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Title: The roles of FoxO1 in the insulin target organs

Abstract
Type 2 diabetes is caused by the dysfunction of pancreatic β cells as well as the insulin resistance in peripheral tissues. However, recent genetic studies revealed that β cell failure is also accounted by the insulin resistance in β cell itself. To clarify the molecular mechanism of insulin resistance, we need to understand intracellular insulin signaling. The forkhead transcription factor FoxO1 is a downstream effector of insulin signaling, and a direct target of Akt. We have been studying the roles of FoxO1 in various insulin target organs, such as liver, skeletal muscle, adipose tissue, hypothalamus, vessels, and pancreas. In this seminar, I will focus on FoxO1 in pancreatic cell differentiation. We have shown that transgenic mice expressing a constitutively active FoxO1 specifically in pancreas have abnormal α / β cell composition, increased duct structures, reduced exocrine acinar cells, islet hypervascularities, and increased islet innervation. Conversely, pancreas specific FoxO1 knockout mice have increased insulin-positive duct-associated cells and exhibit improved glucose tolerance. We propose that FoxO1 plays important roles in pancreatic β cell differentiation and/or neogenesis. Manipulation of FoxO1, either genetically or pharmacologically, may contribute to the development of new strategies to treat diabetes.