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Oral presentation

Reactive oxygen species induce tyrosine phosphorylation of and Src kinase recruitment to NO-sensitive guanylyl cyclase

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Soluble guanylyl cyclase (sGC) is a cytosolic enzyme that converts GTP into the second messenger cGMP in a nitric oxide (NO)-dependent manner. Other factors controlling this key enzyme are intracellular proteins such as Hsp90 and PSD95, which bind to sGC and modulate its activity, stability and localization. To date little is known about the effects of posttranslational modifications of sGC though circumstantial evidence suggests that reversible phosphorylation may contribute to sGC regulation. Here we demonstrate that inhibitors of protein tyrosine phosphatases (PTP) such as pervanadate and bpV(phen) as well as reactive oxygen species such as H_2O_2 induce specific tyrosine phosphorylation of the β_1 but not of the α_1 subunit of sGC. Tyrosine phosphorylation of sGCβ_1 is also inducible by pervanadate or H_2O_2 in intact PC12 cells, rat aortic smooth muscle cells and in rat aortic tissues indicating that tyrosine phosphorylation of sGC may also occur *in vivo*. We have mapped the major tyrosine phosphorylation site to position 192 of β_1 where it forms part of a highly acidic phospho-acceptor site for Src-like kinases. In the phosphorylated state, pTyr192 exposes a docking site for SH2 domains and efficiently recruits Src and Fyn to sGCβ_1 thereby promoting further phosphorylation of the enzyme. Our results demonstrate that sGC is subject to tyrosine phosphorylation and interaction with Src-like kinases, revealing an unexpected crosstalk between the NO/cGMP and tyrosine kinase signaling pathways at the level of sGC.