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Poster presentation

Interaction between hsp90 and soluble guanylyl cyclase: physiological significance and mapping of the domains mediating binding

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Heat shock protein 90 (hsp90) regulates stability and function of many client proteins including members of the NO-cGMP signaling pathway. Soluble guanylyl cyclase (sGC), which is the main intracellular receptor of NO, was recently reported to be an hsp90 interacting partner. In the present study, we show that hsp90 binds to both subunits of the most common sGC form, $\alpha_1\beta_1$. Characterization of the region of hsp90 required to bind each subunit in immunoprecipitation experiments, revealed that residues 310-456 of hsp90 interact with both α_1 and β_1. The region of β_1 responsible for binding to hsp90β was mapped using *in vitro* binding assays and immunoprecipitation experiments and found to lie in the regulatory domain. The physiological importance of the hsp90/sGC interaction was investigated by treating rat smooth muscle cells (RASMC) with the hsp90 inhibitors radicicol (RAD) and geldanamycin (GA) and determining both sGC activity and protein levels. Long-term (24 or 48 hr) inhibition of hsp90 resulted in a strong decrease of both α_1 and β_1 protein levels, as well as sGC activity. Moreover, incubation of smooth muscle cells with the proteasome inhibitor MG132 blocked the GA-induced downregulation of sGC. We conclude that the α_1 and β_1 sGC interact with the M domain of hsp90 and that this interaction regulates the pool of active sGC by affecting the protein levels of the two subunits.