TIPS

IL-33/sST2 axis in The Cardiovascular System: A Brief Review

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Abstract

IL-33 is a type of cytokine and a new member of the IL-1 family labeled as an alarmin, which is released under stressful settings. IL-33 is a biomechanically induced protein and is mainly produced by cardiac fibroblasts and is expressed by various cell types after pro-inflammatory stimulation. Although the physiological role of IL-33 as a nuclear factor is not fully understood, it seems to be involved in transcriptional suppression via binding to nucleosomes and regulating the density of chromatins. It can play different roles, from progression to protection against a disease, depending on the type of the disease. Its signaling happens by means of the sST2 receptor. sST2 is a mechanically induced protein of the cardiac muscle. The IL-33/ST2 axis plays an important role in various illnesses such as cardiovascular diseases and can be a potential target for disease treatment. This review provides an overview of different aspects of IL-33 and its related receptor, sST2 along with the role of IL-33/sST2 axis in different cardiovascular diseases.

Molecular characterization of IL-33

CInterleukin 33 is an intracellular nuclear factor that focuses on the nucleus by its terminal amines and can be attached to the heterochromatins (1). Although the physiological role of IL-33 as a nuclear factor is not fully understood, it seems to be involved in transcriptional suppression via binding to nucleosomes and regulating the density of chromatins (2). The human IL-33 gene is on chromosome 9, which codes for 270 amino acids (3). The IL-33 gene contains 7 coding exons which produces a protein of approximately 31 kDa (1).

IL-33 is a cytokine that increases Th2 response (4-9) and has a central role in controlling immune response in the skin and the gastrointestinal (GI) tract. This cytokine has the ability to activate the cells of innate and adaptive immunity. It can play different roles, from progression to protection against a disease, depending on the type of the disease. According to recent findings, the IL-33 / ST2 pathway is a new therapeutic strategy that can be targeted in treatment or prevention of many inflammatory diseases (4).

Sources of IL-33

IL-33 is expressed in various cells especially the fibroblasts, endothelial and epithelial cells (3). It is also expressed in some organs, including stomach, lung, central nervous system and skin and less in the heart, kidneys, pancreas, spleen, and lymphatic tissues (10).

Receptors of IL-33

This cytokine is known as a new member of the IL-1 family which attaches to its receptor ST2. The ST2 receptor was introduced two decades ago, but remained as an orphan receptor until recent studies led to the discovery of IL-33 as the endogenous ligand of this receptor (7). ST2 gene is

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located on human chromosome 2 (11). In fact, ST2 is a member of the IL-1R / TLR superfamily and has three isoforms: soluble form or sST2, which is expressed in embryonic tis-sues, mammary tumors, and fibroblasts (12). Trans membrane form or ST2L which is a membrane-anchored long form and is restricted to the surface of Th2 cells and mast cells (7) and the variant form or ST2V, which is expressed mainly in the GI organs such as the stomach, large and small in¬testine, and spleen (13).

The sST2 protein, which is further discussed in this study is a form of ST2 that has lost 3 exons as a result of secretion into the extracellular environment. Normally, sST2 is in human serum; where it acts as a Decoy receptor by connecting to free IL-33 (14). The level of sST2 increases in different inflammatory responses and limits the effects of IL-33 in cardiovascular disease, arthralgia and allergic diseases (15-19).

ST2 expression

ST2 receptor is expressed by a variety of cells including: Group 2 Innate lymphoid cells (ILC2s) (20), T helper 2, mast cells (20, 21) and some regulatory T cells. These cells are from the early IL-33 targets. Mast cells are present in many tissues which can be activated by IL-33 in order to liberate intermediating molecules (21).

Release of IL-33 from different cells

Initially, IL-33 is produced in an inactive form inside the cell and transforms into a mature and active form when released from the cell (7). IL-33 is released into the extracellular environment at its full length and size, during necrosis or direct discharge from a healthy cell. By activating the apoptosis pathway, IL-33 is disabled under the enzymatic cleavage of caspase 3 or 7. Full-length secreted IL-33 can be transformed in to an active form by further processes. Cathepsin G and elastase, the two serine proteases are accountable for this transformation (20).

Function of IL-33

IIL-33 increases the Th2-dependent immune responses by binding to its dimeric receptor, and thus exerts its biological activity. This receptor is a complex of ST2L and receptor accessory protein (3). sST2 prevents the IL-33 and ST2L interactions and limits its biological activity.

IL-33 exerts opposite roles in various diseases. On one hand it reduces atherosclerosis and protects against helminthic (3), obesity (22) and cardiac remodeling (10). On the other hand it can develop illnesses such as asthma and atopic dermatitis (3).

In detail, IL-33 signaling is as follows:

IL-33, which is released during cellular necrosis, binds to the ST2/IL-1RAcP hetrodimeric receptor in the cell membrane and as a result activates the receptor. Following the activation of this receptor, some pathways will be activated:

1- Phospholipase D (PLD)-sphingosine kinase (SPHK) pathway that increases the kF nuclear factor (NF-Kb).

2- MAPK (mitogen-activated protein kinase) pathway that Increases the production of Th2 cytokines (10).

Recently, reports of IL-33 expression in smooth muscle cells of the coronary arteries (7), coronary artery endothelium (23), endothelial cells non-HEV (24, 25), adipose tissue (22, 26) and cardiac fibroblasts have been provided which can indicate the role of IL-33 in various cardiovascular diseases (27).

Anti-apoptotic effects of IL-33

IL-33 reduces cardiomyocytes apoptosis. Adding sST2 alone does not induce apoptosis in cases where cell apoptosis is stimulated and the important point is the anti-apoptotic and cardioprotective properties of IL-33 which can be blocked by the sST2 receptor (28).

IL-33 also regulates the expression of anti-apoptotic proteins and regulates the activation of NF-KB, which itself controls apoptosis. Survivin, XIAP, cIAP1, cIAP2, Bcl-2 and Bcl-xL are anti-apoptotic proteins that are regulated by NF-KB (29, 30). In fact, IL-33 activates NF-KB, which plays multiple roles in life and apoptotic death in cells (7, 27). NF-KB signaling in the heart regulates cardiac hypertrophy (31).

According to an in vivo and in vitro study, it has been proven that some of the anti-apoptotic proteins of the IAP family are increased due to the

physiological effects of IL-33 (28)

These IPA proteins can also be regulated by NF-KB and improve cellular life (29, 30). Based on Western blotting analysis, IL-33 increases the expression of anti-apoptotic proteins in hypoxia conditions applied to cardiomyocytes of animal models and addition of sST2 reduces the effects of IL-33. These results indicate that IL-33 can improve life of cardiomyocytes cells by regulating the IAP family of proteins and decreasing cassia-3 cleavage (28).

Improved hemodynamic parameters affected by IL-33

IL-33 improves cardiac function after ischemia-reperfusion myocardial injury in rats. It also improves many hemodynamic parameters, including: cardiac index, systolic and diastolic dp/dt max, stroke volume, ejection fraction, stroke work, arterial elasticity, time constant of exponential decay, maximal power and preload adjusted maximal power.

According to this information, it can be concluded that IL-33 not only reduces apoptosis and fibrosis but also improves cardiac contractility (28).

sST2 as a potential cardiovascular biomarker

Concentration of sST2 is known to be a prognostic factor in the prognosis of heart failure (HF). Myocardial insults, remodeling and neurohormonal activation are involved in the development process of HF in a complex manner. A large number of biomarkers have been identified at various stages of these pathways that can provide important biological information regarding the clean-up processes or assistance in predicting, identifying, classifying risks, and more importantly in monitoring HF. Among these biomarkers is the sST2 receptor (32).

During cardiovascular stresses, including acute and chronic HF, concentration of sST2 in blood circulation increases and has a close relation with the complications of left ventricular remodeling and poor cardiac prognosis (33, 34). sST2 is a biomarker of cardiovascular disease and this concept is the result of clinical studies that show a rapid increase in the serum level of sST2 one day after heart attacks and is directly related to creatine kinase and inversely related to left ventricular ejection fraction (LVEF) (18).

Many studies show the diagnostic value of measuring serum sST2 levels in various cardiovascular diseases and it is stated that high levels of sST2 in cardiovascular patients are a strong predictor of mortality and HF (4).

IL-33 level is likely to be low in cardiovascular patients which may be due to an increase in sST2 level. On the other hand, determining small amounts of IL-33 is not applicable with available laboratory methods (35).

Stimulating IL-33/ST2 signaling pathway in cardiovascular diseases

There are many human studies that indicate the importance of the sST2 biomarker in poor efficacy of HF(36) and MI patients (37, 38). sST2, as a decoy receptor, might reduce IL-33 signals in an in vivo environment, thereby exacerbating the activity of the heart. In this scenario, stimulating the IL-33/ST2 signaling pathway can be useful in patients with high levels of sST2, with this condition that the pro-inflammatory properties of IL-33 should be prevented in short-term treatment (28).

Therapeutic potentials of IL-33 in acute cardiac injuries

IL-33 connects to the ST2L isoform, activates the NF-KB signaling (7) and has the ability to control cell death (39). After MI, cell apoptosis occurs in cardiomyocyte cells (40). Preventing apoptotic cell death in cardiomyocytes can improve the function of the heart (40-42). Thus it can be argued that IL-33 regulates inappropriate cardiac function after MI. The cardioprotective effect of IL-33 was ruled out in mice lacking ST2 gene which means these effects depend on ST2 signaling pathway. This information reveals the different effects and therapeutic potential of IL-33 in acute cardiovascular events (28).

sST2 in MI and HF

Elevated serum levels of sST2 was reported in patients diagnosed with myocardial infarction (MI) and HF (3, 18, 36, 37). Regarding sST2 function, it can be postulated that administration of

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IL-33 in patients with HF will provide beneficial and protective effects and will reduce the incidence of HF. Since an increase in sST2 level is associated with low cardiac output and left ventricular function Thus this biomarker can be considered as a predictor of mortality risk in cardiovascular patients (10).

IL-33 and sST2 in fibrosis and cardiac hypertrophy

IL-33 antagonizes phenylephrine and angiotensin II, the two molecules which cause cardiac hypertrophy (27). In animal models of hypertension, treatment with IL-33 reduces fibrosis and cardiac hypertrophy and it is worth noting that these positive characteristics are not seen in mice lacking ST2 completely (27, 28).

The protective effects of IL-33 with neurohormonal endothelin-1 can be limited, a factor that increases the expression of sST2 and inhibits IL-33 signaling with P38 MAP kinase (43).

IL-33 and sST2 in atherosclerosis

In atherosclerotic diseases, immune cells, including monocytes, T cells and mast cells, penetrate the plaques inside the inner wall of the arteries (44). The manifestation of the disease progresses with Th1 immune responses and related cytokines including IL-12 and interferon gamma (45, 46). It is argued that IL-33 can show protective effects in atherosclerosis by shifting the immune responses from Th1 to Th2. In fact, the treatment of animal models with IL-33 significantly reduces the size of atherosclerotic clots in the aortic sinus. Alongside, the macrophage plaques are also reduced. In contrast to mice receiving intraperitoneal injection of sST2 (IL-33 neutralizing), the size of atherosclerotic plaques increased and the level of interferon gamma was also higher. These entries indicate that IL33/ST2 signaling pathway has a protective role in atherosclerosis (1, 10, 47).

Discussion

Signaling cascade of IL-33/ST2 has attained much attention since its discovery. It has been pointed out repeatedly that the serum sST2 predicts cardiac output in patients with AMI and CHF, and thus worsens their condition. The signal derived from the IL-33/ST2 complex has cardio protective properties and affects fibroblasts and myocytes in the heart (27).

Regarding the function of sST2, it can be said that the level of sST2 can be a predictor of mortality risk in cardiovascular patients (3). IL-33 can prevent apoptosis of cardiomyocytes and improve cardiac function after MI. The anti-apoptosis effect of IL-33 has been proven in both in vivo and in vitro environments (28) .

In spite of quite low number of reports published to date, the tie between IL-33/ST2 axis and cardiovascular diseases seem to be clear. Involvement of ST2 appears to be more predictive than IL-33. However, both molecules are crucial in this regard. The IL-33/ST2 pathway can be considered as a new therapeutic strategy for the treatment or prevention of cardiovascular diseases.

Conflict of Interest

None declared.

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