No. 1626

The Prolyl Isomerase Pin1 Increases β Cell Proliferation and Enhances Insulin Secretion

Tomoichiro Asano

Hiroshima University

Summary

The prolyl isomerase Pin1 binds to the phosphorylated Ser/Thr-Pro motif of target proteins and enhances their cis-trans conversion. This report is the first to show that Pin1 expression in pancreatic β cells is markedly elevated by high-fat diet feeding and in ob/ob mice. To elucidate the role of Pin1 in pancreatic β cells, we generated β cell-specific Pin1 KO (βPin1 KO) mice. These mutant mice showed exacerbation of glucose intolerance but had normal insulin sensitivity. We identified two independent factors underlying impaired insulin secretion in the βPin1 KO mice. Pin1 enhanced pancreatic β cells proliferation, as indicated by a reduced β-cell mass in βPin1 KO mice compared with control mice. Moreover, a diet high in fat and sucrose failed to increase pancreatic β cell growth in the βPin1 KO mice, an observation to which up-regulation of the cell cycle protein cyclin D appeared to contribute. The other role of Pin1 was to activate the insulin secretory step. Pin1 KO β cells showed impairments in glucose- and KCl-induced elevation of the intracellular Ca^{2+} concentration and insulin secretion. We also identified salt inducible kinase 2 (SIK2) as a Pin1-binding protein that affected the regulation of Ca^{2+} influx and found Pin1 to enhance SIK2 kinase activity, resulting in a decrease in p35 protein, a negative regulator of Ca^{2+} influx. Taken together, our observations demonstrate critical roles of Pin1 in pancreatic β cells and that Pin1 both promotes β cell proliferation and activates insulin secretion.