

Podocyte and Proteinuria; Upregulation of Integrin-linked Kinase is a Convergent Pathway Leading to Podocyte Dysfunction and Proteinuria

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Integrin-linked kinase (ILK), an intracellular serine/threonine protein kinase that plays a crucial role in the regulation of cell adhesion, extracellular matrix production and epithelial to mesenchymal transition (EMT), has been implicated in various proteinuric glomerular diseases such as nephrotic syndrome or diabetic nephropathy. Recent studies have shown that ILK is essential for podocyte biology in normal physiologic setting, as podocyte-specific ablation results in nephrin redistribution, heavy proteinuria, podocyte detachment and glomerulosclerosis. However, it remains elusive as to the role of ILK in podocyte injury in pathologic conditions. We investigated the regulation and function of ILK in conditionally immortalized podocytes and in murine proteinuric glomerular disease model induced by adriamycin (ADR). We found that ILK expression in podocytes was induced by various injurious stimuli, such as ADR, puromycin, transforming growth factor- β 1 (TGF- β 1) and high glucose condition, in both time- and dose-dependent manner, suggesting that upregulation of ILK is a convergent response after podocyte injury. Ectopic expression of ILK in podocyte via adenoviral vector induced mesenchymal markers such as desmin, fibronectin and α -smooth muscle actin (α -SMA). In addition, ILK-over-expressing podocytes displayed an altered actin cytoskeletal pattern and increased albumin filtration across podocyte monolayer, as demonstrated by a paracellular albumin flux assay. Blockade of ILK activity with a small molecule inhibitor, QLT 0267 suppressed the expressions of fibronectin, α -SMA and Matrix metalloproteinase-9 (MMP-9) induced by TGF- β 1 or ADR treatments. Furthermore, QLT 0267 reduced TGF- β 1 or ADR-mediated albumin filtration across podocyte monolayer. In vivo, heavy albuminuria developed in mice after a single injection of ADR at 12 mg/kg body weight. Remarkably, intraperitoneal injection of QLT 0267 suppressed albuminuria in mice in a dose-dependent manner. QLT 0267 inhibited glomerular induction of ILK, α -SMA and MMP-9 and restored nephrin expression in ADR-injected mice. Upregulation of ILK is convergent pathway leading to podocyte injury and proteinuria, and targeting ILK may be a novel strategy for the therapeutics of various proteinuric glomerular diseases.