Thioredoxin Reductase
Tiyoredoksin Redüktaz

Mini-Review Article / Kısa Derleme

Berivan Tandogan, N. Nuray Ulusu
Hacettepe University, Faculty of Medicine, Department of Biochemistry, Ankara, Turkey

ABSTRACT

Thioredoxin reductase (TrxR, EC 1.6.4.5) is a homodimeric flavoenzyme that catalyzed the reduction of the thioredoxin (Trx). It has been characterized in many bacteria and mammalian organism and categorized under two different types: bacterial and mammalian. Mammalian TrxRs contain an essential selenocysteine residue in the conserved C-terminal sequence. Mammalian TrxRs have three isoforms; cytosolic, mitochondrial and testis-specific. TrxR3, as testis-specific form, have different property than the other mammalian TrxRs. TrxR is involved in many cellular functions including DNA synthesis, redox signaling, antioxidative defence, selenium metabolism and regulation of apoptosis. Because of the many known functions, it is not surprising that this enzyme is a major subject of the many research. TrxR has been purified and characterized from a wide variety of species by using ion-exchange and affinity chromatographies. Notably, TrxR is a target enzyme for cancer drug research due to the relation with apoptosis. In this review we will present the intra- and extracellular biochemical functions of the enzyme and important medical applications in drug development.

Key Words
Thioredoxin reductase, molecular structure, biochemical function, and clinical importance.

ÖZET

Tiyoredoksin redüktaz tiyoredoksinin indirgenmesini katalizleyen homodimerik bir flavoenzimdir. Enzim birçok organizmada karakterize edilmiş ve bakteri ve memeli olmak üzere iki sınıfta toplanmıştır. Memeli TrxR C-ucu aminoasit dizisinde selenosistein içerir. Sitozolde, mitokondride ve testiste olmak üzere memeli TrxR' nin üç izoformu bulunur. TrxR' nin DNA sentezi, redoks sinyali, antioksidatif savunma, selenyum metabolizması ve apoptozun düzenlenmesinde önemli fonksiyonları vardır. Bu nedenle birçok araştırmaya konu olmaktadır. TrxR iyon değiştirici ve afinite kromatografileri kullanılarak çeşitli türlerden saflaştırılmış ve karakterize edilmiştir. Özellikle apoptozdaki fonksiyonundan dolayı kanser araştırmaları için hedef proteindir. Bu derlemede, enzimin hücre içi ve dışındaki biyokimyasal fonksiyonları ve ilaç geliştirme alanındaki medikal önemi sunulmaktadır.

Anahtar Kelimeler
Tiyoredoksin redüktaz, moleküler yapı, biyokimyasal fonksiyon ve klinik önemi.

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Correspondence to: N. Nuray Ulusu, Hacettepe University, Faculty of Medicine, Department of Biochemistry, 06100 Ankara, Turkey
Tel: +90312 324 5885 Fax: +90312 310 0588 E-Mail: nnulusu@hacettepe.edu.tr

INTRODUCTION

Thioredoxin reductase (TrxR, EC 1.6.4.5) is a widely distributed flavoenzyme that catalyzes the NADPH-dependent reduction of thioredoxin (Trx) and many other physiologically important substrates [1,2]. TrxR plays a crucial role in controlling the reduced intracellular redox environment, cellular growth, and apoptosis [3]. Substrate of TrxR, thioredoxin is responsible for maintaining proteins in their reduced state and also serves as electron donors for enzymes such as ribonucleotide reductases, thioredoxin peroxidases (peroxiredoxins) and methionine sulfoxide reductases. It has also co-cytokine and chemokine activities [4]. TrxR play a pathophysiologic role in chronic diseases such as rheumatoid arthritis, AIDS, and certain malignancies and inhibiting TrxR with drugs may lead to new treatments for human diseases [5].

TrxRs are widely expressed in many different tissues and cellular compartments including the nucleus [6,7]. Mammalian TrxRs expressed as three different isoforms; TrxR1 as cytosolic, TrxR2 as mitochondrial, and TrxR3 as testis-specific thiol regulator [8]. TrxR belongs to a family of homodimeric pyridine nucleotide-disulfide oxidoreductases. These enzymes use at least one nonflavin redox center to transfer electrons from reduced pyridine nucleotide to their substrate through FAD [9]. The mammalian TrxRs have mechanistic and sequence identity, including a conserved -Cys-Val-Asn-Val-Gly-Cys- redox catalytic site, to glutathione reductase (GR). The broad substrate specificity of mammalian TrxRs is due to a second redox-active site, a C-terminal -Cys-SeCys- (where SeCys is selenocysteine), that is not found in GR or bacterial-type TrxR [5] The selenocysteine residue (Sec), which essential for the catalytic cycle, is located on a flexible C-terminal arm of the protein and thus represents an attractive binding site for inhibitors [8]. Notably, several electrophilic agents that are used in anticancer treatment, are inhibitors of TrxR [10]. TrxR has been purified and characterized from a wide variety of prokaryotic and eukaryotic species by using anion-exchange chromatography and affinity chromatography on 2′5′-ADP-Sepharose 4B as well as GR [11-13].

Molecular Structure of Thioredoxin Reductase

Evolution has produced two forms of TrxR in nature: bacterial and mammalian. However this classification is not commonly used now. At the present time, classification of TrxR made according to its molecular weight; small TrxRs (subunit size approx. 35 kDa designated L-TrxR) and large TrxRs (subunit size approx. 55 kDa designated H-TrxR) [14-16]. Although these groups are members of the pyridine nucleotide disulfide oxidoreductases flavoproteins and they function as homodimers with each monomer possessing a FAD prosthetic group, a NADPH binding site and an active site comprising a redox-active disulfide, but the amino acid sequences and catalytic mechanisms of the two TrxR types are different [1]. All three mammalian enzymes TrxR1, 2 and 3 contain a reactive and solvent accessible selenocysteine residue [8].

Catalytic Mechanism and Substrate Specificity

TrxR catalyzes the reduction of the small redox protein thioredoxin by NADPH dependent mechanism, as shown below, where Tr(S2) is thioredoxin and Tr(SH)2 is reduced thioredoxin [17].

$$NADPH + H + Tr(S2) \Longleftrightarrow NADP+ Tr(SH)2$$

There is different catalytic mechanism between bacterial and mammalian TrxR as transferring the electrons from FAD-binding site to the protein. In the low Mw enzyme, after reduction of the disulfide by the flavin, the pyridine nucleotide domain must rotate with respect to the flavin domain. By this rotation, pyridine ring move into a new position as adjacent to the flavin ring and exposes the nascent dithiol for reaction with thioredoxin. In the high Mw enzyme, there is a third redox active group (a selenenylsulfide) that shuttles the reducing equivalent from the active site to the protein surface [1].

The substrate spectra of large and small TrxRs are different. TrxRs of higher eukaryotes have a wide substrate specificity that also reduces hydroperoxides, vitamin C or selenite, 5, 5′dithiobis-(2-nitrobenzoate), alloxan, dehydro-ascorbate,

selenodiglutathione, ebselen, S-nitrosoglutathione, alkylhydroperoxides, methylseleninate [4,18-24]. TrxR3 can reduce glutathione disulfide in addition to Trx. This enzyme has therefore been named TGR, indicating its thioredoxin/glutathione reductase activity [8].

Functions of Thioredoxin Reductase

The most important function of the TrxR is catalyzing the NADPH-dependent reduction of thioredoxins. Sulfhydryl groups of Trx have a variety of different functions in biochemical mechanisms and cellular regulation that is capable of regenerating proteins inactivated by oxidative stress [24,25]. The Trx system functions in synthesis of deoxyribonucleotides for DNA synthesis by acting hydrogen donor to ribonucleotide reductase [3,26]. Mammalian TrxRs can recycle dehydroascorbate to ascorbate and ubiquinone to ubiquinol by NADPH-dependent mechanism [27,28]. TrxR from mammalian cells such as calf thymus, calf liver, human placenta, and rat liver efficiently reduced both lipoic acid and lipoamide [29]. Reduced form of Trx is essentially for the formation of the active holoenzyme T7 DNA polymerase [30]. Trx has pleiotropic cellular effects, such as the control of proliferation, redox states and apoptosis, and is often upregulated in malignancy. It is able to regulate vascular endothelial growth factor levels and hence angiogenesis [31]. Trx plays an important role in the regulation of transcription factors and p53 maturation and oppositely affects NF-kappa B and AP-1 activation [32,33]. Trx system has been implicated in many aspects of hormone action and cytokine function [34].

Inhibitors of Thioredoxin Reductase

Mammalian TrxR contains selenocysteine which is a stronger nucleophile and a highly reactive amino acid. The reactivity of Sec is essential for the native catalytic activity of mammalian TrxR [35]. However, the presence of Sec in TrxR at an easily accessible C-terminal position renders the enzyme highly susceptible to irreversible inhibition. The enzyme is inhibited by many clinically used electrophilic compounds; nitrosoureas, aurothioglucose, retinoic acid derivatives arsenic trioxide, motexafin gadolinium, nitrous compounds, flavonoids, platinum and gold compounds [36,37]. Most irreversible inhibitors of TrxR act apparently via a reaction with one or more redox-active residues. Most of curcumin analogs were more potent TrxR inhibitors than natural curcumin. The action was caused by covalent modification of the redox-active residues Cys (497) and Sec (498) in TrxR [38]. The immunostimulatory dinitrohalobenzene compound irreversibly inhibits mammalian TrxR in the presence of NADPH. Inhibition of TrxR after reaction with dinitrohalobenzenes may play a major role in the inflammatory reactions provoked by these compounds [39]. Several quinoids such as diaziquone, doxorubicin, and the quinoneimine 2, 6-dichloroindophenol, were found to be inhibitors of the reduction of 5, 5′-dithiobis-2-nitrobenzoic acid by TrxR [40]. Thiols and selenols easily form complexes with heavy metal ions such as Hg^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+}, and Mn^{2+}. It has been shown that divalent metal ions such as Cd^{2+}, Ni^{2+}, Zn^{2+} have inhibitory effect on mammalian and yeast GR [41]. As GR and TrxR are structurally very similar, divalent metal ions may also inactivate TrxR.

Purification of Thioredoxin Reductase

TrxRs has been purified from a variety of sources, from bacteria to mammalian cells, show great similarity both in physical and kinetic parameters, with different purification folds and yields including rat liver, calf liver and thymus, Fasciola hepatica, bovine adrenal cortex [42-44]. Purification of TrxR is usually achived by ammonium sulphate fractionation [11], Sephadex G-50, DEAE-cellulose, CM-cellulose [42]. TrxRs and GR are belongs to the same oxidoreductase family. Because of this knowledge researchers used similar purification protocols for these enzymes. Both TrxR and GR have been purified very rapidly in high yield by employing 2′, 5′-ADP -Sepharose 4B as affinity columns [11-13]. The two reductases are then separated by hydrophobic chromatography and purified separately to homogeneity [45]. The rat liver mitochondrial TrxR shows a chromatographic behavior different from that of the cytosolic enzyme. The enzyme exhibits a behavior completely different from that of the cytosolic enzyme both on DEAE-cellulose and 2′, 5′-ADP Sepharose chromatography [46]. Mitochondrial TrxR and GR are partially overlapping when eluted from the DEAE-cellulose

column, while the cytosolic enzyme is completely separated from GR, which is eluted at lower salt concentrations [42].

Thioredoxin Reductase in Health and Disease

Expression and function of TrxR and the other oxidant and antioxidant enzymes are modulated by various pathological conditions, and therapeutic interventions. It has been showed that activity of TrxR decreased significantly in diabetic rat heart [47]. Glutathione and thioredoxin systems may participate in the cellular defense against oxidized LDL. Macrophage uptake of oxidized LDL induces a coordinated up-regulation of genes of these systems and this possibly modulates the development of atherosclerosis [48]. Redox Trx and TrxR activities correlated with the disease activity of rheumatoid arthritis patients. TrxR-1 was up-regulated in synovial cells of these patients and this protein suppresses hydrogen peroxide and inhibits apoptosis [49,50].

Human TrxR system is associated with cancer cell growth and anti-apoptosis process [51]. GSH and Trx metabolism are studied in several malign and benign breast diseases, cancer cell lines and various cancer types. All of these studies emphasizes the significance of this system in oxidative stress and its role in cancer, disease occurred by oxidative stress [52-54]. Trx can directly inhibit proapoptotic proteins such as apoptosis signal-regulating kinase 1 [37]. Mutations in the catalytic Sec residue of TrxR are leading to conformational disturb p53 and induction of apoptosis [33]. TrxR activity increase in tumor cells and stimulates their proliferation as well the phenotype changes [2]. TrxR1 deficient cancer cells lose self-sufficiency of growth, manifest a defective progression in their S phase and a decreased expression of DNA polymerase alpha. Thus, TrxR1 is critical for self-sufficiency in growth signals of malignant cells and acts largely as a pro-cancer protein [55].

CONCLUSION

Understanding the relations of the thioredoxin system with other metabolic pathways and their physiological significance is important for a future therapeutic approach. Trx system may in fact already be a target for widely used electrophilic anticancer agents, and additional inhibitors are in development. Because of this reason purification, characterization and understanding the new properties and functions of this enzyme is gaining importance in recent years. In particular, due to the many known roles in carcinogenic process and invasive phenotype of cancer, TrxR have been regarded as interesting targets for chemotherapy. It also may play a role in the pathogenesis of a number of diseases and the effects of clinically used drugs.

In conclusion development of new TrxR inhibitors is beneficial for preventing cancer, autoimmune diseases, and infectious diseases. The complete enzyme system will be major studying subject in future studies.

REFERENCES

[1] C.H. Williams, L.D. Arscott, S. Müller, B.W. Lennon, M.L. Ludwig, P.F. Wang, D.M. Veine, K. Becker, R.H. Schirmer, Thioredoxin reductase two modes of catalysis have evolved. Eur. J. Biochem., 267 (2000) 6110.

[2] P. Zagrodzki, Thioredoxin reductase--a new target for molecular medical investigations, Postepy. Hig. Med. Dosw., 56 (2002) 155.

[3] E.S. Arner, A. Holmgren, The thioredoxin system in cancer, Semin. Cancer Biol., 16 (2006) 420.

[4] E.S. Arner, A. Holmgren, Physiological functions of thioredoxin and thioredoxin reductase. Eur. J. Biochem., 267 (2000) 6102.

[5] D. Mustacich, G. Powis, Thioredoxin reductase. Biochem. J., 346 (2000) 1.

[6] B. Rozell, A. Holmgren, H.A. Hansson, Ultrastructural demonstration of thioredoxin and thioredoxin reductase in rat hepatocytes. Eur. J. Cell Biol., 46 (1988) 470.

[7] Q.A. Sun, L. Kirnarsky, S. Sherman, V.N. Gladyshev, Selenoprotein oxidoreductase with specificity for thioredoxin and glutathione systems. Proc. Natl. Acad. Sci. USA, 98 (2001) 3673.

[8] S. Urig, K. Becker, On the potential of thioredoxin reductase inhibitors for cancer therapy, Semin. Cancer Biol., 16 (2006) 452.

[9] A. Argyrou, J.S. Blanchard, Flavoprotein disulfide reductases: advances in chemistry and function Prog Nucleic Acid Res. Mol. Biol., 78 (2004) 89.

[10] K. Anestal, E.S. Arner, Rapid induction of cell death by selenium-compromised thioredoxin reductase 1 but not by the fully active enzyme containing selenocysteine, J. Biol. Chem., 278 (2003) 15966.

[11] G. Maggioli, L. Piacenza, B. Carambula, C. Carmona, Purification, characterization, and immunolocalization of a thioredoxin reductase from adult *Fasciola hepatica*, J. Parasitol., 90 (2004) 205.

[12] N.N. Ulusu, B. Tandoğan, Purification and kinetic properties of glutathione reductase from bovine liver. Mol. Cell. Biochem., 303 (2007) 45.

[13] B. Tandogan, N.N. Ulusu, Purification and Kinetics of Bovine Kidney Cortex Glutathione Reductase. Protein Pept Lett., 17 (2010) 667.

[14] M.L. Speranza, S. Ronchi, L. Minchiotti, Purification and characterization of yeast thioredoxin reductase. Biochim. Biophys. Acta., 327 (1973) 274.

[15] H. Bauer, V. Massey, L.D. Arscott, R.H. Schirmer, D.P. Ballou, C.H. Williams Jr., The mechanism of high Mr thioredoxin reductase from *Drosophila melanogaster*, J. Biol. Chem., 278 (2003) 33020.

[16] T.W. Gilberger, B. Bergmann, R.D. Walter, S. Müller, The role of the C-terminus for catalysis of the large thioredoxin reductase from *Plasmodium falciparum*. FEBS Lett., 425 (1998) 407.

[17] Z. Cheng, L.D. Arscott, D.P. Ballou, C.H. Williams Jr., The relationship of the redox potentials of thioredoxin and thioredoxin reductase from *Drosophila melanogaster* to the enzymatic mechanism: reduced thioredoxin is the reductant of glutathione in Drosophila, Biochemistry, 46 (2007) 7875.

[18] E.S. Arner, L. Zhong, A. Holmgren, Preparation and assay of mammalian thioredoxin and thioredoxin reductase, Methods Enzymol., 300 (1999) 226.

[19] A. Holmgren, C. Lyckeborg, Enzymatic reduction of alloxan by thioredoxin and NADPH-thioredoxin reductase, Proc. Natl. Acad. Sci. USA. 77 (1980) 5149.

[20] J.M. May, S. Mendiratta, K.E. Hill, R.F. Burk, Reduction of dehydroascorbate to ascorbate by the selenoenzyme thioredoxin reductase, J. Biol. Chem., 272 (1977) 22607.

[21] M. Bjornstedt, S. Kumar, A. Holmgren, Selenodiglutathione is a highly efficient oxidant of reduced thioredoxin and a substrate for mammalian thioredoxin reductase, J. Biol. Chem., 267 (1992) 8030.

[22] G.E. Arteel, K. Briviba, H. Sies, Function of thioredoxin reductase as a peroxynitrite reductase using selenocysteine or ebselen, Chem. Res. Toxicol., 12 (1999) 264.

[23] D. Nikitovic, A. Holmgren, S-nitrosoglutathione is cleaved by the thioredoxin system with liberation of glutathione and redox regulating nitric oxide, J. Biol. Chem., 271 (1996) 19180.

[24] S. Gromer, J.H. Gross, Methylseleninate is a substrate rather than an inhibitor of mammalian thioredoxin reductase. Implications for the antitumor effects of selenium, J. Biol. Chem., 277 (2002) 9701.

[25] A. Holmgren, Thioredoxin and glutaredoxin systems, J. Biol. Chem., 264 (1989) 13963.

[26] A. Koc, C.K. Mathews, L.J. Wheeler, M.K. Gross, G.H. Merrill, Thioredoxin is required for deoxyribonucleotide pool maintenance during S phase, J. Biol. Chem., 281 (2006) 15058.

[27] J.M. May, C.E. Cobb, S. Mendiratta, K.E. Hill, R.F. Burk, Reduction of the ascorbyl free radical to ascorbate by thioredoxin reductase, J. Biol. Chem., 273 (1998) 23039.

[28] T. Nordman, L. Xia, L. Björkhem-Bergman, A. Damdimopoulos, I. Nalvarte, E.S. Arner, G. Spyrou, L.C. Eriksson, M. Björnstedt, J.M., Olsson, Regeneration of the antioxidant ubiquinol by lipoamide dehydrogenase, thioredoxin reductase and glutathione reductase, Biofactors, 18 (2003) 45.

[29] E.S. Arner, J. Nordberg, A. Holmgren, Efficient reduction of lipoamide and lipoic acid by mammalian thioredoxin reductase, Biochem. Biophys. Res. Commun., 225 (1996) 268.

[30] S. Adler, P. Modrich, T7-induced DNA polymerase. Requirement for thioredoxin sulfhydryl groups, J. Biol. Chem., 258 (1983) 6956.

[31] A. Mukherjee, S.G. Martin, The thioredoxin system: a key target in tumour and endothelial cells, Br. J. Radiol., 81 (2008) 57.

[32] H. Schenk, M. Klein, W. Erdbrügger, W. Dröge, K. Schulze-Osthoff, Distinct effects of thioredoxin and antioxidants on the activation of transcription factors NF-kappa B and AP-1, Proc. Natl. Acad. Sci. USA, 91 (1994) 1672.

[33] P.B. Cassidy, K. Edes, C.C. Nelson, K. Parsawar, F.A. Fitzpatrick, P.J. Moos, Thioredoxin reductase is required for the inactivation of tumor suppressor p53 and for apoptosis induced by endogenous electrophiles, Carcinogenesis, 27 (2006) 2538.

[34] C. Biguet, N. Wakasugi, Z. Mishal, A. Holmgren, S. Chouaib, T. Tursz, H. Wakasugi, Thioredoxin increases the proliferation of human B-cell lines through a protein kinase C-dependent mechanism, J. Biol. Chem., 269 (1994) 28865.

[35] L. Zhong, A. Holmgren, Essential role of selenium in the catalytic activities of mammalian thioredoxin reductase revealed by characterization of recombinant enzymes with selenocysteine mutations, J. Biol. Chem., 275 (2000) 18121.

[36] J. Nordberg, E.S. Arner, Reactive oxygen species, antioxidants, and the mammalian thioredoxin system, Free Radic. Biol. Med., 31 (2001) 1287.

[37] K.F. Tonissen, G. Di Trapani, Thioredoxin system inhibitors as mediators of apoptosis for cancer therapy, Mol. Nutr. Food Res., 53 (2009) 87.

[38] Z. Liu, Z.Y. Du, Z.S. Huang, K.S. Lee, L.Q. Gu, Inhibition of thioredoxin reductase by curcumin analogs, Biosci. Biotechnol. Biochem., 72 (2008) 2214.

[39] J. Nordberg, L. Zhong, A. Holmgren, E.S. Arner, Mammalian thioredoxin reductase is irreversibly inhibited by dinitrohalobenzenes by alkylation of both the redox active selenocysteine and its neighboring cysteine residue, J. Biol. Chem., 273 (1998) 10835.

[40] B.L. Mau, G. Powis, Mechanism-based inhibition of thioredoxin reductase by antitumor quinoid compounds, Biochem. Pharmacol., 43 (1992) 1613.

[41] B. Tandoğan, N.N. Ulusu, The inhibition kinetics of yeast glutathione reductase by some metal ions, J. Enzyme Inhib. Med. Chem., 22 (2007) 489.

[42] M. Luthman, A. Holmgren, Rat liver thioredoxin and thioredoxin reductase: Purification and characterization, Biochemistry, 21 (1982) 6628.

[43] A. Holmgren, Bovine thioredoxin system. Purification of thioredoxin reductase from calf liver and thymus and studies of its function in disulfide reduction, J. Biol. Chem., 252 (1977) 4600.

[44] S. Watabe, Y. Makino, K. Ogawa, T. Hiroi, Y. Yamamoto, S.Y. Takahashi, Mitochondrial thioredoxin reductase in bovine adrenal cortex its purification, properties, nucleotide/amino acid sequences, and identification of selenocysteine, Eur. J. Biochem., 264 (1999) 74.

[45] V.P. Pigiet, R.R. Conley, Purification of thioredoxin, thioredoxin reductase, and glutathione reductase by affinity chromatography, J. Biol. Chem., 252 (1977) 6367.

[46] M.P. Rigobello, M.T. Callegaro, E. Barzon, M. Benetti, A. Bindoli, Purification of mitochondrial thioredoxin reductase and its involvement in the redox regulation of membrane permeability, Free Radic. Biol. Med., 24 (1998) 370.

[47] E. Tuncay, A.A. Seymen, E. Tanriverdi, N. Yaras, B. Tandogan, N.N. Ulusu, B. Turan, Gender related differential effects of Omega-3E treatment on diabetes-induced left ventricular dysfunction, Mol. Cell Biochem., 304 (2007) 255.

[48] D. Hagg, M.C. Englund, M. Jernas, C. Schmidt, O. Wiklund, L.M. Hulten, B.G. Ohlsson, L.M. Carlsson, B. Carlsson, P.A. Svensson, Oxidized LDL induces a coordinated up-regulation of the glutathione and thioredoxin systems in human macrophages, Atherosclerosis, 185 (2006) 282.

[49] Y. Kabuyama, T. Kitamura, J. Yamaki, M.K. Homma, S. Kikuchi, Y. Homma, Involvement of thioredoxin reductase 1 in the regulation of redox balance and viability of rheumatoid synovial cells, Biochem. Biophys. Res. Commun., 367 (2008) 491.

[50] H. Lemarechal, Y. Allanore, C. Chenevier-Gobeaux, O.G. Ekindjian, A. Kahan, D. Borderie, High redox thioredoxin but low thioredoxin reductase activities in the serum of patients with rheumatoid arthritis, Clin. Chim. Acta, 367 (2006) 156.

[51] Z.F. Peng, L.X. Lan, F. Zhao, J. Li, Q. Tan, H.W. Yin, H.H. Zeng, A novel thioredoxin reductase inhibitor inhibits cell growth and induces apoptosis in HL-60 and K562 cells, J. Zhejiang Univ. Sci. B, 9 (2008) 16.

[52] A.L. Simons, A.D. Parsons, K.A. Foster, K.P. Orcutt, M.A. Fath, D.R. Spitz, Inhibition of glutathione and thioredoxin metabolism enhances sensitivity to perifosine in head and neck cancer cells, J. Oncol., 2009 (2009) 519.

[53] N.N. Ulusu, B. Tandogan, M.A. Turkoglu, S. Demirer, Is it Useful to Determine Glutathione Peroxidase and Thioredoxin Reductase Activities for Comparisons of Malign and Benign Breast Diseases?, Turk. J. Biochem., 34 (2009) 187.

[54] M. Honeggar, R. Beck, P.J. Moos, Thioredoxin reductase 1 ablation sensitizes colon cancer cells to methylseleninate-mediated cytotoxicity. Toxicol. Appl. Pharmacol., 241 (2009) 348.

[55] M.H. Yoo, X.M. Xu, B.A. Carlson, A.D. Patterson, V.N. Gladyshev, D.L. Hatfield, Targeting thioredoxin reductase 1 reduction in cancer cells inhibits self-sufficient growth and DNA replication, PLoS ONE, 2 (2007) e1112.