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Signalling Networks in Focus

The transforming growth factor-beta/bone morphogenetic protein signalling pathway in adipogenesis

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ABSTRACT

Rising obesity epidemic makes the better understanding of transcription factor networks regulating adipogenesis very challenging. Adipogenesis begins with the commitment of pluripotent mesenchymal stem cells to the adipocyte lineage, followed by terminal differentiation of preadipocytes to mature adipocytes. Among the molecules that influence the decision of progenitor cells to become adipocytes are members of transforming growth factor-beta superfamily and particularly bone morphogenetic proteins. Transforming growth factor-beta and bone morphogenetic proteins exert their biological functions mainly through their downstream molecules, the Smads. Here, we review the role(s) of transforming growth factor-beta/bone morphogenetic protein signalling pathway in adipocyte differentiation. Unravelling the precise mechanism of each molecule/pathway is necessary for developing suitable inhibitors or mimetic agents in order to treat obesity and improve insulin resistance. Current research efforts aim at discovering drugs that reduce fat mass or change the phenotype of adipose tissue into a more thermogenic one.

Signalling network facts

- Adipogenesis is a complex process that includes several stages (proliferation, growth arrest, mitotic clonal expansion, differentiation) until the undifferentiated mesenchymal stem cells develop into mature adipocytes.
- Several members of TGF-β superfamily and BMPs provide instructive cues that induce or inhibit the different stages of adipogenesis via their respective signalling cascades.
- Targeting appropriate components in these pathways may be a promising avenue for the development of alternative therapies of obesity and its related comorbidities.

1. Introduction

Obesity has received an ever growing attention as it is associated with increased prevalence of cardiovascular and metabolic diseases. Obesity is defined by augmented number and size of adipocytes in fat depots throughout the body. Nowadays, adipose tissue is not only considered as energy storage, but as a multiple endocrine organ that regulates energy balance, lipid and glucose metabolism via the secretion of adipokines. In obesity, adipocytes undergo hypertrophy, which leads to an imbalanced secretion of adipokines and induces the development of hyperglycemia, dyslipidemia, insulin resistance and diabetes (Ahima and Lazar, 2008). Several developmental regulators hold crucial roles in adipocyte differentiation. Therefore, improved knowledge on the mechanisms underlying the formation of adipose tissue and its role in energy homeostasis is needed for preventing the growing prevalence of obesity. This review focuses on the role of transforming growth factor-beta (TGF-β) superfamily members, particularly bone morphogenetic proteins (BMPs), in adipogenesis.

2. Structure and function of adipose tissue

There are two functionally and morphologically different types of adipose tissue in mammals: brown adipose tissue (BAT) which is specialized in energy expenditure and white adipose tissue (WAT), an endocrine organ and major site of triglyceride storage (Fonseca-Alaniz et al., 2007). White adipocyte is characterized by a single large lipid droplet, few mitochondria and poor vasculature, while brown adipocyte has numerous lipid droplets, high mitochondrial density with unique expression of uncoupling protein-1 (UCP-1) and rich vasculature. BAT is a thermogenic tissue that promotes energy expenditure and protects from obesity. UCP-1 is exclusively expressed in the inner mitochondrial membrane of brown

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adipocytes and allows proton gradient dissipation as heat. BAT depots are inversely correlated with age, body mass index, exposure to heat and treatment with β-blockers (Cypess et al., 2009). Therefore, BAT depot elevation is a potential therapeutic target for obesity.

3. Adipocyte proliferation and differentiation

Adipose tissue is of mesodermal origin, like muscle and bone. Adipocytes arise from mesenchymal stem cells (MSCs), originally derived from pluripotent embryonic stem cells. Progenitor cells do not accumulate lipids but express the transcription factor peroxisome proliferator-activated receptor γ (PPARγ), an early marker and key modulator of adipogenesis (Lowe et al., 2011). Several developmental molecules including fibroblast growth factors, members of TGF-β superfamily, BMPs and others provide instructive stimuli to guide differentiation and maturation of progenitors (Schulz and Tseng, 2009; Zamani and Brown, 2011). When triggered by these signals MSCs become committed to the adipocyte lineage (i.e. preadipocytes) and follow the stage of proliferation, growth arrest and mitotic clonal expansion. Clonal expansion is followed by a second growth arrest which is characterized by expression of fatty acid-binding protein 4 (FABP4)/Ap2, leptin and other markers (Fig. 1). Early differentiation starts with the production of the CAAT/enhancer-binding proteins (C/EBPs), C/EBPβ and C/EBPδ, which target the promoters of genes encoding adipogenic transcription factors: C/EBPα, PPARγ and the regulator of lipogenic genes sterol regulatory element-binding protein 1 (SREBP1) (Lowe et al., 2011). C/EBPα ignites PPARγ expression which, in turn, promotes C/EBPα expression, creating a positive feedback axis. PPARγ and C/EBPα induce the expression of genes involved in insulin sensitivity, lipogenesis and lipolysis, such as glucose transporter *GLUT4*, *FABP4*, *lipoprotein lipase* (*LPL*), *perilipin*, *adiponectin* and *leptin* (Fig. 1) (Lowe et al., 2011).

4. TGF-β superfamily signalling in adipogenesis

TGF-β superfamily comprises 33 members which exhibit a broad spectrum of actions in several cell types including adipocytes. TGF-βs exert their functions through Smads and the p38 mitogen-activated protein kinase (p38MAPK). Alternative cascades that mediate TGF-β signalling include other members of the MAPK family [extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK)] as well as protein kinase C, phosphoinositide-3 kinase and p70S6 kinase (de Caestecker, 2004). There are 3 classes of Smads: the receptor regulated Smads (R-Smads) which include Smad-1, Smad-2, Smad-3, Smad-5, Smad-8, the common-mediator Smad (Co-Smad) which includes only Smad-4 and interacts with R-Smads to participate in signalling and the inhibitory Smads (I-Smads) that include Smad-6 and Smad-7 which block the activation of R-Smads and Co-Smad (Fig. 2) (Zamani and Brown, 2011).

Signal transduction in adipogenesis begins when TGF-β ligands associate with cognate receptors and activate them by autophosphorylation. Activated receptors potentiate the R-Smads which then bind to the Co-Smad, and the ensuing complex translocates to the nucleus promoting transcription of target genes (Fig. 2) (Hill, 2009). The accumulation of the complex within the nucleus is regulated by the nuclear transporter TAZ (Varelas et al., 2008). Nuclear phosphatases dephosphorylate R-Smads, leading to dissociation of the complexes and recycling of Smads to the cytoplasm (Lin et al., 2006).

The receptors of TGF-βs are transmembrane serine/threonine kinase glycoproteins which are divided into types I and II. Specifically, type I receptors [activin-like kinases (Alk) 2, 3 and 6] are known to bind BMPs while type II receptors [BMPR2, activin type 2A (ActR2A) and ActR2B] have affinity for BMPs (Kishigami and Mishina, 2005). TGF-β superfamily ligands include BMPs, growth differentiation factors (GDFs), activins, nodal, inhibins and TGF-β isoforms which act in an endocrine, autocrine or paracrine manner. Ligands are divided into two main branches based on receptor type interaction (type I or II) and the Smads mediating their signals. TGF-β/activin/nodal branch that signals through Smad-2/3 involves binding to receptor type II, receptor I phosphorylation and activation of either Smad-2 or Smad-3. In contrast, BMPs branch can bind to either type I or II receptors and the ternary complex phosphorylates R-Smads 1/5/8 (Fig. 2) (Zamani and Brown, 2011).

Among members of TGF-β superfamily, TGF-β1 exerts a great influence in adipogenesis. In vitro studies show that TGF-β1 inhibits the early stages of 3T3-L1 (mouse cells that resemble preadipocytes) differentiation into mature adipocytes (Zamani and Brown, 2011), promotes the proliferation of progenitor cells (Choy et al., 2000) and hampers lipid accumulation (Tsurutani et al., 2011). There are conflicting reports in humans; a study of obese women revealed decreased TGF-β1 levels, while others show increased TGF-β1 expression (Zamani and Brown, 2011). In hypertensive patients, circulating TGF-β levels correlate positively with obesity, body mass index and leptin levels (Porreca et al., 2002).

5. BMPs and adipogenesis

BMPs are pleiotropic proteins that regulate processes like cell-fate determination, proliferation, apoptosis and differentiation during embryonic development and adulthood (Schulz and Tseng, 2009; Chen et al., 2004). Among other roles, they affect the differentiation of MSCs to mature adipocytes (Tseng et al., 2008). BMPs comprise a subfamily that includes the 14 currently known BMPs which interact with different types of receptors and mediate their actions through different signalling pathways. Specifically, BMP6 and BMP7 interact with type II receptors (ActR2A, ActR2B) and recruit type I (Alk2, Alk3, Alk6). In contrast, receptor-binding affinity is reversed for BMP2 and BMP4 which preferentially bind to type I receptors (Alk3, Alk6) and recruit type II into heteromeric signalling complexes (de Caestecker, 2004). BMP2 and BMP4 potentiate p38MAPK through phosphorylation of the respective BMPR kinase, activation of TGF-β-associated kinase 1 (TAK1) and phosphorylation of MAPK kinase 6 (MKK6) (Kimura et al., 2000). Below we will focus on the actions exerted by the most important BMPs in adipogenesis.

BMP2 effects in adipogenesis depend on cell type. It promotes osteogenesis in bone-marrow human cells, while stimulating adipogenesis in C3H10T1/2 (mouse cells that resemble MSCs) and 3T3-L1 cells by induction of PPARγ via mainly Smad-1/5/8 and p38MAPK pathway (Sottile and Seuwen, 2000; Hata et al., 2003). Adipogenic effects of BMP2 are mediated by the transcriptional coactivator Schnurri-2 (Shn-2). In experiments with Shn-2-null mice and consequently reduced BMP2 signalling, there was a poor differentiation of embryo fibroblasts into adipocytes and reduced adipose mass (Jin et al., 2006).

BMP4 promotes MSCs commitment to the adipocyte lineage and induces adipogenesis in a dose-dependent manner. This is demonstrated by treating C3H10T1/2 cells with recombinant human BMP4 (Taha et al., 2006). BMP4 also causes a decrease in UCP-1 (Tseng et al., 2008).

BMP3 is known as a negative regulator of osteogenesis. In vitro models revealed that BMP3 stimulates the proliferation of both C3H10T1/2 and 3T3-L1 preadipocytes via TGF-β/activin pathway, while it does not promote the commitment of MSCs or the differentiation of preadipocytes (Stewart et al., 2011).