

Field:

Bioscience/Life Science

Session Topic:

Body fat : hidden organ, new source of hormonal regulation

Speaker:

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Adipose tissue has been considered to be only the site of triglyceride (TG) storage for a long time. Obesity is defined as an increased mass of adipose tissue and is well-known to be associated with a higher risk of cardiovascular and metabolic disorders such as metabolic syndrome, diabetes, dyslipidemia, and coronary heart disease etc. However, the molecular basis for this association could not simply be explained by only the significance of adipose tissue as TG storage site, and therefore it has remained to be clarified for a long time.

In 1993, the first breakthrough was brought by the experimental results reported by Drs. Hotamisrigil and Spiegelman's group that TNF α is secreted from adipocytes in obesity and secreted TNF α impairs insulin action in the liver and skeletal muscle (1). In 1994, the second, though most pivotal, breakthrough was brought by the identification of leptin secreted from adipocytes as causal molecule of ob/ob mice, reported by Dr. Friedman's group (2). Since ob/ob mice exhibit massive obesity, dyslipidemia and diabetes, by identification of leptin, it came to be believed that adipocytes secrete biologically active hormones, which could regulate the whole body glucose, lipid and energy metabolism and also insulin sensitivity. Interestingly, lipoatrophy, apparently opposite state to obesity regarding the mass of adipose tissue, has also been reported to be associated with a higher risk of cardiovascular and metabolic disorders such as diabetes, dyslipidemia, and coronary heart disease etc. The molecular basis for this association has also remained to be elucidated. The third breakthrough was brought by the experimental results that transplantation of the adipose tissue from "normal lean mice" into the lipoatrophic diabetic mice ameliorated their diabetes and dyslipidemia, whereas transplantation of the same amount of the adipose tissue from "obese diabetic mice" into the same lipoatrophic mice even worsened their diabetes and dyslipidemia, reported by Dr. Reitman's group (3). From these data, others and we hypothesized that the adipose tissue from "normal lean mice" could secrete "good" hormones, which could ameliorate diabetes and dyslipidemia, whereas the adipose tissue from "obese diabetic mice" could secrete "bad" hormones, which could worsen diabetes and dyslipidemia. Moreover, others and we also hypothesized that lipoatrophic diabetes could be resulted from lack of "good" hormones, while obese diabetes could be resulted from both decreased "good" hormones and increased "bad" hormones .

To identify "good" hormones, we searched molecules secreted from adipocytes, whose expression was increased in "normal lean mice" as compared with "obese diabetic mice". And then, to clarify whether these candidate secreted molecules indeed could be "good" hormones,

we infused these candidate secreted molecules into lipoatrophic diabetic mice or obese diabetic mice, and then analyzed the effects on glucose/lipid metabolism.

Before we had completed these experiments, Dr. Shimomura in Drs Goldstein and Brown's group reported that replenishment of leptin into lipoatrophic diabetic mice could ameliorate their hyperglycemia, at least in part (4). We found that decreased expression of adiponectin correlates with hyperglycemia in obese mouse models. Moreover, genome-wide scans mapped a susceptibility locus for type 2 diabetes and metabolic syndrome to chromosome 3q27, where the gene encoding adiponectin is located. Therefore we next examined the effects of adiponectin and found that hyperglycemia in lipoatrophic mice was completely reversed by the combination of physiological doses of adiponectin and leptin, but only partially by either adiponectin or leptin alone. These data suggested that adiponectin and leptin are the two major anti-diabetic hormones secreted from adipocytes (5).

These anti-diabetic effects of adiponectin appear to be mediated via activation of AMP-activated protein kinase (AMPK) (6) and also peroxisome proliferator-activated receptor (PPAR)- α , at least in part. We next reported the cloning of complementary DNAs encoding adiponectin receptors (AdipoR) 1 and 2 by expression cloning (7). We showed by using AdipoR1 and/or AdipoR2 knockout mice that AdipoR1 and R2 serve as the major receptors for adiponectin *in vivo* and play important roles in the regulation of glucose and lipid metabolism, inflammation and oxidative stress *in vivo* (8). Moreover, in the liver AdipoR1 activated AMPK pathways and AdipoR2 activated PPAR α pathways (8). Furthermore, muscle-specific disruption of AdipoR1 revealed that Adiponectin/AdipoR1 regulate PGC-1 α and mitochondria via Ca²⁺ and AMPK/SIRT1 like exercise (9).

Adipose tissue not only serves as the site of TG storage but also participates in the regulation of various types of energy homeostasis as an important endocrine organ that secretes a number of biologically active hormones.

References

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