Kidney International, Vol. 65 (2004), pp. 1968–1969

EDITORIAL

Role of HO-1 in renoprotection: Location, location, location

Heme oxygenase (HO)-1 is a ubiquitously expressed enzyme that is induced by various stimuli, including proinflammatory cytokines/endotoxin, hypoxia, ischemia/reperfusion, heat shock, heavy metals, and other pathophysiologic responses that induce oxidative stress [1, 2]. In many cell types, HO-1 has been shown to play an important role in cellular protection against oxidant-mediated cellular damage. HO-1 is the inducible isoform of heme oxygenase, which catalyzes the degradation of heme (a potent oxidant) to generate carbon monoxide (a vasodilatory gas that has anti-inflammatory properties), bilirubin (an antioxidant derived from biliverdin), and iron (sequestered by ferritin) [1]. Due to the varied properties of HO-1 and its products of heme catabolism, HO-1 has been therapeutically implicated in several disease processes whose pathophysiologies involve inflammation and oxidative stress, including atherosclerosis/vascular injury, hypertension, endotoxic shock, acute renal injury, transplant rejection, as well as others [2]. In recent years, the use of HO-1 gene therapy has become an area of intense investigation.

The kidney is an organ highly vulnerable to damage caused by oxidative stress and reactive oxygen species. Processes contributing to the progression of renal dysfunction into end-stage renal disease include hypertension, diabetes, polycystic kidney disease, and chronic allograft rejection [3]. Other immunologic disorders of the kidneys, ischemic insults, and nephrotoxic drugs also lead to oxidative stress and subsequent renal injury. Antioxidant enzymes, as in many other organs, play important protective roles in the kidney. HO-1 is one of these enzymes induced in the kidney by oxidative stimuli in an effort to resist injury. For example, HO-1 is induced in animal models of acute renal injury such as glycerol-induced renal failure, nephrotoxic serum nephritis, cisplatin nephrotoxicity, and ischemia-induced renal failure [4]. Increased expression of HO-1 has been noted in renal tubules, renal glomeruli, and inflammatory cells infiltrating the kidney, depending on the model studied. Moreover, chemical inhibitors of HO activity and HO-1 null mice [5] have been shown to worsen renal damage in some of these models, suggesting a protective role for HO-1. Even though endogenous HO-1 appears to be protective, an inadequate level or timing of endogenous HO-1 expression could compromise its full cytoprotective ability and not allow complete renoprotection and prevention from progression to renal failure. Thus, modulation of HO-1 expression by exogenous gene transfer is being studied in an attempt to improve the renoprotective capabilities of this cytoprotective enzyme.

In this issue of *Kidney International*, Quan et al [6] take the story a step further to approach the therapeutic application of HO-1 overexpression. Here they show that selective up-regulation of HO-1 gene attenuates oxidative stress caused by angiotensin II in primary cultured cells of the thick ascending loop of Henle (TALH). The TALH segment of the nephron is highly susceptible to ischemic injury because of its location in the oxygen-poor medulla. After infection of the cells with an adenoviral vector expressing human HO-1, the decrease in glutathione levels by angiotensin II was attenuated, and TALH cell injury and DNA damage were diminished. These results are consistent with other reports showing the beneficial effect of HO-1 in blocking inflammatory responses, oxidative injury, and apoptosis in a variety of cell types [2]. However, not all types of cells respond to HO-1 up-regulation in the same way. For instance, when assessing the effect of HO-1 in vascular cells, overexpression can suppress inflammation-induced apoptosis in endothelial cells, in part caused by the generation of HO-1–derived carbon monoxide production [7]. However, in vascular smooth muscle cells (VSMC), a very different response occurs. Infection of VSMC with adenovirus expressing HO-1 leads to apoptosis [8]. Interestingly, in VSMC, this response appears to be related to the generation of bilirubin, not carbon monoxide.

While previous studies have investigated the effect of HO-1 gene therapy in the kidney using an adenoviral approach [9], in our opinion the most critical aspect of the article by Quan et al [6] is the use of a cell type-specific promoter (Na^+-K^+-Cl^- cotransporter, or NKCC2) to drive HO-1 expression in TALH, but not other cell types. Efforts such as these will not only help to target HO-1 expression to cells most vulnerable to the pathophysiologic insult being studied, but will also prevent the collateral injury to bystander cells that may occur when selective targeting is not used. Adding to the excitement of this in vitro work is the fact that the NKCC2 promoter has already been used to target the thick ascending limb of the nephron in vivo [10].

Taking the work of Quan et al together with a multitude of earlier HO-1 studies, we believe that optimizing the

Key words: HO-1, renoprotection, oxidative injury, gene targeting.

cytoprotective ability of HO-1 in gene targeting and gene therapy will depend not only on the products of heme catabolism, but also on (*1*) the specific cell type where HO-1 is being targeted; (*2*) the level of HO-1 overexpression; (*3*) the timing and duration of HO-1 overexpression; and (*4*) and the pathophysiologic stimulus that the cell is being exposed to during HO-1 overexpression. Future studies using this type of selective targeting approach in animal models of disease will help to further elucidate the potential of HO-1 as a renoprotective agent in human disease.

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