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Molecular Regulation of Adipocyte Differentiation

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During the last decade, important efforts have been made to understand the mechanisms controlling adipocyte differentiation and to identify the signals connecting adipose tissue and the whole organism. These studies led us to discover transcription factors and adipocyte specific factors that regulate adipose biology and functions of other organs. These factors also include possible candidates for the links between obesity and its associated insulin resistance. This paper attempts to review the recent advances from research on the control of adipocyte differentiation and on the secreted factors, especially pref 1 and ADSF/resistin that regulates adipose function.

Factors that modulate adipocyte differentiation

Pref-1: Pref-1 was cloned by differential hybridization screening of a preadipocyte 3T3-L1 cDNA library. Pref-1 encodes a protein of 358 amino acids containing six tanderm EGF repeats in the extracellular domain. Constitutively expressing Pref-1 in 3T3-L1 preadipocytes inhibits adipocyte differentiation, whereas, pref-1 antisense expressing cells enhance adipocyte differentiation due to the abolishment of Pref-1 expression. Transgenic mice overexpressing active soluble form of pref-1 in adipose tissue exhibit a substantial decrease in total fat pad weight. Pref-1 transgenic mice with a substantial, but not complete, loss of adipose tissue exhibit hypertriglyceridemia, impaired glucose tolerance, and decreased insulin sensitivity. Pref-1 knockout mice were used to assess the role of Pref-1 in growth and in vivo adipogenesis. Pref-1-null mice display growth retardation, obesity, skeletal malformation, and increased serum lipid metabolites. Furthermore, the phenotypes observed in Pref-1-null mice are present in heterozygotes that harbor a paternally inherited, but not in those with a maternally inherited pref-1-null allele. Taken together, these results demonstrated that Pref-1 expression is tightly associated with adipogenesis in vivo and support the proposed role of Pref-1 as a

negative regulator of the adipogenic process.

ADSF/resistin: ADSF was identified as a cysteine-rich protein expressed and secreted by mature murine 3T3-L1 adipocytes with a unique cysteine repeat motif at the C terminus using microarray analysis. ADSF was also independently isolated by Steppan et al. as a TZD-regulated adipocyte-derived factor, termed resistin using subtractive cloning method. The ADSF/resistin mRNA and protein are exclusively expressed in murine 3T3-L1 adipocytes and adipose tissues. The expression of ADSF/resistin mRNA is dependent on adipocyte differentiation stages. ADSF/mRNA is markedly increased at later stage of 3T3-L1 and primary preadipocyte differentiation into adipocytes in vitro, implicating its potential endocrine effect on adipogenesis. Human homologue of murine ADSF/resistin, having 60% of amino acid identity to that of mouse ADSF/resistin, is shown to be expressed in abdominal human adipose tissue. Unlike to murine ADSF/resistin, human ADSF/resistin mRNA is also detected at high level in preadipocyte and at a low level in differentiated human adipocyte in vitro. Human ADSF/resistin is also detected in human mononuclear cells. These results indicate that the human ADSF/resistin might have more complex functions not only in adipogenesis but also in the metabolic physiology of other target tissues, which have not yet been characterized. Treatment of 3T3-L1 cells with conditioned medium containing ADSF/resistin exhibits an inhibition of murine 3T3-L1 adipocyte differentiation in vitro. The inhibitory function of ADSF/resistin in adipocyte differentiation is likely to be mediated by its increased gene expression resulted from the nutritional and hormonal changes. Taken together, these results provide evidence that ADSF/resistin may function as a regulator mediating the prevalence of obesity and its associated pathogenesis of insulin resistance. Further studies in identifying ADSF/resistin target tissues and its receptor will allow us to investigate the physiological function of ADSF/resistin.

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