Pref-1 and ADSF/resistin Soluble Ingibitors of Adipogenesis

U. C. Berkeley

Hei Sook Sul

Adipocytes are highly specialized cells that play a crucial role in the energy balance by providing ability to synthesize and deposit fat during times of positive energy balance in preparation for periods of food deprivation. The role of adipose tissue as an energy storage organ has been expanded by the discovery of various soluble factors/hormones that are secreted including lepin. However, excess adipose tissue leading to obesity is a major health problem. There is an increase in lipogenesis and storage of fat in adipose tissue that causes hypertrophy. In addition, precursor cells are recruited and converted into mature adipocytes causing hyperplasia. During conversion of preadipocytes to adipocytes. growth arrest and subsequent activation of adipocyte genes by C/EBPa and PPARg transcription factors lead to adipogenesis. During conversion, fibroblastic preadipocytes become rounded lipid filled adipocytes. Various factors in cell-cell communication or cell-matrix interaction may govern whether preadipocytes are kept in an undifferentiated state or to undergo differentiation. I will describe two molecules secreted by adipose tissue, one from stromal vascular preadipocytes and the other from adipocytes, which inhibit adipocye differentiation process.

We cloned Pref-1 (Preadipocyte factor-1), a transmembrane protein with six EGF-repeats at the extracellular domain. Pref-1 is highly expressed in 3T3-L1 preadipocytes, its expression is extinguished during adipose conversion and is not detectable in mature adipocytes. Constitutive expression of Pref-1 blocks

adipocyte differentiation while antisense Pref-1 enhances adipogenesis. We found presence of multiple pref-1 transcripts generated by alternate splicing. We observed processing of the membrane form of Pref-1 to generate a soluble factor of 50 kD corresponding to pref-1 ectodomain which we found biologically active. The artificial membrane form of Pref-1 was not capable of inhibiting adipogenesis. Of the four alternately spliced forms of pref-1, only the two largest forms undergo cleavage in the juxtamembrane region to release the soluble Pref-1. Alternate splicing may be the mechanism that governs the production of biologically active soluble form. We have generated and characterized the pref-1 knockout mice and transgenic mice ectopically expressing pref-1 in an adipocyte-specific manner to demonstrate the role of pref-1 in adipogenesis in vivo.

In addition to Pref-1, we identified an adipocyte-specific, cysteine-rich secreted factor (ADSF). ADSF is not expressed in preadipocytes but marked increased during 3T3-L1 adipocyte differentiation. Constitutive expression of ADSF inhibits adipocyte differentiation. ADSF expression is under tight nutritional and hormonal regulation. When previously fasted animals are fed high carbohydrate diet or when diabetic animals are given insulin, ADSF mRNA levels increased drastically in adipose tissue. Lazar and coworkers also reported this protein as a TZD town-regulated factor contributing to insulin resistance and named it resistin. ADSF/resistin inhibits adipogenesis and may also play a regulatory role in insulin signaling. Studies of these preadipocyte- and adipocyte-specific secretory factors will help us to understand control of adipose formation and function.