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Forum Review Article

Thioredoxin-1 and Endothelial Cell Aging: Role in Cardiovascular Diseases

Joachim Altschmied and Judith Haendeler

Abstract

The thioredoxin-1 (Trx-1) system consists of two oxidoreductases, thioredoxin reductase and Trx-1. Trx-1 is a ubiquitously expressed oxidoreductase. The cellular functions of Trx-1 are wide range. They include protein disulfide reduction, DNA synthesis, protection from apoptosis, redox regulation of a variety of proteins, transcription factors and reduction of H_2O_2, respectively. This review will first focus on the essential role for Trx-1 in different cardiovascular cells, namely smooth muscle cells, endothelial cells, and cardiomyocytes. Thereby, the review will demonstrate the predominant role of Trx-1 to limit oxidative stress directly due to reactive oxygen species scavenging and by protein–protein interaction with key signaling molecules. Second, this review will highlight the role of Trx-1 in cardiovascular aging, focusing on its importance on shear stress and the profound changes with age. Finally, the review will focus on important *in vivo* studies showing a protective role of Trx-1 in different cardiovascular diseases. Thus, the Trx system and Trx-1 could be important future targets to develop clinical therapies for cardiovascular disorders. *Antioxid. Redox Signal.* 11, 1733–1740.

Introduction

The thioredoxin (Trx) system consists of two antioxidant oxidoreductase enzymes, thioredoxin (Trx-1) and thioredoxin reductase. The thioredoxin family includes three proteins, Trx-1, Trx-2, and SpTrx 3–5 (24). They contain a conserved —Cys-Gly-Pro-Cys- active site (cysteine32 and cysteine35 within Trx-1) that is essential for the redox regulatory function of the thioredoxins (24). Trx-1 is ubiquitously expressed in mammalian cells. Genetic targeting of Trx-1 leads to a lethal phenotype (34). The physiological functions of Trx-1 in different types of organisms have evolved from a common fundamental reaction to a large number of different specialized functions. The functions of Trx-1, which depend on the Cys32 and Cys35, can be subdivided into three different functions. The thioredoxin system acts as a H_2O_2-scavenging system and reduces H_2O_2 to H_2O (25). Beside its enzymatic activity as an oxidoreductase, Trx-1 directly interacts with other proteins by forming disulfide bridges such as the apoptosis signaling kinase I and vitamin D_3-upregulated protein 1 (Txnip, also named VDUP-1) (50, 71). Furthermore, Trx-1 translocates into the nucleus under specific stimuli and directly binds different transcription factors and, thereby, modulates their DNA-binding activity [*e.g.*, p53, NFκB, and AP-1 via Ref-1 (18, 20, 21, 67)]. Several studies demonstrated that the mitochondrial Trx-2 is important for apoptosis inhibition and cell growth (39, 45, 76). Recently, Trx-2 was also implicated to play a role in cardiovascular diseases (57). The mechanism, however, by which Trx-2 acts cardioprotective requires further investigation.

The incidence of coronary artery disease increases with age. Aging is one of the major independent risk factors for coronary artery disease. The functional integrity of the endothelial monolayer is essential to prevent vascular leakage and the formation of atherosclerotic lesions. Injury of the endothelial monolayer results in inflammatory remodeling of the vessel wall (48, 49). This process is characterized by invasion of inflammatory cells and proliferation of smooth muscle cells and leads to the development of atherosclerotic lesions (49). In the case of atherosclerosis, the relevant pathology occurs in the coronary arteries. The endothelial cells, which line these arteries, play an important role in the cascade of pathology, and

Cell Biology and Molecular Aging Research, Institute for Molecular Preventive Medicine, University of Duesseldorf, Duesseldorf, Germany.

these cells show profound changes with age (23, 26). However, the molecular mechanisms underlying the process of aging are not well understood. Recent studies suggested that oxidative stress is one major player for aging processes. Moreover, oxidative stress of the vascular wall is a hallmark of atherosclerosis. To defend themselves from oxidative damages, including oxidative and nitrosative stress, vascular cells possess antioxidative enzymes, including endothelial nitric oxide synthase (eNOS), superoxide dismutase, catalase and the thioredoxin system, in order to maintain intracellular levels of reactive oxygen species and reactive nitrogen species (40, 43).

Thus, this review will focus on the role of the thioredoxin system in cardiovascular cells and its role in age-related cardiovascular diseases.

The Thioredoxin System in Cardiovascular Cells

Role of the thioredoxin system in smooth muscle cells

The thioredoxin (Trx) system is highly conserved in almost all species from bacteria to higher eukaryotes (41). Several studies investigated the role for the Trx system and especially Trx-1 in smooth muscle cells. The major findings support the concept of an important function in smooth muscle cell proliferation. In human aortic vascular smooth muscle cells, adenoviral gene transfer of Trx-1 enhanced Trx-1 enzyme activity and significantly increased DNA synthesis (53). Moreover, several growth factors, such as platelet-derived growth factor and epidermal-derived growth factor, increase reactive oxygen species in smooth muscle cells and, thereby, increase proliferation (14, 58). Similarly Schulze *et al*. found that growth factors increase Trx-1 activity in smooth muscle cells (52). Thus, the authors speculate that increased levels of intracellular ROS induced by growth factors may change the binding partners for Trx-1 and induce a translocation of the protein into the nucleus, which could result into modulation of redox-dependent transcription. The hypothesis is further supported by Chyu *et al*. who reported that injury-induced medial vascular smooth muscle cell proliferation of inducible nitric oxide synthase deficient mice was significantly reduced compared with their wild-type littermates (6). An altered AP-1/Ref-1/Trx-1 signaling pathway in aortic smooth muscle cells from inducible nitric oxide synthase-deficient mice was identified as one important mechanism responsible for the reduced growth response. Moreover, a potential role in antioxidant protection against atherosclerosis was suggested for Trx-1 by Okuda *et al*. who demonstrated an intense expression of Trx-1 in the media in human coronary arteries (41). Interestingly, atherosclerotic lesions such as hypercellular lesions and fibrous plaques, which are known to produce various reactive oxygen species, highly expressed Trx-1, suggesting an important antioxidative defense mechanism for Trx-1 in atherosclerosis. In contrast, in smooth muscle cells from streptozotocin-treated rats, as a model of diabetes mellitus, Trx-1 activity was decreased. It has to be noted that in this model the expression of vitamin D3 upregulated protein 1 (Txnip) is increased (53) and therefore, binding of Txnip to Trx-1 is enhanced. Txnip is a Trx-1 interacting protein that inhibits Trx-1 function by binding to its redox-active cysteine residues, Cys32 and Cys35 (38). Another protective mechanism against increased reactive oxygen production induced by Trx-1 has been suggested by Wiesel *et al*. (68) In rat aortic vascular smooth muscle cells, Wiesel *et al*. showed that Trx-1 contributed to the lipopolysaccharide- and interleukin 1ß–induced heme oxygenase (HO)-1 expression mediated by increased AP-1-DNA-binding activity (68). Since the induction of HO-1 in response to cellular stress is believed to be an important protective mechanism, HO-1 represents another target of Trx-1 against increased ROS production.

Role of the thioredoxin system in cardiomyocytes

The second important cell type is the cardiomyocytes in the cardiovascular system. The signal transduction involving Trx-1 and the Trx system is rarely documented in cardiomyocytes. Trx-1 plays an important role in regulation of hemeoxygenase-1 (HO-1) and vascular endothelial growth factor (VEGF). Heme oxygenase (HO) enzymes catalyze the initial reaction in heme catabolism. HO-1 is a cytoprotective enzyme that degrades heme, a potent oxidant, to generate carbon monoxide, biliverdin (subsequently reduced to bilirubin), and iron. HO-1 is an inducible isoform that is upregulated by diverse stimuli, including inflammatory cytokines and factors that promote oxidative stress. HO-1 is cardioprotective in ischemia/reperfusion injury (35, 73), diabetes (33), acute myocardial infarction (32), and atherosclerosis (42). On a molecular level, HO-1 protein expression is upregulated in Trx-1-dependent manner in cardiomyocytes (27), demonstrating the important role for Trx-1 in cardioprotection. Besides the cardioprotective effects of Trx-1 via HO-1 and VEGF induction, Trx-1 promotes cardiomyocyte growth and inhibits apoptosis. Yoshioka *et al*. showed that overexpression of Trx-1 in cardiomyocytes induced protein synthesis in cardiomyocytes by [^{3}H] leucine uptake, demonstrating that increase in Trx protein levels can promote cardiomyocyte growth in the absence of hypertrophic stimuli (74). Overexpression of Trx-1 inhibited H_2O_2-induced apoptosis (66) and recombinant Trx-1 reduced adriamycin-mediated cardiac cytotoxicity (54). Moreover, 17β-estradiol inhibited H_2O_2- and angiotensin II-induced apoptosis in cardiomyocytes in a Trx-1-dependent manner (51), suggesting that Trx-1 might confer cellular defense by scavenging intracellular toxic reactive oxygen species.

Role of the thioredoxin system in endothelial cells

Trx-1 is ubiquitously expressed in endothelial cells (EC) (41). Several studies supported the concept that Trx-1 exerts antiapoptotic functions and is one of the major intracellular scavenging enzymes for H_2O_2 in endothelial cells. The mechanisms described for the anti-apoptotic function of Trx-1 depend either on the post-translational modification of Trx-1 itself or on a change in the binding partners of Trx-1, which will now be discussed in more detail. An important role for Trx-1 in apoptotic processes in endothelial cells was recently demonstrated by our group. We showed that the anti-apoptotic mechanisms of physiological concentrations of reactive oxygen species, which act as signaling molecules, depend on Trx-1 protein expression in human umbilical vein endothelial cells (16). One mechanism for the anti-apoptotic function of Trx-1 in endothelial cells was the post-translational modification of cysteine 69 in Trx-1 by nitric oxide. Therefore, binding of nitric oxide to cysteine 69 in Trx-1 increased the redox-regulatory activity, the ability to reduce intracellular reactive oxygen species and the anti-apoptotic function in endothelial cells (17). Saitoh *et al*.

demonstrated through a genetic screen for ASK1-binding proteins that Trx-1 binds to the N-terminus of the apoptosis signaling kinase 1 (ASK1) via the redox-active cysteines, cysteine 32 and 35 (4, 50). These findings were also demonstrated in endothelial cells. Binding of Trx-1 to ASK-1 inhibited ASK-1 activation and apoptosis induction in bovine aortic endothelial cells (31). These results suggest that association of Trx-1 with ASK1 through the redox-active cysteines is necessary for Trx-1 to inhibit ASK1-induced apoptosis in endothelial cells. Another protective mechanism induced by Trx-1 in microvascular endothelial cells was reported by Das *et al*. who presented that recombinant Trx-1 increased the protein expression of the antioxidative mitochondrial enzyme manganese superoxide dismutase, which catalyzes superoxide radical into H_2O_2 (7). Importantly, since other antioxidative enzymes including copper–zinc superoxide dismutase and catalase were not induced, the effect of Trx-1 on the mitochondrial manganese superoxide dismutase was specific (7). However, upon production of high levels of reactive oxygen species (ROS) from exogenous or endogenous sources, the redox balance is perturbed and endothelial cells are shifted into a state of oxidative stress (45). These excessive high concentrations of ROS directly caused oxidative damage of DNA, lipids, and proteins (13, 30, 43, 56). In endothelial cells, Trx-1 is degraded under conditions of oxidative stress in cathepsin D-dependent manner, which subsequently leads to apoptosis induction. Furthermore, Trx-1 induces angiogenic responses in endothelial cells. Incubation of human coronary aortic endothelial cells with Trx-1 significantly induced capillary-like tube formation. Moreover, resveratrol, a polyphenol compound and naturally occurring phytoalexin, which has been demonstrated to be cardioprotective, increased Trx-1 expression and induced capillary-like tube formation to a similar extent as Trx-1 (27). Finally, the angiogenic effect of sildenafil was attributed to the induction of thioredoxin-1 (Trx-1), hemeoxygenase-1 (HO-1) and VEGF (65).

These findings demonstrate antioxidant, anti-apoptotic and pro-angiogenic abilities of Trx-1 in endothelial cells.

Regulation of Trx-1 by shear stress

The most potent endogenous protective force for endothelial cells is provided by the blood flow itself (named shear stress). Indeed, *in vitro* exposure of endothelial cells to shear stress appears to be one of the most potent inhibitors of endothelial cell apoptosis induced by a variety of stimuli including oxidized lipids, ROS, inflammatory cytokines, and growth factor depletion (9, 10, 19). Most importantly, the occurrence of apoptotic endothelial cells overlaying human atherosclerotic plaques relates to the hemodynamic forces, with high incidence of apoptosis in areas with low or turbulent flow (61). Recently, it was demonstrated that shear stress increased Trx-1 activity in endothelial cells by increasing the amount of S-nitrosylated Trx-1 (22) and in aortic rings by reducing binding to Txnip (72). Overexpression of Trx-1 protects endothelial cells from nitrosative stress induced by excessive nitric oxide exposure by preventing loss of endothelial NO synthase (eNOS) activity (77). Another important mechanism, which accounts for the anti-inflammatory effects of shear stress, is the association of Trx-1 with apoptosis signaling kinase 1 (ASK1) and Txnip. Yamawaki *et al.* demonstrated that a disturbance in the equilibrium of Trx-1/ASK1/Txnip interaction importantly contributed to the activation of JNK and p38 kinase and VCAM1 expression (72), suggesting an important role of Trx-1 on inflammation in endothelial cells.

Taken into account that Trx-1 exerts protective functions on endothelial cells, smooth muscle cells and cardiomyocytes, it is a predictable consequence that Trx-1 should exert cardioprotective functions *in vivo*.

Trx-1 in Cardiovascular Diseases

In this section, the review will summarize studies demonstrating a role for Trx-1 in different animal models for cardiovascular diseases, including hypertrophy, ischemia/reperfusion, diabetes mellitus, and heart failure, respectively (Fig. 1).

Cardiac hypertrophy

The best described protective role for Trx-1 is in cardiac hypertrophy. Several studies support the concept that Trx-1 inhibits cardiac hypertrophy in animal models. Since Trx-1-deficient mice are embryonic lethal, transgenic mice had to be developed with a cardiac-specific overexpression. Yamamoto *et al*. generated transgenic mice with cardiac-specific overexpression of a dominant negative Trx-1 mutant in which the oxidoreductase activity is lost (70). In these mice the activity of endogenous Trx-1 was diminished. The transgenic animals exhibited cardiac hypertrophy with well-maintained LV function under baseline conditions and in response to pressure overload (70). Similar results were obtained by application of Trx-1 antisense into wild-type mice (70). The underlying molecular mechanisms are not completely understood. The antihypertrophic effects of Trx-1 were in part mediated by reactive oxygen species formation, since treatment with an antioxidant reduced cardiac hypertrophy in transgenic mice overexpressing a dominant negative Trx-1 (70). Another mechanism was supported by the study of Yoshioka *et al*. who demonstrated that cardiac hypertrophy induced by transaortic constriction increased endogenous

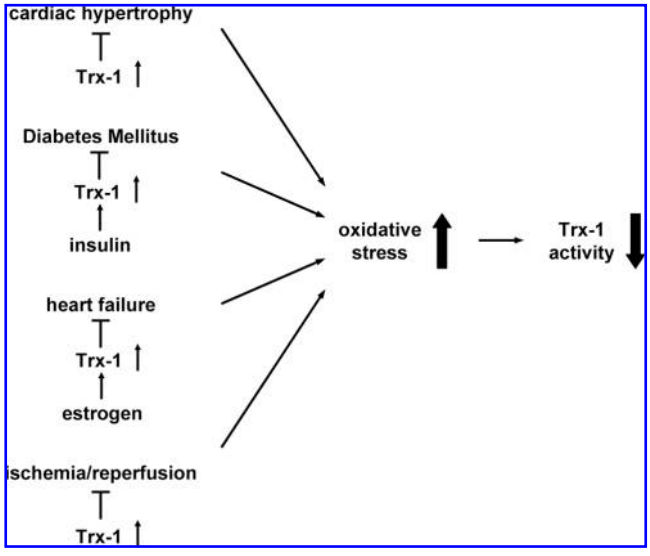

FIG. 1. Role of Trx-1 in cardiovascular diseases.

Trx-1 activity in mice, and cardiac hypertrophy is abrogated by gene transfer of adenoviral Txnip, supporting the concept that reactive oxygen species play a predominant role in cardiac hypertrophy (74). The upregulation of Trx-1 activity could be a defense mechanism to reduce hypertrophy-induced oxidative stress. This defense mechanism seems to be disrupted by Txnip, which inhibits Trx-1 activity by direct binding to the redox-active cysteines of Trx-1. Recently, a reactive oxygen species independent mechanism of Trx-1 was demonstrated in hypertrophy by Kuster *et al*. They showed that α-adreneric receptor-stimulated hypertrophy in ventricular myocytes was not dependent on the peroxidase activity of Trx-1, but on the posttranslational oxidative modification of thiols on Ras (29). Moreover, the hypertrophy-induced increase in reactive oxygen species was only abolished with catalase but retained with Trx-1(29). Therefore, it is tempting to speculate that dependent on the model how cardiac hypertrophy is induced Trx-1 may exert several functions (*e.g.*, scavenging reactive oxygen species or reducing oxidized cysteines). Recently, Ago *et al*. further elucidated the role of Trx-1 on cardioprotection by DNA microarray analysis. Trx-1 induced genes involved in oxidative phosphorylation and TCA cycle (1), suggesting that Trx-1 enhanced mitochondrial functions and thereby functional vitality of the cells. However, enhancing mitochondrial functions can also result in an increase in ROS formation. Thus, the level of reactive oxygen species induced in different models of cardiac hypertrophy may also importantly contribute to the functions and actions of Trx-1.

Ischemia/reperfusion

Human Trx-1 and to a lesser extent catalase inhibited the incidence of ventricular fibrillation during the reperfusion period in an isolated rat heart model. In contrast, superoxide dismutase failed to inhibit ventricular fibrillation, supporting the concept that occurrence of ventricular fibrillation depend on H_2O_2 and not on $O_2^{-\cdot}$ (2). In line with these findings, Turoczi *et al*. demonstrated in isolated working rat hearts that reperfusion of ischemic myocardium resulted in the down-regulation of Trx-1 expression and an increase in reactive oxygen species formation (62). Moreover, the cardioprotective role of Trx-1 in ischemia/reperfusion was further confirmed by data demonstrating that Trx-1 overexpressing mouse hearts displayed significantly improved post-ischemic ventricular recovery and reduced myocardial infarct size compared to their wild-type littermates (62). The role for Trx-1 in ischemia/reperfusion injury was further supported by the study of Kasuno *et al*. who demonstrated in renal ischemia/reperfusion that Trx-1 was retained in the medullary thick ascending limb, the area which is most vulnerable to ischemia/reperfusion injury. Overexpression of Trx-1 in mice abrogated reperfusion injury in the medullary thick ascending limb, indicating that Trx-1 may serve as a defense mechanism against ischemia/reperfusion injury in the kidney. Recently, in an *in vivo* model for ischemia/reperfusion injury, it was demonstrated that administration of human Trx-1 inhibited apoptosis induction in the ischemic/reperfused cardiac tissue. Human Trx-1 was detected throughout the myocardium, providing strong evidence for an uptake of Trx-1 by ischemic/reperfused cardiomyocytes. Furthermore, administration of human Trx-1 reduced myocardial infarct size. The underlying mechanism seems partially dependent on reduced p38 kinase activation. P38 kinase has been demonstrated by several studies to play an important role for ischemia/reperfusion injury (for review, see Ref. 3). Of note, the cardioprotective effect on ischemia/reperfusion injury was enhanced when human Trx-1 was S-nitrosylated prior to administration (60). This is in accordance with data from our group demonstrating that the redox-regulatory activity and the anti-apoptotic function of Trx-1 is increased when Trx-1 is post-translationally modified by nitric oxide on cysteine 69 in endothelial cells (18). Moreover, Kaga *et al*. demonstrated that treatment with resveratrol induced Trx-1, HO-1, and VEGF in the infarcted heart, leading to reduced infarct size and improved cardiac function (28), suggesting that Trx-1 regulates gene transcription through interaction with various transcription factors increasing the antioxidative, the anti-apoptotic and the proangiogenic capacity, depending on the cellular conditions.

Taken together, these findings strongly support that during ischemia/reperfusion the activity of the endogenous Trx system is reduced. This seems to result in an increase in reactive oxygen species, in induction of apoptosis, and therefore to damage of cardiomyocytes and myocardial infarction. Increasing the protein expression of Trx-1 and, thereby, the activity of the Trx system, by overexpression or pharmacological interventions, will protect against ischemia/reperfusion injury.

Diabetes mellitus

Diabetes mellitus is one of the major risk factors for vascular complications. One of the best described animal models for diabetes mellitus is the intraperitoneal injection of streptozotocin into adult rats. In this model, reactive oxygen species formation was drastically increased and vascular Trx-1 activity was decreased. Insulin treatment normalized the Trx-1 activity in these animals (53). Of note, the protein levels of Trx-1 were not different between the diabetic animals and their normal littermates. However, expression of Txnip, the Trx-1 inhibitory binding protein dramatically increased in diabetic animals (53), suggesting that increased binding of Txnip to Trx-1 may account for the reduction in Trx-1 activity in this animal model. Thus, diabetes mellitus is another disease which is accompanied by an increase in reactive oxygen species formation and with a deregulation of the Trx system.

Heart failure

Chronic heart failure is a complex syndrome, in which reactive oxygen species and inflammatory cytokines are important stressors that contribute to the pathogenesis. With respect to reactive oxygen species and inflammatory cytokines, it has to be noted that a C-terminally truncated Trx-1 (Trx80) exists that has cytokine characteristics. Trx80 and Trx-1 are both secreted from cells and show their co-cytokine activities with interleukins. The mechanism how Trx-1 and Trx80 are secreted is not fully understood. It has been reported that Trx-1 follows an ER/Golgi-independent route of secretion which is similar to that of interleukin-1β (for review, see Ref. 37). However, in contrast to interleukin-1β, Trx-1 could not be detected in intracellular vesicles, nor was the secretion processes dependent on ABC transporters. Most importantly, the redox state of Trx-1 did not influence its unconventional export (59). Secretion of Trx and Trx80 occur

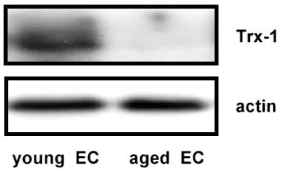

FIG. 2. Trx-1 protein levels are reduced in aged EC. Proteins from young and old EC were resolved by SDS PAGE. Immunoblots were performed with an anti-Trx-1 antibody (*upper panel*). Equal loading was confirmed with actin (*lower panel*).

in conditions of oxidative stress; thus, one may speculate that the secretion of Trx-1 and Trx 80 is a defence system against oxidative stress or other stressors. Indeed, Pekkari *et al*. demonstrated that Trx80 and IL-2 together were strongly synergistic to induce secretion of interferon-γ, and secreted Trx80 induced production of interleukin-12 and enhanced CD14 expression in monocytes (46, 47). These data suggest that Trx80-activated monocytes could be more efficient in phagocytosing apoptotic cells, invasive bacteria, or parasites via the CD14 receptor and the increased CD14 expression may also confer survival advantages for monocytes (46, 47). Moreover, two studies in patients investigated physiological stress response parameters including serum levels of Trx-1. Serum Trx-1 levels were significantly elevated in patients with chronic heart failure of NYHA class II to IV. Trx-1 elevation correlated positively with the severity of New York Heart Association functional class and with increased oxidative stress, but negatively with left ventricular ejection fraction (26, 28). These results suggest an association between Trx-1 secretion and the severity of heart failure. One possible explanation to support the positive association between serum Trx-1 levels and heart failure is that both inflammatory cells and myocytes have increased Trx-1 protein levels during myocarditis (55). Recently, Satoh *et al*. suggested that estrogen improved cardiac contractility and prevented progressive cardiac enlargement in a genetic mouse model of congestive heart failure. The underlying mechanism induced by estrogen included increase in the activity of the Trx system and inhibition of the NADPH oxidase activity, which led to a decrease in oxidative stress in the heart (51). Finally, the authors showed that the increase in the Trx system activity reduced ASK-1-mediated apoptosis (51). Thus, it is tempting to speculate that once again the Trx system acts as a defense mechanism against oxidative stress-induced injury.

Trx-1 and Aging

Aging is a major risk factor for cardiovascular diseases. It has been demonstrated that endothelium-dependent vasodilatation and the basal release of NO are reduced during aging (63, 75). On a molecular level, the reduction of bioavailable NO could be attributed to a downregulation of the phosphorylation and protein expression of eNOS (23). This is in accordance with *in vivo* studies demonstrating a downregulation of eNOS expression in aged rats (4) and in atherosclerotic human vessels (69). Moreover, the loss of eNOS protein expression is paralleled by a reduced Akt protein expression in aged endothelial cells, which may further reduce NO synthesis since Akt is required for eNOS activation (8, 12, 23).

In addition, an increase in ROS production was seen during the process of aging (for review, see Ref. 10). Indeed, there is growing evidence that an accumulation of age-related damage to mitochondria occurs that leads to enhanced ROS formation (11, 15). Enhanced superoxide could therefore directly react with NO to form peroxynitrite. Indeed, vascular peroxynitrite formation increased with age (64). Thus, one may speculate that activity or protein expression of the antioxidative enzymes of endothelial cells is reduced. Indeed, we found that in aged endothelial cells Trx-1 expression is dramatically reduced (Fig. 2). Moreover, application of shear stress was unable to increase eNOS expression in aged endothelial cells (23), further supporting a defect in the antioxidant defence during aging. It has also been demonstrated that endothelial cell apoptosis correlated with aging *in vitro* and *in vivo* (4, 23). The increased apoptosis induction by TNFα in aged endothelial cells was not inhibited by the application of shear stress (23), but was completely blunted by the overexpression of Trx-1 in aged endothelial cells (Fig. 3). These data suggest that Trx-1 can indeed improve endothelial function and rescue endothelial cells from age-induced disorders.

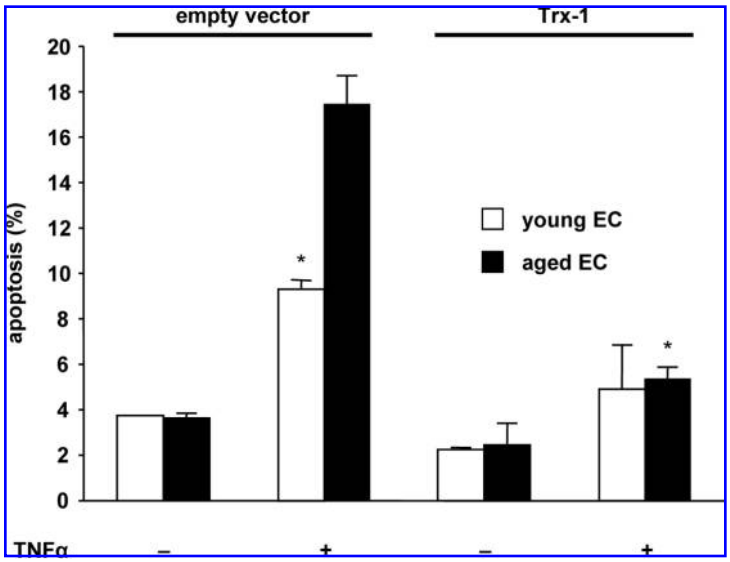

FIG. 3. Overexpression of Trx-1 inhibited TNFα-induced apoptosis in aged EC. Young and old EC were transiently transfected with Trx-1 and apoptosis was induced with 100 ng/ml TNFα. *<p 0.05 versus aged endothelial cells + TNFα.

Conclusions

This review has focused on the role of the Trx system and especially of Trx-1 in cardiovascular systems and in aging processes. Disturbance of the cellular redox balance has a major impact for the development of cardiovascular diseases. Improvement of Trx-1 expression and activity of the Trx system seems to have a cardioprotective effect in several cardiovascular disorders, as summarized in this review. Modulation of cellular redox balance by reactive oxygen species is critically important in the pathogenesis of the cardiovascular disorders, and Trx-1 exerts important protective roles against reactive oxygen species as well as against oxidation of reactive thiol groups in proteins. Moreover, aging, one of the major independent risk factors for cardiovascular diseases, led to an increase in intracellular oxidative stress and to a reduction of Trx-1 expression. Thus, it seems likely that increasing Trx-1 is a promising goal for clinical therapy.

Acknowledgments

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Address reprint requests to:
Judith Haendeler, Ph.D.
Molecular Cell & Aging Research
IUF (Institute for Molecular Preventive Medicine)
At the University of Duesseldorf gGmbH
Auf'm Hennekamp 50
40225 Duesseldorf, Germany

E-mail: juhae001@uni-duesseldorf.de

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