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Structural Mechanism for the Cellular Redox Regulation by the Thiol Specific Antioxidant Proteins

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Recent studies indicate that hydrogen peroxide (H_2O_2), which is one of the reactive oxygen species involved in the oxidative stress, is an intracellular secondary messenger in the signal transduction. A novel family of thiol specific antioxidant (TSA) enzymes with a peroxidase activity shows no sequence homology to previously known antioxidant enzymes. Unlike other antioxidant enzymes these enzymes with a typical molecular weight of 25 KDal do not have any redox cofactors. We determined the crystal structure of a recombinant form of hORF6 that is a human member of the family at 2.0Å resolution. The crystal structure of hORF6 shows two separated domains. The N-terminal domain has a thioredoxin fold and the C-terminal domain folds over the N-terminal domain of the other monomer in a tightly associated dimer of the enzyme. The sulfide group of the active site cysteine (C47) is positioned in the center of a relatively narrow pocket in the surface from which we can imagine the way H_2O_2 accesses the active sulfide group. A couple of positively charged residues interacts with the active sulfide group to lower its pKa. The structure shows that the sulfide group is oxidized to a sulfenic acid that is an intermediate in the substrate reduction mechanism.