***Management of oxidative stress from bacteria to man***

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**Summary:**

Prokarytic and eukaryotic cells are encountered by reactive oxygen species (ROS) and reactive electrophilic species (RES) which are generated inside the cells during respiration or metabolism or supplied externally by toxic compounds, such as antibiotics and xenobiotics. ROS and RES are also implicated in important physiological processes in human cells, such as cell survival, pathogenesis, aging, carcinogenesis and inflammation. Such reactive species are often sensed and transduced by redox-sensitive transcription factors that undergo post-translational thiol modifications, including intra- or intermolecular thiol-disulfide switches or mixed disulfides with low molecular weight thiols (S-thiolations). Thiol-based redox switches activate functions that detoxify reactive species and restore thiol homeostasis while repressing functions that would be deleterious if expressed under oxidizing conditions. The human Keap-Nfr2 pathway and yeast Yap1 transcription factors are examples for well studied regulatory signalling systems involved in sensing and responding of ROS and RES in eukaryotic cells. Intra- or intermolecular disulfide bond formation serves as a regulatory redox switch for several bacterial transcription factors such as *Escherichia coli* OxyR or the two-Cys MarR-type repressor OhrR of *Xanthomonas campestris*. *Bacillus subtilis* encodes redox-sensing MarR-type regulators of the OhrR and DUF24-families that are conserved among Firmicutes and control oxidative stress resistance and virulence functions in pathogenic bacteria. While most characterized members of the OhrR family respond to organic hydroperoxides, the DUF24-family senses electrophiles such as diamide, quinones or aldehydes (1)

Previously, we investigated the global response, post-translational modifications and specific regulatory mechanisms that are induced by reactive electrophilic species (RES) in *Bacillus subtilis,* such as diamide, quinones or aldehydes. In a recent study, we have studied changes in the transcriptome and redox proteome caused by the strong oxidant hypochloric acid in *B. subtilis.* We discovered that the major resistant determinant to NaOCl stress is the OhrA peroxiredoxin and the redox buffer bacillithiol (Cys-GlcN-Malate, BSH) that conferred specific protection against NaOCl toxicity (2). Hypochloric acid caused S-bacillithiolation of the redox-sensing MarR-type repressor OhrR and of four enzymes of the methionine biosynthesis pathway (MetE, YxjG, PpaC and SerA). *S*-bacillithiolation of the OhrR repressor leads to OhrR inactivation and induction of the OhrA peroxiredoxin for NaOCl detoxification. S-bacillithiolation of MetE, YxjG, PpaC and SerA causes hypochlorite-induced methionine starvation. The same mechanism of *S*-glutathionylation of MetE has been described in *Escherichia coli* also leading to enzyme inactivation and methionine auxotrophy. In eukaryotes, protein *S*-glutathionylation has emerged as a major cellular regulatory mechanims and the inactivation of several metabolic enzymes is caused by S-glutathionylation in response to oxidative stress. Thus, our studies discovered conserved roles of the BSH redox buffer in *B. subtilis* in redox regulation and protection of active site Cys residues of essential enzymes against irreversible oxidations as have been described for the glutathione redox buffer in *E. coli* and eukaryotic cells.

(1) Antelmann, H. and Helmann, J.D. Thiol-based redox switches and gene regulation. 2011. *Antioxid Redox Signal.* 14: 1049-63. Review.

(2) Chi, B.K., Gronau, K., Mäder, U., Hessling. B., Becher, D., and Antelmann H. S-bacillithiolation protects against hypochlorite stress in *Bacillus subtilis* as revealed by transcriptomics and redox proteomics. *Mol Cell Proteomics*. 2011 Jul 11. [Epub ahead of print]