Protective Role of Heme Oxygenase-1 Induction against Cellular Oxidative Stress

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Oxidative stresses provoke cellular responses, principally involving transcriptional activation of genes encoding proteins which participate in the defense reactions. One of them is microsomal heme oxygenase-1 (HO-1), the rate-limiting enzyme in heme degradation, as well as the 32-kDa heat shock protein. HO-1 is highly inducible by a vast array of oxidative stress. Accumulating evidence indicates overwhelmingly that induction of HO-1 provides cytoprotective effects in various *in vitro* and *in vivo* models of the oxidative cellular injury. Free heme, which can be liberated from hemeproteins under oxidative conditions, is known to act as a pro-oxidant, leading to generation of oxygen radicals which causes cellular injury. HO-1 catalyzes the decomposition of the pro-oxidant heme into three elements, i.e., iron, biliverdin IXα and carbon monoxide (CO). Iron, which itself is an oxidant, but is directly sequestered and rapidly inactivated by co-induced ferritin. Biliverdin IXα is rapidly converted by biliverdin reductase to bilirubin IXα, which is an anti-oxidant. CO produced from heme by HO can suppress apoptosis of endothelial cells via the activation of p38 MAPK. Thus, in addition to the removal of the pro-oxidant heme, HO produces a series of metabolites from heme which all act as a member of the protective response, and contribute to the suppression of oxidative tissue injuries. The strong adaptive response of HO-1 to various oxidative stimuli suggests an entirely new paradigm for HO-1, and HO-1 should now be recognized as a novel drug target for oxidative tissue injuries. Thus, specific induction of HO-1 by non-stressful stimuli may have important clinical implications. In fact, we have recently reported that recombinant human interleukin (rhIL-11) pretreatment ameliorates hepatic injury induced by carbon tetrachloride (CCl_4), which causes lipid peroxidation of cell membranes, by virtue of its liver specific HO-1 induction. In this symposium, I plan to highlights of CCl_4-induced oxidative tissue injuries and potential therapeutic implications of HO-1 upregulation by rhIL-11.