

Abstract Submission No. : IL-9006

ER-Mitochondrial Crosstalk in Diabetic Kidney Disease

John He
Icahn School of Medicine at Mount Sinai, United States

ABSTRACT

Renal tubular epithelial cell (RTEC) injury contributes to kidney fibrosis and progression of diabetic kidney disease (DKD). However, the major risk factors contributing to RTEC injury in DKD remains unclear. We demonstrate that expression of reticulon 1A (RTN1A) in RTEC is increased in the diabetic kidney and associated with the progression of DKD in human. RTN1A induces RTEC injury in vitro through increasing endoplasmic reticulum (ER) stress. We demonstrate that induction of RTN1A expression specifically in RTEC induces renal fibrosis and decline of renal function in animal models of DKD. Interestingly, we find that RTN1A interacts with several mitochondrial proteins and a published study from others shows that RTN1A is abundantly expressed in the ER-mitochondria contact (EMC), suggesting a potential role of RTN1A in regulation of EMC. To confirm this, we show that overexpression of RTN1A in RTEC induces not only ER stress and but also mitochondrial dysfunction. Tunicamycin, a known ER stress inducer, promotes not only ER stress but also mitochondrial dysfunction in RTEC, which is further aggravated by RTN1A overexpression but improved with RTN1A knockdown. RTN1A also mediates high glucose-induced ER stress and mitochondrial dysfunction in RTEC. In diabetic mice, overexpression of RTN1A in RTEC also increases both ER stress and mitochondrial dysfunction. Among the RTN1A-interacted mitochondrial proteins, hexokinase 1 (HK1) is on the top of the list. RTN1A competes with VDAC1 to bind to HK1 at the mitochondrial outer membrane. Overexpression of RTN1A releases HK1 from VDAC1, leading to the activation of pro-apoptosis and inflammasome pathway. Overall, our study demonstrates that RTN1A-mediated EMC may play a critical role in RTEC injury and progression of DKD.