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Mini Review

Thioredoxin and Its Role in Premature Newborn Biology

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ABSTRACT

Thioredoxin (Trx) is a redox-active protein that has been shown to regulate various cellular processes due to its thiol–disulfide exchange reaction. It has antioxidant properties and also induces the expression of critical antioxidant enzymes such as manganese superoxide dismutase. Trx along with thioredoxin reductase and peroxiredoxins forms a complete system similar to the glutathione system, but with different and divergent functions. This review is a mini-update on key advances in the role of Trx in signal transduction and premature newborn biology. In addition, this mini-update also reviews recently reported prooxidant properties of Trx that relate to anthracycline redox cycling. *Antioxid. Redox Signal.* 7, 1740–1743.

INTRODUCTION

REDOX CONTROL OF CELLULAR FUNCTIONS has become a focus of intensive research in the past few years (3–5, 7, 8, 11, 28, 29, 41, 45, 46). Redox homeostasis of eukaryotes is required to be maintained for optimal metabolic activities (8, 11, 13). Therefore, cells continuously interact with their environment by sensing and responding to stress conditions using complex signaling cascades. For example, birth of an aerobic organism is a significant oxidative stress due to sudden exposure of the newborn to a relatively higher oxidative environment (21% O_2) than that present in the uterus (>3% O_2). Although birth is a physiological process, it involves exposure of the newborn to an oxidative stress condition (4, 11) due to growth and development of the fetus in a relatively hypoxic environment. Therefore, a wide array of antioxidant systems develops during the third trimester of the fetal life that not only protect the newborn, but also allow them to more efficiently generate energy (4, 11).

There are two major redox systems of the cell, glutathione and thioredoxin (Trx), that have dominated research in the field of redox control (8). Trx has been more intensely studied in recent years than glutathione. Glutathione is considered a major redox buffer system of the cell that acts as a sink for reactive species oxygen (14, 24). In addition, glutathione is involved in detoxification via the glutathione transferase system. The glutathione peroxidase system detoxifies peroxides using reducing equivalents from glutathione (1). The Trx system is similar to the glutathione system, but has been shown to have more extensive cellular functions, in addition to its antioxidant properties (17, 28). Additionally, an increasing role of truncated Trx is being recognized in many cellular physiological functions (32). Most importantly, the role of Trx in signal transduction is emerging as a major research area similar to protein phosphorylation. In this review, I will discuss our current understanding of the role of Trx in signal transduction and regulation of gene expression. Additionally, I will discuss our current understanding of the role of Trx in premature newborn biology and the potential areas that need further investigation.

TRX IN SIGNAL TRANSDUCTION

Protein phosphorylation by kinases and dephosphorylation by phosphatases have been shown to regulate major cellular functions via transcription factor activation and gene expression (27, 43, 44). However, recently the importance of thiol-disulfide exchange reactions in the signal transduction and gene expression has been widely recognized as control mechanisms that drive various cellular signaling events. Be-

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sides its antioxidant properties, Trx is perhaps most widely recognized for its role in signal transduction, resulting in transcription factor activation and redox control of cellular functions.

The modulation of nuclear factor-κB (NFκB) activation by Trx via the thiol–disulfide exchange reaction is one of the first described roles of Trx in signal transduction (6, 9, 10, 25). An extensive review in this area has appeared recently (22, 34). Besides a simple thiol–disulfide exchange reaction, Trx has been shown to activate certain components of the MEKK1-JNK signaling pathway, resulting in IκB degradation and NFκB activation (6). These studies demonstrate a far greater role of Trx in signal transduction processes than that of a disulfide-reducing action. Nevertheless, disulfide-reducing action is extremely important in regenerating oxidized proteins, which could render many signaling proteins inactive. Catalytic sites on several enzymes contain critical –SH groups that are susceptible to oxidation during catalysis. Therefore, it is of paramount importance to regenerate oxidatively inactivated proteins, a major function of Trx due to efficient thiol–disulfide exchange reactions. The regulation of apoptosis signal-regulating kinase-1 activity by Trx (37, 45) provided a basis for transduction of redox information to translate into an executable signaling cue, and demonstrated a more relevant role of oxidation–reduction in signal transduction. Additionally, an important role of Trx in activator protein-1 activity has been shown to be mediated by Jab1 (Jun activation domain binding protein) interaction (18). Taken together, the coupling of thiol–disulfide exchange reaction with that of kinase-phosphatase dynamics provides a flexible and executable stress response signal. Therefore, Trx occupies a unique position in the signaling hierarchy of the eukaryotic cell.

Besides these important signal transduction roles of the Trx redox system, several functional roles have been delineated in various physiological processes that deserve mentioning in this review. The redox regulatory role of Trx in lung inflammation (5, 12, 30) and ischemic preconditioning (5, 26, 38, 40) has been extensively worked out and presented in two reviews. The role of Trx in the cardiovascular system has been dealt with in these reviews (38). In addition, the role of the oxidative process in aging and the ameliorating role of Trx in this process have been recently reviewed by Yoshida *et al.* (46). We have previously shown that Trx induces the expression of manganese superoxide dismutase (MnSOD), a critical inducible antioxidant enzyme of the mitochondria. Subsequently, other studies confirmed our finding and suggested that the antioxidant role of Trx is specifically due to its MnSOD-inducing property (2). Although it seems somewhat paradoxical that a reducing agent induces the expression of an antioxidant enzyme, it does demonstrate the crucial role of the redox state of the cell in signal transduction and gene expression. Therefore, induction of MnSOD by Trx is a critical event in the protection of cells and tissues against oxidative stress. These studies suggest that Trx specifically regulates gene expression by modulating signaling events in oxidative stress conditions. Additional studies have shown a protective role of Trx in decreasing brain damage and in attenuating the age-dependent biochemical alterations (16).

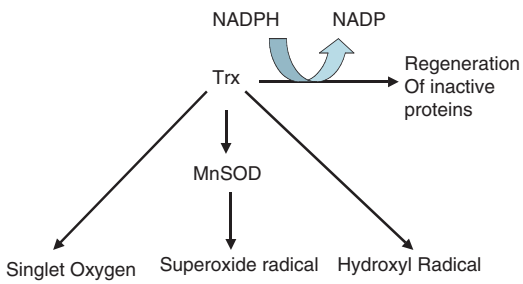

FIG. 1. Antioxidant and activation of oxidatively inactivated proteins. Trx itself quenches singlet oxygen and scavenges hydroxyl radical, but it does not scavenge superoxide anions. However, it induces a critical antioxidant enzyme, MnSOD. Thus, it is an ideal antioxidant that could neutralize all three forms of reactive oxygen species. In addition, by using reducing equivalents from NADPH, it can regenerate oxidatively inactivated proteins. This activation is a major player in the signal transduction and gene expression by Trx.

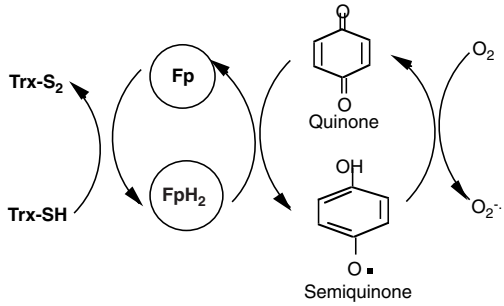

FIG. 2. Possible mechanism of Trx-induced redox cycling of anthracyclines. Redox cycling of the quinone moiety of anthracyclines is shown. The quinone is converted to a semiquinone radical by autooxidation in the presence of molecular oxygen and a flavoprotein enzyme (Fp). The reductive enzyme uses NADPH as the source of reducing equivalents. Reduced Trx (Trx-SH) acts as an electron donor for a bioreductive Fp enzyme that induces redox cycling of the quinone moiety of anthracyclines.

TRX A PROOXIDANT?

We have recently reported that Trx could augment the generation of superoxide radical in combination with anthracyclines (Fig. 1) (35, 36). In addition, Trx was found to increase plasmid DNA damage in combination with anthracyclines, and enhanced p53 DNA binding (35, 36). In the same study, it was also found that Trx alone could provide reducing equivalents to NADPH–cytochrome-p450 reductase that enhanced the activity of this enzyme, suggesting that Trx could enhance the redox cycling of anthracyclines (Fig. 2). In a redox system, both oxidation and reduction occur simultaneously: one molecule is oxidized by donating an electron, whereas the acceptor molecule is reduced by accepting the electron. Therefore, keeping this in perspective, Trx could donate an electron to anthracyclines either alone or with its reductase. This is the first study to demonstrate a prooxidant

role of Trx in anthracycline redox-cycling *in vitro,* as well as in intact cells (35, 36).

ROLE OF TRX IN PREMATURE AND NEWBORN BIOLOGY

Although major advances have been made in elucidating the role of Trx in various biological processes, its role in embryogenesis and newborn biology has not received the required attention. Trx plays a potentially important regulatory role in embryogenesis, early fetal life, and survival of newborn infants. The very fact that Trx knockout mice do not survive beyond embryogenesis attests to the critical role of Trx in early fetal development. Our previous review has covered the role of Trx in fetal and neonatal life in primates, as well as rodents. Additionally, the role of reactive oxygen species in premature and newborn diseases was extensively reviewed by O'Donovan and Fernandes (31). Besides the role of redox and Trx in diseases of the newborn, several excellent reviews presented the important role of redox molecules in fetal and neonatal life (7, 23, 33). Transition of fetal life from a relatively hypoxic environment to a more hyperoxic environment poses an acute oxidative stress in the neonatal life. One of the major complications of the premature lung is due to supplemental oxygen therapy that is routinely administered in critical care units. As the lung is a major target of oxygen therapy, lung physiology is critically altered in a hyperoxic environment. An excellent review by Asikainen and White was presented in the forum issue relating to the role of oxidants in premature and newborn biology (4).

A recent study has demonstrated that cytoplasmic thioredoxin reductase (TR) plays an essential role during embryogenesis, by showing that inactivation of TR1 leads to early embryonic lethality (19). Homozygous mutant embryos displayed severe growth retardation and failed to turn. However, a rather unique observation was that cardiomyocyte growth and proliferation were not affected in mice with heart-specific inactivation of TR1, and the heart of these mice developed normally and appeared healthy. A higher expression of Trx mRNA was observed in the developing cerebellum, olfactory bulb, and dentate gyrus of postnatal rat brains, suggesting an important role of Trx in central nervous system development (20). Additionally, the expression of Trx and TR was shown to be increased during mouse embryogenesis (21). A recent review has summarized the role of redox regulation in lung development and perinatal epithelial function (23). The role of redox state and oxidative stress in preeclampsia is one of the most intensely investigated areas of reproductive biology. This is a disorder of human pregnancy that is associated with premature delivery and fetal growth retardation. Continued research in this area further supports a pivotal role of oxidative stress and redox perturbations as a causal factor in preeclampsia (15, 39, 42).

Although some progress has been made in understanding the role of redox control and the Trx system in the growth and development of embryos, a significant amount of work is necessary to delineate the role of redox control in organogenesis and diseases of the premature and newborns.

ABBREVIATIONS

MnSOD, manganese superoxide dismutase: NFκB, nuclear factor-κB; TR, thioredoxin reductase; Trx, thioredoxin.

REFERENCES

1. Anders MW. Glutathione-dependent bioactivation of haloalkanes and haloalkenes. *Drug Metab Rev* 36: 583–594, 2004.
2. Andoh T, Chock PB, and Chiueh CC. The roles of thioredoxin in protection against oxidative stress-induced apoptosis in SH-SY5Y cells. *J Biol Chem* 277: 9655–9660, 2002.
3. Aro EM and Ohad I. Redox regulation of thylakoid protein phosphorylation. *Antioxid Redox Signal* 5: 55–67, 2003.
4. Asikainen TM and White CW. Pulmonary antioxidant defenses in the preterm newborn with respiratory distress and bronchopulmonary dysplasia in evolution: implications for antioxidant therapy. *Antioxid Redox Signal* 6: 155–167, 2004.
5. Das DK. Thioredoxin regulation of ischemic preconditioning. *Antioxid Redox Signal* 6: 405–412, 2004.
6. Das KC. c-Jun NH_2-terminal kinase-mediated redox-dependent degradation of IkappaB: role of thioredoxin in NF-kappaB activation. *J Biol Chem* 276: 4662–4670, 2001.
7. Das KC. Thioredoxin system in premature and newborn biology. *Antioxid Redox Signal* 6: 177–184, 2004.
8. Das KC and White CW. Redox systems of the cell: possible links and implications. *Proc Natl Acad Sci U S A* 99: 9617–9618, 2002.
9. Das KC, Lewis-Molock Y, and White CW. Activation of NF-kappa B and elevation of MnSOD gene expression by thiol reducing agents in lung adenocarcinoma (A549) cells. *Am J Physiol* 269: L588–L602, 1995.
10. Das KC, Lewis-Molock Y, and White CW. Thiol modulation of TNF alpha and IL-1 induced MnSOD gene expression and activation of NF-kappa B. *Mol Cell Biochem* 148: 45–57, 1995.
11. Dennery PA. Role of redox in fetal development and neonatal diseases. *Antioxid Redox Signal* 6: 147–153, 2004.
12. Ejima K, Layne MD, Carvajal IM, Nanri H, Ith B, Yet SF, and Perrella MA. Modulation of the thioredoxin system during inflammatory responses and its effect on heme oxygenase-1 expression. *Antioxid Redox Signal* 4: 569–575, 2002.
13. Engelhardt JF, Sen CK, and Oberley L. Redox-modulating gene therapies for human diseases. *Antioxid Redox Signal* 3: 341–346, 2001.
14. Fernandes AP and Holmgren A. Glutaredoxins: glutathione-dependent redox enzymes with functions far beyond a simple thioredoxin backup system. *Antioxid Redox Signal* 6: 63–74, 2004.
15. Harma M, Harma M, and Erel O. Oxidative stress in women with preeclampsia. *Am J Obstet Gynecol* 192: 656–657; author reply 657, 2005.
16. Hattori I, Takagi Y, Nakamura H, Nozaki K, Bai J, Kondo N, Sugino T, Nishimura M, Hashimoto N, and Yodoi J. Intravenous administration of thioredoxin decreases brain damage following transient focal cerebral ischemia in mice. *Antioxid Redox Signal* 6: 81–87, 2004.

17. Holmgren A. Antioxidant function of thioredoxin and glutaredoxin systems. *Antioxid Redox Signal* 2: 811–820, 2000.
18. Hwang CY, Ryu YS, Chung MS, Kim KD, Park SS, Chae SK, Chae HZ, and Kwon KS. Thioredoxin modulates activator protein 1 (AP-1) activity and p27Kip1 degradation through direct interaction with Jab1. *Oncogene* 23: 8868–8875, 2004.
19. Jakupoglu C, Przemeck GK, Schneider M, Moreno SG, Mayr N, Hatzopoulos AK, de Angelis MH, Wurst W, Bornkamm GW, Brielmeier M, and Conrad M. Cytoplasmic thioredoxin reductase is essential for embryogenesis but dispensable for cardiac development. *Mol Cell Biol* 25: 1980–1988, 2005.
20. Jeong DW, Kim EH, Kim TS, Chung YW, Kim H, and Kim IY. Different distributions of selenoprotein W and thioredoxin during postnatal brain development and embryogenesis. *Mol Cells* 17: 156–159, 2004.
21. Jurado J, Prieto-Alamo MJ, Madrid-Risquez J, and Pueyo C. Absolute gene expression patterns of thioredoxin and glutaredoxin redox systems in mouse. *J Biol Chem* 278: 45546–45554, 2003.
22. Kabe Y, Ando K, Hirao S, Yoshida M, and Handa H. Redox regulation of NF-κB activation: distinct redox regulation between the cytoplasm and the nucleus. *Antioxid Redox Signal* 7: 395–403, 2005.
23. Land SC and Wilson SM. Redox regulation of lung development and perinatal lung epithelial function. *Antioxid Redox Signal* 7: 92–107, 2005.
24. Li Y, Wei G, and Chen J. Glutathione: a review on biotechnological production. *Appl Microbiol Biotechnol* 66: 233–242, 2004.
25. Matthews JR, Wakasugi N, Virelizier JL, Yodoi J, and Hay RT. Thioredoxin regulates the DNA binding activity of NF-kappa B by reduction of a disulphide bond involving cysteine 62. *Nucleic Acids Res* 20: 3821–3830, 1992.
26. Miyamoto S, Kawano H, Sakamoto T, Soejima H, Kajiwara I, Hokamaki J, Hirai N, Sugiyama S, Yoshimura M, Yasue H, Nakamura H, Yodoi J, and Ogawa H. Increased plasma levels of thioredoxin in patients with coronary spastic angina. *Antioxid Redox Signal* 6: 75–80, 2004.
27. Morton S, Davis RJ, and Cohen P. Signalling pathways involved in multisite phosphorylation of the transcription factor ATF-2. *FEBS Lett* 572: 177–183, 2004.
28. Nakamura H. Thioredoxin as a key molecule in redox signaling. *Antioxid Redox Signal* 6: 15–17, 2004.
29. Nakamura H, Masutani H, and Yodoi J. Redox imbalance and its control in HIV infection. *Antioxid Redox Signal* 4: 455–464, 2002.
30. Nakamura T, Nakamura H, Hoshino T, Ueda S, Wada H, and Yodoi J. Redox regulation of lung inflammation by thioredoxin. *Antioxid Redox Signal* 7: 60–71, 2005.
31. O'Donovan DJ and Fernandes CJ. Free radicals and diseases in premature infants. *Antioxid Redox Signal* 6: 169–176, 2004.
32. Pekkari K and Holmgren A. Truncated thioredoxin: physiological functions and mechanism. *Antioxid Redox Signal* 6: 53–61, 2004.
33. Quintos-Alagheband ML, White CW, and Schwarz MA. Potential role for antiangiogenic proteins in the evolution of bronchopulmonary dysplasia. *Antioxid Redox Signal* 6: 137–145, 2004.
34. Raijmakers MT, Peters WH, Steegers EA, and Poston L. Amino thiols, detoxification and oxidative stress in pre-eclampsia and other disorders of pregnancy. *Curr Pharm Des* 11: 711–734, 2005.
35. Ravi D and Das KC. Redox-cycling of anthracyclines by thioredoxin system: increased superoxide generation and DNA damage. *Cancer Chemother Pharmacol* 54: 449–458, 2004.
36. Ravi D, Muniyappa H, and Das KC. Endogenous thioredoxin is required for redox-cycling of anthracyclines and p53-dependent apoptosis in cancer cells. *J Biol Chem* 2005 Sep 13; [Epub ahead of print] 2005.
37. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, and Ichijo H. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. *EMBO J* 17: 2596–2606, 1998.
38. Shioji K, Nakamura H, Masutani H, and Yodoi J. Redox regulation by thioredoxin in cardiovascular diseases. *Antioxid Redox Signal* 5: 795–802, 2003.
39. Tanir HM, Sener T, Inal M, Akyuz F, Uzuner K, and Sivri E. Effect of quercetine and glutathione on the level of superoxide dismutase, catalase, malonyldialdehyde, blood pressure and neonatal outcome in a rat model of pre-eclampsia induced by *N*ωG-nitro-L-arginine-methyl ester. *Eur J Obstet Gynecol Reprod Biol* 118: 190–195, 2005.
40. Tanito M, Nakamura H, Kwon YW, Teratani A, Masutani H, Shioji K, Kishimoto C, Ohira A, Horie R, and Yodoi J. Enhanced oxidative stress and impaired thioredoxin expression in spontaneously hypertensive rats. *Antioxid Redox Signal* 6: 89–97, 2004.
41. Ueda S, Masutani H, Nakamura H, Tanaka T, Ueno M, and Yodoi J. Redox control of cell death. *Antioxid Redox Signal* 4: 405–414, 2002.
42. Vanderlelie J, Venardos K, Clifton VL, Gude NM, Clarke FM, and Perkins AV. Increased biological oxidation and reduced anti-oxidant enzyme activity in pre-eclamptic placentae. *Placenta* 26: 53–58, 2005.
43. Weston CR, Lambright DG, and Davis RJ. Signal transduction. MAP kinase signaling specificity. *Science* 296: 2345–2347, 2002.
44. Whitmarsh AJ and Davis RJ. Signal transduction by MAP kinases: regulation by phosphorylation-dependent switches. *Sci STKE* 1999: PE1, 1999.
45. Yodoi J. Evolution of thioredoxin and redox signaling research: viewpoint. *Antioxid Redox Signal* 2: 629–630, 2000.
46. Yoshida T, Oka S, Masutani H, Nakamura H, and Yodoi J. The role of thioredoxin in the aging process: involvement of oxidative stress. *Antioxid Redox Signal* 5: 563–570, 2003.

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2. Rommy von Bernhardi , Jaime Eugenín . 2012. Alzheimer's Disease: Redox Dysregulation As a Common Denominator for Diverse Pathogenic Mechanisms. *Antioxidants & Redox Signaling* **16**:9, 974-1031. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
3. Ola Didrik Saugstad. 2010. Oxygen and oxidative stress in bronchopulmonary dysplasia. *Journal of Perinatal Medicine* **38**:6, 571-577. [CrossRef]
4. Eun-Jung Park, Jongheop Yi, Kyu-Hyuck Chung, Doug-Young Ryu, Jinhee Choi, Kwangsik Park. 2008. Oxidative stress and apoptosis induced by titanium dioxide nanoparticles in cultured BEAS-2B cells. *Toxicology Letters* **180**:3, 222-229. [CrossRef]
5. Eun-Jung Park, Jinhee Choi, Young-Kwon Park, Kwangsik Park. 2008. Oxidative stress induced by cerium oxide nanoparticles in cultured BEAS-2B cells. *Toxicology* **245**:1-2, 90-100. [CrossRef]
6. E PARK, K PARK. 2008. Induction of oxidative stress in human Chang liver cells by octachlorostyrene, the persistent and bioaccumulative toxicant. *Toxicology in Vitro* **22**:2, 367-375. [CrossRef]
7. E PARK, K PARK. 2007. Induction of reactive oxygen species and apoptosis in BEAS-2B cells by mercuric chloride. *Toxicology in Vitro* **21**:5, 789-794. [CrossRef]
8. Vittorio Calabrese, Eleonora Guagliano, Maria Sapienza, Mariangela Panebianco, Stella Calafato, Edoardo Puleo, Giovanni Pennisi, Cesare Mancuso, D. Allan Butterfield, Annamaria Giuffrida Stella. 2007. Redox Regulation of Cellular Stress Response in Aging and Neurodegenerative Disorders: Role of Vitagenes. *Neurochemical Research* **32**:4-5, 757-773. [CrossRef]
9. Norihiko Kondo , Hajime Nakamura , Hiroshi Masutani , Junji Yodoi . 2006. Redox Regulation of Human Thioredoxin Network. *Antioxidants & Redox Signaling* **8**:9-10, 1881-1890. [Abstract] [Full Text PDF] [Full Text PDF with Links]