

Research Reveals How Heme Oxygenase-1 Directs the Immune Response after Acute Kidney Injury

New research indicates that an enzyme known to be important in the body's response to kidney injury exerts its protective effects in part by affecting the myeloid cells of the immune system. The findings, which are published in the *Journal of the American Society of Nephrology*, may lead to new kidney-protective treatments.

Heme oxygenase-1 (HO-1) is a cytoprotective enzyme that regulates the inflammatory response to tissue injury by converting highly reactive free heme molecules into carbon monoxide, iron, and biliverdin. People with HO-1 deficiency often experience severe hemolysis, dysregulated inflammation, kidney abnormalities, and premature death.

In an effort to uncover the effects of HO-1 after acute kidney injury (AKI), a team of researchers led by Anupam Agarwal, MD, of the University of Alabama at Birmingham, studied mice lacking expression of HO-1 systemically or in certain immune cells.

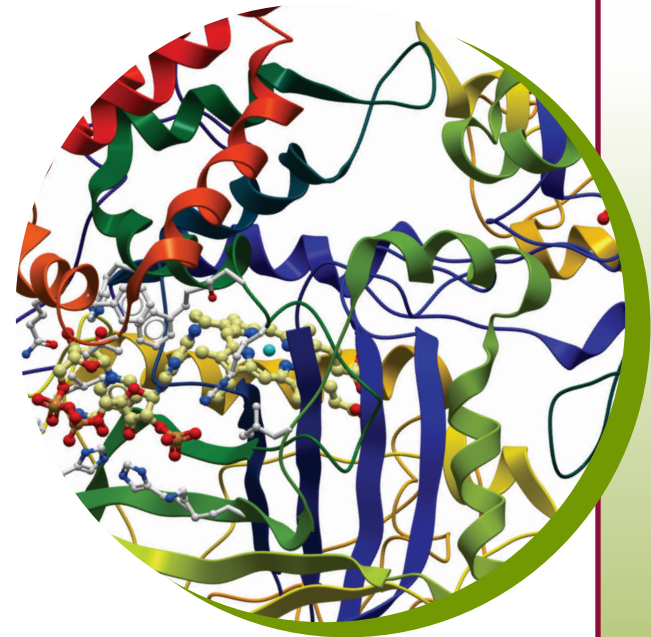
In age-matched male wild-type and HO-1-knockout mice that underwent bilateral renal ischemia for 10 minutes, ischemia-reperfusion injury resulted in significantly worse renal structure and function and increased mortality in the knockout mice. In addition, there were more macrophages and neutrophils in the knockout mice's kidneys after ischemia-reperfusion but a significant decrease in the population of intrarenal resident dendritic cells. Immunofluorescence experiments revealed increased migration of the resident dendritic cell population from the kidneys to the peripheral lymphoid organs in knockout mice compared with wild-type mice. This

effect on renal dendritic cell migration was corroborated in myeloid-specific HO-1 knockout mice subjected to bilateral ischemia. These mice also evidenced impaired kidney recovery and increased fibrosis after injury.

"We utilized HO-1 transgenic mice and cell tracking experiments to demonstrate that HO-1 expression within renal cells is important to protect in the early period after injury, while myeloid expression of HO-1 regulates how these cells traffic throughout the body after injury," said Agarwal.

David Ferenbach, MD, PhD, who was not involved in the study and is a clinical fellow at the University of Edinburgh, noted that an accumulating field of evidence now points to the role of HO-1 as an important protector against AKI and that these latest results offer valuable new information. "Whilst not the headlined finding of the paper, important new data is shown that demonstrates that in animals with a targeted deletion of HO-1 in only myeloid cells, there is still worsened later injury and increased subsequent fibrosis compared to controls," he said. "This validates earlier studies suggesting that despite the widespread tubular induction of HO-1 in response to drugs, the renal macrophage/dendritic cell may be the key cell population mediating the protective effects of HO-1 expression."

Ferenbach noted that some evidence shows that aged mice have reduced levels of HO-1 in kidney cells and an increased susceptibility to renal injury. "It would be very useful to explore in human samples whether there are similar situations where HO-1 levels may fall, and whether these produce injury and scarring problems anal-



ogous to those seen in this paper," he said.

If the study's findings are validated in humans, HO-1 could be an important target in preventing the transition of AKI to chronic kidney disease, said Agarwal. HO-1-based treatments may also have broader clinical applications, although it is important to consider that HO-1 can have disparate functions in different cell types.

"Given the human relevance of HO-1 in AKI and the growing understanding of the myeloid cells in renal health and disease, these studies... provide the foundation for a whole new area of AKI research," noted Gilbert Kinsey, PharmD, PhD, of the University of Virginia, in an accompanying editorial. ●

Industry Spotlight

Ups and Downs in Clinical Trial Results

Several kidney-related drug trials have recently yielded results. ProMetic Life Sciences (Laval, Quebec), announced that it had successfully completed its phase 1b clinical trial of PBI-4050 in patients with chronic kidney disease (CKD).

The randomized double-blind, placebo-controlled, multidose trial was designed to demonstrate the safety and tolerability of PBI-4050, an orally active antifibrotic drug candidate. The trial also determined the pharmacokinetic profile of PBI-4050 while monitoring multiple oral doses during 10 days in patients with stage 3b or 4 stable renal impairment. The trial was performed in a group of eight patients: six patients received PBI-4050, and two received a placebo.

"We are pleased to see that the safety and pharmacokinetic profiles of our lead drug candidate remain unaffected by the severely impaired renal function in the patients tested," said chief medical officer John Moran. "Since fibrosis is the pathological pathway

leading to organ failure and death in many diseases of differing etiologies ... we plan to test the efficacy of this drug in several fibrosis-related conditions." Phase II trials in patients with metabolic syndrome and resulting in type 2 diabetes were expected to begin patient enrollment in April 2015.

Pharmalink AB, a specialty pharmaceutical company based in Sweden, has announced that a phase 2b trial of Nefecon for the treatment of primary IgA nephropathy has met its primary efficacy endpoint at a planned interim analysis. The trial was stopped early with respect to statistical analysis of the endpoint.

The randomized double-blind, placebo-controlled clinical trial assessed the safety and efficacy of two different doses of Nefecon, a new oral modified-release capsule of the corticosteroid budesonide. The corticosteroid was administered daily during a 9-month treatment period to patients with primary IgA nephropathy having persistent proteinuria despite optimized standard-of-care therapy. The trial

was conducted in 62 centers in 10 European countries and was originally intended to recruit 90 patients, but 150 eventually were included.

Bengt Fellström, MD, PhD, professor of nephrology at Uppsala University Hospital, and principal investigator of the Nefecon trial, said, "IgA nephropathy is the most common inflammatory renal disease and in real need of new treatment options. Existing options are insufficient to prevent a significant proportion of patients from progressing to renal failure, with a devastating impact on patients' quality of life."

Zacks Equity reported the results of a phase 2a trial that failed to meet its primary endpoint of progression-free survival in patients with advanced renal cell carcinoma. Shares of Lpath, based in San Diego, "plunged in after-market trading" after the company's announcement of results from a phase 2a study of oncology candidate Asonop, Zacks wrote. The company will decide on the future of the candidate upon completion of the renal cell carcinoma trial. ●