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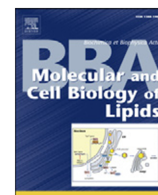

Review

Bone morphogenic proteins signaling in adipogenesis and energy homeostasis ☆

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ABSTRACT

A great deal is known about the molecular mechanisms regulating terminal differentiation of pre-adipocytes into mature adipocytes. In contrast, the knowledge about pathways that trigger commitment of mesenchymal stem cells into the adipocyte lineage is fragmented. In recent years, the role of members of the bone morphogenic protein family in regulating the early steps of adipogenesis has been the focus of research. Findings based on these studies have also highlighted an unexpected role for some bone morphogenic protein in energy homeostasis via regulation of adipocyte development and function. This review summarizes the knowledge about bone morphogenic proteins and their role in adipocyte commitment and regulation of whole body energy homeostasis. This article is part of a Special Issue entitled Brown and White Fat: From Signaling to Disease.

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1. Introduction

During gastrulation several specialized cells such as adipocytes, myocytes and chondrocytes originate from the mesoderm layer [1]. Today it is commonly accepted that with regard to adipocyte development, two types of cells are generated: (i) one that functions as a precursor for white fat, a tissue devoted to store energy in the form of triglycerides for the time of starvation, and (ii) one precursor that gives rise to brown fat, a tissue that burns lipids to produce heat via non-shivering thermogenesis [2–4]. White adipose tissue (WAT) and brown adipose tissue (BAT) are organized to form the adipose tissue organ, a multi-depot organ distributed in our body with a discrete anatomy and a high physiological plasticity [5–7]. WAT can mainly be found in two locations: below the skin (subcutaneous) and in the abdomen (visceral). BAT, was believed to be absent in adult humans, however recently, using fluoro-deoxyglucose (FDG)-positron emission tomography (PET) combined with computer tomography (CT), it was clearly demonstrated that also adult humans possess BAT, which seems to be functional as well [8–11].

Morphologically, white and brown adipocytes differ by their lipid droplet size and abundance. White adipocytes store triglycerides in a single large lipid droplet and contain few mitochondria. On the contrary, brown adipocytes show higher numbers of mitochondria and accumulate triglycerides in several small lipid droplets [12]. The ability of brown adipocytes to dissipate energy is conferred by uncoupling protein 1 (UCP1). This protein is expressed uniquely in BAT, where it uncouples cellular respiration from ATP production, thus dissipating energy as heat [13]. This adaptive non-shivering thermogenesis is important not only for maintaining body temperature, but to some extent, also for the maintenance of body weight. Indeed, genetic ablation of BAT in mice resulted in susceptibility to develop obesity [14], whereas overexpression of UCP1 protected from diet induced obesity [15].

For long time white and brown adipocytes have been assumed to share a common developmental origin as they have a similar differentiation program and a similar expression patter of genes [16]. However, recent studies have clearly demonstrated that brown adipocytes share a common precursor with muscle cells [17]. This is not surprising as both cell types are rich in mitochondria and can perform oxidative phosphorylation as well as adaptive thermogenesis. Actually, the common origin of these two cells was already suggested in 1551 by the Swiss naturalist Konrad Gessner when he described brown adipocytes as neither fat, nor muscle [18]. Almost 450 years later Seale et

Abbreviations: WAT, white adipose tissue; BAT, brown adipose tissue; MSC, mesenchymal stem cell; UCP1, uncoupling protein 1; PRDM16, PR domain containing 16; PPARγ, peroxisome proliferator-activated receptor gamma; BMP, bone morphogenic protein; PGC1, peroxisome proliferator-activated receptor gamma coactivator 1; CtBP, C-terminal-binding protein; SMAD, small mother against decapentaplegic; TGF-β, tumor growth factor-β; ALK, activin receptor-like kinase; BMPR, bone morphogenic receptor; ActR, activin receptor; GDF, grown/differentiation factor; FGF, fibroblast growth factor; WNT, wingless; Rb, retinoblastoma; Pref-1, pre-adipocyte factor-1; C/EBP, CCAAT/enhancer binding protein; RIP140, receptor-interacting protein 140; PG, prostaglandin; HSL, hormone sensitive lipase; CNS, central nervous system; SNS, sympathetic nervous system; VMH, ventromedial hypothalamus; hPSCs, human pluripotent stem cells

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al. [17] confirmed these suggestions by demonstrating that brown adipocytes share a common origin with skeletal muscle cells and have phenotypic features similar to both adipocytes and myocytes. Thus, brown adipocytes can be classified as "adipomyocytes", i.e. muscle cells that have developed the capacity to accumulate lipids.

Initial lineage tracing studies showed that cells expressing engrailed-1 (En1) located in the central dermomyotome can give origin to interscapular brown fat [19]. In addition, brown adipocyte cell precursors were shown to have a myogenic gene expression signature [20]. Finally, through in vivo fate mapping studies, the existence of a common $Myf5^+$ progenitor for both skeletal muscle and brown adipocytes was demonstrated [17]. Myf5 is a key early myogenic transcription factor whose expression was thought to be specific to committed skeletal muscle cells. Notably, the $Myf5^+$ precursor cell population does not give rise to white adipocytes although this concept has been recently challenged [21].

In line with this, the observation that brown adipocytes and muscle cells share a common precursor is the result from myogenin-deficient mice, which suggests that myocyte precursor cells that are not able to terminally differentiate into muscle cells can give rise to brown adipocyte accumulation in skeletal muscle fibers [22].

The factor responsible for the commitment of the $Myf5^+$ precursor cells into brown adipocytes or myocytes has been shown to be PR domain containing 16 (PRDM16) [17]. PRDM16 can control a bidirectional cell fate between muscle and BAT and by repressing the expression of myogenic factors PRDM16 is responsible for the determination of brown adipocytes from the $Myf5^+$ progenitors. Indeed, loss of PRDM16 from brown fat precursors results in an impaired brown fat formation, whereas the expression of myogenic markers is increased [17]. On the other hand, ectopic expression of PRDM16 in myoblast results in the appearance of a brown phenotype [17]. Notably, it was shown that peroxisome proliferator-activated receptor gamma (PPARγ) mediated the effects of PRDM16 and activation of PPARγ was able to convert myogenic cells to white-like adipocytes, whereas conversion into brown adipocytes was possible only by the coexpression of PRDM16. Thus, PRDM16 acts at an early stage to influence a brown lineage decision. Indeed, the expression of PRDM16 has been shown to be regulated by bone morphogenic protein 7 (BMP-7), a factor responsible for trigging commitment of mesenchymal stem cells (MSCs) specifically into the brown adipogenic lineage [23].

In order to repress the myogenic lineage in brown fat precursors, some repressing factors are likely to play an important role. In this respect, PRDM16 has been shown to have the ability to simultaneously activate and repress genes via a mutually exclusive interaction with peroxisome proliferator-activated receptor gamma coactivator 1 α/β (PGC1α/β) or C-terminal-binding protein (CtBP) corepressors [24]. Moreover, it has also been shown that PRDM16 can repress the myogenic signature via mir-193b and mir-365 [25]. By coactivating PPARα, PRDM16 promotes the expression of the cluster mir-193b-365, which blocks the entire program of myogenesis in C2C12 myoblast to promote, under adipogenic conditions, the formation of brown adipocytes. In contrary, blocking mir-193b and/or mir-365 in primary brown preadipocytes results in impaired brown adipogenesis by enhancing RUNX1T1 and increased expression of myogenic markers.

The adipose organ is constantly being remodeled in order to respond to environmental cues. Apart from the population of endogenous brown adipocytes, a second population of inducible brown adipocytes exists (referred to as "brite" or "beige") [26]. Thus, in rodents chronic cold exposure determines the appearance of brite adipocytes in white depots [27–29]. Brite adipocytes are not derived from $Myf5^+$ expressing progenitors [17,30], posing the question from which cellular origin these cells arise. One possibility that was suggested is the transdifferentiation of white to brite adipocytes [31]. However, also separate progenitors, which are negative for Myf5 may exist [21]. These findings are in line with the observation that BAT cells in the interscapular region are genetically different from those localized in WAT depots [32].

In addition to the appearance of brite adipocytes in WAT depots, brown adipocytes have been also identified in skeletal muscle, which might develop from $Myf5^+$ satellite cells to increase the oxidative capacity of the skeletal muscle [33]. Even though it is still unclear to which extend brite cells can participate to energy expenditure, the appearance of brown adipocytes in both WAT and muscle has been suggested to increase energy expenditure and resistance to obesity [34,35]. Thus, therapies aiming to promote these events to counteract obesity need the understanding of brown fat lineage commitment.

Although the discovery of the origin of brown adipocytes is an important finding, the localization and identification of the specific brown fat/myocyte progenitor cells during mouse embryogenesis remains to be established. Thus, it will be important to map the PRDM16 embryonic expression pattern to get insight into both localization and identity of the common precursors during early development. Further cues could be obtained from dissecting the signaling pathways responsible for the spatial and temporal expression of PRDM16. Of note in that respect are the BMP proteins, which are morphogens that play a key role in the development of many tissues, including adipose tissue. In fact, in mice lacking Schnurri-2, a down-stream mediator of the BMP-2 signaling pathways, the development of WAT is dramatically impaired [36]. In contrast the development of BAT is compromised in BMP-7 knock-out mice [23]. Among the BMP proteins, BMP-2 and BMP-4 have been proposed to promote the development of WAT, while BMP-7 has been implicated in the development of BAT [23,36]. BMP-7 has been shown to drive the complete brown fat differentiation program, including PRDM16 expression. Nevertheless, apart from small mother against decapentaplegic (SMAD) transcription factors, the knowledge of the down-stream mediators of the BMP signaling responsible for adipogenesis is limited.

2. Bone morphogenic proteins

Bone morphogenic proteins (BMPs) are pleiotropic members of the transforming growth factor β superfamily (TGF-β). As morphogens, BMPs are synthesized from localized sources from where they diffuse into the surrounding tissue to provide positional information in a dose-dependent manner [37]. Originally identified as factors that induce the formation of bone and cartilage, BMPs have been shown to play an important role in the development and function of many other tissues such as intestine, kidney, muscle, brain and hematopoietic as well as adipose tissue [38]. The activity of BMPs was initially recognized in the 1960s [39]. However, the factors responsible for bone formation stimulation remained elusive until the purification and sequencing of BMP-3 (osteogenin) and the cloning of human BMP-2 and BMP-4 in the late 1980s [40,41]. Since then, around 20 BMP family members have been identified nowadays in vertebrates and invertebrates [42] (Table 1). Of these, BMP-2, BMP-4, BMP-6, and BMP-7 are well-established mediators of both osteogenesis and adipogenesis from mesenchymal stem cells (MSCs) [43]. BMPs are secreted as precursor protein dimers that are cleaved by proteinases to yield the mature active form of the protein [44]. BMPs bind to serine–threonine kinase receptors that transduce their signal to the nucleus via SMAD proteins [45].

3. Bone morphogenic protein receptors

Two types of serine–threonine kinase receptors are required to transduce BMP signaling: type I and type II receptors. Both receptors have a short extracellular domain, a single membrane-spanning domain and an intracellular domain containing a serine–threonine kinase domain [46]. The specificity of BMP binding to type I receptors is affected by type II receptor. Moreover, BMP-receptor binding and signaling activity can be regulated by co-receptor factors [46].

With respect to BMP type I receptors, seven receptors have been identified, which are referred to as activin receptor-like kinase (ALK-1 to ALK-7). These seven receptors are further classified into

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