

Editorial

Mechanisms of Heart Failure in Type 2 Diabetes Mellitus

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The prevalence of Type 2 diabetes mellitus and the metabolic syndrome has increased dramatically and globally over last decades. Type 2 diabetes results from insulin resistance and metabolic syndrome is also known as insulin resistance syndrome, linking to obesity, hyperglycemia, dyslipidemia and hypertension. The metabolic syndrome is a high risk factor for type 2 diabetes and cardiovascular dysfunction and failure. Humans are now facing a crisis for healthcare problem medically and economically; therefore, understanding the mechanisms responsible for insulin action and insulin resistance has become crucial to develop promising therapeutic interventions and control diabetes and metabolic syndrome.

With the completion of human and mouse genomic projects, we begin to understand that about 25,000 genes and their encoding proteins govern the biological function of a cell, and it also has accumulated a large amount of information as to how genes function within a cell and their malfunctions result in diseases. One of the most important recent findings in biology is the molecular basis of longevity control. The key elements regulating longevity, from worm to fruit fly, are components or mediators that are involved in insulin action, of which downstream PI3K, protein kinase B (known as Akt), and the forkhead transcription factor FoxO1 are key in this set of regulation. We recently summarized how insulin acts, via PI3K and Akt activation, on FoxO1 protein and controls gene expression and energy metabolism in cells and organs of animals, which advance our understanding the physiological role of insulin action and FoxO in animals, while dysregulation of insulin at the levels of Akt and FoxO1 regulation can result in diabetes and heart failure [1].

The storage and release of energy during feeding and fasting are essential processes for development, growth, and survival, in which insulin plays a central role in promoting energy storage by activating a set of intracellular signaling cascades and activate or inactivate the hormone-responsive gene profiles that integrate to the metabolic pathways and maintain a steady levels of blood glucose and lipids. Dysregulation of insulin action causes insulin resistance, a primary contributor for metabolic syndrome including diabetes, obesity, and cardiovascular diseases. Over the last decade, we have significantly contributed to the development of important concepts in the field of insulin signal transduction and the molecular basis of regulation of

gene expression and energy metabolism. Genetic studies in worm *C. elegans* indicated that the insulin/IGF-1 signaling pathway via PI-3-kinase→protein kinase B/Akt→Forkhead transcription factor FoxO1 (FKHR) plays a key role in regulating longevity and metabolism. Our early studies demonstrated that the evolutionarily conserved signaling pathway regulates expression of a number of genes in mammalian liver cells. Using the IGF-binding protein-1 (IGFBP-1) gene as a model in cell-based experiments, our studies elucidated that insulin suppresses transcriptional expression of a set of genes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase that govern hepatic glucose production, via an insulin response element (IRE) in the gene's promoter region, and that signaling from PI-3 kinase and protein kinase B is necessary and sufficient in mediating the inhibitory effect of insulin through the IRE-sequence. My research then further demonstrated that FoxO1 interacts with the IRE in vitro and activates gene transcription of IGFBP-1 while mediating insulin inhibition on the gene expression in hepatocytes. In a collaboration with Dr. Phillip Cohen at the University of Dundee, we demonstrated that activation of protein kinase B/Akt in cells in response to insulin/IGF-1 phosphorylates FoxO1 at Thr²⁴, Ser²⁵⁶, and Ser³¹⁹, and phosphorylation of Ser²⁵⁶ primes phosphorylation of FoxO1 at other serine or threonine residues, such as Thr²⁴ and Ser³¹⁹, thus stimulating nuclear export of FoxO1, impairing its DNA binding activity, and executing the function of insulin on gene transcriptional profiling [2]. The pioneering work provides a general and fundamental mechanism by which insulin inhibits and/or promotes gene expression and regulates glucose and lipid metabolism, as well as many other unidentified cellular functions.

Cell-based studies on FoxO protein shed new insights on the molecular basis of insulin action, but the physiologic roles of FoxO in the regulation of gene expression and metabolic homeostasis in animals and its potential pathological role in disease processes in humans remain elusive and necessitate further investigation. Our studies revealed that insulin receptor substrates -1 and -2 (IRS-1, 2) are two major mediators of insulin action and regulate a series of covalent modifications of FoxO proteins in cells and tissues of mice via phosphorylation and ubiquitination. With the employment of a wide range of genetic and biochemical approaches, as well as molecular, cellular, animal and even human systems, we are to define the physiologic and pathological role of IRS and FoxO proteins in health and disease, and to further determine how dysregulation of the IRS→FoxO pathway alters metabolic homeostasis and predisposes diabetes when insulin signaling fails under different cellular and environmental contexts. We hypothesize that defects in any of the steps along the IRS-PI3K-Akt-FoxO signaling cascade can result in insulin resistance and diabetes, which serves as a major mechanism of pathogenesis of Type 2 diabetes and cardiovascular failure, by altering intracellular signaling and gene transcriptional profiling. In supporting this concept, our recent studies demonstrated that mice lacking IRS1 and IRS2 in the liver developed hyperglycemia and insulin resistance [3] and mice lacking IRS1 and IRS2 in the heart

developed heart failure [4], by largely impairing the PI3K, Akt and Foxo1 signaling cascade.

The long-term goal of my research is to study the molecular mechanisms of insulin signal transduction, insulin resistance and associated cardiovascular dysfunction aiming at therapeutic interventions for diabetes and cardiovascular medicine. My laboratory is focused on cellular signaling and gene transcriptional regulation of metabolic homeostasis by the PI3K→Akt→FoxO pathway, with the hope of understanding how the dysregulation of this pathway in insulin/IGF-1 action causes liver damage, cardiovascular dysfunction, and pancreatic beta cell failure, leading to diabetes, obesity, and heart failure. My research encompasses three areas: 1) Decoding the mechanism of insulin resistance and associated cardiovascular dysfunction. Excess nutrients (e.g. high fat diet) cause insulin resistance. Investigating how nutrient-mediated signaling activates novel intracellular mediators and then attacks the insulin→IRS→Akt→FoxO signaling pathway can provide a powerful platform for therapeutic intervention in treatment of diabetes and cardiovascular disorders. The discovery of small compounds (e.g. metformin), peptides, nucleotides, or stem cells that can increase gene expression of IRS or promote FoxO phosphorylation and ubiquitination could promote drug development or provide us with new insights for understanding the mechanism of insulin resistance and its complication. 2) Defining the roles of each of the FoxO proteins (FoxO1, 3, and 4) in insulin signaling and insulin resistance, through the creation of cell lines and animal models in which these proteins are either eliminated by a genetic “knock-out” or increased by overexpression. This will also include studies utilizing the techniques of tissue specific gene inactivation or activation (knock-in) to determine the role of FoxO in various tissues [5], including classic target tissues for insulin action such as the liver, heart, and adipose tissue, as well as other organs, such as pancreas, brain, and vessels. 3) Exploring new players mediating the action of insulin and other hormones, such as glucagon and angiotensin II, and identifying novel therapeutic targets and intervention in control of cellular metabolism and survival. We

have taken advantage of IRS and FoxO genetic models and a variety of approaches, including genomics, proteomics, and metabolomics, to better define the physiological connections between metabolic and survival events and FoxO proteins in intracellular signaling networks. The fundamental mechanisms of understanding insulin action and insulin resistance involving in the regulation of IRS and FoxO genes will provide a novel strategy for therapeutic development and potential cures for treating human diseases, including but not limited to, diabetes and cardiovascular failure in the future.

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