

Oxidative stress-dependent structural and functional switching of a human 2-Cys peroxiredoxin isotype II that enhances HeLa cell resistance to H₂O₂-induced cell death

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Although biochemical properties of 2-Cys peroxiredoxins (Prxs) have been extensively studied, their real physiological functions in higher eukaryotic cells remain obscure and certainly warrant further study. Here, we demonstrate that hPrxII, a cytosolic isotype of human 2-Cys Prx, has dual functions as a peroxidase and a molecular chaperone, and that these different functions are closely associated with its adoption of distinct protein structures. Upon exposure to oxidative stress, hPrxII assumes a high molecular weight (HMW) complex structure that has a highly efficient chaperone function. However, the subsequent removal of stressors induces the dissociation of this protein structure into low MW proteins and triggers a chaperone-to-peroxidase functional switch. The formation of a HMW hPrxII complex depends on the hyperoxidation of its N-terminal peroxidatic Cys residue as well as on its C-terminal domain, which contains a 'YF-motif' that is exclusively found in eukaryotic 2-Cys Prxs. A C-terminally truncated hPrxII exists as a slow and oligomeric protein species and does not respond to oxidative stress. Moreover, this C-terminal deletion of hPrxII converted it from an oxidation-sensitive to a hyperoxidation-resistant form of peroxidase. When functioning as a chaperone, hPrxII protects HeLa cells from H₂O₂-induced cell death, as measured by a terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay and fluorescence-activated cell sorting analysis.