Toll-Like Receptor Signaling
Defensive or Offensive for the Heart?
Masatsugu Hori, Kazuhiko Nishida

The majority of cardiovascular diseases cause progressive deterioration, mainly resulting from accumulation of vascular and myocardial tissue damage. A growing body of evidence indicates that oxidative stress and the inflammatory response are involved as triggers or mediators of these tissue injuries. It is well known that atherosclerosis is an inflammatory disease preferentially occurring in lesion-prone areas. Bacterial infections such as Chlamydia pneumoniae and cytomegalovirus could cause the inflammatory response of the coronary arteries, and accumulation of macrophages in the vascular wall promotes plaque formation. In myocardial infarction, infiltration of macrophages and neutrophils may modify myocardial injury even after reperfusion. It is also reported that inflammatory cytokines and growth factors are activated in either ischemic or nonischemic chronic heart failure. In such progressively deteriorating conditions, both oxidative stress and the inflammatory response are synergistically involved, causing a vicious cycle of progression of injury. These considerations support the hypothesis that inflammatory response is involved in most progressive cardiovascular diseases.

The innate immune system is the first line of defensive mechanisms that protect hosts from invading microbial pathogens. The Toll-like receptor (TLR) family plays a fundamental role in the innate immune response. In 1997, vertebrate homologs of the Drosophila spp transmembrane pattern recognition receptor “Toll” were identified and termed TLRs. Among the 11 human TLRs identified to date, TLR1, -2, -4, -5, and -6 are all present on the plasma membrane. TLR1, -2, -4, and -6 recognize lipids, whereas TLR5 recognizes protein ligands. Among those, TLR4 recognizes specific components of Gram-negative bacteria lipopolysaccharide (LPS) and is well known as the LPS receptor. It is of particular interest that TLR4 binds not only to bacterial LPS but also to endogenous tissue fragments such as extracellular matrix breakdown products, e.g., hyaluronan fragment and fibronectin extra domain A (EDA), and certain types of heat shock proteins. When TLR4 binds to the specific ligands, it activates the innate immune response.

In this issue of Circulation Research, Timmers et al report that knockdown of TLR4 reduces the extent of left ventricular remodeling and preserves systolic function without affecting infarct size after myocardial infarction in mice. In the noninfarcted area, interstitial fibrosis and myocardial hypertrophy are reduced in TLR4-deficient mice. In contrast, in the infarcted area, collagen density is increased, accompanied by fewer macrophages and lower cytokine expression levels, and matrix metalloproteinase (MMP)2 and MMP9 activities are markedly attenuated. From these results, the authors conclude that TLR4 plays a causal role in postinfarct maladaptive ventricular remodeling though the underlying molecular mechanism remains unclear.

What are the endogenous TLR4 ligands in the infarcted heart? The fibronectin EDA expression levels in the infarct area were much higher compared with those in sham hearts, indicating that EDA could be a candidate ligand responsible for TLR4 signaling after myocardial infarction. However, other extracellular matrix breakdown products and/or heat shock proteins could also be candidates as endogenous ligands for selective subtypes of the TLR family. Although heat shock protein (HSP)60 can activate nuclear factor (NF)-κB by binding to either TLR2 or TLR4, HSP60 mRNA levels did not differ between infarct and remote areas, suggesting that HSP60 is not a pivotal player in the left ventricular remodeling. Instead, various endogenous products other than EDA may also activate the TLR4 in myocardial infarction.

When TLR4 is activated, reactive oxygen species are produced and inflammatory cytokines and nitric oxide are released. Reactive oxygen species can also induce the expression of cytokines and chemotaxis of leukocytes and initiate complement activation. These cascades are tightly linked with TLR4-induced oxidative stress in ischemic heart disease. It is widely accepted that NF-κB plays a key role in activation of the inflammatory response to oxidative stress; NF-κB induces tumor necrosis factor (TNF)-α and other inflammatory cytokines, which may induce apoptosis but also may cause a hypertrophic response in myocardial cells. This, the reduced myocardial hypertrophy in the remote area of the infarcted heart observed in TLR4 deficient mice, may be in part a result of reduced expression level of TNF-α. Lower MMP2 and MMP9 activities and increased collagen density in the infarct area of TLR4-deficient mice also indicate that TLR4 defectiveness reduces extracellular matrix degradation, causing collagen accumulation. These considerations strongly suggest that increased expression of TLR4 in ischemic hearts mediates maladaptive left ventricular remodeling after myocardial infarction.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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The intracellular signal transduction pathways of the TLRs, however, are not fully elucidated. Activation of each subtype of the TLR family may stimulate a number of signaling pathways, some of which are common among subtypes, whereas others may be specific to a particular TLR subtype. The cytoplasmic adaptor molecules of TLRs include myeloid differentiation primary response protein 88 (MyD88), Toll/IL-1R homology domain-containing adaptor protein, Toll/IL-1R homology domain-containing adaptor inducing interferon β (TRIF), and TRIF-related adaptor molecule. MyD88 is a universal adaptor that activates the inflammatory pathway. In MyD88-dependent pathway, transforming growth factor β-activated kinase 1 (TAK1), a mitogen-activated protein kinase (MAPK) kinase kinase (MAPKKK), activates 2 downstream pathways involving the inhibitor of NF-κB kinase (IKK) complex and the MAPK family, p38 and c-Jun NH2-terminal kinase. The IKK complex catalyzes the phosphorylation of IκB proteins, which leads to the translocation of NF-κB to the nucleus and subsequently results in transcription of genes encoding proinflammatory cytokines and chemokines. It has also been reported that there is a crosstalk between TLR signaling and the phosphoinositide 3 kinase (PI3K)/Akt signaling and the phosphoinositide 3 kinase (MAPKKK), activates 2 downstream pathways involving the inhibitor of NF-κB kinase (IKK) complex and the MAPK family, p38 and c-Jun NH2-terminal kinase. The IKK complex catalyzes the phosphorylation of IκB proteins, which leads to the translocation of NF-κB to the nucleus and subsequently results in transcription of genes encoding proinflammatory cytokines and chemokines. It has also been reported that there is a crosstalk between TLR signaling and the phosphoinositide 3 kinase (PI3K)/Akt signaling pathway,7 and, thus, stimulation of TLR4 signaling can result in activation of PI3K/Akt signaling. A large body of evidence supports the cardioprotective role of PI3K/Akt signaling8; the PI3K/Akt signaling pathway may serve as an endogenous negative feedback regulator of TLR signaling, and PI3K/Akt signaling may contribute to less maladaptive remodeling in TLR4-deficient mice. In addition to TAK1, several other MAPKKK, such as apoptosis signal-regulating kinase 1 (ASK1), may be involved in the TLR4 signaling pathway. ASK1 is a reactive oxygen species-sensitive MAPKKK that activates NF-κB. Because (1) ASK1-deficient cells have defects in LPS-stimulated p38 and TNF-α activation,9 (2) ASK1-deficient mice exhibit reduced cardiac remodeling after myocardial infarction,10 and (3) PI3K is involved in downregulation of ASK1 during LPS-induced TLR4 signaling,11 there may be another crosstalk between ASK1 and the TLR signaling pathway. Thus, TLR4 signaling may orchestrate these signaling networks including other inhibitory regulators, eg, suppressor of cytokine signaling 1 and A20.2

TLR4 inhibition may be a novel therapeutic strategy for maladaptive left ventricular remodeling in patients with ischemic heart failure. However, direct inhibition of TLR4 may not be a promising therapeutic avenue because TLR4 inhibition may lead to a functional loss of the innate immune mechanism, and, thus, the prognosis after myocardial infarction may not be improved. On the other hand, inhibition of TNF-α with antibodies has failed to improve the prognosis of patients with chronic heart failure.12,13 Thus, to achieve the therapeutic goal, more comprehensive and precise mechanisms underlying the maladaptive remodeling of the heart should be elucidated. Recently, antiinflammatory effects of hydroxymethylglutaryl-coenzyme A reductase inhibitor, statin attracts a great deal of attention in controlling the inflammatory response in atherosclerosis. Of note, it is reported that fluvastatin attenuates increased TLR4 expression in blood monocytes from patients with chronic heart failure.14 Thus, the antiinflammatory effect of statin, known as a pleiotropic effect, may in part be mediated by a TLR4-dependent pathway. This may suggest a therapeutic possibility in targeting the TLR-mediated inflammatory response in progressive cardiovascular diseases. However, the double-edged effects of TLR4 signaling pathways should be taken into account to strike a vein of gold in the therapeutic strategy.

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References


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