Received: 2 September 2018 | Revised: 2 November 2018 | Accepted: 25 November 2018

DOI: 10.1111/obr.12822

WILEY obesityreviews

Beyond the bone: Bone morphogenetic protein signaling in adipose tissue

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Funding information
NIH/NHLBI, Grant/Award Numbers: HL30568 and HL81397

Summary

The bone morphogenetic proteins (BMPs) belong to the same superfamily as related to transforming growth factor β (TGFβ), growth and differentiation factors (GDFs), and activins. They were initially described as inducers of bone formation but are now known to be involved in morphogenetic activities and cell differentiation throughout the body, including the development of adipose tissue and adipogenic differentiation. BMP4 and BMP7 are the most studied BMPs in adipose tissue, with major roles in white adipogenesis and brown adipogenesis, respectively, but other BMPs such as BMP2, BMP6, and BMP8b as well as some inhibitors and modulators have been shown to also affect adipogenesis. It has become ever more important to understand adipose regulation, including the BMP pathways, in light of the strong links between obesity and metabolic and cardiovascular disease. In this review, we summarize the available information on BMP signaling in adipose tissue using preferentially articles that have appeared in the last decade, which together demonstrate the importance of BMP signaling in adipose biology.

KEYWORDS

adipogenesis, bone morphogenetic protein (BMP), obesity

1 | INTRODUCTION

Obesity and overweight have reached pandemic levels in the United States; 35.0% of men and 40.4% of women were obese[1] in 2013 to 2014. If the current trend continues, it is estimated that 38% of the world population will be overweight and 20% will be obese[2] by 2030, and 85% of the adults in the United States will be either overweight or obese.[3] The societal and individual burden of obesity increases significantly if we also take into account the strong links between obesity and metabolic and cardiovascular disease.[4,5]

Obesity results from an imbalance between intake and expenditure of energy.[4,5] White adipose tissue (WAT) is responsible for the storage of energy[6] and has a relevant role in the production of adipokines and hormones.[7] WAT consists of white adipocytes containing big lipid droplets that displace the nuclei and other organelles to the periphery of the cells. Brown adipose tissue (BAT), on the other hand, consists of brown adipocytes containing multiple small lipid droplets. BAT is a highly vascularized tissue that dissipates energy by generating heat, potentially contributing to the elimination of excess of calories.[6,8] A third kind of adipocytes are referred to as "beige" or "brite" (brown-in-white) adipocytes[9] in that they are able to transition from white-like to brown-like adipogenesis, a process referred to as "browning" that occurs in response to specific stimuli such as beta-agonists.[10-12]

White adipogenesis and brown adipogenesis are regulated by numerous signaling pathways, which have been extensively reviewed in recent publications.[13-16] The bone morphogenetic proteins (BMPs) and their modulators are relatively late additions to the field of adipose regulation. The BMPs belong to the same superfamily of growth factors as growth/differentiation factors (GDFs), transforming growth factor β (TGFβ), activins, nodal, and anti-Müllerian hormone.[17,18] The BMPs were first discovered because of their ability to induce ectopic

bone formation in soft tissue by Urist and Strates[19] and were later purified by Wang et al[20] and cloned by Wozney et al.[21] BMP signaling is critical in many developmental processes such as the determination of the body axis, germ layer specification, organ development, and cell differentiation.[22-25] BMP signaling relies on binding of BMPs to type I and II BMP receptors (Figure 1), which triggers an array of intracellular mediators including the canonical SMAD pathway.[26] The BMPs and GDFs activate the SMAD1/5/8 pathway through the type I receptors, ie, activin receptor–like kinases (ALKs) 1, 2, 3, or 6, in combination with the BMP receptor type II, or the activin receptor type IIA or IIB.[22-26] In this review, we summarize the available information on BMP signaling in adipose tissue, which together demonstrate the importance of the BMP signaling pathways in adipose biology.

1.1 | Bone morphogenetic proteins

The BMPs that have been linked to adipogenesis so far belong to four BMP subgroups[26]: BMP2/4, BMP9/10, BMP5-8, and BMP3. The information that is available pertains mostly to individual BMP signaling components (Table 1 and Figure 2) and less to potentially overlapping effects and mutual regulation of BMPs, BMP modulators and receptors.

1.1.1 | Bone morphogenetic protein 2

BMP2 is expressed in human adipose tissue, at higher levels in visceral than subcutaneous WAT, and in overweight and obese individuals than in lean individuals.[27] However, the role of BMP2 remains somewhat

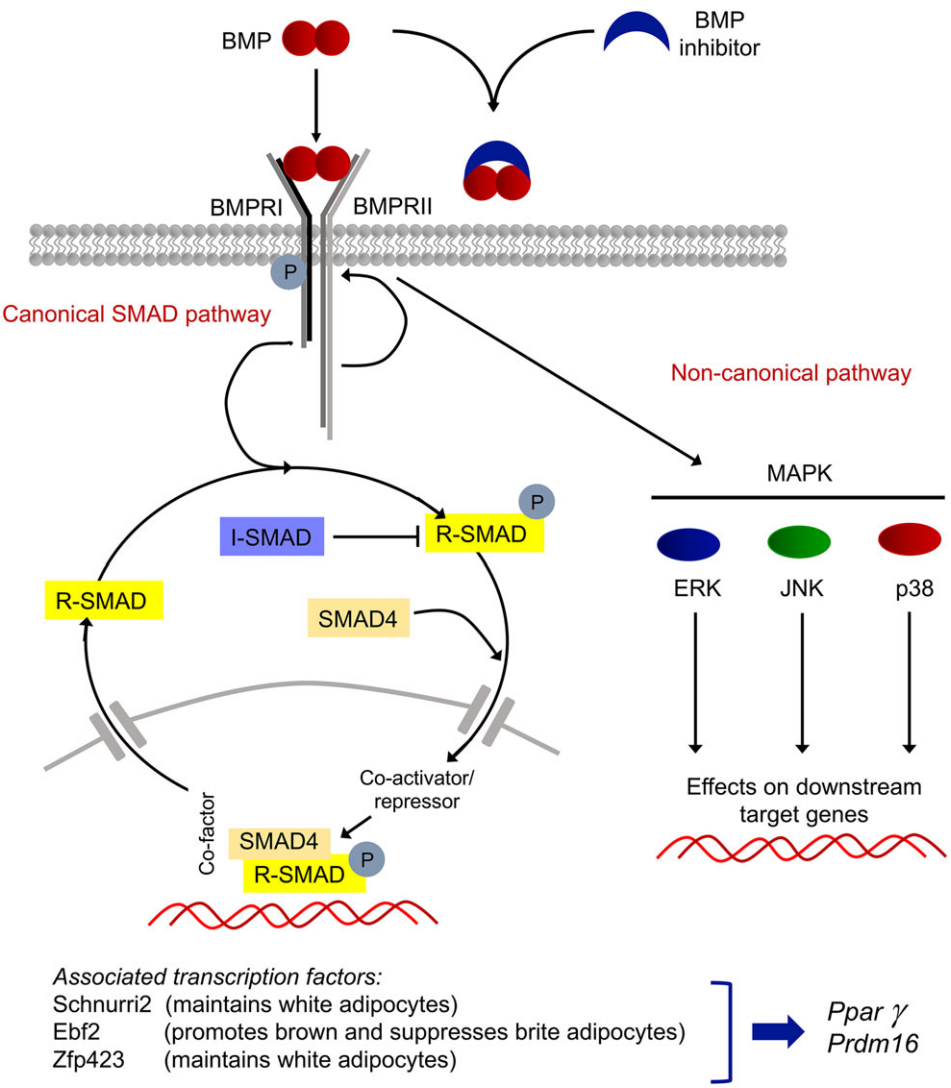

FIGURE 1 Schematic overview of the BMP signaling system and associated transcription factors relevant for adipogenesis. Top: BMP dimers bind to a complex consisting of BMPRI and BMPRII or are sequestered by BMP inhibitors. In canonical BMP signaling, the type II receptor phosphorylates (activates) the type I receptor, which in turn activates regulatory SMAD1/5/8. The R-SMADs combine with SMAD4, a co-SMAD, and enter the nucleus to regulate gene expression together with the appropriate coactivators and repressors. The R-SMADs can also be inhibited by the I-SMADs. In noncanonical BMP signaling, MAPK, ERK, JNK, and p38 are activated. Bottom: Transcription factors known to affect adipocyte differentiation. BMP, bone morphogenetic protein; BMPRI, BMP type I receptor; BMPRII, BMP type II receptor; Ebf2, early B-cell factor 2; ERK, extracellular signal–regulated kinase; I-SMAD, inhibitory SMAD; JNK, Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; p38, p38 mitogen–activated protein kinase; Ppary, peroxisome proliferator–activated receptor γ; Prdm16, PR domain containing 16; R-SMAD, regulatory SMAD; Zfp423, zinc finger protein 423 [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Proposed functions of BMP components

Type	Component	Proposed Functions
BMPs	BMP2	•Linked to WAT (27, 28) (h, m) •May have metabolic effects (28) (m) •Adipogenic effects vary in different progenitor cells (h, m)
	BMP4	•Essential for white adipogenesis (45, 46) (m) but is important UCP1 induction in BAT (57) (h) •Increases with cold exposure (58) (m) •Promotes adipocyte differentiation (51-55) (h, m)
	BMP6	•Increases in BAT with cold exposure (58) (m) •Induces brown-like characteristics in progenitor cells (63) (m, c)
	BMP7	•Essential for brown adipogenesis (63, 71) (m) •Stimulates adipose "browning" (72) (h) •Possible effect on food intake (66, 70) (m)
	BMP8b	•Increases with cold exposure and high-fat diet (58, 74) (m)
	BMP3	•Stimulates proliferation of progenitor cells (75) (m)
	BMP14	•Adipocyte-specific overexpression decreases body fat (80) (m)
Inhibitors	Gremlin	•Silencing of Gremlin-1 promotes adipogenic differentiation and brown-like characteristics in progenitor cells (55, 86) (h, m)
	Noggin	•Contradictory results
	MGP	•Strongly expressed in preadipocytes (94) (h)
	Follistatin	•Induced during brown differentiation and cold exposure (96, 97) (m)
	BAMBI	•Negative regulation of adipogenesis (107) (m)
	Chordin-like	•Overexpression protects against diet-induced obesity (109) (m)
	Follistatin-like	•Decreases during adipogenic induction (110) (m) •Increased in tissue of obese mice and serum of obese individuals (111) (h, m) •Gene deletion reduces body fat (112) (m)
Receptors	BMPRIA (ALK3)	•Higher adipose expression in obese individuals (113) (h) •Deletion in brown precursors led to less BAT (65) (m) •Overexpression, together with that of BMPRIB, promotes adipogenesis (114) (m)
	BMPRII	•Increased in adipose tissue of obese patients (115) (h)
	ActRIIB	•Blockade activates BAT function (117) (m)

Abbreviations: ActR, activin receptor; BAMBI, BMP and activin membrane bound inhibitor; BAT, brown adipose tissue; BMP, bone morphogenetic protein; BMPR, BMP receptor; h, human; m, mouse; MGP, matrix Gla protein; UCP1, uncoupling protein 1; WAT, white adipose tissue.

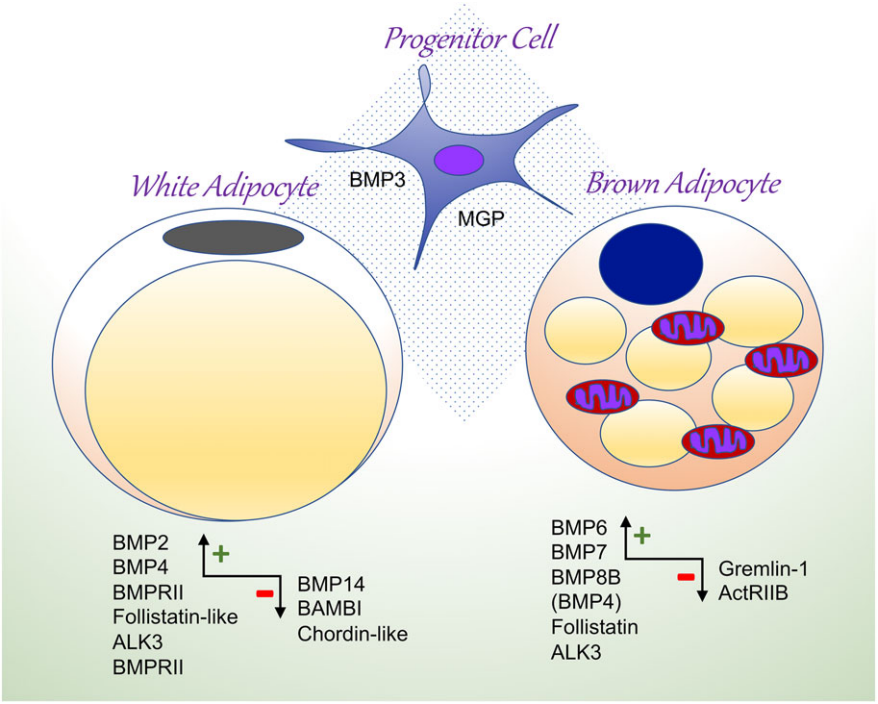

FIGURE 2 Schematic summary of BMP action on white and brown adipocytes based on current knowledge. The + and − signs indicate largely stimulating and inhibitory action, respectively. ActRIIB, activin type IIB receptor; ALK, activin receptor–like kinase; BAMBI, BMP and activin membrane–bound inhibitor; BMP, bone morphogenetic protein; BMPRII, BMP type II receptor; MGP, matrix Gla protein [Colour figure can be viewed at wileyonlinelibrary.com]

ambiguous. Mouse studies have implicated BMP2 in white adipogenesis, in that ablation of *Schnurri2*, a gene targeted and activated by BMP2, reduced white but not brown adipose mass.[28] The *Schnurri2* ablation also resulted in an increase of blood insulin and a decrease of blood glucose,[28] which suggest that BMP2 has metabolic effects. In addition, BMP2 also targets[29] Zfp423, responsible for the maintenance of the characteristics of white adipocytes and the suppression of brite activation.[30]

Numerous studies have examined the effects of BMP2 on adipogenic differentiation in various adipose progenitor cells. C3H10T1/2 transfected with BMP2 preferentially differentiated into osteoblast-like cells, although a large number of adipocytes were also obtained.[31] However, in adipogenic medium, BMP2 preferentially induced adipogenic differentiation[32] suggesting that the effect of BMP2 may be dependent on context and type of delivery. The induction of adipogenesis in C3H10T1/2 cells by BMP2 takes place through activation of peroxisome proliferator–activated receptor γ (PPARγ) via SMAD and p38MAPK signaling.[33]

In adipose-derived stromal cells, BMP2 supports both adipogenic and osteogenic differentiation. In one study, addition of BMP2 to human adipose–derived stromal cells inhibited osteogenic differentiation in cells from six out of eight donors but enhanced it in cells from the remaining two donors.[34] Similar inconsistencies were also seen in other studies. Two studies showed that BMP2 was unable to induce osteogenesis in adipose-derived stromal cells[35,36] whereas a third study showed strong osteogenic effects.[37] Possible contributing factors to these inconsistencies may be variability in the source of BMP2 and biological activity.

The results in human mesenchymal cells (hMSCs) were more proadipogenic. A combination of BMP2 and 3-isomethyl-1-methylxanthine (IBMX) induced a sixfold increase in adiponectin expression[38] even though the effect in human cells was also influenced by the donor.[39] In hMSC from bone marrow cultured in adipogenic medium, treatment with BMP2 increased PPARγ activation, regardless of the origin of the cells.[40] Similarly, in 3T3-L1 adipocytes, BMP2 enhanced insulin-mediated uptake of glucose through PPARγ and glucose transporter type 4 (GLUT4).[41] When combined with insulin-like growth factor, BMP2 was even able to induce adipocyte differentiation in tendon stem cells.[42]

There is only one study proposing a possible relationship of BMP2 with brown adipogenesis. Salisbury et al[43] suggested involvement of BMP2 in the activation and expansion of progenitors of brown adipocyte–like cells in the perineurium of peripheral nerves. Injection of BMP2 stimulated an increase of noradrenalin that in turn resulted in an increase of cells expressing the beta3 adrenergic receptor that migrated from the nerves and then transitioned through a brown-like adipogenic state. Finally, BMP2 was found to form heterodimers with BMP7, which promoted the phosphorylation of the SMAD1/5/8 without affecting the MAPK pathway[44] although it is unclear whether these heterodimer affects adipogenesis.

1.1.2 | Bone morphogenetic protein 4

Overall, BMP4 is mostly known to be associated with WAT in mice. BMP4 induces the transcription[29] of Zfp423, which favors stability of white adipocytes and prevents the activation of brite.[30] Qian et al demonstrated that overexpression of BMP4 in adipose tissue, as mediated by a *Bmp4* transgene, led to a general reduction of visceral WAT and adipocyte size.[45] The investigators observed a decrease in the expression of brown adipocyte developmental- and mitochondrial-related genes in BAT, whereas the expression increased in WAT.[45] However, these results conflict somewhat with those of Modica et al[46] who reported that overexpression of BMP4 in the interscapular BAT, as mediated by an adenovirus containing the *Bmp4* gene, promoted a brown-to-white adipogenic shift by impairing the acquisition of functional thermogenesis and decreasing free fatty acid oxidation and oxygen consumption. The lipid droplets in BAT were larger and the expression of uncoupling protein 1 (UCP1) was lower, even after 24 hours of cold exposure, in mice injected with *Bmp4*-containing virus compared with control mice.[46] The apparent contradiction between the studies may be explained by the fact that the transgene used by Qian et al[45] was regulated by the promoter of the *Fatty acid–binding protein 4* (*Fabp4*) gene (also known as *Adipocyte protein 2*, *aP2*), which is also expressed in cells other than adipocytes,[47,48] whereas Modica et al[46] used the *Adiponectin* promoter. It is also likely that the effect of BMP4 is influenced by the dose, location in the tissues, and fat depot.[45,49]

BMP4 may be involved in the insulin response since deletion of adipose *Bmp4* in mice results in reduced insulin sensitivity along with increased adiposity.[45] Furthermore, correlations between high serum levels of BMP4 and high degrees of diabetes, adiposity and insulin sensitivity have been reported in patients.[46] Similar results were obtained in two models of insulin resistance in mice (*db*/*db* and high-fat fed), where the serum levels of BMP4 increased in parallel with the serum insulin levels.[50]

Several studies have shown that BMP4 regulates adipogenesis in vitro even though the patterns of induction seem to differ between cell models. Suenaga et al[51] reported that expression of BMP4 increases in 3T3-L1 preadipocytes before they differentiate into adipocytes and that the increase in BMP4 is required for the differentiation to occur. However, committed A33 preadipocytes expressed BMP4 in parallel with activation of SMAD1/5/8 during proliferation, whereas BMP4 expression diminished when they reached confluence.[52] When BMP4 was blocked by Noggin, the committed proliferating A33 cells lost their preadipocyte phenotype,[52] further indicating a need of BMP4 to maintain commitment.

In uncommitted C3H10T1/2 cells, however, BMP4 expression increased when the cells reached confluency[52] and treatment with BMP4 induced adipogenic commitment. However, certain threshold concentration of BMP4 was required: 10 ng/mL showed no effect, whereas both 50 and 100 ng/mL resulted in adipocyte differentiation.[53] Induction of BMP4 has also been reported in primary human preadipocytes undergoing differentiation.[54] It is believed that adipogenic commitment caused by BMP4 is mediated by the nuclear entry of the zinc finger protein 423 (ZNF423) transcription factor, which leads to PPARγ induction.[55] Interestingly, BMP4 causes the loss of the platelet-derived growth factor receptor β (PDGFRβ) at the same time that adipose markers appear in both pericytes and C3H10T1/2 cells,[56] suggesting that BMP4 might play a role in connecting the vascular system to the adipose tissue.

The role of BMP4 in BAT is less well studied but has been reported to induce UCP1 expression in human adipose stromal cells (ASCs) when combined[57] with BMP7. Despite its strong association with whitening, BMP4 expression in BAT increases the response to cold exposure.[58] Brown preadipocytes treated with BMP4 have reduced expression of mitochondrial genes, and decreased oxygen consumption and basal lipolysis, which results in larger lipid droplets.[46] BMP4 is able to form heterodimers with BMP7, which reportedly have higher activity in bone than the correspondent homodimers,[59] but

their effects in white adipogenesis and brown adipogenesis remain to be studied. Finally, BMP4 activity may be subject to gender differences since estrogen depletion upregulates BMP4 in adipose tissue and BMP4 stabilizes the estrogen receptor α and estrogen signaling in WAT.[60]

1.1.3 | Bone morphogenetic protein 6

There is only limited research available on the role of BMP6 in adipogenesis, and the results are mixed. BMP6 is highly homologous with BMP7 but displays a 20-fold higher affinity to ALK3 (also known as BMP receptor IA, BMPRIA) than BMP7 and a stronger resistance to inhibition by Noggin.[61] Under cold conditions, the expression of BMP6 was shown to increase in BAT.[58] In addition, BMP6 was able to convert C2C12 murine precursor cells into adipocytes under proadipogenic conditions with induction of BAT markers, resulting in a bioenergetics profile similar to that of brown adipocytes.[62] In brown preadipocytes, however, BMP6 increased lipid accumulation but did not increase expression of brown adipose genes.[63] In intramuscular preadipocytes from chicken, BMP6 expression was enhanced during adipogenic differentiation,[64] and in 3T3-L1 adipocytes, BMP6 increased expression of PPARγ, which enhanced GLUT4 and insulin-mediated uptake of glucose.[41]

1.1.4 | Bone morphogenetic protein 7

BMP7 is the BMP that is most strongly linked to brown adipogenesis. Gene deletion of *Bmp7* in mice reduced BAT at birth[63] with up to 70%. Interestingly, lack of ALK3 (BMPRIA), which mediates BMP7 signaling, also results in impaired cervical BAT formation due to alterations in the progenitor cells.[65] Furthermore, lean C57BL/6J mice that were fed a high-fat diet and treated with BMP7 via subcutaneous osmotic minipumps for 4 weeks at 21°C showed an increase in BAT volume and UCP1 expression.[66] There was also a dose-dependent increase in fat oxidation and energy expenditure.[66] Two different mouse models of obesity, *db*/*db* mice and C57BL/6J mice fed with high-fat diet, that were treated with intraperitoneal injections of BMP7 for a month showed a reduction in body weight and body fat as well as improved glucose levels and reduced inflammation, when compared with their respective controls.[50]

There is evidence that BMP7 controls, through SMAD signaling, both Zfp423 and Ebf2, which have different effects on adipogenesis.[67-69] The proposed model of BMP function has two parts: In the first part, Zfp423 binds to Ebf2 and acts as a transcriptional corepressor of crucial Ebf2-target genes, such as *Prdm16*, resulting in the suppression of the overall thermogenic gene program in white adipocytes.[30] In the second part, BMP7 prompts a Smad1/4 interaction with Zfp423, which results in the activation of *Ppary* expression and adipogenesis. This way, Zfp423 is sequestered from Ebf2, permitting Ebf2 to drive the thermogenic gene program of BAT.[30]

However, the effect of BMP7 on body weight might not be limited to its role in the induction and maintenance of BAT. Two studies have suggested that it affects food intake, although with some contradictions. Townsend et al[70] observed that administration of a BMP7-containing adenovirus to diet-induced obese mice reduced their food intake and consequently the weight of the mice. It was estimated that 75% of the weight reduction was due to decreased food intake and 25% to increased BAT activation. On the other hand, Boon et al[66] described that mice treated with BMP7 via subcutaneous osmotic minipumps for 4 weeks increased their food intake. The contradictory effects may be due to differences in BMP7 administration or the duration or the dose of the respective treatments. Another possibility is that the increase in BAT leads to an increase in energy dissipation, which in turn enhances the need for energy and stimulates food intake. Together, the findings point to a possible role of BMP7 in the regulation of food intake although further research is needed to support this.

In vitro studies also supported a role of BMP7 in brown adipogenic differentiation. Tseng et al[63] showed that brown preadipocytes enhanced expression of UCP1 and mitochondrial biogenesis in response to BMP7 more than to any other BMP. In addition, BMP7 induced commitment of mesenchymal stem cells (MSCs) to the brown adipogenic lineage[63] and increased mitochondrial activity in mature brown adipocytes by increasing fatty acid uptake and oxidation, without increasing the number of mitochondria.[71] BMP7 may play a role in the browning of WAT, as suggested by the finding that BMP7 increases the expression of brown and beige markers as well as metabolic activity in human ASCs.[72] In C3H10T1/2 cells, BMP7 also coordinates a panel of insulin signaling components and is able to rescue brown adipogenesis in cells with defective insulin signaling.[73]

1.1.5 | Bone morphogenetic protein 8B

Preferential expression of BMP8b was recently reported in BAT in mice,[74] unlike the BMP8A isoform, which was enriched in WAT. The expression of BMP8B increased after high-fat diet or cold (4°C) exposure.[58,74] It was also expressed in the hypothalamus where it acted as a thermogenic protein together with AMP-activated protein kinase in key hypothalamic nuclei.[74] Mice with *Bmp8b* gene deletion exhibited altered BAT with enlarged lipid droplets, impaired thermogenesis, and susceptibility to diet-induced obesity.[74] Interestingly, the adipose expression of BMP8B showed gender differences. BAT of females had higher BMP8B expression than that of males, and males injected with diethylstilbestrol (estrogen analog) exhibited an increase in body weight and BMP8B expression.[58]

1.1.6 | Bone morphogenetic protein 3

Despite being a BMP, the action of BMP3 is mediated in a way resembling that of TGFβ. It binds to activin receptor type IIB (ActRIIB), which, together with ALK4, activates the SMAD2/3 pathway.[75] In vivo, increased BMP3 expression has been associated with the C57BL/6J mice that gained the most weight in response to a high-fat diet.[76] However, in C3H10T1/2 or 3T3-L1 cells, BMP3 stimulated proliferation rather than adipogenic differentiation.[75] BMP3 has also been identified as a key factor in a model of maternal protein restriction model of visceral adiposity.[77]

1.1.7 | Bone morphogenetic protein 3b

BMP3b (also referred to as GDF10) increased in the mesenteric adipose tissue of mice with diet-induced obesity[78] and transgenic mice with adipose overexpression of BMP3b (as directed by the *aP2* promoter) appeared to be protected against diet-induced obesity.[79]

This would be consistent with the findings in 3T3-L1 cells that BMP3b suppresses adipogenesis and that BMP3b is expressed at higher levels in preadipocytes than in mature adipocytes.[78] Thus, it may function as feedback mechanism to limit adipogenesis in abdominal obesity.[78]

1.1.8 | Bone morphogenetic protein 14

BMP14 (also referred to as GDF5) is higher in interscapular BAT than in any kind of WAT in mice. Adipose-specific *Bmp14*-transgenic mice driven by the *aP2* promoter has less adipose tissue and smaller adipocytes than control mice, despite no difference in food intake.[80] Furthermore, blood glucose levels were reduced in the *Bmp14* transgenic mice compared with controls, while oxygen consumption and energy expenditure were increased.[80] Conversely, dominant-negative GDF5 mutant mice fed a high-fat diet gained more weight than controls while oxygen consumption and energy expenditure decreased.[80] In vitro, BMP14 increased progressively in 3T3-L1 preadipocytes during adipogenic induction,[81] and promoted brown adipogenesis in cells from BAT and subcutaneous WAT, but not from visceral WAT.[80]

1.2 | Inhibitors and modulators of BMP signaling

A limited number of studies have examined the possible roles of BMP inhibitors and modulators in adipogenic differentiation and adipose metabolism, leaving this field largely open for future investigations. The available information suggests that the modulators of BMP signaling play a relevant role in the adipose tissue, with differences in their effects on WAT and BAT (Table 1 and Figure 2).

1.2.1 | Gremlin

There are two isoforms of Gremlin. Gremlin-1 is the most studied isoform and has been shown to bind[82,83] BMP2, BMP4, and BMP7. Both isoforms were upregulated[46] by BMP4 and might have a limiting effect on adipogenesis. Gremlin-1 was more expressed in omental fat than in its subcutaneous counterpart[84] but increased in the subcutaneous adipose tissue of individuals with hypertrophic obesity.[55] In these individuals, its expression correlated positively with that of BMP4 in whole adipose tissue and in individual adipocytes.[55] The disappearance of Gremlin-1 promoted adipogenic differentiation in vitro. In 3T3-L1 cells undergoing adipogenesis, Gremlin-1 expression gradually disappeared over a few days,[85] and when Gremlin-1 was silenced using siRNA in human preadipocytes, PPARγ was greatly induced.[55] Furthermore, expression of the brown adipocyte markers ZIC1 and UCP1 and mitochondrial content increased with the silencing[55] of Gremlin-1.

The other isoform, Gremlin-2, was reduced in the epididymal adipose tissue of C57BL/6J mice subjected to high-fat diet, as well as in *ob*/*ob* mice and *db*/*db* mice.[86] Gremlin-2 also declined in 3T3-L1 cells upon adipogenic induction. Cells overexpressing Gremlin-2 accumulated less lipids than control cells, whereas knockdown of Gremlin-2 increased the adipogenic potential.[86]

1.2.2 | Noggin

In vitro experiments have shown that Noggin binds a wide range of BMPs, including at least[87] BMP2, BMP4, BMP5, BMP6, BMP7, BMP13, and BMP14. In addition, its expression was induced by BMP4 signaling,[46] potentially establishing feedback regulation. The few studies available suggest that the effect on adipogenic differentiation of Noggin varies from cell to cell. In bone marrow MSCs, Noggin treatment promoted adipogenesis,[88] whereas in human stromal cells, Noggin had an inhibitory effect on adipogenic differentiation if added prior to full differentiation.[54] It has also been found that expression of Noggin is reduced or eliminated in differentiated cells, whether they are adipocytes or cardiac/skeletal myocytes,[55,89] which suggests that modulation by Noggin may be most important during the early cell differentiation. Elevated plasma levels of Noggin levels have been reported in spontaneously obese mice and patients[88] with body mass index (BMI) > 27 although the mechanistic connection between circulating Noggin and the adipose tissue remains to be clarified.

1.2.3 | Matrix Gla protein

Matrix Gla protein (MGP) is best known for its ability to limit arterial calcification and vascular malformations, in part through inhibition[90-93] of BMP2, BMP4, and BMP7. Nevertheless, microarray analysis in human adipocytes showed that MGP was strongly expressed in preadipocytes but decreased in the secretome during their differentiation to adipocytes.[94] MGP expression was also depot dependent, with higher expression in the omental than in the subcutaneous adipose tissue.[95]

1.2.4 | Follistatin

Follistatin binds BMP2, BMP4, BMP6, and BMP7 and activin and promotes BAT characteristics.[96,97] It was expressed in cold-induced BAT in mice[96] and during adipogenic differentiation of mouse brown preadipocytes and mouse embryonic fibroblasts (MEFs).[96] MEFs from mice with *Follistatin* gene deletion had decreased expression of the brown adipocyte markers UCP1 and PR domain containing 16 (PRDM16), which was reversed when Follistatin was added.[96] Conversely, BAT from *Follistatin* transgenic mice had enhanced expression of UCP1 and PRDM16 and an increased amount of interscapular BAT.[98] In addition, WAT from *Follistatin* transgenic mice showed an increase in brown/beige adipogenic markers.[98] A study in obese and nonobese women showed that Follistatin mRNA levels in WAT were reduced in obesity but increased in subcutaneous WAT after weight loss.[99]

1.2.5 | Myostatin

Myostatin, also known as GDF8, blocks BMP7 activity in CH10T1/2 and 3T3-L1 cells by binding to its receptor, the ActRIIB, apart from having direct effects[100,101] on SMAD2 and SMAD3. The inactive form of myostatin, before its propeptide is removed, is also referred[102] to as follistatin-like 3. Mice with *Myostatin* gene deletion exhibit less adipose tissue and higher muscular mass,[103] whereas *Myostatin* transgenic mice have normal body composition with a reduction in adipocyte size.[104] Specific deletion of myostatin in muscle decreased the fat mass and improved insulin sensitivity, whereas a similar deletion in adipose tissue reduced in serum free fatty acids but without change in body composition.[102] Absence of Myostatin has also been linked to increases in expression of brown and brite markers[105,106] and BMP7.

1.2.6 | BMP and activin membrane–bound inhibitor

BMP and activin membrane–bound inhibitor (BAMBI) is a membrane-bound modulator of paracrine factors that regulate adipogenesis such as TGFβ, BMP, and Wnt. It serves as a negative regulator of adipogenesis and is downregulated in a mouse model of diet-induced obesity.[107] Similarly, suppression of BAMBI in porcine preadipocytes promotes adipogenic differentiation.[108]

1.2.7 | Chordin-like

The Kielin/chordin-like protein inhibits both TGFβ and activin signals while enhancing BMP signaling. Kielin/chordin-like transgenic mice were protected from high-fat diet–induced obesity, had higher body temperature (almost a full degree), and oxidized more glucose than control mice.[109] These transgenic mice exhibited high levels of UCP1 and PPARγ in the epididymal WAT.[109]

1.2.8 | Follistatin-like

Follistatin-like is distantly related to Follistatin.[110] It was enriched in 3T3-L1 preadipocytes and decreased as adipogenesis induction occurs; conversely, it reappeared when adipocytes were dedifferentiated.[110] A significant increase of follistatin-like was observed in adipose tissue of *ob*/*ob* mice as well as in the serum of overweight and obese individuals.[111] Mice with deletion of Follistatin-like 3 had enhanced glucose tolerance and insulin sensitivity and their perigonadal visceral fat pad was reduced in size.[112]

1.3 | BMP receptors

1.3.1 | ALK3 (BMPRIA)

ALK3 is known to bind and mediate signals from multiple BMPs.[26] A study in a cohort of 941 type 2 diabetic patients and 944 nondiabetic controls showed that its expression was higher in visceral than in subcutaneous fat, regardless of gender.[113] When analyzed by weight, BMPRIA expression in overweight and obese individuals was higher than in lean subjects and increased in the adipose tissue of type 2 diabetics.[113] ALK3 expression correlated directly with both BMI and percent body fat.[113] In mice, specific deletion of *Alk3* in cells expressing Myf5, a marker of brown adipocytes and the smooth muscle lineages, showed a strong reduction in constitutive BAT.[65] The mice were born with reduced BAT mass, which remained significantly smaller into adulthood. The newborn mice exhibited reduced body temperature, whereas adults had an impaired response to cold temperatures.[65] Overexpression of ALK3 and ALK6 (also known as BMPRIB) in C3H10T1/2 cells promoted adipogenic differentiation, even in the absence of changes[114] in BMP2 and BMP4.

1.3.2 | Type II receptors

BMPRII and ActRIIB

A study in 930 patients with type 2 diabetes and 900 nondiabetic controls showed that BMPRII expression was increased in the subcutaneous adipose tissue versus the visceral adipose tissue.[115] Furthermore, the BMPRII levels were increased in the visceral and subcutaneous adipose tissue of overweight and obese patients as compared with lean patients.[115] The findings might be consistent with cellular findings that targeting BMPRII negatively regulated porcine preadipocytes.[116] In contrast, when mice were treated with antibodies against ActRIIB, the effect was selectively observed in the BAT. The BAT mass increased along with the brown adipocyte size, whereas no changes in WAT were reported.[117] The treated mice were protected against hypothermia and had an increased oxygen consumption and CO_2 release.[117]

1.4 | Unanswered questions and perspectives

So far, the available information suggests that BMP signaling has an important role in the adipose tissue. Some members of the BMP family seem to act preferentially in one type of adipose tissue and others may be relevant for specific fat depots. BMP2/4 appears to have links with WAT and the antagonists Gremlin and Noggin, whereas BMP6/7/8B and 14 connect with BAT and the antagonists Follistatin, Myostatin, and Chordin-like.

Most studies have focused on one or two members of the BMP family but have failed to take into consideration the relationships that exist between many of the BMPs. For example, the details of the relationship between BMP4 and BMP7 remain unclear. As outlined earlier, both have been reported to act on brown adipocytes, whereas the single action of BMP4 seems specific for WAT. It is possible that BMP4/7 and BMP2/7 heterodimers play a role, that there is competition between the two BMPs for specific receptors, or that a temporal relationship exists between BMP4 and BMP7 where one of the BMPs has to "prime" the brown adipocytes prior to the action of the other.

The addition or removal of one BMP agonist or antagonist often affects the expression of other agonists or antagonists thereby upsetting the overall BMP activity. To fully evaluate the effect of an addition or removal, we would have to know what BMP balance would be optimal for each fat depot. The perfect BMP balance is likely affected by age, gender, and adipose location and adds another dimension to BMP signaling that will require additional studies in mice and humans.

The BMP system might serve as an interface between adipose metabolism and diabetes. On one hand, diabetes induces BMP4 in the adipose tissue[118] and the vascular endothelium.[119] On the other hand, transgenic and systemic BMP4 enhances glucose-stimulated insulin secretion and ameliorates glucose tolerance in mice through ALK3 signaling in beta cells.[120] This might be a platform for crosstalk that could be used for modulation of diabetic complications in obesity. It would also be interesting to know if modulation of BMP signaling in the vascular endothelium affects adipocyte differentiation and metabolism.

The role of BMP inhibitors in obesity and obesity complications has not been well studied. Even though the BMP inhibitors regulate BMPs, the extent and circumstance of inhibition will depend on protein characteristics and the respective affinities for different BMPs and other binding partners, as well as the surrounding matrix and cellular localization. Considering all the "moving parts" in the BMP system, it may be necessary to develop a systems biology approach to account for the combined results of simultaneous actions. Such an approach might also be useful to identify and understand the relative importance of BMP target genes in adipose tissue.

Whether or not the possibility of BAT activation in humans to reduce body fat is feasible or effective still needs further evaluation. Theoretically, BAT activation would lead to an increase of energy expenditure and modify the balance between energy intake/expenditure. However, the exact volume of human BAT remains unknown, and there are conflicting reports on whether or not BAT activation, even at its full capacity, would be enough to significantly affect energy expenditure.[121] Attempts to activate BAT through adenoceptor agonists proved to be effective in mice but did not yield similar results in clinical trials because of lack of bioavailability.[122] Whether the direct use of BMPs and their inhibitors can be more effective in reducing body fat remains to be seen.

Once adipose BMP signaling is better understood, we would have a better perspective on what could be done in regard to BMP modulation as a treatment. It might be possible to create agonists and antagonists with select molecular properties that could target specific BMP components. Such molecular therapeutics might be used for systemic delivery via the blood stream, for local delivery through expression in the local endothelium, diffusion from depots in the adipose tissue, or transplantation of genetically modified stem cells or adipocytes. Since BMPs and their extracellular inhibitors have been implicated in gradients in tissue formation and development,[123] it is possible that this principle could be mimicked for local treatments.

Thus, a full understanding of adipose BMP signaling would provide a window into adipose development and metabolism and allow for the development of new strategies targeting obesity and metabolic imbalance.

ACKNOWLEDGEMENT

Funding for this work was provided in part by NIH/NHLBI: grant numbers HL30568 and HL81397 (K.I.B.).

CONFLICT OF INTEREST

Drs Blázquez-Medela, Jumabay, and Boström have nothing to disclose.

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How to cite this article: Blázquez-Medela AM, Jumabay M, Boström KI. Beyond the bone: Bone morphogenetic protein signaling in adipose tissue. *Obesity Reviews*. 2019;1–11. https://doi.org/10.1111/obr.12822