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EDITORIAL

Protease mediated tubular injury: A new direction in acute renal failure?

In this issue of *Kidney International*, Carmago, Shah, and Walker present evidence that meprin A, a metalloprotease present in the brush-border of tubular epithelial cells, plays a key role in hypoxic/ischemic acute renal tubular injury in rats [1]. This is an exciting observation that may signal a new direction in the pathogenesis of acute renal failure.

Meprin is an acronym for **me**tallo-**p**eptidase from **r**enal tissue [reviewed in 2, 3]. The enzyme was first isolated by Bond et al from tubular brush-border membranes prepared from kidneys of BALB/c mice. Two isoforms of meprin have been identified, meprin A and meprin B, that exhibit significant differences in amino acid composition, catalytic activity, and substrate specificity. Both meprins exist as disulfide-linked, oligomeric, membrane-bound, glycoproteins containing one zinc atom and three calcium ions per 85 kD subunit. Meprin A (the better characterized and more active isoform) is able to degrade a variety of biologically active peptides and proteins potentially relevant to renal injury, including α-atrial natriuretic peptide transforming growth factor (TGF-α), endothelin I, big endothelin I, bradykinin, and angiogensin I and II. Meprins are inhibited by the classical inhibitors of metalloproteinases such as ethylenediaminetetraacetic acid (EDTA) but not by inhibitors of serine, cysteine, or aspartic proteinases. Important for this discussion, the naturally occurring peptide hydroxamate, actinonin, is a potent inhibitor of rat meprin A.

The first hint that meprin might play an important role in renal pathophysiology appeared in 1985, when Beynon and Bond reported that the kidney is the only major organ that exhibits significant meprin activity [4]. Importantly, human kidney does contain meprin, albeit at lower levels than rat or mouse kidney. The story unfolds nicely from there, although with an interval of nearly 10 years. In 1994, Kaushal, Walker, and Shah purified a matrix-degrading, 350 kD, neutral metalloproteinase from rat kidney cortex [5]. Surprisingly, amino acid sequence determination of the N-terminal and two internal fragments of the purified proteinase showed it to be identical to the meprin A subunit. In addition, they reported that meprin is the major neutral endopeptidase in rat kidney, accounting for 5% or more of the total tubular protein. Shortly after that, Trachtman et al reported that following either bilateral renal artery clamping or glycerol-induced actute renal failure, mouse strains exhibiting normal meprin activity developed more severe renal structural and functional injury than mouse strains with low meprin activity [6]. Subsequently Walker, Kaushal, and Shah demonstrated that meprin A could cleave the basement membrane component nidogen [7]. They also reported that following renal ischemia-reperfusion in rats, meprin A undergoes a translocation from the tubular brush-border membrane to the cytoplasm and tubular basement membrane. In the current paper, Carmago, Shah, and Walker first demonstrate that exogenously added meprin is cytotoxic to porcine proximal tubular cells (LLC-PK1) and Madin-Darby canine kidney (MDCK) cells in culture. Interestingly, this toxicity is not mediated by cell detachment. They then show that kidney slices (used because cultured renal cell lines do not express meprin) are protected from hypoxia-reoxygenation injury by the specific meprin inhibitor, actinonin. Finally, and most exciting, is their observation that treatment of rats with actinonin provides both histological and functional protection of the kidney following 40 minutes of renal ischemia. Taken together, these studies provide convincing evidence for a pathogenic role for meprin A in hypoxic/ischemic acute renal tubular injury in rats.

As with most good research, this study raises more questions than it answers. For basic scientists, the primary question is, how does meprin mediate its cytotoxic effects? One possibility is the degradation of some protein or peptide critical for tubular cell function or survival. In this light, the ability of meprin A to degrade endothelin, atrial natriuretic peptide, TGF-α, angiotensin I and II, and bradykinin might be considered. Perhaps the shift of meprin from the tubular brush-border to the basement membrane impedes tubular regeneration and repair by degradation of one or more components of the extracellular matrix. Alternatively, meprin could produce a cytotoxic peptide. These and other possible mechanisms will no doubt be examined, hopefully in the near future. Additional important questions for clinical nephrologists include the following: Does inhibition of meprin attenuate the reduction in renal function associated with ischemia-reperfusion injury in humans? Does meprin-mediated cytotoxicity contribute to other types of acute renal injury? If the answer to either of these questions is "yes," then meprin could be a lucrative target for therapeutic intervention in such pathologies.

Key words: meprin, protease-mediated injury, actinonin, metalloprotease, acute renal failure.

The path from the lab bench to the bedside is littered with promising ideas that ultimately did not play out. Clearly, the jury is still out on the role of meprin and the therapeutic potential of meprin inhibitors in acute renal failure. However, to paraphrase the protagonist in Mary Shelly's famous novel, *Frankenstein*, "Good science, however erroneously directed, scarcely ever fails in ultimately turning to the solid advantage of mankind." I look forward to reading about the "solid advantages" that I predict will result from the continuation of this interesting and exciting work.

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