IL-33: a Janus cytokine

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ABSTRACT

Interleukin (IL) 33, a member of the IL-1 family, is the ligand of ST2 that is expressed mainly on activated Th2 cells and mast cells. IL-33 can skew a predominantly Th1 cell population to a mainly Th2 cells phenotype in vivo. IL-33 messenger RNA is expressed early during infection of the intestinal-dwelling nematode *Trichuris muris* in mice. IL-33 treatment enhances resistance to *Trichuris* infection. IL-33 also effectively attenuates sepsis by mobilising the innate cells, neutrophils, to the site of infection, helping to clear the pathogens. Thus, IL-33 may be evolutionally preserved for the host defence against infections. IL-33 can reduce an ongoing atherosclerosis in ApoE$^{-/-}$ mice and attenuate adipocytes mainly by inducing the production of type II cytokines. In contrast, IL-33 can also exacerbate allergy and the inflammation in collagen-induced or serum-induced arthritis. Hence, IL-33 is a double-edged sword, and targeting IL-33 should be approached with caution.

There has been considerable interest in the recently discovered cytokine, IL-33. IL-33 was identified[1] as a new member of the interleukin (IL)-1 cytokine family, which also includes IL-1α, IL-1β, IL-18 and IL-1Ra. Human IL-33 was detected in epithelial cells, fibroblasts[1] and endothelial cells of the inflamed tissues from patients with rheumatoid arthritis and Crohn's disease.[2] In rodents, IL-33 mRNA was detected in various tissues and organs including spleens and the central nervous system.[1] Different from IL-1 and IL-18, full-length IL-33 is bioactive and released most probably through cell necrosis and triggers inflammation in an autocrine or paracrine fashion.[3] IL-33 signals via a heteromeric receptor that consists of ST2 and the IL-1R accessory protein.[4] ST2,[5] also known as T1,[6] the membrane form of protein encoded by the *ST2* gene, is expressed on most cells especially on mast cells[7] and activated Th2 cells.[8] *ST2* is alternatively spliced to produce a soluble form (sST2), which acts as a decoy receptor.[9]

IL-33/ST2/IL-1R-associated kinase (IRAK) accessory protein coupling activates the MyD88/IRAK1/IRAK4 complex, which then activates the Mitogen-activated protein kinase kinase (MAPKK), Extracellular signal-regulated kinase (ERK), p38 and JUN N-terminal kinase (JNK), leading to the enhanced production of IL-5, IL-13, CCL5, CCL17 and CCL24. Down stream of the MyD88 complex, IL-33 also triggers the PLD/SpHK (phoshopholipase D/sphingosine kinase) complex, leading to calcium influx and the degradation of Inhibitor of kappa B (IKB), and then the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and the production of IL-1β, IL-3, IL-6, TNFα, CXCL2, CCL2, CCL3, Protaglandin D (PGD) and leukotriene B (LTB).[2] This signalling pathway naturally results in a complex range of biological functions. Some of the key functions in the disease context are summarised below. The evidence presented in this review is based mainly on the findings of my own research group rather than a comprehensive review of the current literature.

THE ROLE OF IL-33 IN INFECTIONS

Infection is the major driver of the evolution of the immune system. The preservation of IL-33 in the immune response suggests that IL-33 could play an important role in the defense against infection. During the experimental intestinal nematodes (*Trichuris muris*) infection in mice, IL-33 message is markedly elevated soon after infection. Treatment of the infected mice with recombinant IL-33 led to accelerated clearance of the worm burden. This is accompanied by marked increase in the number of mucus-producing goblet cells in the gut and the shortening of the caecal crypt length.[10] The protective effect of IL-33 in this infection model is associated with the activation of TSLP (thymic stromal lymphopoietin), which in turn enhances the Th2-mediated anti-parasitic immunity.

Recently, we have shown that IL-33 can also protect mice against experimental sepsis.[11] Mice undergoing caecal ligation and puncture developed acute polymicrobial sepsis, which was markedly attenuated by treatment with recombinant IL-33. IL-33 also elevated neutrophil influx into the peritoneum and greatly increased bacterial clearance. It turns out that IL-33 blocked the expression of the G-protein-coupled receptor kinase 2 (GRK2), which was upregulated by the Toll-like receptor signalling triggered during sepsis. The expression of GRK2 normally leads to the inhibition of the expression of CXCR2 on neutrophils and reduces neutrophil migration.[12] Thus, IL-33, by blocking GRK2 expression, reverses this process and leads to the influx of neutrophils to the site of infection and bacterial clearance. Importantly, neutrophils from patients who did not recover from sepsis expressed significantly less CXCR2 compared to those who eventually recovered from sepsis. Furthermore, the non-survivors also have more sST2 in their serum compared to the survivors. Since sST2 is a decoy receptor of IL-33, these finding suggests that IL-33 may be associated with a favourable outcome in clinical sepsis.

IL-33 ATTENUATES ATHEROSCLEROSIS

In common with other members of the IL-1 family, IL-33 is expected to play a significant

role in inflammation. One such example is in experimental atherosclerosis.

Atherosclerosis is a chronic inflammatory disease of the vasculature commonly leading to myocardial infarction and stroke. IL-33 and ST2 are present in the normal and atherosclerotic vasculature of mice and humans. IL-33 can reduce atherosclerosis development in ApoE$^{-/-}$ mice on a high-fat diet.[13] While control Phosphate buffered-saline (PBS)-treated mice developed severe and inflamed atherosclerotic plaques in the aortic sinus, lesion development was profoundly reduced in IL-33-treated animals. IL-33 also markedly increased levels of IL-4, IL-5 and IL-13 but significantly decreased the concentrations of interferon γ in serum and lymph node cell culture supernatants. IL-33 treatment also elevated the levels of total serum IgA, IgE and IgG_1 but decreased $IgG_{2a,}$ consistent with a Th1-to-Th2 switch. IL-33-treated mice also produced significantly increased elevated anti-ox-LDL antibodies. Conversely, mice treated with soluble ST2 developed significantly larger atherosclerotic plaques in the aortic sinus of the ApoE$^{-/-}$ mice compared to control IgG-treated mice.[13]

Chronic low-grade inflammation of adipose tissue likely contributes to the metabolic consequences of obesity. The cytokine IL-33 and its receptor ST2 are expressed in adipose tissue. Mice lacking endogenous ST2 fed a high-fat diet had increased body weight and fat mass, impaired insulin secretion and glucose regulation compared to wild-type (WT) controls.[14] Furthermore, administration of recombinant IL-33 to genetically obese (*ob/ob*) mice led to reduced adiposity, decreased fasting glucose and improved glucose tolerance. IL-33 induced production of Th2 cytokines and reduced expression of adipogenic and metabolic genes in adipose cultures in vitro. IL-33 also induced the polarisation of adipose tissue macrophages towards an alternatively activated (M2) phenotype, a lineage associated with protection against obesity-related metabolic events. Thus, IL-33 may also play a protective role in the development of adipose tissue inflammation during obesity.

These results demonstrate that IL-33 may provide a novel therapeutic approach in the treatment or prevention of atherosclerotic vascular disease and obesity. However, in inflammatory disease, IL-33 is a double-edged sword, as demonstrated below.

IL-33 INDUCES AIRWAY INFLAMMATION

Patients with chronic asthma have elevated concentrations of IL-33 protein in their lungs.[15] In ovalbumin-induced experimental asthma in mice, injection of IL-33 intraperitoneally led to markedly enhanced eosinophilia and macrophage accumulation in the lungs. In contrast, ST2$^{-/-}$ mice developed attenuated airway inflammation, IL-5 production and eosinophila. Moreover, IL-33 administration induced the Th2-like cells and exacerbated airway inflammation in both IL-4$^{+/+}$ and IL-4$^{-/-}$ mice. Thus, IL-33 polarises a population of Th2-like cells, which could subsume the function of conventional Th2 cells and play a critical role in allergic diseases.[15]

IL-33 alone, inoculated intranasally, induced profound airway inflammation.[16] This is due to the activation of M2, which plays a crucial role in type 2 immunity. IL-33 changed the quiescent phenotype of alveolar macrophages towards an M2 phenotype that expressed a mannose receptors, IL-4Rα, and produced high levels of CCL24 and CCL17 during IL-33-

Table 1 The role of IL-33 in diseases

Disease	Role of IL-33	Reference
Infections		
Leishmania major infection	Anti-ST2 antibody enhances disease resistance in mice.	8
Trichuris muris infection	IL-33 confers resistance in mice.	10
Pseudomonas aeruginosa	Soluble ST2 exacerbates keratisis induced by *P aeruginosa*.	21
Toxoplasma gondii	IL-33 protects against *T gondii*.	22
Respiratory syncytial virus infection	Anti-ST2 antibody reduces pulmonary inflammation in mice	23
Allergic diseases		
Asthma	IL-33 level is elevated in clinical and experimental asthma.	15 24
	Anti-ST2 antibody attenuates disease in mice.	25
	IL-33 exacerbates experimental asthma in mice.	15
Allergy and anaphylaxis	In the presence of IgE, IL-33 induces anaphylactic shock.	26
Dermatitis, rhinitis and conjunctivitis	IL-33 causes degranulation of IgE-primed mast cells in the skin.	26 27
	IL-33 level increased in skin of these patients.	28
Cardiovascular disease		
Myocardial infarction and heart failure	Serum ST2 levels increased in myocardial infarction and heart failure.	29, 30
	IL-33 protects experimental heart failure.	31
Atherosclerosis	IL-33 attenuates atherosclerosis in mice, whereas soluble ST2 exacerbates the disease.	13
Obesity	IL-33 exerts protective metabolic effects in obesity.	14 32
Central nervous system disease		
Glioblastoma	ST2 expression decreased in glioblastoma samples.	33
Subarachnoid haemorrhage	ST2 and IL-33 are detected in the cerebrospinal fluid.	34
Alzheimer's disease	IL-33 gene expression decreased in brains of patients with Alzheimer's disease.	35
Pain	IL-33 induces cutaneous and articular hypernociception.	36
Autoimmune diseases		
Arthritis	IL-33 and ST2 are increased in the synovium in rheumatoid arthritis.	17
	sST2 attenuates collagen-induced arthritis in mice.	37
	IL-33 exacerbates collagen-induced arthritis and autoantibody induced arthritis.	17 20
Systemic sclerosis	IL-33 and ST2 expression are increased in the skin lesion of patients; IL-33 exacerbates the disease.	27
Inflammatory bowel disease	IL-33 is upregulated in colonocytes of ulcerative colitis.	38 39

IL, interleukin.

induced airway inflammation. Neutralisation of M2-derived CCL24 led to an amelioration of IL-33-induced eosinophilia in the lungs. Moreover, depletion of alveolar macrophages reduced IL-33-induced airway inflammation. In addition, the attenuated Ovalbumin (OVA)-induced airway inflammation in $ST2^{-/-}$ mice was associated with a decrease in M2 differentiation. In vitro, IL-33 amplified the polarisation of alveolar and bone marrow-derived macrophages towards an M2 phenotype by increasing the expression of Arginase-I and Ym1 as well as the production of CCL24 and CCL17 in an IL-4Rα- and ST2-dependent manner. Similarly, IL-33 enhanced the production of CCL24 and CCL17 by human macrophages. Taken together, the IL-33/ST2 signalling pathway plays a significant role in the selective polarisation of M2 and chemokine production, which contributes to innate and antigen-induced airway inflammation.

IL-33 EXACERBATES EXPERIMENTAL ARTHRITIS

IL-33 is expressed by human synovial fibroblasts and induced by inflammatory cytokines.[17] Mice lacking ST2 develop significantly impaired clinical parameters of collagen-induced arthritis (CIA) and attenuated collagen-specific proinflammatory cytokines such as IL-17, TNFα, interferon γ and antibody production. Conversely, the injection of IL-33 into WT but not $ST2^{-/-}$ mice exacerbated the disease together with elevated proinflammatory cytokine and antibody secretions. Furthermore, mast cells play a pivotal role in the IL-33-mediated disease exacerbation. Mast cells express high levels of ST2 and directly respond to IL-33 to produce a wide spectrum of inflammatory cytokine and chemokines in vitro.[18 19] In vivo, IL-33 injection significantly exacerbated CIA in $ST2^{-/-}$ mice engrafted with WT but not $ST2^{-/-}$ mast cells.[17]

IL-33 can also exacerbate anti-glucose 6-phosphate isomerase autoantibody-induced arthritis (AIA).[20] Mice lacking ST2 developed attenuated AIA and reduced expression of articular proinflammatory cytokines. Conversely, treatment of WT mice with IL-33 significantly exacerbated AIA and markedly enhanced proinflammatory cytokine production. However, IL-33 failed to increase the severity of the disease in mast cell-deficient or $ST2^{-/-}$ mice. Furthermore, mast cells from WT, but not $ST2^{-/-}$ mice, restored the ability of $ST2^{-/-}$ recipients to mount an IL-33-mediated exacerbation of AIA. IL-33 also enhanced auto-antibody-mediated mast cell degranulation in vitro and in synovial tissue in vivo. Together, these results demonstrate that IL-33 can enhance autoantibody-mediated articular inflammation via promoting mast cell degranulation and proinflammatory cytokine production. Since IL-33 is derived predominantly from synovial fibroblasts, this finding provides a novel mechanism whereby a host tissue-derived cytokine can regulate effector adaptive immune response via enhancing innate cellular activation in inflammatory arthritis.

Together, these findings demonstrate that IL-33 is a critical proinflammatory cytokine for inflammatory joint disease by promoting arthritogenic cellular and humoral immune responses as well as mast cell activities. Therefore, IL-33 may be a new target not only for allergy but also for rheumatoid arthritis.

CONCLUSION

This review provides a brief summary of the role of IL-33 in some of the diseases studied so far. A more comprehensive review has been presented earlier[2] and updated in table 1.

IL-33 contributes to the host defense against parasite, fungal, bacterial and virus infections. IL-33 also reduces type I inflammation but is a potent inducer of type II cytokines and promotes M2 macrophage phenotype, and as such, contributes to allergic diseases. The unexpected finding that IL-33 also exacerbates arthritic disease, generally associated with Th1 and Th17, is likely due to the unique feature of IL-33 in activating mast cells that express high density of ST2.[7] The role of IL-33 in cancer and neurological diseases remains to be explored.

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Notes