Thioredoxin system-mediated persulfidation of Cys residues controls protein function and protects them from oxidative stress

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In the field of Redox Biology, protein cysteine persulfidation (P-Cys-SSH) and polysulfidation (P-Cys-SS_xH) is gaining increasing attention as an important regulatory element of protein functions. Initially it was proposed to be mainly the result of hydrogen sulfide's biological actions, but recently the Akaike laboratory demonstrated that these modifications can be produced enzymatically via pathways that does not require H_2S.

We demonstrated that protein Cys per/polysulfidation is highly regulated via the NADPH-dependent reducing machineries, the thioredoxin and glutathione systems.

We have shown that persulfidation has a regulatory role on a number of protein functions and recently we also obtained evidence that these modifications have important protein protecting functions in cells and *in vivo*. In cellular systems a substantial fraction of important thiol proteins (such as peroxiredoxins, PTP1B, PTEN, KEAP1 or Hsp90) are present in their persulfidated state, which we propose is a preemptive mechanism to prevent them from overoxidation during oxidative stress. We demonstrated that protection is due to formation of perthio-sulfenic, sulfinic and sulfonic acid derivatives (Cys-$SSO_{1\text{-}3}H$), which can be reduced back by the thioredoxin system to the corresponding functional native thiol forms when the stress is over.

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