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The role of Interleukin-1 in the pathogenesis of heart disease

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Abstract

IL-1 consists of two distinct ligands (IL-1 α and IL-1 β) with indistinguishable biological activities that signal through the IL-1 type I receptor (IL-1RI). A naturally occurring IL-1 receptor antagonist (IL-1Ra) binds to IL-1RI without initiating signal transduction and prevents IL-1 signaling, competitively inhibiting IL-1-mediated responses. Emerging evidence suggests that the balance between IL-1 agonists and antagonists plays an essential role in a variety of cardiovascular conditions. IL-1 may play a role in atherothrombotic disease by promoting formation of atheromatous lesions, enhancing vascular inflammation, and triggering plaque destabilization. Following myocardial infarction, IL-1 critically regulates the inflammatory response and is involved in the development of adverse remodeling by enhancing expression of matrix metalloproteinases. IL-1 signaling may also be an essential mediator in the pathogenesis of heart failure by suppressing cardiac contractility, promoting myocardial hypertrophy and inducing cardiomyocyte apoptosis. The present review summarizes current available data showing the significant role of IL-1 signaling in heart disease and raising the possibility that IL-1 inhibitors (such as anakinra, a nonglycosylated recombinant human IL-1Ra) may be clinically useful agents in patients with certain cardiovascular conditions.

Keywords

interleukin-1; myocardial ischemia; cardiac fibrosis; hypertrophy; remodeling; inflammation

The IL-1 family of cytokines

IL-1, the prototypic pro-inflammatory cytokine, was originally described as the first “endogenous pyrogen” because it exerts fever-inducing effects in both rabbits and humans [27]. IL-1 consists of two distinct ligands (IL-1 α and IL-1 β) with high sequence homology and indistinguishable biological activities [74], [2], [5], [71], [50]. Both IL-1 α and IL-1 β are synthesized as large precursor proteins. Pro-IL-1 α is biologically active and is cleaved by calpain to generate the mature protein; both forms of IL-1 α remain intracellular unless released by a dying cell. In contrast, pro-IL-1 β is biologically inactive until it is enzymatically cleaved by the IL-1 β -converting enzyme (ICE, caspase-1) to generate the active 17.5 kDa protein (p17) [111]. Although most of the IL-1 β precursor localizes in the cytosol, a fraction translocates into secretory lysosomes where it co-localizes with procaspase-1 [3]. In resting cells procaspase-1 is bound to an inhibitory molecule that prevents its activation; however, in activated cells conversion of procaspase-1 to caspase-1 is triggered by a molecular complex termed the “IL-1 β inflammasome” [75]. Generation of active caspase-1 results in processing of the IL-1 β precursor and secretion of mature active IL-1 β .

Both IL-1 α and IL-1 β bind to two primary receptors: the IL-1 type I receptor (IL-1RI) associates with the IL-1 receptor accessory protein (IL-1RAcP) forming a complex that transduces a signal and is responsible for most IL-1-mediated actions. In contrast, the type II IL-1 receptor (IL-1RII) lacks an intracellular signaling domain and does not initiate signaling when IL-1 binds. Thus, IL-1RII serves as a decoy receptor acting as a “molecular trap” for its ligand [18], [19], [73] (Figure 1).

The same cells that produce IL-1 α and IL-1 β synthesize the third member of the family, a naturally occurring competitive IL-1 receptor antagonist (IL-1Ra). IL-1Ra exists in three intracellular (icIL-1Ra1, icIL-1Ra2 and icIL-1Ra3) and one secreted isoform (sIL-1Ra). Binding of IL-1Ra to IL-1RI appears to be unable to recruit IL-1RAcP, does not initiate signal transduction, and prevents IL-1 signaling, competitively inhibiting IL-1-mediated responses [28].

After IL-1 α and IL-1 β , the third agonist member of the IL-1 family that was identified is IL-18 [87], [112]. IL-18 shares many properties with IL-1 β : it is synthesized as an inactive precursor that requires cleavage by caspase-1 to generate the biologically active protein. IL-18 acts through binding to the IL-18 receptor (IL-18R), which forms a complex with IL-18RAcP initiating signaling [29]. Recently, six additional members of the IL-1 family were identified on the basis of sequence homology, three-dimensional structure and receptor binding properties [6]. Discovery of the new members resulted in adoption of a new nomenclature. The new ligands were systematically named as IL-1 family, member 5 (IL-1F5), IL-1F6, IL-1F7, IL-1F8, IL-1F9 and IL-1F10, while IL-1 α , IL-1 β , IL-1Ra and IL-18 became IL-1F1, IL-1F2, IL-1F3 and IL-1F4, respectively [105]. However, the old members of the family (IL-1 α , IL-1 β , IL-1Ra and IL-18) are still usually referred by their original names. In addition, IL-33 has been identified as another member of the IL-1 family (IL-1F11), that signals through the orphan IL-1 receptor ST2 [97].

Interleukin-1: an essential mediator in inflammatory and reparative responses

IL-1 is the prototypic multifunctional inflammatory cytokine and both IL-1 α and IL-1 β exert complex biological effects by modulating gene expression and behavior in a wide variety of cell types [26]. IL-1 is consistently induced and activated following tissue injury and appears to play an essential role in many inflammatory conditions [28], including sepsis, rheumatoid arthritis and inflammatory bowel disease. Activation of IL-1RI triggers multiple and sequential phosphorylations that result in nuclear translocation of transcription factors. Post-receptor amplification is responsible for the potent effects of IL-1 signaling despite the relatively low expression of IL-1RI on many cell types. IL-1 consistently activates protein kinases that phosphorylate serine and threonine residues, which are the targets of the Mitogen-Activated Protein Kinase (MAPK) family. These events are associated with rapid phosphorylation of Inhibitor of κ B (IkB), which is degraded by the proteasome system leading to translocation of Nuclear Factor (NF)- κ B to the nucleus [98]. IL-1 also enhances nuclear binding of c-jun and c-fos, the two components of Activator Protein (AP)-1. NF- κ B and AP-1 sites are present in the promoter regions of many IL-1-inducible genes.

Through activation of the NF- κ B system, IL-1 signaling initiates transcription of a wide variety of inflammatory genes, including chemokines, pro-inflammatory cytokines [78], adhesion molecules [76], colony-stimulating factors, and mesenchymal growth factor genes. In addition, expression of inducible Nitric Oxide Synthase (iNOS), type 2 cyclooxygenase (COX)-2, and type 2 phospholipase A2 (PLA2) is exquisitely sensitive to IL-1. As a result, some of the IL-1-induced biological effects are mediated through prostaglandins or nitric oxide. Through the induction of chemokine and adhesion molecule expression, IL-1 facilitates infiltration of

injured tissues by inflammatory leukocytes. In addition, IL-1 signaling regulates reparative processes by modulating gene expression in fibroblasts and smooth muscle cells and by altering the Matrix Metalloproteinase (MMP)/Tissue Inhibitor of Metalloproteinases (TIMP) balance.

IL-1 function in tissues is regulated not only by modulation of its local concentration, but also through caspase-1-mediated activation, the presence of its functional receptors, and by the expression of its inhibitor, IL-1Ra. The important role of IL-1Ra in the maintenance of tissue homeostasis is emphasized by the development of spontaneous arterial inflammation [85] and chronic inflammatory arthropathy [47] in IL-1Ra null mice. IL-1Ra is typically produced in abundance; however, occupation of a small proportion of IL-1RI receptors by IL-1 is sufficient to produce a significant biological effect. Thus, IL-1 signaling in injured tissues is dependent on the local balance between the agonists, IL-1 α and IL-1 β , and their antagonist, IL-1Ra. Such a relation between IL-1 agonists and antagonists is an important determinant of the course of inflammatory diseases.

The inflammatory reaction in healing myocardial infarction

More than 1.5 million Americans suffer an acute infarct every year; approximately one fourth of all deaths are due to acute myocardial infarction [109]. Cardiac muscle necrosis is associated with inflammatory cascade that clears the infarct from dead cells and matrix debris, and ultimately results in replacement of the damaged tissue with scar [37]. Cells dying by necrosis release their intracellular contents and initiate an intense inflammatory response by activating innate immune mechanisms. Cell surface receptors sense endogenous ligands released upon tissue injury as “danger signals” and activate cytokine and chemokine-mediated pathways. Activation of the complement cascade, generation of reactive oxygen species (ROS) and Toll-like receptor (TLR)-mediated signals play a significant role in triggering the post-infarction inflammatory response by activating the NF- κ B system, resulting in upregulation of chemokines and increased expression of adhesion molecules by endothelial cells. Chemokines are secreted into the subendothelium and are also displayed in the luminal surface of endothelial cells, where they bind to chemokine receptors expressed by circulating leukocytes [38]. This interaction results in integrin-mediated adhesion, followed by diapedesis of leukocytes into the subendothelial space. Once within the infarcted tissue, infiltrating leukocytes clear the infarct from dead cells and matrix debris and, through the induction of cytokines and growth factors, regulate extracellular matrix metabolism and activate mesenchymal cells. Fibroblast and endothelial cell proliferation marks the transition from the inflammatory to the proliferative phase of healing. Inflammatory leukocytes undergo apoptotic death and are cleared from the infarcted area; removal of “dead corpses” plays an important role in resolution of inflammation by inducing the expression of inhibitory mediators, such as Transforming Growth Factor (TGF)- β and Interleukin (IL)-10 that suppress inflammatory cytokine and chemokine synthesis [39], [35], [121]. Furthermore, activation of TGF- β signaling induces fibroblast-to-myofibroblast transdifferentiation and promotes extracellular matrix deposition in the infarcted area [13]. Maturation of the scar follows. Infarct myofibroblasts become apoptotic and neovessels acquire a muscular coat [95], [120], while uncoated vessels regress. A mature scar is formed containing cross-linked collagen and a relatively small number of cells [30].

As the infarct heals, profound changes in ventricular architecture and geometry are noted, also referred to as “ventricular remodeling” [92], [88]. Post-infarction remodeling involves both the necrotic zone and the non-infarcted segments of the ventricle and results in chamber dilation, cardiac hypertrophy, increased sphericity of the ventricle and a marked deterioration in cardiac function [16]. Remodeling is linked to heart failure progression and is associated with poor prognosis following myocardial infarction [116], [107]. The extent of adverse remodeling depends on the size of the infarct but is also directly affected by the pathologic and structural changes associated with infarct healing [49]. Inflammatory pathways appear to play

an essential role in the pathogenesis of adverse remodeling by modulating the qualitative characteristics of the scar, by altering the composition of the extracellular matrix and by mediating fibrous tissue deposition in the infarct border zone and the non-infarcted areas. In addition, enhanced inflammatory activity may be directly involved in the development of serious and potentially lethal acute complications, such as cardiac rupture.

IL-1 induction in healing infarcts

Experimental studies have suggested that members of the IL-1 family are markedly and consistently upregulated in the infarcted heart. IL-1 β induction has been reported in rodent models of reperfused [46], [25] and non-reperfused [23] infarction. Furthermore, a clinical investigation showed that serum IL-1 β levels were elevated in patients with acute myocardial infarction within the first few hours after the onset of chest pain [41]. However, other studies failed to document increased IL-1 β levels in patients with myocardial infarction: IL-1 β levels were not increased in a small group of patients with complicated infarction (Killip class 3 and 4) and in patients treated with thrombolytics [81]. Despite the marked local upregulation of IL-1 β in the infarcted myocardium, elevation of IL-1 β in the serum may be more difficult to detect due to binding of the cytokine to large proteins such as α 2 macroglobulin, complement, and the soluble type II IL-1 receptor [26]. Moreover, serum normally contains approximately 0.8–2.5 ng/ml of soluble IL-1RII, which preferentially binds IL-1 β compared with IL-1 α or IL-1Ra [40]. On the other hand significant elevation of serum IL-1Ra levels was noted in patients with acute myocardial infarction [65] and preceded the release of markers of necrosis [90]. Plasma IL-1Ra levels correlated with the extent of cardiomyocyte loss [91] and with the severity of hemodynamic and clinical impairment in patients with acute myocardial infarction [100]. Increased IL-1 Ra expression was immunohistochemically detected in ischemic cardiomyocytes of the infarct border zone [11].

IL-1 exerts crucial effects on most cell types involved in cardiac injury and repair

IL-1 exerts pleiotropic effects on the infarcted myocardium. Extensive evidence suggests that IL-1 exerts pro-apoptotic and hypertrophic effects on cardiomyocytes, while depressing cardiac contractility. IL-1 β , alone or in combination with IFN- γ and TNF- α , induces cardiomyocyte apoptosis, associated with activation of Bak and Bcl-xL through pathways involving nitric oxide (NO) [54]. Furthermore, IL-1 β induces cardiomyocyte hypertrophy [89] upregulating atrial natriuretic factor (ANF) and suppressing expression of calcium regulatory genes [110]. IL-1 β depresses cardiac function through NO-dependent [99] and NO-independent pathways and inhibits the β -adrenergic agonist-mediated increase in cardiac myocyte contractility and cAMP accumulation [42]. Although the significance of IL-1-mediated suppression of function in most cardiac pathologic conditions remains poorly defined, evidence suggests that, along with TNF- α , IL-1 β is an essential mediator in sepsis-induced contractile dysfunction [62].

Beyond its effects on cardiomyocytes, IL-1 is also capable of modulating behavior and gene expression of most cell types involved in infarct healing (Figure 2). Through its activating effects on both leukocytes and endothelial cells, IL-1 is an essential mediator in leukocyte trafficking. IL-1 stimulation enhances adhesion molecule expression by endothelial cells and activates integrin-mediated pathways facilitating neutrophil and mononuclear cell transendothelial migration [9], [44]. In addition, IL-1 markedly upregulates chemokine synthesis by both mononuclear and endothelial cells promoting leukocyte chemotaxis in sites of injury [104], [103].

Moreover, IL-1 is capable of modulating fibroblast phenotype and activity. IL-1 β diminishes the capacity of mitogen-stimulated fibroblasts to synthesize DNA and exerts its effects at the G1/S interphase by altering the expression of cardiac fibroblast cyclins and cyclin-dependent kinases and by preventing phosphorylation of the retinoblastoma gene product [61]. IL-1 signaling appears to promote matrix degradation by enhancing MMP synthesis, while reducing collagen deposition [106].

The effects of IL-1 on angiogenesis remain poorly understood and somewhat controversial. Although an early investigation showed that IL-1 is an inhibitor of endothelial cell growth both *in vitro* and *in vivo* [21], several studies suggested that IL-1 exerts angiogenic actions. IL-1 inhibition suppressed neovascularization in three distinct rat models of angiogenesis [20], [48]. The mechanisms responsible for the angiogenic properties of IL-1 remain unknown. Both direct effects and actions mediated through enhanced production of angiogenic mediators, or upregulation of their receptors may be involved. IL-1 β increased the capability of human dermal microvascular endothelial cells to form tubular structures when overlaid with collagen gels [96] and increased MMP-2 expression by cardiac microvascular endothelial cells [80] directly enhancing their matrix-degrading potential. Furthermore, IL-1 β stimulated synthesis of VEGF and its receptor flk-1 in cardiac microvascular endothelial cells [77].

IL-1 plays an important role in adverse remodeling following infarction

The marked upregulation of IL-1 in the ischemic heart [46], [25], [41] and its pleiotropic effects on most cell types involved in cardiac injury and repair suggest that it may play an essential role in the infarcted and remodeling myocardium. Experimental investigations have suggested that IL-1 signaling has deleterious effects on the infarcted heart mediated through several distinct pathways:

a. IL-1 may enhance cardiomyocyte apoptosis in the ischemic myocardium.

Both *in vitro* and *in vivo* studies suggest that IL-1 mediates pro-apoptotic signals enhancing cardiomyocyte injury in the ischemic heart. IL-1 β stimulation activates apoptotic pathways in neonatal rat cardiomyocytes [54]. Moreover, overexpression of human IL-1Ra through gene transfection in heterotopically transplanted rat hearts undergoing ischemia and reperfusion significantly decreased infarct size, attenuating cardiomyocyte apoptosis [108] and reducing post-ischemic upregulation of Bax, Bak and caspase-3. In addition, both early (immediately after ischemia) and delayed (24h after coronary occlusion) treatment with recombinant human IL-1Ra (anakinra) reduced cardiomyocyte apoptosis and prevented cardiac dilation in mouse and rat models [1]. *In vitro* experiments showed that incubation of rat cardiomyocytes with anakinra was associated with a significant reduction of apoptosis during simulated ischemia/reperfusion.

b. IL-1 signaling enhances the post-infarction inflammatory response.

The prominent pro-inflammatory actions of IL-1 appear to play an essential role in regulation of the post-infarction inflammatory response. IL-1Ra gene transfection resulted in significantly reduced infiltration of the ischemic heart with neutrophils [108]. Furthermore, our experiments demonstrated that IL-1RI null mice had reduced dilative remodeling, associated with markedly decreased peak cytokine and chemokine mRNA expression in the infarcted heart and attenuated infiltration of the infarcted zone with neutrophils and macrophages [14]. The greatly diminished neutrophil density in IL-1RI null infarcts may reflect both decreased recruitment of neutrophils and their increased susceptibility to apoptosis. IL-1 strongly prolongs neutrophil survival by inhibiting their apoptotic death [17]. The pro-inflammatory actions of IL-1 may enhance injury through several distinct pathways. First, IL-1

signaling may enhance synthesis of other inflammatory mediators promoting cytokine-induced cardiomyocyte apoptosis. Second, enhanced neutrophil infiltration may directly cause death of viable cardiomyocytes. Third, IL-1-mediated inflammatory activity may increase matrix remodeling of the ventricle, activating protease-induced matrix degradation. Our findings showed that suppressed inflammation in ischemic IL-1RI null hearts was not associated with less extensive infarction, suggesting that endogenous IL-1 does not exacerbate cardiomyocyte injury [14]. Thus, the mechanisms of protection in IL-1RI null mice do not appear to involve attenuation of ischemic cardiomyocyte injury.

- c. IL-1 regulates the reparative response and mediates adverse remodeling by altering MMP expression and activity.

In addition to its effects on inflammatory cells and cardiomyocytes, IL-1 also modulates phenotype and gene expression of fibroblasts, the main cells involved in reparative responses. Our study demonstrated that the suppressed inflammatory reaction in IL-1RI null infarcts was followed by an attenuated fibrotic response. Myofibroblast accumulation in the infarcted area was significantly lower in IL-1RI $-/-$ infarcts in comparison with wildtype animals. In addition, expression of the key pro-fibrotic mediator TGF- β [12] was significantly reduced, and collagen deposition was markedly decreased, in both the healing scar and the peri-infarct area of IL-1RI $-/-$ hearts. In the absence of IL-1 signaling, reduced fibrotic remodeling of the infarcted ventricle may be due to an attenuated inflammatory reaction and to the loss of direct stimulatory IL-1-mediated effects on cardiac fibroblast phenotype and function. IL-1 β directly enhances fibrous tissue deposition by upregulating expression of Angiotensin II type 1 (AT1) receptors on cardiac fibroblasts [43] and by stimulating fibroblast migration [79]. Beyond its pro-inflammatory and fibrogenic properties, IL-1 also promotes extracellular matrix remodeling by enhancing cardiac fibroblast MMP expression [106]. IL-1 β stimulation induced MMP-3, MMP-8 and MMP-9 mRNA synthesis by isolated mouse cardiac fibroblasts, while downregulating TIMP-2 and TIMP-4 expression levels. In the complex and dynamic environment of the infarct, where cellular behavior is regulated by a variety of mediators, the contribution of direct IL-1-mediated actions on fibroblast protease expression and extracellular matrix remodeling is difficult to assess. In comparison with wildtype animals, IL-1RI null mice exhibited a decrease in MMP-2 and MMP-3 expression in both the infarcted and remote remodeling myocardium, supporting the *in vivo* relevance of IL-1-mediated effects on synthesis of matrix-degrading proteases.

Our experiments demonstrated that the cellular and molecular alterations observed in IL-1RI null infarcts result in significant attenuation of dilative remodeling following infarction. Protection from adverse remodeling in the absence of IL-1 signaling was not due to enhanced cardiomyocyte survival. Despite the marked suppression of the post-infarction inflammatory response in infarcted IL-1RI null animals, infarct size was comparable with wildtype mice, suggesting that IL-1-mediated inflammatory activity does not accentuate ischemic injury. However, suppression of inflammation may be protective by reducing fibrotic remodeling of the infarcted ventricle. Decreased collagen deposition and reduced MMP synthesis in the remodeling non-infarcted myocardium of IL-1RI null hearts may indicate attenuated interstitial remodeling. Fibrosis is often associated with enhanced matrix degradation indicating active remodeling of the interstitial space [7]. IL-1RI gene disruption appears to abrogate both events resulting in decreased activity in the remodeling interstitial space and attenuated ventricular dilation. These concepts are consistent with the findings by Murtuza et al. who demonstrated that IL-1 inhibition through transplantation of skeletal myoblasts overexpressing IL-1Ra decreased adverse remodeling by reducing interstitial fibrosis and by attenuating MMP-2 and MMP-9 upregulation in the infarcted heart [82]. Thus, the beneficial effects of defective IL-1

signaling in post-infarction remodeling may be mediated both through suppression of the inflammatory response and through the loss of direct IL-1-mediated actions on matrix metabolism and cardiac fibroblast function.

Does IL-1 also exert protective effects on the infarcted heart?

The bulk of experimental evidence suggests that IL-1 signaling exerts deleterious effects on the infarcted and remodeling heart. However, because of their pleiotropic actions, pro-inflammatory cytokines are also capable of exerting protective effects on ischemic cardiomyocytes that may depend on the context of the experimental model. Thus, *in vitro* studies have demonstrated that TNF- α confers resistance to hypoxic injury in the adult mammalian cardiac myocyte [83], while *in vivo* studies have suggested that endogenous TNF-signaling protects cardiomyocytes from apoptosis in a mouse model of myocardial infarction [63]. Furthermore cytokine signaling may critically regulate pathways essential for cardiac repair following infarction.

Evidence suggesting protective effects of IL-1 β on ischemic cardiomyocytes is lacking. However, a study using a single intraperitoneal injection with a neutralizing antibody to inhibit IL-1 β immediately after coronary ligation in a model of non-reperfused infarction showed a significant increase in the occurrence of cardiac rupture, associated with suppressed collagen accumulation in the infarct-related area. This alteration in the composition of the scar resulted in enhanced dilative remodeling [51]. The findings of this study contradict several investigations that demonstrated attenuation of adverse remodeling in mice with disruption of IL-1 signaling [15] and in animals receiving IL-1 antagonists [108], [1], [82]. The following important considerations may explain the conflicting findings. First, selective inhibition of specific inflammatory mediators may be more effective in reperfused infarcts, which exhibit early and intense activation of inflammatory pathways. In contrast, non-reperfused infarcts show delayed and suppressed inflammation; IL-1 inhibition in this context may critically impair the healing response. Second, timing of the intervention is a key determinant of outcome. IL-1 exerts distinct effects on many different cell types involved in all phases of the healing response. Early inhibition of IL-1 signaling is more likely to inhibit the inflammatory cascade, whereas late inhibition may predominantly abrogate the direct actions of IL-1 on fibroblasts. Third, effectiveness of IL-1 inhibition may depend on the specific agent used to neutralize IL-1 activity. Fourth, the spatial localization of the inhibitory strategy may critically affect the outcome. Selective inhibition of inflammatory mediators in the infarct border zone and the remodeling myocardium may contribute to effective containment of the post-infarction inflammatory response [36], reducing fibrotic remodeling and attenuating chamber dilation. In contrast, interventions selectively targeting the infarcted area are likely to be less predictable, because excessive inhibition of the inflammatory response may result in formation of a defective scar.

IL-1 signaling in the pathogenesis of coronary artery disease

Beyond its role in remodeling of the infarcted heart, IL-1 signaling may also play a role in the pathogenesis of atherothrombotic coronary disease by modulating cholesterol metabolism, by promoting formation of atheromatous lesions, by enhancing vascular inflammation, and by facilitating plaque rupture [60], [4].

The effects of IL-1 signaling on cholesterol metabolism remain poorly understood. Chronic inflammation was found to be associated with adverse lipid profiles in many conditions (such as obesity, diabetes and the metabolic syndrome), and pro-inflammatory cytokines may affect lipid metabolism [58]. IL-1Ra $-/-$ mice fed with an atherogenic diet had significantly increased levels of total cholesterol and premature development of fatty liver when compared with wildtype animals [57]. In addition, IL-1 signaling appears to exert atherogenic actions

independent of any effects on cholesterol metabolism. Short term treatment with recombinant IL-1Ra reduced fatty streak formation in both male and female apolipoprotein E (ApoE) $-/-$ mice fed with an atherogenic diet without interfering with lipid metabolism [31]. On the other hand reduction of IL-1Ra levels in IL-1Ra $+/-$ ApoE $-/-$ animals to approximately 50% of those in IL-1Ra $+/+$ ApoE $-/-$ mice was associated with enhanced early atherosclerotic lesion development [56]. In addition, IL-1Ra overexpression attenuated atheromatous lesion formation in low-density lipoprotein receptor (LDLR) $-/-$ mice fed with a high cholesterol/high fat diet containing cholate [24]. In contrast, LDLR $-/-$ /IL-1Ra $-/-$ mice had a tendency to develop early foam cell lesions when fed with a diet rich in cholesterol and cholate [24]. Thus, endogenous IL-1Ra appears to suppress atherosclerosis; this concept is supported by a significant association between single vessel coronary artery disease and an IL-1Ra gene polymorphism in a Caucasian population undergoing coronary angiography [34].

Evidence suggests that IL-1 may also activate pathways leading to plaque rupture and thrombosis [68]. IL-1 upregulation in the atheromatous lesion may induce Monocyte Chemoattractant Protein (MCP)-1 and Macrophage-Colony Stimulating Factor (M-CSF) synthesis promoting monocyte recruitment and activation. In addition, IL-1 enhances MMP synthesis in the plaque inducing matrix degradation and contributing to plaque destabilization [66]. IL-1 may also exert direct pro-thrombotic actions by enhancing endothelial tissue factor expression [8], [10]. These concepts are supported by clinical investigations demonstrating that subjects carrying the TT genotype of the IL-1 β gene had a decreased risk of myocardial infarction. Mononuclear cells from volunteers carrying the T allele exhibited attenuated IL-1 β release and reduced expression of tissue factor upon stimulation with lipopolysaccharide [52]. In addition, the haplotype H3 of the gene encoding for IL-1Ra (*IL1RN*) was associated with reduced *IL1RN* mRNA levels and an increased incidence of myocardial infarction [113]. However, the significance of genetic variations within the IL-1 cluster in the incidence of coronary events remains controversial. A recent prospective study evaluated seven gene polymorphisms within the IL-1 superfamily gene cluster and found no association between the gene variants tested and the risk of atherothrombotic events [119].

IL-1 signaling and neointimal formation after vascular injury

Inflammatory mediators play an important role in neointimal hyperplasia following arterial injury and may be critically involved in the pathogenesis of restenosis after balloon angioplasty. Several components of the IL-1 system (including IL-1 β , IL-1Ra and IL-1RI) are markedly induced in balloon-injured vessels [115]. IL-1 signaling in the vascular neointima may play a role in activation, migration and proliferation of smooth muscle cells through direct actions [67] and via upregulation of other growth factors or cytokines [93]. Several investigations have suggested an essential role of IL-1 in neointimal formation. IL-1RI null mice exhibited attenuated neointimal hyperplasia following common carotid artery ligation [94]. In contrast, IL-1Ra null mice exhibited enhanced neointimal formation following femoral artery injury [55]. Thus, the balance between endogenous IL-1 agonists and antagonists may play an important role in the development of neointimal hyperplasia following vascular injury. Studies investigating the relation between IL-1 cluster gene polymorphisms and the development of restenosis have produced contradictory results. Allele 2 of the IL-1Ra gene (*IL1RN*) was associated with a lower incidence of angiographic restenosis in a Caucasian population undergoing coronary stent implantation for symptomatic coronary artery disease [59]. In contrast, a comprehensive prospective investigation failed to establish a relation between several IL-1 cluster gene variants and the incidence of restenosis following coronary angioplasty [118].

IL-1 signaling and hypertrophic cardiac remodeling

Cardiac hypertrophy is associated with activation of IL-1 signaling in both animal models and human patients. In experimental models of pressure overload IL-1 β expression is upregulated in the hypertrophied heart [117], predominantly localized in endothelial cells and interstitial macrophages [102]. IL-1 β expression becomes more pronounced with decompensation and development of congestive heart failure [102]. On the other hand patients with cardiac hypertrophy due to aortic stenosis exhibit significant upregulation of cardiac IL-1 β expression [114]. Despite the extensive associative data linking IL-1 expression with cardiac hypertrophy and the strong *in vitro* evidence demonstrating that IL-1 signaling activates hypertrophic pathways in cardiomyocytes, the role of endogenous IL-1 in the pathogenesis of cardiac hypertrophy remains poorly understood.

Development of mice overexpressing IL-1 provided insight into the hypertrophic actions of the cytokine. Mice with ubiquitous overexpression of human IL-1 α showed prominent left ventricular hypertrophy and congestive heart failure leading to death within 2 weeks after birth. Transgenic mice with a cardiomyocyte-restricted overexpression of human IL-1 α exhibited concentric left ventricular hypertrophy with a preserved systolic function suggesting that cardiac expression of IL-1 is sufficient to induce hypertrophy [86].

IL-1 in myocarditis and dilated cardiomyopathy

Inflammatory cytokines are thought to be essential mediators in the induction and development of the immune processes associated with acute myocarditis [84]. Several lines of evidence suggest an important role for IL-1 signaling in the pathogenesis of myocarditis. First, IL-1 expression is markedly upregulated in experimental models of autoimmune myocarditis. Coxsackie virus-induced myocarditis in mice is associated with infiltration of the heart by inflammatory cells that secrete IL-1 and TNF [64]. Persistently elevated IL-1 β expression was noted in the chronic stage of myocarditis in a mouse model of postmyocarditis dilated cardiomyopathy induced by the encephalomyocarditis virus [101]. Second, increased IL-1 β mRNA levels were found in endomyocardial biopsies from patients with viral myocarditis [45] and idiopathic dilated cardiomyopathy [114]. Third, IL-1RI null mice were protected from the development of autoimmune myocarditis [32]. Fourth, IL-1Ra administration had beneficial effects in experimental models of inflammatory cardiomyopathy. Direct injection of a plasmid vector expressing human IL-1Ra into the hearts of mice with coxsackieviral (CVB3) myocarditis decreased myocardial inflammation and reduced mortality [69]. In addition, hydrodynamics-based delivery of plasmid encoding IL-1Ra-immunoglobulin gene suppressed the inflammatory response in a model of rat autoimmune myocarditis [70].

The IL-1 system as a therapeutic target in cardiovascular disease

Extensive experimental evidence suggests an essential role for IL-1 signaling in cardiovascular disease. IL-1 is a crucial mediator in atherosclerosis, may be associated with plaque destabilization in acute coronary syndromes and is critically involved in the pathogenesis of post-infarction remodeling. In addition, IL-1 signaling plays an important role in cardiac hypertrophy and in myocarditis. Thus, the IL-1 pathway seems to be a promising therapeutic target in a variety of cardiovascular conditions.

The availability of anakinra, a nonglycosylated recombinant human IL-1Ra, has enriched our therapeutic armamentarium with an agent that, much like endogenous IL-1Ra, binds to IL-1RI competitively inhibiting IL-1 signaling. Anakinra has been approved by the United States Food and Drug Administration for treatment of patients with rheumatoid arthritis who have failed one or more disease modifying anti-rheumatic drugs. The significant role of IL-1 signaling in a variety of cardiovascular conditions raises the possibility that anakinra may be a clinically

useful agent in patients with heart disease [33]. A recent investigation demonstrated that anakinra administration improved vascular and left ventricular function and attenuated nitrooxidative stress in patients with rheumatoid arthritis [53]. In addition, an ongoing proof of concept clinical trial, the MRC-ILA-HEART study will explore the effects of IL-1 antagonism using a 14-day course of anakinra on markers of inflammation in patients with non-ST segment elevation myocardial infarction [22]. It is hoped that this study will provide new information on the effectiveness of IL-1 inhibition in suppressing inflammation in patients with acute coronary syndromes.

Patients with several distinct cardiovascular conditions may benefit from therapies targeting the IL-1 system. In patients with acute coronary syndromes IL-1 inhibition may stabilize atherosclerotic plaques preventing future events and may also attenuate adverse cardiac remodeling reducing the incidence of heart failure. In acute myocarditis IL-1 neutralization may reduce inflammatory injury and protect from the development of dilative cardiomyopathy. In patients with myocardial hypertrophy IL-1 antagonism may reduce progression of the disease. Targeting the IL-1 system may also be effective in reducing the incidence of restenosis in patients undergoing percutaneous coronary interventions. Although experimental studies identified the IL-1 system as a promising therapeutic target in heart disease several important considerations need to be taken into account:

- a. Certain chronic cardiovascular conditions (such as atherosclerosis and cardiac hypertrophy) may require long-term IL-1 inhibition to achieve clinically significant results. Although anakinra is relatively well-tolerated, chronic IL-1 targeting may carry significant risk by suppressing the response to tissue injury and by increasing vulnerability to infections and the incidence of malignancy. Thus, in these cases the risk may outweigh any benefit and chronic anti-IL-1 therapy may not be a realistic goal.
- b. The detrimental effects of targeted anti-TNF- α strategies in patients with heart failure [72] suggested that attempts to inhibit inflammatory pathways, may carry significant risk even when supported by a strong rationale and extensive experimental evidence. Cytokines are highly pleiotropic agents with complex and often contradictory actions; targeted cytokine neutralization may also inhibit protective pathways in cardiomyocyte survival and cardiac repair.
- c. Acute myocardial infarction represents one of the most promising opportunities for the therapeutic use of IL-1 antagonists. The extensive use of percutaneous coronary interventions following infarction offers the possibility for direct implementation of IL-1-targeted therapies in the infarcted area. Short-term IL-1 inhibition with anakinra may exert beneficial effects on the infarcted heart by stabilizing the atherosclerotic plaques, by attenuating cytokine-induced cardiac dysfunction, by reducing matrix degradation, and by suppressing cardiomyocyte apoptosis. These effects may result in reduction of recurrent coronary events and in attenuation of adverse remodeling. However, the use of anti-inflammatory strategies in myocardial infarction is often a double-edged sword: IL-1 inhibition in the infarcted heart may reduce inflammatory injury while delaying clearance of dead cells from the infarct. In addition, targeting of the IL-1 system may exert beneficial effects in the remodeling non-infarcted myocardium while delaying and suppressing formation of a supportive scar in the center of the infarct. Thus, temporal and spatial considerations are essential in order to design a successful therapeutic strategy.

Conclusions

The IL-1 system has a central role in cardiovascular pathology and represents a promising therapeutic target for patients with a variety of cardiovascular conditions. However, the pleiotropic effects of the members of the IL-1 family, the myriad of diverse mediators activated in cardiac disease and the complexity of clinical scenarios have hampered our efforts to translate our mechanistic knowledge into therapy. Understanding the molecular pathways involved in regulation of IL-1 signaling is essential for designing optimal therapeutic strategies for cardiovascular diseases, but should also be coupled with deep understanding of the pathophysiology of each condition.

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Figure 1.

IL-1 signaling is mediated through the type I IL-1 receptor (IL-1RI). After IL-1 (either IL-1 α or IL-1 β) binding to IL-1RI, the IL-1R accessory protein (IL-1RAcP) forms a complex with IL-1/IL-1RI. This results in signal transduction. In contrast, IL-1 binding to the type II receptor (IL-1RII) does not transduce a signal; this receptor serves as a “decoy” trapping IL-1 molecules and regulating activity of the cytokine. IL-1 signaling is also regulated by IL-1 Receptor antagonist (IL-1Ra). Binding of IL-1Ra to IL-1RI fails to recruit IL-1RAcP, does not initiate signal transduction, and prevents IL-1 signaling, competitively inhibiting IL-1-mediated responses.

Figure 2.

IL-1 signaling modulates phenotype and function of all cell types involved in infarct healing. IL-1 suppresses cardiac function and induces cardiomyocyte hypertrophy and apoptosis. Beside its effects on cardiac myocytes, IL-1 signaling exerts pro-inflammatory actions activating leukocytes, inducing expression of cytokines, chemokines and adhesion molecules in endothelial cells, and promoting infiltration of the infarcted myocardium with inflammatory cells. In addition, IL-1 modulates fibroblast function by enhancing MMP expression. These actions are critically involved in cardiac injury, repair and remodeling following myocardial infarction.