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Proinflammatory cytokines in heart failure: double-edged swords

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Abstract Increased circulating and intracardiac levels of proinflammatory cytokines have been associated with chronic heart failure. Following an initial insult, the increased production of proinflammatory cytokines, including TNF-α, IL-6, IL-1, and IL-18, jeopardizes the surrounding tissue through propagation of the inflammatory response and direct effects on the cardiac myocyte structure and function. Cardiac myocyte hypertrophy, contractile dysfunction, cardiac myocyte apoptosis, and extracellular matrix remodeling contribute enormously to the development and progression of chronic heart failure. Despite the identification of efficacious pharmacological regimens and introduction of mechanical interventions, chronic heart failure remains among the leading causes of mortality worldwide. To introduce novel therapeutic strategies that modulate the inflammatory response in the context of the failing heart, it is of prime importance to determine the contributions of TNF-α, IL-6, IL-1, and IL-18 in mediating cardiac adaptive and maladaptive responses, as well as delineating their downstream intracellular signaling pathways and their potential therapeutic implications.

Keywords Chronic heart failure · Immunopathogenesis · Cardiac myocyte hypertrophy · Contractile dysfunction · Cardiac myocyte apoptosis · Extracellular matrix remodeling · Proinflammatory cytokines

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Introduction

Cytokines are low molecular weight proteins, which function as mediators of immune and inflammatory reactions. These mediators are involved in, but not limited to, recruiting cells to inflammatory sites and stimulating cell division, proliferation, and differentiation [1]. Increased circulating and intracardiac levels of proinflammatory cytokines have been associated with chronic heart failure [2–5]. In addition, coronary artery disease (CAD) and dilated cardiomyopathy (DCM), the most common causes of chronic heart failure, are believed to be of an inflammatory origin.

Viral infection, the leading cause of myocarditis, has been implicated in the pathogenesis of DCM [6]. In animal models, acute viral myocarditis might progress to chronic persistent myocarditis, with the resultant induction of autoimmune processes in genetically susceptible strains [7]. Endogenous ligands that are released from damaged or stressed tissues provoke inappropriate Toll-like receptor

(TLR) signaling, causing sterile inflammation and contributing to the activation of auto reactive B and T cells. Elevated levels of proinflammatory cytokines play a prominent role in immediate host defense against microbial pathogens; however, sustained overexpression of tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-18 correlates with disease severity and chronicity, induction of autoimmune myocarditis, and progression to DCM [8–10]. Atherosclerosis is now considered to be an inflammatory disease characterized by activation of the innate and adaptive immune responses [11, 12]. Proinflammatory cytokines contribute to the formation of atherosclerotic plaque and progression of plaque instability [13].

Following an initial insult, i.e. infectious or noninfectious myocarditis or acute myocardial infarction, the increased production of proinflammatory cytokines endangers nearby cells altering cardiac myocyte structure and function. In response to injurious insults, cardiac structural cells contribute further to production of proinflammatory cytokines [5]. When various cytokines are expressed in sufficiently high levels, they are capable of modulating cardiovascular performance in an autocrine, paracrine, juxtacrine, or endocrine fashion.

In attempt to determine the biological activities of individual cytokines, extensive experimental studies have been described in the medical literature. However, in the context of the failing heart, the complex interaction among various cytokines and neurohormonal mediators determine the net outcome [3, 14]. Thus, the reductionist findings in experimental studies do not directly apply to clinical observations.

Increased levels of TNF-α, IL-6, IL-1, and IL-18 have been described repeatedly in patients with chronic heart failure, showing a positive correlation with disease severity [2–5]. Their association in the development and progression of the underlying diseases, i.e. CAD [8–10] and DCM [11–13], is also well established. With respect to the development and progression of heart failure, cardiac myocyte hypertrophy, contractile dysfunction, cardiac myocyte apoptosis, and extracellular matrix remodeling play prominent roles. It is, therefore, of great significance to determine the precise contribution of TNF-α, IL-6, IL-1, and IL-18 to the cardiac adaptive and maladaptive responses. The present review addresses the current knowledge of the immunopathogenic roles of the aforementioned cytokines in the context of the failing heart, as well as their downstream intracellular signaling pathways and their potential therapeutic implications.

TNF-α

TNF-α is a 157-amino acid cytokine, which is produced by a wide variety of the immune and nonimmune cells in response to inflammatory and infectious stimuli [15]. Cardiac structural cells are capable of producing TNF-α, while mechanical stresses including pressure and volume overload [16, 17], ischemia–reperfusion injury [18, 19], and endotoxemia [20, 21] serve as the initial stimulus. Based on experimental models, there is a wide variety in biological activities of TNF-α, which has both physiological and pathological effects. In order to understand its seemingly paradoxical effects, one must pay attention to the time of exposure, concentration, and micro-environmental milieu [22–24].

At one end of the spectrum, the favorable outcomes are dominant, and the physiological concentration of TNF-α regulates local defense mechanisms and provokes regional tissue homeostasis [25–27]. TNF-α gene is expressed rapidly and temporally in response to environmental stresses. Subsequently, TNF-α exerts its protective effects as an autocrine and/or paracrine mediator [23]. At the other end of the spectrum, devastating maladaptive effects become prominent. At higher concentrations, TNF-α acts primarily in an endocrine manner which results in cachexia [28] and contributes to the pathogenesis of multiple organ failure [29], intravascular coagulation and thrombosis [30], and severe sepsis/septic shock [31]. The deleterious effects of prolonged exposure to high concentration of TNF-α on myocardial structure and function have been well established.

TNF-α exerts its biological activities through two specific cell membrane receptors, tumor necrosis factor receptor type 1 (TNFR1), and type 2 (TNFR2) [32]. TNFR1 (p55), which is expressed dominantly, mediates the majority of cytotoxic and deleterious effects, whereas TNFR2 (p75) appears to be responsible for mediating the cytoprotective effects in the heart [33–35]. Following insertion into the cell membrane, both receptors are proteolytically cleaved and form circulating soluble receptors (sTNFR) [36]. The biological role of the sTNFR is not well-defined. It has been suggested, however, that sTNFR at low concentration may bind to, stabilize, and prolong the biological activities of circulating TNF-α, whereas high concentrations of sTNFR may have a buffering action antagonizing excessive TNF-α in the circulation [37, 38].

Cytoprotective effects

TNF-α-treated hearts prior to induction of ischemia–reperfusion injury release lesser amounts of LDH, which has a linear correlation with cell membrane disruption [22, 39]. The cytoprotective effects of TNF-α might be due to induction of manganous superoxide dismutase (MnSOD), which neutralizes and detoxifies the cytotoxic oxygen free radicals [40, 41], and upregulation of heat-shock proteins

(HSP), including HSP-27, HSP-30, HSP-70, and HSP-72 [42–44]. It is suggested that preinduction of heat-shock proteins inhibits excessive myocardial TNF-α production and attenuates myocardial dysfunction following ischemia–reperfusion injury [45–47]. The aforementioned mechanisms have an early and rapid onset and protect the cardiac myocytes by attenuating the extent of the injurious insults.

Maladaptive responses

Cardiac myocyte hypertrophy

TNF-α signaling has a more delayed onset of actions, which assists in cardiac myocyte growth and adverse ventricular remodeling following injurious insults [48]. Cardiac-restricted overexpression of secreted [49] and transmembrane [50] form of TNF-α induce cardiac myocyte hypertrophy and reexpression of the fetal gene program. Looking at all the relevant facts, TNF-α can influence the expression of both IL-1 and IL-6 [51], and these proinflammatory cytokines also stimulate hypertrophic growth response [52, 53]. Although TNF-α expression has an excessively rapid onset and offset [22], the sequential activation of IL-1 and IL-6 continue and propagate its effects.

It has been demonstrated that cardiac-restricted overexpression of TNF-α increases the myocardial rennin angiotensin system activity, as demonstrated by increased angiotensin-converting enzyme (ACE) mRNA expression, increased angiotensin II protein level, and decreased angiotensin receptor mRNA and protein levels consistent with its desensitization and receptor down-regulation [54]. Following administration of losartan, an angiotensin type I receptor antagonist, TNF-α-induced hypertrophic growth response is significantly attenuated [54]. TNF-α, similar to angiotensin II, induces the generation of reactive oxygen intermediates (ROIs) in a dose-dependent manner. The addition of antioxidants to the culture medium inhibits TNF-α-induced hypertrophic growth response [55]. These results indicate that the functional cross-talk between TNF-α and rennin angiotensin system results in hypertrophic growth response in part via the generation of ROIs in cardiac myocytes.

Contractile dysfunction

TNF-α plays a central role in depression of myocardial contractility through discrete time-dependent mechanisms (Fig. 1). *Early* cardiodepressant effect, which is manifested within minutes, is the consequences of nitric oxide (NO)-dependent and sphingomyelinase-dependent signaling. The former leads to NO and subsequent cGMP generation via

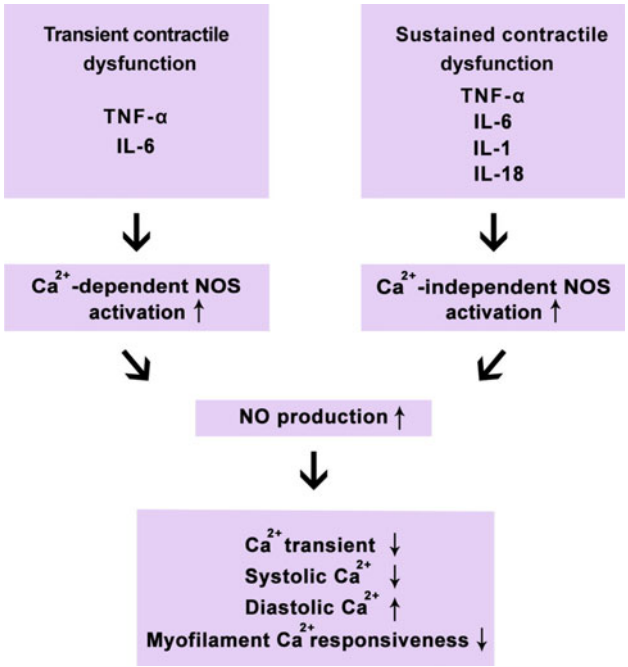

Fig. 1 Cytokine-mediated contractile dysfunction through discrete time-dependent mechanisms. TNF-α and IL-6 cause immediate transient contractile depression through induction of Ca^{2+}-dependent NOS. All four proinflammatory cytokines, i.e. TNF-α, IL-6, IL-1, and IL-18, contribute to the late phase of sustained contractile impairment through induction of Ca^{2+}-independent NOS. Increased NO production, as the final common pathway, alters intracellular Ca^{2+} homeostasis, resulting in profound systolic and diastolic impairment. NOS, nitric oxide synthase; NO, nitric oxide

Ca^{2+}-dependent nitric oxide synthase (NOS) activation. In the presence of N-methyl-L-arginine (L-NMA), an NOS inhibitor, the myocardial function is improved [56]. The latter leads to rapid increase in free sphingosine level which, similar to its exogenous analog D-sphingosine, has negative inotropic effect on isolated cardiac myocytes. Furthermore, enzymatic blockage of sphingosine production reverses TNF-α-mediated myocardial depression [57]. It is postulated that NO-independent defect of β-adrenoreceptor signal transduction is partially responsible for the early depressant effects of TNF-α [58]. This proposition is supported by decreased production of cAMP in response to isoproterenol in the presence of TNF-α, which is not improved following L-NMA administration [58].

Delayed cardiodepressant effect of either basal [59–61] or stimulated [62, 63] myocardial function, which is developed in several hours to days, is the direct result of NO production by activation of Ca^{2+}-independent, inducible isoform of nitric oxide synthase (iNOS). From a physiological standpoint, low concentration of NO controls coronary vascular tone [64], regulates basal myocardial function through its positive inotropic and chronotropic properties [59], and prevents platelet aggregation [65],

whereas pathologically high concentration of NO results in profound systolic and diastolic dysfunction [66].

Reduced calcium availability or sensitivity, as the final common pathway, contributes to both basal and catecholamine-stimulated contractility deficits [58]. Sphingosine blocks the ryanodine receptor which in turn disrupts L-type channel-induced calcium release by the sarcoplasmic reticulum [67]. TNF-α-induced sphingosine production decreases calcium transients causing both immediate and temporary contractile dysfunction [57] (Fig. 2). High levels of NO mediate myofilament desensitization to intracellular calcium, which results in sustained contractile dysfunction [68].

Cardiac myocyte apoptosis

TNF-α induces apoptosis in cardiac myocytes [69], which contributes to the progressive left ventricular (LV) wall thinning and adverse cardiac remodeling [24, 70, 71]. At the molecular level, sustained overexpression of TNF-α activates both intrinsic and extrinsic apoptotic pathways and leads to progressive loss of anti-apoptotic proteins [69] (Fig. 3). Engagement of TNFR1 initiates cardiac myocyte apoptosis [34]. TNF-α-induced extrinsic apoptotic pathway is mediated through complex I and complex II formation. The intracytoplasmic portion of TNFR1 recruits cytoplasmic proteins TNFR1-associated via death domain (TRADD) and TNFR-interacting serine-threonine kinase 1 (RIP1). Complex I is composed of TNFR-associated factor 2 (TRAF2) plus TRADD-RIP1 compound. Complex II is composed of Fas-associated death domain (FADD) and caspase-8 plus cytosolic TRADD-RIP1 compound, not in association with the death domain of TNFR1. Complex I formation provokes NF-κB and JNK activation which have quite the opposite effects. NF-κB activation has an anti-apoptotic property and inhibits enzymatic activity of caspase-8 by caspase-8 inhibitor c-FLIP$_L$. While JNK activation accelerates c-FLIP$_L$ degradation and promotes apoptotic cell death. In other words, the balance between NF-κB and JNK activation determines whether cell survives or dies [69].

Bid, a direct substrate of caspase-8, connects the extrinsic and intrinsic signaling pathways. Cleaved Bid translocates to the mitochondria, where it triggers the release of proapoptotic mediators, most important cytochrome c. Upon cytochrome c release, caspase-9 and caspase-3 are proteolytically activated in a sequential manner. Upon activation, caspase-3 triggers downstream proapoptotic signaling pathways, which result in

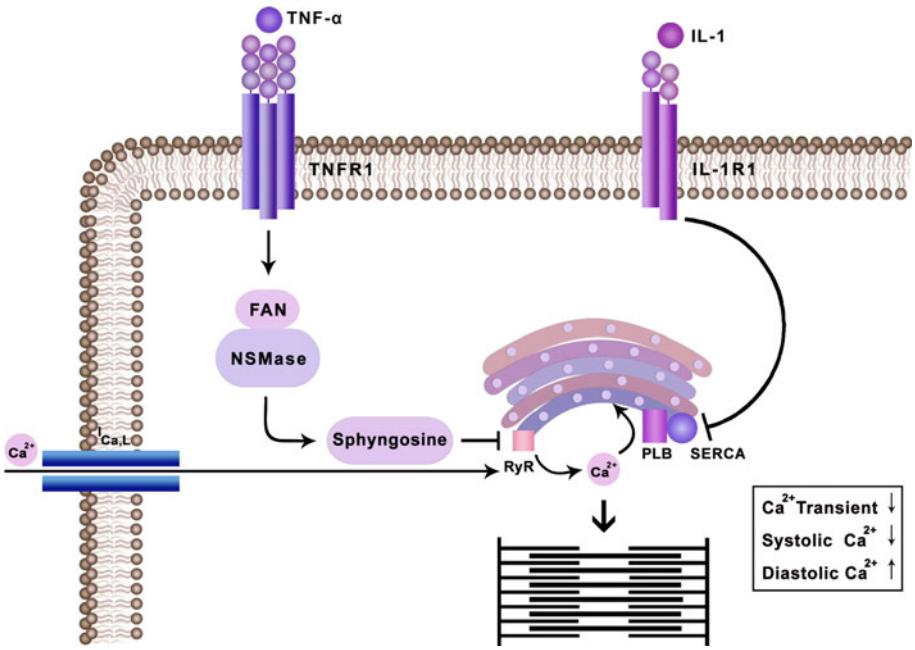

Fig. 2 Cellular mechanisms underlying NO-independent contractile dysfunction. TNF-α-induced sphingosine production inhibits calcium-induced calcium release from the RyRs located in the sarcoplasmic reticulum (SR), causing immediate contractile dysfunction. Chronic exposure to increased level of IL-1 decreases the expression of SERCA and PLB at both the transcript and protein levels. Decreased level of SERCA is responsible for impaired removal of cytosolic Ca^{2+} and a subsequent decrease in sarcoplasmic reticulum Ca^{2+} release. Alterations in Ca^{2+} homeostasis, as demonstrated by decreased Ca^{2+} transient and impaired systolic Ca^{2+} release and diastolic Ca^{2+} removal, alter sarcomere dynamics and function leading to profound systolic and diastolic dysfunction. FAN, factor associated with neutral sphingomyelinase; NSMase, neutral sphingomyelinase; RyR, ryanodine receptor; SERCA, sarcoplasmic reticulum Ca^{2+}-ATPase; PLB, phospholamban; $I_{Ca,L}$, inward Ca^{2+} current; TNFR1, tumor necrosis factor receptor type 1; IL-1R1, interleukin-1 type I receptor

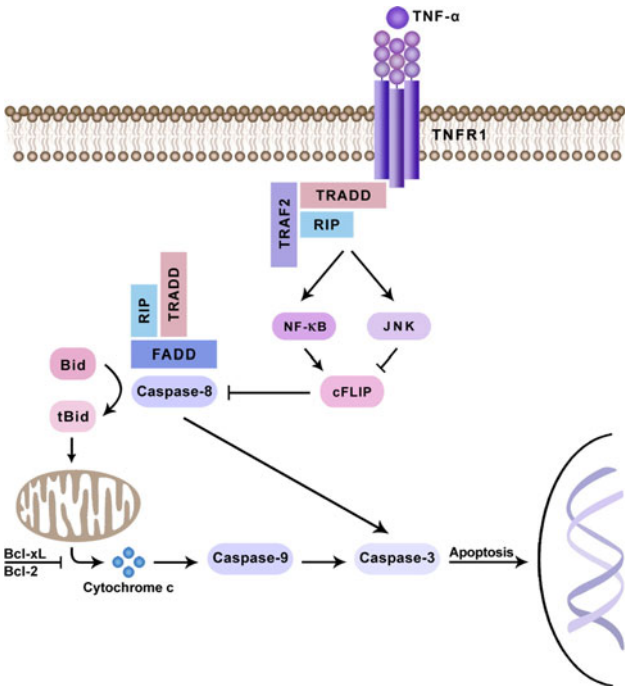

Fig. 3 TNF-α-induced apoptotic cell death through both extrinsic and intrinsic apoptotic pathways. Engagement of TNFR1 initiates TNF-α-induced extrinsic apoptotic pathway. The formation of TRADD/RIP1/TRAF2 complex in direct association with TNFR1 provokes NF-κB and JNK activation which have quite the opposite effects on caspase-8 inhibitor c-FLIP. Cytosolic TRADD/RIP1/FADD complex interacts with caspase-8 and thereby enhancing its enzymatic activity. Bid, a direct substrate of caspase-8, connects the extrinsic and intrinsic signaling pathways. Cleaved Bid triggers the release of cytochrome c from the inner membrane of mitochondria. The consequential activation of caspase-9 and caspase-3 results in DNA fragmentation and apoptotic cell death. TNFR1, tumor necrosis factor receptor type 1; TRADD, TNFR1-associated via death domain; RIP, TNFR-interacting serine-threonine kinase; TRAF2, TNFR-associated factor 2; FADD, Fas-associated death domain; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; JNK, c-Jun N-terminal kinase; cFLIP, cellular caspase-8 (FLICE)-like inhibitory protein; tBid, truncated Bid

DNA fragmentation and protein cleavage. Sustained TNF-α signaling empowers the pro-apoptotic forces, while weakens the cellular defense mechanisms by progressive depletion of cytoprotective proteins (e.g. Bcl-2, c-FLIP, C-IAP-1). Bcl-2 resides in the outer mitochondrial membrane and its progressive loss leads to mitochondrial release of pro-apoptotic mediators. c-FLIP and c-IAPs inhibit caspase-8 and caspase-3 activation, respectively. In their absence, intrinsic and extrinsic apoptotic pathways can be activated without hindrance. Accordingly, overexpression of cytoprotective Bcl-2 in the context of sustained TNF-α signaling (bitransgenic mice), either normalizes or significantly reduces the cytosolic levels of intrinsic apoptotic pathway components. However, Bcl-2 overexpression does not fully compensate for progressive cardiac myocytes apoptosis, since it has no effect on the extrinsic apoptotic pathway [69].

In addition, the prominent role of sphingolipid-signaling pathway in apoptotic cell death has recently become evident. TNF-α activates neutral sphingomyelinase (NSMase) through factor associated with neutral sphingomyelinase (FAN), which results in proapoptotic ceramide and sphingosine production [72]. Expression of a dominant-negative FAN attenuates, whereas overexpression of wild-type FAN aggravates ischemia–reperfusion-induced cardiac myocyte death. Exogenous ceramide administration induces considerable cell death in dominant-negative FAN-expressing cells indicating the importance of sphingolipid cascade activation in induction of cardiac myocyte apoptosis [72]. Apparently, TNF-α-induced cardiac myocyte apoptosis is mediated through multiple complex intracellular mechanisms.

Extracellular matrix remodeling

Myocardial extracellular matrix (ECM) is mainly composed of a complex network of fibrillar collagen [73], which provides the physical scaffolding for the spatial organization of cells into functional tissues as well as a dynamic microenvironment for cell signaling [74]. Alterations in the collagen abundance, isoforms, cross-links, architecture, and turnover have been demonstrated to play a central role in cardiac remodeling and progressive LV dysfunction [74, 75]. Cardiac fibroblasts are the main source of fibrillar collagen in the heart [76, 77]. TNF-α decreases collagen synthesis and procollagen mRNA expression in neonatal and adult rat cardiac fibroblasts in vitro [78]. TNF-α causes imbalance between extracellular matrix synthesis and degradation through dysregulation of degradative enzymes, matrix metalloproteinases (MMPs), and the multifunctional endogenous inhibitors, tissue inhibitors of MMPs (TIMPs), which is a major determinant of pathological ECM remodeling [79]. These effects are largely influenced by the duration of exposure, which ranges from increased fibrillar collagen degradation to excessive fibrillar collagen deposition. In short term, TNF-α-induced activation of MMPs leads to enhanced degradation of ECM components which promotes progressive LV dilation [80, 81]. In long term, increased TIMP expression and the resultant decrease in MMP activity [80] as well as the indirect effects of sustained TNF-α expression, including increased angiotensin type I receptor (AT_1) density on cardiac fibroblasts [82], increased cardiac fibroblast sensitivity to profibrotic effects of angiotensin II [83], and increased TGF-β expression [80], result in excessive collagen deposition and increased LV stiffness. Both TNF-α and MMPs serve as potential therapeutic targets to prevent ventricular remodeling and heart failure; treatment with adenoviral vector expressing soluble TNFR1 [81], soluble TNFR2 fusion protein [84], and

competitive MMP inhibitor [85] has proven to be of benefit. TNF-α-mediated activation of NF-κB and the AP-1 family of transcription factors has been proposed to modulate the MMP-1, MMP-3, MMP-7, MMP-9, and MMP-13 and TIMP-1 and TIMP-2 gene expression at the transcriptional level [86], an effect which could be suppressed by the use of transcription factor inhibitors [87, 88].

IL-6

IL-6-related cytokines, including IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), and cardiotrophin-1 (CT-1), are pleiotropic cytokines with redundant properties. These cytokines are expressed in a wide variety of tissues and organs, mediating proliferation, growth, differentiation, survival and apoptosis signals and are crucial during embryogenesis and subsequently throughout life [89–92].

Without exception, all the members of the IL-6 superfamily share gp130 as the central signal transducer subunit. To some extent, this may explain the underlying mechanisms of redundancy in their functions [92]. Ligand-receptor complex formation, either transmembrane receptor or soluble receptor, leads to gp130 dimerization that triggers downstream signaling cascades including Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, Ras/Raf/mitogen-activated protein kinase (MAPK)/ERK kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway, and phosphoinositide 3-kinase (PI3K)/Akt pathway [89, 91] (Fig. 4).

There are wide discrepancies in cumulative findings of clinical and experimental studies; it is not clear whether IL-6-related cytokines either improve or deteriorate the cardiovascular performance. Although numerous studies have been performed in this regard, the results are inconclusive. To explain the reported inconsistencies, though not entirely satisfactory, the following statements should be considered. *First*, IL-6-related cytokines are closely interrelated and show redundancy. Thus, in vitro studies on individual cytokines may show poor correlation with clinical studies in which a complex and sophisticated network of cytokines have been activated. *Second*, recent studies demonstrate the interaction between cytokines and neurohormonal mediators [3, 14], which share JAK/STAT [93], MAPK [94], and PI3K [94] as their common final intracellular pathways. Therefore, excessive elaboration of neurohormonal mediators within context of the failing heart masks the cytoprotective effects of IL-6 related cytokines. *Third*, although the discrete signal transduction pathways are well defined, the complex interactions among them are widely debated. Attempts to clarify the regulatory functions of downstream signaling molecules will further explain the diversity of gp130-mediated biological activities and strengthen the links between experimental findings and clinical observations.

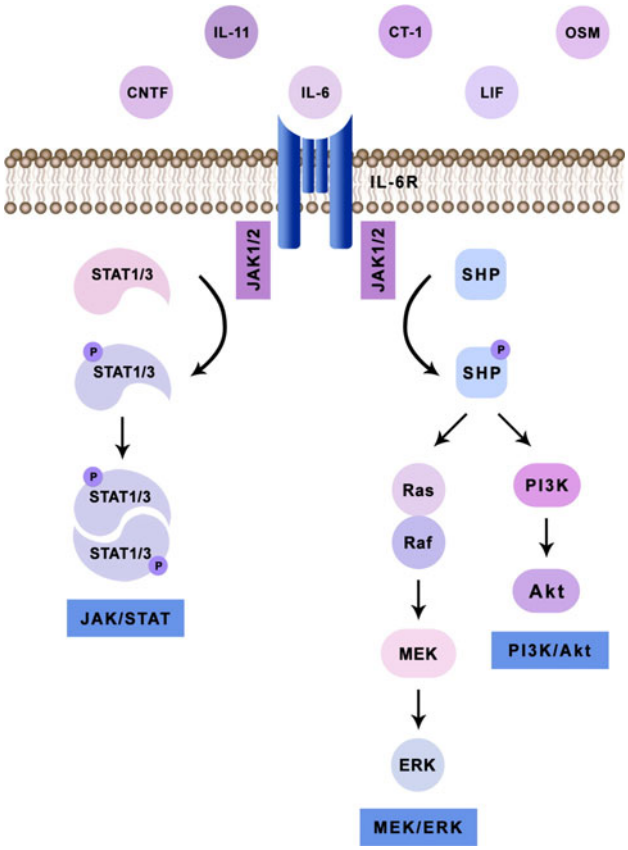

Fig. 4 The divergent intracellular signaling pathways of the IL-6 superfamily of cytokines. LIF, leukemia inhibitory factor; OSM, oncostatin M; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; JAK, Janus kinase; STAT, signal transducer and activator of transcription; MEK, ERK kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase; SHP, Src homology 2 (SH2) domain-containing protein tyrosine phosphatase; IL-6R, interleukin-6 receptor

Cytoprotective effects

Activation of gp130 exerts cytoprotective effects and improves cardiac myocyte survival via inhibition of apoptotic signaling pathways [94]. The following discussion provides compelling evidence in 4 different areas including ischemia–reperfusion injury, hemodynamic overload, doxorubicin-induced cardiotoxicity, and inflammatory heart diseases.

IL-6 treatment of cardiac myocytes prior to induction of ischemia–reperfusion injury is associated with decreased reperfusion-induced mitochondrial depolarization, swelling and loss of structural integrity, increased mitochondrial

Ca^{2+} loading, and decreased cytosolic Ca^{2+} transients. IL-6 preconditioning exerts its beneficial effects through PI3K/Akt-mediated activation of iNOS. Administration of PI3K inhibitor attenuates both iNOS induction and IL-6-dependent protection [95]. Administration of CT-1, either prior to ischemia or at the time of reperfusion, improves cardiac myocyte survival. It has been shown that both cultured adult cardiac myocytes and intact heart ex vivo considerably benefit from CT-1, represented by decreased cell death and reduced infarct size/zone at risk ratio, respectively [96]. Its beneficial effects are blocked by the administration of p42/p44 MAPK inhibitor [96].

In an in vivo murine model of acute myocardial infarction, ischemic and healthy cardiac myocytes show increased levels of STAT3 phosphorylation. Administration of JAK2 inhibitor prior to induction of myocardial infarction results in decreased STAT3 phosphorylation and increased caspase-3 activity and Bax expression [97]. Ischemic preconditioning of the heart exerts potent cardioprotective effects, as demonstrated by improved post-ischemic ventricular function, reduced infarct size, and decreased apoptotic cell death. At the molecular level, JAK2 and STAT3 phosphorylation are increased; the antiapoptotic *BCL2* gene expression is upregulated, whereas the proapoptotic *BAX* gene expression is down-regulated. JAK2 inhibitor has the ability to completely reverse the aforementioned findings [98].

Following acute pressure overload, dilated cardiomyopathy is rapidly developed in gp130 cardiac-specific knockout mice. In comparison to control mice, the prevalence of cardiac myocyte apoptosis is markedly increased. What draws attention is the compensatory hypertrophic growth response in control mice with intact gp130 signaling pathway, which magnifies its beneficial role in cardiac myocyte adaptation and survival [99]. In fact, cardiac myocyte loss contributes significantly to the transition from compensatory LV hypertrophy to overt heart failure [100].

Cardiac toxicity is a unique characteristic of the anthracycline antibiotics, doxorubicin [89]. LIF pretreatment significantly reduces doxorubicin-induced myocyte apoptosis. Following LIF administration, PI3K and Akt kinase activities are partially restored, doxorubicin-induced caspase-3 activation is totally inhibited, and protective function of Bcl-xL is improved [101]. Transgenic mice with cardiac-specific overexpression of STAT3 show prolonged survival following doxorubicin administration [102, 103], whereas cardiomyocyte-specific deletion of STAT3 renders cardiac myocytes more vulnerable to doxorubicin-induced cardiotoxicity [104].

Mice with a cardiomyocyte-restricted STAT3 deletion are particularly susceptible to LPS-induced myocardial inflammation. Accordingly, apoptotic cell death and TNF-α secretion are increased significantly. Advanced age mice demonstrate increased cardiac fibrosis and spontaneous development of heart dysfunction [104]. Cardiac-specific gp130-knockout mice show increased susceptibility to viral infection of cardiac myocytes, demonstrating the major role of gp130 signaling in mediating the survival signal. Specific inhibition of the STAT3 signaling pathway blocks the cytoprotective effects of CT-1, whereas specific inhibition of the other two pathways, i.e. MEK/ERK1/2 and PI3K/Akt signaling, has no effect [105].

To summarize, current evidence points to the importance of 3 major signaling cascades as the mediator and regulator of gp130-induced cytoprotective effects; however, their exact contributions are not clear.

Maladaptive responses

Cardiac myocyte hypertrophy

IL-6-related cytokines, with the subsequent activation of gp130 signaling, contribute to cardiac myocyte hypertrophic growth response [94]. Continuous activation of gp130 signaling in double transgenic mice overexpressing both IL-6 and IL-6 receptor (IL-6R) is associated with cardiac myocyte hypertrophy, measured in terms of cardiac myocyte size, cardiac weight, and LV wall thickness [53]. Neither IL-6 nor IL-6R overexpression alone is sufficient to induce detectable myocardial abnormalities due to low expression level of IL-6R in cardiac myocyte [106]. Cultured neonatal cardiac myocytes, incubated with IL-6 and soluble form of IL-6R, become hypertrophied, emphasizing the importance of IL-6-IL-6R complex formation for signal initiation [53]. On the other hand, LIF receptor is abundantly expressed in cardiac myocytes, with exogenous addition of LIF and CT-1 being sufficient to elicit hypertrophic growth response [107, 108]. LIF and CT-1 are shown to predominantly increase myocardial cell length with the addition of new sarcomeric units in series rather than myocardial cell width [109]. Furthermore, transgenic mice with cardiac-specific overexpression of STAT3 develop myocardial hypertrophy with no additional stimuli [110].

To gain better insight into the underlying intracellular mechanisms, overexpression or inactivation of various components of gp130-mediated signaling pathways have been studied. A growing body of evidence points to STAT3 as the central transducer of hypertrophic growth response; however, a few studies credit MAPK/ERK and PI3K cascades with complementary and regulatory roles [110–114].

Cultured murine cardiac myocytes overexpressing wild-type STAT3 demonstrate augmented STAT3 phosphorylation following LIF stimulation. Administration of a

MAPK inhibitor has no effect on STAT3 phosphorylation; however, gene expression and protein synthesis are substantially reduced even in cells overexpressing STAT3 [115]. It has been demonstrated that MAPK activity is required for maximal transcriptional activity of JAK/STAT cascade [94, 116, 117]. On the contrary, following CT-1 stimulation, the negative regulatory role of ERK1/2, as the inhibitor of STAT3 phosphorylation, has been reported [113, 118]. The cross-talk between STAT3 and ERK1/2 seems to modulate CT-1-induced cardiac myocyte hypertrophy and serve as an intrinsic regulatory mechanism [113].

PI3K is reported to be involved in the regulation of gp130-dependent signaling pathways. Following administration of wortmannin, a specific PI3K inhibitor, MAPK activation is attenuated and LIF-induced gene expression, protein synthesis, and kinase activation are inhibited; however, STAT3 phosphorylation remains unaffected [112]. Various parameters of hypertrophic cell growth, including cell size, gene expression, protein synthesis, and myofilament reorganization, have been measured following specific blockade of the MAPK/ERK, JAK/STAT, and PI3K pathways with MEK, JAK2, and PI3K inhibitors, respectively. The results indicate the priority of MAPK/ERK cascade over JAK/STAT and PI3K pathways in gp130-mediated cardiac myocyte hypertrophy [114].

Pressure and volume overload produce morphologically distinct types of cardiac myocyte hypertrophy. In fact, intracellular signaling pathways have been shown to be differentially activated. It is suggested that stimulus-specific heterogeneity in the signaling pathways determine either eccentric, maladaptive cardiac hypertrophy or concentric, adaptive cardiac hypertrophy to ensue [119].

Contractile dysfunction

IL-6 is a potent mediator of myocardial depression, which in turn potentiates the cardiodepressant effects of TNF-α and IL-1 [120] (Fig. 1). Similar to TNF-α, acute exposure to IL-6 decreases intracellular Ca^{2+} transients and the amplitude of cell contraction within a few minutes. The early depressant effect is attributed to enhanced Ca^{2+}-dependent NOS activity in cardiac myocytes. Pretreatment with L-NMA completely inhibits the IL-6-induced contractile dysfunction, whereas subsequent addition of L-arginine restores the depressed cell contraction [121]. Prolonged exposure to IL-6 decreases cardiac contractility via enhanced de novo synthesis and activation of Ca^{2+}-independent iNOS [122]. The negative inotropic effect of IL-6 is the result of JAK2/STAT3-mediated activation of iNOS [122].

Extracellular matrix remodeling

LIF and CT-1 have been demonstrated to stimulate cardiac fibroblast proliferation in vitro [123, 124]. Pretreatment with antibodies for gp130, LIF receptor, or CT-1 significantly inhibits basal as well as CT-1-induced cardiac fibroblast growth. A reciprocal interaction has also been reported between CT-1/gp130/LIF receptor and endothelin-1 (ET-1)/ET type A (ET_A) receptor axis [123]. Collagen synthesis, assessed by [^{3}H] proline incorporation into cardiac fibroblasts, has been shown to increase upon exogenous CT-1 stimulation [123]. In contrast, IL-6 and LIF significantly reduce collagen synthesis and total collagen content in adult cardiac fibroblasts, respectively [78, 124]. Following experimental induction of acute myocardial infarction, IL-6 and MMP-9 mRNA levels increase significantly in the infarcted and border regions, whereas decreasing IL-6 mRNA levels from the infarcted to the remote noninfarcted regions correlates negatively with increasing MMP-2 and TIMP-1 mRNA levels, being highest in the noninfarcted region [125]. In cardiac fibroblast cultures, IL-6 increases, whereas LIF decreases, MMP activity, as demonstrated by gelatin zymography [78, 124]. Treatment of adult cardiac myocytes and fibroblasts with gp130 ligand OSM increases TIMP-1 production, with no effect on the expression of constitutively expressed MMP-1, MMP-2, MMP-3, MMP-9, and TIMP-2. In the same experimental study, IL-6, LIF, and CT-1 exert no effect on the expression of the studied MMPs and TIMPs [126].

IL-1

The IL-1 superfamily of cytokines comprises IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-18, and the newly discovered IL-33. IL-1α and IL-1β are structurally distinct molecules with indistinguishable biological functions, which share common intracellular signaling cascades through IL-1 type I receptor (IL-1R1). IL-1α and IL-1β are produced as precursor peptides, which are cleaved by caspase-1 or the IL-1 converting enzyme (ICE) to form the active molecules. These pleiotropic cytokines function as mediators of innate immunity responses which are mainly produced by macrophages, monocytes, and dendritic cells [127]. IL-1Ra is an endogenous regulator of IL-1 activity with potential anti-inflammatory properties. It competitively occupies IL-1R and interrupts intracellular signal transduction [128].

In response to various injurious insults, cardiac structural cells are triggered to produce IL-1 as well as other proinflammatory cytokines [129–132]. The deleterious maladaptive effects of IL-1 have been the focus of interest in the majority of experimental studies. However, beneficial effects of IL-1 have also been reported.

Cytoprotective effects

IL-1 pretreatment reduces myocardial ischemia reperfusion injury [133–135]. IL-1 preconditioning results in polymorphonuclear leukocyte (PMN) accumulation and H_2O_2 generation in myocardium. The preceding oxidant stress induces increased glucose-6-phosphate dehydrogenase (G6PD) activity, which provides cytoprotective effects against the subsequent oxidant insult [133]. Increased Cu/ZnSOD, MnSOD, catalase, and glutathione peroxidase activities and HSP-27 overexpression provide additional protection [134].

Maladaptive responses

Cardiac myocyte hypertrophy

IL-1 is involved in myocardial hypertrophic growth response, which partially compensate for environmental stresses. The expression of IL-1β is increased in pressure [136] and volume [137] overload-induced cardiac hypertrophy. Both in vitro [138–140] and in vivo [52, 141] experimental studies provide proof of the direct effect of IL-1 on cardiac myocyte hypertrophy; however, the complex interaction between myocyte and nonmyocyte cells and the intracellular signaling pathways have not been fully identified.

Mice with cardiac-specific overexpression of IL-1α after birth shows concentric LV hypertrophy with preserved LV systolic function [141], while constitutively increased levels of IL-1α even before birth produce cardiac myocyte hypertrophy and heart failure [52]. IL-1β induces growth of isolated cultured cardiac myocyte [138, 139], whereas it inhibits cultured cardiac fibroblast proliferation [138]. Hypertrophic growth response accompanies increased fetal gene (atrial natriuretic factor and β-myosin heavy chain) and decreased calcium regulatory gene (sarcoplasmic reticulum Ca^{2+}-ATPase, calcium release channel, voltage dependent calcium channel) expression [52, 139]. The hypertrophic effect of IL-1 is NO-independent [138, 139], which appears to be mediated through a tyrosine kinase signaling pathway [138]. IL-1-induced growth effect is inhibited by tyrosine kinase inhibitor, whereas the addition of NOS, protein kinase C (PKC), and cyclooxygenase inhibitors has no substantial effect [138].

Contractile dysfunction

In vitro studies have demonstrated that IL-1, in synergism with TNF-α, exacerbates cardiac myocyte [60, 142] and intact heart [61] contractile dysfunction. IL-1 produces delayed and prolonged phase of decreased myocardial contractility, emphasizing the necessity for de novo gene expression, protein synthesis, and recruitment of secondary mediators [143] (Fig. 1). The underlying mechanism(s) has not been uniformly elucidated and both NO-dependent and NO-independent mechanisms have been proposed (Fig. 2).

IL-1, in parallel with other proinflammatory cytokines, augments the expression of cardiac myocyte iNOS [144–146]. The subsequent increase in NO production dampens cardiac myocyte [60, 146, 147] and intact heart [61, 148] contractile function, which can be attenuated with isoform nonselective [60, 61, 146, 147] and selective [148] inhibitors of NOS. NO may directly inhibit the mitochondrial activity in cardiac myocytes [146, 149], with the resultant energy depletion and contractile dysfunction [147]. Increased glucose consumption and lactate production, and decreased cellular ATP content are blocked by addition of an NOS inhibitor. However, neither the administration of cGMP donor nor an inhibitor of cGMP-dependent protein kinase reverses the metabolic, electrophysiological, and contractile derangements [147]. These results point to the direct non-cGMP dependent cardiodepressant effects of IL-1-induced NO production.

Alterations in Ca^{2+} homeostasis, rather than NO-mediated pathways, have been shown to mediate the cardiodepressant effect of IL-1. Chronic exposure to IL-1β reversibly decreases basal and stimulated contractility and the amplitude of calcium transients [150]. Altered calcium handling of cardiac myocytes is evidenced by decreased expression of genes involved in the regulation of Ca^{2+} homeostasis, namely phospholamban and sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), at both the transcript and protein levels [150, 151]. There is a growing body of evidence from experimental and clinical studies to support the fundamental role of altered SERCA/phospholamban interactions in the failing heart [152, 153]. Either decreased level of SERCA or increased inhibition of its activity by phospholamban is responsible for impaired removal of cytosolic Ca^{2+} and a subsequent decrease in sarcoplasmic reticulum Ca^{2+} release, which are the characteristic features of cardiac diastolic and systolic dysfunction. Adenoviral gene transfer of SERCA2a in the transitional phase from compensated hypertrophy to heart failure restores systolic and diastolic function to normal levels [154]. Besides, overexpression of SERCA2a in failing hearts results in improved survival, normalized LV volumes, and increased phosphocreatine/ATP ratio [155]. In addition to the paramount importance of altered Ca^{2+} homeostasis, the shift from α-MHC toward β-MHC gene expression [52, 139], which signifies the structural changes in myofibrillar protein composition, might contribute to modified contractile properties.

Cardiac myocyte apoptosis

IL-1 induces programmed cell death in cultured cardiac myocytes through NOS induction [156]. Following administration of an NOS inhibitor, increased levels of iNOS mRNA and NO metabolites are reversed, while apoptotic cell death is completely blocked [156, 157]. NO-mediated apoptosis seems not to be driven by cGMP-dependent mechanisms, as evidenced by the lack of antiapoptotic effect of cGMP-dependent protein kinase inhibitor. IL-1-induced apoptosis is mediated, at least in part, by generation of reactive nitrogen species in the presence of oxygen free radicals, caspase activation, and alteration in the cellular balance of Bak and Bcl-xL. Apoptotic cell death is attenuated by antioxidants and caspase inhibitor administration, which further support the proposed mechanisms [156].

In line with the aforementioned evidence, the antiapoptotic property of anakinra, an exogenous recombinant human IL-1Ra, has been demonstrated in models of ischemia–reperfusion injury [158, 159] and acute myocardial infarction [160]. The resultant reduction in cardiac myocyte apoptosis leads to reduced infarct size and signs of favorable ventricular remodeling. The anti-apoptotic property of anakinra is partly due to decreased expression of pro-apoptotic mediators, namely Bax, Bak, and caspase-3 with no significant effect on the expression of anti-apoptotic mediator Bcl-2 [158, 159]. Furthermore, anakinra inhibits caspase-1 and caspase-9 activities as a mixed competitive and noncompetitive enzyme inhibitor [160].

Extracellular matrix remodeling

IL-1 exerts a potent antiproliferative effect on cultured cardiac fibroblasts [138]. IL-1β serves as a robust stimulus of adult cardiac fibroblast migration; TNF-α substantially enhances, whereas TGF-β1 strongly inhibits, the migratory response to IL-1β [161]. IL-1β induces a selective down-regulation of fibrillar collagen synthesis, as demonstrated by decreased expression of procollagen α_1(I), α_2(I), and α_1(III) mRNA and increased expression of procollagen α_1(IV), α_2(IV), and fibronectin mRNA [78]. IL-1β treatment increases collagen breakdown through induction of proMMP-2 and proMMP-3 mRNA expression and increased MMP activity, with specific increases in both the proenzyme and active enzyme bands corresponding to MMP-2, MMP-9, and MMP-13 [78]. IL-1β increases MMP-2 transcription and activity in cultured cardiac fibroblasts, an effect which could be inhibited by the NOS inhibitor L-NMMA [162]. PKC isoforms (α, β1, ζ, and θ) differentially activate ERK1/2, JNKs, and NF-κB, which have been shown to be differentially regulated in IL-1β-induced MMP-2 and MMP-9 expression and activity [163]. IL-1β-mediated activation of NF-κB and the AP-1 family of transcription factors might be responsible for IL-1β-induced MMP-1, MMP-3, MMP-7, MMP-9, and MMP-13 and TIMP-1 and TIMP-2 gene expression at the transcriptional level [86], as demonstrated by decreased MMP-1, MMP-2, and MMP-9 levels following administration of MAPK and NF-κB inhibitors [163, 164].

IL-18

IL-18, originally identified as IFN-γ inducing factor, is a proinflammatory cytokine with pleiotropic biological effects on immune, infectious, and inflammatory processes. IL-18 belongs to the IL-1 superfamily of cytokines with structural, rather than functional, homology to IL-1. Furthermore, the IL-18 receptor complex and its intracellular signaling pathways are closely analogous to IL-1. Similar to IL-1α and IL-1β, IL-18 is synthesized as a biologically inactive precursor (pro-IL-18), which is processed by ICE to form the bioactive mediator [165].

IL-18 shares functional similarities with IL-12 as a key element of both innate and adaptive immunity [165, 166]. IL-18, in synergism with IL-12, stimulates IFN-γ production by T cells, natural killer (NK) cells, and macrophages. The synergistic function of IL-18 and IL-12 is partly due to simultaneous activation of transcriptional factors involved in IFN-γ gene expression. IL-12 is an essential prerequisite for IL-18R induction on naïve T cells. Subsequently, IL-12 and IL-18 stimulate the reciprocal upregulation of their receptors, which in combination with antigenic engagement of T-cell receptor (TCR), direct T-cell differentiation toward T_H1 lineage [166]. Although the biological effects of IL-18 are mainly due to enhanced IFN-γ production, IFN-γ-independent mechanisms have also been identified.

Myocardial structural cells, including endothelial cells, smooth muscle cells, and cardiac myocytes, are able to produce IL-18 in response to ischemia–reperfusion injury, acute myocardial infarction [167], and endotoxemia [168]. The emerging body of evidence represented herein deals with the direct role of IL-18 in mediating the cardiovascular maladaptive responses. Its indirect impacts through IFN-γ-dependent mechanisms are beyond the scope of the current literature.

Maladaptive responses

Cardiac myocyte hypertrophy

IL-18 has been demonstrated to induce cardiac myocyte hypertrophy, which provides early functional compensation followed by eventual decompensation and heart

failure. In vitro treatment with IL-18 results in phosphorylation of the translational regulatory proteins, increased total protein synthesis and cell surface area, and enhanced fetal gene expression and protein synthesis [169]. The critical role of IL-18 in the cardiac growth response has been demonstrated in an in vivo model of chronic pressure overload. IL-18 knockout mice showed blunted hypertrophy in association with reduced expression of contractile-, hypertrophy-, and remodeling-associated genes [170].

PI3K/PDK1/Akt/GATA4 signaling pathway has been demonstrated to relay IL-18-induced hypertrophic growth response [169, 170]. In support of the above findings are in vivo models of cardiac specific PI3K [171] and Akt [172] overexpression, which result in increased cardiac myocyte size and concentric LV hypertrophy. Akt phosphorylation leads to its nuclear translocation, which augments GATA4 DNA binding activity with the subsequent increase in target gene expression. NF-κB, p38 MAPK, JNK, and ERK activation has been spotted in IL-18-treated cardiac myocytes in vitro; however, their inactivation does not interfere with cardiac myocyte growth [169]. This result runs contrary to the previous experimental studies in which the transcriptional factor NF-κB [173] and members of the MAPK cascade [174–176] are implicated as main regulators of cardiac myocyte growth.

Contractile dysfunction

Daily administration of IL-18 seems to be sufficient to compromise contractile function and β-adrenergic responsiveness in healthy mice [177, 178]. Furthermore, IL-18 neutralization attenuates LPS-induced myocardial dysfunction [168]. The ability of IL-18 to stimulate proinflammatory cytokines with known cardiodepressant effects, i.e., TNF-α, IL-1α, IL-1β, IL-6 [179–181], and IFN-γ [182], has been postulated as the plausible underlying mechanism. IL-18 has been shown to induce NO synthesis [181, 183], which mediates myocardial dysfunction either directly or as a consequence of IL-18-mediated proinflammatory cytokines production (Fig. 1). Moreover, IL-18 enhances intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression [184, 185], induces neutrophilic cell infiltration [186], and activates cytotoxic T lymphocytes [187, 188], all of which contribute to aggravated myocardial inflammation and the severity of contractile dysfunction.

In support of the aforementioned statement, improved contractile function following IL-18 neutralization is associated with reduced myocardial IL-1β production and ICAM-1/VCAM-1 expression [168]. However, neither increased cardiac infiltration of leukocytes nor increased endothelial leukocyte adhesion or ICAM-1 protein synthesis has been documented in IL-18-treated mice [177]. Additionally, either daily administration of IL-18 [177] or IL-18 neutralization in an in vivo model of LPS-induced myocardial dysfunction [168] fails to make a significant difference in TNF-α mRNA and protein levels in the cardiac tissue.

The direct effects of IL-18 on Ca^{2+} homeostasis, rather than its indirect effects, may contribute to contractile dysfunction. Increased peak Ca^{2+} transients and diastolic Ca^{2+} concentration consistent with reduced myofilament responsiveness to Ca^{2+} has been demonstrated in vitro [177]. However, the precise mechanisms of altered Ca^{2+} homeostasis are not well identified.

Cardiac myocyte apoptosis

IL-18 is a proinflammatory cytokine with proapoptotic properties. Programmed cell death might be attributed indirectly to IL-18-induced TNF-α, IL-1β, IL-6 [179–181], and NO production [189], which contributes to cardiac myocyte apoptosis. More important, IL-18 induces apoptotic cell demise via the extrinsic and intrinsic signaling pathways [190]. A comprehensive description of the common mechanisms of apoptosis has been provided previously (Fig. 3). Engagement of death receptors, i.e., TNFR1 and Fas, initiates extrinsic signaling pathway. IL-18 induces proapoptotic Fas, Fas-L, and TNFR1 expression in endothelial cells [190, 191], NK cells [192], and T_H1 cells [187]. The increased Fas and Fas-L promoter activities are mediated through NF-κB activation [190]. Of note, IL-18 activates caspase-8 and caspase-3 and inhibits the caspase-8 inhibitor c-FLIP, further potentiating the extrinsic signaling pathway [190]. On the other hand, the release of mitochondrial cytochrome c initiates intrinsic signaling pathway. IL-18 has been noted to activate Bid, which promotes cytochrome c release, and to increase caspase-9 activation. Furthermore, IL-18 alters the expression of Bcl-2 family proteins in favor of apoptosis [190].

In addition, a novel signal transduction pathway has been identified in IL-18-mediated cardiac endothelial cell apoptosis. IL-18 induces phosphatase and tensin homolog (PTEN) expression via p38MAPK/NF-κB signaling pathway [193]. PTEN is a tumor suppressor, which negatively regulates PI3K/Akt signaling pathway [194]. Akt functions as a prosurvival kinase through activation of antiapoptotic and inhibition of proapoptotic signaling molecules [195]. PTEN dephosphorylates phosphatidylinositol-3,4,5-triphosphate (PI3P), a substrate for PI3K-dependent Akt phosphorylation and activation [194].

In stark contrast to the aforementioned reports, IL-18-treated cardiac myocytes show no sign of increased susceptibility to apoptotic cell death [169]. The antiapoptotic property of IL-18 is mediated in part by phosphorylation of

Bcl2-antagonist of cell death (BAD), which prevents it from inactivating anti-apoptotic members of the Bcl-2 family [196, 197]. Therefore, it has been suggested that IL-18-induced apoptosis might be cell specific.

Extracellular matrix remodeling

IL-18 stimulates fibronectin expression in adult cardiac fibroblasts, an effect which is blocked by either anti-IL-18 neutralizing antibodies or IL-18BP:Fc chimera. IL-18-induced fibronectin expression has been shown to be independent of other proinflammatory cytokines (i.e. TNF-α and IL-1β) and growth factors (i.e. TGF-β and CTGF). IL-18 induces fibronectin expression via PI3K-Akt-dependent NF-κB activation [198]. In murine models of left ventricular pressure and volume overload, there is a parallel increase in IL-18 and osteopontin expression and the subsequent interstitial fibrosis and diastolic dysfunction. IL-18 induces osteopontin expression in cultured cardiac fibroblasts, while anti-IL-18 neutralizing antibodies abolish this effect [199].

Conclusions

Chronic heart failure is among the leading causes of mortality worldwide. Approximately 2% of adult population are diagnosed with moderate or severe systolic dysfunction [200] with an incidence rate of 10 per 1000 population after the age of 65 [201]. The number of patients with established heart failure tends to increase in parallel with improved management of the underlying cardiovascular diseases. Despite the identification of efficacious pharmacological regimens targeting neurohormonal activation and introduction of mechanical interventions, chronic heart failure remains to be a leading cause of hospitalization and poses a considerable financial challenge to health care resources worldwide [202]. Therefore, the introduction of novel therapeutics as adjunctive to conventional pharmacotherapy has been a topic of intensive research.

In the past two decades, numerous experimental and clinical investigations provide powerful evidence to support a role for immune system dysregulation, and in particular the pathogenic role of proinflammatory cytokines, in the development and progression of heart failure. Experimental studies mainly fall into three categories including genetically manipulated models of "gain of function" and "loss of function", exogenous addition of cytokines, either alone or in combination with their soluble receptors, and pharmacological inhibition of cytokine-mediated intracellular signaling pathways. Accordingly, the complex nature of immunopathophysiological mechanisms in mediating the adaptive and maladaptive responses has become increasingly evident. The substantial impact of proinflammatory cytokines on cardiac myocyte hypertrophy, contractile dysfunction, cardiac myocyte apoptosis, and extracellular matrix remodeling could be of immense significance for designing novel therapeutic strategies to delay the progression of heart failure. Neutralization of proinflammatory cytokines and inhibition of intracellular signaling pathways and subsequent gene expression are among the most promising therapeutic strategies in the near future.

A number of proinflammatory cytokines (i.e. TNF-α and IL-6) are believed to play either physiological or pathological roles depending on their concentrations and the acuteness versus chronicity of the primary insult. The results of large, well-designed, randomized, double-blind, placebo-controlled clinical trials of anti-TNF-α therapies, i.e. infliximab [203] and etanercept [204], showed either neutral or even detrimental effects of such treatment. It has been postulated that reduction of TNF-α concentration to below the physiological levels may have blocked its beneficial cytoprotective effects, emphasizing on the pleiotropic nature of proinflammatory cytokines in mediating both adaptive and maladaptive responses [205]. In addition, infliximab-induced antibody and complement-dependent cytotoxicity [206] and caspase-dependent apoptosis [207] could have resulted in detrimental effects on TNF-α-expressing cardiac myocytes [205]. Due to the irreversible nature of cardiac myocyte apoptosis and ECM remodeling, anti-cytokine therapy would probably benefit those patients in whom these processes are not yet begun or are in their earliest stages. Therefore, further studies are needed to determine the best type and optimal dosage of anti-TNF-α therapy, as well as the specific subgroups of patients who might benefit the most [205]. Given the relative contribution of other proinflammatory cytokines and chemokines to the deleterious maladaptive responses in the context of the failing heart, the lack of clinical benefit is also probably due to the highly selective nature of the adopted strategies, underlining the inherent complexity and redundancy of the immune system [208, 209].

The dual role of proinflammatory cytokines in mediating both beneficial and detrimental effects might have hindered the development and clinical implementation of anti-inflammatory therapeutic modalities. Given the pleiotropic nature of proinflammatory cytokines, complete blocking of an individual mediator may actually result in adverse clinical outcomes. Based on the results of experimental studies, TNFR1 gene ablation blunts TNF-α-induced cardiomyopathy, whereas ablation of TNFR2 gene exacerbates heart failure and reduces survival [34]. Therefore, it could be hypothesized that the clinical benefit of anti-cytokine therapy resides in balancing the disturbance in the cytokine network and its receptor-mediated signaling,

rather than inhibition of one specific cytokine. Furthermore, given the considerable redundancy in the characteristic features of proinflammatory cytokines, the introduction of highly specific anti-inflammatory strategies has proved to be futile [205]. Therefore, to tackle various components of the immune system, the employment of broad spectrum anti-inflammatory strategies, including nonspecific immunomodulation therapy [210], intravenous immunoglobulin [211], pentoxifylline [212, 213], and immunoadsorption [214], has received much attention in the recent years.

In the present review, the current knowledge on the immunopathogenic roles of the most studied proinflammatory cytokines, including TNF-α, IL-6, IL-1, and IL-18, in mediating cardiac myocyte hypertrophy, contractile dysfunction, cardiac myocyte apoptosis, and extracellular matrix remodeling have been summarized. The pleiotropic properties of proinflammatory cytokines underline the importance of identifying and effective targeting of cell-specific intracellular signaling pathways specified for relaying the undesirable effects. Thus, the systemic and local consequences of such immunomodulation could be minimized to a great extent. Furthermore, to overcome their redundant activities, several elements of the inflammatory response could be simultaneously modulated by targeting the intracellular signaling molecules which are shared among various cytokines. Cognizance must also be taken of the differential roles of proinflammatory cytokines in the stepwise progression of disease from the initial insult to the clinical syndrome of heart failure. Although sustained overexpression of TNF-α, IL-1, and IL-18 has been demonstrated to be involved in the pathogenesis of myocarditis and DCM [7–10], the potential benefit from TNF-α and IL-1β blockade is limited to the onset of the disease [215]. Similarly, the vast majority of experimental studies have been performed in relatively acute models of myocardial infarction, where inhibition of the inflammatory response during the infarct healing process has been proven to be of therapeutic value [216, 217]. Intervention directed at proinflammatory cytokine signaling could potentially provide efficacious treatment of heart failure; however, the current knowledge has not yet been applied to clinically applicable protocols. In order to delineate the therapeutic potential of proinflammatory cytokines in heart failure, a greater understanding of their physiological and pathological roles with emphasis on identifying the key signaling pathways and regulatory molecules is mandatory.

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