ANTIOXIDANTS & REDOX SIGNALING
Volume 9, Number 6, 2007

DOI: 10.1089/ars.2007.1529

Forum Review

Thioredoxin1 as a Negative Regulator of Cardiac Hypertrophy

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ABSTRACT

Excessive reactive oxygen species (ROS) play an important role in the development of cardiac hypertrophy. In contrast, antioxidants scavenge ROS, thereby maintaining the reduced environment of cells and inhibiting hypertrophy in the heart. Thioredoxin1 (Trx1) not only functions as a major antioxidant in the heart but also interacts with important signaling molecules and transcription factors, thereby attenuating cardiac hypertrophy. This review will discuss the molecular mechanisms by which Trx1 exerts antihypertrophic effects in the heart.
Antioxid. Redox Signal. 9, 679–687.

INTRODUCTION—THIOREDOXIN

Reactive oxygen species (ROS), generated by mitochondrial electron transport leakage (19, 37), NAD(P)H oxidases (12, 83), xanthine oxidase (76), and uncoupled nitric oxide synthases (87), have been implicated in the pathogenesis of cardiac hypertrophy and heart failure. On the other hand, antioxidants, such as glutathione, thioredoxin (Trx) (81, 93, 103), superoxide dismutase (19, 82), catalase (43, 53), glutathione peroxidase (59), and thioredoxin peroxidase (peroxiredoxin) (58), reduce ROS, thereby playing protective roles in the heart.

Trx is a major antioxidant in cardiac myocytes, along with the tripeptide glutathione (Glu–Cys–Gly) (31, 65, 69, 74, 103). In mammals, there are at least three members of the Trx family (99): Trx1, Trx2 (the mitochondrially localized form), and Sptrx (sperm Trx, also designated $p32^{TrxL}$); all of them have dithiol in the catalytic site (–Cys–Gly–Pro–Cys–; Cys at 32 and 35 in Trx1). Trx reduces thiol groups in redox-sensitive proteins by oxidizing itself to form a disulfide bond between the two cysteines in the catalytic site (32, 65, 69, 74; Fig. 1). The oxidized Trx is reduced and regenerated by Trx reductase and NADPH. Thus, Trx, Trx reductase, and NADPH, collectively called the Trx system, operate as a powerful protein disulfide oxidoreductase system (Fig. 1). Trx1 reduces peroxiredoxin, which catalyzes H_2O_2 to produce water (42) (Fig. 1). Since H_2O_2 is a stable ROS and is involved in the pathogenesis of various cardiovascular diseases (10, 12, 50), thus antioxidant effect of Trx1 should be an important function of Trx in the heart. In addition, Trx1 physically interacts with various intracellular signaling molecules and transcription factors, thereby regulating their activities. The cellular activity of Trx1 is regulated by various mechanisms, such as the total expression level, localization (nucleus or cytosol), protein–protein interaction, and post-translational modification (2). The purpose of this review is to summarize the cardiac function of Trx1, with a special emphasis on antihypertrophic effects of Trx1 in the heart.

TRX1 SUPPRESSES CARDIAC HYPERTROPHY IN MICE

Since Trx1 is a major antioxidant and because oxidative stress is implicated in the pathogenesis of cardiac hypertrophy, Trx1 is expected to suppress hypertrophy in the heart and vascular smooth muscle cells. However, Trx1 promotes cell growth in some cell types, such as cancer cells (8, 65, 74, 104). In order to clarify whether Trx1 promotes or inhibits cardiac hypertrophy *in vivo*, we made transgenic mice with cardiac-specific overexpression of Trx1 (Tg-Trx1) and catalytically defective Trx1 harboring the substitution of Cys32Ser/Cys35Ser (Tg-DN-Trx1) (103). Interestingly, overexpression of the catalytically inactive Trx1, which suppressed the activity of endogenous Trx1 and increased ROS in hearts, induced cardiac hypertrophy at

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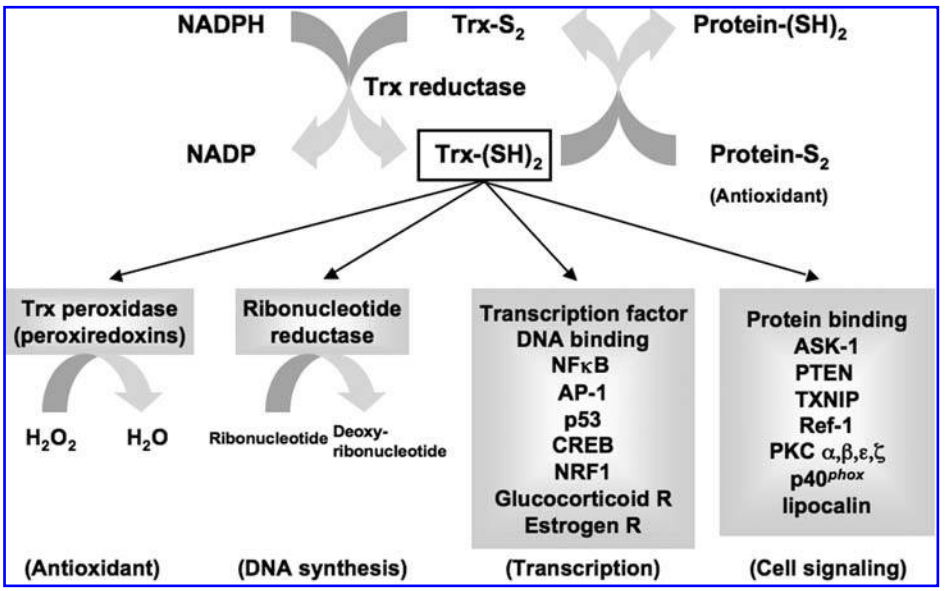

FIG. 1. Trx1 is an antioxidant having diverse functions. Besides its role as an antioxidant, Trx1 has a wide variety of functions, including stimulation of DNA synthesis, regulation of transcription factor activity, and modulation of intracellular signaling pathways.

baseline and exacerbated oxidative stress and hypertrophic responses induced by transverse aortic constriction (TAC) (103). On the other hand, baseline cardiac hypertrophy was never observed in Tg-Trx1 mice, and cardiac hypertrophy induced by TAC was significantly suppressed in Tg-Trx1 mice (103). These findings clearly indicate that Trx1 suppresses cardiac hypertrophy both at baseline and under stresses.

THE MODES OF ANTIHYPERTROPHIC EFFECTS OF TRX1

Increasing lines of evidence suggest that cardiac hypertrophy is regulated not only by positive regulators, such as mechanical forces and autocrine/paracrine factors, but also by endogenous negative regulators of cardiac hypertrophy (23). The negative regulators may be classified broadly into two groups according to their timing of activation (23) (Fig. 2). The first group of negative regulators is always active and suppresses cardiac hypertrophy even at baseline (constitutive). Importantly, their expression and/or activity can be suppressed by hypertrophic stimuli. This group of molecules includes GSK3β, class II histone deacetylases (HDACs), and peroxisome proliferator activated receptors (PPARs) (23). Molecules belonging to the other group are characterized by the fact that their expression is normally low, but is induced following hypertrophic stimulation (inducible). These molecules act as negative feedback regulators, and include ANP/BNP, ICER, SOCS3, MCIP, S100β, and PICOT (23, 40).

Judging from available experimental results, Trx1 is an endogenous negative regulator of cardiac hypertrophy with properties of both constitutive and inducible types. In the absence of stresses, a reduced form of Trx1 binds to and negatively regulates some intracellular signaling molecules which positively mediate cardiac hypertrophy, such as Ras, apoptosis signal-regulating kinase-1 (ASK-1), and phosphatase and

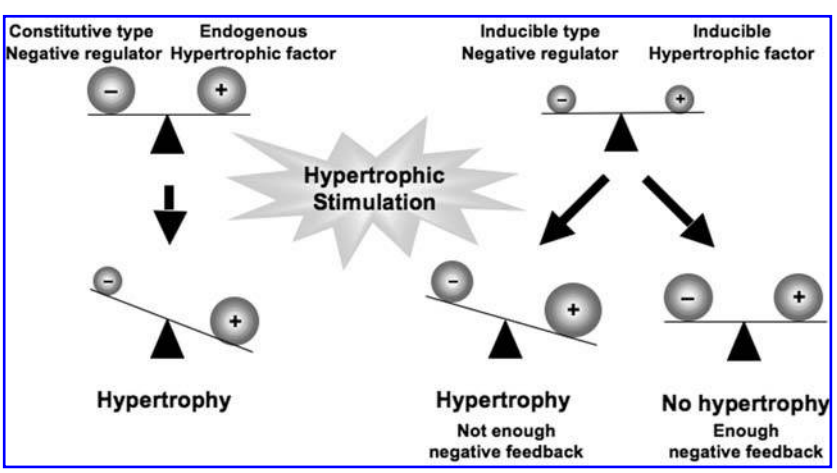

FIG. 2. Models of negative regulators of cardiac hypertrophy. Negative regulators of cardiac hypertrophy are classified into two groups. The constitutive negative regulator is always active under normal conditions, thereby persistently blocking the development of cardiac hypertrophy. However, it is suppressed in the presence of hypertrophic stimuli, and removal of the negative constraint leads to cardiac hypertrophy. The inducible negative regulator is upregulated in the presence of hypertrophic stimuli and functions as a negative feedback regulator. If the activity of the inducible negative regulator is enough to counteract the stimulus, cardiac hypertrophy may be completely suppressed.

TABLE 1. MOLECULAR AND PATHOPHYSIOLOGIC REGULATION OF TRX1 EXPRESSION

Upregulators	*References*	*Comments*
TNFα	65, 68	
$TGF\beta_1$/Smad7	5	
Estrogen	17, 51, 57	
Prostaglandin E1	102	
Geranylgeranylacetone	28, 29, 71	A natural plant constituent, an anti-ulcer drug
Tamocapril	105	An angiotensin-converting enzyme
Resveratrol	41	A polyphenolic compound, a major component of red grapes
Sulforaphane	90	A natural isothiocyanate that is highly concentrated in broccoli sprouts
tert-Butylhydroquinone (tBHQ)	45	Major metabolites of butylated hydroxyanisole
Adriamycin	81	An anti-cancer drug
cis-Diammine-dichloroplatinum	79	CDDP, an anti-cancer drug
Suberoylanilide hydroxamic acid (SAHA), MS-275	94	Histone deacetylase inhibitor only in normal cells (see below)
TPA (PMA)	48	Phorbol ester, a PKC activator
H_2O_2	22, 77	Low conc. (10 and 50 μ*M*) of H_2O_2 for 6 h
cAMP	102	Forskolin, an activator of adenylate cyclase dibutylyl cAMP, a cyclic AMP analog
Nitric oxide (cGMP)	4	
UV/radiation	16, 33, 77	
Heat shock	52	HSF2-dependent
Hypertrophy (pressure overload)	103	
Heart failure	39, 46	Plasma in patients
Ischemia/reperfusion	13	
Myocarditis, cardiomyopathies	66	
Hypoxia/ischemia	24, 64, 86	Plasma in patients with myocardial infarction/brain around injured region
Atherosclerotic plaques	70, 85	
Exercise	84	Peripheral blood mononuclear cells
Downregulators	*References*	*Comments*
Cathepsin D	21	Protein degradation
H_2O_2	21	Protein degradation at 100 μ*M* H_2O_2 for 6 h: mRNA levels are not changed.
Suberoylanilide hydroxamic acid (SAHA)	9	Histone deacetylase inhibitor only in transformed cells
cis-Diammine-dichloroplatinum	93	CDDP, anti-cancer drug
Hypertension	91	Spontaneously hypertensive rats (SHR) Stroke-prone SHR (SHRSP)

tensin homolog (PTEN) (see below), thereby constitutively suppressing cardiac hypertrophy. However, under pathological conditions, which are often accompanied by enhanced ROS generation, Trx1 is oxidized to form a disulfide bond between the two cysteines in the catalytic site and thus inactivated (32, 65, 69, 74). Additional ROS-mediated modifications, such as a disulfide bond between Cys-62 and Cys-69, decrease the accessibility of Trx1 to Trx reductase (98). A mixed disulfide bond between Cys-73 and glutathione (11) also attenuates Trx1 activity. ROS may also promote degradation of Trx1 through a cathepsin D-dependent mechanism (21). Inactivation of Trx1 by these post-translational modifications elicits direct activation of the Trx1-interacting molecules, thereby leading to cardiac hypertrophy. Thus, Trx1 suppresses cardiac hypertrophy as a constitutive negative regulator in the unstimulated heart, and inactivation of Trx1 could be a mechanism mediating cardiac hypertrophy.

Importantly, Trx1 expression is further enhanced under stressed conditions, such as pressure-overload (103), ischemia (64, 93), and cardiac failure (39, 46). The promoter of the *trx1* gene contains a series of stress-responsive elements, such as oxidative responsive element (89), antioxidant responsive element (44) and heat shock responsive element (52). It has been shown that a wide variety of stresses induce Trx1 expression in many cell types (Table 1). It should be noted that some molecules induce Trx1 expression in some cases but suppress it in others: the difference may depend on cell types, cell conditions, or strength of stimulation. Trx1 upregulated by stresses functions as a negative feedback regulator against many cellular responses (23, 65), including TAC-induced cardiac hypertrophy (103). Because upregulated Trx1 is translocated into the nucleus in response to some stresses, Trx1 may function not only in the cytosol but also in the nucleus to suppress cardiac hypertrophy (27, 67). Thus, in the

following, we will discuss both cytoplasmic and nuclear mechanisms by which Trx1 inhibits cardiac hypertrophy.

TRX1 TARGETS IN THE CYTOSOL/PLASMA MEMBRANE

Ras, a small GTP-binding protein

Ras has a redox-sensitive cysteine at residue 118. ROS, produced upon hypertrophic stimuli, such as angiotensin II and stretch, oxidize the thiol group in the cysteine to form a mixed disulfide bond with glutathione (S-SG; glutathionylation). Since Cys-118 is involved in the interaction with the guanine nucleotide, its redox modification could directly affect the exchange of GTP/GDP, thereby regulating activity of Ras (1, 73). The enhanced Ras-mediated signaling induces a hypertrophic response in the heart (101). Trx1 keeps Ras in the reduced and inactive state, thereby suppressing cardiac hypertrophy both in mice (103) and in adult rat ventricular myocytes (49) (Fig. 3).

ASK-1, a MAP kinase kinase kinase

Apoptosis signal-regulating kinase 1 (ASK-1), a serine/threonine kinase upstream of p38/JNK (36), plays a critical role in mediating apoptosis and hypertrophy in the heart (38). The reduced form of Trx1 physically interacts with ASK-1 and suppresses its kinase activity (78). Trx1 may also promote degradation of ASK-1 by ubiquitination (55). In response to hypertrophic stimuli, increased production of ROS oxidizes Trx1 and sequesters it from ASK-1, which would then be activated (78), leading to cardiac hypertrophy and apoptosis (30) (Fig. 4).

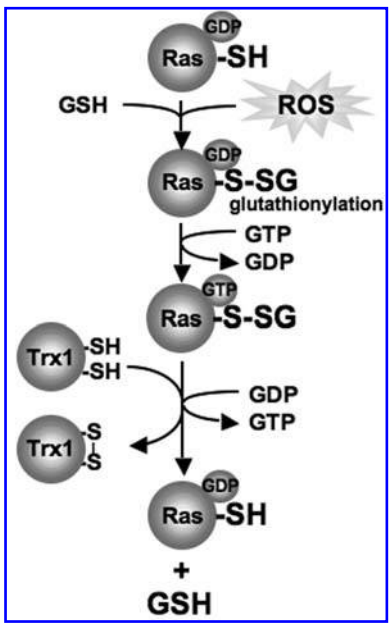

FIG. 3. ROS-mediated activation of Ras. ROS induce glutathionylation of Ras, which appears to increase the affinity of Ras for GTP, thereby activating Ras. Trx1 keeps Ras in a reduced and inactive state.

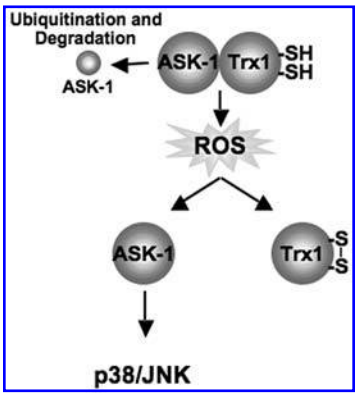

FIG. 4. ROS-mediated activation of ASK-1 through oxidation of Trx1. The reduced form of Trx1 interacts directly with ASK-1, inhibits its activity, and promotes degradation of ASK-1 through an ubiquitin-mediated mechanism. ROS oxidize Trx1 and sequester Trx1 from ASK-1, which would then be activated.

PI3K/Akt and PTEN

The PI3K/Akt pathway plays an important role in determining cell size, and exerts both growth-promoting and anti-apoptotic effects in many cell types (14, 80). In the heart, this signaling pathway is likely to mediate physiological hypertrophy, such as exercise-induced hypertrophy, rather than pathological hypertrophy, such as pressure overload-induced hypertrophy (61, 97). DeBosch *et al*. (15) recently reported, using *akt1*$^{-/-}$ mice, that Akt-mediated signaling antagonizes, rather than mediates, pathological hypertrophy. PTEN is a lipid phosphatase that attenuates the activity of the PI3K/Akt pathway (63). PTEN has a critical cysteine at residue 212 in the C2 lipid-binding domain. It is reported that Trx1 forms a disulfide bond with the cysteine of PTEN through Cys32 in its catalytic site, leading to attenuated phosphatase activity of PTEN and activation of the PI3K/Akt signaling pathway in NIH3T3 cells (63) (Fig. 5). Recent evidence

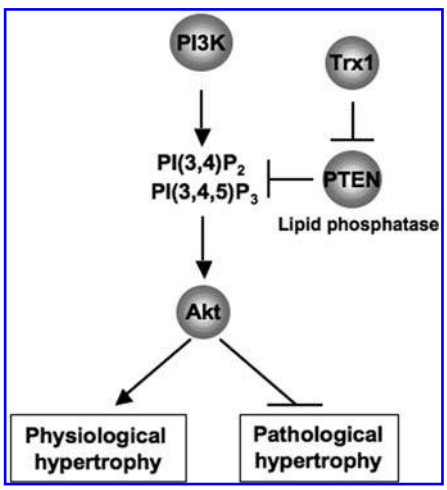

FIG. 5. Mechanism of activation of Akt through inhibition of PTEN by Trx1. Trx1 interacts directly with PTEN, and inhibits its lipid phosphatase activity, thereby activating Akt.

suggests that the PI3K/Akt/PTEN signaling complex is localized not only in the cytosol but also in the nuclear compartment (54). The Akt localized in the nucleus antagonizes hypertrophy of cardiac myocytes (92). In addition, ischemic preconditioning induces nuclear translocation of Trx1, which may stimulate cell survival signals through PI3K/Akt in the nucleus (56). Although it remains unknown as to how Trx1 affects the activity of nuclear PTEN in cardiac myocytes, Trx1 may activate the PI3K/Akt pathway in the nucleus through inhibition of PTEN, which in turn may attenuate pathological hypertrophy, as observed in Tg-Trx1 mice (103). At present, the causative role of Trx1 in mediating physiological hypertrophy remains to be shown. Therefore, it will be interesting to test whether upregulation of Trx1 and subsequent activation of Akt are involved in the development of exercise-induced cardiac hypertrophy.

TRX1 TARGETS IN THE NUCLEUS

Although Trx1 has no apparent nuclear localization signals, it is translocated into the nucleus in response to stresses, thereby modulating the activity of transcription factors (26, 27, 60, 88, 100). The molecular mechanism by which Trx1 is actively transported into the nucleus is not fully understood. Because Trx1 interacts with importin α either directly (20) or indirectly through Trx1-binding protein-2 (TBP-2) TXNIP, a Trx1-interacting protein (67), the nuclear translocation of Trx1 may be mediated by these molecules. Our preliminary results suggest that significant levels of Trx1 are localized in the nucleus of cardiac myocytes even under unstimulated conditions. Thus, it is speculated that regulation of nuclear transcription factors by nuclear Trx1 may play a significant role in mediating its antihypertrophic actions. To identify the target molecules transcriptionally regulated by Trx1, we conducted DNA microarray analysis using Tg-Trx1 mouse hearts (3).

Genes transcriptionally upregulated by Trx1

Trx1 enhances the transcriptional activity of nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) in some cells, including HeLa and COS-7 cells (26, 27, 60, 100). Since both NF-κB and AP-1 are related to cardiac hypertrophy (47, 75), one might expect that NF-κB and AP-1 would be activated in Tg-Trx1 mice, leading to cardiac hypertrophy. However, according to our DNA microarray analyses and subsequent transcription factor binding site (TFBS) analyses, specific binding sequences for these transcription factors were not frequently found in the promoter regions of the genes that are either up- or down-regulated in Tg-Trx1 mouse hearts (3). Thus, it is unlikely that Trx1 increases the transcriptional activity of NF-κB and AP-1 in cardiac myocytes. In addition, the microarray analysis showed that a greater number of genes are downregulated rather than upregulated when a higher-fold change is used as a cut-off (3). This observation suggests that Trx1 does not induce global upregulation of transcriptional mechanisms in the heart. It remains to be investigated whether the downregulated genes with high-fold changes are involved in the antihypertrophic actions of Trx1.

The DNA microarray analysis also revealed that PPARγ coactivator-1α (PGC-1α) and a series of genes related to oxidative phosphorylation and the TCA cycle were upregulated in the Tg-Trx1 mouse heart (3) (Fig. 6). Consistently, cAMP response element binding protein (CREB), a transcription factor known to upregulate PGC-1α (25), and nuclear respiratory factor 1 (NRF1) were identified as transcription factors whose activity is enhanced by Trx1 in the heart (3). Since Akt phosphorylates/activates both CREB and NRF1 (62, 72), and because Trx1 activates Akt through inactivation of PTEN

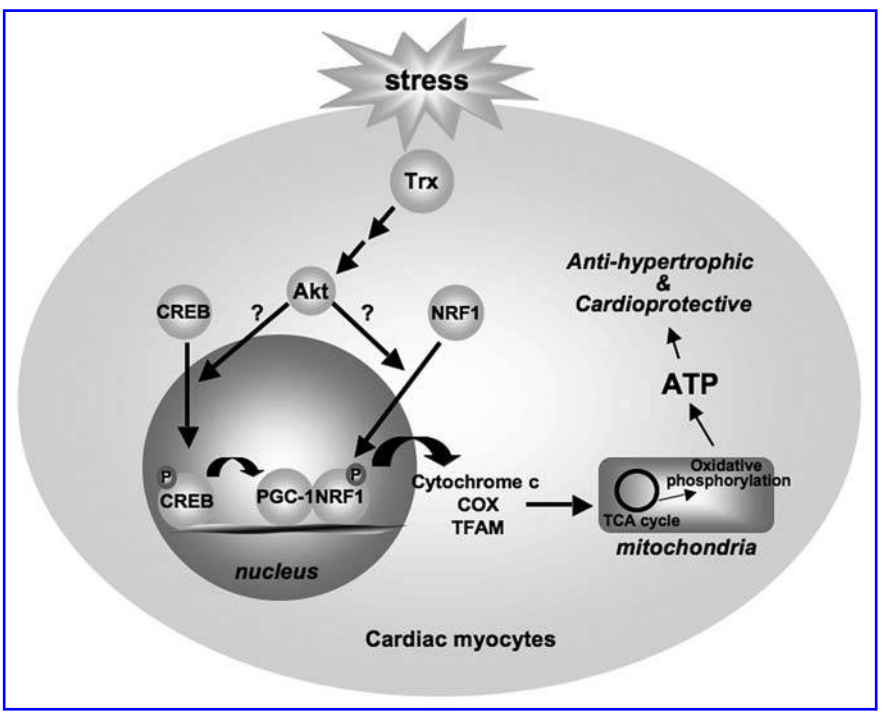

FIG. 6. Transcriptional induction of mitochondrial genes by Trx1. Akt, activated by Trx1 (possibly through PTEN inhibition), may phosphorylate CREB and NRF1 and induce nuclear translocation. CREB upregulates expression of PGC-1α, a critical coactivator of NRF1. NRF1 and PGC-1α induce expression of mitochondrial genes related to oxidative phosphorylation, the TCA cycle, and mitochondrial transcription factor A (TFAM), all of which, in turn, enhance mitochondrial functions.

(63), Trx1 may stimulate the transcriptional activity of CREB and NRF1 through Akt-induced phosphorylation of these transcription factors (Fig. 6). PGC-1α and NRF-1, major regulators of mitochondrial biogenesis and respiration, play an important role in maintaining the normal cardiac metabolism (18, 35). During the development of cardiac hypertrophy, the metabolic process to supply acetyl-CoA, the energy source of the TCA cycle, shifts from fatty acid oxidation to glucose-mediated metabolism (6, 95), and downregulation of PGC-1α during hypertrophy may account for the metabolic switch (7, 18, 34, 35). Thus, Trx1 may protect the heart from various stresses, such as hypertrophy and ischemia/reperfusion, by maintaining mitochondrial function through activation of CREB and subsequent upregulation of PGC-1α/NRF1 (Fig. 6).

CONCLUSION

Trx1 has a wide variety of cellular functions, not only as an antioxidant but also as a regulator of diverse signaling pathways through direct interaction with intracellular signaling molecules and transcription factors. Through these functions, Trx1 appears to prevent the development of cardiac hypertrophy under both basal and stimulated conditions. Trx1 is a promising molecule for use in clinical therapy, because it is of small size and structurally stable, and can function both intracellularly and extracellularly, which would allow administration of Trx1 either directly into the myocardium or into the coronary circulation. Furthermore, Trx1 functions as not only an antihypertrophic but also an anti-apoptotic regulator in the heart. It should be noted, however, that administration of Trx1 could potentially stimulate cancer through its growth-promoting and/or anti-apoptotic effects (96). In order to alleviate such potential problems, the detailed downstream molecular mechanism by which Trx1 confers advantages specifically to the heart should be identified. Further investigations are needed for us to apply our knowledge regarding the potentially salutary effects of Trx1 to treatment for cardiovascular patients.

ACKNOWLEDGMENTS

The authors thank Daniela Zablocki for critical reading of the manuscript. This work was supported in part by U.S. Public Health Service Grants HL 59139, HL67724, HL67727, HL69020, and HL 73048 and by the American Heart Association grant 0340123N. TA is supported in part by a Research Fellowship from the Uehara Memorial Foundation, Japan.

ABBREVIATIONS

AP-1, activator protein-1; ASK-1, apoptosis signal-regulating kinase 1; CREB, cAMP response element binding protein; HDAC, histone deacetylase; NF-κB, nuclear factor κB; NRF1, nuclear respiratory factor 1; PGC-1α, PPARγ coactivator-1α; PPAR, peroxisome proliferator-activated receptor; PTEN, Phosphatase and Tensin homolog; ROS, reactive oxygen species; TAC, thoracic aortic constriction; TFBS, transcription factor binding site; Tg-Trx1, transgenic mice with cardiac specific thioredoxin1-overexpression; Trx, thioredoxin; TXNIP, thioredoxin-interacting protein.

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Date of first submission to ARS Central, December 6, 2006; date of acceptance, January 13, 2007.

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