# Emerging role of interleukin-1 in cardiovascular diseases

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**short title**
IL-1 in cardiovascular diseases

**summary**

There is an increasing evidence linking disbalance between various proinflammatory mediators and higher risk of cardiovascular events and pathologies. Likewise, some of the cardiovascular diseases lately appeared to have an autoimmune component. Interleukin-1 (IL-1), a master regulator of diverse inflammatory processes in higher eukaryotes and the key player in numerous autoimmune disorders including rheumatoid arthritis, diabetes mellitus or systemic sclerosis, has recently been proved to be involved in development of several cardiovascular diseases as well. This report aims to give a summary on current knowledge about the IL-1 signaling pathways and about the implication of IL-1 and the IL-1 receptor antagonist (IL-1Ra) in some of the diseases of the cardiovascular system.

**key words**

interleukin-1, interleukin-1 receptor antagonist protein, signal pathways, cardiovascular diseases

## Introduction

Nowadays, inflammation is well established as a crucial component of diverse chronic diseases and interleukin-1 (IL-1), a proinflammatory cytokine with pleiotropic biological effects, appears to be one of the key players of various inflammation-linked disorders. Currently, the role of interleukin-1 in rheumatoid arthritis, Alzheimer disease (Nicoll *et al.* 2000; Rainero *et al.* 2004) and associated vascular dementia (Yucesoy *et al.* 2006), diabetes mellitus, periodontitis (Lopez *et al.* 2005), systemic sclerosis (Kawaguchi 1994; Kawaguchi *et al.* 2006), autoimmune encephalomyelitis (Sutton *et al.* 2006) and cerebral infarction (Um *et al.* 2005) is well accepted.

Interleukin-1 was first described in 1972 as a lymphocyte-activating factor (Gery and Waksman 1972) and later was shown to exert a variety of effects including induction of inflammation, body temperature increase, stimulation of proliferation of T and B cells, induction of acute phase proteins and prostaglandin or regulation of hematopoesis. Its activities are not restricted to the immune system; interleukin-1 is involved also in the regulation of blood calcium levels, stimulation of proliferation of various cells, regulation of blood pressure or modulation of sleep. However, IL-1 represents one of the most important mediators of the inflammatory response that induces a cascade of proinflammatory effector molecules. It is thus not surprising that reports of evidence are accumulating that interleukin-1 is involved in pathogenesis of certain cardiovascular diseases, mainly due to its proinflammatory potential. Multiple studies revealed that effects of IL-1 on cardiac myocytes include structural and functional alterations like hypertrophy (Isoda *et al.* 2001; Thaik *et al.* 1995), regulation of MAP kinase pathway and induction of expression of

inducible nitric oxide synthase (iNOS) (Fichera *et al.* 2004; Singh *et al.* 1996), induction of the vasodilatator peptide adrenomedullin (Horio *et al.* 1998) or vascular endothelial growth factor (VEGF) induction (Tanaka *et al.* 2000). Certain IL-1 gene variations have been associated with overexpression of inflammatory mediators and also with increased risk of cardiovascular events (Florez *et al.* 2006; Francis *et al.* 1999; Iacoviello *et al.* 2005; Kornman 2006; Kornman *et al.* 2004; Kornman *et al.* 1999; Lai *et al.* 2006; Momiyama *et al.* 2001). Current knowledge about the involvement of interleukin-1 proteins in various cardiovascular diseases is reviewed throughout this text.

**The biology of IL-1**

Interleukin-1 is a term for two distinct but related proteins, interleukin-1α and interleukin-1β, encoded by two separate genes. Both of them are produced in consequence of stress or cell injury as 31-kDa precursors which undergo proteolytical cleavage by specific proteases during the process of maturation. The major interleukin-1 producing cells are macrophages, but many other cells like neutrophils, lymphocytes, dendritic cells, keratinocytes, endothelial cells, hepatocytes, fibroblasts or muscle cells have been shown to synthesize IL-1. Main target cells of IL-1 actions are primarily cells of the immune system such as monocytes, lymphocytes, granulocytes, dendritic cells, but this cytokine can affect many other cells like epithelial cells, fibroblasts, endothelial cells or smooth muscle cells.

The three-dimensional structure of IL-1α and IL-1β is composed of 12 antiparallel beta-strands arranged into a beta-trefoil. Both of the IL-1 proteins

lack the signal peptide and if secreted, the secretion proceeds along a non-conventional secretory pathway differing from the classical endoplasmic reticulum-Golgi route (Rubartelli *et al.* 1990). IL-1α and β use the same membrane receptor (IL-1R) to trigger the signal transduction pathway leading to activation of NF-κB or AP-1.

Despite all of the structural and functional similarities these two forms of IL-1 possess different features and play partly different roles in the organism. Unlike IL-1β both the IL-1α precursor molecule (amino acids 1-271) and the mature protein (amino acids 113-271) generated by calpain cleavage are biologically active and able to bind to membrane receptors (Mosley *et al.* 1987). IL-1α is constitutively expressed by many cell types under physiological conditions and its synthesis is stimulated during inflammation, on the contrary, IL-1β is not produced unless the cell receives an inflammatory signal and also its cleavage by caspase-1 is a tightly regulated process. Moreover, while mature IL-1β is released from cells via an ATP-dependent non-classical secretory pathway including $P2X_7$ receptors and pannexin-1 (Ferrari *et al.* 1997; Pelegrin and Surprenant 2006), the release of IL-1α seems to employ a different pathway dependent on copper ions and protein product of the S100A13 gene (Mandinova *et al.* 2003). Nonetheless, the secretion of mature IL-1α from human cells is a rare event and the protein is usually not detected in body fluids of healthy individuals. To exert its biological activity and interact with the IL-1 receptor, the IL-1α precursor needs to be inserted into the plasma membrane due to myristoylation on specific lysine residues (Stevenson *et al.* 1993). It is now accepted that the major part of the IL-1α precursor remains localised

intracellularly. A nuclear localization sequence is present within the precursor molecule and this points toward a specific function of IL-1α in the cell nucleus (Maier *et al.* 1994; Wessendorf *et al.* 1993). Conversely, mature IL-1β is the secreted form of IL-1.

It seems that some of the biological functions are shared by both IL-1 forms and some of them are not. In particular, the striking difference in regulation, processing, tissue-specific expression, subcellular localization and compartmentalization of IL-1α and IL-1β isoforms suggests the differential function and physiological role of these molecules (Beissert *et al.* 1998; Hacham *et al.* 2002; Kavita and Mizel 1995; Nakae *et al.* 2001; Song *et al.* 2003). However, only few studies have evaluated the relationship of IL-1α and IL-1β in parallel with pathophysiology of various diseases. Therefore, the precise differencies in roles of these two forms of IL-1 have not been clarified yet and many questions concerning the possible redundancy of IL-1 remain open.

IL-1-mediated inflammatory effects can be abolished by an effective natural inhibitor, IL-1 receptor antagonist (IL-1Ra). IL-1Ra joins both IL-1 proteins in the so-called IL-1 family of proteins cognate in the terms of structural and evolutionary relationship. There are both soluble and intracellular isoforms of IL-1Ra. The soluble IL-1 receptor antagonist molecule binds the IL-1 receptor, but this interaction does not lead to the activation of the signaling pathway. It is synthesized primarily in monocytes and macrophages, but might be produced in various other cell types. The function of the intracellular IL-1Ra (icIL-1Ra) isoforms remains unclear, but type I icIL-1Ra has been demonstrated

to interact with the third component of the COP9 signalosome CSN3 and inhibit activity of CSN-associated kinases as well as IL-1α-mediated release of IL-6 and IL-8, displaying thus unique anti-inflammatory activities inside the cells (Banda *et al.* 2005). Recently, Dewberry *et al*. (2008) reported that type I icIL-1Ra promotes endothelial cell proliferation by modulating CDK2 activity and retinoblastoma (Rb) protein phosphorylation.

Nowadays, the recombinant non-glycosylated form of IL-1Ra, anakinra, is used for treatment of rheumatoid arthritis and is tested also for IL-1 inhibition during acute gout (So *et al.* 2007), diabetes mellitus (Tellez *et al.* 2005) or familial cold autoinflammatory syndrome (Metyas and Hoffman 2006).

**The IL-1 signaling pathways**

Interleukin-1 triggers a complex network of signaling pathways which are influenced by a variety of regulatory proteins and target expression of a significant number of genes (Fig. 1).

Extracellular IL-1 is recognized and bound by the type I transmembrane IL-1 receptor which forms a complex with the IL-1 receptor accessory protein (IL-1RAcP) (Greenfeder *et al.* 1995), adaptor MyD88 (Muzio *et al.* 1997), Tollip (Burns *et al.* 2000) and kinases IRAK-1 (Croston *et al.* 1995) and IRAK-4 (Li *et al.* 2002; Lye *et al.* 2004). Upon IL-1 binding to the receptor, IRAK-1 becomes phosphorylated on Thr-209 and Thr-387 (supposedly by IRAK-4) and autophosphorylated within the so-called ProST region (**pro**line-, **s**erine-, **t**hreonine-rich) (Croston *et al.* 1995; Kollewe *et al.* 2004; Yamin and Miller 1997), interacts with tumor recrosis factor receptor-associated factor (TRAF6)

(Cao *et al.* 1996) presumably through TIFA protein (TRAF-interacting protein with a forkhead-associated domain) (Ea *et al.* 2004; Takatsuna *et al.* 2003) and leaves the receptor. Pellino-1, a homologue of *Drosophila* adaptor protein Pellino, is recruited (Jiang *et al.* 2003) and thus a new intermediate complex IRAK-1-IRAK-4-TRAF6-Pellino-1 is formed. Subsequently, IRAK-4 and Pellino-1 leave the complex and TRAF6 undergoes polyubiquitinylation (Wang *et al.* 2001) that brings about its activation. At the cytoplasmic membrane, another complex is formed that consists of IRAK-1, TRAF6, transforming growth factor-β-activated kinase 1 (TAK1) and two TAK-1-binding proteins TAB1 and TAB2 (Ninomiya-Tsuji *et al.* 1999; Takaesu *et al.* 2001) or alternatively TAK1, TAB1 and TAB3 (Cheung *et al.* 2004). Afterwards, phosphorylated IRAK-1 is ubiquitinylated and degraded in proteasomes, TAB2 becomes phosphorylated and TAB1 promotes autophosphorylation of TAK-1 and thus its activation (Kishimoto *et al.* 2000). Phosphorylation of TAK1 and TAB2 then facilitates the translocation of this complex from the membrane to the cytosol (Jiang *et al.* 2002).

As a result of all these events, NF-κB inhibitor (IκB) becomes phosphorylated on serine residues -32 and -36 by MEKK1 kinase (Lee *et al.* 1997), covalently modified by TRAF6-mediated and Ubc13/Uev1A-dependent ubiquitinylation at lysine-63 (Deng *et al.* 2000) and targeted to proteasome for degradation. NF-κB transcription factor is thus made available and enters the nucleus where it activates transcription of target genes. Alternatively, the signal triggered by IL-1 is mediated by MAP kinases and AP-1 since the TAK-1 kinase

is able to activate both MKK4-JNK and MKK6-p38 pathway as well (Yamaguchi *et al.* 1995).

Among the proteins whose synthesis is induced by IL-1 there are proinflammatory cytokines (IL-6, TNF) and mediators (cyclooxygenase, inducible nitric oxide synthase), acute phase proteins (C-reactive protein, complement factors) or growth factors (FGF; reviewed in (Dinarello 1996)).

The IL-1 signaling pathway is very similar to that triggered by the Toll-like receptors (TLR) involved in the innate immunity. Also both IL-1R and TLR contain the evolutionary conserved intracellular TIR domain that is crucial for interactions of the receptors with adaptors mediating the signal from outside.

Aside from the signaling pathways triggered by IL-1 from the cell surface, there has been an evidence of IL-1α activity in the cell nucleus. As mentioned above, IL-1α can be found in the nucleus since the precursor (but not the mature protein) contains a nuclear localization sequence (Wessendorf *et al.* 1993). This sequence is situated within the so-called N-terminal peptide of IL-1α (IL-1αNTP) that is cleaved from the precursor by calpain in the process of IL-1α maturation. However, IL-1αNTP is evolutionarily well conserved among vertebrates, suggesting that it is more than a byproduct of IL-1α cleavage. Both IL-1α precursor protein and IL-1αNTP are commonly found in the cell nucleus and we previously demonstrated that IL-1α interacts with nuclear histone acetyltransferase complex p300/PCAF via its N-terminal part (Buryskova *et al.* 2004). Results confirming the role of IL-1α precursor and NTP in transcriptional activation were observed by others as well (Werman *et al.* 2004). IL-1αNTP was also shown to be associated with elements of the RNA splicing apparatus and

to induce apoptosis in malignant cells (Pollock *et al.* 2003). The translocation of IL-1α to the nucleus is mediated by HAX-1 protein which appears to interact with IL-1α by three different segments (Kawaguchi *et al.* 2006). Moreover, the IL-1α precursor, but not the mature protein, can regulate the human endothelial cell migration *in vitro* (Mcmahon *et al.* 1997). All these results suggest that the IL-1α precursor or its N-terminal peptide might have a specific function in the cell nucleus. However, this “intracrine“ activity of IL-1α is still poorly understood.

Interestingly, a small group of „dual-function“ proteins that are active both extracellularly and within the cell nucleus has been described recently (Carriere *et al.* 2007). From this point of view, interleukin-1α resembles to the high-mobility group box 1 (HMGB1) protein that has been found associated with nuclear chromatin (Agresti and Bianchi 2003) but acts also as a proinflammatory cytokine (Wang *et al.* 1999a; Wang *et al.* 1999b), and interleukin-33, a cytokine from the IL-1 family promoting the Th2 response but acting also as a nuclear transcriptional repressor (Carriere *et al.* 2007; Gadina and Jefferies 2007). The latter molecule has been recently found to be involved in cardiovascular disease as well (Kakkar and Lee 2008).

Negative regulation of the IL-1 pathway can occur at multiple levels. Outside the cytoplasmic membrane, the functional concentration of IL-1 can be decreased by action of an inactive IL-1 receptor type II which lacks the TIR domain and does act as a kind of decoy target for IL-1, preventing its binding to IL-1R type I. Furthermore, IL-1Ra that is unable to trigger the IL-1R-mediated pathway can competitively occupy the IL-1 receptors and therefore is able to abrogate the signaling. Inside the cell, two naturally occuring variants of IRAK

but lacking the kinase activity, IRAK-M and IRAK-2, can also inhibit the IL-1/TLR signaling (Janssens and Beyaert 2003; Kobayashi *et al.* 2002). Regulation of the IRAK kinase activity is further provided by the mechanism of alternative splicing. IRAK-1b, an alternatively spliced version of IRAK-1, is not efficient in NF-κB activation and does not become phosphorylated and degraded in response to IL-1. This prolonged stability of IRAK-1b may lead to the replacement of IRAK-1 by IRAK-1b in the signaling complex and attenuate the IL-1 signaling pathway (Jensen and Whitehead 2001). Another splice variant of IRAK1 lacking exon 11, IRAK-1c, associates with MyD88, Tollip and TRAF6 but acts as a negative regulator by its inability to be phosphorylated by IRAK-4 and subsequently autophosphorylated (Rao *et al.* 2005). Further suggested negative regulators of the IL-1 signaling pathway are Smad6, PP2Cβ-1 and PP2Cε. Binding of Smad6 to Pellino-1 prevents its involvement in the signaling (Choi *et al.* 2006). TAK-1-mediated signaling can be inhibited via TAK-1 dephosphorylation by PP2Cβ-1 isoform of protein phosphatase PP2C (Hanada *et al.* 2001). Another member of the PP2C family, PP2Cε, might be involved in the attenuation of TAK-1 function as well (Li *et al.* 2003).

**IL-1 and atherosclerosis**

Coronary arterial disease is a chronic disease that results from the formation of an atheromatous plaque in the artery (so called atherosclerosis - "hardening of the artery") and subsequent reduction of arterial lumen diameter. Death can occur through myocardial infarction, cerebrovascular events and renal failure. The classical risk factors for atherosclerosis include elevated LDL

cholesterol level, smoking, obesity, diabetes or sedentary lifestyle. However, in the course of time it has become evident that atherosclerosis may also have autoimmune components and that many cytokines are likely to participate in the pathogenesis of this disorder especially in people lacking classical risk factors. Current data show clearly that atherosclerosis is associated with activation of the inflammatory processes and with systemic increase of proinflammatory molecules such as IL-1, IL-6, TNF or C-reactive protein and thus it turns from a disease caused by a simple accumulation of lipids into a complex disorder influenced by the inflammatory response of the arterial wall (reviewed in (Libby 2002)). The proatherogenic effect of IL-1 is attributed to its ability to modulate a number of key events involved in the complex inflammatory process of atherogenesis such as the vessel wall inflammation, leukocyte chemotaxis and adhesion or plaque rupture (Bochner *et al.* 1991; Libby *et al.* 1995; Von Der Thusen *et al.* 2003; Waehre *et al.* 2004).

The involvement of interleukin-1 during atherogenesis could be exemplified by its ability to promote atheromatous plaque instability due to upregulation of matrix metalloproteinases at the site of plaque formation. Increased levels of proinflammatory cytokines IL-1 and TNF as well as the chemokine IL-8 are found within the atheromatous plaque (Apostolopoulos *et al.* 1996; Tipping and Hancock 1993) together with matrix metalloproteinases that are synthesized by smooth muscle cells, endothelial cells and macrophages (Galis *et al.* 1995; Rajavashisth *et al.* 1999b). These zinc-dependent endopeptidases have the capacity to degrade various components of extracellular matrix (reviewed in (Newby 2005)) and indeed, they are capable to

induce collagen breakdown in atheromatous plaques (Shah *et al.* 1995). The matrix metalloproteinases have been shown to be upregulated by IL-1 and other proinflammatory cytokines in smooth vascular cells, endothelial cells and macrophages (Galis *et al.* 1994; Hanemaaijer *et al.* 1993; Herman *et al.* 2001; Rajavashisth *et al.* 1999a; Rajavashisth *et al.* 1999b) and inversely, their induction in smooth muscle cells can be inhibited by IL-1Ra (Lee *et al.* 1995). Increased expression of matrix metalloproteinases induced by proinflammatory cytokines such as IL-1 might therefore promote destabilization of atheromatous plaques and may lead to thrombosis (Galis *et al.* 1995).

Further proatherogenic potential of IL-1 is attributed to the ability of this cytokine to modulate cell adhesion and subsequent monocyte infiltration into the subendothelial space. According to Kirii *et al*. (2003), the absence of IL-1ß decreases the severity of atherosclerosis in apoE deficient mice, possibly through decreased expressions of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1) in the aorta. These adhesion-promoting molecules are likely to attract monocytes to the arterial intima. Following adhesion, monocytes enter the intima, differentiate into macrophages and then change into foam cells, that is one of the key steps in atherogenesis.

Moreover, IL-1 has been shown to influence the metabolism of plasma levels of cholesterol and serum amyloid A (SAA), both of which are frequently associated with atherogenesis. Following the atherogenic diet, mice lacking IL-1α showed a reduced SAA level and a lower atherosclerotic lesion area when compared to wild type mice, despite a higher total cholesterol level (Kamari *et al.* 2007). Interestingly, the anti-atherogenic effect of IL-1α knock-out was

stronger that the result of IL-1β deficiency, whose atheroprotective effect was described previously (Kirii *et al.* 2003). The early lesion formation was enhanced specifically by IL-1α having origin in bone marrow cells, most probably macrophages. On the contrary, this bone marrow-derived IL-1α had no effect on cholesterol levels (Kamari *et al.* 2007). The involvement of IL-1 in cholesterol metabolism is supported by results showing elevated levels of plasma cholesterol in mice lacking the IL-1 receptor antagonist (Isoda and Ohsuzu 2006).

Excessive angiogenesis in consequence of VEGF induction by IL-1 may be important in atherosclerosis as well. IL-1α stimulates secretion of VEGF in a dose-dependent manner and promotes angiogenesis in mice injected subcutaneously with IL-1α (Salven *et al.* 2002). Similarly, VEGF can be induced by IL-1β as well (Voronov *et al.* 2003) presumably due to the upregulation of hypoxia inducible factor-1α (HIF-1α), a major transcription factor for VEGF (Thornton *et al.* 2000), but IL-1β-mediated proangiogenic activity independent on VEGF induction was observed in monocytes treated with osteopontin too (Naldini *et al.* 2006). Since osteopontin is abundantly expressed in the atheromatous lesions (Giachelli *et al.* 1993), its interaction with the proinflammatory cytokine IL-1β could possibly contribute to the growth of atherosclerotic lesions and destabilization of the atheromatous plaques.

Up to the present, there have been reported numerous links between angiogenesis and inflammation that consist in vascular permeability increase, activation of the endothelium, cell migration and differentiation and of course influence of a range of cytokines and regulatory factors. Joint action of

angiogenesis and inflammation has been reported in a number of diseases including osteoarthritis (reviewed in (Bonnet and Walsh 2005)), rheumatoid arthritis (Paleolog 2002) or lung diseases (Walsh and Pearson 2001); however, the direct link between formation of new vessels and development or clinical outcome of atherosclerosis has not been established until now (Khurana *et al.* 2005).

According to recent genetic studies, certain polymorphisms in IL-1 genes are known to influence the plasma levels of C-reactive protein (Berger *et al.* 2002; Latkovskis *et al.* 2004). Elevated levels of C-reactive protein, a classical acute phase protein, indicate an increased risk of atherothrombotic and cardiovascular events (Danesh *et al.* 2004; Danesh *et al.* 2000) Studies in Italian, Chinese and Korean populations confirmed association of some of the interleukin-1 gene cluster polymorphisms with ischemic stroke (Iacoviello *et al.* 2005; Lai *et al.* 2006; Lee *et al.* 2004).

Other recent works have shown that certain bacterial species such as *Chlamydia pneumoniae, Helicobacter pylori* and *Porphyromonas gingivalis* aggravate atherosclerotic lesion development in animal models and that infectious agents including those that cause periodontal disease may also play an important role (Epstein *et al.* 1999; Hoge and Amar 2007; Chi *et al.* 2004). Bacterial infection triggers release of IL-1 by two different mechanisms: antigenic bacterial products such as lipopolysaccharide (LPS) stimulate IL-1 release from cells via Toll-like receptors and alternatively, recognition of bacteria via pattern recognition receptors such as CD-14 enhances IL-1 release from macrophages. Certain IL-1 gene polymorphisms can influence the process

of coronary artery disease in patients with *Chlamydia pneumoniae* infection and can lead to an increased risk of myocardial infarction (Momiyama *et al.* 2001). An epidemiological association between periodontitis and cardiovascular diseases has been reported in multiple studies as well (Kornman and Duff 2001; Kornman *et al.* 1999).

The key importance of IL-1 as a proatherogenic factor is further supported by other studies that point out the role of IL-1 receptor antagonist in the process of atherogenesis. A study by Merhi-Soussi *et al*. (2005) demonstrates that the IL-1/IL-1Ra ratio plays a critical role in the pathogenesis of vascular inflammation and atherosclerosis. Indeed, mice homozygous for the null mutation of IL-1Ra develop lethal arterial inflammation (Nicklin *et al.* 2000). It has been also shown that frequency of allele 2 of the IL-1RN gene coding for IL-1Ra is increased in patients with single vessel coronary artery disease and IL-1RN allele distribution is different in single and multiple coronary arterial diseases (Francis *et al.* 1999). Furthermore, the IL-1 receptor antagonist was demonstrated to inhibit neointima formation after coronary artery injury (Isoda *et al.* 2003; Morton *et al.* 2005) and to be involved in metabolism of cholesterol (Isoda and Ohsuzu 2006). IL-1Ra$^{-/-}$ knock-out mice are unable to synthesize mRNA of cholesterol 7α-hydroxylase, an enzyme that is involved in cholesterol conversion into bile acid, and display increased plasma cholesterol levels compared to mice with normal IL-1Ra expression (Isoda and Ohsuzu 2006). Thus, deficiency in the IL-1 receptor antagonist obviously has a proatherogenic potential and these observations point again toward the significance of IL-1 as an important agent in atherogenesis.

When it comes to obesity that is a classical risk factor for atherosclerosis, it has been shown that besides many other activities affecting nearly all organ systems, the perivascular white adipose tissue (pWAT) acts as an important source of secreted cytokines, chemokines and various metabolically active molecules such as TNF-α, TGF-β, leptin, adiponectin, MCP-1, IL-8, IL-6, IL-1 or IL-1Ra. Since the distance of pWAT from the vascular wall has been estimated to be less than 100 μm, the factors produced by perivascular adipocytes could interact with the blood vessels and contribute to progression of atherosclerosis by facilitating infiltration of leukocytes and monocytes, promoting angiogenesis and enhancing smooth muscle cell proliferation (Henrichot *et al.* 2005; Thalmann and Meier 2007).

Interestingly, serum levels of IL-1Ra are over 7-fold elevated in obese patients (Meier *et al.* 2002) and adipose tissue acts as an important source of IL-1Ra (Juge-Aubry *et al.* 2003). Although it seems that the overexpressed IL-1Ra may act against inflammation and should therefore represent a benefit, it seems that due to its metabolic activities, the increased production of the antagonistic protein is likely to promote resistance to leptin, weight gain and insulin resistance (Meier *et al.* 2002; Somm *et al.* 2005).

**IL-1 and myocardial infarction**

Apart from the initiation and progression of atherosclerosis, inflammation plays a role also in activation of the coagulation process that contributes to the development of myocardial infarction. This cardiac event usually occurs when a blood clot formed in the artery after the atheromatous plaque rupture blocks the

heart artery and the heart muscle starves of oxygen. Patients with myocardial infarction show significantly elevated levels of proinflammatory cytokines including IL-1, IL-6 or TNF (Guillen *et al.* 1995; Miyao *et al.* 1993) and also of the IL-1 receptor antagonist (Patti *et al.* 2004).

It has been shown that interleukin-1β enhances expression of tissue factor and induces procoagulant activity (Schwager and Jungi 1994). According to Iacoviello *et al*. (2005), certain polymorphisms in the IL-1β gene can be associated with incidence of myocardial infarction at young age, probably due to the inflammation-activated blood coagulation. However, Momiyama *et al*. (2005) states more precisely the IL-1β gene polymorphism to be associated with myocardial infarction only in patients with *Chlamydia pneumoniae* seropositivity.

Prolonged ischemia or oxygen shortage in consequence of an insufficient blood supply may result in damage and necrosis of myocardial cells. Such an event is likely to be followed by sterile inflammation triggered by a variety of molecules released from dying cells. A recent report by Chen *et al*. (2007) shows that the IL-1R-MyD88 pathway is involved in the sterile inflammatory response that could contribute to the development of many diseases including cardiovascular disorders. This inflammatory response is mediated by neutrophils recruited to the site of injury and requires an intact IL-1R signaling on none-bone-marrow-derived cells. In this pathway, IL-1α appears to be the key cytokine mediator. In IL-1R$^{-/-}$ and MyD88$^{-/-}$ knock-out mice, the sterile inflammatory response mediated by neutrophils is markedly reduced while monocyte recruitment to the site of injury remains relatively intact. Therefore, blocking the IL-1α action in order to reduce the extent of tissue damage might

not impair the host defense responses mediated by monocytes (Chen *et al.* 2007).

During the postinfarct period, many functional and morphological changes can occur within the heart. Adverse remodeling with left-ventricular dilatation represents a postinfarct complication that involves a number of functional changes and may lead to heart failure. One of the therapeutical approaches to the treatment of the infarcted heart that was used succesfully in experimental animals is the transplantation of skeletal myoblasts. However, the survival of the grafted cells might be reduced by the acute inflammatory response mediated by IL-1β (Suzuki *et al.* 2004). Recently, Murtuza *et al*. (2004) showed that transplantation of skeletal myoblast secreting IL-1Ra results in the improvement of systolic function, attenuation of adverse remodeling and reduction in myocyte hypertrophy. Moreover, in mice lacking the IL-1 receptor type I, adverse remodeling of the infarcted heart is markedly decreased due to a reduced collagen deposition in the absence of IL-1 signaling (Bujak *et al.* 2008). Targeting IL-1 as a molecule modulating the pathological heart remodeling could therefore have important clinical relevance (Murtuza *et al.* 2004).

Though, interleukin-1 might be involved also in cardiac repair mechanism. In human cardiac cells, IL-1α along with other inflammatory mediators upregulates the production of plasminogen activator inhibitor 1 (PAI-1) (Macfelda *et al.* 2002). Previous studies showed that treatment with PAI-1 prevents the cardiac rupture after myocardial infarction in mice (Heymans *et al.* 1999). Thus, IL-1α might contribute to the wound healing and cardiac repair after the stroke.

**IL-1 and myocarditis**

Myocarditis is a disease that may have an autoimmune background and is accompanied by the infiltration of inflammatory cells in the myocardium and subsequent inflammation of the heart muscle. In most cases it is caused by infection with various viruses (enterovirus, coxsackie virus, cytomegalovirus, poliovirus, influenza virus and others) and apparently, IL-1 is involved in this process (Lane *et al.* 1992; Shioi *et al.* 1996). As a model of myocarditis, mice infected with coxsackie virus B3 (CB3) have been established. The major autoantigen in this model is the cardiac myosine (Fairweather *et al.* 2001).

Several studies reported increased levels of IL-1α and IL-1β during coxsackie virus-induced myocarditis (Matsumori *et al.* 1999; Matsumori *et al.* 1994; Okuno *et al.* 2000). IL-1 treatment enhances the CB3-induced myocarditis in genetically resistant mice (Lane *et al.* 1992) and while gene therapy based on plasmids expressing IL-1Ra is effective for treatment of viral myocarditis in tested mice (Lim *et al.* 2002; Nakano *et al.* 2001). Mikami *et al*. (1996) showed that IL-1 together with other proinflammatory mediators such as TNF-α originated from inflammatory cells infiltrating the myocardial lesions and as a consequence of that, inducible NO synthase mRNA and protein were induced specifically after coxsackievirus B3 virus infection in mice. IL-1-mediated activation of iNOS causes excessive production of nitric oxide and subsequent cytotoxicity and negative inotropic effect on myocardial tissue (Finkel *et al.* 1992; Nakano *et al.* 2001; Pinsky *et al.* 1995). Indeed, treatment

with low-dose iNOS inhibitor results in decreased myocardial injury in mice (Mikami *et al.* 1997).

It has been also shown that interleukin-1β can bind to the IL-1 receptors on the surface of dendritic cells and stimulate them to produce cytokines including IL-12, required for activation of autoreactive $CD4^+$ cells that are responsible for the development of autoimmune myocarditis. In IL-$1R^{-/-}$ knock-out mice immunized with a self-peptide, activation of autoreactive $CD4^+$ cells was impaired. These data confirmed the key role of interleukin-1 in pathogenesis of autoimmune myocarditis (Eriksson *et al.* 2003). Fairweather *et al*. (2003) investigated the role of IL-12 on the development of CB3-induced myocarditis. In their experiments they showed that serum levels of IL-1β and severity of inflammation are significantly reduced in coxsackie virus-infected IL-$12^{-/-}$ knock-out mice which directly leads to the conclusion that IL-12 modulates the production of IL-1β. The development of chronic myocarditis that follows the initial phase of acute myocarditis can be suppressed by IL-12-induced IFN-γ in the murine myocarditis model. IFN-γ contributes to reducing the expression of IL-1β in the heart and decreasing the overall severity of the disease (Fairweather *et al.* 2004). During chronic myocarditis, the incidence of cardiac fibrosis and pericarditis is increased in IFN-$\gamma^{-/-}$ knock-out mice and the level of IL-1α and IL-1β in hearts of these mice is elevated (Fairweather *et al.* 2004; Grun *et al.* 2005).

Treatment with digoxin increases the intracardiac production of IL-1 and decreases the survival of mice infected with encephalomyocarditis virus

(Matsumori *et al.* 1999). The latter result should be taken into consideration since this drug has been used for treatment of viral myocarditis**.**

**IL-1 and dilated cardiomyopathy**

Dilated cardiomyopathy is a non-curable disease of the heart muscle during which the heart becomes enlarged and is unable to pump the blood strongly and efficiently. This usually leads to heart failure. In the majority of cases the cause of dilated cardiomyopathy is unknown, however the factors that contribute to the development of this disease are viral infection (coxsackie B viruses), pregnancy, excessive alcohol intake, genetic disorders or autoimmunity.

Patients with dilated cardiomyopathy show elevated levels of IL-1β (Francis *et al.* 1998; Vanderheyden *et al.* 2005) that is produced by endothelial cells and by myocytes themselves (Francis *et al.* 1998). On the contrary, the IL-1Ra gene expression is significantly lower in patients with dilated cardiomyopathy as compared to controls (Westphal *et al.* 2008). Therefore, this imbalance between the proinflammatory mediator IL-1β and its antagonistic molecule IL-1Ra could underlie the pathogenesis and progression of dilated cardiomyopathy. Besides the potential enhancement of the inflammation in the heart tissue, the action of IL-1 and IL-1-induced cytokines on heart muscle cells can induce cardiodepressant effects (Cain *et al.* 1999; Gulick *et al.* 1989; Matsumori *et al.* 1999) that can be attenuated by beta-adrenergic blockers (Ichihara *et al.* 2006; Prabhu *et al.* 2000).

## Conclusion

Both IL-1α and IL-1β are cytokines with pleiotropic effects in vertebrate organism and the cytokine network, that they make part of, regulates many essential processes. Current data support the notion that both IL-1 isoforms together with their negative regulator IL-1Ra play an essential role in development of various cardiovascular diseases including atherosclerosis, myocardial infarction, myocarditis, dilated cardiomyopathy, infective endocarditis or chagasic cardiomyopathy. IL-1 gene variations that are associated with overexpression of inflammatory mediators correlate also with increased risk of cardiovascular events.

Actions of the proteins belonging to the IL-1 family on circulatory system are complex and imbalance between the agonists and IL-1Ra might have an important impact on the cardiovascular function. So far, it was demonstrated that these molecules may be involved in regulation of inflammation, angiogenesis, coagulation processes or cholesterol metabolism, they mediate chemotaxis and facilitate adhesion (Table 1). Furthermore, IL-1 along with other proinflammatory cytokines as well as proteins induced by these are present in the myocardium of infants with congenital cardiac defects such as tetralogy of Fallot or ventricular septal defects (Qing *et al.* 2003). Taking into account the current wide application of cytokine antagonists like IL-1Ra/anakinra in treatment of serious autoimmune disorders, these therapeutic antagonists should be studied also from the point of view of the influence of disbalanced cytokine levels on the cardiovascular system. An example of a succesful application of IL-1Ra production in local tissues that yielded promising results

might be the transplantation of myoblasts secreting IL-1Ra that had leaded to improvement of the postinfarct myocardial function (Murtuza *et al.* 2004), another might be the IL-1Ra gene therapy treatment of viral myocarditis (Lim *et al.* 2002; Nakano *et al.* 2001).

Taken together, there is a considerable evidence of implication of IL-1α, IL-1β and IL-1Ra in the cardiovascular system and its various pathologies. However, future research on this field will be needed in order to elucidate the complex action of IL-1 on cardiovascular system in its whole extent.

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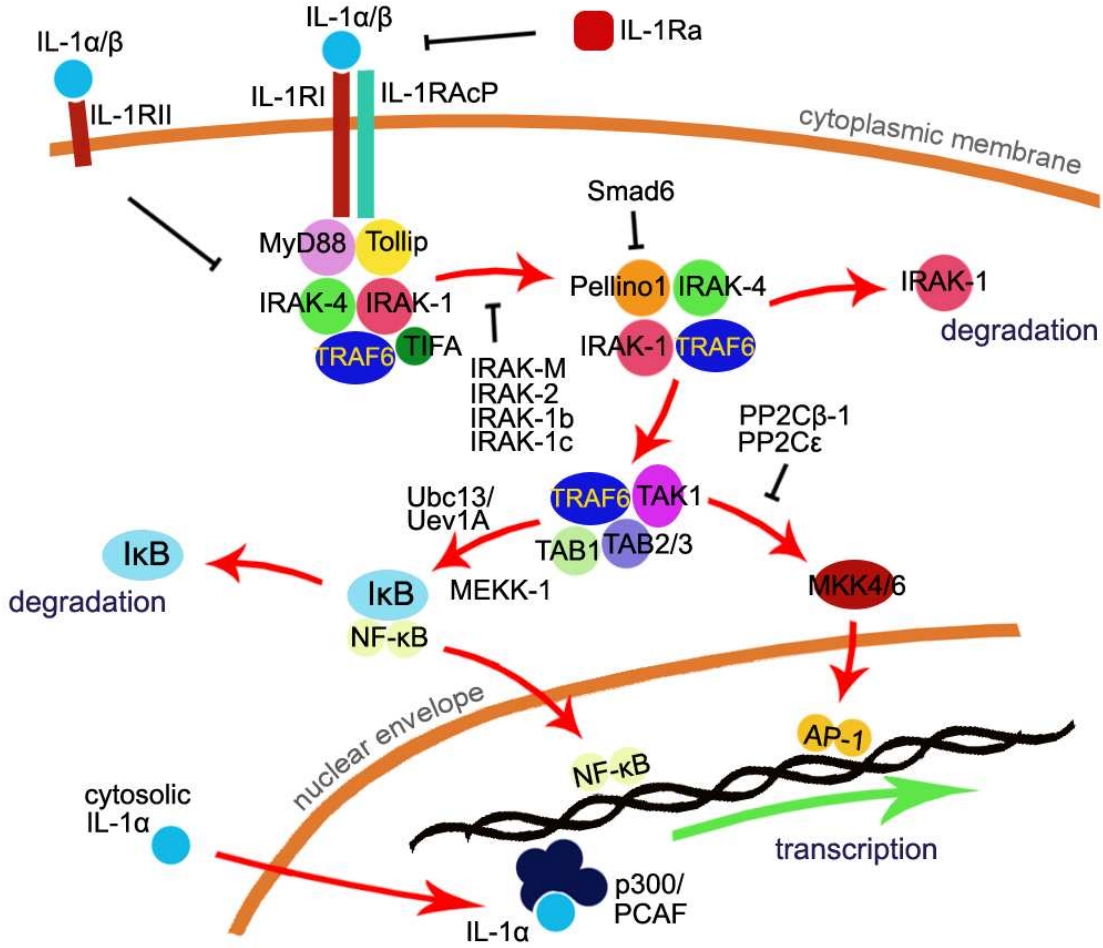


**Figure 1.** The IL-1 signaling and its negative regulation

| biological effect | molecule involved | corresponding mechanism | disease/ disorder | citation |
|---|---|---|---|---|
| proadhesive activity | IL-1b | stimulation of adhesion-promoting molecules (VCAM-1) | atherosclerosis | Kirii *et al.*, 2003 |
| atheromatous plaque destabilization | IL-1a, IL-1b | upregulation of matrix metalloproteinases | atherosclerosis | Rajavashisth *et al.*,1999a,b; Galis *et al.*,1995 ; Shah *et al.*, 1995 |
| modulation of cholesterol plasma level | IL-1a, IL-1b | SAA induction | atherosclerosis | Kamari *et al.*, 2007; Merhi-Soussi *et al.*, 2005 |
| stimulation of angiogenesis | IL-1a, IL-1b | VEGF induction | atherosclerosis | Salven *et al.*, 2002; Voronov *et al.*, 2003 |
| vessel wall inflammation | IL-1a, IL-1b | induction of inflammatory pathways through IL-1R I | atherosclerosis | Nicklin *et al.*, 2000 |
| induction of procoagulant activity | IL-1b | stimulation of tissue factor expression | myocardial infarction | Schwager and Jungi 1994 |
| tissue damage, disease aggravation | IL-1a | mediation of sterile inflammation | myocardial infarction | Chen *et al.*, 2007 |
| enhancement of adverse remodeling | IL-1b | modulation of collagen deposition | myocardial infarction | Bujak *et al.*, 2000; Murtuza *et al.*, 2004 |
| myocardial dysfunction, disease aggravation | IL-1a, IL-1b | iNOS induction | myocarditis | Lim *et al.*, 2002; Mikami *et al.*, 1996; Nakano *et al.*, 2001 |
| development of the disease | IL-1b | IL-12-mediated activation of autoreactive CD4+ cells | autoimmune myocarditis | Eriksson *et al.*, 2003 |

**Table 1.** Mechanisms of involvement of the IL-1 molecules in cardiovascular disease