FOXO TRANSCRIPTION FACTORS IN TYPE 2 DIABETES

The forkhead box O family consists of FoxO1, FoxO3, FoxO4 and FoxO6 proteins in mammals. They share a common structural motif, namely the “forkhead box” or “winged helix” domain that is responsible for binding to chromatin DNA in the nucleus of cells. FoxO proteins act as nuclear transcription factors that mediate the inhibitory action of insulin or insulin-like growth factor on key functions in diverse pathways including cell metabolism, proliferation, differentiation, oxidative stress, cell survival and senescence, autophagy and aging in mammals. Genetic mutations in FoxO genes or abnormal expression of FoxO proteins are associated with metabolic disease, cancer or altered lifespan in humans and animals. My laboratory focuses on the studies of FoxO1 in glucose and lipid metabolism. FoxO1 is abundantly expressed in the liver and its transcriptional activity is tightly regulated by insulin. Insulin inhibits FoxO1 activity via a distinct mechanism by altering its subcellular redistribution. We showed that insulin signaling bifurcates at FoxO1 in the liver to govern two metabolic pathways, namely gluconeogenesis and very low-density lipoprotein (VLDL) assembly. This effect helps synchronize hepatic insulin signaling to simultaneously adjust the rates of hepatic glucose production and VLDL secretion in response to nutrient availability. Such FoxO1-dependent mechanism seems pivotal for the liver to rapidly adapt to metabolic shift between fasting to feeding states for maintaining normal glucose and lipid homeostasis. Our studies provided mechanistic insights into how FoxO1 orchestrates insulin action on hepatic glucose and lipid metabolism in healthy individuals, and how FoxO1 dysregulation, resulting from insulin resistance, contributes to the dual pathogenesis of hyperglycemia and hyperlipidemia in obesity and type 2 diabetes. We screened for small molecule drugs against FoxO1, demonstrating that pharmacological FoxO1 inhibition translated into a significant beneficial effect on glucose and lipid metabolism in mice with diabetic dyslipidemia. Our studies characterize FoxO1 as a potential therapeutic target for improving blood glucose and lipid profiles in type 2 diabetes.

Biography

H Henry Dong is the Professor of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, USA. He is a member of American Diabetes Association. He is serving as an Editorial Board Member of Journal of Biological Chemistry, Molecular Metabolism, and Journal of Diabetes and its Complications.

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