REVIEW

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

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Abstract

Interleukin (IL)-1 consists of two distinct ligands, IL-1α and IL-1β, 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 the 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.

Key words: interleukin-1, myocardial ischemia, cardiac fibrosis, hypertrophy, remodeling, inflammation.

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THE IL-1 FAMILY OF CYTOKINES

Interleukin (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 (Dinarello 1999). IL-1 consists of two distinct ligands, IL-1α and IL-1β, with high sequence homology and indistinguishable biological activities (Allan et al. 2005; Auron et al. 1984; Huising et al. 2004; Lomedico et al. 1984; March et al. 1985). Both IL-1α and IL-1β are synthesized as large precursor proteins. Pro-IL-1α is biologically active and is cleaved by calpain to generate the mature protein; both forms of IL-1α remain intracellular unless released by a dying cell. In contrast, pro-IL-1β is biologically inactive until it is enzymatically cleaved by the IL-1β-converting enzyme (caspase-1) to generate the active 17.5-kDa protein (p17) (Thornberry et al. 1992). Although most of the IL-1β precursors localize in the cytosol, a fraction translocates into secretory lysosomes, where they co-localize with procaspase-1 (Andrei et al. 1999). In resting cells, procaspase-1 is bound to an inhibitory molecule that prevents its activation; however, in activated cells the conversion of procaspase-1 to caspase-1 is triggered by a molecular complex termed the "IL-1β inflammasome" (Martinon et al. 2002). The generation of active caspase-1 results in processing of the IL-1β precursor and secretion of mature active IL-1β.

Both IL-1α and IL-1β 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 (Colotta et al. 1993; Colotta et al. 1994; Mantovani et al. 2001) (Fig. 1).

The same cells that produce IL-1α and IL-1β 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 ren-

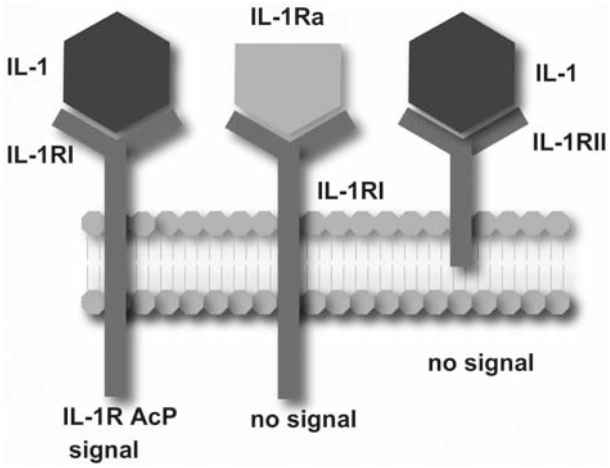

Fig. 1. IL-1 signaling is mediated through the type I IL-1 receptor (IL-1RI). After IL-1 (either IL-1α or IL-1β) binding to IL-1RI, the IL-1R accessory protein (IL-1RAcP) forms a complex with IL--1/IL-1RI. This results in signal transduction. In contrast, IL-1 binding to the type II receptor (IL-1RII) 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.

der IL-1RA unable to recruit IL-1RAcP, does not initiate signal transduction, and prevents IL-1 signaling, competitively inhibiting IL-1-mediated responses (Dinarello 2000).

After IL-1α and IL-1β, the third agonist member of the IL-1 family that was identified is IL-18 (Okamura et al. 1995; Ushio et al. 1996). IL-18 shares many properties with IL-1β; 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 (Dinarello 2007). Recently, six additional members of the IL-1 family were identified on the basis of sequence homology, three-dimensional structure, and receptor binding properties (Barksby et al. 2007). Discovery of the new members resulted in adoption of a new nomenclature. The new ligands were systematically named as IL-1 family members 5 (IL-1F5), IL-1F6, IL-1F7, IL-1F8, IL-1F9, and IL-1F10, while IL-1α, IL-1β, IL-1Ra, and IL-18 became IL-1F1, IL-1F2, IL-1F3, and IL-1F4, respectively (Sims et al. 2001). However, the old members of the family (IL-1α, IL-1β, IL-1Ra, and IL-18) are still usually referred to 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 (Schmitz et al. 2005).

IL-1: AN ESSENTIAL MEDIATOR IN INFLAMMATORY AND REPARATIVE RESPONSES

IL-1 is the prototypic multifunctional inflammatory cytokine and both IL-1α and IL-1β exert complex biological effects by modulating gene expression and behavior in a wide variety of cell types (Dinarello 1996). IL-1 is consistently induced and activated following tissue injury and appears to play an essential role in many inflammatory conditions (Dinarello 2000), 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 family. These events are associated with rapid phosphorylation of inhibitor of κB (IκB), which is degraded by the proteasome system, leading to translocation of nuclear factor (NF)-κB to the nucleus (Schreck et al. 1991). IL-1 also enhances nuclear binding of c-jun and c-fos, the two components of activator protein (AP)-1. NF-κB and AP-1 sites are present in the promoter regions of many IL-1-inducible genes.

Through activation of the NF-κB system, IL-1 signaling initiates the transcription of a wide variety of inflammatory genes, including chemokines, pro-inflammatory cytokines (Matsushima and Oppenheim 1989), adhesion molecules (Marui et al. 1993), colony-stimulating factors, and mesenchymal growth factor genes. In addition, the expressions of inducible nitric oxide synthase, type 2 cycloxygenase, and type 2 phospholipase A2 are 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 atrix 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 (Nicklin et al. 2000) and chronic inflammatory arthropathy (Horai et al. 2000) 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 bal-

ance between the agonists IL-1α and IL-1β 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 (Tavazzi 1999). Cardiac muscle necrosis is associated with an inflammatory cascade that clears the infarct from dead cells and matrix debris and ultimately results in replacement of the damaged tissue with scar (Frangogiannis 2006). 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, and Toll-like receptor-mediated signals play a significant role in triggering the post-infarction inflammatory response by activating the NF-κB 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 (Frangogiannis 2007). 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 of 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; the removal of "corpses" plays an important role in the resolution of inflammation by inducing the expression of inhibitory mediators, such as transforming growth factor (TGF)-β and IL-10, that suppress inflammatory cytokine and chemokine synthesis (Frangogiannis et al. 2000; Frangogiannis 2008; Zymek et al. 2007). Furthermore, activation of TGF-β signaling induces fibroblast-to-myofibroblast transdifferentiation and promotes extracellular matrix deposition in the infarcted area (Bujak et al. 2007). Maturation of the scar follows. Infarct myofibroblasts become apoptotic and neovessels acquire a muscular coat (Ren et al. 2002; Zymek et al. 2006), while uncoated vessels regress. A mature scar is formed containing cross-linked collagen and a relatively small number of cells (Dobaczewski et al. 2006).

As the infarct heals, profound changes in ventricular architecture and geometry are noted, also referred to as "ventricular remodeling" (Opie et al. 2006; Pfeffer and Braunwald 1990). 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 (Cohn et al. 2000). Remodeling is linked to heart failure progression and is associated with poor prognosis following myocardial infarction (St John Sutton et al. 1994; White et al. 1987). The extent of adverse remodeling depends on the size of the infarct, but is also directly affected by the pathological and structural changes associated with infarct healing (Huebener et al. 2008). Inflammatory pathways appear to play an essential role in the pathogenesis of adverse remodeling by modulating the qualitative characteristics of the scar, altering the composition of the extracellular matrix, and 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-1β induction has been reported in rodent models of reperfused (Dewald et al. 2004; Herskowitz et al. 1995) and non-reperfused (Deten et al. 2002) infarction. Furthermore, a clinical investigation showed that serum IL-1β levels were elevated in patients with acute myocardial infarction within the first few hours after the onset of chest pain (Guillen et al. 1995). However, other studies failed to document increased IL-1β levels in patients with myocardial infarction; IL-1β levels were not increased in a small group of patients with complicated infarction (Killip class 3 and 4) and in patients treated with thrombolytics (Munkvad et al. 1991). Despite the marked local upregulation of IL-1β in the infarcted myocardium, elevation of IL-1β in the serum may be more difficult to detect due to binding of the cytokine to large proteins such as α2 macroglobulin, complement, and the soluble type II IL-1 receptor (Dinarello 1996). Moreover, serum normally contains approximately 0.8–2.5 ng/ml of soluble IL-1RII, which preferentially binds IL-1β compared with IL-1α or IL-1Ra (Giri et al. 1994). On the other hand, significant elevation of serum IL-1Ra levels was noted in patients with acute myocardial infarction (Latini et al. 1994) and preceded the release of markers of necrosis (Patti et al. 2004). Plasma IL-1Ra levels correlated with the extent of cardiomyocyte loss (Patti et al. 2005) and the severity of hemodynamic and clinical impairment in patients with acute myocardial infarction (Shibata et al. 1997). Increased IL-1Ra expression was immunohistochemically detected in ischemic cardiomyocytes of the infarct border zone (Bonetti et al. 2008).

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-1β, alone or in combination with interferon γ and tumor necrosis factor (TNF)-α, induces cardiomyocyte apoptosis, associated with activation of Bak and Bcl-xL through pathways involving nitric oxide (NO) (Ing et al. 1999). Furthermore, IL-1β induces cardiomyocyte hypertrophy (Palmer et al. 1995), upregulating atrial natriuretic factor and suppressing the expression of calcium regulatory genes (Thaik et al. 1995). IL-1β depresses cardiac function through NO-dependent (Schulz et al. 1995) and NO-independent pathways and inhibits the β-adrenergic agonist-mediated increase in cardiac myocyte contractility and cAMP accumulation (Gulick et al. 1989). Although the significance of IL-1-mediated suppression of function in most cardiac pathological conditions remains poorly defined, evidence suggests that, along with TNF-α, IL-1β is an essential mediator in sepsis-induced contractile dysfunction (Kumar et al. 1996).

Beyond its effects on cardiomyocytes, IL-1 is also capable of modulating the behavior and gene expression of most cell types involved in infarct healing (Fig. 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 (Bevilacqua et al. 1985; Hakkert et al. 1991). In addition, IL-1 markedly upregulates chemokine synthesis by both mononuclear and endothelial cells, promoting leukocyte chemotaxis to sites of injury (Sica et al. 1990a; Sica et al. 1990b).

Moreover, IL-1 is capable of modulating fibroblast phenotype and activity. IL-1β 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 (Koudssi et al. 1998). IL-1 signaling appears to promote matrix degradation by enhancing MMP synthesis while reducing collagen deposition (Siwik et al. 2000).

The effects of IL-1 on angiogenesis are 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* (Cozzolino et al. 1990), several studies suggested that IL-1 exerts angiogenic actions. IL-1 inhibition suppressed neovascularization in three distinct rat models of angiogenesis (Coxon et al. 2002; Hu et al. 1994). 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-1β increased the capability of human dermal microvascular endothelial cells to form tubular structures when overlaid with collagen gels (Romero et al. 1997) and increased MMP-2 expression by cardiac microvascular endothelial cells (Mountain et al. 2007), directly enhancing their matrix-degrading potential. Furthermore, IL-1β stimulated the synthesis of VEGF and its receptor flk-1 in cardiac microvascular endothelial cells (Maruyama et al. 1999).

IL-1 PLAYS AN IMPORTANT ROLE IN ADVERSE REMODELING FOLLOWING INFARCTION

The marked upregulation of IL-1 in the ischemic heart (Dewald et al. 2004; Guillen et al. 1995; Herskowitz et al. 1995) 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.

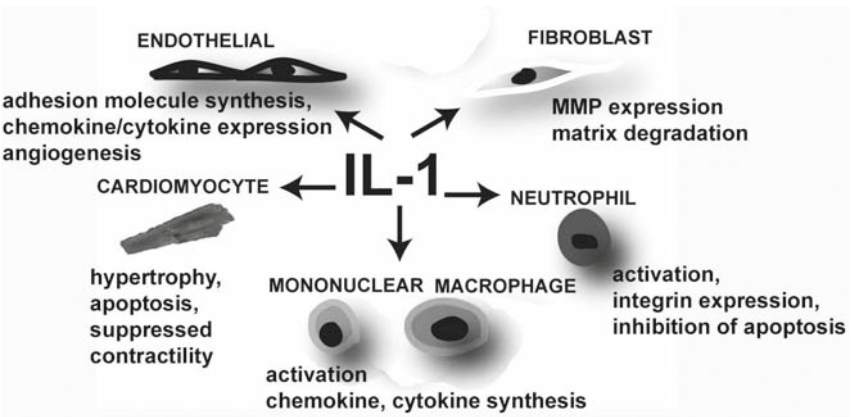

Fig. 2. IL-1 signaling modulates phenotype and function of all cell types involved in infarct healing. IL-1 suppresses cardiac function and induces cardiomyocyte hypertrophy and apoptosis. Beside its effects on cardiac myocytes, IL-1 signaling exerts pro-inflammatory actions, activating leukocytes, inducing the expression of cytokines, chemokines, and adhesion molecules in endothelial cells, and promoting infiltration of the infarcted myocardium by 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.

Both *in vitro* and *in vivo* studies suggest that IL-1 mediates pro-apoptotic signals enhancing cardiomyocyte injury in the ischemic heart. IL-1β stimulation activates apoptotic pathways in neonatal rat cardiomyocytes (Ing et al. 1999). 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 (Suzuki et al. 2001) and reducing post-ischemic upregulation of Bax, Bak, and caspase-3. In addition, both early (immediately after ischemia) and delayed (24 h after coronary occlusion) treatment with recombinant human IL-1Ra (anakinra) reduced cardiomyocyte apoptosis and prevented cardiac dilation in mouse and rat models (Abbate et al. 2008). *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 the regulation of the post-infarction inflammatory response. IL-1Ra gene transfection resulted in significantly reduced infiltration of the ischemic heart by neutrophils (Suzuki et al. 2001). 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 (Bujak et al. 2008a). 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 (Colotta et al. 1992). The pro-inflammatory actions of IL-1 may enhance injury through several distinct pathways. First, IL-1 signaling may enhance the 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 (Bujak et al. 2008a). 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 wild-type animals. In addition, expression of the key pro-fibrotic mediator TGF-β (Bujak and Frangogiannis 2007) 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-1β directly enhances fibrous tissue deposition by upregulating the expression of angiotensin II type 1 receptors on cardiac fibroblasts (Gurantz et al. 2005) and by stimulating fibroblast migration (Mitchell et al. 2007). Beyond its pro-inflammatory and fibrogenic properties, IL-1 also promotes extracellular matrix remodeling by enhancing cardiac fibroblast MMP expression (Siwik et al. 2000). IL-1β 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 wild-type 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 the 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 that of wild-type 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 (Berk et al. 2007). 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 attenuating MMP-2 and MMP-9 upregulation in the infarcted heart (Murtuza et al. 2004). 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 (Nakano et al. 1998), while *in vivo* studies have suggested that endogenous TNF signaling protects cardiomyocytes from apoptosis in a mouse model of myocardial infarction (Kurrelmeyer et al. 2000). Furthermore, cytokine signaling may critically regulate pathways essential for cardiac repair following infarction.

Evidence suggesting protective effects of IL-1β on ischemic cardiomyocytes is lacking. However, a study using a single intraperitoneal injection with a neutralizing antibody to inhibit IL-1β 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 (Hwang et al. 2001). The findings of this study contradict several investigations that demonstrated attenuation of adverse remodeling in mice with disruption of IL-1 signaling (Bujak et al. 2008b) and in animals receiving IL-1 antagonists (Abbate et al. 2008; Murtuza et al. 2004; Suzuki et al. 2001). 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, the 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 (Frangogiannis et al. 2005), 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 the 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 (Apostolakis et al. 2008; Kleemann et al. 2008).

The effects of IL-1 signaling on cholesterol metabolism are poorly understood. Chronic inflammation was found to be associated with adverse lipid profiles in may conditions (such as obesity, diabetes, and the metabolic syndrome) and pro-inflammatory cytokines may affect lipid metabolism (Isoda and Ohsuzu 2006). IL-1Ra$^{-/-}$ mice fed an atherogenic diet had significantly increased levels of total cholesterol and premature development of fatty liver compared with wild-type animals (Isoda et al. 2005). 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 an atherogenic diet without interfering with lipid metabolism (Elhage et al. 1998). 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 (Isoda et al. 2004). In addition, IL--1Ra overexpression attenuated atheromatous lesion formation in low-density lipoprotein receptor (LDLR)$^{-/-}$ mice fed a high-cholesterol/high-fat diet containing cholate (Devlin et al. 2002). In contrast, LDLR$^{-/-}$/IL-1Ra$^{-/-}$ mice had a tendency to develop early foam cell lesions when fed a diet rich in cholesterol and cholate (Devlin et al. 2002). 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 (Francis et al. 1999).

Evidence suggests that IL-1 may also activate pathways leading to plaque rupture and thrombosis (Libby et al. 1995). IL-1 upregulation in the atheromatous lesion may induce monocyte chemoattractant protein-1 and macrophage-colony stimulating factor synthesis,

promoting monocyte recruitment and activation. In addition, IL-1 enhances MMP synthesis in the plaque, inducing matrix degradation and contributing to plaque destabilization (Lee et al. 1995). IL-1 may also exert direct pro-thrombotic actions by enhancing endothelial tissue factor expression (Bevilacqua et al. 1984; Bevilacqua et al. 1985b). These concepts are supported by clinical investigations demonstrating that subjects carrying the TT genotype of the IL-1β gene had a decreased risk of myocardial infarction. Mononuclear cells from volunteers carrying the T allele exhibited attenuated IL-1β release and reduced expression of tissue factor upon stimulation with lipopolysaccharide (Iacoviello et al. 2005). 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 (van Minkelen et al. 2009). 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 (Zee et al. 2009).

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-1β, IL-1Ra, and IL-1RI) are markedly induced in balloon-injured vessels (Wang et al. 2000). IL-1 signaling in the vascular neointima may play a role in the activation, migration, and proliferation of smooth muscle cells through direct actions (Libby et al. 1988) and via upregulation of other growth factors or cytokines (Raines et al. 1989). 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 (Rectenwald et al. 2000). In contrast, IL-1Ra null mice exhibited enhanced neointimal formation following femoral artery injury (Ing et al. 1999). 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 (Kastrati et al. 2000). 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 (Zee et al. 2003).

IL-1 SIGNALING AND HYPERTROPHIC CARDIAC REMODELING

Cardiac hypertrophy is associated with the activation of IL-1 signaling in both animal models and human patients. In experimental models of pressure overload, IL-1β expression is upregulated in the hypertrophied heart (Xia et al. 2009), predominantly localized in endothelial cells and interstitial macrophages (Shioi et al. 1997). IL-1β expression becomes more pronounced with decompensation and the development of congestive heart failure (Shioi et al. 1997). On the other hand, patients with cardiac hypertrophy due to aortic stenosis exhibit significant upregulation of cardiac IL-1β expression (Vanderheyden et al. 2005). 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-1α showed prominent left ventricular hypertrophy and congestive heart failure leading to death within two weeks after birth. Transgenic mice with a cardiomyocyte-restricted overexpression of human IL-1α exhibited concentric left ventricular hypertrophy with a preserved systolic function, suggesting that cardiac expression of IL-1 is sufficient to induce hypertrophy (Nishikawa et al. 2006).

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 (Neumann et al. 1993). 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 (Lane et al. 1993). Persistently elevated IL-1β expression was noted in the chronic stage of myocarditis in a mouse model of postmyocarditis dilated cardiomyopathy induced by the encephalomyocarditis virus (Shioi et al. 1996). Second, increased IL-1β mRNA levels were found in endomyocardial biopsies from patients with viral myocarditis (Han et al. 1991) and idiopathic dilated cardiomyopathy (Vanderheyden et al. 2005). Third,

IL-1RI mull mice were protected from the development of autoimmune myocarditis (Eriksson et al. 2003). 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 (Lim et al. 2002). In addition, hydrodynamics-based delivery of plasmid encoding IL-1Ra-immunoglobulin gene suppressed the inflammatory response in a model of rat autoimmune myocarditis (Liu et al. 2005).

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 (Fearon and Fearon 2008). A recent investigation demonstrated that anakinra administration improved vascular and left ventricular function and attenuated nitro-oxidative stress in patients with rheumatoid arthritis (Ikonomidis et al. 2008). 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 (Crossman et al. 2008). 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. In these cases the risk may thus 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 (Mann 2005) 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 of 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, attenuating cytokine-induced cardiac dysfunction, reducing matrix degradation, and suppressing cardiomyocyte apoptosis. These effects may result in a reduction of recurrent coronary events and 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 the IL-1 system may exert beneficial effects in the remodeling non-infarcted myocardium while delaying and suppressing the formation of a supportive scar in the center of the infarct. Thus temporal and spatial considerations are essential in designing 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 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 the regulation of IL-1 signaling is essential for designing optimal therapeutic strategies for cardiovascular diseases, but it should also be coupled with a deep understanding of the pathophysiology of each condition.

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