Minireview

Roles of IL-33 in the Pathogenesis of Cardiac Disorders

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Impact statement

The cytokine interleukin-33 (IL-33) is expressed in diverse cardiac cell types. There have been some reports on the role of IL-33 in myocardial injury. But the roles of IL-33 vary in different myocardial disorders, and there are few comprehensive reviews of IL-33's contributions to distinct myocardial injuries. This article summarizes evidence concerning the role of IL-33 in cardiac inflammation, heart transplantation, hypertensive heart disease, coronary atherosclerotic heart disease, myocardial infarction, and diabetic cardiomyopathy (DCM). This article provides novel insights into the roles of IL-33 in cardiomyopathy and clues for a possible strategy in cardiomyopathy therapy.

Abstract

Interleukin-33 (IL-33) is a member of the IL-1 cytokine family and is believed to play important roles in different diseases by binding to its specific receptor suppression of tumorigenicity 2 (ST2). In the heart, IL-33 is expressed in different cells including cardiomyocytes, fibroblasts, endothelium, and epithelium. Although many studies have been devoted to investigating the effects of IL-33 on heart diseases, its roles in myocardial injuries remain obscure, and thus further studies are mandatory to unravel the underlying molecular mechanisms. We highlighted the current knowledge of the molecular and cellular characteristics of IL-33 and then summarized its major roles in different myocardial injuries, mainly focusing on infection, heart transplantation, coronary atherosclerosis, myocardial infarction, and diabetic cardiomyopathy. This narrative review will summarize current understanding and insights regarding the implications of IL-33 in cardiac diseases and its diagnostic and therapeutic potential for cardiac disease management.

Keywords: IL-33, heart transplantation, hypertensive heart disease, myocardial infarction, coronary atherosclerotic heart disease, diabetic cardiomyopathy

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Introduction

The heart pumps oxygen- and substrate-enriched blood to the body's organs and tissues,[1] and it is not surprising that cardiac diseases are among the leading causes of global morbidity and mortality. Cardiac injuries can be initiated by various causes, such as diabetes, hypertension, infection, hypoxia, atherosclerosis, and valvular heart disease. Importantly, cardiomyopathy and consequential heart failure are the leading causes of death and are major contributors to the worldwide healthcare system's burden.[2,3] However, due to the poor regenerative ability of the heart following injury currently available treatments often fail to effectively treat heart failure.

IL-33 was identified in 2005 as an IL-1 family cytokine and a T-helper type 2-associated immune response inducer.[4] Knowledge of the roles of IL-33 and its damage-associated molecular patterns increases our understanding of disease and homeostasis.[5] Subsequently, an increasing number of studies have demonstrated a pivotal role for IL-33 in disease progression by binding to its receptor growth stimulus-expressed gene 2 protein (ST2). When discovered, interleukin-33 (IL-33) was characterized as a potent driver of type 2 immunity and implicated in parasite clearance, as well as asthma, allergy, and lung fibrosis.[6] IL-33 plays a fundamental role in tissue repair, fibrosis, immune rejection, and homeostasis, as the importance of type 2 response has emerged.[4] In addition, IL-33 can be expressed in different parenchymal cells and play different roles in different tissues and organs.

IL-33 is expressed in different cardiac cells. It was reported that tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-1β significantly increased both protein and mRNA levels of IL-33 in primary human adult cardiac fibroblasts, cardiac myocytes, coronary artery smooth muscle cells, vascular endothelial cells, and macrovascular (aortic and coronary artery) and heart microvascular endothelial cells *in vitro*.[7]

In this review, we aim to elucidate the biological characteristics of IL-33 and provide a systematic analysis of the IL-33 implication in heart injuries, focusing on the regulatory mechanism and the associated pathological conditions.

Biological characteristics of IL-33

Discovery and structure of IL-33

IL-33 was first described as DVS27 in cerebral arteries vasospasm in canine models of hemorrhage in 1999 and was recognized as a nuclear factor abundantly expressed in human high endothelial venules of lymphoid organs in 2003.[8] In 2005, Schmitz *et al.* demonstrated DVS27 to be a cytokine of the IL-1 superfamily by analyzing the protein sequence databases and named it IL-33.[9] In 2007, new studies identified IL-33 as a chromatin-associated cytokine.[10] In humans, the *IL-33* gene is located on chromosome 9 and encodes a protein of 270 amino acids (aa) with a molecular weight of 30 KD while in mice, the *IL-33* gene is located on chromosome 19 encoding a 266 aa protein corresponding to a molecular weight of 29.9 KD, and the gene contains eight exons in both humans and mice.[9] The IL-33 protein is structured into the N-terminus (aa 1–65, containing a nuclear localization sequence and a chromatin-binding domain), the central "sensor" domain (aa 66–111), and the C-terminus (aa 112–270, IL-1-like cytokine domain).[11] Its N-terminal domain contains a helix-turn-helix (HTH)-like motif that can bind to chromatin and histones to regulate gene transcription, while the C-terminus can bind to its receptor to mediate the intracellular signaling and is responsible for its cytokine-like activities.[10,12] Thus, IL-33 acts as a nuclear transcription factor that regulates gene expression and acts as a cytokine to mediate biological effects.[10]

Source of IL-33 in the heart

IL-33 protein is constitutively distributed in the nucleus of multiple types of cells including endothelial cells, epithelial cells, and fibroblasts.[11,13] Also, a variety of immune cells, such as macrophages, mast cells, and eosinophils, can express IL-33.[14–16] Moreover, parenchymal cells such as hepatocytes and cardiomyocytes can also produce IL-33.[17,18] During the resting state, IL-33 is mainly expressed in the nucleus,[19] whereas, it is activated and released into the extracellular space under cellular stress conditions.[20,21] Moreover, the expression of IL-33 is upregulated during cellular stress or inflammation exposure such as radiation, chemotherapy, pathogenic organisms, or tissue transplantation.[5]

The receptor of IL-33

The IL-33 receptor is the growth stimulus-expressed gene 2 protein (ST2), which was discovered in embryonic fibroblasts of BALB/c-3T3 in 1989 and was also named "tumor suppressor protein 2" in later studies.[22,23] ST2 is a member of the Toll-like receptor/IL-1 receptor family present on human chromosome 2 and has two major different isoforms as a result of alternative splicing from two different promoters: transmembrane ST2 (ST2L) and a soluble ST2 (sST2).[24]

The functional IL-33 receptor, ST2L is mainly expressed in Th2-type immune cells, including M2-type macrophages, innate lymphoid cell type 2 (ILC2), mast cells, eosinophils, and regulatory T cells (Tregs).[25–27] After release from cells, IL-33 binds to a heterodimeric complex composed of ST2L and IL-1 receptor accessory protein (IL-1RAcP) on the cell surface, thereby activating downstream signaling pathways.[28,29]

The sST2 lacks the transmembrane sequence and thus is secreted into the extracellular space where it binds to IL-33 and mainly serves as a decoy receptor.[30] IL-33 and its receptor sST2 are thought to be independent predictors possibly associated with poor prognosis for heart failure.[31,32]

Role of IL-33 in cardiac disease

IL-33 in CVB3 viral injury in cardiac infection

Coxsackievirus B3 (CVB3) infection is the most common cause of mouse viral myocarditis. Interestingly, IL-33 mRNA expression was significantly elevated during both acute and chronic CVB3 myocarditis. In acute viral myocarditis (7 days of infection) of CVB3-induced BALB/c mice, IL-33 overexpression markedly increased $ST2L^+$ $F4/80^+$ macrophage cells and $ST2L^+$ $CD4^+$ T cells, while IL-4 neutralizing antibody treatment antagonized the protective effect of IL-33.[33] Another study demonstrated that IL-33 exerted a cardioprotective effect by inducing Th (T helper) 2 type immune response in acute viral myocarditis mice.[34] In the chronic stage (35 days after infection), CVB3 infection caused autoimmune heart disease, and recombinant IL-33 (rIL-33) administration in these animals increased inflammatory factors such as IL-33, IL-1β, and IL-6, induced eosinophilic pericarditis, and reduced heart function in untreated mice.[35–37] During the acute phase of cardiac infection, the th1-type immune response has a pro-inflammatory effect, and enhancing the Th2-type immune response inhibits the Th1-type immune response and limits inflammation, while excessive Th2-type immune response activation also causes chronic low-grade inflammation and fibrosis.[38–40] Collectively, these results indicate that in the acute phase of cardiac infection, IL-33 may inhibit inflammation by inducing Th2-type immune response and macrophage M2 polarization, while in the chronic phase, IL-33 can induce eosinophil infiltration and increase inflammatory cytokine levels and result in dilated cardiomyopathy.

IL-33 in heart transplantation

Only a few studies have investigated the role of IL-33 in heart transplantation. In this regard, high levels of IL-33 in the heart and circulation were observed in humans and mice during the rejection period following heart transplantation. According to Yin *et al.*, recombinant IL-33 (rIL-33) administration prolonged the mean survival time of mice subjected to heart transplantation from 7.2 days to 21.7 days compared to phosphate-buffered saline (PBS) treatment.[41] In addition, the same study also revealed that IL-33 treatment induced an increase in Th2-type cytokines in the spleen and heart while reducing IFN-γ levels, therefore, promoting immune tolerance in heart allografts. Moreover, Li *et al.* observed that IL-33 promoted metabolic programming of macrophages that are associated with reparative and regulatory functions in cardiac transplants, and IL-33 deficiency in the graft caused pro-inflammatory $iNOS^+$ macrophage upregulation and accelerated graft loss, whereas local IL-33 supplementation inhibited chronic rejection.[42]

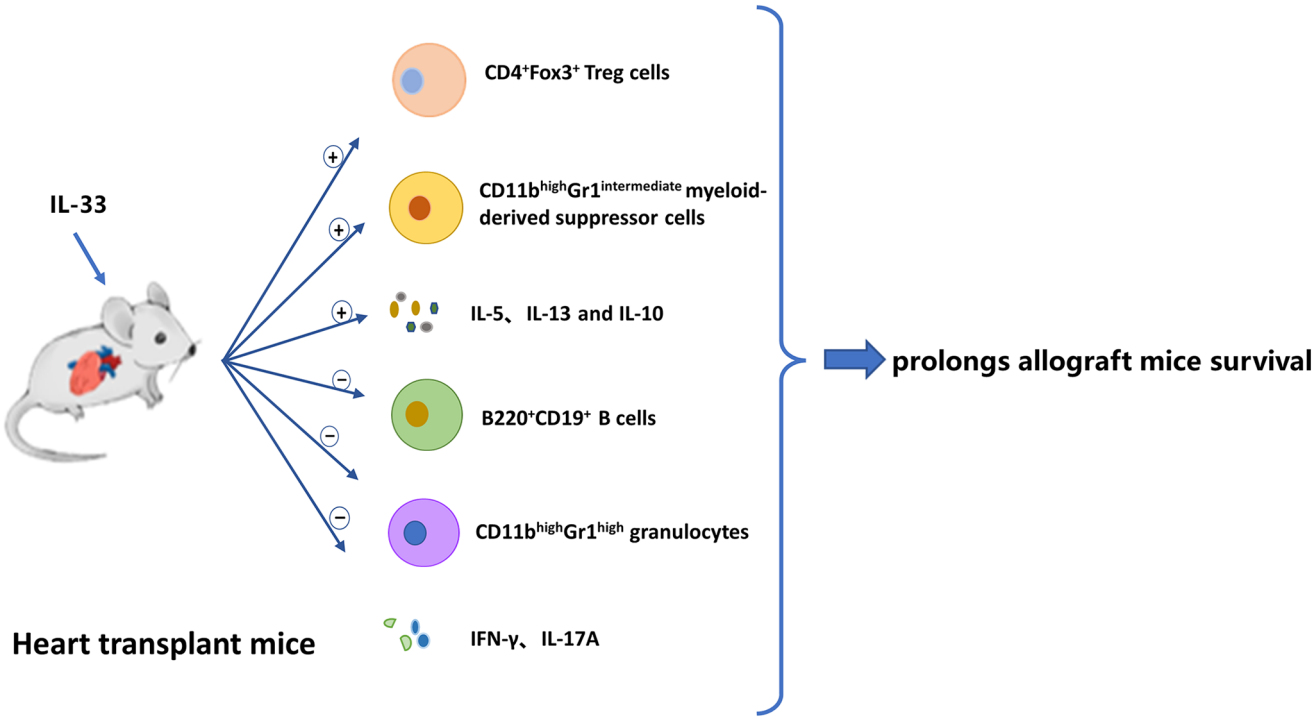

Figure 1. The survival of mice receiving heart transplant. IL-33 promotes cardiac allograft survival by inducing the proliferation of $CD4^+$ $Foxp3^+$ Treg cells and bone marrow-derived $CD11b^{high}$ $Gr1^{intermediate}$ cells, increasing the levels of the anti-inflammatory cytokines IL-5, IL-13, and IL-10; reducing the $B220^+$ $CD19^+$ B cells and $CD11b^{high}Gr1^{high}$ granulocytes and decreased the pro-inflammatory cytokine IL-17A and IFN-γ.

Another study demonstrated that intravenous administration of IL-33 to transplant recipient mice promoted cardiac allograft survival by suppressing chronic allograft inflammation.[43] Cells isolated from the cardiac allografts and spleens of IL-33-treated mice produced less pro-inflammatory cytokine IL-17A and more anti-inflammatory cytokines IL-5, IL-13, and IL-10 than cardiomyocytes and splenocytes from saline-injected control mice. IL-33 also induced the proliferation of $CD4^+$ $Foxp3^+$ Treg cells and bone marrow-derived $CD11b^{high}$ $Gr1^{intermediate}$ cells, and reduced $B220^+$ $CD19^+$ B cells and $CD11b^{high}Gr1^{high}$ granulocytes versus the control mice. Collectively, these results suggest the development of a Th2-type immune response that promotes allograft survival. In support of this possibility, a study by Simeonovic *et al.* also reported that the shift of the Th1-type immune response to the Th2-type immune response promoted cardiac allograft survival, improved transplant tolerance, and alleviated post-transplant cardiac atherosclerosis.[44] The collective results of these studies indicate that IL-33 prolongs heart transplant recipient survival mainly by regulating the proliferation of immune cells and the levels of cytokines in transplanted mouse hearts (Figure 1).

IL-33 in hypertensive heart disease

Hypertension is a common risk factor for cardiomyopathy[45] and IL-33 is expressed in the heart and related blood vessels. Therefore, it is not surprising that some studies have revealed alterations in the IL-33 and its receptor in this pathology. For instance, it has been reported that in wild-type mice, cardiac pressure overload leads to increased expression of IL-33 and sST2, and rIL-33 treatment reduces hypertrophy and decreases mouse mortality.[46] However, IL-33 or ST2-null mice demonstrated greater left ventricular hypertrophy and cardiac fibrosis, and decreased survival following cardiac pressure overload than their wild-type littermates,[46] suggesting that the lack of IL-33 or its receptor ST2 confers cardiac pressure overload vulnerability in these mice, indicating a protective role of IL-33. In addition, sST2 overexpression promoted hypertension-induced cardiac injury, while ST2L overexpression reduced blood pressure and improved myocardial hypertrophy in hypertensive mice,[47] further supporting the decoy role of sST2 and the protective role of IL-33 via its receptor ST2L. Furthermore, cardiac endothelial cell-derived IL-33 improved cardiomyocyte hypertrophy and reduced the systemic inflammatory response by binding ST2L.[47] Moreover, cardiomyocyte-specific deletion of ST2 or endothelial-specific deletion of IL-33 aggravated pressure overload-induced cardiac hypertrophy. Thus, these studies indicate that the crosstalk between IL-33 and its receptor ST2L was cardioprotective, while competitive binding of IL-33 by sST2 blunted IL-33-ST2L binding in hypertension-induced heart injury.

IL-33 in coronary atherosclerotic heart disease

The most common cause of myocardial infarction, coronary atherosclerosis is a chronic inflammatory condition caused by vascular stenosis and obstruction of the major vessels that supply the heart resulting in myocardial ischemia and hypoxia. Atherosclerosis is characterized by excessive lipid deposition in the arterial intima, and lipid peroxidation-induced macrophage foam cell formation is believed to play a key role in the development of coronary atherosclerosis.[48]

Interestingly, *in vitro* studies revealed that IL-33 promotes the efflux of intracellular free cholesterol and phospholipids while reducing macrophage-derived foam cells formation by inducing ERK1/2 phosphorylation and increasing IL-10 and ATP-binding cassette transporter A1 (ABCA1).[49] Moreover, IL-33 was reported to reduce macrophage foam cells mainly by regulating the expression of key proteins implicated in the uptake and efflux of cholesterol, reducing the uptake of acetylated and oxidized low-density lipoprotein.[50] Together, these mechanisms lowered both total and esterified intracellular cholesterol content and enhanced cholesterol efflux. IL-33 also attenuated foam cell formation by inducing the production of IL-5 and antibodies directed against oxidized low-density lipoprotein.[51] In addition, IL-33 could also promote M2-polarization of macrophages by binding to the T-cell surface receptor ST2L and increasing the production of Th2-type cytokines in atherosclerosis[52] thereby suppressing inflammation. IL-33 also reduced arterial plaque inflammation and suppressed the development of coronary atherosclerosis by promoting Treg cell expansion. Thus, the data reviewed here suggest that IL-33 and its receptor ST2L protect against coronary atherosclerosis by decreasing macrophage foaming formation by decreasing intracellular cholesterol, and by ameliorating chronic inflammation.

The formation of atherosclerotic plaques results in the stenosis of the affected vessels. Interestingly, in patients with coronary heart disease, increased serum IL-33 levels were associated with recurrent stenosis after coronary stenting, independent of the clinical presentation and the number and type of stents.[53] This increases in IL-33 could be due to the efforts of the body, albeit unsuccessful, to overcome the restenosis. In a cohort study, where the patients were stratified according to the clinical manifestation of coronary heart disease, serum sST2 concentrations were increased appreciably in patients with ST-segment elevation myocardial infarction, and to predict mortality in the cohort.[54] Thus, increases in the serum levels of IL-33 and sST2 are associated with adverse outcomes in coronary artery disease.

Similar to B-type natriuretic peptide (BNP), serum levels of sST2 and IL-33 were also reported to be associated with major adverse cardiovascular events in patients with acute myocardial infarction undergoing percutaneous coronary intervention.[55] This finding is an indication that serum sST2 and IL-33 levels have potential value in predicting adverse cardiovascular events in patients with acute myocardial infarction undergoing coronary intervention. Conversely, in another study in patients with coronary heart disease, serum IL-33 was significantly lower in patients with acute myocardial infarction and unstable angina pectoris than in those with stable angina.[56] Moreover, IL-33 was found to be lower in patients with single-, double-, or triple-vessel lesions than in healthy volunteers without coronary artery disease.[56] As summarized above, IL-33 favors the Th2 response by inducing the secretion of Th2-type cytokines and M2 polarization of macrophages. These mechanisms can slow inflammation and thereby stabilize the developing plaque. Thus, reduced IL-33 levels are more likely to be associated with plaque rupture and thromboembolism, a major complication of atherosclerosis imposing a heightened risk of myocardial and cerebral ischemia and infarcts. Serum IL-33 paralleled sST2 levels in the patients with coronary heart disease; indeed, serum sST2 may be a better indicator of the severity of coronary heart disease as increased sST2 levels were associated with negative outcomes in both chronic heart failure and acute myocardial infarction patients.[57,58] As shown in Figure 2, IL-33 plays a protective role in atherosclerosis by decreasing cholesterol plaques and limiting stenosis and vessel lesions by enhancing cholesterol efflux and reducing foamy macrophage. Thus, IL-33 could be used as a diagnostic, therapeutic, and prognostic biomarker in coronary artery disease.

IL-33 in myocardial infarction

During the early stage (4–7 days) of myocardial infarction in mice induced by coronary artery ligation, IL-33 was found to effectively activate Th2-type cytokines, reduce the inflammatory cytokines TNF-α and IL-1β, and alleviate the early inflammatory and profibrotic responses in the heart.[59] However, in the chronic stage (after 7 days), IL-33 administration significantly increased myocardial eosinophil infiltration, enlarged infarct size, and promoted cardiac rupture versus saline control. These adverse actions suggest that although in the acute stage of myocardial infarction, IL-33 promoted repair and suppressed inflammation during the chronic stage, a sustained high level of IL-33 could induce a Th2-type inflammatory response and excessive remodeling which would aggravate cardiac fibrosis and heart failure. This scenario is supported by significantly increased sST2 and IL-33 levels in patients with acute myocardial infarction as compared to normal healthy controls, with a further increase in patients with heart failure.[60]

Moreover, protein contents of IL-33 and ST2 increased in a mouse myocardial infarction model, whereas a reduced-deubiquitinase USP17-mediated IL-33 degradation improved cardiomyocyte apoptosis.[61] In a rat myocardial infarction model, treatment with bisoprolol, a beta-blocker, for 4 weeks improved cardiac function and reduced serum sST2 levels, and decreased infarct size when compared with the placebo group.[19] In support of these findings, Chen *et al*. showed in a rat myocardial infarction model that both eplerenone (an aldosterone receptor antagonist) and anakinra (an IL-1 receptor antagonist) decreased myocardial mRNA expression of sST2, IL-6, MCP-1, and collagen.[62] Even though both studies showed that these drugs had no significant effect on the IL-33 level, they significantly enhanced IL-33/ST2 signaling and decreased sST2 expression. As a decoy receptor for IL-33, sST2 can block the binding of IL-33 with ST2L. Collectively, the IL-33/ST2L axis has a dual role in myocardial infarction, as shown in Figure 3.

Role of IL-33 in DCM

DCM is a condition with unclear etiopathogenesis that is a significant cause of morbidity and mortality in diabetic patients and is marked by anatomical and physiological alterations of the myocardium.[63,64] The loss of cardiomyocytes in DCM is mainly mediated via apoptosis where endoplasmic reticulum (ER) stress and autophagy play critical roles.[65] Interestingly, it was observed that in diabetic (db/db) mice, IL-33 alleviated DCM by regulating ER stress

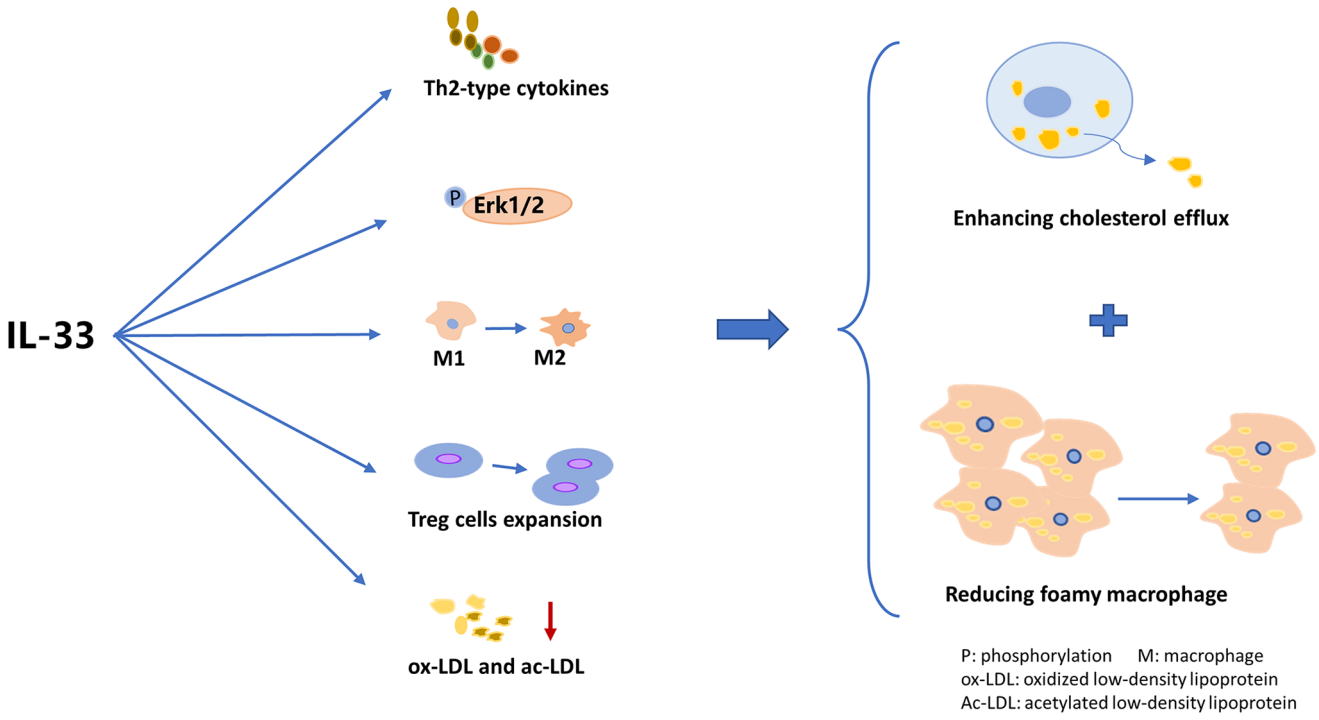

Figure 2. IL-33 protects against coronary atherosclerotic disease. IL-33 enhances cholesterol efflux and reduces foamy macrophages via induction of Th2-type cytokines, increasing the expression of phosphorylated Erk1/2, promoting Treg cell amplification and M1 and M2 polarization of macrophages, thereby reducing the production of oxidized low-density lipoprotein and acetylated low-density lipoprotein.

and autophagy via the insulin-like growth factor–binding protein 3.[66] Following IL-33 treatment, these mice exhibit decreased ER stress-related apoptosis and myocardial lipid accumulation, and improved diastolic function. Moreover, in mice with diabetes mellitus, IL-33 protein expression was significantly decreased, while IL-33 overexpression alleviated cardiac fibrosis and improved cardiac function.[67] In addition, the same study also revealed that IL-33 decreased cardiomyocyte apoptosis by reducing protein kinase C BII protein (PKCβII) activity while enhancing diacylglycerol kinase ζ (DGK-ζ) activity in the presence of both high glucose and hypoxia-reoxygenation injury.

Interestingly, the level of the sST2 was also reported to be altered in diabetic patients. For instance, it was observed that serum sST2 levels were higher in diabetic patients than in healthy controls and that sST2 levels were even higher in patients with versus without diastolic dysfunction.[68] In addition, elevated serum levels of sST2 were associated with the occurrence of adverse cardiovascular events and predicted mortality in patients with diabetes and acute coronary syndrome.[69] Thus, elevated sST2 is associated with the degree of cardiac injury and could serve as a biomarker for, cardiac injury. Collectively, these studies indicate that the IL-33/ST2L axis may have protective effects on myocardial injury in diabetes mellitus.

IL-33 in other cardiac diseases

The cardioprotective effects of IL-33 are reported in many other cardiac diseases including rheumatic heart disease (RHD), acutely decompensated heart failure (ADHF), cardiac arrhythmia, acute aortic syndrome, and myocardial oxidative stress. Angiotensin II was shown to promote IL-33 and ST2L expression by stimulating transforming growth factor (TGF)-β to induce fibrosis in RHD while angiotensin-converting enzyme inhibitor inhibited the production of angiotensin II, which in turn promoted the binding of IL-33 to ST2L and alleviated cardiac fibrosis.[70] Thus, IL-33 and ST2L might play a protective role in RHD. In patients with ADHF, elevated sST2 correlates directly with ADHF severity, and powerfully and independently predicts an increased risk of heart failure complications including arrhythmia, pump failure, and death.[71] And IL-33/ST2L axis was thought to protective effect in ADHF. Anoxia/reoxygenation assault on the myocardium-induced myocardial oxidative stress accompanied by apoptosis of the cardiac cell and enhanced protein kinase CβII protein (PKCβII) and Janus kinase (JNK) phosphorylation levels which were all recovered following treatment with IL-33.[72] However, in JNK-deficient or PKCβII siRNA-interfered cardiomyocytes, IL-33 treatment did not show corresponding protective effects, indicating that IL-33 improved myocardial injuries possibly through the PKCβII/JNK signaling pathway.[72] In systemic sclerosis, an increase in IL-33 and sST2 are associated with the involvement of the heart such as cardiac diastolic dysfunction, and the sST2 exhibited a negative linear correlation with diastolic dysfunction.[73] Another study also revealed increased IL33 and sST2 in systemic sclerosis patients that are associated with microvascular damage.[74] It was reported that serum

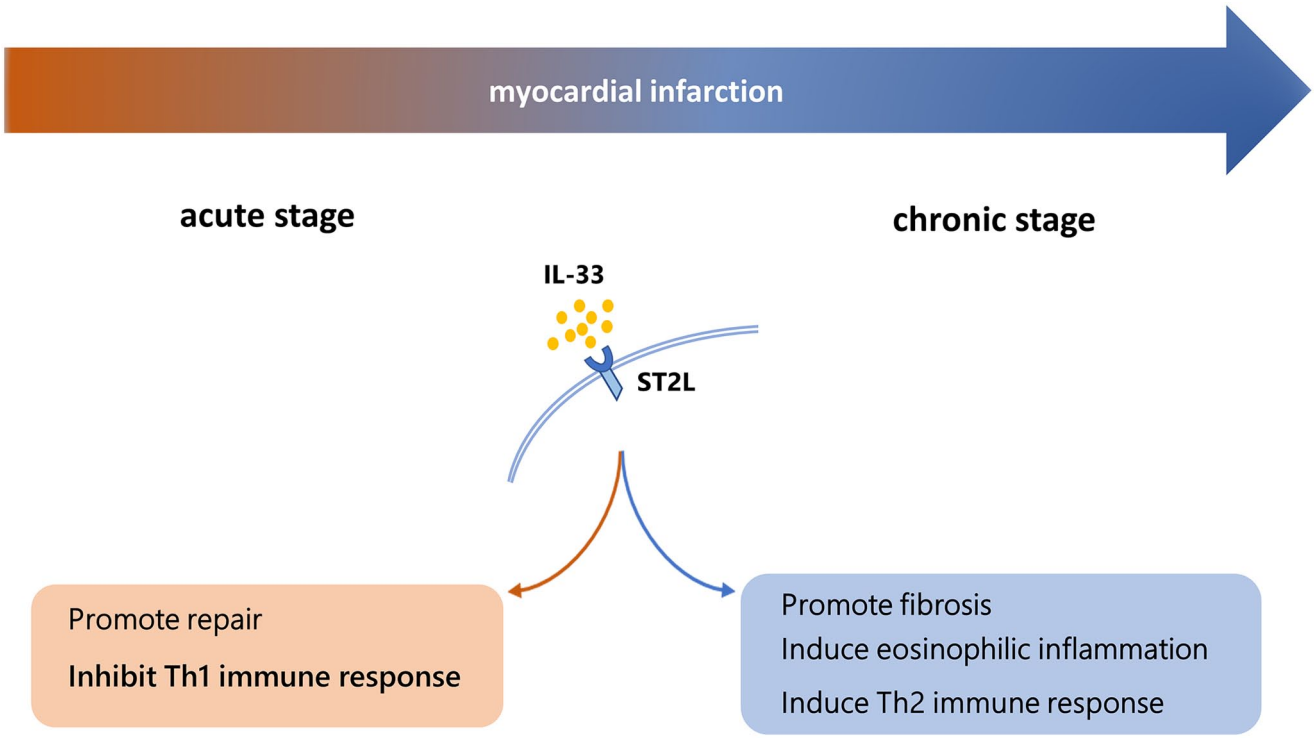

Figure 3. Summary of IL-33 actions in myocardial infarction. In the acute stage of myocardial infarction, IL-33 promotes cardiac repair and inhibits the Th1 immune response, while in the chronic stage, IL-33 induced fibrosis, eosinophilic inflammation, and the immune response by binding its receptor ST2L.

sST2 and IL-33 were dramatically higher in atrial fibrillation patients than in healthy volunteers.[75] In idiopathic inflammatory myopathies (IIMs), there was a correlation between the levels of sST2 and IL-33 and the clinical symptoms.[76] The concentration of sST2 was found to be significantly higher in the IIM group compared to healthy subjects, while the concentration of IL-33 did not exceed the detection limit in this group. These data suggest that an increase in IL-33 and sST2 might indicate the involvement of the heart and/or microvasculature in systemic sclerosis.

Conclusions

Preclinical and clinical evidence on the role of IL-33 in heart disease shows that IL-33 and its receptor ST2 often are elevated after cardiac injury. Although IL-33 is implicated in myocardial inflammation and fibrosis, it undeniably also has important protective roles, for example, inhibiting acute injury and facilitating repair. However, the role of IL-33 and ST2 in heart disease is not yet fully understood. For example, the different roles of IL-33 in different immune environments over the course of disease progression require further clarification.

AUTHORS' CONTRIBUTIONS

JCJ wrote the main manuscript text; JXM, LCL, WLN, and WYQ: checked the draft; LXJ and ZZ provided funding support; TRS: conceived the planning subject. All authors reviewed the manuscript.

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DECLARATION OF CONFLICTING INTERESTS

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