Public Abstract
First Name:SANJIB
Middle Name:
Last Name:BHATTACHARYYA
Adviser's First Name:KENT
Adviser's Last Name:GATES
Co-Adviser's First Name:
Co-Adviser's Last Name:
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Molecular Basis of Protein Tyrosine Phosphatase Inhibition by Biologically Important Small Molecules with Relevance to Cell Signaling Pathways
Sanjib Bhattacharyya

Dr. Kent S. Gates, Dissertation Supervisor

ABSTRACT

Protein tyrosine phosphatase 1B (PTP1B) is an abundant mammalian enzyme present ubiquitously in the cell. PTP1B has been characterized as a central player in the insulin and leptin signaling pathways. Peracetic acid is a strong oxidant molecule produced by several bacterial hydrolase, perhydrolase, haloperoxidase, lipase enzyme and few mammalian decarboxylase enzymes. Here we presented the evidence that peracetic acid and other organic peroxide can reversibly inactivate the PTPs function in low nanomolar concentration and that the inactivation is potent in presence of cellular reducing agent, glutathione. The result shows that peracetic acid posses the characteristic of ROS and other cell signaling messengers like H2O2 to survive inside the cell under reducing condition. The condition how peracetic acid is produced inside the cell is not yet known. Our study shows that peracetic acid has the potential to regulate the PTPase function and indicate that peracetic acid might act as a third messenger or secondary oxidant in insulin signaling pathways if generated during that time frame. Lipid peroxide (13S)-hydroperoxyoctadecanoic acid (13S-HPODE) which is a dietary metabolite is known to prolong the phosphorylaion of endothelial growth factor (EGF). Our in vitro study demonstrates that 13S-HPODE can inhibit the PTPase function in an identical manner as H2O2 and could be the probable mechanism for increased EGF phosphorylation.
Oltipraz is a cancer preventive agent which is currently undergoing clinical phase trial II. Oltipraz triggers its chemo preventive action by the inducing of cell protecting enzymes, generally known as phase II enzyme by interacting with keap-Nrf2 pathways. Keap1 is a redox sensitive enzyme and it can interact with electrophile like oltipraz. Oltipraz also causes activation of ERK pathways, NF-ÎºB transcription factor and several other important biological pathways. We are the first to establish that oltipraz inhibits PTPs function like other cys-dependent proteins by reversible chemical modification. Two distinct studies show that PTPs inhibition and oltipraz, both individually can lead to the activation of NF-ÎºB. Our study raises the possibility that oltipraz mediated PTPs inhibition might have the potential to trigger the NF-ÎºB activation.
Hydrogen sulfide signaling has started getting attention in various aspects of cellular disease and therapeutics. H2S can cause upregulation of various kinase phosphorylation pathways such as Akt in case of pro-angiogenesis. Mechanism for many of the H2S mediated signaling pathways is not yet known. Our preliminary study shows that H2S metabolite sulfate (SO32-) can individually and by combination with other reactive oxygen species inactivate the PTPase function. Characterization of those combined species yet need to be determined. Our work implicates the importance of metabolism of endogenous H2S relevant to PTPase function during cell signaling.