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Oxidative stress induces CHIP-mediated ubiquitination and roteasomal degradation of soluble guanylyl cyclase

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Oxidative stress attenuates the NO-cGMP pathway, e.g. in the vascular system, through scavenging of free NO radicals by superoxide $O_2^{\bullet-}$, by inactivation of soluble guanylyl cyclase (sGC) via oxidation of its central Fe^{2+} ion, and by down-regulation of sGC protein levels. While the former pathways are well established, the molecular mechanisms underlying the latter are still obscure. Using oxidative sGC inhibitor ODQ we demonstrate rapid down-regulation of sGC protein in mammalian cells. Co-incubation with proteasomal inhibitor MG132 results in accumulation of ubiquitinated sGC whereas sGC activator BAY 58–2667 prevents ubiquitination. ODQ-induced down-regulation of sGC is mediated through selective ubiquitination of its b subunit, and BAY 58–2667 abrogates this effect. Ubiquitination of sGC-b is dramatically enhanced by E3 ligase CHIP. Our data indicate that oxidative stress promotes ubiquitination of sGC b subunit through E3 ligase CHIP, and that sGC activator 58–2667 reverts this effect, most likely through stabilization of the heme-free b subunit. Thus the deleterious effects of oxidative stress can be counter-balanced by an activator of a key enzyme of vascular homeostasis.