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Heme oxygenase-1 ameliorates kidney ischemia-reperfusion injury in mice through extracellular signal-regulated kinase 1/2-enhanced tubular epithelium proliferation

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ABSTRACT

Heme oxygenase (HO)-1 confers transient resistance against oxidative damage, including renal ischemia-reperfusion injury (IRI). We investigated the potential protective effect of HO-1 induction in a mouse model of renal IRI induced by bilateral clamping of the kidney arteries. The mice were randomly assigned to five groups to receive an intraperitoneal injection of PBS, hemin (an HO-1 inducer, 100 μmol/kg), hemin + ZnPP (an HO-1 inhibitor, 5 mg/kg), hemin + PD98059 (a MEK-ERK inhibitor, 10 mg/kg) or a sham operation. All of the groups except for the sham-operated group underwent 25 min of ischemia and 24 to 72 h of reperfusion. Renal function and tubular damage were assessed in the mice that received hemin or the vehicle treatment prior to IRI. The renal injury score and HO-1 protein levels were evaluated via H&E and immunohistochemistry staining. Hemin-preconditioned mice exhibited preserved renal cell function (BUN: 40 ± 2 mg/dl, creatinine: 0.53 ± 0.06 mg/dl), and the tubular injury score at 72 h (1.65 ± 0.12) indicated that tubular damage was prevented. Induction of HO-1 induced the phosphorylation of extracellular signal-regulated kinases (ERK) 1/2. However, these effects were abolished with ZnPP treatment. Kidney function (BUN: 176 ± 49 mg/dl, creatinine: 1.54 ± 0.39 mg/dl) increased, and the tubular injury score (3.73 ± 0.09) indicated that tubular damage also increased with ZnPP treatment. HO-1-induced tubular epithelial proliferation was attenuated by PD98059. Our findings suggest that HO-1 preconditioning promotes ERK1/2 phosphorylation and enhances tubular recovery, which subsequently prevents further renal injury.

1. Introduction

HO-1 plays a cytoprotective role in the modulation of tissue responses to injury in several pathophysiological states [1]. HO-1 is induced in several forms of acute kidney injury (AKI), including ischemia-reperfusion injury (IRI) [2], nephrotoxin-induced renal injury [3], transplantation-associated tissue injury [4], acute glomerulonephritis [5] and non-renal tissue injury [6]. Previous studies have indicated that HO-1 is induced in the kidney by various renal toxins or stressors, and HO-1 plays an important role in renal protection. The first human patient with HO-1 deficiency to be reported suffers from growth failure, anemia, tissue iron deposition, lymphadenopathy, leukocytosis, and an increased sensitivity to oxidant injury [7]. Moreover, renal tubular injury and subsequent proteinuria and hematuria are observed in patients with an HO-1 defect [8]. In an animal model of HO-1 deficiency, mice lacking the gene frequently die in utero, and the animals that survive to term display a phenotype similar to that of the HO-1-deficient boy [9]. Conversely, gene transfer can induce overexpression of HO-1, which prolongs kidney isograft survival, improves renal function and attenuates tubular injury resulting from IRI [10]. HO-1 may

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