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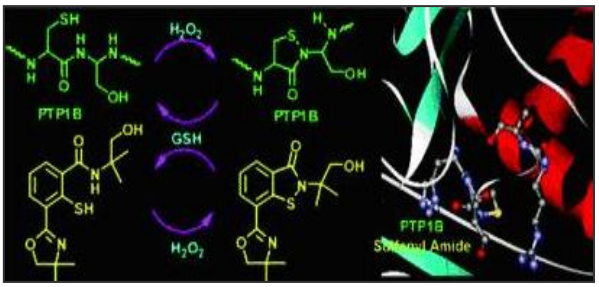
Redox Regulation of Protein Tyrosine Phosphatase 1B - Synthetic Model Uncovers Key Enzyme's Secrets

- Dr. G. Mugesh, IPC

Protein tyrosine phosphatases (PTPs) regulate signal transduction pathways involving tyrosine phosphorylation and these enzymes have been implicated in the development of cancer, diabetes, rheumatoid arthritis, and hypertension. In particular, the structure and function of the mammalian protein tyrosine phosphatase 1B (PTP1B) have attracted significant interest in recent years due to the importance of this enzyme in insulin signaling. The reaction mechanism of PTP1B involves a nucleophilic attack of a catalytically active cysteine residue (Cys215) at a phosphotyrosine (pTyr) substrate, resulting in a covalent phospho-cysteine intermediate that is subsequently hydrolyzed by a water molecule.



Recent studies suggest that the cellular redox state is involved in regulating tyrosine phosphatase activity through the reversible oxidation of the catalytic cysteine to the corresponding sulfenic acid (Cys-SOH). Although many cysteine-containing enzymes protect their active site from overoxidation and irreversible inactivation by forming an internal disulfide bond with a second cysteine residue within the active site or a mixed disulfide bond with external thiols, the sulfenic acid intermediate produced in response to PTP1B oxidation is rapidly converted into a sulfenyl amide species (Salmeen et al. Nature **2003**, 423, 769-773; van Montfort et al. Nature **2003**, 423, 773-777). This novel and unusual protein modification is believed to protect the active site cysteine from irreversible oxidation to sulfinic or sulfonic acids.

G. Mugesh and his graduate student, Bani Kanta Sarma, at the Department of Inorganic and Physical Chemistry, Indian Institute of Science, have synthesized the first successful chemical model that clearly demonstrates the chemistry underlying the cyclization reaction of PTP1B sulfenic acid intermediate to the unusual sulfenyl amide species. The quantitative conversion of the sulfenic acid to the sulfenyl amide even in the presence of thiols, as demonstrated in this study, supports the assumption that the PTP1B enzyme would produce the sulfenyl amide species in the reducing environment of the cell.

The article titled, "Redox Regulation of Protein Tyrosine Phosphatase 1B (PTP1B): A Biomimetic Study on the Unexpected Formation of a Sulfenyl Amide Intermediate" by Bani Kanta Sarma and G. Mugesh appeared in the July 18, 2007 issue of Journal of the American Chemical Society, 129 (8872-8881).

For more details, see: http://dx.doi.org/10.1021/ja070410o