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Src tyrosine kinase in diabetic kidney disease

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Diabetic kidney disease is the leading cause of end-stage renal disease and is the result of persistent hyperglycemia. Activation of multiple signaling pathways such as angiotensin II (AngII) and transforming growth factor-beta (TGF-beta) in diabetic kidney disease induces excessive extracellular matrix accumulation, results in renal fibrosis. TGF-beta is an important mediator of organ fibrosis, and AngII-mediated renal fibrosis is mediated by TGF-beta signaling.
Epidermal Growth Factor Receptor (EGFR) is a receptor tyrosine kinase that is known to regulate many cellular processes such as proliferation, differentiation, cytoskeleton regulation and transcription. Previous studies have shown that EGFR is also associated with renal fibrosis mediated by AngII and TGF-beta.
Src is a non-receptor tyrosine kinase that affects multiple tyrosine signaling pathways, including cytoskeletal dynamics. Src can inactivate RhoA by mediating tyrosine phosphorylation and activation of p190Rho-GAP, thereby inhibiting cell adhesion and destroying the actin cytoskeleton. Recent study showed that EGFR/Src mediated tyrosine phosphorylation of synaptopodin in podocytes accelerates the binding of serine / threonine phosphatase to calcineurin. This leads to loss of 14-3-3 binding, resulting in synaptopodin degradation and ultimate loss of stress fibers in podocytes.
In STZ-diabetic mice model, albuminuria, increased Src and EGFR phosphorylation, glomerular collagen accumulation and podocyte loss were inhibited by the Src inhibitor, PP2. This data indicated that Src plays an important role in the pathway of high glucose-Src-EGFR signaling for collagen accumulation in diabetic mice model.
Thus, many studies from in vitro and animal models, src may be a novel therapeutic target for diabetic kidney disease.