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Does soluble guanylyl cyclase need a chaperone?

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Two commonly accepted features of soluble guanylyl cyclase (sGC): its lack of "partners" and its exclusive-cytoplasmic localization were recently challenged. Several proteins that bind directly to sGC have now been identified. The molecular chaperone Hsp70 is one of these sGC-interacting proteins. Hsp70 modulates sGC activity, but apparently requires other associated proteins or co-factors for its sGC-activating effect. Other members of the molecular chaperones family appear to interact with sGC as well.

One of our aims is to determine the physiological relevance of the sGC-Hsp70 association. So far, Hsp70 has not been described as a classical activator, rather it is known for assisting the folding of nascent polypeptides or the association of multi-domains proteins, including potentially sGC. Because Hsp70 and Hsp90 form a chaperone machinery that modulates various signaling pathways and because Hsp90 participates in the processing, trafficking and maturation of nitric oxide synthase (NOS), we postulate that the Hsp70-Hsp90 machinery could modulate the NO-sGC pathway.

In particular, we wanted to determine whether the chaperone machinery could have a role in translocation of sGC to the plasma membrane and in its maturation/degradation. To define the role of the chaperone machinery, we blocked Hsp90 ATPase activity. We observed a decrease in sGC activity in particulate and soluble fractions of cells treated with Hsp90 inhibitors. This decrease in activity was accompanied by a paralleled decrease of sGC levels in the soluble fraction but not in the particulate fraction or cell homogenates. Subcellular fractionation indicated that the levels of sGC in cytosol and the plasma membrane were greatly reduced in the presence of Hsp90 inhibitors. These results not only confirmed that sGC can be associated with the plasma membrane but also suggest that Hsp90 is involved in translocation of sGC to the membrane and its maturation/degradation. We are currently investigating the mechanisms of this Hsp90-dependent modulation and the involvement of Hsp70 and other chaperones.

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