Nephro-2013

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Nephrology & Therapeutics

July 29-31, 2013 Embassy Suites Las Vegas, USA

The role of endoplasmic reticulum stress in the chronic inflammatory response in kidney disease

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Abstract

Endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) have been shown to be important in the chronic inflammatory process via activation of nuclear factor-κB and activating protein 1(AP1) stimulation. UPR activation also has been shown to occur or be required for the differentiation of a number of cellular components of the immune system including T-cells, plasma cells, macrophages and in myofibroblast differentiation. We have determined the presence of both a UPR response and a chronic inflammatory response in our models of acute and chronic kidney disease. We want to determine if ER stress and subsequent UPR induction results in this chronic inflammatory response through IRE1 mediated nuclear factor-κB signaling. The tunicamycin model is a model of ER stress induced acute kidney injury. We show that tunicamycin leads to a chronic inflammatory response characterized by T-cell infiltration. Further, this T-cell infiltrate is reduced in mice treated with the ER stress inhibitor 4-PBA along with down regulation of the expression of a number of UPR response genes including GRP78, CHOP and TDAG51. Further, in a model of chronic kidney disease, the Dahl S rat, we have observed a similar chronic inflammatory response characterized by T-cell infiltration and linked to the development of salt-sensitive hypertension and proteinuria. This T-cell infiltrate was inhibited by the ER stress inhibitor, 4-PBA (1g/kg/day), treatment. Thus, it appears that the ER stress response and UPR activation are part of the chronic inflammatory response associated with renal injury in both acute and chronic disease.

Biography

Jeffrey G. Dickhout received his PhD from McMaster University. He trained as a Postdoctoral Fellow with Dr. Allen W. Cowley Jr. in Physiology at the Medical College of Wisconsin. 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 has published over 25 peer-reviewed papers. The overall goal of his research is to better understand the relationship between renal dysfunction and cardiovascular disease.