ACUTE KIDNEY INJURY NOVEL PROTECTIVE ROLE OF H-FERRITIN

Transgenic mice with targeted deletion of the ferritin heavy chain (FtH) in renal proximal tubules are more susceptible to acute kidney injury (AKI) than their wild-type littermates, according to findings just published by researchers at the University of Alabama at Birmingham, USA. “These findings underscore the importance of FtH expression in proximal tubules as a protective response during AKI,” states lead investigator Anupam Agarwal.

Injury caused by reactive oxygen species is pivotal in the development and progression of AKI, and free catalytic iron is a major generator of reactive oxygen species. Although the liver and intestines are key sites of iron homeostasis, the role of the kidney in iron metabolism is relatively unstudied. To address this shortfall, Agarwal and co-workers conditionally deleted *Fth1*—which encodes an intracellular protein that stores and releases iron—in renal proximal tubules, the kidney region most susceptible to damage in AKI. The researchers assessed the effects of *Fth1* knockout in two models of AKI, glycerol-induced rhabdomyolysis and cisplatin nephrotoxicity.

Fth1^{PT-/-} mice with rhabdomyolysis-induced AKI displayed increased mortality, and renal outcomes were worse in both models, as shown by elevated serum creatinine levels and increased numbers of tubular casts and necrotic tubules, versus wild-type mice. Knockout of *Fth1* aggravated AKI despite increased levels of heme oxygenase 1 (HO-1), a protective antioxidant protein, indicating that HO-1 is unable to provide renal protection in the absence of FtH. Levels of the iron-trafficking protein ferroportin were also markedly lower in *Fth1*^{PT-/-} mice than in wild-type mice, regardless of the presence or absence of AKI, suggesting that FtH directly regulates the expression of ferroportin and, therefore, controls iron trafficking *per se*.

This study substantiates the deleterious effect of free iron in AKI and defines the proximal tubule as the main site of iron-induced renal injury, as well as highlighting the pivotal role of proximal tubule FtH in iron metabolism and trafficking. Agarwal adds, “Our data corroborate iron sequestration as a novel preventive and/or therapeutic modality in AKI”.

David Holmes

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