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Research
Background
Over seven million Japanese are estimated to have
diabetes mellitus, a serious and costly disease.
Diabetes causes several major complications, such as
blindness, kidney failure, leg and foot amputations,
and cardiovascular diseases. People with diabetes
have a decreased ability to secrete sufficient insulin, a
hormone that allows glucose to enter cells and be
converted to energy. If diabetes is not controlled well,
excess glucose remains in the blood and damages a lot
of organs through vessels throughout the body. The
long-term goal of our research is to develop better
care for those with diabetes. To achieve this, we are
focusing on the following projects:

1. The role of autophagy in β-cell homeostasis
   Common features of type 2 diabetes mellitus are
   progressively decreased pancreatic β-cell function
   and β-cell mass, resulting in insufficient insulin
   secretion. We have shown that dysfunction of cellular
   autophagy occurs in islets of diabetic patients as well
   as mice under metabolic stress, such as high-fat-fed
   mice and db/db mice, and that autophagy-deficient
   mutant mice exhibit impaired glucose tolerance,
   partly due to the lack of a compensatory increase in
   β-cell mass. In addition, we have recently found that
   the forced expression of human IAPP, which is
   thought to cause β-cell failure in diabetic patients,
   caused deterioration of glucose tolerance in mice with
   a β-cell-specific autophagy defect, indicating that
   increased autophagy may enhance the toxic potential
   of hIAPP in diabetic patients. Now, we are exploring
   further molecular mechanisms of how autophagic
dysfunction is induced in β-cells under conditions of
   metabolic stress, and what role autophagy has in
   regulating β-cell survival and/or replication.

2. Regulation of glucose profiles by zinc signals
   Zinc is an essential nutrient for living organisms
   because its deficiency causes growth retardation,
imunodeficiency, hypogonadism, and neuronal and

Figure 1: Role of β cell autophagy in insulin resistance
sensory dysfunctions. Intracellular zinc homeostasis is controlled via coordinated regulation of zinc influx and efflux, where zinc transporters have essential roles. Recent genome-wide association studies (GWAS) have demonstrated that common variants of SLC30A8 increase susceptibility to type 2 diabetes. SLC30A8 encodes zinc transporter-8 (ZnT8), which delivers zinc from the cytoplasm into insulin granules. In order to uncover the roles of ZnT8 and its pathological implications, we have generated β-cell-specific Slc30a8−/− deficient mice. We demonstrated that zinc co-secreted with insulin suppressed hepatic insulin clearance. Our study highlighted a novel role of zinc-mediated intra-organ communication, referred to as "zinc flow", between the pancreas and the liver.

We are currently investigating further molecular factors underlying the role of zinc in pathological conditions of lifestyle-related diseases.

3. Understanding the progression of atherosclerosis in diabetic patients

Patients with type 2 diabetes mellitus are at high risk of developing cardiovascular diseases. However, it largely remains unknown which risk factors in diabetic conditions contribute to the progression of atherosclerosis because diabetic patients have many risk factors, such as hyperglycemia accompanied by insulin resistance, hyperinsulinemia, hypertension, and hyperlipidemia. In order to quantify the adhesion of monocytes to the endothelium, which is one of the earliest events in naturally occurring experimental animal models of atherosclerosis in vivo, we have established a new en face method for optimal observation of endothelial surface (NEMOes). This method allows us to observe the entire surface of the endothelium with a clear focused image, and thus to quantify the number of monocytes adhering to every region of rodent thoracic aorta. Using this NEMOes method, we are uncovering how each risk factor contributes to the progression of atherosclerosis, which would lead to new therapeutic approaches for preventing and curing cardiovascular diseases in patients with type 2 diabetes.

4. Investigating mechanisms of insulin resistance in muscle and liver

In most Asian countries, type 2 diabetes can easily develop in subjects with normal body mass index (BMI) (<25 kg/m²), in contrast to the case in European countries and the USA, although the mechanisms that induce metabolic disorders in normal-weight subjects are not fully understood.

It has been shown that ectopic fat accumulation in muscle and liver induces insulin resistance in these organs, independent of obesity. We have measured intramyocellular lipid (IMCL) and intrahepatic lipid (IHL), using proton magnetic resonance spectroscopy (1H-MRS), in order to investigate the role of ectopic fat accumulation in insulin resistance, and found that a short period of calorie restriction and exercise therapy decreased IHL and IMCL, respectively, suggesting that dietary and exercise intervention in metabolic diseases may directly decrease ectopic fat and improve metabolic states in liver and muscle, independent of body weight reduction.

On the basis of these findings, we hypothesized that diet and physical activity directly regulate intracellular lipid accumulation and insulin sensitivity in muscle and liver independently of obesity. To test this hypothesis, we have recently evaluated tissue-specific insulin resistance in muscle and liver of non-obese diabetic patients by using a euglycemic hyperinsulinemic clamp with a glucose tracer, searching for determinants of insulin resistance, such as ectopic fat and lifestyle factors. We also generated a mouse model of physical inactivity and investigated how physical inactivity regulates IMCL and insulin sensitivity in muscle. This approach will help us to understand the pathophysiology of metabolic disorders in non-obese diabetic subjects and bring new insight for treatment beyond the idea of body weight reduction.

References