Role of interleukins in heart failure with reduced ejection fraction

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ABSTRACT

Heart failure (HF) is the leading cause of morbidity and mortality in developed countries, and it is the primary cause of mortality in the elderly worldwide. The processes of inflammatory response activation, production and release of pro-inflammatory cytokines, activation of the complement system, synthesis of autoantibodies, and overexpression of Class II major histocompatibility complex molecules contribute to the HF development and progression. High levels of circulating cytokines correlate with the severity of HF, measured with the use of New York Heart Association’s classification, and prognosis of the disease. In HF there is an imbalance between pro-inflammatory and anti-inflammatory cytokines. Concentrations of several interleukins are increased in HF, including IL-1β, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, and IL-18, whereas the levels of IL-5, IL-7, or IL-33 are down-regulated. Concentrations of inflammatory mediators are associated with cardiac function and can be HF markers and predictors of adverse outcomes or mortality. This review presents the role of interleukins, which contribute to the HF initiation and progression, the importance of their pathways in transition from myocardial injury to HF, and the role of interleukins as markers of disease severity and outcome predictors. (Anatol J Cardiol 2019; 22: 287-299)

Keywords: interleukins, heart failure, interleukin-1, interleukin-6, interleukin-33

Introduction

Heart failure (HF) is an insufficiency of the cardiac output to fulfill the demands of organs and tissues. It can represent the end-stage of several cardiovascular diseases, including ischemic disease, myocardial infarction, or myocarditis, which lead to pathological changes in the myocardium. HF is the leading cause of morbidity and mortality in developed countries, and it is the primary cause of mortality in the elderly worldwide. Its typical clinical presentations include shortness of breath, fatigue, and impaired exercise tolerance. Despite several improvements in the management of HF, it is still an incurable and a progressive disease. Its 5-year mortality has been estimated to range between 50% and 70% in the American population.

The mechanisms of the HF development are complicated, and several factors have been implicated in its pathophysiology. Many studies confirmed that HF is not only a “pump illness”. In fact, it is a systemic disease, and persistent overactivation of different compensatory systems, such as the renin–angiotensin and β-adrenergic system, is one of the most relevant causes of HF. Nevertheless, the use of inhibitory agents blocking those systems did not influence morbidity and mortality satisfactorily, which may suggest that we still miss some significant pathways. Several trials demonstrated that the process of inflammation might be responsible for the initiation and progression of HF. Inflammation can be defined as the biological response to tissue injury or irritation. Immune activation may be the result of direct stimulation by foreign antigens, such as in viral myocarditis, or can be indirect, caused by cardiac injury and subsequent exposure to self-antigens, which could be responsible for the response against the heart. Recurrent and sustained immune system activation is implicated in the left ventricular hypertrophy and its progression to HF. Chemical transmitters playing role in mediating the inflammatory signaling from the site of local injury to whole body are known as cytokines. Cytokines recruit cells to the site of inflammation, stimulate cell division, proliferation, and differentiation. In HF there is an activation of the immune system, production and release of autoantibodies, pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), and complement system recruitment. High levels of circulating cytokines correlate with the severity of HF, measured with the use of the New York Heart Association (NYHA) classification, and prognosis of the disease. They also cause the altera-
tions in the heart function due to the increase of cardiomyocyte apoptosis, cardiac hypertrophy, and matrix metalloproteinase activation (4, 7). The process of T-cell migration to the left ventricle was shown as important in the HF development (8); however, its mechanisms are not well known. An overexpression of TNF-α leads to the development of dilated cardiomyopathy in animal studies (9), which implies that cytokines themselves may cause the initiation and progression of HF.

The processes of the inflammatory response activation, production, and release of pro-inflammatory cytokines, activation of the complement system, production of autoantibodies, and overexpression of Class II major histocompatibility complex molecules contribute to the HF pathogenesis. However, the treatment with several immune pathways inhibitors did not improve the HF outcomes. TNF-α inhibitors had no positive effect on patients’ survival. In fact, high doses of infliximab, a chimeric monoclonal antibody to TNF-α, were found to increase the mortality rate (10, 11). Several trials demonstrated a decreased inflammatory factors concentration after colchicine application. However, it did not improve the clinical state of HF patients (12). The use of nonspecific immunomodulation therapy in HF demonstrated beneficial effects only in some groups of patients (13). On the other side, the levels of inflammatory cytokines did not decrease after traditional therapy was used in acute HF decompensation, even when clinical parameters showed improvement (14). What is more, the use of amiodarone has been associated with up-regulated concentrations of TNF-α in serum (15).

This review presents the role of interleukins, which contribute to the HF initiation and progression, the importance of their pathways in transition from myocardial injury to HF, and the role of interleukins as markers of disease severity and outcome predictors.

**Interleukin-1β and its receptor as a therapeutic target in HF and myocardial infarction**

Interleukin-1β (IL-1β) is a pro-inflammatory cytokine, which triggers up-regulation of several downstream signaling molecules involved in immune response. After binding to its receptor, multiple adaptor proteins are recruited, including the myeloid differentiation factor 88 (MyD88), which activate the IL-1R associated kinases (IRAks) and tumor necrosis factor receptor-associated factor 6 (TRAF-6). These all cause the activation of several transcriptional factors. IL-1 triggers transcriptional and posttranslational alterations in sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) and overexpression of nitric oxide synthase (NOS) (16). IL-1 signaling pathway and downstream effector molecules are presented in Figure 1. Myocardial injury induces the synthesis of a macromolecular structure, denoted inflammasome, which is responsible for the cleavage of pro-IL-1β by caspase-1, and therefore activates IL-1β. IL-1β initiates the migration of leukocytes to the site of cardiac insult and triggers the synthesis of other cytokines. The IL-1β concentration was proportional to the ischemia duration in the studies on mice (17).

**Figure 1.** IL-1 Signaling pathway and downstream effector molecules
IL-1R - interleukin-1 receptor; IL-1RAcP - IL-1 receptor accessory protein; TIR - Toll/interleukin-1 receptor kinase; MyD88 - myeloid differentiation factor 88; IRAK - IL-1R associated kinase; TRAF-6 - tumor necrosis factor receptor-associated factor-6; SERCA - sarcoplasmic/endoplasmic reticulum calcium ATPase; NOS - nitric oxide synthase; TNF-α - tumor necrosis factor-α

IL-1β has been implicated in cardiac remodeling after ischemia and in changes in ventricles contractility and relaxation. The level of IL-1β was proportional to the NYHA’s functional class and was regardless of the cause of HF (18). Studies demonstrated that even more patients had elevated concentrations of IL-1 soluble receptor/receptor antagonists than IL-1 (18). An overexpression of IL-1, which caused alterations in myocardium, was noted in sepsis (19) and viral myocarditis (20). Moreover, inhibiting this cytokine suppressed the progression to HF (21). Treatment with IL-1β promoted contractile dysfunction in cell culture and in vivo studies, and it reduced the LV contractility reserve, evaluated according to the responsiveness to isoproterenol, which is a β agonist. Moreover, the negative influence of IL-1β was reversible (22). IL-1β blocker administration in acute ischemia in animal model prevented from the left ventricle dysfunction, even when used 10 weeks after injury (22, 23). The injection of patients’ plasma, which suffered from acute HF to healthy mice, caused a development of diastolic dysfunction (24, 25). Moreover, treatment with anakinra, which is an IL-1 receptor antagonist, or an IL-1β antibody, protected from the cardiac function depression (23, 25). The administration of plasma from stable systolic HF patients resulted in a lower contractile reserve, whereas the contractile function was unchanged (24).
Patients with rheumatoid arthritis treated with anakinra had a better systolic and diastolic function of ventricles, greater increase in coronary flow reserve, and improved endothelial function, whereas the use of triamcinolone did not affect the myocardial function (26). Similar results were observed in clinical trials VCU-ART (27) and VCU-ART2 (28), which aimed to verify the effect of anakinra on patients with the ST-segment elevated myocardial infarction (STEMI) treated with primary percutaneous coronary intervention. These studies demonstrated a lower level of inflammatory transmitters, better cardiac function, and decreased extent of pathological remodeling in patients administered with anakinra. However, it did not have an impact on myocardial infarction recurrence or the infarct size. VCU-ART3 is a still continued double-blind randomized clinical trial, which evaluates the effect of high doses of anakinra in comparison to standard doses of anakinra and measures the effects on the acute rise and fall of the plasma C-reactive protein (CRP) levels during the first 14 days after myocardial infarction. Patients with the non-STEMI injected with anakinra had a lower level of CRP, but also, unfortunately, an unchanged infarct size and a higher risk of adverse cardiac events (29). Mice administered with a recombinant human IL-1 receptor antagonist after treatment with doxorubicin (30) or chest irradiation (31) had preserved myocardial systolic and diastolic function. Losartan, which is an angiotensin II receptor antagonist, prevented the depression of the cardiac function after the IL-1 treatment in an animal model (32).

**Interleukin-6 and its antagonists as potential therapeutic options in HF**

Interleukin-6 (IL-6) is a pleiotropic cytokine implicated in thymocytes, macrophages, and natural killer cells activation; B- and T-cell differentiation; and inducing the acute-phase proteins synthesis (33). This cytokine initiates the leucocyte infiltration; however, a prolonged inflammation can change into destructive response causing tissue fibrosis. IL-6 acts through the IL-6 receptor (IL-6R), which is detected only in some cell types, such as hepatocytes or leukocytes. After IL-6 binds to IL-6R, the ubiquitously expressed glycoprotein 130 receptor subunit (gp130) is recruited to form a complex. However, another pathway known as trans-signaling has been revealed, which uses a soluble form of IL-6R (sIL-6R). This receptor binds IL-6 with a similar affinity. This dimer can associate with gp130 on cells not expressing IL-6R. IL-6 trans-signaling is pro-inflammatory, while classic IL-6 signaling via the membrane-bound IL-6R has anti-inflammatory properties. The gp130 receptor subunit activates three pathways, including the Janus kinase/signal transducer and activator of the transcription 1/3 (JAK/STAT1/3) pathway, which seems to be the most important in the HF development, Ras/mitogen-activated protein/extracellular signal regulated kinases (Ras/MEK/ERK1/2), and the phosphatidylinositol-3-kinase (PI3K)/Akt pathway (34). Janus kinases are a family of tyrosine kinases linked with the cytoplasmic domain of cytokine and growth factor receptors. After the activation, JAK proteins phosphorylate and recruit STAT proteins whose phosphorylation leads to their homodimerization, and eventually to their translocation to the nucleus or mitochondria (35).STAT3 activates the Survivor Activating Factor Enhancement (SAFE) pathway, which is an intrinsic protective signaling program limiting cell death activated by the heart and triggers ischemic post-conditioning, which prevents the reperfusion injury to occur. The downstream proteins of the JAK/STAT3 pathway are among others cyclin D1, E1, p21, Fas, Bcl-xL, Bcl-2, Mcl-1, or the vascular endothelial growth factor (VEGF). This pathway may also be activated by several factors, including high-density lipoproteins, prostaglandins, bradykinin, leptin, insulin, erythropoietin, adrenoreceptors, cannabinoid agonists, opioids, resveratrol, or biogenic amines present in red wine, including ethanolamine and melatonin (36). The IL-6 signaling pathway and downstream effector molecules are presented in Figure 2. Studies revealed the presence of a decoy receptor, sgp130, which is an endogenous inhibitor of the IL-6 trans-signaling (37). IL-6 inhibited the sarcoplasmic reticulum Ca²⁺ ATPase (SERCA2) via the transcriptional mechanism (38) and decreased the expression of beta- and alpha-myosin heavy chain and cardiac-alpha-actin in cell culture (39).

The levels of IL-6 and soluble IL-6-type receptors were elevated in patients with HF (7) and were proportional to the NYHA

![Figure 2. Downstream signaling of IL-6](Image)
functional class (6, 18) and function of either the left or right ventricle (40, 41). A higher number of patients had an increased IL-6 than the sIL-6R level (18). Moreover, studies revealed the overexpression of their genes in ischemic and nonischemic end-stage HF (42). The IL-6 concentration depended on the etiology of HF. It was significantly increased in patients with HF caused by ischemic heart disease and cardiomyopathy than in those affected by valvular heart disease or hypertensive heart disease (43). IL-6 was linked with the sympathetic nervous system activation and correlated with a poor outcome (44). Jug et al. (45) showed that IL-6 was an independent predictor of prognosis, even better than hsCRP in patients with a chronic stable HF. However, the Corona Trial did not demonstrate a correlation between the level of IL-6 and the endpoints, which were cardiovascular mortality, myocardial infarction, or stroke in patients with chronic symptomatic systolic HF (46). Nevertheless, sgp130 was associated with mortality from all causes (46). IL-6 was an independent predictor of systolic pulmonary artery pressure in patients with advanced HF (47). An increased IL-6 level was associated with a higher HF risk in people without previous cardiovascular diseases (48).

In in vitro studies, IL-6 suppressed the systolic function in isolated hamster papillary muscles through the myocardial NOS pathway (49). In animal studies, IL-6 had a negative inotropic effect on myocardium. Its administration resulted in cardiac dilation and the reduction of skeletal muscle mass (50). gp130 played a role in cardiac fibroblast growth, neovascularization, and wound healing (51). The loss of gp130 has been implicated in the cardiac dilation caused by pressure overload (52). Nevertheless, the overexpression of gp130 led to ventricular hypertrophy through the trans-signaling process (53). Activation of the SAFE pathway was required for the cardioprotective effect of ischemic pre- and post-conditioning. Ischemic post-conditioning induced the activation of JAK1, JAK2, STAT1, and STAT3, and the inhibition of this pathway impaired the development of ischemic tolerance (54). The loss of STAT3 resulted in neovascularization alterations, enhanced fibroblast proliferation, HF progression, increased mortality, higher susceptibility to myocardial ischemia/reperfusion injury and infarction, raised apoptotic cell rate, and enhanced infarct size (55). A similar effect was obtained in IL-6-knockout mice, in which the ischemic post-conditioning-induced activation of JAK/STAT was down-regulated, and the infarct size was not reduced (56). Chronic activation of STAT3 through IL-6 and gp130 in subacute infarction was responsible for inflammation, left ventricular rupture, and HF development (57).

The use of an IL-6 and a gp130 antagonist led to a decreased expression of atrial natriuretic peptide (ANP) and beta-myosin heavy chain in isolated cardiomyocytes, reduction of its surface area, and lower proliferation of fibroblast in cardiomyocyte/fibroblast coculture. Fibroblasts, which synthesized angiotensin II (AngII), stimulated the IL-6 production. Losartan, which is an AT-1 receptor antagonist, neutralized the influence of IL-6 and prevented myocyte hypertrophy and fibroblast proliferation (58).

Tocilizumab is an anti-human IL-6R monoclonal antibody. It binds to both the soluble and membrane-bound IL-6R (59), and this may be the cause of several serious side effects, including neutropenia and increased susceptibility to infections (60). Another issue that questions the use of tocilizumab in patients with HF is the fact that it leads to increased cholesterol levels and decreased statin effects. However, the concentration of lipoprotein(a), which is a known marker of cardiovascular diseases, was lower after the treatment (60).

The effect of IL-6 may be both positive and negative, depending on the duration of this cytokine activation. IL-6 synthesis restricted to short period after the injury is curative and could protect and preserve the myocardium, while a prolonged synthesis and over-production result in ventricular dilation and HF development. Classical, membrane-bound signaling has been associated with the favorable, anti-inflammatory influence of IL-6, whereas the noxious pro-inflammatory pathway is mediated by trans-signaling. The anti-inflammatory role of IL-6 varies upon the dose, duration, and moment of initiation of its administration and type of receptor stimulated.

Interleukin-8 associated with a worse clinical prognosis in patients with HF

Interleukin-8 (IL-8) is a key mediator associated with inflammation, which is encoded by the CXCL8 gene. IL-8 plays a role in angiogenesis, neutrophil and granulocyte chemotaxis, and phagocytosis stimulation, and it is induced by several stimuli such as shear stress, ischemia, hypoxia, and other factors that activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway (61). IL-8 is synthesized by cells with toll-like receptors, including macrophages, epithelial cells, smooth muscle cells, and endothelial cells. In human heart, IL-8 is localized mainly in cardiomyocytes (62).

IL-8 concentration was up-regulated in patients with HF compared to healthy controls (7, 63, 64). Increased IL-8 concentrations have been related with a worse clinical prognosis in patients with HF (65). However, a small study on explanted hearts from patients with end-stage HF showed down-regulated IL-8 mRNA levels in patients with HF compared to healthy donors (62). The IL-8 concentration was demonstrated to be a predictor of the HF development after myocardial infarction (66). High levels of IL-8 were associated with less improvement in left ventricular function during the first 6 weeks after STEMI. The IL-8 level was not proportional to peak troponin T concentration or infarct size after 6 weeks, which suggested that IL-8 might not be implicated in the process of necrosis (67).

Interleukin-10 improved the myocardial function and protected from adverse cardiac remodeling

Interleukin-10 (IL-10) is an anti-inflammatory cytokine produced in macrophages, activated T cells and B cells, or mast cells. IL-10 inhibits pro-inflammatory cytokines and matrix metalloproteinases synthesis. It regulates the growth, differentia-
tion, and function of cytotoxic and helper T cells, B cells, natural killer (NK) cells, granulocytes, dendritic cells, mast cells, keratinocytes, and endothelial cells. IL-10 blocks the infiltration of monocytes and macrophages into the injured site and is a strong repressor of pro-inflammatory cytokines (68).

The IL-10 level was increased in patients with HF compared with healthy people (69) and correlated positively with the NYHA class (70). However, another study demonstrated that the concentration of IL-10 was not altered in patients with HF (71). In studies on mice, IL-10 had a cardioprotective effects. The lack of the IL-10 gene resulted in a worse myocardial function and up-regulated cardiac myocyte apoptosis in animals with iso-terenol- and aortic constriction-induced hypertrophy compared with wild types. IL-10 knockout mice treated with recombinant IL-10 showed an improved systolic function, reversed cardiac remodeling, decreased caspase-3 activation, lowered hypertrophic and inflammatory gene expression, and raised anti-apoptotic Bcl2 concentration. IL-10 acted through STAT3, and it suppressed the nuclear factor-κB activation and blocked the STAT3 inhibition. A persistent STAT3 activation had effects similar to IL-10 administration, a lowered ANP, B-type natriuretic peptide (BNP), and TNF-α gene expression (71).

Several studies demonstrated the important role of IL-10 in pathophysiological pathways after myocardial infarction. The IL-10 level was up-regulated after myocardial ischemia and reperfusion injury in studies on animals, and the highest concentration reached 96–120 hours after the reperfusion (72). IL-10 inhibited infiltration of inflammatory cells and expression of pro-inflammatory cytokines in the myocardium, improved myocardial function, and protected from adverse cardiac remodeling in acute myocardial infarction in animal models (73, 74). IL-10 knockout mice demonstrated a worse left ventricular function, fibrosis, and cardiomyocyte apoptosis (74). The IL-10 administration led to down-regulation of p38 mitogen-activated protein kinase activation, reduced expression of the cytokine mRNA-stabilizing protein Hur, a decreased metalloproteinase-9 (MMP-9) activity, and inhibited fibrosis after myocardial infarction. IL-10 was responsible for increased STAT3 phosphorylation and subsequently up-regulated capillary density in the heart (75). Silencing the Hur gene resulted in an improvement in the systolic function, similarly to IL-10. It reversed cardiac remodeling, down-regulated the TGF-β, MMP-9, and p53 expression, inhibited myocyte apoptosis, and reduced the infarct size (74, 75). Moreover, IL-10 up-regulated the VEGF-A expression in cell culture through the STAT3 pathway and promoted the mobilization of bone marrow endothelial progenitor cells (75). IL-10 suppressed pathological autophagy in response to Ang II treatment via the PI3K/Akt/mTORC1 pathway (76). Atorvastatin administration enhanced the IL-10 concentration, reduced the TNF/IL-10 ratio, inhibited cardiac remodeling, and improved the systolic function in rats with HF caused by myocardial infarction (77). Regular exercise increased the IL-10 levels in both humans (78) and rats (79).

**Interleukin-17 implicated in adverse cardiac remodeling**

Interleukin-17 (IL-17) is a pro-inflammatory cytokine, which is synthesized by T helper cells, macrophages, dendritic cells, NK, natural killer T, lymphoid tissue inducer and γδ-T cells. IL-17 stimulates the production of several cytokines, which eventually results in neutrophils and monocytes recruitment to the site of inflammation (80). IL-17 acts via several pathways, including the NF-κB -DNA pathway, mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), and p42/p44 Extracellular signal Regulated Kinases (ERK) pathways (81). IL-17 cooperates with interferon-γ (IFN-γ) in the inflammatory response activation and stimulates several cytokines synthesis, including IL-6, IL-8, C-C motif chemokine ligand 5 (CCL5), C-X-C motif ligand 1 (CXCL1), C-X-C motif ligand 10 (CXCL10), complement component 5a (C5a), and soluble intercellular adhesion molecule-1 (ICAM-1) (82).

The IL-17 concentration was increased in patients with HF compared with healthy controls and correlated with the NYHA class (83). Single nucleotide polymorphisms in the IL-17 gene has been implicated with HF development risk. rs8193037 in IL-17 was an independent risk factor of ischemic and nonischemic HF, whereas rs4819554 in IL17RA was a predictor of cardiovascular mortality in patients with congestive HF (84). Several alterations in the IL-17/gp130-JAK-STAT have been demonstrated in end-stage HF. The expression of non-receptor tyrosine-protein kinase (TYK2), STAT3, and suppressor of cytokine signaling-1 (SOCS3) were reduced, whereas the expression of phospho-glycoprotein 130 (phospho-gp130) and SOCS1 were up-regulated in comparison with healthy people (85). IL-17 has been implicated in adverse cardiac remodeling after myocarditis and its progression to dilated cardiomyopathy in the mouse model (86). IL-17 contributed to the process of cardiac fibrosis, activation of matrix metalloproteinases, and enhanced cardiac cell death. IL-17 led to increased NOS (iNOS) synthesis and subsequently endothelium injury (87). It enhanced the release of pro-inflammatory cytokines, such as IL-1 and IL-6 (88), and decreased intracellular calcium levels (89).

**Pro-inflammatory role of interleukin-18**

Interleukin-18 (IL-18) is a pro-inflammatory cytokine, which is a member of the IL-1 superfamily. It is produced by macrophages, monocytes, keratinocytes, and other cells. IL-18 cooperates with IL-12 in activating cell-mediated immunity. IL-18 up-regulates the synthesis of several cytokines, including IFN-γ by NK cells and T cells (90). IL-18 has been implicated in fibroblast and smooth muscle cell proliferation and migration through the activation of the JNK and PI3-kinase pathways in *in vitro* studies (91). Interestingly, acetylsalicylic acid blocks fibroblast migration, reactive oxygen species generation, MMP9 activation, and reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) inhibition (92). IL-18 activates GATA4, which is a member of the GATA family of zinc finger transcription factors, and therefore, it up-regulates the expression of ANP in cardiomyocytes, among others (93). IL-18 also stimulates the activation of NF-κB, p38 MAPK, and ERK. IL-18 plays a role in apoptosis through both the extrinsic
and intrinsic pathway (94) and increases pro-apoptotic effects of TNF-α and enhances the caspase-3 activation (95).

The concentrations of IL-18 mRNA and protein were increased in myocardium in patients with ischemic cardiomyopathy. The expression of IL-18-binding protein (IL-18BP) mRNA was reduced in end-stage HF, whereas the IL-18 receptor α chain (IL-18Ra) level was up-regulated in both ischemic and dilated cardiomyopathy (96). The IL-18 concentration was an independent risk factor of mortality in elderly patients with HF (97). The expression of IL-18, IL-18Ra, and IL-18 mRNA were up-regulated in pressure overload-induced hypertrophy and subsequent HF in animals, whereas the IL-18BP concentration was unchanged in hypertrophied hearts and reduced in HF. Also in in vitro pressure overload models, the expression of IL-18 and IL-18Ra were increased. The IL-18 inhibition attenuated hypertrophy (97). Mice treated with IL-18 presented with cardiac hypertrophy, reduced left ventricular ejection fraction, enhanced end-diastolic pressure, up-regulated expression of ANP mRNA, and decreased β-adrenergic responsiveness to isoproterenol (98). Inhibiting the IL-18 pathway prevented the HF development (25). Moreover, cardiomyocytes incubated with recombinant IL-18 demonstrated an enhanced cell surface area, and increased ANP and BNP concentration and Akt activation (97). IL-18 knockout mice, which underwent pressure overload, demonstrated attenuated ventricular dilatation (99).

**Cardioprotective effect of interleukin-33 in HF development and progression**

Interleukin-33 (IL-33) is a member of the IL-1 superfamily. This protein is constitutively expressed in the nuclei of endothelial cells in both small and large blood vessels, in epithelial cells, smooth muscle cells, fibroblasts, and keratinocytes (100). IL-33 acts through IL-1 receptor-like 1 (IL1RL1, ST2) and IL-1 receptor accessory protein (IL-1RAcP) dimeric receptor complex, which promotes the activation of NF-κB and MAPK pathways. Two isoforms of the IL-33 receptor have been discovered, denoted a soluble (sST2) receptor and membrane-bound (ST2L) receptor, which are present in cardiomyocytes and fibroblasts. sST2 is a soluble decoy receptor, which is a mechanically induced cardiomyocyte protein and inhibits anti-hypertrophic effects of IL-33 (101). IL-33 by signaling via the MyD88, IRAK-1/4, and TRAF activates the Th2 type immune responses. In endothelial cells, IL-33 stimulates the synthesis of IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1/CCL2), vascular cell adhesion molecule-1 (VCAM-1), ICAM-1 and endothelial selectin (E-selectin), increases the vascular permeability and promotes angiogenesis (102). The IL-33 signaling pathway and downstream effector molecules are presented in Figure 3. IL-33 inhibits the atherosclerotic plaques formation via the induction of IL-5 and ox-LDL antibodies (103) and decreases adiposity, lowers fasting glucose, and improves glucose and insulin tolerance in obesity as revealed by studies on animals (104). In myocardium, it is produced mainly in cardiac fibroblasts in response to mechanical stress (105). IL-33 prevents angiotensin II- and phenylephrine-induced hypertrophy. Moreover, IL-33 activates NF-κB and blocks the phosphorylation of inhibitor of NF-κB caused by angiotensin II or phenylephrine (105). IL-33 plays a dual role, and under certain circumstances, it can act both as a pro-inflammatory or anti-inflammatory protein.

A previous study demonstrated a decreased concentration of IL-33 in patients with HF in comparison with healthy controls (106). Another study indicated that both IL-33 and ST2 were down-regulated in patients with unstable HF submitted to Left Ventricular Assist Device (LVAD) Support compared to those with stable HF. The ST2 expression was proportional to markers of inflammation. Treatment with LVAD resulted in an increase of IL-33 and ST2 level, and therefore, it was hypothesized that the IL-33/ST2 pathway was implicated in mechanical unloading and probably in inhibiting adverse remodeling (107). However, a recent study showed that the serum level of IL-33 was increased in patients with HF, whereas its bioactivity was reduced (108). IL-33 was
proportional to serum concentration of oxidative stress markers, whereas the IL-33/sST2 ratio was inversely proportional to the malondialdehyde (MDA) level. IL-33 directly down-regulated the MDA and reactive oxygen species production and enhanced the superoxide dismutase activity in cultured cells stimulated by angiotensin II (108).

Mice administered with IL-33 demonstrated decreased hypertrophy, cardiac remodeling, fibrosis, and a better survival rate after the pressure overload (105). Under hypoxic conditions, cardiomyocytes incubated with IL-33 expressed a higher level of antiapoptotic proteins, including XIAP, cIAP1, and survivin. IL-33 used in rats subjected to the ischemia–reperfusion injury led to a decreased caspase synthesis and therefore prevented apoptosis. It reduced the infarct size and fibrosis, and improved the systolic function. These effects were not seen in ST2 knockouts animals, and therefore, positive IL-33 effects could be mediated through the ST2 pathway (101).

IL-33 knockout mice subjected to pressure overload presented with more severe hypertrophy, reduced fractional shortening, adverse fibrosis, inflammation, poorer prognosis, and an increased level of natriuretic peptides RNA, including BNP and C-Myc. They also showed an up-regulated level of Th1 cytokines mRNA expression and infiltration of inflammatory cells in myocardium (109). Animals treated with IL-33 demonstrated lower expression of natriuretic peptides RNA (105). Studies on animals showed that the mRNA levels of IL-33 were enhanced in the heart up to 12 weeks after the infarction, whereas the sST2 expression was up-regulated in the first week and reduced at 4 weeks after the infarction. The level of sST2 mRNA was correlated with the expression of inflammatory, including IL-6, TNF-α, TGF-β and MCP-1, and fibrosis markers (110).

Studies on animals revealed that the lack of ST2 led to a more pronounced systolic dysfunction, left ventricular hypertrophy, adverse remodeling, myocardial fibrosis, and worse survival in both ischemic and nonischemic HF (105). SST2 competed with ST2L for IL-33 binding, inhibiting the interaction of IL-33 and ST2L. Clinical trials revealed that serum sST2 levels predicted an adverse outcome and death in patients with myocardial infarction or chronic HF (111). ST2L mediated the effect of IL-33 on Th2-dependent inflammatory processes, whereas sST2 has been implicated in the attenuation of Th2 inflammatory responses. Moreover, an increased concentration of sST2 in healthy subjects preceded adverse outcomes (112). The change in the ST2 level in patients with acute HF was predictive of 90-day mortality and was independent of BNP or N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration (113).

Other interleukins playing an important role in HF

Interleukin-5 (IL-5) is a cytokine, implicated in the growth and differentiation of eosinophils and B cells. It plays a role in the immunoglobulin production and eosinophil activation. It is synthesized by Type 2 T helper cells and mast cells (114). The IL-5 plasma concentration was reduced in patients with HF and inversely proportional to disease duration in the NYHA Class III and IV in patients with ischemic cardiomyopathy (64). The expression of IL-5 in heart was down-regulated in mice after myocardial infarction (115).

Interleukin-7 (IL-7) acts as a hematopoietic growth factor, promoting the maturation of multipotent hematopoietic stem cells into lymphoid progenitor cells. It is produced by stromal cells in the thymus and bone marrow, fibroblastic reticular cells in T-cell zones of lymph nodes, dendritic cells, epithelial cells, hepatocytes, intestinal epithelial and epithelial goblet cells, and neurons. IL-7 is responsible for the development, homeostasis, and survival of B cells, T cells, and NK cells (116). This interleukin was down-regulated in patients with HF (64). Local IL-7 synthesis played an important role in growth and maintenance of CD8+ T cells in heart, which have been implicated in myocardial damage in chronic Chagas’ disease cardiomyopathy (117).

Interleukin-9 (IL-9) is a cytokine that plays a role in regulating the differentiation of hematopoietic cells, their proliferation, and prevention of cell death. IL-9 stimulates T, B, and NK cells and the mast cell growth and function, and it induces the Th2 cytokine production. Its secretion by mast cells, NK cells, Th2, Th17, Treg, ILC2, and Th9 cells is stimulated by IL-2, IL-4, IL-25, IL-33, and TGF-β, among others. IL-9 acts through the STAT pathway (118). This cytokine was increased in patients with HF and was negatively proportional to the left ventricular ejection fraction (64). The presence of IL-9 in blood was found to be a risk factor of adverse outcome in patients with HF, and it was correlated with an impaired cardiopulmonary functional capacity (119). IL-9 acted through activating the Gp130/JAK/STAT pathway protecting from progression to HF (120).

Interleukin-13 (IL-13) is produced by CD4 cells, eosinophils, basophils, mast cells, NK cells, NK T cells, and lymphoid tissue associated with the gastrointestinal tract. IL-13 stimulates the immunoglobulin E (IgE) class switching, mediates synthesis of IgE in B cells, up-regulates the CD23 and MHC Class II expression, and modulates the resistance to intracellular parasites. It has been implicated in B-cell maturation and differentiation, reduction of the macrophage activity, and therefore inhibiting the production of pro-inflammatory cytokines (121). Plasma concentration of IL-13 in HF patients was up-regulated in comparison to healthy people. It was positively correlated with the NYHA functional class, brain natriuretic peptide and CRP levels, and negatively correlated with the left ventricular ejection fraction (122).

Conclusion

HF is a systemic disease with a multifactorial etiology. A great amount of studies demonstrated that the activation of inflammation is implicated as an important factor in the initiation and progression of HF. The immune system plays an important role in myocardial remodeling, hypertrophy, apoptosis, and fibrosis. In HF, there is an imbalance between pro-inflammatory and anti-in-
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<td>Involved in cardiac remodeling after ischemia</td>
<td>Promoted contractile dysfunction and reduced LV contractility reserve</td>
<td>Decreased contractile function and reduced LV contractility reserve</td>
<td>Prevented from LV dysfunction</td>
<td>Protected from depression of cardiac function</td>
<td>↑ proportional to NYHA functional class</td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>If restricted to short period after the injury-cardioprotective; when prolonged-ventricular dilation and HF development</td>
<td>If restricted to short period after the injury-cardioprotective; when prolonged-ventricular dilation and HF development</td>
<td>Decreased contractile function and reduced LV contractility reserve</td>
<td>Prevented from LV dysfunction</td>
<td>Cardioprotective effect of ischemic pre- and post-conditioning</td>
<td>↑ proportional to NYHA functional class</td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>Key mediator associated with inflammation</td>
<td>?</td>
<td>?</td>
<td>Worse myocardial function and up-regulated cardiac myocyte apoptosis</td>
<td>↑ or ↔; proportional to NYHA functional class</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>Anti-inflammatory; cardioprotective effects</td>
<td>Suppressed pathological autophagy</td>
<td>Inhibited infiltration of inflammatory cells; improved myocardial function; protected from adverse cardiac remodeling</td>
<td>Worsened left ventricular function, increased fibrosis, and cardiomyocyte apoptosis</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-17</td>
<td>Pro-inflammatory</td>
<td>?</td>
<td>Adverse cardiac remodeling; activation of matrix metalloproteinases; enhanced cardiac apoptosis</td>
<td></td>
<td>↑ proportional to NYHA functional class</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-18</td>
<td>Pro-inflammatory</td>
<td>Enhanced cell surface area, increased ANP and BNP concentration and Akt activation</td>
<td>Cardiac hypertrophy, reduced left ventricular ejection fraction, enhanced end-diastolic pressure, up-regulated expression of natriuretic peptides</td>
<td>Prevented from HF development; attenuated ventricular dilatation</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-33</td>
<td>Dual role, pro-inflammatory or anti-inflammatory</td>
<td>Prevented from hypertrophy, increased level of antiapoptotic proteins</td>
<td>Decreased hypertrophy, reduced infarct size and fibrosis, improved systolic function after ischemia–reperfusion injury</td>
<td>More severe hypertrophy, reduced fractional shortening, adverse fibrosis, inflammation, poorer prognosis, and increased level of natriuretic peptides</td>
<td>↑; especially in patients with unstable heart failure</td>
<td>Serum soluble decoy receptor (sST2) levels predicted adverse outcome and death</td>
<td></td>
</tr>
</tbody>
</table>

HF = heart failure; LV = left ventricular; NYHA = New York Heart Association
Interleukins in HF with reduced EF


Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.


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