

# Is obesity an absolute evil? Increase in adipose tissue does not always decrease insulin sensitivity

Obesity reflects an increase in adipose tissue mass. An increase in the amount of adipose tissue predisposes individuals to metabolic disorders. Metabolic syndrome has been defined by several study groups (i.e., International Diabetes Federation, World Health Organization and National Cholesterol Education Program/Adult Treatment Panel III), and is characterized by central obesity, hypertension, elevated blood glucose and dyslipidemia. The underlying pathogenesis is presumably closely related to insulin resistance.

However, the precise mechanisms of insulin resistance caused by obesity have not been fully elucidated. Accumulation of adipose tissue implies metabolic malfunction *per se*, and causes insulin resistance in the body. Dysfunction of adipose tissue has been attributed to several factors including free fatty acid (FFA), endoplasmic reticulum (ER) stress, oxidative stress, inflammation, hypoxia and fibrosis<sup>1</sup>.

The efflux of FFA from hypertrophic adipose tissue accumulates in organs, such as the liver, skeletal muscles and pancreas. Reduction of insulin sensitivity in the peripheral tissue as a result of FFA deposits is called 'lipotoxicity'. Nutrient excess results in a hypersynthesis of metabolic proteins to deal with the spillover of glucose and lipids in the blood, which might cause misfolded proteins that accumulate in the cytosol and elicit ER stress. ER stress provokes FFA release from adipocytes into the circulation, and reduces the activity of the insulin signaling pathway in target

tissues/organs, such as adipose tissue and liver. It also promotes inflammatory gene expression. The generation of reactive oxygen species facilitated by the increased  $\beta$ -oxidation of FFA and/or increased glucose catabolism induces oxidative stress. Cumulative oxidative stress decreases the activity of the insulin signaling pathway and mitochondrial function. Another typical feature of obesity is low-grade inflammation. Adipose tissue hypertrophy and macrophage infiltration results in the secretion of a variety of pro-inflammatory adipokines, such as tumor necrosis factor alpha, interleukin-6, monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, resistin and visfatin. As a consequence, systemic insulin resistance emerges in the setting of obesity. The expansion of adipose tissue facilitates the development of adipose tissue hypoxia and expression of hypoxia-inducible genes, which trigger pro-inflammatory cytokine release, adipocyte necrosis and macrophage invasion. Normally, hypoxia induces fibrosis in adipose tissue. The subsequent progressive rigidity of adipose tissue causes insulin resistance. Adipose tissue inflammation and necrosis also cause tissue fibrosis and insulin resistance. The reduced capacity of adipose tissue to store lipids leads to negative consequences including oxidative stress and ectopic lipid accumulation. We found that insulin resistance was accelerated when lipid storage in adipose tissue was artificially prevented<sup>2</sup>.

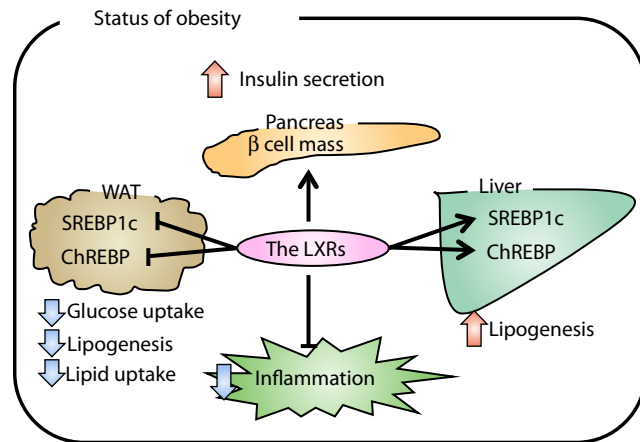
Obesity induces insulin resistance and metabolic disorders as aforementioned. However, some overweight individuals have no metabolic disorders at all, whereas others have extremely severe metabolic disorders. The reason for this discrepancy remains obscure.

Recently, Beaven *et al.*<sup>3</sup> found that liver X receptor (LXR)  $\alpha\beta$ -deficient *ob/ob* mice were obese, but showed improved insulin sensitivity compared with *ob/ob* mice. LXRs are oxysterol-activated nuclear receptors that play an important role in lipid and glucose metabolism by influencing sterol regulatory element-binding protein-1c expression and facilitating *de novo* lipogenesis of triglycerides. Ligand activation of LXRs contributes to hepatic steatosis, and could potentially facilitate hepatic insulin resistance. LXRs also reduce the activity of inflammatory signaling pathways.

The role of LXRs in the pathogenesis of diabetes and insulin resistance remains unclear, although LXRs reportedly modulate metabolic and inflammatory pathways. LXR-null mice are known to be resistant to diet-induced obesity, thus it has been difficult to elucidate the function of LXRs in the setting of obesity.

Beaven *et al.*<sup>3</sup> solved this problem by breeding mice deficient in both LXR $\alpha$  and LXR $\beta$  onto the genetic obese LEP background (*ob/ob* LXR  $\alpha\beta^{-/-}$  [LOKO] mice). Interestingly, their total bodyweights were as heavy as *ob/ob* mice up to 24 weeks-of-age. However, LOKO mice showed dramatic improvement in insulin sensitivity, and were protected against hepatic steatosis. The livers of LOKO mice weighed less than those of *ob/ob* mice as a result of less hepatic lipid accumulation. The expression of hepatic lipogenesis genes, such as *Srebp1c*, *Scd1* and *Fas*, was decreased in the livers of LOKO mice. The lipogenic program in the liver of LOKO mice is therefore subdued. The expression of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and carbohydrate response element-binding protein (ChREBP- $\beta$ ), key players in lipogenesis and insu-

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**Figure 1** | Schematic diagram of the liver X receptors (LXRs) involved in glucose and lipid metabolism. The LXRs in the setting of obesity play an important role of metabolism of glucose and lipid. ChREBP, carbohydrate response element binding protein; SREBP1c, sterol regulatory element-binding protein; WAT, white adipose tissue.

lin resistance, were reduced in the livers of LOKO mice. These results are consistent with those of Gao *et al.*<sup>4</sup>

Intriguingly, the weight of white adipose tissue (WAT) in LOKO mice was heavier than that in *ob/ob* mice. Expression of lipogenesis and lipid uptake genes associated with WAT was robustly augmented in LOKO mice. The expression of PPAR $\gamma$  and ChREBP- $\beta$  genes and their targets, such as aP2 and Rgs-16, was greater in LOKO WAT than in *ob/ob* WAT. The expression of genes associated with insulin sensitivity was also enhanced in WAT of LOKO mice.

The plasma glucose level in LOKO mice was higher than that in *ob/ob* mice before and after glucose load. However, the insulin level in LOKO mice was lower than that in *ob/ob* mice. The hyperinsulinemic euglycemic clamp study showed that the glucose infusion rate and the insulin-stimulated glucose disposal rate in the peripheral tissues were greater in LOKO mice compared with those in *ob/ob* mice. LOKO mice therefore had better insulin sensitivity in the body. Furthermore, hepatic glucose production was reduced in LOKO mice.

The pancreatic  $\beta$ -cell mass in LOKO mice was reduced compared with that in *ob/ob* mice because of decreased  $\beta$ -cell proliferation. Insulin secretion in islets isolated from *ob/ob* mice was not affected

by LXR $\beta$  deficiency, hence LXRs do not play an essential role in insulin secretion. Despite the superior insulin sensitivity in LOKO mice, their glucose intolerance was affected by the relative lack of insulin for their severe obesity.

The amount of macrophage infiltration into WAT was not different between LOKO mice and *ob/ob* mice, whereas the gene expression of pro-inflammatory and circulating inflammatory mediators in LOKO mice were increased compared with that in *ob/ob* mice. These observations suggest that inflammation might not be associated with insulin sensitivity in LOKO mice, although it is generally believed that inflammation facilitates insulin resistance.

LXRs act as physiological suppressors of PPAR $\gamma$  and ChREBP- $\beta$  pathways, thereby modulating glucose homeostasis. In contrast, LXRs activate PPAR $\gamma$  and ChREBP- $\beta$  pathways in the liver of obese individuals.

Taken together, LXRs are key players in glucose and lipid metabolism, especially in the setting of obesity (Figure 1). The results of the study by Beaven *et al.*<sup>3</sup> are interesting and exciting, and also raise many questions. Why do the activities of PPAR $\gamma$  and ChREBP- $\beta$  differ between the liver and WAT despite systemic ablation of LXRs? What switches PPAR $\gamma$  and ChREBP- $\beta$  on or off in each

tissue? What is the energy expenditure in LOKO mice if they consume the same amount of food as *ob/ob* mice? How much does brown adipose tissue (BAT) contribute to energy expenditure in LOKO mice? Because unchanged body-weight between LOKO mice and *ob/ob* mice might come from function failure of BAT<sup>5</sup>. How much does skeletal muscle—an important tissue that mediates the effect of insulin—affect glucose and lipid metabolism in LOKO mice? Why does inflammation not affect insulin resistance in LOKO mice?

Some of the aforementioned questions might be answered by examining conditional knock-out models using LOKO mice; for example, specific deficiency of LXRs in the liver, WAT, BAT, skeletal muscle,  $\beta$ -cells or macrophages. Insight into these mechanisms could guide the development of novel therapies for the metabolic syndrome.

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