A genetic model of adult type 2 diabetes mellitus of fetal origin

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Altered fetal environments increase the risk of global pandemic type 2 diabetes mellitus, but the underlying mechanisms are poorly defined due to the lack of genetic models. Genome-wide gene profiling and real time PCR analyses demonstrate that many transforming growth factor-β (TGFβ) superfamily genes are expressed during development, and are then progressively down-regulated to undetectable levels in adult islet cells. Pancreas-specific deletion of the TGFβ family member bone morphogenetic protein receptor type 1a (Panc cKO) reduced expression of the key cell-cell interaction molecule E-cadherin in developing islets and transiently impaired their architecture. Postnatally, Panc cKO mice displayed glucose intolerance after a short episode of metabolic stress and their islets had an abnormal expression profile of approximately 700 genes. Among them, there was striking overexpression of tryptophan hydroxylase 1 gene, encoding the rate-limiting enzyme catalyzing the production of 5-hydroxytryptamine (5-HT), which emerges as a critical regulator of β-cell function and proliferation. Aging Panc cKO mice exhibited reduced expression of several key regulators of β-cell function, significantly lower fasting insulin and higher pancreatic insulin content, and spontaneous glucose intolerance. Hence we demonstrate that modifying gene expression during fetal development leads to adult diabetes, which provides a novel genetic model for mechanistic studies.

Biography

Fang-Xu Jiang is the Head of Islet Cell Development Program, the University of Western Australia and has extensive experience in medical research both in Australia and China. His Program is completely committed to identify a regenerative therapy for type 1 diabetes and subtypes of type 2 diabetes. In addition to molecular genetic studies of diabetes, as example above, several stem cell research programs are also actively pursued under his leadership, that are sought broader international collaborations.