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ER stress inhibitor therapy offers protection from acute kidney injury through the repression of CHOP/GADD153

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ER stress has been shown to be associated with acute kidney injury (AKI) from a variety of causes including radio contrast, cisplatin, antibiotics and ischemia. We investigated if therapy with a known ER stress inhibitor, 4-Phenylbutyrate, would prevent AKI induced by the nucleoside antibiotic tunicamycin. Tunicamycin injection (I.P., 0.5 mg/kg) in the C57BL/6 mouse lead to AKI characterized histologically as acute tubular necrosis (ATN) occurring in the proximal convoluted tubule of the cortex as well as in the straight proximal tubule (Pars Recta) of the outer medullary stripe. This damage included tubular epithelial cell vacuolization, appearance of apoptotic nuclear as demonstrated by TUNEL staining, ER stress marker expression including nuclear CHOP/GADD153 expression and ultrastructural degeneration of the epithelial cells with intact basement membrane. Pre-treatment of these animals with 4-Phenylbutyrate (1 g/kg/day), before tunicamycin injection, prevented the pathological findings of ATN described above, significantly lowered the tubular injury score and repressed ER stress marker expression. 4-Phenylbutyrate therapy also repressed CHOP/GADD153 expression and normalized Pars Recta ultrastructure. Mechanistic experiments conducted in human proximal tubular cells demonstrated that the tunicamycin-induced ATN response was medicated by CHOP/GADD153. Genetic disruption of CHOP/GADD153 in the C57BL/6 mouse prevented tunicamycin-induced AKI. In conclusion, CHOP/GADD153 appears to be a viable molecular target for the inhibition of AKI. Investigations are ongoing to determine if this result may be generalized to AKI of diverse etiology including ischemia due to chronic heart failure.

Biography

Jeffrey G Dickhout received his PhD from McMaster University. He was the inaugural holder of the Division of Nephrology Junior Researcher award. He is currently an Assistant Professor in the Department of Medicine, Division of Nephrology at McMaster University and St. Joseph's Healthcare Hamilton. His research program is currently supported by the Canadian Institutes of Health Research. He also holds the McMaster University, Department of Medicine Internal Career Research Award. He has published over 25 peer-reviewed papers.

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