Abstract

Chronic kidney disease (CKD) affects around 14% of the global population and the number of affected individuals is expected to continue to rise. Current management is focused on improving cellular lipid metabolism and mitochondrial function, or to reduce ER stress and tubular glucose reabsorption, and have gained attention, suggesting an important role of these metabolic pathways as therapeutic targets for CKD.

We and others demonstrated that ATP-binding cassette A1 (ABC1)-mediated cholesterol ester-induced podocyte injury plays a major role in the progression of glomerular diseases of metabolic and non-metabolic origin, including diabetic kidney disease (DKD), renal disease associated with Alport Syndrome (AS) and focal segmental glomerulosclerosis (FSGS). Overexpression of ABC1 or pharmacological induction of ABCA1 (ABCA1) is sufficient to paratively rescue glomerular injury in proteinuric mice, suggesting that ABCA1 may represent novel therapeutics for patients with CKD. Interestingly, these ABCA1's were developed to compete with oxysterol binding to oxysterol-binding protein (OSBP) like 7 (OSBP7), a member of a group of lipid-binding proteins involved in movement of lipids between membranes. Recent studies suggest a role for OSBP7 in cholesterol transfer from the endoplasmic reticulum (ER) to the Golgi, in cholesterol efflux and in the regulation of ABCA1 expression. However, if OSBP7 is expressed in the kidney and it is involved in the preservation of ER function has not been explored.

In this study, we demonstrate that OSBP7 is expressed in podocytes isolated from wildtype and Col4a3/- mice, an experimental mouse model of chronic kidney disease. Western blot analysis revealed that OSBP7 protein levels are reduced in kidney cortex of Col4a3/- mice, so OSBP7 Podocytes and HEK293 cell lines were established using siRNA yielding these cells deficient in OSBP7. HEK cells do not express ABCA1 making them a valuable tool to study the ABCA1 independent effects of OSBP7. so OSBP7 podocytes and HEK293 cells show increased levels of ER stress, cytotoxicity and apoptosis. Overexpression of OSBP7 in Col4a3/- podocytes lead to a reduction in apoptosis levels further indicating a beneficial role of OSBP7 in podocytes. Future studies will address the role of OSBP7 in podocyte lipid trafficking in chronic kidney disease that may lead to the identification of novel therapeutic targets for the treatment of this prevalent and costly disease.

Hypothesis

OSBP7 deficiency causes ABCA1-independent ER stress thus linking OSBP7 deficiency to podocyte injury and CKD progression.

Proposed Mechanism

Methods

Immunofluorescence: Podocytes were grown on glass slides in 6-well plates at 33C, and differentiated for 14 days at 37C, then fixed and exposed to immunoperoxidase or anti-OSBP7 antibodies and imaged by fluorescent microscopy.

Results

Conclusions

• Determine the role of OSBP7 in modulating ABCA1-dependent cholesterol export in podocytes.
• Analyze the lipid trafficking consequences of OSBP7 deficiency in podocytes.

Future Directions

References

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