2 axis in helminth infections is summarized in Table 4.

**IL-33/ST2 ambivalent functions in the lung during helminth infections.** In a mouse model of lung granuloma induced by *Schistosoma mansoni* eggs, ST2 deficiency downregulated the production of IL-4 and IL-5 and granuloma assembly, which is related to an influx of polymorphonuclear leukocytes (66). These data suggest a protective role of IL-33 via a Th2-dependent immune response. This result was strengthened by the observation of higher

TABLE 4 The IL-33/ST2 axis during helminth diseases

Disease or pathogen	Species involved	Principal findings	Reference
<i>Schistosoma mansoni</i>	Mouse	ST2-deficient mice exposed to <i>S. mansoni</i> eggs showed decrease in production of IL-4 and IL-5 and formation of pulmonary granulomas	66
	Human	Serum IL-33 was significantly elevated in patients with acute <i>S. japonicum</i> infection; IL-33 was significantly correlated with number of eosinophils and duration of infection	67
	Mouse	The IL-33 quickly induced after infection induced prompt expansion of IL-13-producing type 2 innate lymphoid cells, which are associated with airway contraction	70
<i>Nippostrongylus brasiliensis</i>	Mouse	IL-33 was overexpressed in lungs of <i>N. brasiliensis</i> -infected mice and was dependent on trefoil factor 2	69
	Mouse	IL-33-dependent production of IL-4, IL-5, and IL-13 in nuocytes in response to <i>N. brasiliensis</i>	73
	Mouse	IL-33-deficient mice showed limited elimination of <i>N. brasiliensis</i> and decreased production of IL-13 by Th2 innate lymphoid cells	72
	Mouse	ST2 <sup>+</sup> innate lymphoid cells participated in effective expulsion of <i>N. brasiliensis</i> by production of IL-4, IL-6, and IL-13	75
	Mouse	The transcriptional determinant Gfi1 promoted development of type 2 innate lymphoid cells and controlled their responsiveness to <i>N. brasiliensis</i> lung infection/inflammation; type 2 innate lymphoid cells showed preferential responsiveness to IL-33 via a Gfi- and IL-1rl1-dependent mechanism	91
<i>Strongyloides venezuelensis</i>	Mouse	IL-33 was produced by alveolar epithelial cells following <i>S. venezuelensis</i> infection, with IL-33-dependent induction of IL-5 and IL-13 by natural helper cells	71
<i>Angiostrongylus cantonesis</i>	Mouse	IL-33 and ST2 were overexpressed in brains of <i>A. cantonesis</i> -infected mice, with production of IL-5 and IL-13 by splenocytes and cerebral mononuclear cells	80
<i>Trichuris muris</i>	Mouse	Expression of IL-25 and IL-33 observed in mast cells during invasion by <i>H. polygyrus bakeri</i> or <i>T. muris</i>	76
	Mouse	IL-33 expressed during invasive intestinal <i>T. muris</i> infection in association with production of IL-4, IL-9, and IL-13	78
<i>Trichinella spiralis</i>	Mouse	Expression of IL-33 observed in cytoplasm of intestinal epithelial cells following invasive intestinal <i>T. spiralis</i> infection in mice, in association with Th2 cytokine response	79
<i>Litomosoides sigmodontis</i>	Mouse	ST2 deficiency in BALB/c mice led to significantly increased levels of peripheral blood microfilariae and filarial progeny without affecting adult worm burden following chronic <i>L. sigmodontis</i> infection; increased <i>L. sigmodontis</i> -associated microfilaremia in ST2-deficient mice due to an impaired splenic clearance of microfilariae	77

IL-33 levels in the serum of patients with acute schistosomiasis due to *Schistosoma japonicum* than in healthy subjects (67). A significant correlation was shown between the IL-33 level and eosinophil blood counts, as well as schistosomiasis disease duration (67). IL-33 was shown to be increased in the plasma of Malian patients infected with *Schistosoma haematobium* 9 weeks after treatment and was associated with increased intracellular IL-13 expression in eosinophils and disease recovery (68).

After *Nippostrongylus brasiliensis* infection in mice, IL-33 was overexpressed in lung epithelium, alveolar macrophages, and inflammatory dendritic cells in a trefoil factor 1-dependent pathway (69), leading to IL-13 secretion by nuocytes and airway hyperreactivity. Thus, IL-33 plays a deleterious role, in favoring an allergic response in this model (13). Using ST2- or IL-25 receptor-deficient mice or doubly deficient mice, IL-33 was found to induce airway hyperreactivity, whereas IL-25 induced slower and less potent responses (70). Similar to *N. brasiliensis*, *Strongyloides venezuelensis* infection (or chitin intranasal administration, which mimics parasitic invasion) increased IL-33 levels in alveolar epithelial cells, with IL-5 and IL-13 production by natural helper cells. However, in this model, IL-33 induced lung eosinophilic inflammation and played a protective role, since IL-33-deficient mice showed an impaired capacity to expel the worms from the lungs (71).

**Role of the IL-33/ST2 axis in secondary lymphoid organs during helminth infections.** In the liver, spleen, bone marrow, and mesenteric lymph nodes, Th2 innate lymphoid cells proliferate in response to IL-25 and IL-33 early after *N. brasiliensis* invasion *in vivo* (72–74). These cells are known as the major source of IL-13 and induce the induction of resistin-like beta (RELMp) and the recruitment of eosinophils, which contribute to worm clearance (72–74). The lack of IL-13 and the worm persistence in IL-33-deficient mice confirmed the pivotal role of IL-33 in the induction of a protective immunity that depends on innate lymphoid cells in the liver (72). Similarly, ST2<sup>+</sup> innate lymphoid cells have been recently described in a new type of secondary lymphoid organ associated with adipose tissue in the peritoneal cavity, fat-associated lymphoid clusters (FALC). In response to *N. brasiliensis*, these cells produce high levels of IL-5, IL-6, and IL-13, increase IgA production, and favor goblet cell hyperplasia, leading to worm expulsion (75). After invasion with two other worm species, *Heligmosomoides polygyrus bakeri* or *Trichuris muris*, the mast cells were described as regulators of IL-25 and IL-33 expression. Therefore, these cells could play a critical role in the development of a specific protective mucosal immunity during parasitic infections mediated by IL-33 (33, 76).

In ST2-deficient BALB/c mice infected with the filarial nema-

TABLE 5 IL-33/ST2 axis during protozoan diseases

Disease or pathogen	Species involved	Principal findings	Reference(s)
<i>Plasmodium falciparum</i>	Human	Plasma IL-33 increased in <i>P. falciparum</i> -infected children vs noninfected children; IL-33 level was positively correlated with parasitic charge	83
<i>Toxoplasma gondii</i>	Mouse	Increased susceptibility to cerebral infection by <i>T. gondii</i> in ST2 <sup>-/-</sup> mice that was associated with increased iNOS, TNF- $\alpha$ , and IFN- $\gamma$ production	85
<i>Leishmania major</i>	Mouse	IL-4-, IL-5-, and IL-10-expressing Th2 ST2 <sup>+</sup> lymphocytes and parasites accumulated in chronic cutaneous lesions experimentally infected with <i>L. major</i>	86, 87
	Mouse	Increased Th1 response without alteration of Th2 response following blockage of anti-ST2-Fc antibody treatment in experimentally infected mice vs control mice	88
<i>Leishmania donovani</i>	Mouse	BALB/c mice experimentally infected with <i>L. donovani</i> showed higher IL-33 in serum, with presence of IL-33 <sup>+</sup> cells and ST2 <sup>+</sup> cells in liver; ST2-deficient mice showed reduced hepatic parasitic burdens and reduced hepatomegaly vs wild-type controls	89
	Human	Higher level of IL-33 in serum of patients with visceral leishmaniasis than in healthy donors; presence of IL-33-positive cells in liver biopsy specimens from <i>Leishmania</i> -infected patients	89

tode *Litomosoides sigmodontis*, the level of peripheral blood microfilariae was significantly increased, whereas the *L. sigmodontis* adult worm burden was not affected (77). Therefore, the IL-33/ST2 pathway seems important for the splenic clearance of microfilariae from the peripheral blood and could be interesting in therapies intended to block the transmission of filarial disease (77).

**IL-33 and the protective immune response against intestinal worms.** In the mouse intestine, IL-33 is rapidly induced after *Trichuris muris* invasion and biases T cell polarization toward a Th2 response characterized by the production of IL-4, IL-9, and IL-13 (78). IL-33 thus plays a crucial role in the initiation of a protective antihelminth intestinal immunity, as shown by the improved *T. muris* worm expulsion in response to recombinant IL-33 in susceptible mice (78). Similarly, in response to *Trichinella spiralis*, IL-33 is constitutively expressed in intestine epithelial cells and contributes to the development of Th2 immunity depending on mast cells through ST2/MyD88 activation. In addition, after *T. spiralis* epithelial cell invasion, IL-33 translocates from the cytoplasm into the nucleus in safe, neighboring intestine epithelial cells through an innate mechanism independent of ST2 and MyD88, suggesting a nuclear function of IL-33 or regulation of its expression in intestinal cells (79). In skeletal muscles, where *T. spiralis* completes its life cycle, the parasite load is increased in ST2-deficient mice (79). Therefore, IL-33 could repress extra-intestinal invasion through the promotion of Th2 responses in lymph nodes that drain muscles (79).

**IL-33 is neuro-protective during angiostrongyliasis.** Finally, IL-33 and ST2 are overexpressed in the brain in mice infected with *Angiostrongylus cantonensis* (80, 81). In this model, splenocytes and mononuclear brain cells responded to IL-33 through production of IL-5 and IL-13, both of which contribute to eosinophilic meningitis induced by *A. cantonensis* (80, 81). The injection of a monoclonal anti-ST2 antibody 3 days postinfection with further injections every 5 days led to a significant reduction of IL-5 blood levels and of eosinophil influx in the meninges (82). Thus, blocking the IL-33/ST2 axis could be beneficial in minimizing the neurological damage caused by this parasitic infection (82). In summary, the IL-33/ST2 pathway is activated in numerous tissues, where it manages the initiation and progression of a Th2 immune response that can promote protective worm expulsion.

## PROTOZOAN INFECTIONS AND INVOLVEMENT OF THE IL-33/ST2 AXIS

A few studies have reported the role of the IL-33/ST2 axis in protozoan diseases, but a crucial role for IL-33/ST2 axis has been recently acknowledged during malaria, toxoplasmosis, and leishmaniasis (Table 5).

**IL-33 levels are increased during malaria.** During *Plasmodium falciparum* malaria, serum IL-33 levels are significantly higher in children with or without complications than in noninfected children (83). IL-33 levels are correlated with parasite load and strongly decrease with parasite clearance. The sequestration of infected erythrocytes or merozoite liberation from schizonts could amplify IL-33 production in endothelial cells, contributing to malaria pathogenesis (83).

**The IL-33/ST2 axis protects mice from TH1-induced damages in the brain during toxoplasmosis.** During toxoplasmosis, cytokines and chemokines are regulated with a delicate balance between a necessary Th1 response for the control of parasite proliferation and a Th2 regulating response to limit the pathology due to an exacerbated deleterious Th1 response (84). ST2 was overexpressed in the brains of mice infected with *Toxoplasma gondii* (85). In BALB/c mice, ST2 deficiency increased susceptibility to cerebral infection characterized by an increased parasite load and more severe encephalitis due to increased levels of iNOS, TNF- $\alpha$ , and IFN- $\gamma$ . Thus, IL-33 could play a regulatory role in the Th1/Th2 balance in this murine model of infection (85).

**The IL-33/ST2 pathway during leishmaniasis.** In BALB/c mice, infection with *Leishmania major* induces the differentiation of T helper cells into two populations of Th2 effector cells in lymphoid organs depending upon ST2 expression (86). ST2<sup>+</sup> CD4<sup>+</sup> lymphocytes secrete IL-4, IL-10, and IL-5, whereas ST2<sup>-</sup> CD4<sup>+</sup> T lymphocytes express IL-4 and IL-10 but not IL-5 (86). There are few ST2<sup>+</sup> Th2 lymphocytes in lymphoid organs, but they are enriched in cases of chronic ulcerative cutaneous lesions (which concentrate parasites) in BALB/c mice (87). The injection of a blocking antibody or an ST2-Fc fusion protein to inhibit the ST2 pathway does not impair Th2 cytokine production but improves the ability of CD4<sup>+</sup> T lymphocytes to produce IFN- $\gamma$  in response to IL-12. Thus, IL-33 seems to induce repression of the protective



Th1 response rather than the induction of Th2 cytokines during cutaneous leishmaniasis, as observed during murine tuberculosis (58, 88). During visceral leishmaniasis, a granulomatous response develops in the liver, with a delicate balance between an efficient Th1 response and a regulating Th2 environment with sequential recruitment of myeloid and lymphoid cells, which finally control the hepatic parasite load. We observed overexpression of both IL-33 and ST2 in liver granulomas during visceral leishmaniasis in an experimental mouse infection model with *Leishmania donovani* as well as in human patients with severe leishmaniasis (89). The ST2 deficiency in BALB/c mice infected with *L. donovani* is associated with overexpression of protective Th1 cytokines and a stronger influx of myeloid cells in the liver, which leads to better control of the hepatic parasite load. In contrast, repetitive intraperitoneal injections of recombinant IL-33 led to a drastic repression of key Th1 cytokines and impaired myeloid recruitment in the liver. The IL-33/ST2 axis is thus associated with Th1 repression rather than Th2 induction in the liver during visceral leishmaniasis, as observed during cutaneous leishmaniasis (89). Therefore, IL-33 appears to be a potent regulatory cytokine during visceral leishmaniasis in susceptible hosts. Moreover, elevated IL-33 serum levels in patients with progressive visceral leishmaniasis compared with healthy donors indicate IL-33 as a possible soluble marker in human leishmaniasis (89).

## CONCLUDING REMARKS

The IL-33/ST2 axis is crucially involved in various infections in humans and animals, and it plays a pivotal role in the development of infectious disease mechanisms. The double-edge functions of the IL-33/ST2 axis may provide insights for its therapeutic uses in various infectious diseases. Further studies will be required to correlate the animal model findings with experiences in human patients and to ascertain the role of the IL-33/ST2 axis in infection and immunity.

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