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REVIEW

Progress of Research into the Interleukin-1 Family in Cardiovascular Disease

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Abstract: Inflammatory factors, such as the IL-1 family, are generally acknowledged to be involved in systemic diseases and IL-1α and IL-1β, in particular, have been linked to cardiovascular disease with IL-18, IL-33, IL-36, IL-37 and IL-38 yet to be explored. The current review aims to summarize mechanisms of IL-18, IL-33, IL-36, IL-37 and IL-38 in myocardial infarction, hypertension, arrhythmia, valvular disease and aneurysm and to explore the potential for cardiovascular disease treatment strategies and discuss future directions for prevention and treatment.

Keywords: cardiovascular disease, interleukin-1 family, myocardial infarction, hypertension, arrhythmia

Introduction

Cardiovascular disease (CVD) often occurs in middle-aged or older patients[1,2] and CVD morbidity and mortality are on the rise along with global aging.[3–5] In addition, the population of CVD patients has become younger as obesity, poor lifestyle, dietary habits and substance abuse (cocaine, e-cigarettes) increase in the youthful population.[6] Countries in the Asian region, such as China and India, have the highest global burden of CVD due to their large population bases.[7,8] Therefore, mechanisms of CVD pathogenesis require urgent attention.

A great deal of research has allowed us to conclude that inflammatory responses are involved in human physiological and pathological processes.[9–13] The interleukin-1 family has numerous family members that stimulate inflammation-related genes and contribute to intestinal diseases, tumors, rheumatoid arthritis, liver and kidney diseases, skin diseases and neurological disorders[14–19] and have been shown to affect human metabolism, sleep, appetite and mood.[20] The interleukin-1 family can be broadly divided into two types, pro-inflammatory, IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ, and the anti-inflammatory, IL-1Ra, IL-36Ra, IL-37 and IL-38.[21] Recent studies have focused on IL-1 and its isoforms, IL-1α, IL-1β and IL-1Ra[22–26] but other family members also deserve scrutiny. IL-18 drives myeloid-derived suppressor cell production and suppresses T-cell responses to promote multiple myeloma.[27] IL-33 mediates microglia synaptic phagocytosis in central nervous system development.[28] Targeted inhibition of IL-36 signaling is used to treat pustular psoriasis[29] and both IL-37 and IL-38 suppress allergic disease, with the former binding maternal anti-alopecia homolog 3 and entering the nucleus to affect gene transcription,[30] and the latter antagonizing the ERK1/2 and NF-κB pathways and upregulating host defense genes.[31] The interleukin-1 family has been linked to CVD and IL-1α creates a pro-thrombotic microenvironment by inducing IL-6 production while IL-1β drives inflammation during atherosclerosis.[32] Low-grade chronic inflammation mediated by IL-1 is involved in vascular aging, and increased expression of IL-1Ra has been observed in the elderly.[33] IL-1 also affects L-type calcium channels through altered gene expression or IL-1R signaling to trigger heart failure.[34] CVD-related mechanisms of IL-1 have been extensively reported and will not be repeated here. Instead, the focus will be on the mechanisms of IL-18, IL-33, IL-36, IL-37 and IL-38 in CVD and development of therapeutic strategies will be discussed.

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Regulation of Interleukin-1 Family in Cardiovascular Diseases

Myocardial Infarction

Thrombosis, coronary spasm and atherosclerotic plaque erosion due to acute rupture of coronary atherosclerotic plaque are common causes of coronary heart disease. All may lead to coronary occlusion, distal myocardial blood supply obstruction and myocardial infarction (MI).[35,36] Myocardial injury results in the secretion of cytokines by fibroblasts to mediate inflammatory responses.[37] Mild inflammatory responses facilitate myocardial repair while excessive responses lead to cardiac adaptive remodeling and systolic dysfunction, precipitating the condition of heart failure.[38]

MI involves the formation of the leukocyte NLRP3 inflammasome in the infarcted area and the activation of IL-1β and IL-18 in the presence of caspase-1.[39] Cardiomyocytes express and activate IL-18 but not IL-1β, even in the presence of high-dose stimulation.[39] IL-18 has been shown to be involved in vascular fibrosis and the promotion of atherosclerotic plaques[40] and is considered to be a predictor of inflammation risk in MI patients.[41] IL-18 acts synergistically with IL-12 and IL-15 to induce IFN-γ secretion, enhance TH1-type immune responses and induce post-MI fibrosis.[42,43] IL-18 also triggers release of adhesion molecules, GM-CSF and iNOS, and promotes vascular endothelial cell apoptosis, inhibits cardiac contractile function and induces myocardial fibrotic remodeling.[44,45] IL-18 is cross regulated with inducers of extracellular matrix metalloproteinase (EMMPRIN), promoting MMP-9 release, amplifying and exacerbating MI.[46] Silencing of EMMPRIN reduced myocardial remodeling by IL-18.[43] Moreover, targeted inhibition of the IL-18/TGFβ1/P-SMAD2/3 pathway in a model of MI reduced synthesis of the pro-fibrotic proteins, EDA-Fibronectin, Periostin, Vimentin and α-SMA.[47] Similar results were reported for a mouse model of ischemia-reperfusion (I/R). IL-18 blockade reduced infiltration of monocytes and CD4+ T cells in the mouse myocardium, TH17 cell differentiation was inhibited and I/R injury attenuated.[48] The conclusion can be drawn from previous studies that elevated post-MI IL-18 exacerbates disease progression. Blockade of the IL-18 signaling pathway appears beneficial but further studies are needed to observe long-term effects.

Many tissues express IL-33. Cardiac fibroblasts are responsible for their synthesis within the heart.[49,50] The IL-33 receptor, ST2, has a soluble isoform, sST2, which often acts as a decoy receptor, and the alternative, ST2L to which IL-33 binds and forms an active complex with IL-1R accessory protein.[49] Current studies have focused on the IL-33/ST2 axis. IL-33 enriches regulatory T lymphocytes (Tregs) in mouse models of MI and I/R via IL-33/ST2 and increases Sparc expression to promote collagen maturation and maintain cardiac integrity.[51,52] Binding of IL-33 to ST2 amplified the group 2 innate lymphocyte (ILC2) population, including IL-13, Areg and BMP-7. IL-13 promotes M2-type macrophage polarization, BMP-7 inhibits TGF-β1 signaling and Areg acts on cardiomyocytes. These factors work together to alleviate post-infarction myocardial fibrosis.[53] However, Mia et al found that blockade of the IL-33/ST2 signaling pathway in an MI model attenuated Yap/Taz-induced conversion of cardiac fibroblasts to myofibroblasts, attenuating myocardial fibrosis.[54] Thus, IL-33 has the potential to exacerbate myocardial injury. The influences of IL-33 on MI remain controversial and further exploration is required.

IL-36 has four isoforms with different impacts on MI, three agonists, IL-36α, IL-36β and IL-36γ, and one natural inhibitor, IL-36Ra.[55,56] IL-36γ upregulates macrophage CD36 expression via the phosphatidylinositol 3-kinase pathway, amplifying the inflammatory response and promoting uptake of oxidized low-density lipoprotein to stimulate foam cell formation and atherogenesis.[57] Indeed, targeted inhibition of the IL-36(α/β)/IL-36R pathway attenuated oxidative damage to the vascular endothelium and VCAM-1 and ICAM-1 expression in an I/R mouse.[58] IL-36 has hitherto received little attention with respect to MI and isoform functions require characterization.

IL-37 is a cytokine with anti-inflammatory effects which is elevated in the peripheral blood of MI patients.[59] IL-37 amplified Tregs and suppressed TH1 and TH17 cells in PBMC of 129 infarct patients, exerting a protective effect.[60] Injection of induced cardiosphere overexpressing IL-37 into an I/R model reduced myocardial infarct size, improved left ventricular function and downregulated pro-inflammatory cytokines.[61] Moreover, IL-37 contributed to increased proportions of M2-type macrophages and reduced infiltration by pro-inflammatory macrophages and collagen deposition in the myocardium of an MI model, perhaps due to inhibition of NOTCH1 and NF-κB signaling pathways.[62,63] IL-37 also mediated lipid metabolism via the IL-1R8/TLR4/NF-κB signaling pathway to reduce MI.[64] In conclusion, IL-37 influences CD4+ T cell typing, promotes macrophage transformation and regulates lipid metabolism during MI. The

IL-37 amplification of Tregs is similar to the IL-33/ST2 signaling pathway and research is necessary to demonstrate whether these two cytokines engage in cross-talk.

IL-38 is considered anti-inflammatory in various diseases[31,65,66] and inhibited the NLRP3 inflammasome and NF-κB and MAPK signaling pathways downstream of IL-36 to block vascular injury during MI.[67] Anti-inflammatory effects also result from IL-38 stimulation of the IL-1RAPL1/JNK/AP1 pathway[68] and IL-38 promotes the M1 to M2 phenotypic switching in macrophages.[69] The IL-38 receptor has yet to be characterized along with the site of macrophage binding (Figure 1).

Hypertension

Hypertension is a common and complex clinical syndrome with multiple pathological mechanisms,[70] often caused by low-grade chronic inflammation of the kidney and blood vessel walls.[71,72]

Chronic kidney disease is associated with CVD[73] and IL-18, a product of NLRP3 inflammation, has been demonstrated to be involved in the initiation and maintenance of renal inflammation.[71,74,75] IL-18 stimulates ICAM-1 and VCAM-1 secretion by vascular endothelial cells to precipitate renal inflammation and hypertension and to mediate leukocyte aggregation, causing damage to the vascular endothelium. Three signaling pathways are involved, IL-18/Src/ERK, IL-18/PI3K/AKT and IL-18/MyD88/TRAF/IRAK/NF-κB.[73] However, whether IL-18, like the NLRP3 product, IL-1β, has a role in mediating central system inflammation and causing salt-sensitive hypertension is far from clear.[76] IL-18

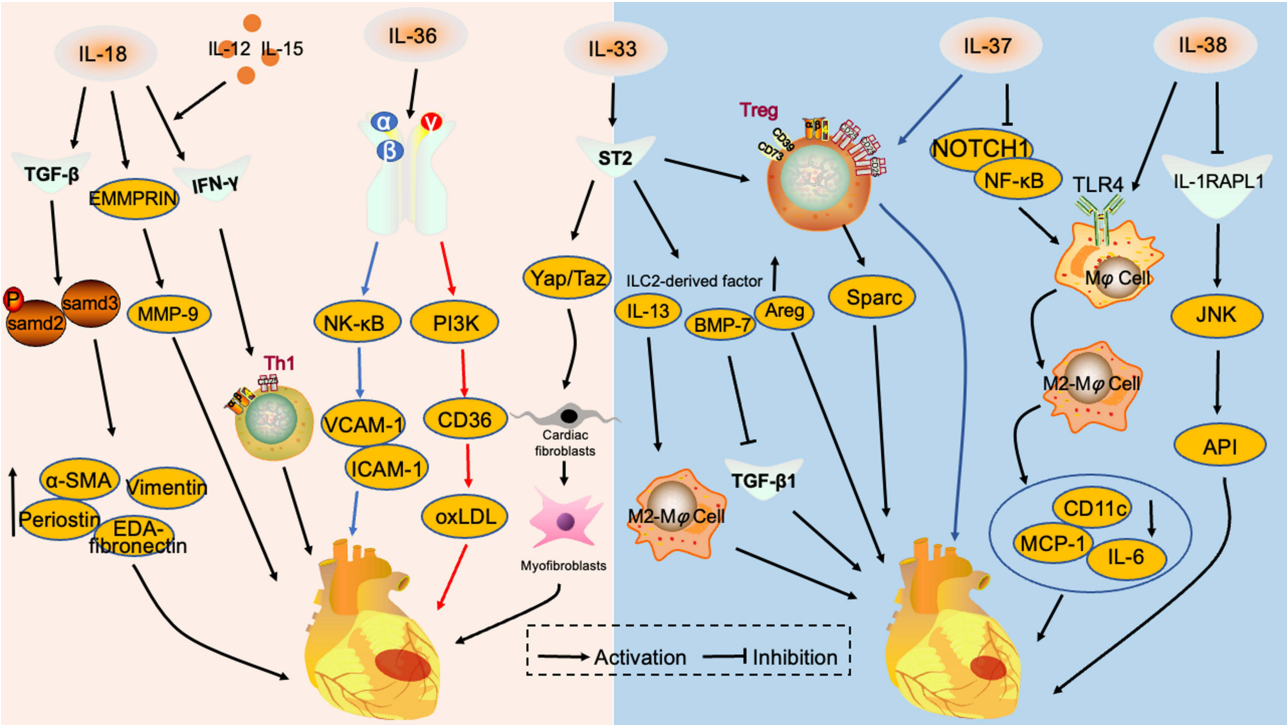

Figure 1 Interleukin 1 family in myocardial infarction. IL-18 promotes the expression of pro-fibrotic proteins, EDA-Fibronectin, Periostin, Vimentin and α-SMA, by activating the TGF-β/P-samd2/3 signaling pathway and cross-regulates with EMMRPRIN to promote MMP-9 release. IL-18 acts synergistically with IL-12 and IL-15 to induce IFN-γ release and enhances TH1-type immune responses. These mechanisms aggravate myocardial infarction. IL-36α/β promotes VCAM-1 and ICAM-1 release through NF-κB signaling pathway and aggravates endothelial cell injury. IL-36γ upregulates CD36 through the PI3K signaling pathway, promotes oxLDL secretion and aggravates atheromatous plaque progression. IL-33 stimulates ST2 receptors and activates the Yap/Taz signaling pathway, promoting conversion of cardiac fibroblasts to myofibroblasts. IL-33 binds to ST2 and amplifies the group 2 innate lymphocyte population, including IL-13, Areg and BMP-7. IL-13 promotes M2-type macrophage polarization, BMP-7 inhibits the TGF-β1 signaling pathway and Areg acts directly on cardiomyocytes. IL-37 inhibits NOTCH1 and NF-κB signaling pathways, promotes the M2 conversion of macrophages and reduces the secretion of pro-inflammatory factors and chemokines, inhibiting myocardial infarction progression. IL-38 binds to the IL-1RAPL1 receptor to exert anti-inflammatory effects through the JNK/AP1 signaling pathway and alleviate myocardial infarction.

Abbreviations: TGF-β, transforming growth factor-β; α-SMA, α-Smooth muscle actin; EMMRPRIN, extracellular matrix metalloproteinase inducer; MMP-9, matrix metalloproteinases-9; IFN-γ, interferon-γ; NF-κB, nuclear factor kappa B; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; PI3K, phosphatidylinositol 3-kinase; oxLDL, oxidized low-density lipoprotein; ST2, growth ST imulation expressed gene 2; BMP-7, bone morphogenetic protein 7; Sparc, secreted protein acidic and rich in cysteine; TLR4, toll-like receptor 4; MCP-1, monocyte chemoattractant protein-1; IL-1RAPL1, interleukin 1 receptor accessory protein-like 1; Treg, regulatory T cells; JNK, c-jun N-terminal kinase; API, activator protein 1.

connects kidney disease and hypertension and elevated IL-18 has been associated with arterial stiffness in patients with metabolic syndrome, weakening the elastic reservoir effect of the artery and increasing late systolic blood pressure.[40] IL-18 is a promising therapeutic target in hypertension and its mechanism merits further scrutiny.

Blood pressure correlates with structural changes to the left ventricle and higher blood pressure puts mechanical strain on cardiac myocytes.[77] IL-33 was elevated when myocardial endothelial cells were subject to mechanical stretch. It binds to the ST2L receptor, producing an anti-hypertensive, anti-myocardial hypertrophy effect. By contrast, the sST2 receptor competes for IL-33 binding, antagonizing this effect.[78] Heterodimerization of ST2L and IL-1RAcP in the presence of IL-33 activates NF-kB and AP-1 to promote hypertension.[79] IL-33 restored perivascular adipose tissue (PVAT) activity mediated by eosinophils and vascular anti-constriction to reverse hypertension in a model of obesity.[80] Roles of IL-33/ST2 in hypertension remain controversial and the impact of IL-33 on PVAT merits further attention.

Obesity is a common cause of high blood pressure.[81–83] IL-36 stimulated the MAPK (p42/p44) pathway, promoting increased intestinal mucus secretion and intestinal commensal *A. muciniphila* abundance to reduce diet-induced weight gain in mice.[84] IL-36 influence on blood pressure was not studied during the above work but the gut microbiome is known to correlate with hypertension.[85–88] IL-36 may influence blood pressure by an effect on gut microbes. Nishikawa suggested that IL-36 aggravates acute kidney injury and exacerbates hypertension through upregulation of NF-κB, TNF-α and IL-6 activities.[89] The effect ofIL-36 on other organs should be considered in the context of treatment strategies for hypertension.

IL-37 has been shown to be associated with hypertension,[90] regulating immune cell differentiation and inhibiting inflammatory factor release.[91] IL-37 may reduce vascular endothelial damage during hypertension by mediating NO bioavailability while reducing NADPHO-associated products.[92] Mice injected with recombinant IL-37 had reduced secretion of the inflammatory factors, IL-1β, CXCL-1 and TNFα, in epididymal adipose tissue and improved systemic insulin resistance status. A similar effect was observed in human adipocytes and AMPK and the mTOR signaling pathway have been implicated.[93] The protective effect of IL-37 in hypertension appears largely due to inhibition of inflammatory factor release.

There is a paucity of reports demonstrating direct effects of IL-38 on hypertension but its anti-inflammatory and hyperlipidemia modulating effects may be involved.[31,94] IL-38 inhibited human adipocyte differentiation and reduced secretion of inflammatory cytokines, IL-1β and MCP-1,[95] and IL-38 reduction of joint inflammation involved the NF-κB signaling pathway also known to be involved in hypertension.[96,97] Macrophages, smooth muscle cells and vascular endothelial cells also release IL-38 under apoptotic conditions and affect the circulatory Bcl-2/Bax/Caspase-3 signaling pathway, attenuating hyperlipidemia.[68,94] No direct relationship between IL-38 and hypertension has yet been shown but this molecule does seem to ameliorate the disorder (Figure 2).

Arrhythmias

Arrhythmias occur alone or as a complication of various types of heart disease and in severe cases increase the risk of death.[98] Inflammatory leukocytes may cause arrhythmias by switching phenotypes or interfering with conduction between cardiomyocytes.[99]

Increased IL-18 in the peripheral circulation has been associated with atrial fibrillation and could be considered a potential therapeutic target.[100,101] Indeed, the QT interval in sickle cell cardiomyopathy patients was strongly correlated with plasma IL-18 and IL-18 increased susceptibility to ventricular arrhythmias, perhaps through the NF-κB signaling pathway.[102] Inhibition of IL-18 via a binding protein improved cardiac diastolic function and targeting this molecule may be beneficial for patients at risk of sudden cardiac death.

IL-37 level correlated with the type of atrial fibrillation (AF), levels being lower in patients with paroxysmal and persistent AF than in those with permanent AF.[103] IL-37 treatment decreased IL-6 and CRP secretion in in vitro experiments.[103] Thus, IL-37 appears to have a protective effect in AF, perhaps through inhibition of the NF-κB signaling pathway.

Targeting the inflammatory response may be an appropriate therapeutic foundation for the treatment of atrial fibrillation.

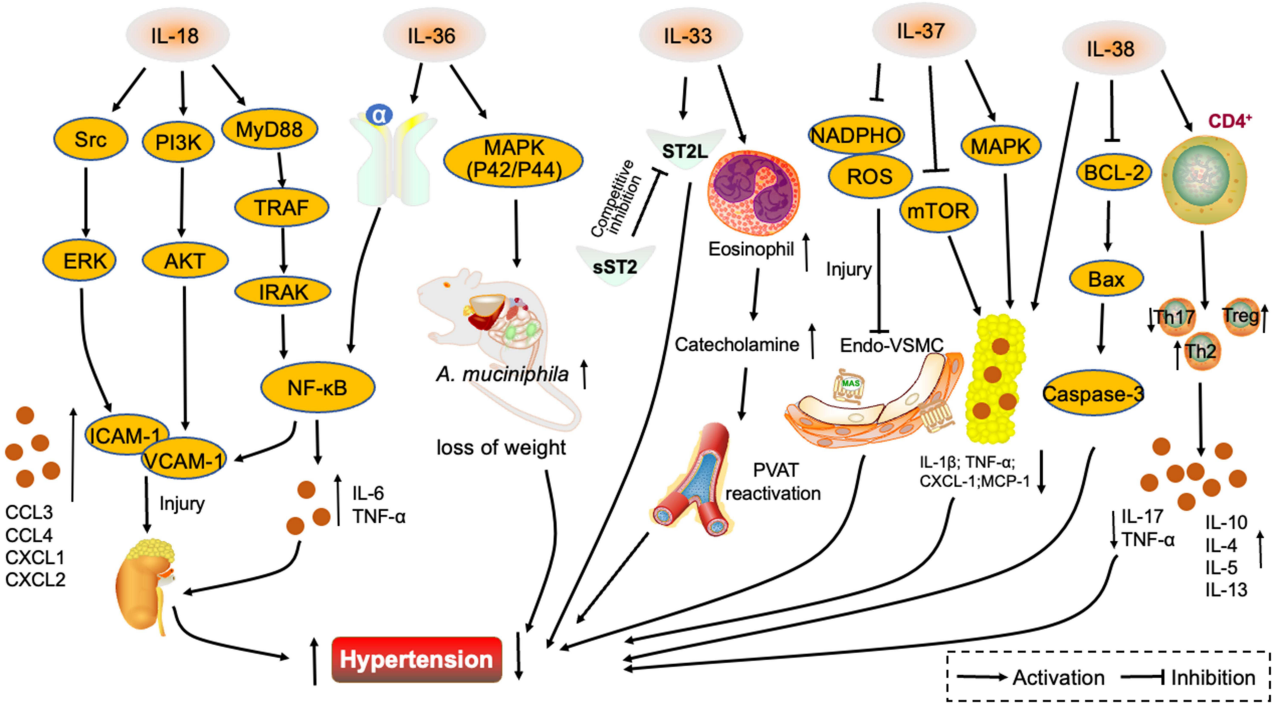

Figure 2 Interleukin 1 family in hypertension. IL-18 promotes VCAM-1 and ICAM-1 secretion through three signaling pathways, Src/ERK, PI3K/AKT and MyD88/TRAF/IRAK/NF-κB. Renal vascular endothelial injury is exacerbated and hypertension promoted. IL-36α stimulates the NF-κB signaling pathway, IL-6 and TNF-α are secreted, renal vasculature damaged and hypertension aggravated. IL-36 activates the MAPK signaling pathway, upregulates *A. muciniphila* abundance, regulates lipid metabolism and lowers blood pressure. Competitive binding of IL-33 by sST2 receptors attenuates the protective effect of IL-33/ST2L on blood pressure. IL-33 also promotes an increase in eosinophils, catecholamine secretion, perivascular adipose tissue activity and results in the attenuation hypertension. IL-37 attenuates the damage of NADPHO metabolites on vascular endothelium, while activating the MAPK signaling pathway and inhibiting the mTOR pathway, attenuating inflammatory factor secretion in adipose tissue and alleviating hypertension. IL-38 reduces inflammatory factor secretion in adipocytes and inhibits the BCL-2/Bax/Caspase-3 signaling pathway while binding to CD4+ T cells, decreasing Th17 ratio and upregulating Th2 and Treg ratios and controlling blood pressure.

Abbreviations: Src, tyrosine protein kinase; ERK, extracellular regulated protein kinases; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; MyD88, myeloid differentiation factor 88; TRAF, tumor necrosis factor receptor-associated factor; IRAK, interleukin-1 receptor-associated kinase; NF-κB, nuclear factor kappa B; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; CCL3, chemokines-3; CCL4, chemokines-4; CXCL1, chemokine (C-X-C motif) ligand 1; CXCL2, chemokine (C-X-C motif) ligand 2; TNF-α, tumor necrosis factor-α; MAPK, mitogen-activated protein kinase; *A. muciniphila, Akkermansia muciniphila*; ST2L, the membrane-bound isoform; sST2, soluble protein; PVAT, perivascular adipose tissue; NADPHO, nicotinamide adenine dinucleotide phosphate oxidase; ROS, reactive oxygen species; mTOR, mammalian target of rapamycin; BCL-2, B cell lymphoma protein-2; Bax, apoptosis proteins; Caspase-3, cysteine aspartate protease 3; Treg, regulatory T cells; MCP-1, monocyte chemoattractant protein-1.

Valvular Heart Disease

Valvular heart disease is common in industrialized countries, and the incidence rate in the United States is approximately 2.5%.[104] Surgery is the best option for patients with end-stage disease.

IL-18 is expressed in the aortic valve and correlates with aortic stenosis.[105] IL-18 induced the conversion of valvular interstitial cells to myofibroblasts and induced osteopontin (OPN) secretion via NF-κB to accelerate valve calcification.[106] HO-1 and FPN were also activated through the p38 MAPK/ERK1/2 signaling pathway, promoting phagocytosis and degradation of erythrocytes by M1-type macrophages, exacerbating valvular calcification.[107]

IL-33 and sST2 were found to be elevated in peripheral blood from patients with non-rheumatic aortic disease and α-SMA, OPN and ST2 were co-expressed, demonstrating that IL-33 induces phenotypic transformation of valvular mesenchymal cells through the NF-κB and p38 MAPK pathways and exacerbates aortic lesions.[108] Moreover, IL-33 binding to ST2 receptors activated valvular interstitial cells and promoted mesenchymal transformation of valve endothelial cells, contributing to mitral mucinous tumor degeneration.[109]

IL-37 was found to be expressed in both aortic disease and mitral valve disease but with lower levels at the site of aortic stenosis.[110] Recombinant IL-37 attenuated the osteogenic response in valves by inhibiting the NF-κB and ERK1/2 signaling pathways and reducing bone morphogenetic protein-2 and alkaline phosphatase release.[111]

IL-18 and IL-33 appear to facilitate valvular calcific disease via specific protein activating effects while IL-37 was protective. However, the paucity of relevant literature and the lack of mature animal models means that further research is needed to consolidate these conclusions.

Aneurysms

Aneurysms, whether thoracic or abdominal aortic, are extremely dangerous and aortic dissection is a fatal hazard.[112] The pathophysiological basis concerns inflammatory cascade and extracellular matrix breakdown due to arterial injury.[113]

IL-18 has recently been found that to enhance OPN expression in the intima, leading to the release of matrix metalloproteinases from macrophages and decreased collagen and elastin which exacerbates the progression of abdominal aortic aneurysms.[114] Obesity is a pre-disposing factor for cardiovascular disease, including aneurysms, and changes in PVAT may form part of the underlying mechanism.[115,116] Adipocytes and PVAT were found to bind IL-18r and Na-Cl cotransport protein (NCC) at the sites of abdominal aortic aneurysm lesions which enhanced IL-18 binding to macrophages, arterial smooth muscle cells and vascular endothelial cells, exacerbating endothelial injury and promoting disease progression. IL-18r and NCC were found to act synergistically and also participated independently in the pathophysiology of abdominal aortic aneurysms.[117]

Animal experiments have shown beneficial effects of IL-33.[118] Activation of the IL-33/ST2 signaling pathway amplifies Tregs to inhibit inflammatory factors and chemokines such as IL-6 and MCP-1 in smooth muscle cells while M2 macrophage conversion is promoted. However, Tregs are crucial for this mechanism and in their absence, the protective effect was lost (Figure 3).

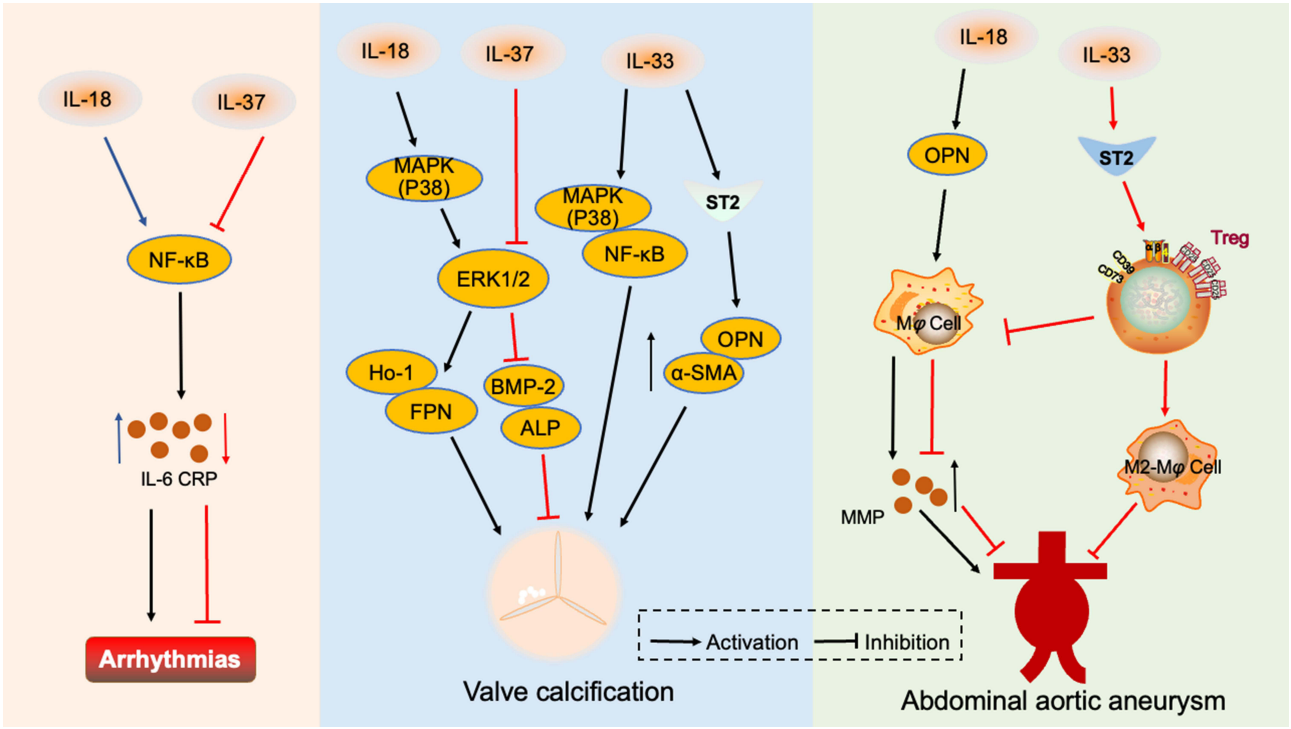

Figure 3 Interleukin 1 family in other cardiovascular diseases. IL-18 activates the NF-κB signaling pathway, causing the release of inflammatory factors and inducing arrhythmia. However, IL-37 reduces the incidence of arrhythmia by inhibiting the NF-κB pathway. IL-18 activates the MAPK(p38)/ERK1/2 signaling pathway, promotes HO-1 and FPN secretion, and accelerates valve calcification. IL-33 mediates the MAPK(p38)/ NF-κB signaling pathway and promotes OPN and α-SMA secretion through IL-33/ST2, which aggravates valve calcification. IL-37 inhibits ERK1/2 and reduces BMP-2 and ALP release, thus reducing valve calcification. IL-18 promotes the secretion of OPN which causes macrophages to secrete MMP and aggravates abdominal aortic aneurysm. IL-33 binds to the ST2 receptor and enriches Treg, to exert an inhibitory effect on abdominal aortic aneurysm by inhibiting macrophage MMP secretion and promoting macrophage conversion to the M2 phenotype.

Abbreviations: NF-κB, nuclear factor kappa B; CRP, c-reactive protein; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular regulated protein kinase 1/2; HO-1, heme oxygenase-1; FPN, ferroportin; ST2, growth ST imulation expressed gene 2; OPN, osteopontin; α-SMA, α-Smooth muscle actin; BMP-2, bone morphogenetic protein 2; ALP, alkaline phosphatase; MMP, matrix metalloproteinases; Treg, regulatory T cells.

IL-18 appears to promote aneurysm development and the relationship between IL-18 and PVAT could provide new treatment options. IL-33 is a protective factor despite its aggravating effect on CVD. IL33/ST2 pathway specificity in aneurysmal awaits further clarification.

Prospect and Future

IL-18 promotes several cardiac diseases through multiple pathways and statins, eg, atorvastatin, commonly prescribed for coronary heart disease have lipid-lowering effects and inhibit the NLRP3 inflammasome to reduce IL-18 secretion.[119] Other drugs such as remifentanil and baicalin[120,121] may also inhibit IL-18. In addition, NCC inhibitors such as hydrochlorothiazide, have potential value in limiting the progression of abdominal aortic aneurysms. Interleukin receptors may thus be a suitable focus for therapeutic research and interactions between IL-18 and other cytokines require attention. IL-18 acts synergistically with IL-1 to exacerbate systemic acute infectious inflammation[122] and a synergistic interaction between IL-22 and IL-18 in the prevention and treatment of rotavirus infection was also found by Zhang.[123] However, synergistic effects of IL-18 with other inflammatory factors have been little reported and should be considered when designing drugs.

While focusing on the therapeutic potential of IL-33 for CVD its harmful effects should also be kept in mind. IL-33 induced eosinophilic pericarditis through the IL-33 receptor[124] and the beneficial effects of IL-33 in CVDs, such as hypertension, are attenuated by its sST2 decoy receptor. Promising effects of IL-33 injections have been reported for hypertension but the resulting splenomegaly does significantly limit its therapeutic potential.[80] Several IL-33 blocking strategies signaling are feasible with anti-IL-33 mAb, anti-ST2 or sST2 being under development for asthma and COPD.[125,126] In addition, the hybrid factor, IL-233, a complex of IL-2 and IL-33, enhances the protective effect of Tregs and ILC2 in AKI and prevents I/R injury.[127]

IL-36 inhibitors are currently used for psoriasis[29] and effect on blood pressure, via modulation of metabolic patterns and gut microbiota, and on vascular endothelial damage, demonstrate the therapeutic potential for CVD. Elevated urinary IL-36α and enhanced IL-36α staining in renal biopsy samples are found in AKI[89] and a contrasting increase in IL-36γ in *P. aeruginosa* infection-mediated lung injury.[128] IL-36β enhances disease progression in a mouse model of colitis by promoting the Th2 response while decreasing the Foxp3+ Tregs response.[129] Different isoforms of IL-36 mediate disease in different ways and attention should be paid to its subtypes.

IL-37 and lL-38 suppress the secretion of inflammatory factors, inhibit macrophage polarization and transport and modulate immunity. Recombinant IL-37 enhances mesenchymal stem cells for the treatment of SLE.[130] Probiotics and prebiotics increase IL-38 gene expression and reduce airway inflammation to control asthma.[131] Positive effects of IL-37 and IL-38 have been shown in animal models of CVD but have been little studied in hypertension, valvular disease, aneurysms and arrhythmias and deserve further investigation.

Conclusion

The interleukin-1 cytokines, IL-18, IL-33, IL-36, IL-37 and IL-38, have been linked to CVD. IL-18 and IL-36 promote the development of MI, hypertension, calcific valve disease and aneurysm by inducing release of inflammatory factors, chemokines, adhesion factors, related proteins and promoting lipid deposition. By contrast, IL-37 and IL-38 inhibit the above pathways and exert a protective effect. IL-36 increases the abundance of intestinal flora and reduces hypertension. Controversy surrounds the protective and promotional role of CVD by IL-33. Further elucidation of mechanisms, regulatory relationships and effector targets is needed for therapeutic development.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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