Proteinuria: it is time to look beyond the proximal tubule

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TUBULOINTERSTITIAL FIBROSIS is a prominent feature of end-stage kidney disease. However, the mechanism of tubulointerstitial injury preceding chronic kidney disease remains to be undetermined. The degree of proteinuria has been utilized as a surrogate marker for prognosis and response to medical therapy in glomerular diseases. Proteinuria was proposed to induce progression by facilitating tubulointerstitial inflammation and fibrosis. Controversial hypotheses were put forward in regard to the mechanism of proteinuria-induced progression in glomerular diseases (1). It was suggested that increased protein trafficking as a result of albumin overload in the proximal tubule epithelial cells facilitates tubulointerstitial inflammation and fibrosis that is observed in proteinuric states independent of the glomerular pathology. Another hypothesis proposes that proteinuria-induced tubulointerstitial injury originates from tubular alterations as a result of encroachment of the glomerulotubular junction caused by glomerular crescents. However, there is a little doubt that in vivo and in vitro exposure to high concentrations of albumin result in production of proinflammatory and profibrogenic molecules in the proximal tubule cells (3, 4, 10).

The role of proximal tubule in albumin endocytosis renders it the focus of attention in proteinuric states. Proximal tubule epithelial cells handle 3–5 g of albumin in the glomerular filtrate via receptor-mediated endocytosis (9). In in vitro and in vivo albumin overload models, it was demonstrated that albumin endocytosis in the proximal tubule through megalin and cubilin receptor complex trigger production of proinflammatory and profibrogenic mediators such as transforming growth factor-β1 (TGF-β1), regulated on activation normal T-expressed and presumably secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), endothelin, and NF-κB that results in tubulointerstitial inflammation, fibrosis, and tubular apoptosis (10). Despite the convincing in vitro data, glomerular proteinuria models in mice with mosaic knockout of megalin and cubilin receptor complex trigger production of proinflammatory and profibrogenic mediators such as transforming growth factor-β1 (TGF-β1), regulated on activation normal T-expressed and presumably secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), endothelin, and NF-κB that results in tubulointerstitial inflammation, fibrosis, and tubular apoptosis (10). Despite the convincing in vitro data, glomerular proteinuria models in mice with mosaic knockout of megalin and cubilin receptor complex trigger production of proinflammatory and profibrogenic mediators such as transforming growth factor-β1 (TGF-β1), regulated on activation normal T-expressed and presumably secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), endothelin, and NF-κB that results in tubulointerstitial inflammation, fibrosis, and tubular apoptosis (10). 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labeled network. Therefore, the profibrogenic and proinflammatory effect of albumin overload in CCDs may explain the lack of protective effect of isolated megalin deletion in proximal tubules.

This study not only enhances our understanding of mechanism of proteinuria-induced tubulointerstitial damage but also paves the way for future studies to dissect the trafficking of albumin in CCD. The future questions include the role of clathrin and adaptor molecules in albumin handling in CCD. Despite >80% of inhibition in 24p3R expression with small interfering RNA, the decrease in albumin uptake was ~30%, which brings the possibility of another receptor contributing to albumin endocytosis in CCD. The possible cross talk between 24p3R and sodium channels in CCDs may reveal an overlap between albumin endocytosis and trafficking of sodium channels. If so manipulating the overlapping pathways may attenuate tubulointerstitial damage and hypertension in proteinuric states.

Future research will shed light to the mechanism proinflammatory/profibrogenic response involved in albumin endocytosis in distal nephron and whether blocking this pathway may lead to promising therapies to halt progression of the glomerular diseases.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: E. E. conception and design of research; E. E. analyzed data; E. E. interpreted results of experiments; E. E. drafted manuscript; E. E. edited and revised manuscript; E. E. approved final version of manuscript.

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