Molecular Basis of Protein Tyrosine Phosphatase Inhibition by Biologically Important Small Molecules with Relevance to Cell Signaling Pathways

Sanjib Bhattacharyya

Dissertation Supervisor, Dr. Kent S. Gates

ABSTRACT

Protein tyrosine phosphatase 1B (PTP1B) is an abundant mammalian enzyme and well known to be as a central player in the insulin and leptin signaling pathways.

Peracetic acid is a strong oxidant molecule, endogenously produced by mammalian decarboxylase enzymes. Here we have presented the evidence that peracetic acid can reversibly inactivate the PTPs function in nanomolar concentration and the inactivation is potent in presence of glutathione. Our *in vitro* study demonstrates that 13S-HPODE (lipid peroxide), a dietary metabolite of linoleic acid can also inhibit the PTPase function in an identical manner as H_2O_2.

Oltipraz is a cancer preventive agent and currently undergoing clinical phase trial II. Oltipraz potentiates its chemo preventive action by the inducing of cellular detoxifying enzymes. Our work shows that oltipraz inhibits PTPs function like other cys-dependent proteins by reversible covalent modification. Our study also raises the possibility that oltipraz mediated PTPs inhibition might have the potential to trigger the NF-κB activation.

Hydrogen sulfide signaling has started getting attention in various aspects of cellular disease and therapeutics. Mechanism for many of the H_2S mediated signaling pathways is not yet known. Our work implicates that the metabolites of endogenous H_2S has potential to regulate the PTPase function during cell signaling.