Exogenous Thioredoxin Reduces Inflammation in Autoimmune Myocarditis

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Levels of reactive oxygen species (ROS) are tightly regulated in mammalian cells. A variety of enzymes produce ROS, including NAD(P)H oxidase, xanthine oxidase, glucose oxidase, myeloperoxidase, the family of nitric oxide synthases, and mitochondrial enzymes. Low levels of ROS such as superoxide or hydrogen peroxide regulate highly specific targets. In the cardiovascular system, for example, ROS serve as signaling molecules, mediating vascular endothelial growth factor signal transduction, activating matrix metalloproteinases, and regulating cell cycle phosphatases. Host defenses that protect against oxidative stress include small antioxidant molecules such as ascorbate, α-tocopherol, glutathione, and thioredoxin (Trx), as well as antioxidant enzymes such as superoxide dismutase, catalase, paraoxonase, glutathione reductase, glutathione peroxidase, and Trx reductase.

However, excessive oxidative stress—caused by either increased ROS production or inadequate antioxidant defenses—can lead to cardiovascular diseases. For example, genetic deficiency of glutathione peroxidase-1 is associated with increased levels of vascular hydrogen peroxide and arterial thrombosis. Another example of an imbalance in oxidant stress occurs when elevated levels of angiotensin II trigger excess ROS production by the vascular NAD(P)H oxidase Mox1, contributing to decreased nitric oxide bioavailability, endothelial dysfunction, and atherogenesis. Additionally, increased levels of ROS generated by xanthine oxidase in the heart impair cardiac energetics, playing a role in the development of cardiomyopathy. Finally, ROS may play a critical role in autoimmune myocarditis.

Autoimmunity is surprisingly common in patients with cardiomyopathy: Up to 20% of all idiopathic dilated cardiomyopathies are associated with autoantibodies and other autoimmune markers. Triggers of autoimmune myocarditis include (1) molecular mimicry, in which viral antigens structurally similar to myocardial antigens activate lymphocytes to recognize and attack the host, and (2) cryptic epitopes, in which myocardial inflammation alters the processing and presentation of normal host antigens. These exogenous or endogenous antigens then stimulate an immune response directed against the host myocardium, driven by B and T lymphocytes, natural killer cells, neutrophils, and monocytes. Effectors released by autoreactive immune cells include perforin, granzyme B, and autoimmune directed against myocytes. Neutrophils and monocytes infiltrating into inflamed myocardium express NAD(P)H oxidase and myeloperoxidase, enzymes capable of generating high levels of ROS.

ROS may play a role at multiple steps in autoimmune pathways. Cryptic epitopes can be produced by highly reactive hydroxyl anions that oxidize amino acids or DNA bases, generating novel antigens such as 8-hydroxyguanosine. Cryptic epitopes also may be produced by cytotoxic radicals that damage cells, releasing sequestered antigens. ROS can activate antigen presentation by dendritic cells. Excessive oxidant stress can regulate the activity of intracellular transcription factors, leading to the release of inflammatory cytokines and chemokines that regulate leukocyte trafficking into the heart. Finally, ROS can kill cells by necrosis or apoptosis, leading to further myocardial injury.

In this issue of Circulation, Liu and colleagues examine the effects of Trx therapy for autoimmune myocarditis in mice. Building on prior published work demonstrating that Trx protects the myocardium from ischemia and drug toxicity, these investigators hypothesized that Trx should inhibit myocarditis by decreasing protein oxidation, chemokine signaling, and leukocyte trafficking. In an elegant set of experiments, the authors administered exogenous Trx or decreased endogenous Trx in mice injected with myosin. The results of their study support their hypothesis: Trx does indeed decrease myocarditis, but the mechanism of action is unclear.

Trx might affect any one of a number of pathways that lead to autoimmune myocarditis:

1. Scavenging ROS. One simple explanation for the beneficial effect of exogenous Trx is that Trx scavenges radicals such as hydroxyl radical and hydrogen peroxide that would otherwise oxidize proteins, lipids, and DNA. Supporting this theory, Liu and colleagues found in their present study that Trx decreases levels of the oxidized DNA base 8-hydroxyguanosine. Trx thus may ameliorate myocarditis by blocking the formation of novel oxidized antigens or by blocking the release of sequestered antigens from cardiac myocytes injured by cytotoxic levels of ROS.

2. Reducing oxidized targets. Trx is a component of an antioxidant system that includes Trx, Trx reductase, and...
NADPH.

The reduced form of Trx interacts with oxidized proteins, reduces the target protein, and is itself oxidized. Trx reductase then uses the reducing equivalents of NADPH to convert oxidized Trx to reduced Trx, which then can reduce additional targets. For example, reduced Trx interacts with and reduces specific transcription factors such as nuclear factor-κB, p53, and AP1.

Liu and colleagues found in their present study that Trx treatment suppressed expression of macrophage inflammatory protein-1α, which is regulated by nuclear factor-κB. Trx thus may inhibit myocardial inflammation by modulating expression of inflammatory genes.

3. Modulating signal transduction cascades. Trx also has redox-independent effects. Trx can bind to apoptosis signal–related kinase 1 (ASK1), inducing ubiquitination and degradation of ASK1, thereby decreasing apoptosis mediated by ASK1.

Trx also interacts with vitamin D3–upregulated protein, which may modulate cell differentiation and growth.

The present study by Liu et al did not examine the effect of Trx on myocardial apoptosis but did detect less myocyte necrosis in Trx–treated mice. Trx may thus limit myocarditis by promoting cell survival.

The study by Liu et al also raises intriguing but unanswered questions. The authors showed that treatment with mutant Trx lacking active site cysteine residues has no effect on myocarditis. Is the redox activity of Trx responsible for its beneficial effects, or are the cysteine residues needed to interact with the targets of Trx? Cells exposed to oxidant stress can secrete Trx; other cells can transport Trx from the extracellular space into the cytoplasm. Does Trx act outside or inside cardiovascular cells to alleviate myocardial inflammation? If exogenous Trx acts inside its target cells, how does Trx gain access to the intracellular compartment? Finally, what are the specific protein targets of Trx in autoimmune myocarditis?

Whatever the precise mechanism, the demonstration that Trx ameliorates myocardial inflammation has important clinical implications. Antioxidant therapy may be beneficial in patients with autoimmune myocarditis and perhaps with other autoimmune disease as well. Additional preclinical studies are needed before Trx therapy is ready for clinical trials. Nevertheless, these intriguing and important animal studies support the concept that the balance of oxidative stress and antioxidant defenses is an important therapeutic target in autoimmune diseases.

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References


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