INTRODUCTION

Doxorubicin (DOX) is one of the most widely used and successful antitumor drugs and is prescribed for treatment of a variety of cancers, including both solid tumors and leukemias. Unfortunately, despite its broad effectiveness, its cumulative and dose-dependent cardiac toxicity has been a major concern of oncologists in cancer therapeutic practice for decades. Cardiac inflammation and generation of oxidative stress are known to contribute to DOX-induced cardiomyopathy. Cytokine release mediated by activation of the innate immune system is believed to be involved in the pathogenesis of DOX-induced cardiotoxicity. The innate immune system has long been regarded as the first line of defense against foreign pathogens. Toll-like receptors (TLRs) are a part of the innate immune system and are germline-encoded receptors involved in the cardiac stress reaction. They are key components of the innate immunity and are activated in response to pathogens as well as non-pathogenic components of damaged tissues. Among the TLR family, TLR4 is the most extensively studied in the pathogenesis of cardiomyopathy. TLR4 activation not only triggers an inflammatory response but also results in extracellular matrix degradation and causes a vicious cycle of which the outcome is cardiomyopathy. On the other hand, TLR4 deficiency improves left ventricular function and attenuates key pathophysiological mechanisms in DOX-induced cardiomyopathy. Consequently, any substance that blocks the TLR4 receptor or disrupts its signaling may provide protection against cardiomyopathy in DOX-treated patients. Statins are currently-marketed reductase inhibitors that are used to reduce levels of LDL; they also have other beneficial effects including decrease of oxidative stress and vascular inflammation. More recently, statins have been shown to inhibit the TLR4-mediated inflammatory response in individuals with a specific TLR4 genotype. It is possible that these agents could be used off-label to diminish the likelihood of doxorubicin cardiotoxicity, permitting higher doxorubicin doses. We propose the hypothesis that statins can prevent doxorubicin-induced cardiomyopathy.
mia/reperfusion injury, heart failure, cardiac hypertrophy and atherosclerosis. Among the TLRs, TLR4 has been investigated most extensively. This receptor is expressed by cardiomyocytes with and has been shown to contribute to myocardial contractility dysfunction during sepsis. TLR4 activation resulting from a variety of ligands such as pathogen-associated molecular patterns, heat shock proteins and oxidized LDL may lead to a pro-inflammatory response in the heart. It has been shown that TLR4 can modulate left ventricular hypertrophy, myocyte contractility and myocardial ischemia-reperfusion injury and it plays a role in inflammatory responses including septic shock syndrome. Stimulation of TLR4 by circulating lipopolysaccharide (LPS) during sepsis is one of the mechanisms by which Gram-negative sepsis reduces the ejection fraction and creates heart failure. Interestingly, TLR4 has also been shown to mediate the elevation of interleukin-6 and 8 (IL6 and 8) secretion from human coronary artery endothelia stimulated by LPS. TLR4 activation not only triggers an inflammatory response but also results in extracellular matrix degradation and causes a vicious cycle of which the outcome is cardiomyopathy. Activation of inflammatory cytokines and nuclear factor κB (NF-κB) as well as augmented expression of inducible nitric oxide synthase (iNOS) are the major consequences of stimulation of these TLRs. In addition, it has been reported that expression of TLR4 is augmented in the myocardium from patients with heart failure, and TLR4 is involved in the genesis of myocardial hypertrophy.

**HYPOTHESIS**

Although the exact mechanism of DOX-induced cardiomyopathy is not completely understood, numerous current findings suggest that cardiac inflammation and generation of oxidative stress play an important role in its pathology. Toll-like receptors are a part of the innate immune system and are involved in the cardiac stress reaction. TLR4 is relevant in cardiac inflammation signaling and DOX-induced cardiomyopathy. Antagonism of TLR4 may modulate DOX-induced cardiomyopathy and potentially lessen the deleterious processes that lead to pathogenesis of cardiovascular diseases such as DOX-induced cardiomyopathy. On the other hand, TLR4 deficiency improves left ventricular function and attenuates key pathophysiological mechanisms that cause DOX-induced cardiomyopathy in comparison with wild-type.

**Evaluation of hypothesis**

To test this hypothesis we offer following methods:

1. Oral or intraperitoneal administration of statins (e.g. Simvastatin or Atrovastatin) to animals before and during DOX treatment, and evaluation of oxidative stress and inflammatory markers in their sera in comparison to control group.

2. Simultaneous addition of statins and DOX to cultured rat cardiomyocytes and evaluation of toxicity in comparison to DOX alone in control cultures.

3. Since statins are FDA-approved HMG-CoA reductase inhibitors and are known to be safe drugs in humans, it is possible to evaluate this hypothesis in Doxorubicin-treated patients.

**Experimental data**

A study on humans demonstrated an enhancement of TLR4-positive circulating monocytes in patients with acute coronary syndrome. Furthermore, increased TLR4 expression was observed in cardiomyocytes isolated from humans and animals with cardiomyopathies. Recently, Raid et al. reported that in TLR4-deficient mice (carrying a deletion of the TLR4 gene), treatment with Doxorubicin improved left ventricular function and attenuated key pathophysiological mechanisms that cause DOX-induced cardiomyopathy in comparison with wild-type.

**DISCUSSION**

Several lines of evidence support the role of TLRs in various cardiovascular diseases such as DOX-induced cardiomyopathy. There is growing interest in therapeutics targeting TLRs and components of the downstream pro-inflammatory signaling cascade. Antagonism of these TLRs may modulate the inflammatory response and potentially lessen the deleterious processes that lead to pathogenesis of cardiovascular diseases such as DOX-induced cardiomyopathy. On the other hand, TLR4 deficiency improves left ventricular function and attenuates key pathophysiological mechanisms in DOX-induced cardiomyopathy. Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are a class of drugs that lower cholesterol level by inhibiting the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. However, benefits from statin therapy appear to exceed their cholesterol-lowering effect. A recent study has shown that statins inhibit the TLR4-mediated inflammatory response in individuals with a specific TLR4 genotype. In addition, statin treatment results in inhibition of NF-κB activity and subsequent reduction of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and IL-6. Furthermore, statins inhibit LPS-mediated activation of human peripheral mononuclear cells and endothelial cells. TLR4 is the main receptor for LPS and statins suppress LPS-induced up-regulation of TLR4. Given the potential of genomics for identifying people in a target population who are most likely to benefit from specific drugs or who are most at risk of side effects, it is notable that the efficacy of pretreatment with pravastatin, a member of the statin family, in preventing cardiovascular events proved higher in carriers of the TLR4 Asp299Gly polymorphism than in non-
Statins influence TLR4 expression and signaling via inhibition of protein prenylation. These observations imply interaction with innate immune mechanisms as a potential mechanism by which statins mediate anti-inflammatory effects. It has been indicated that simvastatin attenuates the up-regulation of TLR4 and 2 on the surface of monocytes by more than half after LPS administration. This suppression of TLR4 and TLR2 expression was associated with decreased circulating concentrations of TNF-α, monocyte chemoattractant protein-1 (MCP–1) and C-reactive protein (CRP). Thus, statins could provide an additional level of cardioprotection by modulating TLR4 activity, secondary to its well-established effects on hyperlipidemia. The reduction of inflammatory cytokines by statins has been convincingly demonstrated in clinical studies. Several small, prospective studies have evaluated the effect of statin treatment on inflammatory markers in patients with coronary artery endothelial cells by LPS. Cardiovasc Res. 2003;107(19):2416-2421.

Most of these trials have noted a significant decrease in concentrations of inflammatory markers after treatment with a statin for 16 weeks to 12 months in patients with ischemic and non-ischemic cardiomyopathy. In view of these diverse findings, we propose that the manipulation or intervention of TLR4-mediated immune responses by statins is a potential treatment for attenuating Doxorubicin-induced cardiomyopathy.

REFERENCES


