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Interaction of NO-sensitive guanylyl cyclase with Src-like kinases

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NO-sensitive guanylyl cyclases (soluble guanylyl cyclase, sGC) are among the key regulators of intracellular cGMP concentration. The mechanisms underlying NO-mediated activation of sGC are quite well understood, however, little is known about the fine-tuning of sGC activity through alternative mechanisms such as protein phosphorylation. Several reports have demonstrated the reversible phosphorylation of sGC on serine/threonine residues, and it has been speculated, though not experimentally proven, that sGC might also be phosphorylated on tyrosine residues. Using broad-spectrum phosphatase inhibitors we were able to demonstrate tyrosine phosphorylation at Tyr192 of the β_1 subunit of human sGC in COS1 cells. This residue forms part of a sequence segment (YEDL) representing a preferential binding site for SH2 domains of Src-like kinases. Pull-down assays and co-immunoprecipitation experiments showed that Src can indeed bind via its SH2 domain to pTyr192 of β_1 indicating that tyrosine phosphorylation of sGC may be followed by recruitment of Src-like kinases to the phosphorylated β_1 subunit. In support of this hypothesis, immunofluorescence studies showed a colocalization of overexpressed sGC and Src at the plasma membrane of COS1 and Hela cells. Together, our results point to an unexpected crosstalk between tyrosine kinase pathway(s) and the NO/cGMP signalling cascade which may result in translocation of the predominantly cytosolic sGC to the cytosolic face of the plasma membrane.