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REVIEW
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The Role of Interleukin-6 Family Members in Cardiovascular Diseases

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Cardiovascular disease is one of the main causes of human mortality. Cytokines play crucial roles in the development of cardiovascular disease. Interleukin (IL)-6 family members are a series of cytokines, including IL-6, IL-11, IL-30, IL-31, OSM, LIF, CNTF, CT-1, CT-2, and CLC, that regulate multiple biological effects. Experimental and clinical evidence shows that IL-6 family members are closely related to cardiovascular diseases such as atherosclerosis, hypertension, aortic dissection, cardiac fibrosis, and cardiomyopathy. This review mainly discusses the role of IL-6 family members in cardiovascular disease for the sake of identifying possible intervention targets for cardiovascular disease prevention and treatment.

Keywords: cardiovascular diseases, IL-6 family cytokines, atherosclerosis, coronary artery disease, cardiac remodeling

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INTRODUCTION

Currently, cardiovascular diseases (CVDs) are the leading cause of human death and morbidity worldwide. They not only threaten the safety and quality of life of patients but also place a heavy burden on society (1, 2). Inflammation plays an important role in CVD, and markers of inflammation can predict future CVD events (3).

The interleukin-6 family comprises IL-6, IL-11, IL-30, IL-31, and non-IL molecules, including oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), and cardiotrophin-like cytokine (CLC). They are characterized by sharing the common receptor subunit glycoprotein 130 (gp130) and sharing the structure of four-helices with an up-up–down-down topology.

A large number of studies have confirmed that IL-6 has both proinflammatory and anti-inflammatory effects via different IL-6Rs. The receptor complexes of IL-6 are composed of IL-6R or soluble IL-6R and gp130. It seems that the proinflammatory effect mainly relies on trans-signaling mediated by sIL-6R and that the anti-inflammatory effect mainly depends on membrane-bound IL-6R (4–7). IL-6 induces Th17 differentiation, suppresses Treg differentiation, and stimulates the polarization of M2 macrophages (8–10). Lymphocytes, monocytes/macrophages, adipocytes, and hematopoietic and endothelial cells are the cellular sources of IL-6 (11). The gp130 protein is expressed in almost all tissues (12).

IL-11 is reported as a pro- and anti-inflammatory cytokine. The signal transduction process of IL-11 is similar to that of IL-6, and the IL-11/IL-11R complex needs to be formed before gp130 can be activated. Additionally, there are both classic and trans-signaling pathways through IL-11R or sIL-11R complexes (13, 14). The cellular sources of IL-11 are T cells, B cells, macrophages, cardiac myocytes, etc. The main source of IL-11 is not clear. It can induce Th2 and Th17 differentiation, suppress Th1 differentiation and inhibit macrophage activity (13).

IL-30 is the p28 subunit of IL-27 but has some functions that are independent of IL-27. IL-30 is a natural antagonist of gp130, so IL-30 may offer a therapeutic strategy against inflammation (15, 16). IL-30 has been shown to inhibit the differentiation of Th1 and Th17 cells (17). IL-30 is secreted by activated macrophages and splenocytes (18).

IL-31 is a proinflammatory cytokine that activates the receptor complex of IL-31RA and OSMR. IL-31 induces Th1 and inhibits Th17 differentiation *in vitro* (19, 20). IL-31 is secreted by T cells and granulocytes, especially Th2 cells (21).

OSM has been shown to bind to both the gp130/OSMR complex and gp130/LIFR complex and shows proinflammatory effects (22–24). *In vitro* experiments have shown that OSM inhibits the proliferation of Th17 cells and induces dendritic cell (DC) maturation and Th1 polarization (25, 26). It is secreted by activated monocytes/Møs, DCs, neutrophils, T lymphocytes, and hematopoietic cells in the bone marrow (22).

LIF is an anti-inflammatory cytokine that binds to the gp130/LIFR complex (27). LIF is highly produced by Treg cells in both humans and mice. LIF inhibits inflammation by promoting Treg differentiation and inhibiting Th17 cell differentiation (28).

CNTF binds to CNTFR and then induces heterodimerization of gp130 and LIFR, which is involved in signal transduction (29). The cellular source and its role in the immune response remain to be studied.

CT-1 plays an anti-inflammatory role and binds to the complex of gp130 and LIFR and possibly requires the CT-1R subunit in neuronal cells (30, 31). CT-1 mRNA is expressed in the adult human heart, skeletal muscle, ovary, colon, prostate, and testis. CT-1 is mainly secreted by cardiac nonmyocytes in the heart. However, the cellular source still needs to be studied (31–33).

CLC or the heterodimeric cytokine cardiotrophin-like cytokine:cytokine-like factor-1 (CLC:CLF-1) binds to CNTFR and then interacts with gp130/LIFR, which subsequently has a proinflammatory role (34–36). Evidence has shown that CLC is secreted by circulating lymphocytes and can stimulate B cells, activate Møs, and promote monocyte numbers (37–39).

The signaling pathways of IL-6 family members are similar but distinct because of their similar but distinct receptor complexes. One major signaling pathway is the activation of Janus kinase (JAK) tyrosine kinase family members, leading to the activation of the signal transducers and activators of transcription (STAT) transcription factors, mostly STAT3. Another major signaling pathway is the JAK-SH2 domain tyrosine phosphatase 2 (SHP2)-mitogen-activated protein kinase (MAPK) pathway (23, 40–43). The detailed pathways are illustrated in **Table 1**.

INTERLEUKIN-6 FAMILY MEMBERS AND CARDIOVASCULAR DISEASE

Increasing evidence demonstrates that inflammation plays an important role in the development of cardiovascular disease (51–54). IL-6 family members modulate the immune response and inflammatory activity and then participate in the development of cardiovascular diseases (41, 55, 56).

Interleukin-6 Family Members and Atherosclerosis, Coronary Artery Disease

Atherosclerosis is the leading cause of coronary artery disease (CAD). It causes life-threatening events such as thrombosis as well as the rupture or erosion of atherosclerotic plaques (57). Atherosclerosis is a chronic inflammatory disease, so many researchers have focused on the potential mediators that initiate and maintain this vascular disease (58).

The progression of carotid atherosclerosis is positively correlated with the elevation of IL-6 (59). IL-6 plays an important role in regulating the downstream inflammatory responses that contribute to the development of atherosclerosis (60, 61). IL-6 perpetuates vascular inflammation by promoting smooth muscle cell (SMC) proliferation and migration, endothelial dysfunction and the recruitment and activation of inflammatory mediators, which result in atherosclerotic plaque development and plaque destabilization (61, 62). Higher IL-6 measured at 24 h after ST-elevation myocardial infarction (STEMI) is associated with a larger infarct size and diminished cardiac function measured at 4 months. IL-6 can be a potential biomarker for STEMI prognosis and a target for improving prognosis (63). Clinical data show that IL-6 is a biomarker of mortality from unstable CAD (64). The increase in IL-6 levels has a strong relationship with future cardiac events and CAD mortality in anginal syndrome or healed myocardial infarction patients (65). The use of tocilizumab, an IL-6 receptor antagonist, reduces the inflammatory response in non-STEMI (NSTEMI) patients, which may be beneficial to patients but still needs further study (66). Canakinumab is a monoclonal antibody against IL-1β and can modulate the IL-6 pathway to decrease the major adverse cardiovascular event (MACE) rate (67). On the one hand, experimental atherosclerosis studies show that treatment with recombinant IL-6 (rIL-6) promotes early atherosclerosis in C57Bl/6 and ApoE-deficient mice. The rIL-6-treated mice showed higher plasma levels of proinflammatory cytokines such as TNFα and IL-1β, which can promote the development of fatty streaks by enhancing the accumulation of foam cells. In addition, proinflammatory cytokines can activate macrophage-monocytes so that cell migration into the intima, lipid uptake, and low-density lipoprotein (LDL) oxidation are increased (68). On the other hand, IL-6 has an atheroprotective effect because lifetime IL-6 deficiency leads to more severe atherosclerosis rather than inhibition of plaque formation. It is believed that lifetime deficiency of IL-6 breaks the balance of IL-6 and IL-10 and thus promotes the development of atherosclerosis (69, 70). OSM is expressed in atherosclerotic lesions and promotes SMC proliferation, migration and extracellular matrix synthesis, which may contribute to atherosclerosis progression. OSMR-β deficiency alleviates atherosclerosis and plaque instability. Serum OSM levels are elevated in CAD patients compared to those without CAD (71–73). Nevertheless, chronic administration of OSM can attenuate the development of plaques and improve plaque severity in APOE*3Leiden.CETP mice. The possible mechanisms might involve regeneration of the endothelial barrier, induction of SMC proliferation, and a reduction in the inflammatory Ly-6CHigh monocyte subset. Patients with higher serum OSM have increased post incident coronary heart

TABLE 1 | The receptor complexes and pathways of IL-6 family members.

	Receptors complexes	Pathways	Role in immune response	Cellular source	References
IL-6	IL-6R/sIL-6R+gp130	JAK1,JAK2,TYK2, STAT3,STAT1, MAPK, PI3K	Induce Th17 differentiation Suppress Treg differentiation stimulate the polarization of Mø	Lymphocytes, monocytes/ Mø, adipocytes, hematopoietic and endothelial cells	(5–11, 44–47)
IL-11	IL-11R/ sIL-11R +gp130	JAK, STAT3, MAPK, PI3K	Induce Th2, Th17 differentiation Suppress Th1 differentiation Inhibit Mø activity	T cells, B cells and other cell types Main source is unclear	(13, 14, 48)
IL-30	gp130	STAT1,STAT3, MAPK	Inhibit Th1,Th17 differentiation	activated Mø splenocytes	(15–18)
IL-31	IL-31RA+OSMR	STAT1, STAT3, STAT5, PI3K, MAPK	Indude Th1, inhibit Th17 differentiation	Th cells	(19, 21)
OSM	gp130+OSMR or gp130+LIFR	JAK,STAT, MAPK, PI3K, PKCδ	Inhibit Th17 activation induces dendritic cell maturation and Th1 polarization	Activated Monocytes/Mø, DCs, neutrophils,T-lymphocytes. Hematopoietic cells in the bone marrow	(22, 23, 25, 26)
LIF	gp130+LIFR	JAK1,JAK2, TYK2, STAT1,STAT3,STAT5, PI3K, MAPK	Prompt Treg differentiation Inhibit Th17 differentiation	Tregs	(27, 28)
CNTF	CNTFR+gp130+LIFR	JAK, STAT1,STAT3, MAPK, PI3K	-	-	(29, 49, 50)
CT-1	LIFR+gp130 or LIFR+gp130+CT-1R	JAK1, JAK2, TYK2, STAT1, STAT3, STAT5, MAPK, PI3K	Inhibit M1 polarization Prompt M2 polarization	Cardiac nonmyocytes	(30–33)
CLC	CNTFR+LIFR+gp130	JAK1, JAK2, TYK2, STAT1, STAT3, STAT5, MAPK, PI3K	Stimulate B cell Activate Mø Promote monocytes number	circulating lymphocytes	(34, 35, 37–39)

Mø, macrophages; DC, dendritic cell.

disease survival probability (74). Because OSM can activate both gp130/OSMR receptor complex and gp130/LIFR receptor complex. The selective inhibition of OSMR-β might be a potential therapeutic target. Further study is needed. In a rabbit model, LIF can retard the progression of atherosclerosis because it can reduce macrophages in the neointima of uninjured arteries and can regulate iNOS activity to maintain beneficial levels of nitric oxide (NO) (75, 76). CT-1 promotes the development of atherosclerotic lesions because it can induce the migration and proliferation of vascular smooth muscle cells and collagen-1 production. It can stimulate inflammatory responses, and the formation of foam cells is correlated with CD36 and ACAT1 upregulation in macrophages (77). ApoE and CT-1 double knockout (DKO) mice have smaller atherosclerotic lesions than ApoE KO mice. CT-1 deficiency induces atheroprotective immune cells, including Bregs, Tregs and B1a cells. Moreover, CT-1 deficiency is beneficial to plaque stability because DKO mice have an increased collagen content in the aortic sinus, a significant reduction in MMP9 expression and necrotic core area and an increase in the fibrous cap thickness in atherosclerotic roots. The present study demonstrates the inhibition of CT-1 attenuates atherosclerosis progression and development. But the application in patients still needed to be studied (78). Cardiotrophin-like cytokine factor 1 (CLCF1) upregulates scavenger receptor A 1 (SR-A1) expression, which is the major mechanism of the increase in lipoprotein uptake, inducing the formation of macrophage-foam cells. A murine experiment indicated that SR-A1 deficiency decreased atherosclerotic lesions (44, 79). Kim, Jun W et al. have engineered CLCF1 variants that can inhibit or activate CNTFR. The application of it in atherosclerosis might be meaningful research (80).

Interleukin-6 Family Members and Hypertension

Hypertension is a leading cause of cardiovascular events, which contributes greatly to mortality and disability. With the increased understanding of immunology, evidence that the immune system may lead to hypertension is increasing (81).

The inhibition of IL-6 attenuates the development of salt-sensitive hypertension in rat models. IL-6 KO mice have a lower mean arterial pressure (MAP) than WT mice. The deletion of IL-6 can prevent the activity of the JAK2/STAT3 pathway, which plays a role in Ang II-induced hypertension (82–84). The circulating levels of IL-6 have a positive relationship with blood pressure (85). Clinical data indicates that the hypomethylation of the IL-6 gene promoter may increase the risk of essential hypertension by upregulating the expression of IL-6 (86). CT-1 is significantly increased in untreated hypertensive patients compared with normotensive subjects (87, 88). SA study showed that excess CT-1 may contribute to inappropriate left ventricular growth in hypertension patients (89). Research on other IL-6 family members associated with hypertension remains to be conducted. Aortic stiffness is measured by pulse wave

velocity (PWV) and can predict cardiovascular morbidity and mortality in hypertension patients. Clinical data shows a positive relationship between IL-6 and PWV (90–93). Du, Bing et al. showed that the LDLr-/- mice had larger PWV and *ex vivo* intrinsic mechanical properties, which means that LDLr-/- mice had arterial stiffness. IL-6 from aortic perivascular adipose tissue (PVAT) plays a critical role in promoting arterial stiffness. What's more, the inhibition of IL-6 can attenuate arterial stiffness, and the treatment of IL-6 can aggravate (94).

Interleukin-6 Family Members and Aortic Aneurysms and Aortic Dissection

Aortic aneurysms are dilations of the aorta larger than 50% of the normal aorta diameter (95). Abdominal aortic aneurysms (AAAs) and thoracic aortic aneurysms (TAAs) are the most common aortic aneurysms (96). Acute aortic dissection (AD) is a rare disease but has high mortality. The blood penetrates the aortic wall layers and creates a so-called false lumen (FL), which is a cavity within the medial layer. The FL and true lumen (TL) are separated by dissection membranes. The rupture of the FL or a second tear in the dissection membrane would cause serious consequences (97).

The expression of IL-6 is increased in β-aminopropionitrile (BAPN)-induced AD rat models. Circulating plasma IL-6 levels are elevated in AAA patients. Experimental data support that aortic aneurysms can secrete IL-6 (98–100). Paige et al. found that selective inhibition of the IL-6 trans-signaling pathway can decrease aortic rupture and death in 2 AAA mouse models, which shows us a potential therapeutic target for AAA (101). The expression of IL-6 is increased in AD rat models. IL-6 may enhance the expression of MMP-2 and may promote extracellular matrix degradation of the vascular wall, which promotes the formation of AD (98). Lv, Xiao-Chai et al. found that plasma IL-6 level is elevated in postoperative delirium (POD) patients after aortic dissection surgery. Thus, plasma IL-6 values can be used to evaluate AAD patients' POD outcomes (102). Besides, the high level of IL-6 and D-dimer has predictive value in assessing the poor prognosis after acute Stanford type A aortic dissection surgery (103). IL-11 is significantly increased in thoracic AD and can be a potential biomarker for AD (104). OSM is a proinflammatory mediator and is upregulated in abdominal AD patients. Thus, it may contribute to the development of aortic aneurysms (105, 106). The level of CT-1 is higher in AAA tissues. CT-1 can stimulate aortic endothelial cells to overproduce MMP-1, which leads to ECM degradation. These mechanisms are associated with the formation and progression of AAA (107, 108).

Interleukin-6 Family Members and Cardiac Remodeling

Cardiac fibrosis is characterized by the excessive deposition of extracellular matrix (ECM) proteins that results in the expansion of the cardiac interstitium, which is a common pathophysiologic companion of most myocardial diseases. It is related to cardiac dysfunction, arrhythmogenesis, and adverse outcomes (109, 110). Cardiomyopathy is a disease that weakens the heart muscle, attenuating the heart's ability to pump blood and possibly leading to heart failure (HF) (111). HF is a complex clinical syndrome that is caused by structural or functional impairment of ventricular filling or ejection of blood (112). Proinflammatory cytokines trigger a series of pathological responses, such as oxidative stress, endothelial dysfunction, induction of myocyte apoptosis, and hypertrophy, which ultimately leads to cardiomyocyte dysfunction (113).

An experimental study showed that IL-6 plays a central role in myocardial fibrosis that depends on the activation of the MAPK and CAMKII-STAT3 pathways. IL-6 is a downstream signal of hypoxia-induced mitogenic factor (HIMF), and its inhibition can prevent fibroblast activation (114). In addition, the overexpression of IL-6 increases TGF-β1-mediated MMP2/MMP3 signaling to induce myofibroblastic proliferation, differentiation, and fibrosis (115). IL-6 KO mice had a lower degree of cardiac fibrosis. Thus, anti-IL-6 can be a potential therapeutic target for decreasing cardiac fibrosis (116). The expression of IL-11 is positively related to myofibroblast numbers and is higher in mice with cardiac fibrosis than in wild-type mice (117). Anti-IL-11 treatment can attenuate the profibrotic effect on the heart of transverse aortic constriction (TAC) mouse model (118). Interestingly, Obana et al. found that IL-11 attenuates cardiac fibrosis in mouse models after myocardial infarction through the activation of STAT3 (119). Thus, when faced with different diseases, the appropriate application of IL-11 or its antagonist is a potential therapeutic target and needs further investigation. The antifibrotic effects of OSM are achieved by inhibiting the TGF-β1-mediated activation of cardiac fibroblasts in TAC mouse models (120). LIF cDNA injection was found to attenuate cardiac fibrosis in mice after myocardial infarction (121). Chronic administration of LIF improves the heart function of mice (122). Therefore, LIF may be a novel treatment for cardiac fibrosis. López et al. found that CT-1 can be a biomarker of myocardial fibrosis (123). CT-1 is believed to promote the development of cardiac fibrosis by upregulating Gal-3 through the ERK 1/2 and STAT3 pathways (124).

Clinical data have demonstrated that idiopathic dilated cardiomyopathy patients with higher serum IL-6 have a lower ejection fraction and worse prognosis (125). Serum IL-6 concentration is increased in patients with takotsubo cardiomyopathy (126). IL-6 KO mice with dilated cardiomyopathy showed better cardiac function and less myocardial cell apoptosis than WT mice with dilated cardiomyopathy because of the inhibition of STAT3 (127). The inhibition of IL-6/STAT3 signaling pathway may offer a new target for cardiomyopathy. Diabetic cardiomyopathy mice exhibited increased OSM. Moreover, OSM-treated diabetic mice exhibit worse cardiac function. Knockout of the OSM receptor Oβ attenuated dilated cardiomyopathy injury by inhibiting the B-Raf/MEK/ERK cascade (128). OSM is consistently upregulated in dilated cardiomyopathy patients and mouse models. OSM protects the damaged myocardium by inducing dedifferentiation. However, prolonged stimulation with OSM prompts the progression of HF in dilated cardiomyopathy (129). The plasma levels of CT-1 are increased in hypertrophic

cardiomyopathy and are associated with the severity of left ventricular hypertrophy (130). The expression of CT-1 is increased in the acute stage of Chagas disease (131). The plasma level of CT-1 is increased in dilated cardiomyopathy patients with congestive HF compared to control subjects (132).

An observational study showed that higher IL-6 plasma levels were found in half of HF patients and were associated with reduced left ventricular ejection fraction (LVEF), atrial fibrillation, and poorer clinical outcomes (133, 134). Genetic deletion of IL-6 alleviates left ventricular dysfunction through the STAT3 pathway in a transverse aortic constriction-induced pressure overload-HF mouse model (135). Moreover, the inhibition of IL-6/STAT3 by raloxifene can attenuate inflammation in the same model (136). Higher plasma IL-11 levels predict poor outcomes in HF patients (137). Plasma OSM levels are elevated in HF patients with reduced ejection fraction (HFrEF) (138). Kubin, Thomas et al. found that OSM is the key modulator of HF that induces cardiomyocyte dedifferentiation and contractility loss through the MAPK cascade in a mouse model of left anterior descending coronary artery (LAD) ligation (129). LIF mRNA is elevated in the left ventricle of congestive HF patients, and the circulating LIF level is increased with the deterioration of congestive HF (139, 140). Moreover, the upregulation of LIF in the ventricle was reproduced in the Dahl salt-sensitive (DS) rat chronic HF model (141). Myocardial and circulating CT-1 levels are increased in HF patients and are positively correlated with HF patient mortality, which can be used as a biomarker for determining prognosis (124, 142–144). CT-1 upregulates galectin-3 (Gal-3) via the ERK 1/2 and STAT3 pathways to promote cardiac fibrosis and hypertrophy, which are involved in the development of HF (124). López, Natalia et al. illustrate that LIFR is downregulated in spontaneously hypertensive rats HF model that attenuates the cytoprotection of CT-1. The upregulation of LIFR might be a potential target (145).

Interleukin-6 Family Members and Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia and leads to detrimental consequences. Increasing evidence supports that inflammation plays a crucial role in the pathophysiology of AF (146, 147). Thus, the process of inflammation is a potential therapeutic target for AF.

Amdur et al. found that elevated levels of IL-6 are associated with an increased risk of AF in chronic kidney disease (CKD) patients, which suggests that IL-6 can serve as an inflammatory biomarker for AF in CKD patients (148). Also, IL-6 levels are associated with AF in CAD patients (149). Elderly patients who received recombinant human IL-11 were observed to have an increased incidence of AF (150). OSM is increased in atrial tissue of AF patients with thrombus (151). Patients with higher levels of CT-1 have more frequent AF relapse (152). The correlation between the IL-6 family and AF still needs further study.

TABLE 2 | The expression of IL-6 family members on cardiovascular diseases.

Disease	IL-6	IL-11	OSM	CT-1	Reference
AS	Increase	-	Increase	Increase	(59, 71, 78)
CAD	Increase	-	Increase	-	(63, 73)
Hypertension	Increase	-	-	Increase	(85, 87, 88)
AA, AD	Increase	Increase	Increase	Increase	(98–100, 104, 105, 108).
Cardiomyopathy	Increase	-	increase	Increase	(126, 129, 131, 132)
AF	Increase	Increase	Increase	Increase	(148, 151, 152)
Myocarditis	-	-	-	Increase	(158)

AS, atherosclerosis; CAD, coronary artery disease; I/R, ischemic-reperfusion; AA, arterial aneurysm; AD, aortic dissection; AF, atrial fibrillation.

Interleukin-6 Family Members and Myocarditis

Myocarditis is an uncommon but potentially life-threatening heart disease (153). Myocarditis induces a broad range of pathological immune processes in the heart, which causes structural and functional abnormalities (154).

IL-6 plays a key role in the development of autoimmune heart disease, possibly by upregulating complement C3. IL-6 KO mice with autoimmune myocarditis showed a reduction in inflammatory responses, the proliferation of autoreactive CD4+ T cells, and the expression of ICAM-1 and VCAM-1, which reduced myocarditis susceptibility (155). IL-6 is crucial for Th17 differentiation through the induction of retinoic acid receptor-related orphan nuclear receptor, which is a critical event in the onset of experimental autoimmune myocarditis (EAM). The blockade of IL-6R inhibits the initiation of EAM (156). Adequate levels of IL-6 attenuate the damage from viral infection in the early stage of inflammation. Nevertheless, overexpression of IL-6 aggravates viral myocarditis (157). CT-1 is expressed in cardiac myocytes infected with Coxsackievirus B3 (CVB3) and induces pathologic responses in acute myocarditis. However, the early expression of CT-1 might have a protective effect on cardiac myocytes by inhibiting TNF-α and IL-1α expression (158).

Interleukin-6 Family Members and Cardiac Ischemia Reperfusion Injury

Reperfusion of the myocardium can induce further cardiomyocyte apoptosis after cardiac ischemia, such as occurs with myocardial infarction or heart transplantation (159). Many studies have shown that myocardial apoptosis mediated by inflammation is one of the crucial processes of ischemia-reperfusion (I/R) injury (160, 161).

IL-6 prompts the development of infarction after cardiac I/R injury, whereas IL-6 deficiency attenuates I/R injury. However, the beneficial effects cannot be explained by modification of other inflammatory mediators, coagulation activation, or neutrophil influx. The related mechanisms need to be further explored (162). The administration of IL-11 has a protective effect on the heart from I/R injury via the STAT3 pathway. Thus, it can be a potential therapeutic target against I/R injury (163,

TABLE 3 | Regulation of IL-6 family members on cardiovascular disease.

Disease	IL-6	IL-11	OSM	LIF	CT-1	CLC	Reference
AS	Aggravate	-	Controversial	Alleviate	Aggravate	Aggravate	(44, 60, 71, 74, 75, 77)
CAD	Aggravate	-	Alleviate	-	-	-	(65, 74)
Hypertension	Aggravate	-	-	-	Aggravate	-	(83, 89, 135)
AA, AD	Aggravate	-	Aggravate	-	Aggravate	-	(98, 101, 105–108)
Cardiac fibrosis	Aggravate	Controversial	-	Alleviate	Aggravate	-	(114–117, 121, 122, 124)
Myocarditis	Aggravate	-	-	-	Controversial		(155, 156, 158)
Cardiomyopathy	-	-	-	-	Controversial		(129)
I/R	Aggravate	Alleviate	Alleviate	Alleviate	Alleviate		(162–170)

AS, atherosclerosis; CAD, coronary artery disease; I/R, ischemic-reperfusion; AA, arterial aneurysm; AD, aortic dissection; AF, atrial fibrillation.

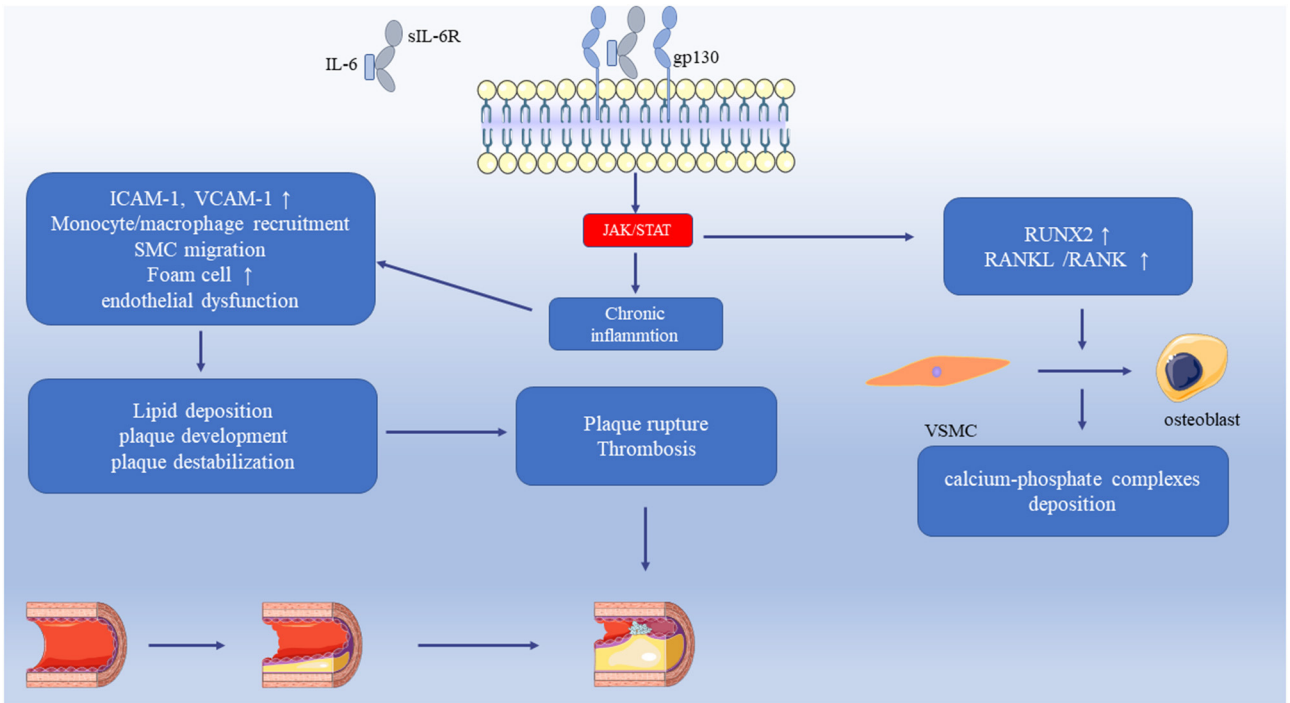

FIGURE 1 | The relationship between IL-6 and atherosclerosis, MI, and vascular calcification. The IL-6 trans-signaling activates the JAK/STAT pathway that leads to chronic inflammation. It increases the adhesion molecules in the vasculature, endothelial dysfunction, the recruitment of monocytes/macrophages, and SMC migration. Monocytes uptake LDL and transform into foam cells that accelerate the progression of atherosclerosis. These pathological processes cause lipid deposition, plaque development, and plaque destabilization. With increasing severity of atherosclerosis, the plaque ruptures, and thrombosis result in myocardial infarction. IL-6 upregulates RUNX2 and RANKL/RANK, which induces the differentiation of VSMC to osteoblast and then induces the calcium-phosphate complexes deposition. JAK, Janus Kinase; STAT, Signal transducers and activators of transcription; LDL, Low-density lipoprotein; RUNX2, Runt-related transcription factor 2; RANKL, Receptor activator of NF-κB ligand; SMC, Smooth muscle cell; VSMC, Vascular smooth muscle cell.

164). OSM is thought to be an important factor for tissue repair after cardiac I/R injury because it upregulates monocyte-chemoattractant-protein (MCP-1) expression and stimulates the proliferation of fibroblasts (165). Experimental data show that OSM protects the heart against cardiac I/R injury through the regulation of mitochondrial biogenesis, cardiomyocyte apoptosis, and insulin sensitivity in diabetic mice (166). OSM can alleviate cardiac dysfunction and reduce the infarct size in mice partly through the Notch3/Akt and AMPK/PGC-1α pathways (167). Pretreatment with LIF has a protective effect on the heart against cardiac I/R injury (168). The significant protective effect that CT-1 has on the heart after I/R injury depends on the activation of the p42/p44 MAPK pathway (169, 170).

Interleukin-6 Family Members and Other Cardiovascular Diseases

IL-6 family members are also associated with other cardiovascular diseases, such as ventricular fibrillation, congenital heart disease (CHD), and vascular calcification.

Elevated IL-6 serum levels are correlated with the occurrence of spontaneous ventricular tachyarrhythmia and ventricular fibrillation in implantable cardioverter-defibrillator (ICD)-recipient patients with CAD and idiopathic dilated cardiomyopathy (171). The IL-6 variant rs1800795 is associated with CHD among Chinese Han people (172). Moreover, serum IL-6 levels are higher in CHD groups than in control groups (173, 174). Myocardial IL-11 and IL-6 levels are elevated in CHD children and downregulate the microRNA-199a-5p-mediated unfolded protein response through the STAT3 pathway (175). CT-1 is induced in CHD patients and is negatively correlated with arterial oxygen saturation (176). Clinical data show serum IL-6 levels are elevated in hemodialysis patients and chronic kidney disease patients with vascular calcification (177–180). IL-6 promotes vascular calcification by inducing the differentiation of VSMCs into osteoblast-like cells. IL-6/STAT3 pathway upregulates *RUNX2* gene expression, which is an important transcription factor of the differentiation of osteoblast (181). The activation of IL-6-mediated receptor activator of NF-κB ligand(RANKL) plays a crucial role in the development of vascular calcification. And the anti-IL-6 treatment can reduce the SMC calcification (182–184). Moreover, Lee, Guan-Lin et al. also showed the inhibition of IL-6 can attenuate the VSMC calcification (185).

CONCLUSION

This review describes the molecular receptors of the IL-6 family members, related signaling pathways, and their role in the regulation of inflammation. IL-6 family signal transduction is similar and is dominantly mediated by STAT3. The expression and regulation of IL-6 family members in cardiovascular disease are summarized in **Tables 2**, **3**. Some family members, especially IL-6, have both pro- and anti-inflammatory effects through different receptors and pathways. Thus, the selective inhibition of trans-signaling rather than global inhibition might be a future therapeutic strategy. Cytokines affect the progression of cardiac pathology by regulating complex signaling networks. We illustrated the relationship between IL-6 and atherosclerosis, MI, and vascular calcification in **Figure 1**. Further research is needed to discover potential therapeutic targets and biomarkers for cardiovascular disease.

AUTHOR CONTRIBUTIONS

YF and DY wrote this article. ZW, HP, XL, MW, YX, JYu, JZ, MZ, SX, WP, and ZY searched the literature. JYe and JW provided ideas and financial support. All authors contributed to the article and approved the submitted version.

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