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BASIC RESEARCH

Inhibitor of FLC–THP binding prevents AKI in myeloma kidney

A proof-of-concept study showing that intraluminal cast formation is involved in the pathogenesis of acute kidney injury (AKI) from cast nephropathy supports the therapeutic potential of targeting this pathogenetic step in the management of renal failure in patients with multiple myeloma.

The development of cast nephropathy involves binding of Tamm–Horsfall glycoprotein (THP) to the CDR3 region of immunoglobulin free light chains (FLCs) in the distal nephron. The formation of intraluminal casts obstructs tubular fluid flow and can lead to the development of AKI and progressive renal failure. In their study, Wei-Zhong Ying and colleagues first identified amino acid sequences in the CDR3 region of FLCs that are critical for coprecipitation with THP, by using a yeast 2-hybrid system and mutagenesis experiments. They then used data generated by these experiments to synthesize a cyclized inhibitor peptide, which prevented binding of FLCs to THP.

To investigate the hypothesis that inhibition of FLC–THP binding might prevent AKI arising from cast nephropathy, the researchers administered either vehicle or the cyclized inhibitor peptide to rats 2 h before and 24 h after an injection of cast-forming human FLCs. Histological examination of kidney tissue at 48 h revealed a significantly lower number of intraluminal casts in peptide-treated rats than in vehicle-treated rats. Administration of inhibitor peptide, but not vehicle, also prevented the functional manifestations of AKI.

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The researchers also performed a rescue experiment, in which rats received the inhibitor peptide or vehicle several hours after administration of FLCs. After 48 h, mean serum creatinine level in inhibitor peptide-treated rats had not increased significantly from baseline levels and was significantly lower than that of vehicle-treated rats. Histological analysis also demonstrated a significantly lower number of casts in the peptide-treated group. “The goal of this research has always been to understand this disease process at the molecular level, then translate the findings through an animal model and ultimately back to the human condition”, explains researcher Paul Sanders. “We think we have developed a novel inhibitor that can prevent or mitigate renal failure from cast nephropathy in humans, although achieving the goal of translating this information back to the bedside remains for future studies.”

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