GSK3β: a key regulator of glomerular podocyte injury in diabetic kidney disease

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Keywords: GSK3β hyperactivity, Diabetic Podocyte Injury, Senescence

Published: 14 December 2023

Background: Emerging evidence suggests that glycogen synthase kinase (GSK3β), a critical transducer downstream of the insulin signaling pathway, acts as a convergent point for myriad pathways implicated in kidney injury, repair, and regeneration (1-3). However, its role in the pathogenesis of diabetic kidney disease remains highly controversial and was examined here (4, 5).

Methods: Mouse podocytes were cultured under non-permissive conditions and exposed to a diabetic milieu containing high ambient glucose and insulin in the presence of proinflammatory stimulation. Cells were additionally subjected to GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with tideglusib, a highly-selective small molecule inhibitor of GSK3β. Podocyte injury was assessed and signaling pathways examined.

Results: Upon diabetic insult, podocytes demonstrated prominent signs of cytopathic changes, marked by loss of homeostatic marker proteins like synaptopodin, increased oxidative stress and apoptosis, and stress-induced premature senescence, as evidenced by increased staining for the acidic senescence-associated-β-galactosidase activity, amplified formation of γH2AX foci, and elevated expression of mediators of senescence signaling, like p21 and p16INK4a. Podocyte injury was associated with a reduction in inhibitory phosphorylation of GSK3β, denoting GSK3β hyperactivity. In podocytes overexpressing S9A, diabetic podocytopathy was worsened, concomitant with a desensitized insulin signaling activity, enhanced senescence response, impaired Nrf2 antioxidant response and the ensued exacerbation of oxidative damages. Conversely, GSK3β knockdown potentiated the insulin signaling, reinforced Nrf2 antioxidant response, and suppressed senescence, resulting in an improvement in podocyte injury. This protective effect was mimicked by tideglusib co-treatment, suggesting that GSK3β hyperactivity plays a key role in mediating diabetic podocytopathy.

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Conclusion: Our findings indicate that GSK3β hyperactivity contributes to glomerular podocyte injury in diabetic kidney disease, suggesting that therapeutic targeting of GSK3β may represent a novel strategy for the treatment of diabetic kidney disease.

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