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Title: Lung expression levels and subcellular localization of heme oxygenase-1 (HO-1) modulate recovery from hyperoxia in neonatal mice

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Body: HO-1, an integral membrane protein of the endoplasmic reticulum, is inducible in response to oxidative stress and is cytoprotective. However, it can translocate to the nucleus under oxidative stress. Although moderate levels of HO-1 are cytoprotective, very high levels are associated with oxygen cytotoxicity. To understand how expression levels and subcellular localization of HO-1 modulate its cytoprotective function, lung-specific transgenic mice overexpressing high or low levels of full-length (cytoplasmic, FL(H) or FL(L)) or C-terminally truncated (nuclear, TR) HO-1 were generated. Newborn mice were exposed to 95% O2 for 3 days and some were allowed to recover in room air. Although the FL(L) lung had decreased protein oxidation and preserved lung architecture after recovery from hyperoxia, the FL(H) lung had increased alveolar wall thickness with type II cell accumulation. The TR lung showed reduced poly(ADP-ribose) (PAR) hydrolysis associated with direct binding of HO-1 to poly(ADP-ribose) glycohydrolase (PARG) during recovery. Neonatal hyperoxia adversely affected pulmonary function in the TR and FL(H) adult lung. In addition, the FL(H) showed the most significant lung lesions compared to all other transgenic lines. We conclude that low cytoplasmic HO-1 levels protect against hyperoxia-induced lung injury by reducing lung oxidative damage, whereas high cytoplasmic HO-1 levels worsen lung function via increased type II cell proliferation, leading to alveolar wall thickness and decreased lung function. In addition, increased nuclear HO-1 in type II cells exacerbated hyperoxic lung injury due to inhibition of PAR-dependent DNA repair.