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Clinical evidence regarding factors linking metabolic abnormal obesity to pancreatic β-cell dysfunction

In the past few decades, the prevalence of obesity has increased not only in Western countries, but also in Asia. Obesity is frequently accompanied by unhealthy adipocyte expansion; this results in a condition known as metabolic abnormal obesity, in which lipid spillover and abnormal adipocytokine secretion from adipose tissue elicit insulin resistance, a hallmark of type 2 diabetes mellitus[1]. In addition, several studies have suggested that metabolic abnormal obesity might contribute to the development of pancreatic β-cell failure, another hallmark of type 2 diabetes (Figure 1). Although most clinical data supporting this scenario of type 2 diabetes development are from studies in rodents, it might also be applicable to humans. Even though Asian people generally have less severe obesity than white people, they are susceptible to developing metabolic abnormal obesity. Also, Asian people are believed to be susceptible to β-cell failure[2]. Thus, this scenario might apply not only to white people, but also to Asian people. Indeed, several recent studies suggested that this scenario might be applicable to Asian people. Here, we introduce recent findings regarding this topic.

In type 2 diabetic model rodents, the deterioration of insulin secretion is caused by the deterioration of insulin secretion from individual β-cells and decreased β-cell mass. A reduction of β-cell mass has been observed in studies of autopsy samples from humans with type 2 diabetes; however, these studies did not provide definitive clinical information on the autopsy samples. Recently, Inaishi *et al.*[3] investigated β-cell mass using autopsy samples from Japanese individuals with available data on oral glucose tolerance tests carried out at annual health check-ups. The authors found that β-cell mass decreased significantly in association with worsening glucose tolerance before the onset of type 2 diabetes. Although there have been conflicting reports regarding the relationship between α-cell mass and glucose tolerance[3,4], this study showed that a decrease of β-cell mass seems to be a fundamental feature of β-cell failure in patients with type 2 diabetes. In addition, Fujikawa *et al.*[5] assessed longitudinal β-cell function from before the onset of diabetes type diagnosed by oral glucose tolerance test to after the deterioration of glucose tolerance. They found that β-cell function in individuals with obesity deteriorated faster than in those without obesity. These results clearly show that obesity worsens β-cell function in humans.

Obesity-induced β-cell dysfunction might be mediated by free fatty acids and by several adipokines produced by adipose tissue[6]. The deterioration of β-cell function as a result of free fatty acids is known as lipotoxicity. Chronic exposure of β-cells to free fatty acids enhances intracellular oxidative stress and endoplasmic reticulum stress, and reduces autophagic flux, resulting in β-cell dysfunction. This might be a primary factor linking obesity and β-cell dysfunction; adipocytokines could also play a more important role in the development of β-cell dysfunction than expected.

Leptin is an adipocytokine that mainly acts on the central nervous system to increase food intake and energy expenditure. In general, obese individuals show elevated leptin levels, probably due to the presence of leptin resistance[7]. Several reports have shown that leptin has effects on several tissues, including pancreatic β-cells. Most data have shown that leptin inhibits insulin secretion through increased K^+ current and somehow inhibits β-cell growth[8]. Clinically, however, circulating leptin concentrations positively correlate with insulin levels due to the presence of insulin resistance[7], and thus the direct action of leptin on β-cells in humans has not yet been fully clarified. Recently, Morioka *et al.*[9] investigated a soluble form of the leptin receptor (soluble Ob-R) in Japanese patients with type 2 diabetes, and found that soluble Ob-R levels were independently associated with decreased β-cell function. Soluble Ob-R is believed to reflect systemic leptin activity, and therefore these data support the theory that leptin inhibits β-cell function.

Another well-known adipocytokine is adiponectin. In contrast to most adipocytokines, serum adiponectin levels are inversely associated with adiposity. Adiponectin improves insulin sensitivity in muscle and the liver. In addition, this hormone has anti-atherosclerotic effects[10]. Many studies have shown that adiponectin enhances insulin secretion *in vitro* or in rodents[11]; however, the effects of adiponectin on β-cell function considering insulin sensitivity in humans has not been elucidated yet. Recently, Nakamura *et al.*[12] clinically assessed the relationship between serum adiponectin levels and β-cell function in Japanese individuals, using the disposition index, and found a positive association between adiponectin level and β-cell function. This finding supports the hypothesis that adiponectin has a positive effect on β-cell function in humans.

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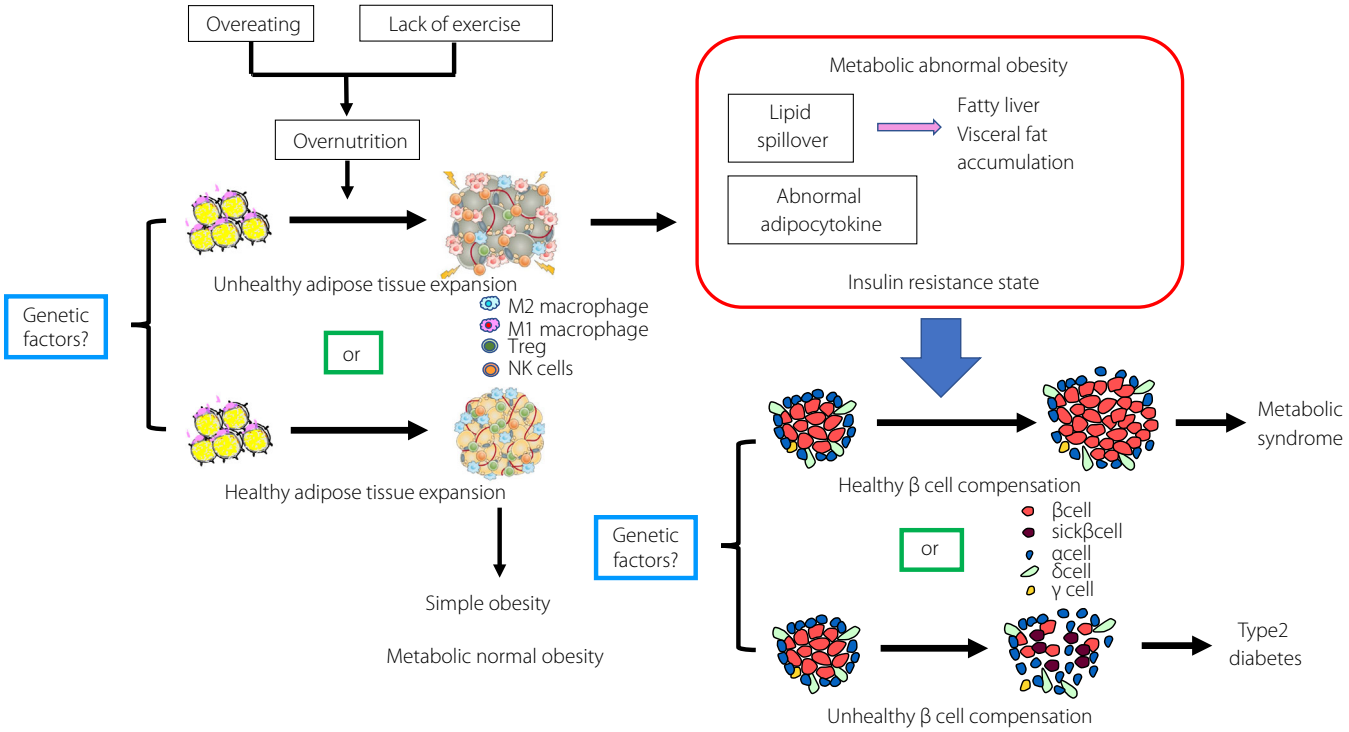

Figure 1 | Mechanism linking adipocyte dysfunction to pancreatic β-cell dysfunction in the development of type 2 diabetes mellitus. This figure shows the estimated mechanism of the development of type 2 diabetes mellitus. Overeating and lack of exercise results in overnutrition. In the overnutrition state, to save the excess energy, expansion of adipose tissue occurs. In healthy expanded adipose tissue, anti-inflammatory macrophage, M2 macrophage and regulatory T cells (Treg) tend to accumulate, and vascular density is sufficient to supply the energy and oxygen to tissue. Instead, in unhealthy expanded adipose tissue, inflammatory macrophage, M1 macrophage and natural killer (NK) cells tend to accumulate and vascular density is insufficient. Unhealthy adipose tissue expansion causes lipid spillover from adipocytes, and results in fatty liver and visceral fat accumulation, and also causes abnormal secretion of adipocytokine. These changes induce systemic insulin resistance. In patients with insulin resistance, healthy β-cells expand and increase in insulin secretion from each islet to compensate for insulin resistance. In contrast, unhealthy β-cells cannot compensate for insulin resistance, thus reducing its mass and decreasing insulin secretion.

Adipsin is an adipocytokine whose impact on β-cells has only recently been identified. Lo *et al.*[13] investigated the phenotype of mice deficient for the adipsin gene, and found that these mice showed glucose intolerance caused mainly by decreased insulin secretion from β-cells. In addition, administering adipsin to these mice resulted in improved glucose intolerance as a result of increased insulin secretion. These data clearly suggest that adipsin is an adipocyte-secreted factor that plays a major role in enhancing β-cell function. Indeed, Zhou *et al.*[14] investigated the levels of serum adipsin in Chinese individuals, and found that these levels were lower in patients with type 2 diabetes than in individuals with normal glucose tolerance. This result confirms that adipsin plays an important role in β-cell function in humans, although it has not yet been determined if adipsin links obesity and β-cell function.

Here, we introduce recent findings regarding the factors linking obesity and β-cell function in humans. However, the cellular mechanisms underlying the effect of each adipocytokine and the interactions of each factor have not been clarified yet. Further research progress in this field is essential and will contribute to the identification of new drug targets for type 2 diabetes.

DISCLOSURE

HW has given speeches on behalf of Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Dainippon Sumitomo Pharma, Eli Lilly, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho, Kyowa Hakko Kirin, Terumo Corp and Takeda, and has received research support from Abbott Japan, Astellas Pharma, Boehringer Ingelheim, Daiichi Sankyo, Dainippon Sumitomo Pharma, Kissei Pharma, Kowa, Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho, Soiken, Taisho Toyama Pharmaceutical and Takeda.

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