Systems Biology of Hydrogen Peroxide Mediated Signaling

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The past several years have seen growing evidence for the key roles of thiol-based redox processes in major metabolic pathways. Thiol-based redox processes regulate a variety of biological functions, such as protection against oxidative stress, signal transduction, protein folding and modification. While mechanistically similar, thiol-dependent redox processes involve structurally distinct families of enzymes called thiol oxidoreductases. We developed thiol oxidoreductases identification approach and identified a whole set of thiol oxidoreductases in 852 completely sequenced organisms including yeast thiol oxidoreductases set, and demonstrated that number of thiol oxidoreductases is linearly growing with proteome size [1]. Such trend is typical for signaling machinery components in the cell. Further experimental analysis of computation results shown a key role of thiol peroxidases, subfamily of thiol oxidoreductases, in hydrogen peroxide (H_2O_2) mediated signaling in *Saccharomyces cerevisiae* [2]. This type of signaling is a critical process in nearly all organisms. Environmental or metabolically formed H_2O_2 is thought to regulate cellular processes by direct oxidation of numerous cellular proteins, whereas antioxidants, most notably thiol peroxidases, are thought to reduce peroxide and inhibit H_2O_2 response. We found that *Saccharomyces cerevisiae* cells lacking all eight thiol peroxidases were viable and withstood redox stresses. They transcriptionally responded to various redox treatments, but were unable to activate and repress gene expression in response to H_2O_2. Further studies involving redox transcription factors suggested that thiol peroxidases are major regulators of global gene expression in response to H_2O_2. Our data suggest that thiol peroxidases sense and transfer oxidative signals to the signaling proteins and regulate transcription, whereas a direct interaction between H_2O_2 and other cellular proteins plays a secondary role.

1. Fomenko D.E.*, Gladyshev V.N.* (2012) Comparative genomics of thiol oxidoreductases reveals widespread and essential functions of thiol-based redox control of cellular processes. *Antioxid Redox Signal*, 16, 193-201 (* co-corresponding authors).

2. Fomenko D.E.*, Koc A., Agisheva N., Jacobsen M., Malinouski M.Y., Rutherford J.C., Siu K.L., Jin D.Y., Winge D.R., and Gladyshev V.N.* (2011) Thiol peroxidases mediate specific, genome-wide regulation of gene expression in response to hydrogen peroxide. *PNAS*, 108, 2729-2734 (* co-corresponding authors).

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