Protein tyrosine phosphatase 1B deficiency in podocytes protects against hyperglycemia-induced renal injury

Author(s)

Yoshihiro Ito[1], Ahmed Bettaieb[1], MingFo Hsu[1], Shinichiro Koike[1], Aline Mello[1], Fawaz G. Haj[1]

Authors affiliation(s)

University of California Davis[1], CA, USA

Abstract

Diabetic nephropathy is one of the most devastating complications of diabetes, and growing evidence implicates podocyte dysfunction in disease pathogenesis. Protein tyrosine phosphatase 1B (PTP1B; encoded by PTPN1) is an established metabolic regulator in vivo but its metabolic functions in podocytes remains unexplored. To that end, we generated podocyte-specific PTP1B knockout (pod-PTP1B KO) mice and determined alterations under normoglycemia and streptozotocin (STZ)- and high fat diet (HFD)-induced hyperglycemia. pod-PTP1B KO mice displayed significant improvement in renal function and glucose homeostasis under STZ- and HFD-induced hyperglycemia. Consistent with these findings, podocyte PTP1B deficiency was associated with increased renal insulin signaling and enhanced autophagy with corresponding decrease in inflammation and fibrosis. These effects were recapitulated in E11 murine kidney podocytes with lentiviral-mediated PTP1B knockdown, consistent with being cell-autonomous. Moreover, reconstitution of PTP1B in knockdown cells reversed the improved insulin signaling and autophagy demonstrating that they were likely a consequence of PTP1B deficiency. Together, these findings identify PTP1B in podocytes as a significant contributor to signaling events following hyperglycemia-induced damage, and suggest that PTP1B inhibition in podocytes may be of value in combating podocytopathies.