FS 1－1

A New Development in the NAD World：Therapeutic Potential of SIRT 1 and NAMPT-Mediated Systemic NAD Biosynthesis in Type 2 Diabetes

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In the pathogenesis of type 2 diabetes mellitus (T 2 DM), a delicate balance between insulin sensitivity and secretion is compromised by both environmental and genetic factors. While our current life style with nutrient-dense diets and the lack of enough exercise appears to cause an explosive epidemic of obesity and insulin resistance, people who manifest insulin resistance do not necessarily develop T 2 DM, implicating that the dysfunction of pancreatic β cells might play a critical role in the development of T 2 DM. Aging is one of the greatest risk factors for developing T 2 DM. It has been shown that a progressive decline in β cell function in the elderly is a major contributing factor to the pathophysiology of T 2 DM. Therefore, factors that contribute to age-associated changes in β cell function could also contribute to the pathogenesis of T 2 DM. One such factor is the mammalian nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase SIRT 1. For the past several years, there has been an increasing interest in SIRT 1 as a new therapeutic target for T 2 DM. Because SIRT 1 absolutely requires NAD for its activity, mammalian NAD biosynthesis has also drawn much attention in the field of metabolism. Indeed, we have demonstrated that the NAD biosynthesis mediated by nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting NAD biosynthetic enzyme in mammals, plays a critical role in the regulation of β cell function.

Based on our research, we have recently developed a novel concept for the systemic regulation of metabolism and aging in mammals, named "NAD World." The NAD World comprises two critical components: NAMPT-mediated systemic NAD biosynthesis as a driver that keeps up the pace of metabolism, and SIRT 1 as a mediator that executes regulatory effects in various organs/tissues in response to changes in systemic NAD biosynthesis. Strikingly, nicotinamide mononucleotide (NMN), a product of the NAMPT reaction and a novel plasma metabolite, plays an important role in the regulation of NAD biosynthesis and tissue functions at a systemic level. In mice, plasma NMN levels are significantly reduced with advanced age so that SIRT 1 activity in the most sensitive tissues, such as pancreatic β cells, is significantly affected. Indeed, NMN administration can restore normal glucose tolerance in mice with naturally occurring and diet-induced diabetes. This new concept of the NAD World provides important insights into a systemic regulatory mechanism that fundamentally connects metabolism and aging and also conveys the ideas of functional hierarchy and frailty for the regulation of metabolic robustness and aging in mammals.

FS 1－2

Lipid Mediated Insulin Resistance

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In this talk I will discuss the use of novel MRS methods to assess insulin stimulated glucose metabolism in humans and the relation between insulin sensitivity and lipid content in muscle and liver. I will present our studies using MRS techniques to examine mitochondrial function in human muscle non-invasively. Specifically I will review the use of ^{13}C MRS to assess rates of mitochondrial oxidation and ^{31}P MRS to assess rates of ATP synthesis.

I will then discuss the application of these methods to assess mitochondrial function in muscle of healthy lean in elderly subjects to examine the potential role of mitochondrial dysfunction in the pathogenesis of insulin resistance associated with aging.

I will review our studies on the relation between hepatic steatosis and hepatic insulin resistance in type 2 diabetic patients. Finally, I will review our recent studies on the relation between muscle insulin resistance and the early development of the metabolic syndrome. Specifically, I will review data on abdominal fat content and hepatic steatosis in different ethnic groups as assessed by MRS abd whole body MRI techniques.