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Heme Oxygenase 1 as a Therapeutic Target in Acute Kidney Injury

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Abstract

A common clinical condition, acute kidney injury (AKI) significantly influences morbidity and mortality, particularly in critically ill patients. The pathophysiology of AKI is complex and involves multiple pathways including inflammation, autophagy, cell cycle progression, and oxidative stress. Recent evidence suggests that a single insult to the kidney significantly enhances the propensity to develop chronic kidney disease. Therefore, generation of effective therapies against AKI are timely. In this context, the cytoprotective effects of heme oxygenase 1 (HO-1) in animal models of AKI are well documented. HO-1 modulates oxidative stress, autophagy, and inflammation, and regulates the progression of cell cycle via direct and indirect mechanisms. These beneficial effects of HO-1 induction during AKI are, in part, mediated by the by-products of the HO reaction (iron, carbon monoxide, and bile pigments). This review highlights the recent advances in the molecular mechanisms of HO-1–mediated cytoprotection and discusses the translational potential of HO-1 induction in AKI.

Keywords

acute kidney injury (AKI); heme oxygenase 1 (HO-1); renal failure; translational research; cytoprotection; pathophysiology; oxidative stress; inflammation; cell cycle regulation; autophagic response; biomarker; *HMOX1*; review

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Background

Acute kidney injury (AKI) is a common clinical condition, particularly in critically ill patients, that is associated with increased morbidity, mortality, and hospital cost.[1–3] Given the diversity of insults, lack of a reliable early biomarker, and markedly heterogeneous nature of pathways involved in the pathophysiology of AKI, identification and implementation of novel therapeutic options (apart from conservative measures and kidney replacement therapy) has remained elusive. Heme oxygenase 1 (HO-1) is an inducible enzyme with potent anti-oxidant, anti-inflammatory, and anti-apoptotic attributes[4–6] that was first recognized as a rapid and protective response in the context of rhabdomyolysis and heme pigment–induced AKI.[7] Extensive evidence has demonstrated the beneficial effects of HO-1 to be mediated via the breakdown of heme, a vigorous pro- oxidant molecule, and the generation of protective products–namely, carbon monoxide (CO), biliverdin with the subsequent formation of bilirubin, and ferritin via iron release from the heme moiety.[6] These findings have been reported in multiple animal models of AKI, including nephrotoxins, sepsis, kidney transplantation, and ischemia-reperfusion (IR)–mediated AKI among others, and also corroborated in human studies where HO-1 promoter polymorphism (leading to variable levels of HO-1 expression) is associated with several clinical conditions including AKI.[8–13] Despite the overwhelming evidence that highlights the promising nature of HO-1 induction as a therapeutic target, the translational aspects of HO-1 application in human AKI settings are yet to be investigated. Such a limitation is based on multifaceted challenges, which will be discussed in this review along with potential solutions and recent advances in the field.

Case Vignette

A 42-year-old man with no major past medical history is brought to the hospital after work equipment fell on his legs at a construction site. Per reports, he was unable to extricate himself and only received medical attention three hours following the accident. On presentation, his vital signs were stable and his physical examination revealed multiple bruises on both lower extremities. He was oliguric, and imaging revealed no evidence of bone fractures. Laboratory evaluation found multiple biochemical abnormalities. Serum creatinine was 4.2 (reference range, 0.4–1.2) mg/dL (corresponding to an estimated glomerular filtration rate (eGFR) of 16 mL/min/1.73 m^2 based on the MDRD [Modification of Diet in Renal Disease] Study equation) up from a previous creatinine measurement obtained during an annual evaluation of 1 mg/dL (eGFR, 82 mL/min/1.73 m^2). Serum urea nitrogen was 56 (reference range, 5–22) mg/dL; potassium, 6.1 (reference range, 3.1–5.1) mMol/L; phosphorus, 8.3 (reference range, 2.4–5) mg/dL; calcium, 7.1 (reference range, 8.4–10.4) mg/dL; serum creatine kinase, 81,000 (reference range, 25–190) U/L; and troponin, 0.01 (reference range, 0.00–0.039) ng/mL. Urinalysis was notable for dark urine, protein (1+), and blood (3+) with no red blood cells. Further urine analysis revealed the presence of myoglobin. He was diagnosed with rhabdomyolysis-induced AKI, intravenous fluid administration was initiated, and he was admitted to the intensive care unit. Over the course of his hospital stay, his urine output improved, his electrolyte abnormalities resolved, and his serum creatinine decreased to 1.2 mg/dL (eGFR, 66 mL/min/1.73 m^2).

Acute kidney injury from rhabdomyolysis was first described by Bywaters and Beall, who noted dark urine, reduction in urinary output, hyperkalemia, and ultimately death in victims of crush injuries at the time of the London blitz in World War II.[14] Interestingly, the first evidence for a protective role for HO-1 was demonstrated in rhabdomyolysis-induced AKI by Nath and colleagues some fifty years later.[7] The field has since grown exponentially and expanded to multiple other organ systems and disciplines. There are several excellent reviews that discuss the cytoprotective nature of HO-1 in kidney physiology and disease states. [15–19] The elegant review by Courtney and colleagues discussed the role of HO-1 in mediating protection during kidney diseases, with emphasis on transplantation.[15] The focus of this current review is to highlight key aspects of the mechanisms by which HO-1 confers protection during AKI, and to discuss the most recent translational advances in this field.

Pathogenesis

Mechanisms of HO-1–Mediated Cytoprotection in AKI

Immunomodulation During AKI—The inflammatory response plays a key role in the pathogenesis and resolution of AKI. Exaggerated inflammation following an acute insult leads to increased severity of AKI, incomplete recovery, and increased propensity to progress to CKD. This unfettered immune response has been well documented in AKI following IR, rhabdomyolysis, and sepsis.[20–24] Studies in animal models have identified a prominent role for both innate and adaptive immune mechanisms. Of these, innate immune cells, such as macrophages, dendritic cells (DC), and neutrophils are the primary responders to the acute insult and continue to remain on the forefront of research in the AKI field. Interestingly, studies demonstrate an important immunomodulatory role for HO-1 in these cells.[25–28] Global HO-1 knockout mice and HO-1–deficient humans demonstrate increased leukocytosis, erythrophagocytosis, hepatosplenomegaly, and renal tubulointerstitial injury with inflammatory cell infiltration and fibrosis, underscoring the anti-inflammatory actions of HO-1.[25, 29–31] Global HO-1–deficient mice also express high levels of circulatory monocyte chemoattractant protein 1 (MCP-1) in the quiescent state and following AKI (Table 1).[32] Additionally, macrophages that express HO-1 polarize towards the anti-inflammatory phenotype, secrete anti-inflammatory cytokines (eg. IL-10), and express reparative genes that are critical for tissue recovery after AKI.[28, 33] Additionally, the beneficial effects of IL-10 expression are dependent on HO-1 expression and activity.[34, 35] Following IR, macrophages that accumulate in the injured kidney of HO-1–deficient mice express significantly higher levels of the cytokine IL-6, while expressing low levels of the anti-inflammatory cytokine IL-10.[33, 36] These findings were recapitulated using an animal model of unilateral ureteral obstruction, highlighting the salutary effect of HO-1 in the immune responses during AKI.[37, 38]

The actions of HO-1 are not confined to the regulation of cellular gene expression and maturation of immune cells (eg. DC), but also extend to their ability to migrate.[33, 39–41] Previous studies have demonstrated that following AKI, global HO-1 deficiency leads to increased accumulation of macrophages in the injured kidney.[37] A recent study by Hull et al demonstrated that deletion of HO-1 in myeloid cells (macrophages, neutrophils, and dendritic cells) facilitates the egress of these cells from the injured kidney to peripheral

lymphoid tissue, presumably for antigen presentation and amplification of the immune response.[33] They confirmed these findings using multiple models, including a syngeneic kidney transplantation utilizing fluorescent protein–labeled HO-1–deficient donor kidneys into a wild-type mouse, and bilateral IR in a transgenic mouse with specific deletion of HO-1 in the myeloid cells. This study provided evidence to suggest that manipulation of HO-1 expression in the myeloid cells may be an exciting avenue to minimize the immune response following IR and transplant-associated AKI. Interestingly, CO was also able to exert this inhibitory effect on the migration of DC.[41, 42] Additionally, HO-1 expression in antigen-presenting cells such as DC is required for optimal regulatory T cell function, which has been shown to facilitate recovery following AKI.[26, 43]

It should be noted that while the aforementioned studies utilized genetic manipulation of HO-1, some of these findings were also recapitulated using by-products of the HO reaction. For instance, CO inhibits T cell proliferation via downregulation of IL-2 and caspase activity, thereby dampening inflammation.[44] In addition, numerous studies using chemical and pharmacologic modulators of HO-1 expression and/or activity have confirmed these immunoregulatory effects of HO-1 during AKI (Table 2).[4, 26, 45–50]

The constitutive isoform of the enzyme, HO-2, also plays an important role in immunomodulation. Global HO-2 deficiency leads to a dysregulated inflammatory response and subsequently impairs the reparative response following injury.[51, 52] Recent studies have demonstrated that deletion of HO-2 in macrophages significantly impedes their phagocytic ability and promotes expression of inflammatory genes, while downregulating the expression of anti-inflammatory markers leading to diminished wound healing.[53] Interestingly, these deleterious effects were reversed by supplementation of biliverdin.[53, 54] These results highlight the importance of HO enzyme activity in the modulation of immune responses following injury.

Cell Cycle Regulation—The inherent capacity of the injured kidney to recover from an acute insult is vital for maintaining homeostasis. The key mechanisms that drive the reparative process include upregulation of anti-oxidant defense systems, inhibition of oxidative stress and associated apoptosis, and finally regeneration of the injured tubules. The latter process is finely orchestrated by a group of proteins having roles in cell cycle regulation, namely cyclins and cyclin-dependent kinases (CDKs). The cell cycle is a meticulously controlled process that occurs under both physiologic and pathophysiologic conditions. It consists of a cyclic pathway of specific phases: G1 (gap 1), S (DNA synthesis), G2 (gap 2), and M (mitosis). The progression of each phase into the next is tightly regulated by the expression of specific cyclins and CDKs, ultimately determining cell cycle arrest or proliferation. Interaction of a cyclin with its respective CDK leads to phosphorylation of target proteins, which in turn initiates or restricts progression into the next phase of the cell cycle. This complex system is further controlled by the expression of CDK inhibitors, INK4a/ARF (inhibitor of kinase 4/alternative reading frame), and the Cip/Kip (interacting protein/kinase inhibitory protein) family of proteins.

During AKI, seminal studies have delineated a critical role for these proteins in mitigating injury. In this connection, Megyesi et al demonstrated that during cisplatin-induced AKI,

expression of p21 (a member of Cip/Kip family) was significantly upregulated in the kidney, associated with an inhibition of cell cycle progression, and subsequently led to marked reduction in injury during ischemia reperfusion and cisplatin nephrotoxicity.[55, 56] Following these studies, Nath and colleagues were the first to identify a direct regulatory effect of p21 expression by HO-1 in the kidney .[57] They demonstrated a beneficial effect of HO-1 and p21 expression in tubular injury mediated by heme, TNF- α, and serum deprivation.[57, 58] Studies utilizing transgenic mice deficient in p21 or HO-1 confirmed a protective role for these proteins in IR- and cisplatin-induced AKI.[4, 55, 56, 59] In the quiescent state, tubular cells constitutively express low levels of p21, which is rapidly co-induced with HO-1 upon injury in vitro.[57] In cells that constitutively overexpress HO-1, basal p21 expression was reported to be elevated and associated with diminished hyperplastic growth and cell cycle arrest in the G0/G1 phase of the cell cycle. Further work demonstrated that p21 induction is dependent on HO activity, in that inhibition of HO activity was observed to lead to marked reduction in p21 expression and increased apoptosis following injury.[57] These findings suggest that the by-products of the HO reaction may contribute to regulation of p21 (Figure 1). In fact, studies demonstrate an inducible effect of iron on p21 expression, which is abolished in the presence of an iron chelator, deferoxamine.[58] In addition, CO is also capable of eliciting a similar response.[58] Another heme-iron–containing protein, myoglobin, also promotes cell cycle arrest, an effect that reversed in the presence of deferoxamine.[60] Recent evidence suggests that HO-1–mediated p21 regulation is not only confined to tubular epithelial cells, but also extends to mesangial cells in the kidney.[61]

Interestingly, biliverdin reductase A (BVRA), a key enzyme in the heme oxygenase system, also mediates a dominant role in cell cycle regulation. Kim et al demonstrated that BVRA knockdown leads to marked reduction in the expression of cyclin D1 and phosphorylated pRb, whereas it increases the expression of p16 (member of INK4 family), leading to premature cellular senescence.[62] Another inhibitor of the INK4 family of proteins, p18, which arrests the cell cycle at the G1 phase, was shown to be protective during cisplatin nephrotoxicity.[63] Recent evidence also suggests that p18 expression is regulated by HO-1 expression, in that HO-1 upregulates p18 expression while inhibition of HO activity was found to ablate such induction during cisplatin injury.[64]

Taken together, HO-1–mediated cell cycle regulation plays a pivotal role in tubular injury and repair during AKI. A recent study by Kashani and colleagues identified two novel urinary biomarkers (insulin-like growth factor-binding protein 7 [IGFBP7] and tissue inhibitor of metalloproteinases 2 [TIMP2]) for AKI using a multicenter observational study involving large cohort of critically ill patients (about 700).[65] Interestingly, both of these markers are potent inducers of G1 cell cycle arrest, underscoring the mechanistic role of cell cycle regulation in the pathogenesis of AKI.[65] Additionally, studies have identified a significant role for maladaptive repair in the induction and progression of CKD. Given the increasing evidence for the convergence of AKI to CKD, regulation of cell cycle provides an interesting avenue for the generation of effective therapeutics for AKI and the prevention of CKD as reported from the Bonventre laboratory.[66]

HO-1 Regulates Autophagic Response During AKI

Autophagy refers to an evolutionarily conserved and physiologically regulated intracellular degradation process by which cytoplasmic components (eg, damaged organelles, protein aggregates, and other macromolecules) are sent to the lysosome for breakdown and ultimate disposal.[67, 68] Recent data suggests that autophagy is induced in several animal models of AKI, including IR, nephrotoxin and immunosuppressive agent-mediated injury[69, 70]. Additionally, the presence of autophagosomes in the transplanted human kidney underscores the relevance of this pathway in injury-mediated responses.[71] Increasing evidence suggests that in quiescent cells, constitutively activated autophagy serves as a physiologic homeostatic process. However, under stress conditions such as AKI, autophagy induction may promote survival or converge into apoptotic cell death depending on the extent of injury and activation of pro-survival pathways.[69] Interestingly, evidence gathered over the past decade identifies HO-1 as a potent regulator of autophagy.[72–74] Proximal tubules deficient in HO-1 display elevated basal autophagy, as evident by increased accumulation of autophagic vesicles and expression of light chain 3 (LC3)-II and beclin.[72] This increased activity is presumably to maintain cellular homeostasis and is reflective of an oxidative environment (increased levels of heme, oxidized proteins, and lipid peroxidation) in the absence of HO-1. Following cisplatin administration, absence of HO-1 expression is linked with failed autophagy induction and converges into increased apoptosis, underscoring the effect of cumulative stress in the interplay between autophagy and apoptosis. On the other hand, HO-1 overexpression in kidney epithelial cells during cisplatin nephrotoxicity delays the autophagic response and concomitantly inhibits apoptosis.[72] Whether this delayed response is attributed to decreased generation of reactive oxygen species (ROS) and heme content is not known. Another mechanism by which HO-1 regulates autophagy is through inhibition of beclin expression, a key protein responsible for autophagy initiation.[73, 74] These studies suggest that the cellular fate, as determined by the competence or perturbation of autophagy, is an HO-1 mediated process, and targeting the HO system may provide effective strategies against AKI.

Oxidative Stress and HO-1

Irrespective of the etiology of injury, oxidative stress is a common denominator in the AKI pathogenesis. Oxidative stress results when the cellular anti-oxidant machinery is exhausted by an overwhelming imbalance in the accumulation of oxidants, such as ROS. These reactive species contain an oxygen atom with an unpaired valence electron, which quickly interacts with various functional groups and propagates a vicious cycle of free radical generation, ultimately culminating in amplified cellular oxidative stress and death. Nath and colleagues provided the first evidence for the cytoprotective role of HO-1 in vivo during AKI.[7] This elegant study demonstrated for the first time that following glycerol induced rhabdomyolysis (a model in which oxidative stress is a predominant pathogenic mechanism), HO-1 is quickly induced in the kidney, and prior induction of HO-1 with hemoglobin ameliorates injury. Furthermore, this functional protection is abrogated in the presence of tin protoporphyrin, an HO enzyme activity inhibitor, underscoring the HO-1 mediated beneficial response to oxidant injury.[7] This study propelled investigators to determine protective mechanisms modulated by HO-1 during oxidant injury in other organ

systems as well. Indeed, it is clear now from multiple studies that oxidative stress induces HO-1, and such induction mediates protection during AKI in animal models.

The salutary beneficial effect of HO-1 expression during oxidative stress is twofold. First, HO-1 catalyzes the breakdown of heme, a potent pro-oxidant and a noxious stimulus that amplifies oxidative insult in several models of injury. Heme is an integral functional component of several proteins, intracellular and extracellular, that are involved in cellular homeostasis. Cellular heme levels are maintained at 100 nM through two opposing processes, namely, synthesis and degradation. While heme synthesis is regulated by aminolevulinic acid (ALA) synthase activity, the enzymatic degradation of heme is managed by HO enzymes. During injury (ischemic or nephrotoxic), destabilization of heme proteins, which are ubiquitous in cells, leads to a significant increase in free heme. Heme is lipophilic and freely permeates the lipid membranes (plasma and organellar), causing oxidization of lipids and accentuating oxidative stress (Figure 2). Furthermore, heme not only stimulates the generation of hydrogen peroxide in tubular epithelial cells but also amplifies oxidative stress through interaction with hydrogen and lipid peroxides to form potent pro-oxidant ferryl forms of heme.[75] Animal models using global or kidney specific HO-1-deficient mice confirm the damaging role of heme in kidney injury.[59, 76, 77] Moreover, patients with rhabdomyolysis and acute intermittent porphyria who use hematin develop severe AKI, supporting the clinical relevance of heme burden and injury.[78, 79] Furthermore, genetic HO-1 deficiency in humans results in significantly higher levels of heme in the plasma and renal tubulointerstitial injury.[29, 79, 80]

While heme is required for the optimal function of metabolic enzymes such as cytochrome c oxidase and NOS, free heme also impairs the activity of several enzymes including glucose-6-phosphate dehydrogenase and glutathione reductase.[79] Mitochondrial-targeting of HO-1 in kidney epithelial cells leads to decreased expression of multiple subunits of cytochrome c oxidase without altering basal mitochondrial function.[81] Additionally, these cells demonstrate significant protection against hypoxic and oxidative insults, as evident by reduced ROS generation and apoptosis.[81] Interestingly, a few studies demonstrate a protective role for low-dose heme infusion during IR-induced injury and attribute these effects to the induction of HO-1.[82]

The second salutary effect of HO activity is the generation of by-products that possess anti-oxidant and anti-apoptotic properties. The bile pigments, bilirubin and bilverdin, scavenge free radicals such as peroxynitrite, inhibit lipid peroxidation, and, thereby, mitigate oxidative stress.[83, 84] Additionally, the cyclic interconversion of biliverdin to bilirubin mitigates oxidative stress through sequestration of hydrogen peroxide during the reaction.[84, 85] Bilirubin also suppresses the activity of NADPH (educed nicotinamide adenine dinucleotide phosphate) oxidase, a major source of ROS during oxidative insults.[86, 87] Interestingly, ligation of the bile duct during glycerol-induced rhabdomyolysis leads to mitigation of AKI, suggesting a beneficial role for bilirubin during injury.[88] Furthermore, neonatal Gunn rats demonstrate increased resistance to free radical injury, an effect that is attributed to increased bilirubin.[89] Additional studies have demonstrated that exogenous bilirubin supplementation provides marked protection against oxidative stress during AKI, validating the anti-oxidant effect of this metabolite.[90, 91] Another by-product of the HO reaction is CO,

a powerful anti-apoptotic and anti-inflammatory molecule (Figure 2). Endogenous CO production is exclusively mediated by the HO enzymes. However, exogenous supplementation is achieved through inhalation of CO (usually at 250 ppm) or by treatment with CO releasing molecules (CORMs). Studies using both these modes of CO supplementation in vivo have demonstrated that CO is capable of mitigating oxidative stress through direct and indirect mechanisms. It has to be noted, however, that supra-therapeutic levels of CO may also amplify ROS generation through its interaction with mitochondrial proteins such as cytochrome c oxidase, which hinders its potential as a therapeutic intervention.

In summary, research over the past few decades has provided indisputable evidence of HO-1 as a beneficial anti-oxidant during AKI. Mechanistically, HO-1 converts a toxic oxidative microenvironment to an anti-oxidant and reparative milieu that facilitates recovery from injury. Therefore, current research efforts must be directed toward translating these pre-clinical studies to generate effective therapies aimed at inducing this cytoprotective enzymatic system in humans with AKI.

Recent Advances

HO-1: The Murine Versus Human Paradox

Introduction of HO-$1^{-/-}$ mice transformed this field of research by providing a valuable tool for investigating various aspects of HO-1 gene regulation and its role in injury settings.[30] Several pathologic findings obtained in these transgenic mice have been corroborated in patients with human HO-1 deficiency.[101, 102] Despite such remarkable advances in this field, certain limitations to fully explore the potential of HO-1 as a therapeutic target still remain.

First, the global deletion of HO-1 did not allow for meticulous examination of different cell types and dissecting their sequential and temporal effects following injury. To overcome this limitation, and by taking advantage of Cre-Lox site-specific recombinase technology, mouse models have been developed that are deficient or overexpress HO-1 in proximal tubular cells (most susceptible to different forms of insults) or myeloid cells.[76, 103] These novel animal models would allow for a more in-depth analysis of the mechanisms that are involved with cellular injury, inflammation, and repair in AKI as it relates to HO-1. Furthermore, they will provide valuable information on the role of cell-specific HO-1 expression in cross-talk of tubular and inflammatory cells, and the contribution of each cell type during injury and repair.

Second, HO-1 gene expression is regulated differently in mice and humans[104, 105]. These dissimilarities include contrasting responses to various stimuli such as hypoxia, heat shock, hyperosmolarity, and cytokines such as interferon γ. In addition, the molecular mechanisms of human HO-1 gene regulation by an intronic enhancer that facilitates HO-1 gene expression via chromatin looping have not been shown in the rodent HO-1 genes.[104, 105] These limitations prompted generation of a novel “humanized” transgenic mouse model, consisting of the human HO-1 gene in addition to its regulatory regions on a HO-$1^{-/-}$ background.[77] This study confirmed rescue of the pathologic phenotypes observed in HO-$1^{-/-}$ mice via functional presence of the human HO-1 gene (Figure 3). These mice

should serve as an important tool to study the mechanisms of human HO-1 gene regulation in vivo and should enable identification of novel therapeutic agents to target HO-1 expression in AKI.

Micro-RNA and HO-1

The discovery of micro-RNAs (miRNAs) in the past two decades has led to an exciting new field of investigation.[106, 107] These miRNAs are small, non-coding RNA molecules that are involved in gene silencing and post-transcriptional regulation of gene expression.[108] They have been shown to have essential roles in many forms of kidney diseases [109, 110]. Also, miRNAs may regulate HO-1 gene expression. This notion has been confirmed in different cell lines including podocytes, renal proximal tubular cells, and endothelial cells, among others.[111–117] In contrast, there is also evidence that HO-1 expression modulates certain miRNAs.[118, 119] Such reciprocal interactions and regulatory involvements between HO-1 and miRNAs provides an innovative platform for further investigation that could lead to identification of novel pathways and potential therapeutic targets in different clinical settings, including AKI and other kidney diseases.

HO-1 Gene Polymorphisms

Translational efforts to study effects of HO-1 expression in human diseases have identified polymorphisms in the 5' flanking region of the HO-1 gene[120]. These include a $(GT)_n$ dinucleotide length polymorphism and two single-nucleotide polymorphisms (SNPs), G(-1135)A and T(-413)A.[120] Among these the $(GT)_n$ polymorphism in the promoter region has been extensively studied in different clinical conditions[120–123]. Shorter $(GT)_n$ repeats ($n < 27$) are associated with greater HO-1 expression and confer protection against many diseases.[124–126] Within the context of kidney diseases, HO-1 promoter polymorphism is associated with IgA nephropathy, transplant rejection, patency of arteriovenous fistula, and progression of CKD.[127–132] More recently, a study examined such polymorphism and its relationship with development of AKI in patients undergoing cardiac surgery. Importantly, the authors found that longer $(GT)_n$ repeat (associated with lower HO-1 expression) in these patients led to increased risk of AKI following cardiac surgery.[13] It should be noted that some studies did not find any significant association between the HO-1 promoter polymorphism and disease development or progression.[133–135] However, more elaborate recent meta-analysess were performed to address this issue, and after careful review of the literature and accounting for various methods of randomization, the authors have corroborated the protective effects of HO-1 promoter polymorphisms.[121, 122] Furthermore, these studies identified potential confounding factors, such as age, race, gender and preexisting conditions/risk factors, that need to be accounted for during design and interpretation of these studies. In this age of precision medicine, taking these factors into consideration would potentially enable a more personalized approach to patients.

Iron and AKI

Iron is an absolute requirement for life, but can also pose deleterious effects via participation in the Fenton reaction and generation of ROS. Recently, the role of the kidney in iron handling and metabolism has gained significant attention.[136, 137] Based on experimental and human studies, iron is increasingly recognized to be a major culprit in AKI.[138–140] To study

iron trafficking and its role in AKI, we recently generated a novel transgenic mouse model with conditional deletion of heavy chain ferritin (FtH) in renal proximal tubules.[100] Interestingly, these mice exhibit significantly higher levels of HO-1 expression both under basal and injury conditions. However, despite such significantly higher levels of HO-1, FtH deletion has been associated with worse kidney function and morphologic changes in two different models of AKI.[100] These results underscore the crucial significance of FtH co-expression during HO-1 induction to safely sequester the released iron from the breakdown of heme and prevent its participation in the Fenton reaction. Clinical studies have further corroborated these findings. Recently, Leaf et al. conducted a prospective cohort of 250 patients undergoing cardiac surgery and found a direct relationship between plasma catalytic iron levels and higher likelihood of AKI, hospital mortality, and postoperative myocardial injury.[139] While results from clinical trials using iron chelators in AKI have not been reported, targeting FtH may represent a novel strategy to sequester iron during AKI.

HO-1 as a Biomarker of AKI

The traditional reliance of clinicians on serum urea nitrogen and/or serum creatinine, as well as urine output, to diagnose AKI has been a major obstacle to the early recognition of this condition as well as potential implementation of therapeutic modalities in a timely manner. Therefore, identification of novel biomarkers in AKI has been a foremost priority in recent years. Several candidates have been identified and many are being evaluated as “point of care” testing in AKI (eg. IGFBP7, TIMP2).[141–143] In this regard, given the localization of the HO-1 enzyme to the endoplasmic reticulum and lack of an identified secretory pathway, the probable role of HO-1 as a biomarker has only recently been examined. Zager and colleagues invesigated urinary and plasma levels of HO-1 in four models of AKI that included ischemia/reperfusion, glycerol-induced rhabdomyolysis, cisplatin nephrotoxicity, and bilateral ureteral obstruction.[144] Interestingly, following AKI, induction of renal HO-1 was found to be accompanied with elevation of its levels in both serum and urine. Moreover, urinary and plasma levels of HO-1 were seen to be significantly higher in ten patients with AKI when compared to ten critically ill patients without AKI and twenty patients with CKD, including ESRD.[144] Such potential to utilize HO-1 as a biomarker in kidney disease is also corroborated by other investigators. For instance, a recent study reported higher levels of urinary HO-1 in patients with type 2 diabetes. Intriguingly, the increment in urinary HO-1 levels in these patients precedes significant proteinuria and also inversely correlates with glomerular filtration rate.[145] Another study found increased levels of plasma HO-1 in patients who developed AKI following cardiopulmonary bypass; this is associated with duration of the bypass, hemolysis, and inflammation.[146] Given the overwhelming reliance on serum creatinine, urine output, and degree of proteinuria to monitor kidney function, the aforementioned findings of plasma and urinary HO-1 are timely and add to our armamentarium of biomarkers of AKI. However, it must also be noted that utilization of HO-1 as a novel biomarker of AKI requires additional investigation. Two major concerns that require in-depth analysis are related to the following. First, the origin of the observed HO-1 in serum and urine following AKI is interesting, as it is known to be localized to the endoplasmic reticulum; this localization raises the question as to whether the observed HO-1 in serum and urine is a mere reflection of cellular damage and release of intracellular proteins, or if it involves a more active cellular secretion pathway. Second, as shown by

Zager and colleagues, the immunoreactive HO-1 in both urine and serum is present as a 16 kDa protein that is likely reflective of a cleavage of the two approximately equal-sized bound helices of HO-1. [144] Further studies are required to validate the functionality of this protein, its precise amino acid sequence, and mechanism(s) leading to such fragmentation.

Summary

The incidence of AKI is growing at an alarming rate and its role in the development of CKD is increasingly recognized, making identification and implementation of novel therapeutics an exigent challenge. The presented case vignette focuses on rhabdomyolysis-induced AKI, and based on seminal findings reported by Nath and colleagues, it is evident that HO-1 is robustly induced in the kidney during rhabdomyolysis.[7] The significance of such induction was elegantly underscored by pre-induction of HO-1 being shown to improve kidney function and survival, and conversely chemical inhibition of HO being obeserved to lead to exacerbation of AKI. These pivotal findings have been corroborated in different animal models of AKI, and more recent human studies have validated these findings.[13] As discussed in this review, HO-1 mediates cytoprotection during AKI through regulation of several different pathways (Box 1). Future studies should aim to utilize the aforementioned transgenic animals to discover novel therapeutics to induce HO-1 in a timely manner to prevent and/or treat AKI. Recognition of early biomarkers will be a valuable asset to expedite these studies. Furthermore, human studies ought to expand our knowledge regarding HO-1 gene polymorphisms in different AKI settings. Knowledge gained from these studies could be implemented to identify patients at higher risk, paving the way towards a more “personalized medicine” approach. There are a number of ongoing clinical trials targeting the HO-1 pathway in the kidney, heart, and other organ systems, or in various phases of completion (ClinicalTrials.gov study numbers NCT01430156, NCT00483587, NCT02142699, and NCT00531856). A broader understanding of how endogenous adaptive responses such as HO-1 can be exploited as an approach to developing new therapeutic strategies in the setting of AKI would allow us to translate findings in the laboratory to the clinic.

BOX 1

Regulatory actions of HO-1 during AKI

Property
Apoptosis
Autophagy
Inflammation
Oxidative stress
Regulation of miRNA
Biomarker function; Endothelial cell integrity
Immune cell trafficking; Regulation of cell cycle

HO-1, heme oxygenase 1; miRNA, microRNA

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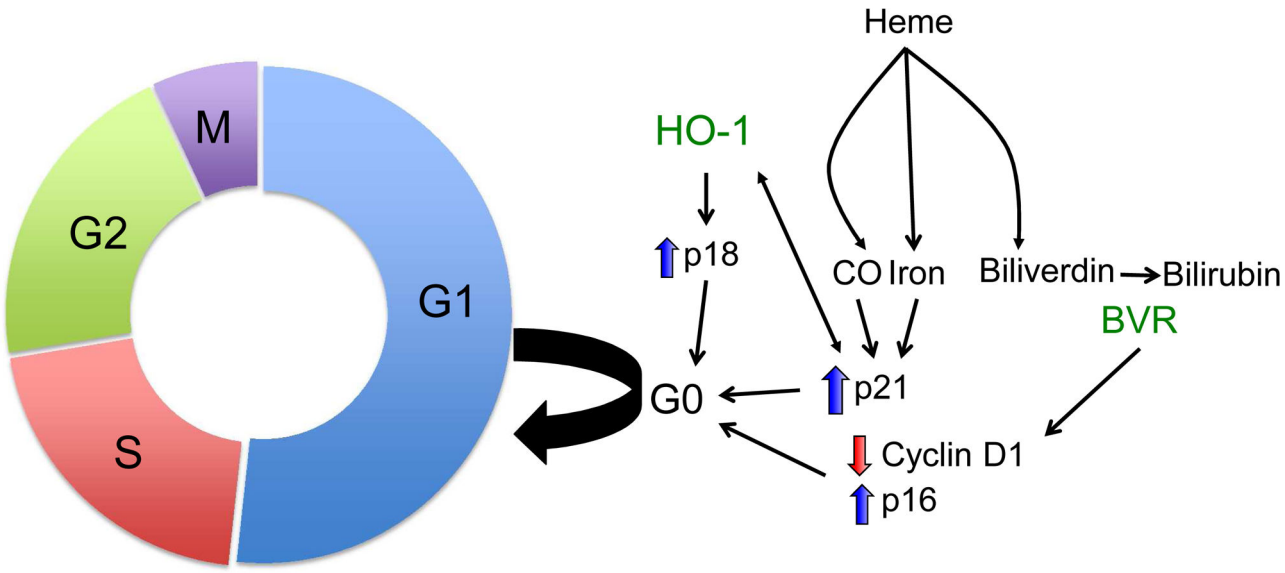

Figure 1.

Heme oxygenase-1 (HO-1) modulates cell cycle progression. HO-1 upregulates the expression of cell cycle regulators p21 and p18, and arrests cell cycle progression from G1 to S phase. By-products of the HO reaction, CO, and iron also mediate arrest via p21. Biliverdin reductase expression leads to cellular senescence via regulation of p16 and cyclin D1.

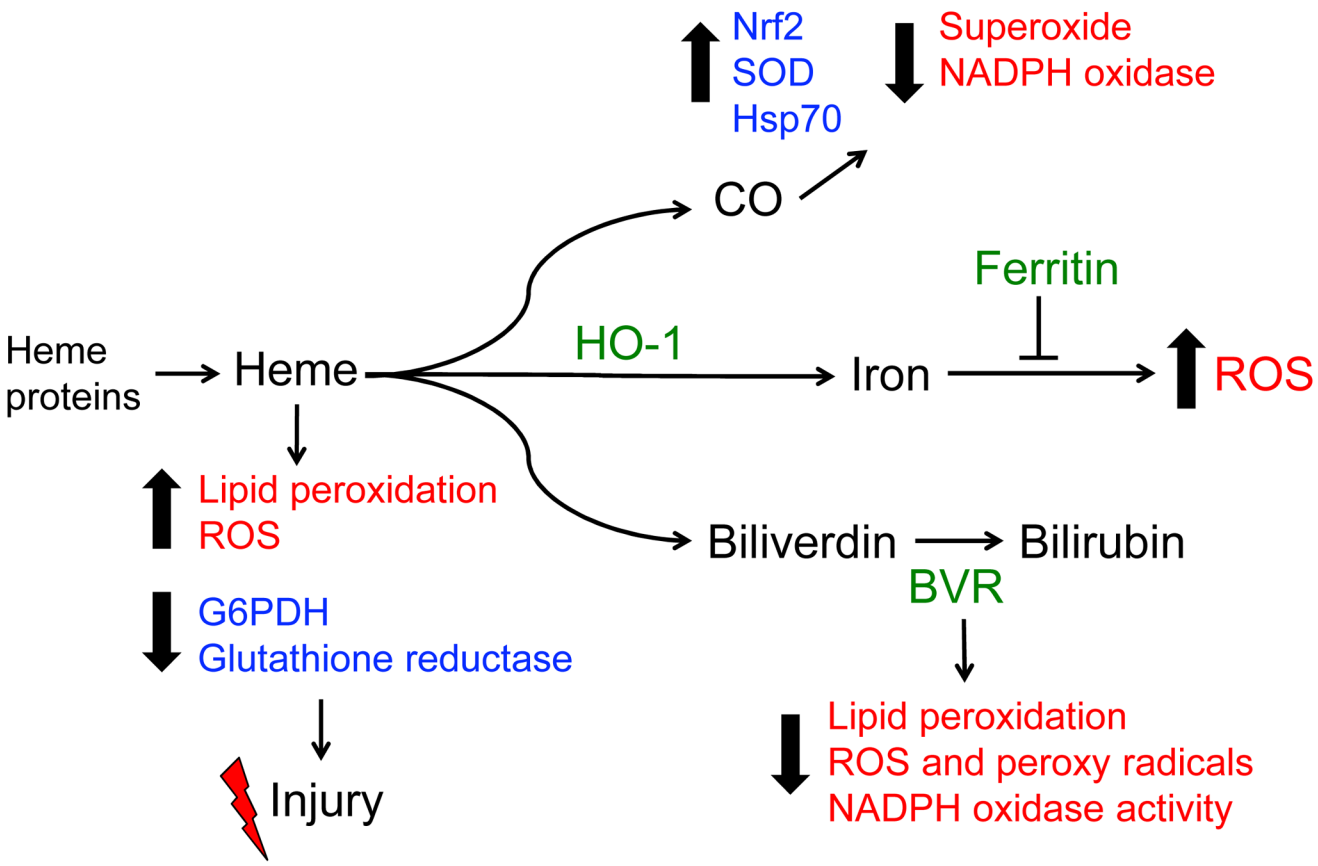

Figure 2.

HO-1 inhibits oxidative stress. HO-1 degrades pro-oxidant heme and generates potent anti-oxidant molecules, bile pigments, and carbon monoxide (CO). Heme amplifies oxidative stress by inducing lipid peroxidation and ROS generation, while inhibiting the activity of glutathione reductase and glucose-6-phosphate dehydrogenase (G6PDH). CO and bile pigments decrease oxidative stress via inhibiting NADPH Oxidase and sequestering ROS. CO also upregulates the anti-oxidant machinery, including superoxide dismutase (SOD), heat shock protein 70 (Hsp70), and activation of Nrf2. Iron released from the reaction is safely sequestered by ferritin, and thereby mitigates ROS generation.

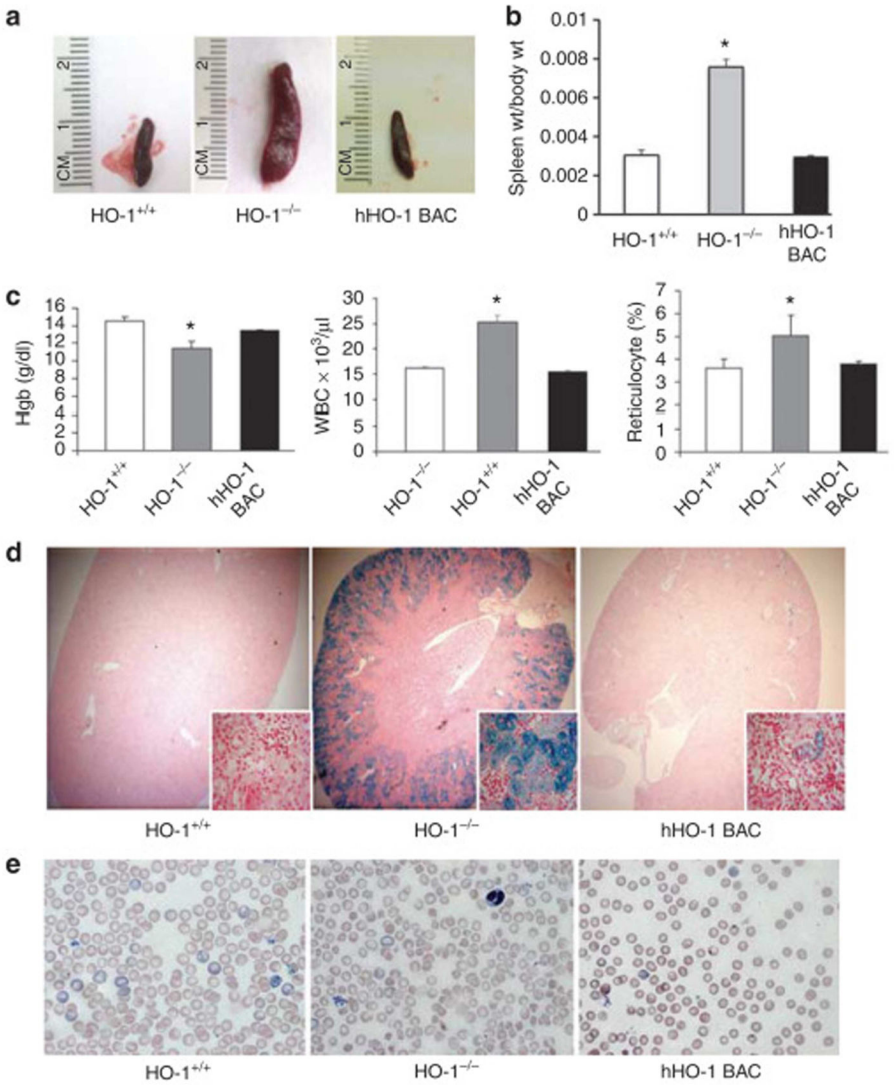

Figure 3.

Human heme oxygenase-1 (HO-1) in hHO-1 bacterial artificial chromosome (BAC) transgenic mice rescues the pathologic phenotype of HO-$1^{-/-}$ mice. Spleens from 25- to 35-week-old HO-$1^{+/+}$, HO-$1^{-/-}$, and hHO-1 BAC transgenic mice were compared for their (**a**) lengths and (**b**) weights (wt). Weights of spleen were normalized to body weight of each animal, and average normalized values were plotted for each group (mean±standard error of the mean). *P<0.05 vs. HO-$1^{+/+}$ and hHO-1 BAC mice. (**c**) Whole blood from 30- to 40-week-old HO-$1^{+/+}$, HO-$1^{-/-}$, and hHO-1 BAC mice were analyzed for hemoglobin (Hgb), leukocyte (white blood cell (WBC)), and reticulocyte counts. *P<0.05 vs. HO-$1^{+/+}$ and hHO-1 BAC mice. (**d**) Prussian blue staining was performed on kidneys from 25- to 35-week-old HO-$1^{+/+}$, HO-$1^{-/-}$, and hHO-1 BAC mice to detect tissue iron. (**e**) red blood cell (RBC) morphology was determined by Wright-Giemsa staining on peripheral blood smears from HO-$1^{+/+}$, HO-$1^{-/-}$, and hHO-1 BAC mice. Reproduced from Kim et al.[77] with permission of the International Society of Nephrology.

TABLE 1

The effects of manipulation of HO-1 or its by-products during AKI

Manipulation	Phenotype	Model	Effect	Ref
HO-1 knockout	Global HO-1 deficiency	Mouse kidney IR	Increased MCP-1, IL-6; reduced IL-10	32, 33
HO-1 knockout	Global HO-1 deficiency	Mouse unilateral ureteral obstruction	Increased MCP-1, IL-6; reduced IL-10	37
Adenovirus-mediated transduction of kidney with HO-1 expression vector	Kidney-specific HO-1 overexpression	Rat kidney IR	Preserved kidney function	11
HO-1 knockout	Global HO-1 deficiency	Mouse cisplatin nephrotoxicity	Worse kidney structural & functional injury	9, 72
HO-1 overexpression	Global HO-1 overexpression	Mouse cisplatin nephrotoxicity, rhabdomyolysis	Preserved kidney structure & function	77
HO-1 knockout in PTCs	PTC-specific HO-1 deficiency	Mouse cisplatin nephrotoxicity	Worse kidney structural & functional injury	76
HO-1 overexpression in PTCs	PTC-specific HO-1 overexpression	Mouse cisplatin nephrotoxicity	Preserved kidney structure & function	76
Adenovirus-mediated transduction of BMDM with HO-1 expression vector	BMDM-specific HO-1 overexpression	LPS/IFN injury	Increased IL-10-1; reduced TNF-α, NO	28
HO-1 knockout in myeloid cells	Myeloid cell–specific HO-1 deficiency	Mouse kidney IR	Egress of kidney dendritic cells to lymph node for antigen presentation	33
GFP-positive, HO-1 knockout mice	Global HO-1 deficiency and GFP expression	Mouse syngeneic kidney transplant	Egress of donor kidney dendritic cells to lymph node for antigen presentation	33
HO-1-overexpressing HEK293	HO-1 overexpression	Human renal epithelial cells	Inhibits ROS generation, autophagy, & apoptosis; promotes cell survival during oxidative stress	72
Mitochondria-targeted HO-1 expression vector in PTCs from HO-1 knockout mice	Mitochondria-specific overexpression of human HO-1 in murine HO-1-deficient PTCs	Mouse PTCs: hypoxia	Inhibits apoptosis & promotes cell survival during hypoxic stress	81
Mitochondria-targeted HO-1 expression vector	Mitochondria-specific HO-1 overexpression	Human renal epithelial cells	Inhibits ROS generation & apoptosis following hypoxia & oxidative stress	81
Gunn rat	Increased bilirubin	Rat hyperoxia	Increased resistance to free radical injury	89
Acute cholestatic liver disease	Increased bilirubin	Rat rhabdomyolysis	Protects against rhabdomyolysis injury	88

Abbreviations: ischemia reperfusion, IR; monocyte chemoattractant protein 1, MCP-1; interleukin, IL; bone marrow–derived macrophages, BMDM; tumor necrosis factor, TNF; nitric oxide, NO; green fluorescent protein, GFP; reactive oxygen species, ROS; Ref, reference; proximal tubular cell, PTC; HO-1, heme oxygenase 1; IFN, interferon; LPS, lipopolysaccharide

TABLE 2

Agents reported to be protective during AKI through HO-1 or its by-products

Agent	Property	Model	Effect	Ref
Methylene chloride	Induction of CO	Rat allogeneic kidney transplant	Reduced anti-donor immunogenicity	41, 42
Cobalt protoporphyrin	Induction of HO-1	Rat allogeneic kidney transplant	Inhibition of DC migration and anti-donor immunogenicity	41
Methylene chloride	Induction of CO	Rat allogeneic kidney transplant	Decrease in DCs, alloreactive and $CD4^+$ T cells and chronic allograft dysfunction	42
CO	250 ppm CO	T Lymphocytes	Inhibits T cell proliferation	44
Cerivastatin*	Induction of HO-1	Rat renal IR	Reduced kidney injury and dysfunction	45
Capsaicin*	Induction of HO-1	Mouse cisplatin nephrotoxicity	Inhibits oxidative stress, inflammation, and kidney injury	46
Adiponectin	Induction of HO-1	Mouse renal IR	Inhibits apoptosis, inflammation and kidney injury	47
Hepatocyte growth* factor	Induction of HO-1	Mouse endotoxemia	Prevention of acute kidney failure	48
Hydrogen gas*	Induction of HO-1	Mouse Sepsis (CLP)	Promotes survival	49
Bardoxolone methyl	Induction of HO-1	Mouse IR	Reduced structural and functional kidney injury	147
Bardoxolone methyl	Induction of HO-1	Mouse aristolochic acid nephropathy	Reduced structural and functional kidney injury	148
Epigallocatechin-3- gallate*	Induction of HO-1	Rat contrast-induced nephropathy	Inhibits oxidative stress and inflammation	149
Epigallocatechin-3- gallate	Induction of HO-1	Mouse unilateral ureteral obstruction	Inhibits oxidative stress and inflammation	150
IL-10*	Induction of HO-1	Mouse LPS-induced septic shock	Anti-inflammatory effect	35
Heme, iron, CO*	Induction of HO-1	TNF-α/cycloheximide, staurosporine, serum deprivation	Increased sensitivity to apoptosis in the absence of HO-1 and p21	58
Myoglobin*	Induction of HO-1, p21	Human renal epithelial cells	Promotes cell cycle arrest	60
Hemin*	Induction of HO-1	Mouse renal epithelial cells	Induces p18 and protects against cisplatin injury	64
Rapamycin	Induction of HO-1	Human renal cancer cells	Inhibits autophagy and apoptosis and promotes cell survival	73
Sorafenib	Induction of HO-1	Human renal cancer cells	Inhibits autophagy and apoptosis	73
Hemoglobin	Induction of HO-1	Rat rhabdomyolysis	Induces HO-1 and protects against rhabdomyolysis	7
Hemin	Induction of HO-1	Rat renal IR	Induces HO-1 and protects against IR	82
Erythropoietin *	Induction of HO-1	Rat chronic tubulointerstitial injury (salt sensitive Dahl rat model)	Induces HO-1 and protects against oxidative stress	151
NGAL	Induction of HO-1	Mouse renal IR	Inhibits azotemia and protects against injury	152
Bilirubin	Increased bilirubin	Rat kidney IR	Improved vascular resistance, tubular function, mitochondrial integrity	90
Carbon monoxide	Increased CO	Pig cardiopulmonary bypass-AKI	Reduced kidney injury and dysfunction	94
CORM-2	Increased CO	Rat sepsis induced AKI	Inhibits oxidative stress, inflammation and kidney injury	96

Agent	Property	Model	Effect	Ref
Bilirubin	Increased bilirubin	Rat endotoxin-mediated toxicity	Inhibits NADPH Oxidase and NOS2 expression and prevents mortality	86

Abbreviations: lipopolysaccharide, LPS; dendritic cells, DC; carbon monoxide, CO; ischemia reperfusion, IR; cecal ligation puncture, CLP; carbon monoxide–releasing molecule 2, CORM-2; HO-1, heme oxygenase 1; NADPH, reduced nicotinamide adenine dinucleotide phosphate; Ref, reference

* reversal/rescue of effect with inhibitors of heme oxygenase activity or supplementation of heme oxygenase by-products.