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Review

Transcriptional factors that promote formation of white adipose tissue

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ABSTRACT

Adipocytes are highly specialized cells that play a major role in energy homeostasis in vertebrate organisms. Excess adipocyte size or number is a hallmark of obesity, which is currently a global epidemic. Obesity is a major risk factor for the development of type II diabetes (T2DM), cardiovascular disease, and hypertension. Obesity and its related disorders result in dysregulation of the mechanisms that control the expression of metabolic and endocrine related genes in adipocytes. Therefore, understanding adipocyte differentiation is relevant not only for gaining insight into the pathogenesis of metabolic diseases, but also for identifying proteins or pathways which might be appropriate targets for pharmacological interventions. Significant advances towards an understanding of the regulatory processes involved in adipocyte differentiation have largely been made by the identification of transcription factors that contribute to the adipogenic process. It is important to note that the developmental origin of white and brown fat is distinct and different precursor cells are involved in the generation of these different types of adipose tissue (reviewed in Lefterova and Lazar, 2009; Seale et al., 2009). Several transcription factors, notably PPARγ, several members of the C/EBP and KLF families, STAT5, and SREBP-1c, have been shown to have significant roles in promoting adipogenesis. More comprehensive reviews on negative and positive regulators of adipogenesis have been published in the past year (reviewed in Christodoulides et al., 2009; Lefterova and Lazar, 2009). Though many proteins are known to negatively regulate adipogenesis, including Wnts, KLFs, the E2F family of transcription factors, CHOP, Delta-interacting protein A, ETO/MTG8, and members of the GATA and forkhead transcription factor families, this review will focus on transcription factors that positively impact the development of white adipose tissue.

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1. Introduction and history

Interestingly, the majority of studies that have identified transcriptional regulators of adipogenesis have been performed in vitro. These studies have been primarily conducted in the 3T3-L1 or 3T3-F442A murine preadipocyte cell lines that were originally generated in the laboratory of Dr. Howard Green at Harvard University (Green and Kehinde, 1975, 1976). In the last 35 years, these cells lines have been used by thousands of investigators world-wide. Many cell types cannot be adequately studied in vitro because the cultured cells do not possess the properties of cells in vivo. However, the preadipocyte cell lines developed by Dr. Green have been extremely useful model systems for adipocyte biologists, and the data obtained in these cells have been validated

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from less mechanistic in vivo studies in the last decade. In vivo, adipocytes have three primary characteristics, which include lipid storage, insulin sensitivity, and endocrine properties. The 3T3-L1 cells have all three of these notable characteristics of fat cells. In addition to being widely used to study adipocyte development, the identity and/or characterization of many adipocyte specific genes have been identified using this cell line.

In the late 1980s, a commentary by Dr. Steven McKnight, now at the Carnegie Institution of Washington, and Dr. M. Daniel Lane at John Hopkins University indicated that C/EBPα was a key metabolic regulator of energy metabolism (McKnight et al., 1989). Numerous studies have since confirmed the role of C/EBPα and other C/EBP family members in energy balance and defined roles for these transcription factors in adipocyte differentiation (reviewed in Farmer, 2006). In 1994, two prominent laboratories independently identified PPARγ as an important modulator of adipocyte differentiation. Studies by Dr. Mitch Lazar's group at the University of Pennsylvania observed the induction of PPARγ during adipogenesis (Chawla et al., 1994), and experiments by Dr. Bruce Speigelman's Laboratory at Harvard Medical School revealed that PPARγ was a transcription factor which bound to an enhancer element in the aP2 promoter and conferred its fat-specific expression (Tontonoz et al., 1994). The early 1990s was also the time that Drs. Michael Brown and Joseph Goldstein from the University of Texas Southwestern identified SREBP-1 (Yokoyama et al., 1993), also termed ADD1, whose expression was observed to play a role in adipocyte determination by the Spiegelman Laboratory (Tontonoz et al., 1993). Since then, several other transcription factors have been found to promote adipocyte development.

Studies of the aP2 gene, and use of its regulatory sequences, have led to significant discoveries in adipocyte biology and metabolic diseases. aP2 is an abundantly expressed adipocyte gene that was first discovered in 1984 (Bernlohr et al., 1984), and one of the earliest studies on PPARγ identified this transcription factor for its ability to bind to an enhancer element in the aP2 promoter and mediate its adipocyte-enriched expression (Tontonoz et al., 1994). Since its discovery, the aP2 promoter has been used by hundreds of laboratories to construct transgenes that have largely fat-specific expression. A lesser known historical fact is that c-fos was also shown to bind to the aP2 promoter just 124 base pairs upstream of the transcriptional start site (Distel et al., 1987). As means of introduction, this was one of the first studies to propose that AP-1 proteins were regulators of adipocyte gene expression.

1.1. AP-1 transcription factors

Members of the activating protein-1 (AP-1) family of transcription factors are well-known regulators of cellular proliferation and differentiation. AP-1 is a collective term referring to dimeric transcription factors composed of c-Jun, Jun-B, Jun-D and c-Fos, Fos-B, Fra-1, or Fra-2 subunits that bind to a common DNA site, the AP-1-binding site (reviewed in Karin et al., 1997). Initial studies by the Spiegelman Laboratory showed that c-Fos was involved in the modulation of aP2 expression (Distel et al., 1987), and accordingly it was shown that the expression of c-Jun, c-Fos, Jun-B, Fos-B, and Fra-1 was induced immediately after the induction of adipocyte differentiation (Stephens et al., 1992, 1993). Although the role of individual AP-1 family members in adipogenesis has not been elucidated, there is strong evidence to indicate the importance of these transcription factors in vivo. Transgenic mice were generated that express a dominant-negative protein that prevents the DNA binding of B-ZIP transcription factors of both the C/EBP and Jun families under the control of the adipose-enriched aP2 enhancer/promoter. These mice have no white adipose tissue throughout life (Moitra et al., 1998). Collectively, these studies suggest that the induction and expression of AP-1 transcription factors play a role in fat cell differentiation.

1.2. STAT (signal transducers and activators of transcription)

In the last decade, several groups have studied the modulation and function of STAT proteins during adipogenesis and in mature fat cells. The STAT family of mammalian transcription factors is comprised of seven proteins (STATs 1, 2, 3, 4, 5A, 5B, and 6) which, in response to stimulation of various receptors, mainly those for cytokines, are phosphorylated on tyrosine residues causing their translocation to the nucleus. Each STAT family member shows a distinct pattern of activation by cytokines and upon nuclear translocation can regulate the transcription of particular genes (reviewed in Darnell, 1997). STATs have been shown to bind to distinct DNA sequences, and this binding regulates the transcription of specific genes (reviewed in Darnell, 1997; Pellegrini and Dusanter-Fourt, 1997). Since the tissue distribution and function of each STAT is unique, the regulation of tissue-specific genes appears to be a physiological role for these proteins (reviewed in Schindler and Darnell, 1995). This hypothesis is supported by numerous reports which demonstrate that specific STATs are activated differently by growth factors and cytokines, and STAT activation can be cell type dependent. In addition, transgenic knockout experiments have revealed crucial roles for each known mammalian STAT (reviewed in Darnell, 1997), and cell-specific functions for STAT family members have also been identified (reviewed in Schindler, 2002).

The first studies on STAT expression in 3T3-L1 cells revealed that STATs 1, 5A and 5B were highly induced during murine adipogenesis (Stephens et al., 1996). Similar results were observed during the in vitro differentiation of human preadipocytes (Harp et al., 2001). In addition, the ectopic expression of C/EBPs β and δ in non-precursor cells results in an induction of adipogenesis (Wu et al., 1996) that is accompanied by an induction in STAT5A and STAT5B protein levels (Stephens et al., 1996). These two STAT5 proteins are also coordinately regulated with both PPARγ and C/EBPα in differentiating 3T3-L1 cells under a variety of conditions (Stewart et al., 1999). In 3T3-F442A preadipocytes, the ability of growth hormone to modulate adipogenesis is attenuated by STAT5 anti-sense oligonucleotides (Yarwood et al., 1999). Also, constitutively active STAT5 is capable of replacing the requirement for growth hormone in adipogenesis of these cells (Shang and Waters, 2003). Ectopic expression of STAT5A confers adipogenesis in 3T3-L1 preadipocytes (Nanbu-Wakao et al., 2002) and in two different non-precursor cell lines (Floyd and Stephens, 2003). Interestingly, STAT5B was not capable of conferring adipogenesis in non-precursor cells (Floyd and Stephens, 2003). Transgenic deletion of STAT5A, STAT5B, or both STAT5 genes in mice resulted in significantly reduced fat pad sizes compared to wild-type mice (Teglund et al., 1998). In primary cultures of adipose tissue from these animals, growth hormone did not stimulate lipolysis as it did in adipocytes from wild-type animals (Fain et al., 1999), suggesting that some of the effects of growth hormone on fat metabolism are dependent on STAT5 proteins. It should be noted that the increased expression of STAT5 proteins is not typically observed until after the induction of C/EBPα and PPARγ (refer to Fig. 1), yet the activation of STAT5 proteins in preadipocytes occurs prior to the induction in expression of PPARγ in 3T3-L1 cells (Floyd and Stephens, 2003). In fact, both STAT5 proteins are tyrosine phosphorylated and translocate to the nucleus within 15 min after the induction of adipogenesis (Baugh et al., 2007; Floyd and Stephens, 2003). Coupled with the observations that STAT5 null mice have fat pads one-fifth normal size (Teglund et al., 1998), the data suggest that activation of STAT5 proteins may be an important driver of adipogenesis both in vitro and in vivo. This hypothesis is also supported by work indicating that one of the PPARγ promoters can be modulated