Journal of Biological Chemistry
Volume ٢٨٣, Issue ٣٢, ٨ August ٢٠٠٨, Pages ٢١٨٩٠-٢١٨٩٨

Regulation of the catalytic activity and structure of human thioredoxin ١ via oxidation and S-nitrosylation of cysteine residues

Hashemy, S.I.[ab], Holmgren, A.[ac]
[a] **Medical** Nobel Institute for Biochemistry, Department of **Medical** Biochemistry and Biophysics, Karolinska Institutet, SE-١٧١ ٧٧ Stockholm, Sweden
[b] Dept. of Biochemistry and Nutrition, **Mashhad University** of **Medical Sciences**, **Mashhad**, Iran
[c] **Medical** Nobel Inst. for Biochemistry, Dept. of **Medical** Biochemistry and Biophysics, Karolinska Institutet, SE-١٧١ ٧٧ Stockholm, Sweden

View references (٦٠)

Abstract

The mammalian cytosolic/nuclear thioredoxin system, comprising thioredoxin (Trx), selenoenzyme thioredoxin reductase (TrxR), and NADPH, is the major protein-disulfide reductase of the cell and has numerous functions. The active site of reduced Trx comprises $Cys^{٣٢}$-Gly-Pro-$Cys^{٣٥}$ thiols that catalyze target disulfide reduction, generating a disulfide. Human Trx١ has also three structural Cys residues in positions ٦٢, ٦٩, and ٧٣ that upon diamide oxidation induce a second $Cys^{٦٢}$-$Cys^{٦٩}$ disulfide as well as dimers and multimers. We have discovered that after incubation with $H_٢O_٢$ only monomeric two-disulfide molecules are generated, and they are inactive but able to regain full activity in an autocatalytic process in the presence of NADPH and TrxR. There are conflicting results regarding the effects of S-nitrosylation on Trx antioxidant functions and which residues are involved. We found that S-nitrosoglutathione-mediated S-nitrosylation at physiological pH is critically dependent on the redox state of Trx. Starting from fully reduced human Trx, both $Cys^{٦٨}$ and $Cys^{٧٣}$ were nitrosylated, and the active site formed a disulfide; the nitrosylated Trx was not a substrate for TrxR but regained activity after a lag phase consistent with autoactivation. Treatment of a two-disulfide form of Trx١ with S-nitrosoglutathione resulted in nitrosylation of $Cys^{٧٣}$, which can act as a trans-nitrosylating agent as observed by others to control caspase ٣ activity (Mitchell, D. A., and Marletta, M. A. (٢٠٠٥) Nat. Chem. Biol. ١, ١٥٤-١٥٨). The reversible inhibition of human Trx١ activity by $H_٢O_٢$ and NO donors is suggested to act in cell signaling via temporal control of reduction for the transmission of oxidative and/or nitrosative signals in thiol redox control. © ٢٠٠٨ by The American Society for Biochemistry and Molecular Biology, Inc.

Reaxys Database Information

|

Indexed Keywords

EMTREE drug terms: cysteine; diamide; hydrogen peroxide; nitric oxide donor; oxidizing agent; proline; s nitrosoglutathione; thiol reagent; thioredoxin; disulfide; insulin; nitric oxide; reactive oxygen metabolite; reduced nicotinamide adenine dinucleotide phosphate; thiol derivative; thioredoxin reductase; thioredoxin reductase ١

EMTREE medical terms: article; catalysis; chemical structure; chemistry; drug effect; human; metabolism; oxidation reduction reaction; protein tertiary structure; time; antioxidant activity; disulfide bond; enzyme active site; enzyme activity; enzyme assay; enzyme structure; enzyme substrate; Escherichia coli; nitrosylation; nonhuman; pH; polyacrylamide gel electrophoresis; priority journal; spectrophotometry

MeSH: Catalysis; Cysteine; Diamide; Humans; Hydrogen Peroxide; Models, Molecular; Nitric Oxide Donors; Oxidants; Oxidation-Reduction; Proline; Protein Structure, Tertiary; S-Nitrosoglutathione; Sulfhydryl Reagents; Thioredoxins; Time Factors
Medline is the source for the MeSH terms of this document.

Engineering controlled terms: Biomechanics; Catalytic oxidation; Mammals; Oligomers; Oxidation; pH; pH effects; Respiratory mechanics