Heme Oxygenase-1 Gene Therapy Provides Cardioprotection Via Control of Post-Ischemic Inflammation: An Experimental Study in a Pre-Clinical Pig Model.

Abstract:
Heme oxygenase-1 (HO-1) is an inducible stress-responsive enzyme converting heme to bilirubin, carbon monoxide, and free iron, which exerts anti-inflammatory and antiapoptotic effects. Although efficient cardioprotection after HO-1 overexpression has been reported in rodents, its role in attenuating post-ischemic inflammation is unclear. This study assessed the efficacy of recombinant adenoassociated virus (rAAV)-encoding human heme oxygenase-1 (hHO-1) in attenuating post-ischemic inflammation in a murine and a porcine ischemia/reperfusion model. Murine ischemia was induced by 45 min of left anterior descending occlusion, followed by 24 h of reperfusion and functional as well as fluorescent-activated cell sorting analysis. Porcine hearts were subjected to 60 min of ischemia and 24 h of reperfusion before hemodynamic and histologic analyses were performed. Human microvascular endothelial cells transfected with hHO-1 displayed an attenuated interleukin-6 and intercellular adhesion molecule 1 expression, resulting in reduced monocytic THP-1 cell...
recruitment in vitro. In murine left anterior descending occlusion and reperfusion, the post-ischemic influx of CD45(+) leukocytes, Ly-6G(+) neutrophils, and Ly-6C(high) monocytes was further exacerbated in HO-1-deficient hearts and reversed by rAAV.hHO-1 treatment. Conversely, in our porcine model of ischemia, the post-ischemic influx of myeloperoxidase-positive neutrophils and CD14(+) monocytes was reduced by 49% and 87% after rAAV.hHO-1 transduction, similar to hHO-1 transgenic pigs. Functionally, rAAV.hHO-1 and hHO-1 transgenic left ventricles displayed a smaller loss of ejection fraction than control animals. Whereas HO-1 deficiency exacerbates post-ischemic cardiac inflammation in mice, hHO-1 gene therapy attenuates inflammation after ischemia and reperfusion in murine and porcine hearts. Regional hHO-1 gene therapy provides cardioprotection in a pre-clinical porcine ischemia/reperfusion model.