

【S2-3】**Molecular Mechanism of Fat Cell Differentiation and It's Impacts on Metabolic Diseases**

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Adipocyte development has an impact on human health issues mainly through the association of obesity with Type II diabetes, hyperlipidemia, hypertension and cardiovascular disorders. Obesity results from excessive food intake and reduced energy expenditure, and such surplus energy is stored in adipose tissue.

Adipocyte differentiation, so called adipogenesis, is a complex process accompanied by coordinated changes in morphology, hormone sensitivity and gene expression. These changes are regulated by several transcription factors, including C/EBPs, peroxisome proliferator-activated receptor (PPAR) γ and ADD1/SREBP1c. These transcription factors interact with each other to execute adipocyte differentiation including lipogenesis and adipocyte-specific gene expression, which are pivotal metabolism in adipocytes. Expression of C/EBP β and δ occurs at the very early stage of adipocyte differentiation, and overexpression of C/EBP α or C/EBP β promotes adipogenesis through cooperation with PPAR γ . PPAR γ , a member of the nuclear hormone receptor family, is predominantly expressed in brown and white adipose tissue. PPAR γ is activated by fatty acid-derived molecules such as prostaglandin J₂ and synthetic thiazolidinediones (TZDs), novel drugs used in type II diabetes treatment. Recent studies using PPAR γ knockout mice indicated that the major roles of PPAR γ are adipocyte differentiation and insulin sensitization. ADD1/SREBP1c, which also appears to be involved in adipocyte differentiation, is highly expressed in adipose tissue and liver, and is also expressed early in adipocyte differentiation. ADD1/SREBP1c stimulates expression of several lipogenic genes, including FAS, LPL, ACC and SCD-1 & -2. Furthermore, ADD1/SREBP1c expression is modulated by the nutritional status of animals and is regulated in an insulin-sensitive manner in fat and liver. Therefore, it is likely that ADD1/SREBP1c is a major player in both fatty acid and

glucose metabolism to orchestrate energy homeostasis.

Adipocytes are highly specialized cells that play a critical role in energy homeostasis. The major role of adipocytes is to store large amounts of lipid metabolites during periods of energy excess and to utilize these depots during periods of nutritional deprivation. Adipocytes also function as endocrine cells by secreting several adipocytokines that regulate whole-body energy metabolism. Adipocytes possess the full complement of enzymes and regulatory proteins required to execute both *de novo* lipogenesis and lipolysis. These two biochemical processes are tightly controlled and determine the rate of lipid storage in adipocytes. Disorders of lipid metabolism involving fatty acid and cholesterol are associated with obesity, diabetes and cardiovascular diseases. To maintain lipid homeostasis, higher organisms have developed regulatory networks involving fatty acid- or cholesterol-sensitive nuclear hormone receptors, such as peroxisome proliferator-activated receptors (PPAR α , PPAR δ and PPAR γ), retinoid X receptors (RXRs), farnesoid X receptor (FXR) and liver X receptors (LXR α and LXR β).

Among nuclear hormone receptors, recent data suggest that LXRs play dynamic roles in regulation of cholesterol and fatty acid metabolism. The LXR family consists of LXR α and LXR β . LXR α is predominantly expressed in liver, adipose tissue, kidney and spleen, whereas LXR β is ubiquitously expressed. LXRs are activated by naturally produced oxysterols, including 22(R)-hydroxycholesterol, 24, 25(S)-epoxycholesterol and 27-hydroxycholesterol, and by the synthetic compound T0901317. LXRs form heterodimers with RXR that directly bind two direct repeat sequences (AGGTCA) separated by four nucleotides (DR4, also known as LXRE). The major physiological role of LXRs appears to be as cholesterol sensors. LXRs regulate a set of genes associated with regulation of cholesterol catabolism, absorption and transport. In addition, a number of studies indicate that LXRs also regulate several genes involved in fatty acid metabolism through either modulating expression of ADD1/SREBP1c or directly binding promoters of particular lipogenic genes including FAS. In support of these observations, LXR α/β -deficient mice show reduced expression of FAS, SCD-1, ACC and ADD1/SREBP1c, which are genes involved in fatty acid metabolism.

Liver and adipose tissues are considered major organs for regulation of lipid metabolism. However, it is uncertain whether LXRs is directly involved in the process of

adipocyte differentiation including adipocyte-specific gene expression or adipogenesis. Very recently, it has been shown that LXR activation elevates lipogenesis in 3T3-L1 cells with increase of lipogenic gene expression.

Recently, we have identified that LXR activation is involved in not only lipogenesis but also adipogenesis with adipocyte-specific gene expression through increase of PPAR γ expression. Activation of LXRs in several preadipocyte cell lines stimulated adipocyte differentiation with increase of lipogenesis. LXR activation with T0901317 preferentially increased expression of lipogenic genes such as ADD1/SREBP1c and FAS, and enhanced expression of adipocyte specific genes such as PPAR γ and aP2 *in vivo* and *in vitro*. Furthermore, suppression of LXR α by small interfering RNA (siRNA) inhibited adipocyte differentiation. These observations suggest that LXRs are involved in both lipid metabolism and adipocyte differentiation in fat tissue.