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Poster presentation

Structural studies of soluble guanylate cyclase

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Soluble guanylate cyclase (sGC) is the primary receptor for nitric oxide (NO), which enhances GTP to cGMP conversion by sGC ~200-fold. The second messenger, cGMP, further modulates the activity of kinases and ion channels and ultimately induces smooth muscle relaxation and vasodilation. In cases of endothelial dysfunction, diminished NO production and insufficient output of the NO-sGC-cGMP pathway contribute to cardiovascular diseases, hepatic and renal failure, and impotence. Compounds that activate sGC (activators/stimulators) offer a promising strategy to treat these diseases.

So far, the structural details underlying sGC activation by NO and/or activators are lacking. The x-ray structures of independent proteins homologous to sGC independent domains have been determined, but there is currently no information on how the different domains assemble and interact in full-length sGC. Furthermore, despite extensive studies, the exact mechanism by which NO and/or activator binding to sGC allosterically activates cGMP production, remains elusive.

Our laboratory has initiated structural studies of sGC to identify the binding site(s) of sGC activators and to determine the mechanism for sGC activation. Here, we will present our latest results combining molecular biology, protein chemistry, x-ray crystallography, and small-angle x-ray scattering.