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REVIEW

Crosstalk between the heart and peripheral organs in heart failure

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Mediators from peripheral tissues can influence the development and progression of heart failure (HF). For example, in obesity, an altered profile of adipokines secreted from adipose tissue increases the incidence of myocardial infarction (MI). Less appreciated is that heart remodeling releases cardiokines, which can strongly impact various peripheral tissues. Inflammation, and, in particular, activation of the nucleotide-binding oligomerization domain-like receptors with pyrin domain (NLRP3) inflammasome are likely to have a central role in cardiac remodeling and mediating crosstalk with other organs. Activation of the NLRP3 inflammasome in response to cardiac injury induces the production and secretion of the inflammatory cytokines interleukin (IL)-1β and IL-18. In addition to having local effects in the myocardium, these pro-inflammatory cytokines are released into circulation and cause remodeling in the spleen, kidney, skeletal muscle and adipose tissue. The collective effects of various cardiokines on peripheral organs depend on the degree and duration of myocardial injury, with systematic inflammation and peripheral tissue damage observed as HF progresses. In this article, we review mechanisms regulating myocardial inflammation in HF and the role of factors secreted by the heart in communication with peripheral tissues.
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INTRODUCTION

Heart failure and the role of inflammation

Cardiovascular diseases are the leading cause of death worldwide, and heart failure (HF) is an important contributor to this statistic.[1] When the heart is under stress or injured, it undergoes structural and functional changes termed cardiac remodeling.[2] These include cardiac hypertrophy, fibrosis, apoptosis and altered metabolism.[3] When an individual suffers from myocardial ischemia, it is intuitively important to re-perfuse the damaged area and re-establish the supply of blood to the damaged area. However, it has also been realized that some cellular events which occur during reperfusion may lead to worse outcomes, a phenomenon termed myocardial ischemia/reperfusion (I/R) injury.[4]

The various mechanisms underlying the detrimental effects of ischemia and subsequent reperfusion are complex and are not fully understood. Nevertheless, a number of clinical and animal studies suggest that inflammation is a key contributor to adverse myocardial remodeling.[4] Broadly speaking, inflammation is a wound-healing process mediated by innate immune cells that recognize microbial and non-microbial sources of danger/stress. Inflammation triggered in the absence of infection is termed 'sterile inflammation'. Multiple studies have highlighted the importance of targeting sterile inflammation in HF.[5–7] Sterile inflammation involves the secretion of inflammatory cytokines and recruitment of innate immune cells, such as neutrophils and monocytes/macrophages. However, prolonged exposure to inflammatory cytokines will exacerbate adverse remodeling and enhance myocardial damage.[8] Importantly, in addition to local adverse effects on cardiac remodeling, ischemia- or I/R-induced inflammation in the heart releases pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-18, into circulation. These, and other so-called cardiokines, can have significant endocrine effects on other tissues, leading to damage in multiple peripheral organs.[9] For example, prolonged exposure to IL-1β and IL-18 can lead to caspase-1-dependent cell death via pyroptosis.[10,11] Thus, crosstalk from the heart to other tissues can elicit multi-organ damage as a consequence of ischemia-induced inflammation.[9] This review highlights the current knowledge of inflammasome activation in the heart and its consequences on other organs.

Mechanisms regulating cardiac inflammation in HF, focus on the NLRP3 inflammasome

The nucleotide-binding oligomerization domain-like receptors with pyrin domain (NLRP3) inflammasome is a cytoplasmic protein complex composed of NLRP, apoptosis-associated

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speck-like protein containing CARD (ASC), a caspase recruitment domain and pro-caspase-1.[12,13] NLRP is composed of C-terminal leucine-rich repeats, a central nucleotide domain (NACHT) and N-terminal effector pyrin domain. Upon recognizing patterns, either from a pathogenic source (pathogen-associated molecular patterns) or from a non-pathogenic source (danger/damage-associated molecular patterns, DAMPs), NLRP will recruit ASC, which, in turn, recruits pro-caspase 1, which will then get activated.[14] Inflammasomes are classified based on NLRPs, which recognize or sense different stimuli.[15] The NLRP3 inflammasome is the most widely studied to date due to its ability to recognize various cellular stressors and its strong relationship with diseases such as HF.[16] The key consequence of inflammasome activation is maturation of pro-inflammatory cytokines, in particular IL-1β and IL-18. The generation of active forms of IL-1β and IL-18 is regulated at two steps: expression of pro-IL-1β and pro-IL-18 is mediated by nuclear factor kappa-light chain enhancer of activated B cells (NF-κB), and processing to the mature form of IL-1β and IL-18 is mediated by active caspase-1 in the inflammasome.[14]

Multiple DAMPs have been found to activate NLRP3 inflammasomes, including monosodium urate, calcium phosphate crystals, cholesterol crystals, amyloid β, hyaluronan, islet amyloid polypeptide, asbestos and silica.[14] However, in HF, we suggest that mitochondria have a critical role in initiating inflammasome activation.[17,18] In HF-associated inflammasome activation, the three main triggers are adenosine triphosphate (ATP), mitochondrial DNA (mtDNA), and reactive oxygen species (ROS) (see Figure 1). When cells undergo death they release ATP. Multiple studies have suggested that ATP directly activates the NLRP3 inflammasome.[19,20] High extracellular ATP levels activate $P2X_7$ purinergic receptors to cause potassium efflux. Low intracellular levels of potassium promote the assembly of NLRP3 and ASC. In addition, it has been suggested that low intracellular potassium will also promote pannexin-1 membrane pore formation, further easing the access of inflammasome activating agents.[21] mtDNA has been established as a DAMP when liberated into the extracellular space.[22,23] It was shown[24] that the translocation of mtDNA to the cytosol was associated with subsequent inflammasome activation. A DNAse treatment reduced secretion of IL-1β in macrophages. It has also been reported[25] that mitochondrial dysfunction and oxidized mtDNA directly activate the NLRP3 inflammasome. Macrophages lacking mtDNA or treated with the oxidized nucleoside 8-OH-dG to confer competitive inhibition had severely attenuated IL-1β secretion. Mitochondrial marker and NLRP3 inflammasome colocalization and a significant activation of NLRP3

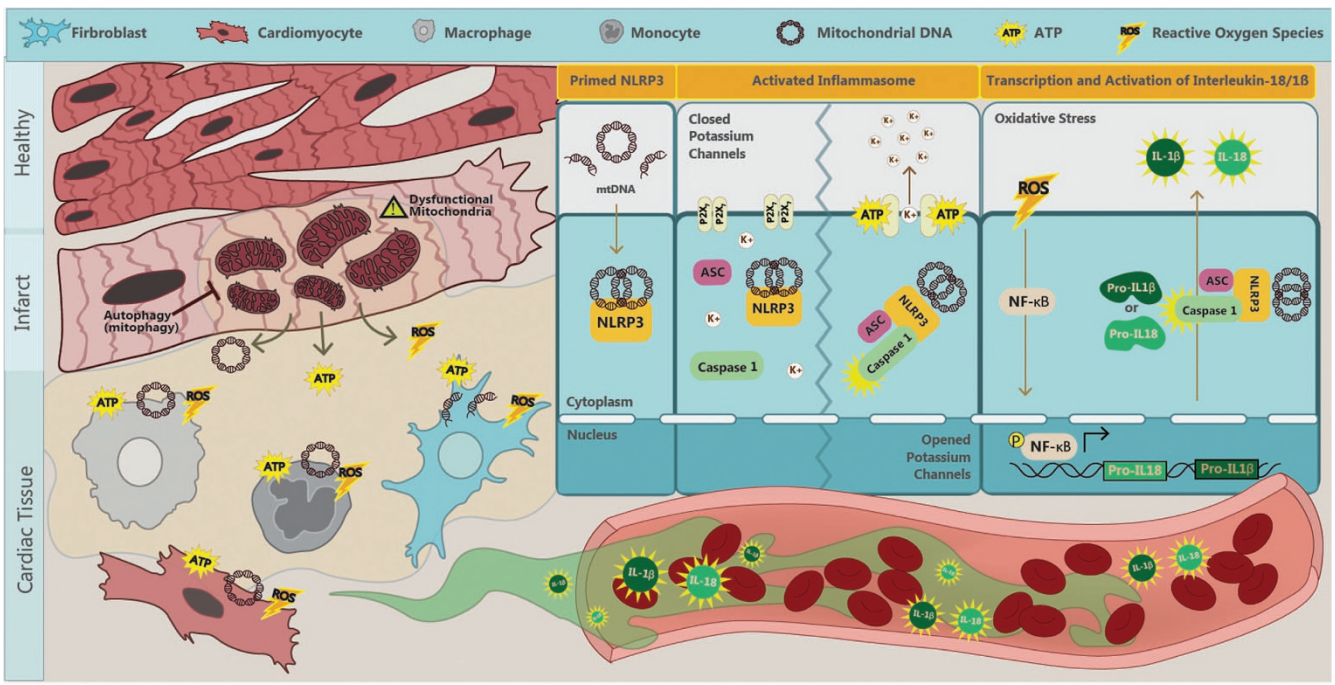

Figure 1 Mechanisms of NLRP3 inflammasome activation in heart failure. Myocardial infarction (MI), ischemia or ischemia/reperfusion (I/R) injury induces cardiomyocytes to release ROS, ATP and mtDNA. ROS mediates autocrine and paracrine activation and nuclear translocation of NF-κB, which regulates the transcription of pro-IL-1β and pro-IL-18. mtDNA directly primes NLRP3 and ATP via binding to $P2X_7$ receptors and leads to potassium efflux, a trigger for the assembly of NLRP3 inflammasome. These collective effects result in activation of the NLRP3 inflammasome-associated caspase-1, which processes pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18 and can exacerbate local inflammation. It can also be released into circulation to mediate endocrine effects. ATP, adenosine triphosphate; IL, interleukin; mtDNA, mitochondrial DNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family, pyrin domain containing 3; ROS, reactive oxygen species; K^+, potassium.

inflammasome upon mitochondrial membrane disruption have been shown.[26] It was reported[27] that activation of the NLRP3 inflammasome in macrophages occurred due to an ATP-mediated ROS-dependent activation of phosphoinositide 3 kinase signaling. ROS stimulates the activation of NF-kB and increases the expression of pro-IL-1β and pro-IL-18.[21]

Mitochondrial regulation by autophagy in the heart

Because all the mediators discussed above (ATP, mtDNA and ROS) may come from mitochondria, our hypothesis is that this organelle has a vital role in inflammasome activation. Thus, mitochondrial integrity is a key limiting factor for NLRP3 inflammasome activation. Furthermore, this may be especially relevant in the heart where cardiomyocytes have a higher mitochondrial content relative to other cell types. Overall, the heart is likely to be highly susceptible to mitochondria-derived DAMPs. Thus, effective regulation of damaged mitochondria is critical. Autophagy is a quality control system mediating degradation of protein aggregates and damaged organelles. Multiple studies have documented the importance of mitochondrial regulation by autophagy, specifically referred to as mitophagy, in HF.[28] Multiples studies have also now established a strong association between autophagy and inflammasome activation. First, stimulating autophagy in macrophages using rapamycin can directly target precursors of IL-1β for degradation. Mice pretreated with rapamycin showed reduced circulating levels of IL-1β following a challenge with an inflammatory stimulus.[29] Using ATG16L1-deficient cells, it was shown that autophagy was involved in endotoxin (lipopolysaccharide)-induced inflammasome activation and increased IL-1β and IL-18 secretion.[30] Another study[31] reported that inflammasomes can be directly sequestered into autophagosomes and destined for autophagic degradation. Nakahira *et al.*[24] reported on the regulation of mtDNA-driven inflammasome activation by autophagy. They deleted genes encoding key autophagy proteins LC3B and Beclin1, and found a significant enhancement in caspase-1 activation and secretion of IL-1β and IL-18. Thus, defective autophagy-mediated quality control mechanisms resulted in enhanced inflammasome activation via the accumulation of damaged mitochondria and reduced inflammasome clearance in both *in vitro* and *in vivo* settings.

Distinct roles of cardiomyocytes, fibroblasts and immune cells in cardiac inflammasome activation

Numerous studies have now established a strong association between inflammasome activation and adverse remodeling in HF. For example, both ASC-KO and caspase-1-KO mice exhibited a significant reduction in infarct zone and fibrosis, as well as improved cardiac function after myocardial I/R injury.[32] As highlighted in Figure 1, it has been proposed that activation of the inflammasome occurs via cell-to-cell communication within heterogeneous cell populations of heart tissue, including cardiomyocytes, fibroblasts and innate immune cells.[6,33] Kawaguchi *et al.*[32] identified that both hematopoietic and non-hematopoietic cells are responsible for secreting IL-1β after myocardial I/R injury, because only chimeric mice with ASC-KO bone marrow on an ASC-KO background showed reduction in infarct zone. They followed up with *in vitro* experiments in which hypoxia/reoxygenation stimulated inflammasome activation in cardiac fibroblasts, but not in cardiomyocytes. This notion was supported by studies in adult cardiomyocytes in which NLRP3 inflammasome activation was inhibited using either siRNA or pharmacological inhibitors. This resulted in fewer cell deaths but not IL-1β secretion.[34] Upon permanent myocardial ischemia in both murine and rat models, myocardial fibroblasts were shown to be the primary source of IL-1β secretion in response to ATP released from damaged neighboring cells.[35] Further work[36] has also supported the notion of non-immune cell-mediated IL-1β and IL-18 secretion. This work concluded that mitochondrial ROS from cardiomyocytes acts as a trigger to prime the NLRP3 inflammasome. Taken together, the data suggest that cardiomyocytes, cardiac fibroblasts and infiltrating immune cells contribute via different roles toward inflammation and cardiac remodeling in myocardial infarction (MI) (Figure 1).

CROSSTALK BETWEEN THE HEART AND ADIPOSE TISSUE

Alterations in adipokine profiles influence the development of HF

There is a well-documented association between obesity and HF.[2] Adipose tissue is clearly an important contributor to inflammation in HF. Multiple studies have established both pro- and anti-inflammatory effects of adipokines.[37,38] In obesity, adipose tissue undergoes changes induced by metabolic stress. It releases more pro-inflammatory cytokines, including IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and less of the anti-inflammatory cytokines, including IL-10 and adiponectin.[39–41] Visceral fat is the most important depot, which responds to metabolic stress in this way. There is a well-established positive correlation between visceral fat levels and HF.[42] However, it is interesting to note that epicardial and pericardial fat depots exhibit a similar phenotype to visceral fat and have been strongly correlated with the progression of adverse cardiac remodeling.[43] McKenney *et al.*[44] observed increased epicardial adipose tissue after MIs, which correlated with a reduced adiponectin level after MI. In their study they compared pigs with or without adipectomy subjected to MI. They observed that the progression of adverse remodeling after the MI was attenuated, and the infarct zone size was diminished in adipectomized animals. This correlates with a previous observation in which a pig with myocardial I/R injury developed improved cardiac function, reduced infarct size and less tumor necrosis factor alpha (TNFα) production with a greater production of IL-10 after intracoronary administration of adiponectin.[45] In summary, whereas it is generally accepted that in obesity, the profile of adipokines from various fat depots mediates detrimental effects on the myocardium, the obesity paradox suggests that these adipokines can confer beneficial effects during post-MI stages of remodeling.[2]

Extensive epidemiological and clinical data suggest that type 2 diabetes increases the risk for HF independently of other risk factors, such as hypertension.[46,47] One potential mechanism is that type 2 diabetes, often associated with obesity, leads to myocardial lipotoxicity that contributes to cell death, and thus, to cardiac dysfunction. Diabetic cardiomyopathy is also characterized by interstitial and perivascular fibrosis. A significant increase in collagen deposition was found around intramural vessels and between myofibers in heart biopsies in patients with diabetes.[48–50] Given that fibrosis is one consequence of inflammation, IL-1β and other inflammatory markers, such as fibrosis, signal the onset and progression of HF in this way.[51–54]

Cardiokine and endocrine effects on peripheral tissues in HF

In recent years, there has been an increased realization of endocrine effects mediated by factors produced and secreted by the heart.[55] Collectively, these are referred to as cardiokines. Ischemic stress results in a substantial change in the profile of cardiokines secreted from the myocardium.[9,55] In particular, upon activation of the inflammasome and infiltration of splenocytes in the infarct zone, the heart will release more pro-inflammatory cytokines.[9] Cardiac fibroblasts have been proposed as the principal source of inflammatory signals in pathological conditions, although cardiomyocytes also contribute to the pro-inflammatory environment in the myocardium by producing different cytokines and chemokines.[56,57] Injured cardiac cells release damage-associated molecular pattern molecules, such as high-mobility group box 1, DNA fragments, heat-shock proteins and matricellular proteins, which instruct surrounding healthy cardiomyocytes to produce inflammatory mediators. These mediators, mainly IL-1β, IL-18, IL-6, MCP-1 and TNFα, in turn activate versatile signaling networks within surviving cardiomyocytes and trigger leukocyte activation and recruitment.

Evidence for myocardial production of TNFα has been controversial.[58,59] However, it is now clear that TNFα can be produced by isolated cardiomyocytes under certain conditions, such as treatment with lipopolysaccharide.[60–63] Similarly, increased expression of TNFα in cardiac myocytes and fibroblasts isolated from failing hearts suggests that if exposed to pathophysiological stimuli, the heart has the capacity to produce TNFα.[64,65] IL-6 can be produced in most cells in the heart, including cardiomyocytes[66,67] and fibroblasts.[68,69] A lipopolysaccharide treatment or hypoxia-reoxygenation stimulated the production of IL-1β in isolated cardiac fibroblasts, while isolated cardiomyocytes did not respond to either treatment.[32] A co-culture of cardiomyocytes with fibroblasts induced by an angiotensin-II treatment secreted much greater levels of IL-6 and TNFα than cultures of fibroblasts alone, indicating that a paracrine action has a vital role in the production of pro-inflammatory cytokines.[70]

Another good example of a cardiokine is atrial natriuretic peptide (ANP), which is produced mainly in the myocardium. Its expression is enhanced during myocardial stretching.[71] ANP has a beneficial role in cardiac remodeling by acting in an autocrine or paracrine manner. For example, treatment with cultured cardiac myocytes with an antagonist of ANP receptor HS-142-1 increased expression of contractile protein genes, such as skeletal-actin and beta-myosin heavy chain, as well as the size of cardiomyocytes.[72] ANP also contributes to oxytocin-induced protection in myocardial ischemia-reperfusion injury by reducing lipid peroxidation in a nitric oxide-dependent mechanism.[73]

ANP receptors are found in adipose tissue and mediate effects, including enhanced lipolysis and energy expenditure, as well as altering adipokine production and release.[74–76] Thus, natriuretic peptides can definitely influence peripheral metabolism by acting on adipose tissue. Therapeutically targeting ANP action may confer metabolic and cardiovascular benefits in the future.[74]

CROSSTALK BETWEEN THE HEART AND SPLEEN: THE CARDIO-SPLENIC AXIS

Neutrophil activation and leukocyte infiltration in the heart are prominent features of MIs that exacerbate inflammatory cytokine release and tissue damage.[77] Indeed, the mononuclear phagocyte network undergoes extensive remodeling after MI. There are different subpopulations of monocytes residing in mice. These are converted from one to another upon inflammatory responses after an MI. Monocytes are generally classified into two categories: migratory monocytes with inflammatory characteristics, which express high levels of Ly6C and CC chemokine receptor CCR2 and low levels of fractalkine receptor CX3CR1 (Ly-6C^{hi},CCR2^{hi}CX3CR1^{low}), and reparative monocytes with anti-inflammatory profiles (Ly-6C^{low},CCR2^{low}CX3CR1^{high}).[78] The exact mechanism of how each phenotype of monocytes regulates the inflammatory response during an MI is complicated and is not resolved.[79] However, under acute MI conditions, monocyte recruitment to the heart is very dynamic and largely dependent on the spleen. The spleen is one of most important lymphoid tissues. It has a role in filtering blood and regulating immune responses to circulating agents.[80] The spleen contains large pools of undifferentiated monocyte reservoirs[80,81] that can undergo splenic hematopoiesis, increasing motility and pro-inflammatory characteristics (Ly-6C^{hi}).[81] Recruitment of reparative monocytes (Ly-6^{low}) ultimately helps resolve inflammation and promote tissue healing.[81,82]

Dendritic cells (DCs), specialized for presenting antigens to T cells, also have an important role in the immune response to an MI.[83] In an acute MI, both DCs and monocytes/macrophages have been shown to positively contribute to tissue healing. Upon an initial cardiac inflammatory response, DCs infiltrate the infarcted area to confer a protective role. This is demonstrated with DC-ablated mice exhibiting greater adverse cardiac remodeling after an MI.[84] In these mice, there was sustained expression of pro-inflammatory cytokines, IL-1β, IL-18 and TNFα, yet reduced IL-10 expression.[84]

Interestingly, under chronic MI conditions, the protective roles of splenocytes become detrimental. Mice with a long-term

MI (8 weeks) showed profound splenic remodeling with a prolonged existence of pro-inflammatory monocytes (Ly-6C^{hi}) and increased expression of alarmins.[85] A splenectomy was performed to investigate the role of splenocytes (splenic monocytes/macrophages and DCs) in the progression of HF-associated inflammation and post-MI remodeling. Intriguingly, mice without spleens showed less cardiac dysfunction. This was associated with attenuated monocytes/DC infiltration in the heart.[85] When splenocytes from the mice with an MI were injected into normal mice, the recipient mice developed left ventricule (LV) dilation, cardiac hypertrophy, systolic dysfunction, myocardial apoptosis and fibrosis.[85] However, the recipient mice did not reveal changes in pro-inflammatory cytokines in circulation, indicating that the adverse cardiac remodeling in chronic MI model was specifically due to splenocytes. Therefore, there is a clear sequential activation of inflammatory responses depending on the duration of MI via splenocyte-mediated crosstalk to the heart (Figure 2).

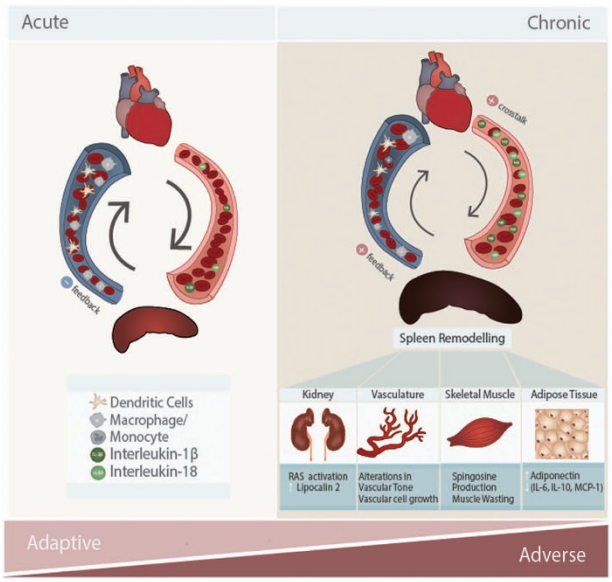

Figure 2 Crosstalk mechanisms in the cardio-splenic axis in heart failure, and their functional consequences on peripheral tissues. In acute myocardial infarction (MI), splenocytes (splenic monocytes/macrophages and dendritic cells) migrate to the heart and mediate protective effects during the inflammatory response. In chronic MI, cardiokines induce dramatic changes in the spleen, such that splenocytes develop inflammatory profiles. This exacerbates existing inflammation in the heart and promotes adverse cardiac remodeling leading to cardiac dysfunction. Inflammatory splenocytes also lead to peripheral organ damage. For example, kidney inflammation results in enhanced activation of the renin-angiotensin system (RAS) and release of lipocalin-2. In vasculature, inflammation results in adverse alterations in vascular tone and vascular cell proliferation. Skeletal muscle is also strongly affected by heart failure, at least in part via inflammation resulting in cellular changes, such as sphingosine accumulation and muscle wasting. In adipose tissue, inflammation results in reduced adiponectin levels and further increased levels of pro-inflammatory adipokines (IL-6, MCP-1, IL-10). IL, interleukin; MCP-1, monocyte chemotactic protein 1.

CROSSTALK BETWEEN THE HEART AND KIDNEY: CARDIO-RENAL AXIS

Multiple clinical studies have suggested that patients with chronic kidney disease experience extremely high mortality rates following acute MI.[86–89] This suggests that there is a strong crosstalk between the kidneys and heart. The association between end-stage renal disease and cardiovascular disease is often termed cardio-renal syndrome.[90] The renin-angiotensin system (RAS), a signaling cascade responsible for regulating blood pressure, has a well-established critical role in cardio-renal syndrome.[91] Ogawa *et al.*[92] reported that nephrectomy in mice with an MI influenced cardiac remodeling after the MI. The combination of nephrectomy and MI resulted in deteriorated left ventricular remodeling and RAS activation, oxidative stress and MCP-1. This observation was similar to transgenic mice overexpressing renin and angiotensinogen after a coronary artery ligation (CAL) surgery.[92] This correlates with previous findings that cardiomyocytes increase the expression of TNFα and IL-1 family through activation of NF-kB and activator protein 1 transcription factor in response to angiotensin II.[93–95]

Other than RAS, a new biomarker has been identified that strongly correlated with cardio-renal syndrome. HF patients with declined renal function exhibit elevated levels of neutrophil gelatinase-associated lipocalin (also known as lipocalin-2)[96]. Neutrophil gelatinase-associated lipocalin levels are strongly correlated with inflammation and cardiac remodeling in HF patients with renal dysfunction.[96] Pro-inflammatory effects of lipocalin-2 are also known to induce endothelial dysfunction[97,98] and promote apoptosis in cardiomyocytes.[99,100]

In addition, cardiokines, such as ANP, can mediate endocrine effects on the kidney.[101] They have effects on electrolyte balance and water excretion in the kidney by increasing glomerular permeability and filtration rate. ANP also antagonizes the deleterious effects of the renin-angiotensin-aldosterone system activation.[101–103] Furthermore, crosstalk between the heart and kidney are evident from the observation that worsening renal function manifests only in end-stage HF and is strongly related to mortality.[104] Although cardio-renal interactions in HF are well established, many questions, especially mechanistic, remain unanswered.

CROSSTALK BETWEEN THE HEART AND SKELETAL MUSCLE

We now appreciate that HF is strongly associated with skeletal muscle wasting, which is typically not associated with general weight loss.[105,106] Skeletal muscle in congestive HF patients shows increased fatigability as well as decreased endurance and exercise capacity.[105,106] Changes evident in muscle include metabolic imbalance, increased degradation of myofibrils and myocyte apoptosis. The signals mediating crosstalk from the heart need to be comprehensively identified.[107,108] One possibility is that generation of TNFα from the failing heart has a detrimental effect on several processes in skeletal muscle. NF-κB is rapidly activated by TNFα in differentiated skeletal

muscle cells, which directly induces skeletal muscle protein loss.[109] Another proposed mechanism is that TNFα induces sphingosine production, which then leads to induction of apoptosis in these cells.[110] In addition, exercise attenuates the local expression of TNFα, IL-1β and inducible Nitric Oxide Synthase (iNOS) in skeletal muscle and decreases the catabolic wasting process in HF patients.[34,111,112] Angiotensin-II is also produced by the heart under conditions of stress and contributes to cardiac hypertrophy and fibrosis.[113] Studies have shown that there is a catabolic effect of angiotensin-II on skeletal muscle, suggesting its role in muscle wasting in HF.[114,115]

THERAPEUTIC APPROACHES TARGETING INFLAMMATION IN HF

As outlined above, myocardial inflammation in HF is often detrimental to peripheral tissues. There have been several studies addressing consequences of manipulating HF-associated inflammation.[116] Targeting TNFα has been extensively studied in numerous clinical trials. Patients who already have severe inflammatory conditions, such as rheumatoid arthritis (RA), were treated with TNFα inhibitors (etanercept, infliximab and adalimumab), which effectively reduced the inflammatory activity and reduced the prevalence of HF complications.[117] The data from two-large-scale trials with more than 2000 HF patients showed that etanercept treatment reduced the risk of mortality or morbidity in HF.[64] Indeed, the US Food and Drug Administration has issued a directive concerning the use of etanercept in the population with HF.[118] However, targeting TNFα using a neutralizing antibody (infliximab) showed no improvement and perhaps even worsened the clinical condition of patients with chronic HF.[119] Other studies indicated that patients treated with high-dose infliximab continued to show a worse outcome compared with other groups.[57,120] Several other agents have also been suggested to have potential as therapeutic tools for chronic HF because of their inhibitory effect on TNFα, including the glutamic acid derivative thalidomide.[121] Thalidomide prevents the accumulation of TNFα by inducing the degradation of TNFα messenger ribonucleic acid transcripts, and thus, protein production.[121] The xanthine derivative pentoxifylline has also been reported to have a role in therapeutic TNFα modulation. Reduced TNFα in the serum of patients treated with pentoxifylline was observed. This correlated with improved peripheral vasodilation and blood hemodynamics.[122] Other studies demonstrated a significant improvement in NYHA functional class in patients treated with pentoxifylline.[123,124] However, the results were not reproduced by another group,[125] suggesting that the significance of

Table 1 Cytokines/chemokines involved in crosstalk between the heart and peripheral organs

Cytokines/Chemokines	*Effect*	*Reference*
IL-1β, IL-18[9,32–35]	Neutrophil activation and leukocyte infiltration	77
	[@Spleen] increasing mobility and inflammatory characteristics of monocytes, and infiltration of DCs to heart	78,80–82
	[@Heart] autocrine production of IL-6, TNFα	71
	Prolonged exposure led to pyroptosis	148,149
IL-6, IL-8, MCP-1[60,67–69]	Pro-inflammatory cytokines	60,67–69
DAMPs, HMGB1, DNA fragments, heat shock proteins, matricellular protein[9,55–57]	[@Heart] autocrine effects to produce pro-inflammatory cytokines; IL-1β, IL-18, IL-6, MCP-1, TNFα	56,57
TNFα[58,59]	Prolonged exposure led to pyroptosis	64,65
	[@Skeletal Muscle] muscle wasting, sphingosine production, induction of apoptosis	109,110
ANP[71]	Paracrine effect: oxytocin production, reducing lipid peroxidation with NO-dependent mechanism	73
	[@Heart] autocrine effect on heart by increasing expression of contractile protein, actin and myosin, and induce hypertrophy	72
	[@Adipose Tissue] enhancing lipolysis and increasing energy expenditure, adipokines production	75,76,150
	[@Kidney] increasing glomerular permeability and filtration rate, antagonizing RAS activation	101–103
IL-6, IL-8, MCP-1[37,38]	Pro-inflammatory cytokines	39–41
IL-10[37,38]	Anti-inflammatory cytokines	39–41
Adiponectin[37,38]	[@Heart] reducing TNFα production, increasing IL-10 production, reducing infarct size	45,55
Alarmins[85]	[@Heart] worsening cardiac dysfunction, inducing myocardial apoptosis, fibrosis	85
Angiotensin-II[91]	[@Heart] inducing cardiac hypertrophy/fibrosis, increasing expression of TNFα, IL-1 family cytokines	70,93,94,113
	[@Skeletal Muscle] muscle wasting	114,115
Lipocalin-2[96]	endothelial dysfunction, cardiomyocyte apoptosis	97–100

Abbreviations: ANP, atrial natriuretic peptide; DAMPs, danger/damage-associated molecular patterns; DCs, dendritic cells; HMGB1, high-mobility group box 1; IL, interleukin; MCP-1, monocytes chemoattractant protein-1; NO, nitric oxide; TNFα, tumor necrosis factor alpha.

targeting TNFα is controversial and requires further exploration.[126] This may be because pleiotropic TNFα effects may be involved in many beneficial physiologic, as well as pathologic, processes. For example, TNFα provides endogenous cyto-protective signals that prevent cardiomyocyte apoptosis following ischemic injury.[127] Additionally, TNF type 1 receptor deficiency was associated with accelerated myocardial death.[128] Overall, the cardiomodulatory effects of TNFα and other cytokines likely depend on factors such as cell type and timing and extent of inhibition.

We propose that IL-1β is a major mediator between HF and peripheral tissues. In fact, multiple studies have targeted IL-1β. Canakinumab, a neutralizing antibody against IL-1β, and anakinra, a recombinant IL-1 receptor antagonist, were shown to exert beneficial effects on acute MI in animal models.[129,130] Several clinical trials identified therapeutic benefits by blocking IL-1β.[131,132] Anakinra successfully reduced adverse remodeling in patients with an MI and reduced the level of C-reactive protein, a common biomarker used to determine the severity of inflammation.[133,134] Patients diagnosed with HF were treated with Anakinra and subjected to exercise performance testing. Two weeks of the Anakinra treatment significantly increased oxygen consumption, decreased carbon dioxide retention and exercise performance with significant reduction in IL-1β, C-reactive protein and IL-6 serum profiles.[135] These correlated with a previous study in which patients with RA treated with Anakinra had improved cardiac function. A single injection of Anakinra resulted in increased blood flow in 3 h.[136] The commercial usage of Anakinra was approved by Food and Drug Administration in 2001. However, it was for treating patients with RA not chronic HF, although multiple studies demonstrated cardiac benefits of Anakinra in treating RA.[137–139]

There also have been therapeutic efforts to target IL-18 and inflammasome activation. A recombinant human IL-18 binding protein and neutralizing antibody for IL-18 have been developed, and initial clinical trials to treat patients with RAs are ongoing.[140,141] In subjects with moderate to severe RA, IL-18 binding protein shows a favorable safety profile and is well tolerated in healthy volunteers. Because IL-18 binding protein stays in circulation much longer than any other inhibitors previously described, it has attracted a lot of attention.[141,142] Antagonists targeting $P2X_7$ receptors have also been tested to potentially block inflammasome activation. Many successful cases have been shown; they limit neuronal damage and lung, liver and kidney injury in several animal models.[143–146] Currently, the safety and efficacy of $P2X_7$ receptor antagonists are being investigated and have progressed to phase 2 clinical trials. However, their main use is to target inflammatory bowel disease, RA and chronic obstructive airway disease.[147]

CONCLUDING REMARKS

Myocardial ischemia- and I/R-induced inflammation involve NLRP3 inflammasome activation. One principal trigger for inflammasome activation is the recognition of mitochondrial DAMPs. This results in the production and secretion of pro-inflammatory cytokines, including IL-1β and IL-18 (Table 1). These and other factors produced by the heart during inflammation can have local effects. They can also crosstalk with other peripheral tissues via endocrine effects. For example, HF is associated with dramatic changes in the spleen, skeletal muscle wasting, alterations in adipose metabolism and kidney function. The extent and significance of bidirectional crosstalk between the heart and other organs may have been underappreciated, but is now becoming more established and may represent a logical focus of therapeutic interventions in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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