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Forum Editorial

Thioredoxin as a Key Molecule in Redox Signaling

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THIOREDOXIN was originally identified in *Escherichia coli* as a hydrogen donor for ribonucleotide reductase, an essential enzyme for DNA synthesis (5). The thioredoxin system is composed of NADPH, thioredoxin reductase, and thioredoxin (4). Oxidized thioredoxin is reversibly reduced by NADPH and thioredoxin reductase. Mammalian thioredoxin reductase contains selenocysteine in the conserved C-terminal sequence and has broad substrate specificity. It reduces many substrates in addition to oxidized thioredoxin. Mammalian cells contain three isoforms of thioredoxin reductase. Rundlöf and Arnér review the roles of thioredoxin reductase in this Forum (13). Peroxiredoxin is a thioredoxin-dependent peroxidase and mammalian cells contain at least six isoforms of peroxiredoxin. Therefore, thioredoxin-related proteins function as antioxidants.

The terminology of "reduction/oxidation (redox) regulation" was originally defined as the thiol-dependent modulation in the DNA binding activity of a transcriptional factor for a gene expression. Now "redox regulation" is widely used to mean the biological responses maintaining the homeostasis against oxidative stresses. Oxidative stresses caused by chemical, physical, or biological stimuli generate reactive oxygen species (ROS) in the cells, and the cellular responses against oxidative stresses transduce the signals to maintain the cellular redox balance. A small amount of hydrogen peroxide by itself plays a crucial role as a second messenger in the signal transduction, and antioxidants such as superoxide dismutase, catalase, and glutathione-dependent enzymes also regulate the redox balance by scavenging ROS. As antioxidants, glutathione-dependent enzymes play major roles in the cells. This is because the intracellular amounts of glutathione are in the millimolar range, whereas intracellular amounts of thioredoxin are in the micromolar range. However, thioredoxin plays a crucial role in the redox regulation of gene expression. This is because the reducing activity of thioredoxin for transcriptional factors such as nuclear factor–κB and activator protein-1 is >1,000-fold higher than that of glutathione. Therefore, thioredoxin is a key molecule in redox signaling. Redox regulation by thioredoxin is deeply involved in the activation of transcriptional factors for the expressions of cellular responsive genes against oxidative stresses and in the signal transduction of oxidative stress-induced apoptosis.

Mammalian cells contain several "thioredoxin family" proteins that share the consensus active-site sequence -Cys-Xxx-Yyy-Cys-. Human original thioredoxin exists mainly in the cytosol and now is sometimes called thioredoxin-1. Thioredoxin-2 is a mitochondria-specific isoform of thioredoxin Not only thioredoxin-1 but also thioredoxin-2 is an essential protein in mammals because knockout mice of each protein are embryonic lethal. In this Forum, Miranda-Vizuete *et al.* review testis-specific thioredoxin family proteins that are expressed tissue-specifically (8). Glutaredoxins are also members of the thioredoxin family, and numbers of the glutaredoxin family members by themselves are growing. Fernandes and Holmgren review glutaredoxins in the present Forum (1). Thioredoxin family proteins may have their specific functions, and the interactions between the member proteins remain to be elucidated in the molecular mechanisms of redox signaling.

Human thioredoxin is secreted from the cells. It was originally cloned as a cytokine-like factor named adult T-cell leukemia-derived factor produced by human T-cell leukemia virus type I-transformed cells (15) or an autocrine growth factor produced by Epstein–Barr virus-transformed cells (17). Truncated thioredoxin is 80 or 84 N-terminal amino acids of human cytosolic thioredoxin and is also secreted from the cells. It shows more cytokine-like activity than thioredoxin. Here Pekkari and Holmgren review the functions of truncated thioredoxin (12). Serum/plasma levels of thioredoxin are elevated in infection, ischemia–reperfusion, and other oxidative stresses and are good markers for monitoring oxidative stresses. In acquired immune deficiency syndrome, the prognosis is much poorer in human immunodeficiency virus-infected individuals with higher plasma levels of thioredoxin compared with those with normal levels of thioredoxin (10). In hepatitis C virus infection, serum levels of thioredoxin can predict the efficiency of interferon therapy (14). Plasma levels of thioredoxin are also elevated in patients with coronary spastic angina (9) and other cardiovascular diseases.

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Human thioredoxin is induced by oxidative stress, and the expression of thioredoxin is also another oxidative stress marker. Liver tissues suffering from oxidative stress in chronic hepatitis C infection overexpress thioredoxin and other oxidative stress markers (6). The promoter region of the thioredoxin gene contains the oxidative responsive element, antioxidant responsive element, xenobiotics responsive element, cyclic AMP responsive element, and SP-1, but no heat shock responsive element (7). Overexpression of human thioredoxin in transgenic mice confers the resistance against a variety of oxidative stresses. Compared with the wild-type C57BL/6 mice, human thioredoxin transgenic mice are more resistant to cerebral infarction, adriamycin-induced cardiotoxicity, thioacetamide-induced acute hepatic injury, influenza virus-induced pneumonia, and inflammatory cytokine- or bleomycin-induced acute lung injury. Moreover, these mice survive longer than control wild-type mice (11). Therefore, induction of endogenous thioredoxin or gene therapy may be beneficial for oxidative stress-associated disorders. Geranylgeranylacetone (GGA), an antiulcer drug, induces thioredoxin-1 as well as heat shock protein-70 (3). GGA attenuates ethanol-induced hepatic cell injury and chemical-induced neuronal cell death by induction of thioredoxin. In contrast, the down-regulation of thioredoxin expression may be associated with the dysfunction in the host defense system. Interestingly, genetic hepertensive rats show decreases in thioredoxin expression in the aorta, heart, and kidney (16).

Exogenous administration of human thioredoxin also attenuates the cell and tissue injury. The molecular mechanisms of how extracellular thioredoxin enters into the cell still remain to be elucidated. However, extracellularly administered thioredoxin inhibits the cell death and ischemia–reperfusion injury. Intraperitoneal administration of thioredoxin also suppresses inflammatory cytokine- or bleomycin-induced lung injury in mice. Intravenous administration of recombinant human thioredoxin attenuates cerebral infarction in mice (2). Now we have started a translational research program to try to treat patients with acute lung injury or acute respiratory distress syndrome by administration of recombinant human thioredoxin protein. Ebselen, a new pharmaceutical compound with an antioxidant effect, facilitates the recycling of ascorbate with the mammalian thioredoxin system (18). Clinical applications of thioredoxin and its related molecules are ongoing.

The review articles and original articles in this Forum will cover the most updated research in the thioredoxin field.

ABBREVIATIONS

GGA, geranylgeranylacetone; ROS, reactive oxygen species.

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