

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 major risk factor for the development of type 2 diabetes mellitus, which currently afflicts 22 million Americans and over 100 million Chinese (Alberti *et al.* 2005, Cornier *et al.* 2008, Roger *et al.* 2011). Importantly, metabolic syndrome is also a significant risk factor for the development of 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 around the world had diabetes, and this number is predicted to rise to 522 million by 2030 (Whiting *et al.* 2011). The estimated costs of diagnosed diabetes in the USA have risen from \$174 billion in 2007 to \$245 billion in 2012 (Herman 2013). Obviously, understanding and controlling metabolic syndrome and associated cardiovascular disorders have far-reaching impacts 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 for developing therapeutic interventions and, thereby controlling metabolic syndrome. In this special issue of *Journal of Endocrinology*, we provide four thematic review articles, which combine discussion of the disease mechanism behind metabolic syndrome with the most recent research from cell-based and animal studies. These reviews address how insulin resistance in different organs contributes to metabolic syndrome at the molecular, biochemical, and physiological levels. In particular,

we largely focus on studies using genetically engineered mouse models, which have provided detailed information with respect to the 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 insulin resistance contribution of each organ to the clinical features of metabolic syndrome.

In the first review of the series, Dr S Guo updates our understanding of the insulin signaling cascade, with an emphasis on the role of phosphatidylinositol-3-kinase (PI3K) in metabolic control (Guo 2014). A key action of insulin on metabolic regulation involves activation of PI3K by association with the insulin receptor substrate 1 (IRS1) and IRS2, and subsequent phosphorylation of Akt → Foxo1. This pathway has a central role in the 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 the suppression of IRS1 and IRS2 in organs following hyperinsulinemia, metabolic inflammation, and overnutrition, may form key mechanisms for metabolic syndrome in humans. Thus, targeting the IRS → Akt → Foxo1 signaling cascade will probably provide a strategy for therapeutic intervention in the treatment of type 2 diabetes mellitus and its complications. Recent studies carried out in Dr Guo's laboratory have further demonstrated that suppression of IRS1 and IRS2 expression and functionality occurs in the liver and heart of animals with insulin resistance and/or type 2 diabetes, suggesting that loss of IRS1 and IRS2 not only contributes to the occurrence of hyperglycemia, but also promotes heart failure and death

in rodents (Qi *et al.* 2013). Clearly, an impaired and/or biased signaling cascade resulting from the loss of IRS1 and IRS2 forms a common mechanism leading to the deactivation of the endogenous protein kinase Akt and activation of Foxo1 in association with the development of type 2 diabetes mellitus and cardiac dysfunction.

Body weight and appetite are tightly controlled by insulin signaling as a result of its interaction with other factors through a complex and multi-level integration process in the central nervous system. Dr Schneeberger and colleagues provide a concise and up-to-date overview of energy homeostasis control by hypothalamic and brainstem neurons (Schneeberger *et al.* 2014). Insulin and/or leptin signaling in hypothalamic neurons, including the AgRP and POMC neurons, has long-term and central roles in suppression of appetite and obesity, as well as in the maintenance of nutrient homeostasis. However, gastrointestinal hormones, such as ghrelin and GLP1, and vagal afferents are also responsible for short-term regulatory mechanisms involved in the suppression of appetite and obesity. This indicates that alternative hormones and/or pathways can be targeted to achieve body weight and appetite control, in addition to pancreas-secreted insulin and the adipocyte-released hormone leptin.

Obesity results from an excessive 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 (Cao 2014). Obesity induces the production of inflammatory cytokines and the infiltration of immune cells into adipose tissue, creating a state of chronic low-grade inflammation, termed metabolic inflammation related to a broad spectrum of pathological conditions, including insulin resistance.

The accumulation of lipids in adipose tissue, muscle, and other organs, via excess energy intake, also provides mechanisms for the build-up of bioactive lipid species that interfere with the insulin signaling cascade. Dr Turner and colleagues report 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, thereby inhibiting the action of insulin on metabolic regulation in muscle. Moreover, an excess amount of the metabolic intermediate acetyl-CoA derived from fatty acid oxidation has a profound effect on gene post-translational modifications,

such as the protein acetylation that epigenetically regulates energy homeostasis.

Overall, it is clear that insulin resistance in each organ contributes differently to the features of metabolic syndrome: obesity results from insulin resistance in the brain; hyperglycemia from insulin resistance in the brain, pancreas, liver, and adipose tissue; hyperlipidemia from insulin resistance in adipose tissue and brain; and hypertension from insulin resistance in, 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 discussed herein are based on rodents, the important mediators and concepts of insulin signaling remain to be validated in humans. With extensive collaborations among basic scientists in academia, clinical investigators in healthcare systems, and R&D researchers in the biopharmaceutical industry, more rational strategies need to be employed for the development of new therapeutics, as well as for better disease control in the future.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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