Japan Academy Prize to:

Takashi Kadowaki
Professor, Graduate School of Medicine, The University of Tokyo

for “Molecular Basis of Type 2 Diabetes and Metabolic Syndrome”

Outline of the work:

Prof. Takashi Kadowaki found earlier from his own clinical/epidemiological research that (1) genetic predisposition, (2) impaired insulin response to glucose, and (3) obesity/insulin resistance are independent risk factors for type 2 diabetes. In the years that followed, while focusing on these three factors, he has continued to make maximum use of his expertise as a physician-scientist in collating and integrating epidemiological, clinical and genomic information from humans and gene expression as well as functional and biochemical information from genetically engineered animal models in an attempt to elucidate the fundamental pathophysiological bases of type 2 diabetes, including the molecular mechanisms of its onset. As described below, Prof. Kadowaki continues to labor at the cutting edge of global research into the molecular basis of type 2 diabetes and the metabolic syndrome. With a focus on insulin and adiponectin signaling, he has conducted a series of research projects related to the discovery of adiponectin receptors and their functional analyses. This work is of particular interest in that it opened up a whole new area of research in which Prof. Kadowaki continues to represent the leading edge.

1. Elucidation of diabetes susceptibility genes

In 1988, Prof. Kadowaki identified a phenotype of diabetes that results from insulin receptor gene aberrations and elucidated one of the molecular bases of the insulin hormone receptor abnormality. He went on to identify multiple insulin receptor abnormalities and contributed through their functional analyses to elucidating the correlation between the structure and the function of the insulin receptor. He has identified multiple subtypes of diabetes associated with mitochondrial DNA 3243 point mutation. In doing so, he established and proposed the pathophysiological concept “diabetes due to mitochondrial DNA aberrations” as a subtype of diabetes, which accounts for about 1% of all diabetes cases. Additionally, Prof. Kadowaki identified type 2 diabetes susceptibility genes in Japanese and Asian populations, and his work remains on the leading edge of research on the “diabetes-susceptible constitutional predisposition” in Japanese and Asian populations.

2. Elucidation of the function of key molecules involved in glucose regulation and their role in the pathogenesis of type 2 diabetes

While it has been widely known that the process of insulin-mediated glucose decrease starts with insulin binding to the insulin receptor, the rest of the process remains largely unelucidated. In 1994, Prof. Kadowaki was the first to engineer a mouse model deficient in the insulin receptor substrate-1 (IRS-1), which represents the second step in the process of insulin-mediated glucose decrease. He showed that the IRS-1-deficient mice were insulin-resistant, thus providing the first evidence of IRS-1 as playing an essential role in insulin action
and glucose metabolism. Prof. Kadowaki hypothesized that other insulin receptor substrates might be involved besides IRS-1 and identified IRS-2. He, then, went on to engineer whole-body and organ-specific IRS-1 and -2 mouse models to elucidate the role of IRS-1 and -2 in various tissues, including skeletal muscle, liver, pancreatic β cells, brain (hypothalamus), and the vascular system. He produced mouse models in which such key molecules as pancreatic β cell-derived glucokinase, NADH shuttle, adipocyte-derived PPAR-γ, and phosphatidylinositol-3 (PI3) kinase were genetically engineered, and clarified their functions and their roles in the pathogenesis of type 2 diabetes and the metabolic syndrome. Regarding the molecular mechanism of insulin resistance associated with obesity, Prof. Kadowaki proposed that normal, small-sized adipocytes secrete insulin-sensitizing hormones, while insulin-sensitizing hormones decrease as the adipocytes become enlarged or in the presence of obesity, thus causing insulin resistance.

3. Discovery of the insulin-sensitizing effect of adiponectin, identification and functional analysis of the adiponectin receptors

Adiponectin was an adipocyte-derived hormone independently discovered by four research groups including Matsuzawa’s. In 2001, Prof. Kadowaki hypothesized that the insulin-sensitizing hormone secreted by the small-sized adipocytes described above is in itself adiponectin and discovered through experiments adding adiponectin to a mouse model of obesity/type 2 diabetes associated with low adiponectin levels that adiponectin is an adipocyte-derived anti-diabetic hormone which increases insulin sensitivity. In 2003, Prof. Kadowaki was the first in the world to identify the adiponectin receptors (AdipoR1/R2) by using expression cloning. AdipoR1 and AdipoR2 are both seven-transmembrane receptors, whose N terminus is internal and whose C terminus is external, and thus have a topology opposite that of GPCRs, and represent a novel receptor family. It is known that AdipoR1 activates AMP kinase, while AdipoR2 activates PPRA-α. In 2007, Prof. Kadowaki produced mice deficient in both AdipoR1 and AdipoR2 and demonstrated that these receptors are essential in the onset of adiponectin action. AdipoR1 inhibits neoglucogenesis, lowers steatogenesis and promotes fatty acid burning through AMPK kinase activation in the liver, and AdipoR2 promotes fatty acid burning in the liver through PPAR-α activation in the liver, thus each improves insulin resistance. In 2010, Prof. Kadowaki found that AdipoR1 activates the longevity gene Sir1 downstream through AMPK kinase activation and that AdipoR1 regulates mitochondrial content and function through mitochondrial master regulator PGC-1α activation, thus promoting glucose/fatty acid burning and modulating exercise tolerance and insulin sensitivity. In obesity, not only the expression of adiponectin but the expression of AdipoR1 and AdipoR2 are decreased, thus leading to the onset of insulin resistance, the metabolic syndrome, and type 2 diabetes. In this regard, Prof. Kadowaki et al. were the first in the world to develop small-molecule adiponectin receptor agonists, and they showed in animal models that these adiponectin receptor agonists markedly improve type 2 diabetes and the metabolic syndrome, thus demonstrating that decreased adiponectin-adiponectin receptor signaling represents the most critical of the mechanisms involved in the onset of lifestyle-related diseases such as type 2 diabetes.

Prof. Kadowaki’s series of research projects that led to the discovery of the insulin sensitizing effects of adiponectin and to the discovery and functional analysis of the adiponectin receptors constitute a highly original research output from Japan and a breakthrough in medical and life science research. At the same time, his achievements have enabled an intrinsic understanding of the molecular mechanisms of the onset of lifestyle-related diseases, providing a basis for radical treatment modalities for type 2 diabetes, which not only causes complications in many patients but also continues to affect an increasing number of individuals. To date, Prof. Kadowaki’s original papers and review articles have been cited more than 35,000 times. Of note, limiting our attention to his adiponectin- and adiponectin receptor-related papers alone, to date they
have received an impressive over 10,000 citations in the literature. As a leading authority in his area of research, which accounts for an annual total of about 2,000 papers, Prof. Kadowaki has received critical global acclaim.

On the basis of his excellent research achievements that led to the elucidation of the molecular basis of type 2 diabetes and the metabolic syndrome, Prof. Kadowaki is eminently deserving to receive the Japan Academy Prize.

References


insulin sensitivity by increasing hepatic IRS-2 expression via macrophage-derived IL-6 dependent pathway. *Cell Metabolism* 13: 401-412, 2011