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# Decoding Insulin Resistance and Metabolic Syndrome for Promising Therapeutic Intervention

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Metabolic syndrome, also known as insulin resistance syndrome, has become a major public health problem worldwide. It consists of obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension. Metabolic syndrome is a high risk factor for the type 2 diabetes mellitus, which currently afflicts 22 millions of Americans and over 100 millions of Chinese population (Alberti, et al. 2005; Cornier, et al. 2008; Roger, et al. 2011). Importantly, metabolic syndrome is also a significant risk factor for cardiovascular disease and two-thirds of patients with diabetes mellitus die of heart failure (Roger et al. 2011). In 2011, an estimated 366 million people had diabetes and this number is predicted to rise to 522 million by 2030 over the world (Whiting, et al. 2011). The estimated costs of diagnosed diabetes in the United States of America have risen to $245 billion in 2012 from $174 billion in 2007 (Herman 2013). Obviously, understanding and controlling metabolic syndrome and associated cardiovascular disorders have far-reaching impact on our healthcare and economic systems that affect the quality of our daily life.

As a first step, understanding the mechanisms responsible for insulin action and resistance is critical to develop promising therapeutic intervention and control metabolic syndrome. In the thematic review section in this issue of the *Journal of Endocrinology*, we provide four review articles, discussing the disease mechanism of metabolic syndrome with the most recent research update from cell-based and animal studies, which address how insulin resistance in different organs contributes to metabolic syndrome at the molecular, biochemical, and physiological levels. In particular, our knowledge is largely focused on studies using genetically engineered mouse models, which have provided with detailed information with respect to inactivation of the insulin signaling cascade in the brain, adipose tissue, pancreas, muscle, and liver, as well as other tissues. Thus, we can determine the contribution of insulin resistance from each organ to the features of metabolic syndrome.

In the first review of the series, Dr. Guo updates our understanding of insulin signaling cascades, with an emphasis on the role of phosphatidylinositide-3-kinase (PI-3K) in metabolic control. A key aspect of insulin on metabolic regulation involves in activation of

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PI-3K by association with the insulin receptor substrate-1 and -2 (IRS1, 2) and subsequent Akt→Foxo1 phosphorylation, which has a central role in control of nutrient homeostasis and organ survival. A large amount of evidence suggests that inactivation of Akt and subsequent activation of the *forkhead/winged helix family* transcription factor Foxo1, through suppression IRS1 and IRS2 in organs following hyperinsulinemia, metabolic inflammation, and over nutrition, may provide key mechanisms for the metabolic syndrome in humans. Thus, targeting the IRS→Akt→Foxo1 signaling cascade will likely provide a strategy for therapeutic intervention in the treatment of type 2 diabetes mellitus and its complications. Recent studies from Guo's lab further demonstrated that suppression of IRS1 and IRS2 expression and functionality are observed in the liver and heart of animals with insulin resistance and/or type 2 diabetes, suggesting that loss of IRS1 and IRS2 not only contributed to occurrence of hyperglycemia, but also promoted heart failure and death in rodents (Qi, et al. 2013). Clearly, impaired and/or biased signaling cascade resulting from loss of IRS1 and IRS2 provides a common mechanism leading to deactivation of endogenous protein kinase Akt and activation of Foxo1 in accompany with development of type 2 diabetes mellitus and cardiac dysfunction.

Body weight and appetite are tightly controlled by the insulin signaling as a result of its interaction with other factors through a complex and multi-level integration process in central nervous system. Dr. Schneeberger *et al.* provide a concise and up-to-date overview of energy homeostasis control by hypothalamic and brainstem neurons. Insulin and/or leptin signaling in hypothalamic neurons, including AgRP and POMC neurons, has long-term and central roles in preventing food intake and obesity, as well as maintaining nutrient homeostasis. However, gastrointestinal hormones, such as ghrelin and GLP-1, and vagal afferents also provide short-term regulatory mechanisms in suppression of appetite and obesity. This indicates that alternative hormones and/or pathways can be targeted to achieve control of body weight and appetite regulation, in addition to pancreas-secreted insulin and the adipocyte-released hormone leptin.

Obesity results from excess proliferation and expansion of adipocytes. Dr. Cao provides a compelling review on how adipose tissue can secrete an array of hormones (adipokines or adipose secretome) that signal key organs to maintain systemic metabolic homeostasis and how dysregulation of this system has been causally linked to a wide range of metabolic diseases. Obesity induces production of inflammatory cytokines and infiltration of immune cells into adipose tissue, creating a state of chronic low-grade inflammation, termed metabolic inflammation that relates to a broad spectrum of pathological conditions, including insulin resistance.

Accumulation of lipids in adipose tissue, muscle, and others, via excess energy intake, also provides mechanisms for the build-up bioactive lipid species that interfere with the insulin signaling cascade. Dr. Tuner *et al.* reviewed that fatty acids, the essential elements of all cells, not only serve as components of cellular structure and fuel substrates, but also act as signaling molecules that activate intracellular protein kinases inhibiting the action of insulin on metabolic regulation in muscle. Moreover, excess metabolic intermediate - acetyl-CoA derived from fatty acid oxidation, has a profound effect on gene post-translational modifications, such as protein acetylation that epigenetically regulates energy homeostasis.

Overall, it is clear that insulin resistance in each organ differently contributes to the features of metabolic syndrome: Obesity is resulted from insulin resistance by the brain; hyperglycemia by the brain, pancreas, liver and fat; hyperlipidemia by the fat and brain; and hypertension by, at least, the vascular endothelial cells. We are hopeful that readers will find the four thematic reviews to be of high interest and that many will be prompted to decipher the mechanism of metabolic syndrome and further develop therapeutic intervention. Although most of the studies here are based on rodents, the important mediators and concepts in insulin signaling remain to be validated in humans. With extensive collaborations among basic scientists in academics, clinical investigators in healthcare system, and R&D researchers in biopharmaceutical industry, more rationale strategies need to be employed for new therapeutic development, as well as better disease control in the future.

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