# Glycogen synthase kinase (GSK) 3beta hyperactivity impairs glomerular podocyte insulin signaling via IRS1 modulation in diabetic kidney disease

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**Background:** Insulin signaling in kidney cells, in particular podocytes, is essential for maintaining kidney homeostasis, independent of glycemic levels. As a critical transducer of insulin signaling, GSK3beta also acts as a convergent point for myriad pathways implicated in kidney injury. However, its role in DKD remains elusive.

**Methods:** Mouse podocytes were exposed to insulin or a type 2 diabetic milieu, following GSK3beta silencing, ectopic expression of a constitutively active GSK3beta mutant (S9A), or treatment with tideglusib, a GSK3beta inhibitor. Podocyte injury was assessed and results validated in kidneys from db/db mice.

**Results:** Upon insulin stimulation, insulin signaling mediators like Akt and GSK3beta, were phosphorylated, associated with increased glucose uptake and expression of GLUT. GSK3beta silencing sensitized insulin signaling, marked by potentiated induction of p-Akt and p-ERK1/2 and enhanced

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glucose uptake and GLUT expression. Conversely, S9A de-sensitized insulin signaling and mitigated GLUT induction and glucose uptake. Among the many insulin signaling transducers, IRS1 co-precipitated and interacted with GSK3beta. Moreover, in silico analysis indicated that IRS1S332, resides in the consensus motifs for phosphorylation by GSK3beta. Indeed, insulin-induced p-IRS1S332 was suppressed by GSK3beta silencing but was enhanced by S9A. Furthermore, in podocytes exposed to a type 2 diabetic milieu, inhibitory p-GSK3betaS9 was suppressed, denoting GSK3beta hyperactivity. This was associated with enhanced p-IRS1S332. Tideglusib treatment counteracted this effect, re-sensitized insulin signaling, and averted diabetic podocyte injury. In db/db mice, expression of p-IRS1S332 was augmented in glomerular podocytes. Based on immunoblotting, the expression ratio of p-GSK3betaS9/GSK3beta in glomeruli was repressed in db/db mice as compared with control mice, denoting GSK3beta hyperactivity, which negatively correlated with the level of p-IRS1S332.

**Conclusion:** Diabetes-associated GSK3beta hyperactivity promotes IRS1 phosphorylation, contributing to insulin signaling desensitization in podocytes. Therapeutic targeting of GSK3beta could re-sensitize insulin signaling in podocytes via regulation of IRS1.

**Keywords:** GSK3beta hyperactivity, Hyperinsulinemia, Diabetic Kidney Disease

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