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Poster presentation

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Nitric oxide-independent vasodilator rescues heme-oxidized soluble guanylate cyclase from proteosomal degradation

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Background

Nitric oxide (NO) is an essential vasodilator. In vascular diseases, oxidative stress attenuates NO signaling by both chemical scavenging of free NO and oxidation and down-regulation of its major intracellular receptor, the α/β heterodimeric heme-containing soluble guanylate cyclase (sGC). Oxidation can also induce loss of sGC's heme and responsiveness to NO.

Results

sGC activators such as BAY 58-2667 bind to oxidized/heme-free sGC and reactivate the enzyme to exert disease-specific vasodilation. Here we show that oxidation-induced down-regulation of sGC protein extends to isolated blood vessels. Mechanistically, degradation was triggered through sGC ubiquitination and proteasomal degradation. The heme-binding site ligand, BAY 58-2667, prevented sGC ubiquitination and stabilized both α and β subunits.

Conclusion

Collectively, our data establish oxidation-ubiquitination of sGC as a modulator of NO/cGMP signaling and point to a new mechanism of action for sGC activating vasodilators by stabilizing their receptor, oxidized/heme-free sGC.