Published in final edited form as:

Cytokine Growth Factor Rev. 2009 ; 20(5-6): 523–531. doi:10.1016/j.cytogfr.2009.10.019.

Emerging Role of Bone Morphogenetic Proteins in Adipogenesis and Energy Metabolism

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Abstract

Bone morphogenetic proteins (BMPs) regulate many processes in embryonic development as well as in the maintenance of normal tissue function later in adult life. However, the role of this family of proteins in formation of adipose tissue has been underappreciated in the field of developmental biology. With the growing epidemic of obesity, improved knowledge of adipocyte development and function is urgently needed. Recently, there have been significant advances in understanding the role of different members of BMP superfamily in control of adipocyte differentiation and systemic energy homeostasis. This review summarizes recent progress in understanding how BMPs specify adipose cell fate in stem/progenitor cells and their potential role in energy metabolism. We propose that BMPs provide instructive signals for adipose cell fate determination and regulate adipocyte function. These findings have opened up exciting opportunities for developing new therapeutic approaches for the treatment of obesity and its many associated metabolic disorders.

1. Introduction

According to the World Health Organization, the continuing surge in the obesity pandemic creates a substantial increase in incidences of metabolic diseases, such as type 2 diabetes mellitus, cardiovascular dysfunction, liver steatosis and cirrhosis, as well as the neurodegenerative Alzheimer's disease and even some cancers (1–4). Treatment of obesity-related morbidities has imposed a huge economic burden on societies, with 147 billion per year estimated to be the annual medical cost of obesity in the US to date (5). Increasing body adiposity is the defining characteristic of obesity. The past two decades have shed considerable light on the understanding of adipocyte biology and function. Originally considered as an inert mass for energy storage, adipose tissue is now seen as an endocrine organ that actively participates in the regulation of whole body energy metabolism (6). Adipokines produced by fat cells, such as leptin and adiponectin, are key mediators of physiological processes in distant organs, such as brain, liver and muscle, where they control appetite, digestion of nutrients, energy expenditure and storage, glucose and lipid metabolism and insulin sensitivity (7–9). Therefore, improved knowledge on the mechanisms underlying the formation of adipose tissue and its role in energy homeostasis is urgently needed to counter the growing epidemic of obesity.

While research on transcriptional regulation of adipocyte differentiation has been a central focus in studies of adipocyte biology, emerging evidence suggests that secreted factors, such

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as cytokines or developmental regulators, play a crucial role in controlling the differentiation of mesenchymal progenitor cells into adipocytes and in regulating adipocyte function and energy metabolism. These cytokines and developmental regulators can modulate expression and activities of specific adipogenic transcriptional regulators. This review will focus on the current understanding of how a group of prominent morphogens, the bone morphogenetic proteins (BMPs), regulates adipose cell fate, white versus brown adipocyte formation, and systemic energy metabolism, as well as their potential use for anti-obesity therapies.

2. Development of adipose tissue

2.1. Function and distribution of adipose tissue

The capacity to store fat as a reservoir of readily available energy in times of scarce nutrient supply is found in most animal species and is conserved throughout evolution. While invertebrates such as the nematode *Caenorhabditis elegans* store lipids in the intestine, and the fruit fly *Drosophila melanogaster* stores excess energy in the “fat body”, only higher organisms have developed a specialized tissue for lipid storage -- the adipose tissue/organ (10). There are two functionally and morphologically different types of adipose tissue in mammals: white adipose tissue is the primary site of triglyceride storage; and brown adipose tissue is specialized in energy expenditure (Figure 1). The white fat cell is characterized by a single large lipid droplet, a nucleus located in close proximity to the cell membrane and low mitochondrial density, while the brown adipocyte features multi-locular lipid inclusions, numerous well-developed mitochondria with the unique expression of uncoupling protein-1 (UCP-1) and resides in rich vasculatures (11). UCP-1 is a 32-kDa protein exclusively expressed in the inner membrane of the mitochondria of brown fat and allows the dissipation of the proton electrochemical gradient generated by respiration as the form of heat. UCP-1 is generally regarded as the defining marker of brown fat, whereas leptin is more highly expressed in white fat than brown fat (Figure 1).

The distribution of fat varies among different species. In humans, white fat is dispersed throughout the body with the subcutaneous and intra-abdominal depots as two major compartments for fat storage. Distribution of these two white fat depots is highly associated with the risk of developing metabolic syndrome (6). Increased accumulation of visceral fat is associated with higher risk for metabolic complication of obesity, while no association is found with increased subcutaneous adiposity (12). Brown fat is primarily a thermogenic tissue that burns fat to generate heat in order to maintain body temperature in cold environment and dissipate excess energy in response to overfeeding (11). In rodents, induction of brown fat promotes energy expenditure, reduces adiposity and protects from diet-induced obesity (13; 14). Conversely, targeted ablation of brown fat results in reduced energy expenditure and increased obesity (15). In newborn humans, significant amounts of brown fat are found in interscapular, axillary, cervical, perirenal, and periadrenal regions (16). The interscapular brown fat disappears shortly after birth, and thus it has traditionally been assumed that there is no functional brown fat present in adult humans. However, this concept has been radically revised during the past few months. In the spring of 2009, five independent teams reported studies using PET-CT (positron emission tomography- computed tomography) imaging to prove conclusively that adult humans have metabolically active brown fat (17–21). The most common location for brown fat in adults is the cervical-supraclavicular depot, and in a small subset of patients, brown fat is also found in the thoracic and paraspinal regions. More importantly, these brown fat depots appear to correlate inversely with body mass index in older people (17), suggesting a critical role of brown fat in human adult energy metabolism and the potential of using brown fat-mediated energy expenditure as an anti-obesity therapy.

2.2. The origin of adipose tissue

Adipose tissue, like muscle and bone, is considered to be of mesodermal origin, although precise lineage tracing studies have not yet been performed (6). Adipocytes develop from mesenchymal stem/progenitor cells, which derive from embryonic stem cells. When triggered by appropriate developmental cues, these cells become committed to adipocyte lineages, i.e. the preadipocytes (Figure 2). In adolescents, both fat cell hypertrophy and hyperplasia occur with the development of obesity (22). The turnover of adipocytes is tightly maintained in a steady state in adults (23). Thus, the adipocyte stem/progenitor cells residing within the stromovascular fraction constantly replenish adipose tissues with newly formed adipocytes. These progenitor cells are characterized by the capacity for self-renewal, and commitment to the adipogenic lineage, which is marked by expression of the transcription factor PPAR γ , an early marker of adipogenesis, but do not accumulate lipids (24). Moreover, a subset of vasculature resident adipose precursor cells possesses the ability to regenerate an entire fat depot and induce *de novo* vascularization. These cells express the surface antigens CD29, CD34, Sca-1, and CD24, and are negative for markers of the hematopoietic lineage (25). As for the development of brown adipose tissue, recent evidence suggests that brown fat and skeletal muscle may share a common early developmental program (26). More recently, Seale *et al.*, used a myogenic marker, myf5, to perform cell fate mapping in the mouse and found that both skeletal muscle and interscapular brown fat, but not white fat, arise from progenitors expressing myf5 (27). In addition to these discrete interscapular brown fat cells, UCP-1-positive brown adipocytes are also found systemically distributed in the body, especially within white fat depots (28) and between muscle bundles (29). Interestingly, these “systemic” brown adipocytes, such as those present in white fat and muscle, are not derived from myf5-expressing precursors (27), suggesting different developmental origins for these different pools of brown fat. Thus, an important unsolved issue in adipocyte biology is the identification of brown fat progenitor cells. Interplay between the progenitor cells and the inductive signal specifies the developmental fate of the precursors into specific adipose cell lineages.

2.3. Molecular controls of adipocyte differentiation

Several developmental signaling molecules implicated in the evolution of mesodermal tissues have been shown to impact the development of adipose tissue. These include nodal, wingless, fibroblast growth factors, members of the transforming growth factor (TGF)- β family, BMPs, and others. These factors are often produced by the microenvironment or niche and provide instructive cues to guide differentiation and maturation of the progenitors (30).

Once the multipotent progenitor cells become committed to the adipocyte lineage, these cells are then referred to as preadipocytes. It is believed that white and brown preadipocytes are predetermined towards differentiation into either one or the other adipose cell type (31). Decisive markers that allow a clear distinction between mesenchymal progenitor and committed preadipocyte are currently unavailable; therefore, the only common phenotypic characteristic of cell culture models of preadipocytes is that they do not undergo differentiation into cell types other than adipocytes. Over the past two decades, considerable progress has been made on defining the transcriptional events controlling differentiation of preadipocytes into mature adipocytes (32;33). Prior to adipogenic transcriptional cascade initiation, both brown and white preadipocytes need to be released from suppression and become committed to terminal differentiation. The known inhibitors of this early adipogenic event include the notch family of epidermal growth factor-like-repeat-containing protein preadipocyte factor-1 (Pref-1) (34), the wingless (Wnt) family of developmental regulators (35), proteins of the retinoblastoma (Rb) family (36;37) and a member of the melanoma-associated antigen family of proteins, functionally resembling RB, named necdin (38). Interestingly, the Rb family of proteins and necdin appear to selectively suppress brown preadipocyte differentiation at the early stage. After release from suppression, the committed preadipocytes then initiate a transcriptional

cascade involving transcription factors CCAAT/enhancer-binding proteins (C/EBPs) and peroxisome proliferator-activated receptor (PPAR) γ to turn on lipid synthesis and other adipocyte-specific programs.

Some factors that underlie brown versus white adipocyte differentiation have been identified, including the zinc-finger binding protein PRDM16 (39), nuclear coactivator PPAR γ coactivator-1 (PGC-1) α (40), members of the pRb protein family, members of the p160 family of coactivators (41;42), the nuclear corepressor RIP140 (43), and others (44). While these transcriptional regulators may indeed play an important role in the determination of adipose cell fate between BAT and WAT, upstream secreted factors that modulate expression and activities of these transcriptional regulators have just begun to be elucidated. One protein family of great interest in the control of brown versus white adipose fate determination is the BMP family. The role of BMPs in adipocyte development is detailed below.

3. BMPs, BMP receptors and signal transduction

3.1. Discovery and members of BMPs

BMPs, although originally named for their ability to induce bone formation, are a group of pleiotropic proteins that regulate processes as diverse as cell fate determination, proliferation, apoptosis, and differentiation during both embryogenesis and adulthood. The discovery of the BMP protein family was initiated in 1945, when Pierre Lacroix hypothesized that a bone derived substance, which he called osteogenin, could initiate bone formation and growth (45). This hypothesis was later confirmed by Marshall Urist's seminal work, which demonstrated that intramuscular implants of cell-free, lyophilized bone extracts could induce *de novo* formation of bone at the site of implantation (46). However, it was not until in the late 1980s that the first individual BMP proteins, BMP-2, -3, and -4, isolated and characterized by Wozney and colleagues (47). BMPs belong to the superfamily of TGF- β proteins, where they form a large subfamily including the currently known 14 BMP proteins, and the growth and differentiation factors (GDFs) (Table 1). BMP homologues are also found in many species, including *daf-4* and *daf-7* in the nematode (*Caenorhabditis elegans*), Univin in the sea urchin (class: *Echinoidea*), decapentaplegic, glass bottom boat 60A, and screw in fruit fly (*Drosophila melanogaster*), VG1 in the African clawed frog (*Xenopus laevis*), as well as Dorsalin-1 in chicken (*Gallus gallus*) (48–50). BMPs are secreted as precursor protein dimers which are cleaved by pro-protein convertases to yield the mature active form of the protein (51;52). Although bone is an important site producing BMPs, most members of this family are expressed in other tissues where they regulate the formation and function of many other organ systems (53–55).

3.2. BMP receptors

While specific receptors for BMPs exist, the binding specificity of these proteins to their receptors is very complex. BMPs can also bind to some receptors of other members of the TGF- β superfamily, namely the activin receptors, with similar affinity. The activation of the BMP signaling cascade requires binding to two receptor types (BMPRs), which then form a hetero-oligomeric complex that relays the signal to downstream targets. Three type 1 receptors are known to bind BMPs, which include the activin receptor like kinases (ALK)-2, ALK-3 (also known as BMPR1A), and ALK-6 (BMPR1B). Similarly, three type 2 receptors possess binding affinity for BMPs, including BMPR2, activin type 2 A receptor (ActR2A), and ActR2B (56). Upon ligand binding, the type 2 receptor, a serine threonine kinase, trans-phosphorylates the type 1 receptor. Once activated, the serine threonine kinase type 1 receptor further activates downstream targets to transduce signals. The specificity of the BMP signal is believed to be regulated by at least four mechanisms: (a) binding affinity of the BMP ligand to the receptor, (b) the stoichiometric composition of the individual receptors in a given cell type, (c) accessory

proteins such as co-receptors (57), and (d) the order of ligand-receptor-complex formation. A BMP ligand can either bind to a single receptor type subunit which then recruits the second subunit, or alternatively bind to a pre-existing loose complex of both receptor types which are activated following association with the BMP ligand. Both possibilities can lead to activation of different downstream signaling pathways, with the Smad (mammalian homologues of the *Drosophila melanogaster* mothers against decapentaplegic) proteins and the p38 mitogen activated protein kinase (p38MAPK) pathways as the two major signaling cascades activated by most BMP ligands (58).

3.3. Signal transduction

While assembly of the hetero-oligomeric receptor complex prior to ligand binding entails activation of the Smad pathway, ligand binding followed by recruitment of the type 2 receptor activates p38MAPK signaling (58). These two pathways represent the canonical signaling cascades that relay ligand-binding to elicit physiological responses in most cell types, although the differential responses largely depend on cell type and other interacting factors within the cell. While the TGF- β proteins and activins can phosphorylate Smad 2 and Smad 3, the proteins of the BMP subfamily are known to phosphorylate Smad 1, 5 and 8, the so called R-Smads (receptor-activated Smads). The specificity of this interaction depends on three-dimensional interaction of the L45 loop of the type 1 BMP receptor kinases which interacts with the compatible L3 loop on the Smad 1, 5, and 8 proteins only (59). Phosphorylated R-Smad then binds to the universal co-Smad, Smad 4, which in turn facilitates the migration into the nucleus and transcriptional activity of the Smad protein. Smad phosphorylation can be antagonized by the inhibitory Smad 6 and Smad 7 proteins, which interfere with the receptor substrate interaction and can thus contribute another layer of signal specificity from BMP ligand to intercellular response (60–63).

As discussed above, BMPs can also activate the p38MAPK signaling cascade, an alternative signaling pathway which has been characterized as an important regulator of energy metabolism directing both mitochondrial biogenesis and insulin-dependent glucose uptake (64;65). The cascade begins with BMP-2 and BMP-4, whose binding leads to phosphorylation of the respective BMP receptor kinase and the activation of MAPK kinase kinase (MAPKKK) TAK1. TAK1 in turn phosphorylates the MAPK kinase MKK6, which can directly phosphorylate p38MAPK (66). Signal transduction from receptor to MAPKKK is mediated by two accessory proteins, TAB1 and XIAP1 which have been shown to modulate signaling downstream of BMP ligand binding (67;68). Although Smad and p38 MAPK pathways represent the main transmitters for BMP binding signals to the nucleus, it should be noted that other signaling cascades have also been implicated in mediating BMPs' signals in different cell types. These alternative pathways include activation of the extracellular signal-related kinase (ERK), the c-Jun N-terminal kinase (JNK), the protein kinase C, the phosphoinositide 3-kinase (PI3K), and the p70S6 kinase (69).

4. Effects of BMPs on development of adipocyte tissue

4.1. Determination of adipose cell fate in mesenchymal stem/progenitor cells

Cell fate determination in the pluripotent stem/progenitor cells is controlled by the integration of cell intrinsic factors with extrinsic cues supplied by the surrounding microenvironment, known as the niche. The concept of a stem cell niche was introduced in 1978, which postulates that stem cells are believed to reside within a microenvironment of defined anatomical structure that helps sustain the typical characteristics of these cells (70). The surrounding cells, forming the niche, not only provide an extracellular matrix as an anchoring point for adhesion of stem cells but also determine stem cell proliferation (i.e. self-renewal) and the differentiation fate of daughter cells. Daughter cells then can either undergo a committing step and terminal

differentiation, or can retain their ability to differentiate into multiple lineages (30). The factors that influence these processes include cell-cell contacts, cell-matrix adhesion, and soluble growth factors - the so called morphogens (71). Morphogens can be secreted from the niche in close vicinity of the stem cells and act as paracrine effectors, or they can be blood-borne growth factors from other endocrine organs throughout the body (Figure 3A). The interplay of these morphogens, and possibly also autocrine factors originating from the stem cell itself, are thought to control progenitor cell preservation, lineage commitment and differentiation.

BMPs are known as one of the niche factors which provide instructive signals to the pluripotent stem cells in proximity or at a distance. During early embryonic development, BMPs form a morphogen gradient to instruct body patterning (72). For example, in the fruit fly, *Drosophila melanogaster*, BMPs have been implicated in embryogenesis following the formation of concentration gradients within the developing embryo (73). The effect of BMPs on formation of fat appears to be evolutionally conserved. The *Drosophila* BMP-7 homologue *glass bottom boat* (gbb-60A) plays an indispensable role in fat body formation, as larvae lacking gbb-60A display severe morphological abnormalities of the fat body (74). Based on the role of morphogens in guiding tissue/organ formation during embryonic development, we speculate that a similar morphogen gradient, presumably established by BMPs and/or other developmental regulators, may instruct the formation of different fat depots distributed in various locations of the body (Figure 3B). Whether BMPs can be directly secreted from different cell types residing in the adipose vasculature or they are secreted at a distant site, and then travel to the adipose tissue via circulation remains to be determined. In addition, the surrounding niche cells could potentially affect ligand binding to the appropriate receptors. Because fat distribution is tightly associated with metabolic phenotype, the embryonic morphogen gradient may influence the susceptibility of developing obesity and other metabolic disorders later in life.

Several lines of evidence have suggested that BMPs provide inductive signals for adipose cell fate determination in mammalian systems (55). The effects of BMPs on adipogenesis appear to depend on the stage of cell development and the dosage of different BMP ligands. In embryonic stem cell-derived embryoid bodies, BMP-4, presumably through interaction with retinoic acid (75;76), can promote adipogenesis (77). In bone marrow stromal cells, the predominant effect of BMPs, in particular BMP-2, is to promote osteogenic differentiation and inhibit adipogenesis (78–82); however, low concentrations of BMPs modestly stimulate adipocyte differentiation (79). The effects of BMPs in the pluripotent mesenchymal cell line C3H10T1/2 are more complex and tightly controlled by the dosages and types of BMPs used in the system as well as by the presence of other extracellular and intracellular factors. The C3H10T1/2 cells are mouse embryonic fibroblasts established from 14- to 17-day-old embryos of the C3H mouse strain (83). These cells functionally resemble mesenchymal stem/progenitor cells that possess the ability to differentiate into multiple lineages, including myoblast, adipocyte, chondrocyte, and osteoblast (84–86). In these cells, low concentrations of BMP-2 and BMP-7 induce adipogenic differentiation whereas high concentrations promote differentiation toward chondrocyte and osteoblast (85;87). Stable expression of cDNAs encoding different BMPs induces C3H10T1/2 cells to differentiate into osteogenic, chondrogenic and adipogenic lineages (86;88). These BMPs appear to have differential effects on adipogenesis in this system, with BMP-4 having the greatest effect on induction of lipid accumulation and expression of markers for mature adipocytes (88).

While these early studies suggest BMPs regulate adipogenesis in the multipotent progenitors, the effect of different BMP members on determination of brown versus white fat cell fate has not been established until recently (Figure 2). Treatment of C3H10T1/2 with BMP-4 has been shown to induce commitment and subsequent differentiation into white adipocytes (89;90).

We have recently discovered that BMP-7 specifically triggers commitment of the multipotent

mesenchymal cells into the brown fat lineage, and implantation of C3H10T1/2 cells treated with BMP-7 into nude mice results in the formation of a UCP-1 positive brown fat pad (91). In NIH-3T3 cells, a cell line with no adipogenic character, both BMP-7 and BMP-4 induce lipid accumulation and expression of adipogenic marker PPAR γ , while only BMP-7 is able to induce expression of brown fat-specific markers, such as PRDM16 and UCP-1 expression. Moreover, BMP-7 in combination with a hormonal induction cocktail and rosiglitazone produces similar effects on other mouse embryonic fibroblast cell lines and primary culture of stromal-vascular fraction isolated from interscapular brown fat (91). Together, these data highlight the fact that BMP-7 can not only trigger commitment of mesenchymal cells to a brown adipocyte lineage, but also can act in concert with other differentiating agents to induce characteristics of brown fat in more primitive fibroblastic cells.

The notion that BMP-7 serves as the inductive signal for brown fat development *in vivo* has also been established. In 1992, Loncar *et al.*, demonstrated that engraftment of mesoderm from E9 rat embryos into the kidney capsule (renal tissue being the main source of BMP-7 in adult animals (92)) results in the implant exclusively differentiating into brown fat (93). The direct evidence for a BMP-7 role in embryonic brown fat development comes from examination of BMP-7 knockout embryos. Both E17.5 and E18.5 embryos of BMP-7 knockout mice show a marked paucity of brown fat and near complete absence of UCP-1 protein (91), suggesting that BMP-7 is absolutely required for formation of functional brown adipose tissue during embryonic development.

4.2. Regulation of adipocyte differentiation in committed preadipocytes

BMPs can also stimulate differentiation in committed preadipocytes. The two most prominent white preadipocyte cell lines are 3T3-L1 and 3T3-F442A. BMP-2 can induce a mature white fat phenotype in both cell lines suggesting that BMPs not only regulate progenitor cell commitment as discussed above, but also promote terminal adipogenic differentiation (94; 95). The transcription factor PPAR γ is a key regulator of the adipogenic process. Some findings suggest a cross talk between BMP signaling and PPAR γ action, since adipogenesis induced by BMP-2 treatment in committed preadipocytes can be further enhanced following the treatment with the PPAR γ agonist rosiglitazone (96). The synergistic effect of BMP-2 and PPAR γ ligand may be explained, at least in part, by the ability of BMP-2 to upregulate PPAR γ expression (97).

BMP-7, as discussed above, triggers progenitor cell commitment towards the brown adipocyte lineage. Furthermore, BMP-7 also promotes brown adipogenesis in committed brown preadipocytes even in the absence of normally required induction cocktail, while it does not affect the differentiation of committed white preadipocytes under the same conditions (91). Taken together, these data suggest that different members of the BMP family exert differential effects on brown versus white adipocyte differentiation, with BMP-2 and BMP-4 as white adipogenic factors and BMP-7 as the unique brown fat inducer (Figure 2).

4.3. Molecular mechanisms

At the molecular level, Hata *et al.* have reported that both Smad1 and p38 MAPK pathways are involved in regulating the expression and activity of PPAR γ during BMP-2-induced adipogenesis in C3H10T1/2 cells (97). In addition, Schnurri (Shn)-2, a zinc finger-containing protein that enters the nucleus upon BMP-2 stimulation, is found to cooperate with Smad1/4 and C/EBP α to induce PPAR γ gene expression (98). Interestingly, Shn-2 knockout mice display reduced white, but not brown, fat mass, suggesting that BMP-2 utilizes the Smad/Shn-2 pathway to regulate white adipogenesis *in vivo*. In committed brown preadipocytes, BMP-7 activates a full program of brown adipogenesis including suppression of adipogenic inhibitors, induction of early regulators of brown fat fate PRDM16 and PGC-1 α , increased expression of

adipogenic transcription PPAR γ and C/EBPs, and mitochondrial biogenesis (91). Interestingly, while BMP-7 is able to activate both Smad and p38 MAPK pathways in brown preadipocytes, activation of p38 MAPK is essential for BMP-7-induced thermogenic program, while this pathway appears to be dispensable for BMP-7's effect on lipid accumulation.

5. Effects of BMPs on systemic energy metabolism

Compared to the substantial amount of data concerning the roles of BMPs in different aspects of embryonic development and morphogenesis, very little is known about the role of BMPs in adipocyte development *in vivo* and in systemic energy homeostasis. This is partially due to embryonic lethality in many of the knockout models of BMPs and/or because severe defects in other tissues/organs overshadow the adipose phenotype. Nevertheless, high expression levels of BMP-3 in white fat positively correlates with increased susceptibility to high fat diet-induced obesity in inbred strain of mice (99). *In vivo* overexpression of GDF-3, a member of the BMP subfamily, increases adiposity and hepatic steatosis in mice fed a high fat diet (100), while GDF-3 deficiency protects mice from diet-induced obesity by selectively targeting white adipose tissue (101). Deletion of myostatin, also known as GDF-8, not only confers muscle hypertrophy but also results in reduced adipose tissue mass (102;103). Lastly, increasing circulating BMP-7 levels by adenoviral-mediated gene transfer results in a significant increase in brown, but not white, fat mass and leads to an increase in energy expenditure and reduced weight gain (91), consistent with the specific role of BMP-7 in brown fat differentiation and function.

As discussed above, the cellular response of BMPs is mediated by ligand binding to the cell surface receptors. Of the different BMP receptor isoforms, BMPRII is particularly interesting to adipocyte development since it has been shown to specialize in adipocyte differentiation *in vitro* (104). Notably, BMPRII binds to BMP-2 and BMP-4 with high affinity, while it exerts low binding capacity to BMP-7 (105). Recently, an increased expression of BMPRII was found in visceral and subcutaneous white fat depots in overweight and obese human subjects (106), consistent with the role of BMP-2 and BMP-4 on formation of white fat. Furthermore, an association of BMPRII-SNPs with obesity-linked quantitative trait loci was identified which could potentially affect the pathophysiology of human obesity. Because mice with whole-body knockout of BMPRII are embryonic lethal (107), we recently generated a conditional knockout model with adipocyte-specific deletion of BMPRII. These mice display a significant reduction in body weight as well as a trend toward reduced fat pad weight on both standard and high fat diets (108). Together, these data suggest a critical, yet complex, role of the BMP superfamily in systemic energy metabolism via regulation of adipocyte development and function.

6. Conclusion

Adipocyte development is a complex process, involving a multitude of interactions between the progenitor cells and inductive signals. Here we have discussed compelling evidence that establishes a critical role of BMPs in adipogenesis and energy metabolism. BMPs are involved in many aspects of adipocyte development, including adipose cell fate determination, differentiation of committed preadipocytes, and function of mature adipocyte. Adipose tissue plays an important role in systemic energy metabolism. It not only serves as an energy reservoir in the form of white fat, but also functions in energy expenditure, which mainly occurs in brown fat. Furthermore, this tissue is also an important source of adipokines that influences appetite, glucose and lipid homeostasis. While detailed mechanisms by which BMPs regulate adipocyte differentiation and function remain to be elucidated, BMPs and their downstream signaling components provide a new avenue to develop potential therapies for the treatment of obesity.

Acknowledgments

We thank A. M. Cypess and K. L. Townsend for a critical reading of the manuscript. T.J.S. is supported by a fellowship from the German Research Foundation. This work was supported in part by an NIH R01 grant DK077097, and research grants from the Eli Lilly Research Foundation, the Harvard Stem Cell Institute, and the Harvard Catalyst/Harvard Clinical and Translational Science Center (to Y.-H. T.).

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Characteristics	White Adipose Tissue	Brown Adipose Tissue
Image (microscopic/ schematic)
Color	Yellow, Ivory	Brown
Vascularization	Arteriole	Multiple Capillaries
Cell size^a	50 to 105 μm^a	38 to 45 μm^a
Fat storage	Unilocular Fat Droplet	Multilocular Fat Droplets
Mitochondria	Few	Abundant
Nucleus	Peripheral	Central
Unique Markers	Leptin ^b	UCP-1
Primary Function	Energy Storage	Energy Expenditure

(a) Cavallini *et al.*; Biomed Pharmacother 2006 Apr;60(3):139-43

(b) Relative expression of leptin is several magnitudes higher in white fat compared to brown fat

Figure 1.
Characteristics of brown versus white adipocytes

Figure 2. Role of BMPs in adipocyte development

Adipocytes arise from multipotent mesenchymal progenitor cells which originally derived from the pluripotent embryonic stem cells. When triggered by specific instructive signals, these progenitors become committed to the adipocyte lineage. While BMP-2 and BMP-4 induces commitment and subsequent differentiation into white adipocyte lineage, BMP-7 drives brown fat cell fate in both mesenchymal progenitor cells and committed brown preadipocytes.

Figure 3. Proposed model of stem cell niche and morphogen gradient controlled adipocyte tissue development

(A) The stem cell niche consists of the surrounding cells (niche cells), the extracellular matrix, and the local microvasculature. Locally secreted morphogens, such as BMPs, and the blood-borne factors affect stem cell fate differentially and depending on their concentration in the microenvironment. The extracellular matrix also represents an important regulator for stem cell function as it forms a natural barrier limiting the accessibility and diffusion of endocrine and paracrine factors. (B) Morphogen gradients are known to regulate multiple developmental processes in the maturing embryo and during adult tissue regeneration. The family of BMP proteins has been implicated in these processes. A localized group of surrounding (stromal) cells secretes instructive factors which then distribute throughout the microenvironment to form a so called “morphogen gradient. Local concentrations are higher at the proximal site and lower at distal regions. This gradient provides distinct effects to the stem cells located at proximal versus distal sites. It is hypothesized that BMPs, and other morphogens, could affect adipose tissue formation in a similar manner. This model could apply to white versus brown adipocyte formation, as well as determination of different white fat depots.

Table 1

Members of the mammalian BMP-subfamily of the TGF- β superfamily and their functional role in development, disease progression and physiology

BMP Ligand Subfamily	Alternative Names	Function
BMP-4	ZYME; BMP2B; OFC11; BMP2B1; MCOPS6	mesenchymal progenitor differentiation, (white) adipogenesis, osteogenesis, chondrogenesis
BMP-2	BMP2a; XBMP2; xBMP-2; MGC114605	mesenchymal progenitor differentiation, (white) adipogenesis, osteogenesis, chondrogenesis
BMP-5	MGC34244	development of trabecular meshwork and optic nerve head; potential role in glaucoma pathogenesis and cartilage development
BMP-6	Vgr-1; DVR-6	early embryonic development; joint integrity
BMP-7	OP-1	brown adipogenesis; early embryonic development and bone formation
BMP-8a	OP-2; FLJ14351; FLJ45264	
BMP-8b	OP-3; PC-8; MGC131757	early embryonic development, possibly bone inductive activity
BMP-12	GDF-7; CDMP-3	specification of neuronal identity in the dorsal spinal cord
BMP-13	KFS; KFSL; SGM1; CDMP2; MGC158100; MGC158101; GDF6	formation of some bones and joints in the limbs, skull, and axial skeleton; mutations lead to colobomata and Klippel-Feil syndrome (KFS)
BMP-14	OS5; LAP4; CDMP1; SYNS2; MP52	cell growth and differentiation in embryonic and adult tissues; mutations associated with acromesomelic dysplasia, Hunter-Thompson type, brachydactyly type C, and chondrodysplasia Grebe type
GDF-1		establishment of left-right asymmetry and in neural development during embryogenesis
GDF-3	Vgr-2	cell growth and differentiation in embryonic and adult tissues
BMP-9	GDF-2	cell growth and differentiation in embryonic and adult tissues; plays a role in adult liver and in differentiation of cholinergic central nervous system neurons
BMP-10	MGC126783	trabeculation of the embryonic heart

BMP Ligand Subfamily	Alternative Names	Function
BMP-11	GDF-11	mesodermal formation and neurogenesis during embryonic development
BMP-15	ODG2; POF4; GDF-9B	oocyte maturation and follicular development
BMP-3	Osteogenin, BMP-3A	induces bone formation; possible role in energy metabolism
BMP-3b	GDF-10; Sumitomo-BIP	skeletal morphogenesis