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Mini Review

# Role of histone acetyltransferases and histone deacetylases in adipocyte differentiation and adipogenesis

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ABSTRACT

Adipogenesis is a complex process strictly regulated by a well-established cascade that has been thoroughly studied in the last two decades. This process is governed by complex regulatory networks that involve the activation/inhibition of multiple functional genes, and is controlled by histone-modifying enzymes. Among such modification enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs) play important roles in the transcriptional regulation and post-translational modification of protein acetylation. HATs and HDACs have been shown to respond to signals that regulate cell differentiation, participate in the regulation of protein acetylation, mediate transcription and post-translation modifications, and directly acetylate/deacetylate various transcription factors and regulatory proteins. In this paper, we review the role of HATs and HDACs in white and brown adipocyte differentiation and adipogenesis, to expand our knowledge on fat formation and adipose tissue biology.



## Introduction

Many studies have established adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. Adipose tissue consists of three types of adipocytes: white, brown and beige (Bartelt and Heeren, 2014). White adipose tissue (WAT) is the main "storage site" of excess energy, primarily in the form of triglycerides, which can then be released as fatty acids when food is scarce (Bartelt and Heeren, 2014). In addition, brown adipose tissue (BAT) dissipates energy as heat production (thermogenesis) in mammals that has for many decades been considered an attractive target to promote weight loss heat, which is mediated by uncoupling protein-1 (UCP1) in the mitochondria (Harms and Seale, 2013). Beige (also called inducible brown, brown-in-white, or brite) adipocytes are found in WAT, develop in white fat in response to various activators (Harms and Seale, 2013; Rosen and Spiegelman, 2014), which have thermogenic capacities as similar with brown adipocytes (Bartelt and Heeren, 2014).

Adipogenesis is a complex process strictly regulated by a well-established cascade of sequence-specific transcription factors. CCAAT/enhancer binding protein-α (C/EBPα) and peroxisome proliferator-activated receptor-γ (PPARγ) were described as two key transcription factors (Rosen and Spiegelman, 2000). PR domain containing 16 (PRDM16) is a key driver of brown fat cell fate (Harms and Seale, 2013). The regulation of adipocyte differentiation and adipogenesis by transcriptional cascade and the role of histone modifications in these processes have been broadly reviewed (Ge, 2012; Musri et al., 2007, 2010; Okamura et al., 2010; Siersbaek et al., 2012).

Epigenetic regulations have become the focus of studies on gene regulation and several biological processes (Mihaylova and Shaw, 2013). The chromatin structure is partly regulated through dynamic modifications of the constituent proteins, primarily histones (Okamura et al., 2010). However, epigenetic regulations also modulate gene expression by modifying non-histone proteins, such as p53, Forkhead transcription factors 1 (FOXO1), and many non-histone sirtuin substrates (reviewed in Martínez-Redondo and Vaquero, 2013). Histone acetylation regulates many cellular processes and specific acetylation marks, either individually or in combination, and produce distinct results (Shahbazian and Grunstein, 2007). Histone acetylation/deacetylation is tightly regulated by the balance of opposing activities between histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Peserico and Simone, 2011). HATs and HDACs regulate a broad and complex array of physiological processes, such as cell proliferation, differentiation, senescence, apoptosis and metabolism (Bai et al., 2008), extension of life span, glucose homeostasis, insulin secre-

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tion, and adipocyte differentiation and metabolism (Backesjo et al., 2006; Chatterjee et al., 2011; Han et al., 2008; Picard et al., 2004; Qiang et al., 2012; Rodgers et al., 2005; Sun et al., 2007; Yang et al., 2013). This review briefly discusses the role of HATs and HDACs in adipogenesis.

## Role of HATs in regulation of white adipocyte differentiation and adipogenesis

Several recent studies provide supporting evidence on the significant role of DNA/histone modifications in the cell fate decision of MSCs (Cherasse et al., 2007; Takahashi et al., 2002). Changes in nucleosome structure affect gene expression by modulating the accessibility of the promoter regions to specific transcription factors (Yoo et al., 2006), and thus, the acetylation of histones H3 (Lys9 and Lys14) and H4 (Lys8 and Lys12) mediated by HATs is associated with transcriptional activation. Peserico and Simone (2011) summarized the discoveries and studies on HATs, and classified them into two groups, HAT A and HAT B, according to mechanisms of catalysis and on cellular localization. The members of the HAT A family are found in the nucleus, where they transfer the acetyl group from Acetyl-CoA to an ε-NH2 group of histone N-tails after assembly into nucleosomes (Peserico and Simone, 2011). The HAT A family can be further divided into three subclasses according to their homology with yeast proteins: GCN5-related N-acetyltransferase (GNAT) superfamily (GCN5, P300/CREB1-binding protein (CBP) associated factor (PCAF), Elp3, and Hpa2), MYST family (Tip60, p300/CBP, MORF, MOZ, and HBO1), and nuclear receptor co-activators (SRC-1, ACTR, and TIF2) (Sterner and Berger, 2000). In contrast, the members of the HAT B family act in the cytoplasm and transfer the acetyl group from Acetyl-CoA to an ε-NH2 group of free histones prior to their deposition in the DNA (Peserico and Simone, 2011).

HATs are important factors of the white adipocyte differentiation process, and are often associated with transcription activators, which increase target gene expression, and promote adipocyte differentiation and adipogenesis (Gao, 2013; Johmura et al., 2008; Kim et al., 2012; Nolte et al., 1998; Steger et al., 2010; Wiper-Bergeron et al., 2007) (Fig. 1a). HAT A members, such as GCN5, p300/CBP, Tip60, and PCAF, also known as K (lysine) acetyltransferase 2B, are associated with transcriptional activation; whereas the functions of the members of HAT B are less clear (Kim et al., 2012).

### *GNAT family*

Mammalian GCN5 and PCAF are all members of the GNAT family of acetyltransferases, which are paralogous histone acetyltransferases important for normal development, cell proliferation, and differentiation. The HAT enzyme, PCAF, is originally identified as a p300/CBP-binding protein, and has a key function in the regulation of myofilament contractile activity, myogenic program, and adipocyte proliferation (Cherasse et al., 2007). PCAF/GCN5-dependent acetylation of C/EBPβ is an important molecular switch in determining the transcriptional regulatory potential of this transcription factor during differentiation of NIH 3T3 and 3T3-L1 pre-adipocytes (Wiper-Bergeron et al., 2007).

### *MYST family*

Tip60 is a member of the MYST family of acetyltransferases, which requires PPARγ for its recruitment to PPARγ target genes in 3T3L1 adipocytes, and is a novel positive adipogenic factor (van Beekum et al., 2008). Recent research identified the co-regulator protein Tip60 as an essential player in adipogenesis (Gao, 2013). During early adipogenesis, p300/CBP as a co-regulator with the glucocorticoid receptor, C/EBPβ, mediator subunit 1, is involved in cell proliferation, development, and differentiation, and includes the gene encoding the master regulator of adipocyte differentiation, PPARγ2 (Steger et al., 2010). Furthermore, studies report that both CBP and p300 are significant for the activation of PPARγ, and the downregulation of CBP/p300 expression significantly reduces adipocyte differentiation (Takahashi et al., 2002). In addition, PCAF and p300 can regulate other transcription factors, such as KLF2, a negative effector of adipogenesis (Ahmad and Lingrel, 2005). The knockdown of HBO1 impaired the ability of 3T3-L1 cells to differentiate into mature adipocytes by inhibiting mitotic clonal expansion. Moreover, the factor for adipocyte differentiation 24 interacts with HBO1 to promote adipogenesis by controlling DNA replication (Johmura et al., 2008).

### *Nuclear receptor coactivators*

Steroid receptor coactivator-1 (SRC-1), activator of thyroid and retinoic acid receptor (ACTR), and transcriptional intermediary factor 2 (TIF-2) are three important nuclear receptor co-activators that display HAT activity. SRC-1 is known to interact with p300/CBP and PCAF, and its HAT domain is located in the C-terminal region. ACTR (also known as RAC3, AIB1, and TRAM-1 in humans) shares significant sequence homology with SRC-1, particularly in the N-terminal and C-terminal (HAT) regions, and in the receptor and co-activator interaction domains (Sterner and Berger, 2000). TIF-2 (also known as GRIP1) is another nuclear receptor co-activator with HAT activity, which also interacts with p300/CBP. Co-expression of HAT SRC-1 with PPARγ enhances the transcriptional activity of the factor and adipogenesis, whereas co-expression of co-repressor nuclear receptor co-repressor (NCoR) suppresses this activity (Nolte et al., 1998). SRC-1 knockdown does not affect adipogenesis, but SRC-2 and SRC-3 promote early human adipogenesis (Hartig et al., 2011). The lack of TIF2 in mice decreases PPARγ activity in WAT and reduces fat accumulation (Picard et al., 2002). Astaxanthin (ASX), an oxygenated carotenoid (xanthophyll), increased the interactions of PPARγ with TIF-2 and SRC-1 in adipogenesis, and blocked the increase in CBP recruitment to PPARγ mediated by rosiglitazone (Inoue et al., 2012). HATs have an important function in the regulation of adipocyte differentiation.

### *MEC-17*

MEC-17, which is a newly discovered acetyltransferase that is conserved from *Tetrahymena* to mammalian species, directly promotes α-tubulin acetylation in vitro and seems to be the major (Akella et al., 2010). Yang and colleagues found that acetylation of α-tubulin, which is the main component of the cytoskeleton, is upregulated during adipogenesis, and that adipocyte development is dependent on α-tubulin acetylation. The acetylation of α-tubulin is under the control of the acetyltransferase MEC-17, and deacetylases SIRT2 and HDAC6 (Yang et al., 2013).

## Role of HDACs in regulation of white adipocyte differentiation and adipogenesis

HDACs are a class of enzymes that remove acetyl groups from an ε-N-acetyl lysine amino acid on a histone or on non-histone proteins (Reuter et al., 2011). HDACs can be grouped into four classes according to their phylogenetic conservation (de Ruijter et al., 2003; Gregoretti et al., 2004). Class I includes HDACs-1, -2, -3, and -8; class II includes class IIA (HDACs-4, -5, -7, and -9) and class IIB (HDACs-6 and -10); and class IV includes HDAC11, all of which are related to the yeast Rpd3, Had1, and Hos3 proteins, respectively, and encompass the classical family of zinc-dependent HDACs. Class III consists of the $NAD^+$-dependent yeast Sir2 homologues, which comprise the sirtuin family (de Ruijter et al., 2003; Haigis