Emerging Role of Bone Morphogenetic Protein 4 in Metabolic Disorders

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Bone morphogenetic proteins (BMPs) are a group of signaling molecules that belong to the TGF-β superfamily. Initially discovered for their ability to induce bone formation, BMPs are known to play a diverse and critical array of biological roles. We here focus on recent evidence showing that BMP4 is an important regulator of white/beige adipogenic differentiation with important consequences for thermogenesis, energy homeostasis, and development of obesity in vivo. BMP4 is highly expressed in, and released by, human adipose tissue, and serum levels are increased in obesity. Recent studies have now shown BMP4 to play an important role not only for white/beige/brown adipocyte differentiation and thermogenesis but also in regulating systemic glucose homeostasis and insulin sensitivity. It also has important suppressive effects on hepatic glucose production and lipid metabolism. Cellular BMP4 signaling/action is regulated by both ambient cell/systemic levels and several endogenous and systemic BMP antagonists. Reduced BMP4 signaling/action can contribute to the development of obesity, insulin resistance, and associated metabolic disorders. In this article, we summarize the pleiotropic functions of BMP4 in the pathophysiology of these diseases and also consider the therapeutic implications of targeting BMP4 in the prevention/treatment of obesity and its associated complications.

Worldwide obesity has more than doubled since 1980. Obesity continues to be the principal driver for the rising prevalence of other comorbidities such as type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), and cardiovascular disease and is a major burden on health care systems globally. Adequate treatment of these complications should preferably address both the underlying causes and the specific consequences of disease. Current therapeutic options slow the progression but may not effectively reverse the underlying anomalies. Recently, bone morphogenetic protein (BMP) signaling has emerged as a new strategy for these problems.

BMPs are members of the TGF-β superfamily of secreted signaling molecules, which includes 33 members in mammals. BMPs play important roles in regulating many cellular and developmental processes such as cell fate determination, cell proliferation, and differentiation (1). In recent years, a broader role for BMPs in metabolic diseases has been characterized in a number of preclinical and clinical studies (Tables 1 and 2), and BMPs are now considered important regulators of both embryonic and adult tissue homeostasis.

BMPs can signal through both canonical and noncanonical pathways. Canonical signaling relies on binding of BMPs to heterotetrameric complexes of type I and type II serine/threonine kinase receptors (2,3), which transduce signals through R-SMADs and co-SMADs, whereas noncanonical pathways include MAPKs, p38, ERK, and JNK. BMP signaling is negatively regulated by I-SMADs intracellularly, whereas secreted BMP antagonists, including GREMLIN 1, NOGGIN, CHORDIN, CHORDIN-LIKE 1, and others, block these pathways extracellularly. Intriguingly, the interaction of these ligands with their receptors and regulators is also shared with TGF-β pathways at multiple levels, giving rise to the remarkable complexity and diversity of BMP functions, which are highly dependent on spatio-temporal regulation in addition to the endocrine properties of the ligands secreted into circulation. Hence, a careful examination of these potentially overlapping signaling pathways is required to understand molecular mechanisms and to evaluate their clinical benefits.

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Table 1—Altered levels of different BMPs in obesity and associated disorders

Diseases	BMPs	Animal studies	Clinical findings
Obesity/T2D/IR	BMP2	Increased serum levels in diabetic rats (62).	Increased serum levels in overweight/obese subjects (63). Increased mRNA levels in WAT and increased serum levels in T2D patients with moderate obesity but not morbid obesity (64). Increased plasma levels in T2D patients (65).
	BMP3b	Increased weight gain along with development of IR in BMP3b$^{-/-}$ mice (66).	
	BMP7	Reduced serum levels in animal models of T2D (67).	Positive correlation of serum levels with HOMA2-%B (insulin secretion index) and fasting insulin (68). Reduced serum levels in T2D subjects (69).
	BMP9	Reduced hepatic mRNA levels in IR rats (70). Reduced hepatic mRNA/protein expression in *db*/*db* and HFD-fed wild-type mice (71).	Reduced hepatic mRNA/protein levels in T2D subjects (71). Reduced circulating levels in MetS patients and associated negatively with FBG, OGTT, HOMA-IR, etc. (72). Reduced circulating levels in T2D patients and associated negatively with FBG, OGTT, HOMA-IR. Also, reduced mRNA/protein levels in muscle and AT of T2D subjects (73). Circulating levels were negatively correlated with HOMA-IR (74).
NAFLD/NASH/liver fibrosis	BMP2	Reduced hepatic mRNA/protein levels in BDL- and CCL_4-treated mice (75).	Reduced protein levels in human fibrotic livers (75).
	BMP6	Increased hepatic mRNA levels in different murine models of chronic liver injury (55).	Increased hepatic mRNA levels in patients with NAFLD (55).
	BMP7	Increased hepatic protein levels followed by a decrease in CCL_4-treated mice (76).	Hepatic protein levels were increased in patients with liver fibrosis, whereas they were reduced in patients with cirrhosis (76). Elevated systemic and hepatic protein levels in patients with liver cirrhosis (77).
	BMP8b		Increased hepatic mRNA levels along with increase in NASH disease stage, level of hepatocellular ballooning, and fibrosis (78).
	BMP9	Highest mRNA levels in HSCs; increased with HSCs activation (79).	Increased hepatic protein levels in patients with acute liver failure, but no change with increased fibrosis stages (79). Reduced plasma levels in patients with decompensated cirrhosis (80). Higher BMP9 levels accompanied advanced stages of liver fibrosis (81).
	BMP10		Reduced plasma levels in patients with decompensated cirrhosis (80).

AT, adipose tissue; BDL, bile duct ligation; FBG, fasting blood glucose; HOMA-IR, HOMA of insulin resistance; MetS, metabolic syndrome; OGTT, oral glucose tolerance test %B, β-cell function.

BMP4: CLINICAL PERSPECTIVES IN METABOLIC DISORDERS

BMP4 was first purified and cloned in 1988 by Wozney et al. (4). It is localized on chromosome 14 and highly conserved between humans and mice (5). Apart from its high expression and critical role in embryogenesis and development, BMP4 is also important for maintenance and function of many adult tissues. Its role in adipose progenitor cell commitment and adipogenic differentiation has been well established (6–8). Mature adipocytes secrete BMP4, which increases with adipocyte expansion. It acts in a paracrine manner to promote metabolically beneficial hyperplastic adipose tissue expansion and to enhance subcutaneous adipose cell oxidative capacity by assuming a beige/brown phenotype during differentiation (9).

Clinical studies have shown that circulating BMP4 levels are increased in obese humans (10–12) and further enhanced in individuals with impaired glucose tolerance and T2D (11). Serum and mRNA (in white adipose tissue [WAT]) levels of BMP4 are positively correlated with adipocyte size (9–11), and BMP4 is secreted by both adipose cells (9) and the endothelial cells in the adipose tissue (13), probably accounting for the increased levels in obesity. Consequently, serum levels are also negatively

Table 2—Alterations in BMP4 and BMP signaling in obesity and associated disorders

Metabolic disorders	BMP4 and receptors	Animal studies	Clinical studies
Obesity/T2D	BMP4		Serum levels increased in obese subjects and were positively correlated with BMI (10). Serum levels increased in obesity, with further increase in T2D patients. Serum levels were positively correlated with adipocyte size, whereas they were negatively correlated with IS (11). Serum levels were positively correlated with visceral AT mass (12). Serum levels were reduced after RYGB in severely obese patients with T2D (82). WAT mRNA levels were inversely correlated with BMI (37).
	BMPR1A	Loss of BMPR1A in brown adipogenic progenitor cells impairs constitutive BAT formation (16). Adipose-specific deletion resulted in reduced macrophage infiltration and improved IS (17). mRNA and protein levels were increased in sWAT and iBAT of $Irs^{-/-}$ and cold-induced mice models (83).	Increased mRNA levels in WAT of overweight/obese subjects. SNPs were associated with obesity and higher *BMPR1A* expression in AT (14).
	BMPR2	BMPR2 knockout mice lose white fat due to cell death (84).	Increased mRNA levels in WAT of overweight and obese subjects. SNPs were associated with obesity and higher *BMPR2* expression in AT (15).
NAFLD/NASH	BMP4	Increased hepatic protein levels in mice fed with HFD (21).	
	ALK6		ALK6 SNP associated with increase in prevalence of NAFLD (22).
	SAMD1/5/8	Hepatocyte-specific ablation results in liver fibrosis (85).	

These data are focused on metabolic associations, but BMP genetic variations have also been shown in other human diseases including cardiovascular disease, lung fibrosis, and certain malformations (86). AT, adipose tissue; iBAT, BAT in the interscapular region; IS, insulin sensitivity; RYGB, Roux-en-Y gastric bypass; sWAT, subcutaneous WAT.

correlated with insulin sensitivity (11). The BMP receptors ALK3 (BMPR1A), ALK6 (BMPR1B), and BMPR2, which are used by BMP4 to transduce its signal, have been studied to understand the complex roles of BMP signaling in the pathophysiology of obesity. *BMPR1A* and *BMPR2* mRNA levels are significantly increased in WAT of overweight and obese subjects, compared with their lean counterparts, and are strongly correlated with BMI as well as with traits of glucose metabolism and insulin levels (14,15).

Additionally, genetic polymorphisms of BMP receptors have been associated with obesity (14,15). Single nucleotide polymorphisms (SNPs) within the *BMPR1A* and *BMPR2* gene have been identified as obesity risk alleles in two cohorts (Leipzig and Sorbs) and related to higher adipose *BMPR1A* and *BMPR2* mRNA levels, respectively (14,15). These data indicate that the SNP effects on obesity and related metabolic parameters might be mediated through effects on adipose mRNA levels. However, it is not known if these SNPs are functional so the biological relevance of these associations in man is unclear, but some support is provided by experimental work in animal models. BMPR1A knockout mice models have shown that BMPs are critical for the formation and thermogenic activity of brown adipocytes, whereas, in white adipocytes, BMPs regulate the endocrine interaction between cells of adipose lineage and immune cells (16,17). Given the involvement of BMP receptors in human obesity and the known ability of BMP7 in reducing appetite in mice (18), attenuated BMP signaling might regulate energy balance via affecting appetite. Townsend et al. (19) demonstrated that deletion of BMPR1A in hypothalamic POMC neurons resulted in hyperphagic mice. However, deletion of BMPR1A did not lead to weight gain due to increased energy expenditure by enhanced sympathetic activation of brown adipose tissue (BAT), which could be due to compensatory increase in BMPR1A expression in non-POMC neurons. BMPR1A signaling has also been shown to play an important role in postnatal establishment of hypothalamic neural circuits critical for leptin-mediated feeding behavior (20). However, BMP7 apparently does not require leptin to mediate its appetite-reducing effects (18). These findings provide evidence for the involvement of BMP receptor signaling in the complex regulatory system connecting central and peripheral pathways in regulating energy balance. This is an intriguing area of investigation, and identification of functional SNPs within these genes

could potentially contribute to both improved risk assessment and the development of targeted therapies.

Liver is another important target of BMPs, and BMP signaling has been reported to be involved in the pathophysiology of hepatic steatosis. Hepatic BMP4 levels are elevated in NAFLD, and administration of BMP4 has been reported to alleviate hepatic steatosis (21). However, no clinical study has yet elucidated the role of BMP4 in hepatic fibrosis to date. Very recently, Thayer et al. (22) described a rare SNP in a BMP type I receptor (ALK6) to be associated with increased prevalence of NAFLD in humans. We (R.K.B., P. Pingitore, M.B., U.S., unpublished data) have observed a significant increase in *BMP4* mRNA levels in the liver of obese individuals with NAFLD/nonalcoholic steatohepatitis (NASH), which are further increased in the presence of T2D (Fig. 1*A*). Furthermore, hepatic *BMP4* levels also reflect the degree of whole-body insulin resistance measured with hyperinsulinemic-euglycemic clamps (Fig. 1*B*).

In this article, we focus on recent findings supporting the importance of BMP4 signaling and action in the pathophysiology of obesity, insulin resistance, and associated comorbidities and also discuss potential therapeutic implications of targeting BMP4 signaling and action in these disorders. Figure 2 provides an overview of our current knowledge of the effects of BMP4 on whole-body insulin sensitivity and glucose homeostasis as well as effects on WAT browning, thermogenesis, and energy homeostasis in vivo.

BMP4 AND METABOLIC DISEASES

Obesity

Obesity is the result of an imbalance between intake and expenditure of energy. WAT is a complex organ responsible not only for energy storage and utilization but also for the secretion of several signaling molecules that impact multiple target organs (23). Among different fat depots, subcutaneous adipose tissue (SAT) is the largest adipose depot and is also considered the least harmful site for excess fat storage. However, SAT has a limited expandability dependent on ability of adipose cells to enlarge (hypertrophy) and/or to recruit new cells (hyperplasia) for storage (24). When SAT storage capacity is exceeded, further caloric overload leads to fat accumulation in ectopic sites as well as in visceral adipose depots. Ectopic fat accumulation is both a marker and driver of the obesity-associated metabolic complications such as dyslipidemia, NAFLD, and insulin resistance. As expected, hypertrophic obesity is associated with reduced recruitment and differentiation of new adipose cells in SAT (25). Therefore, improving the storage capacity of SAT by increasing the recruitment of WAT precursors and/or simultaneously increasing the tissue thermogenesis should decrease the deleterious effect of increased fat accumulation on whole-body homeostasis.

Thiazolidinediones, a class of well-established antidiabetes drugs, increase the storage capacity of SAT while reducing fat accumulation in the visceral depot and liver (26). However, these ligands can only enhance the differentiation of already committed preadipocytes and cannot promote the commitment and recruitment of new adipose cells.

BMP4 Promotes White Adipogenesis

BMP4 plays a key role in the regulation of white adipogenesis by inducing commitment of mesenchymal stem/progenitor cells into the white adipogenic lineage by activating peroxisome proliferator–activated receptor γ (PPARγ) (6,27). Adipogenic commitment by BMP4 is a complicated process that involves dissociation of the intracellular PPARγ transcriptional activator zinc finger protein 423 (ZFP423) complex (28) from the mesenchymal cell canonical WNT1-inducible signaling pathway protein 2 (WISP2), allowing ZFP423 to enter the nucleus with transcriptional activation of PPARγ (29). Moreover, consistent with the well-documented importance of adipose

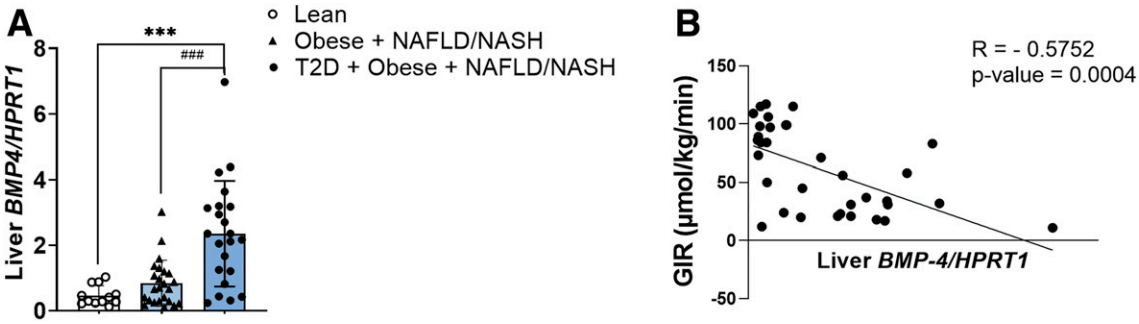

Figure 1—Hepatic BMP4 expression is increased in obese patients with NAFLD/NASH and T2D and is negatively correlated with insulin sensitivity. *A*: Relative mRNA levels of BMP4, measured by quantitative RT-PCR in RNA extracted from liver biopsies of lean patients ($n = 12$; BMI 24.5 ± 0.8 kg/m^2), obese patients with NAFLD/NASH ($n = 24$; BMI 34.2 ± 6.0 kg/m^2), and obese patients with NAFLD/NASH and T2D ($n = 22$; BMI 34.9 ± 5.8 kg/m^2). Data were normalized to hypoxanthine phosphoribosyltransferase 1 (HPRT1) and are expressed as relative fold change (mean ± SD). Statistical significance was assessed using one-way ANOVA and post hoc Tukey test. ***$P < 0.0001$ vs. lean patients; ###$P < 0.0001$ vs. obese patients with NAFLD/NASH. *B*: Association between hepatic BMP4 gene expression (fold) and insulin sensitivity (measured as glucose infusion rate [GIR]) in obese patients with NAFLD/NASH and T2D was analyzed with use of Pearson correlation test.

tissue vessel expansion in modulating adipose tissue growth and development, an interplay between angiogenesis and adipogenesis mediated by BMP4 has also been described (30). BMP4 enhances angiogenesis via promoting precursors to produce proangiogenic cytokines communicating with endothelial cells to promote angiogenic expansion. Several in vitro studies have also demonstrated the proangiogenic effects of BMP4 in endothelial cells via different signaling pathways including RUNX1T1 (31), VEGF/VEGFR2, and angiopoietin/Tie2 (32) and also miRNAs (33). BMP4-induced increase in angiogenesis in adipose tissue also supports a beneficial role in enhancing energy expenditure (34,35). These findings show that BMP4 is a positive regulator of both WAT cell commitment and differentiation as well as of angiogenesis.

BMP4 Signaling and Browning Effects in WAT. BMP4 signaling is essential not only for promoting mesenchymal progenitor cell commitment and subsequent differentiation of white adipose precursor cells but also for the induction of a beige/brown and oxidative phenotype of the SAT adipose cells that would protect against obesity and insulin resistance. In fact, we have found exactly this to happen in mature lean mice undergoing gene therapy with BMP4 targeting the liver to increase circulating levels (36). SAT adopted a beige/brown phenotype, increasing energy expenditure and protecting the mice from becoming obese when placed on a high-fat diet (HFD) (36). Insulin sensitivity was also increased in comparisons with control mice of equal weight.

Whether the target cells are specific adipose progenitor cells or the common white adipose progenitor cells is still unclear. However, we found that maintained BMP4 signaling during differentiation of isolated and undifferentiated human SAT stromal vascular cells promoted their development to a beige/brown phenotype, while early, transiently increased BMP4 signaling is only required for PPARγ activation and subsequent white adipogenic differentiation of these cells (9). Although this is still an unresolved issue, our current concept is that (specific?) human SAT adipose progenitor cells are multipotent and that maintained BMP4 signaling during their adipogenic differentiation drives the beige/brown phenotype. This, in turn, also means that important ambient factors regulating cell BMP4 signaling, including the cell-secreted BMP antagonists GREMLIN 1 and NOGGIN, are important regulators of the final differentiation phenotype.

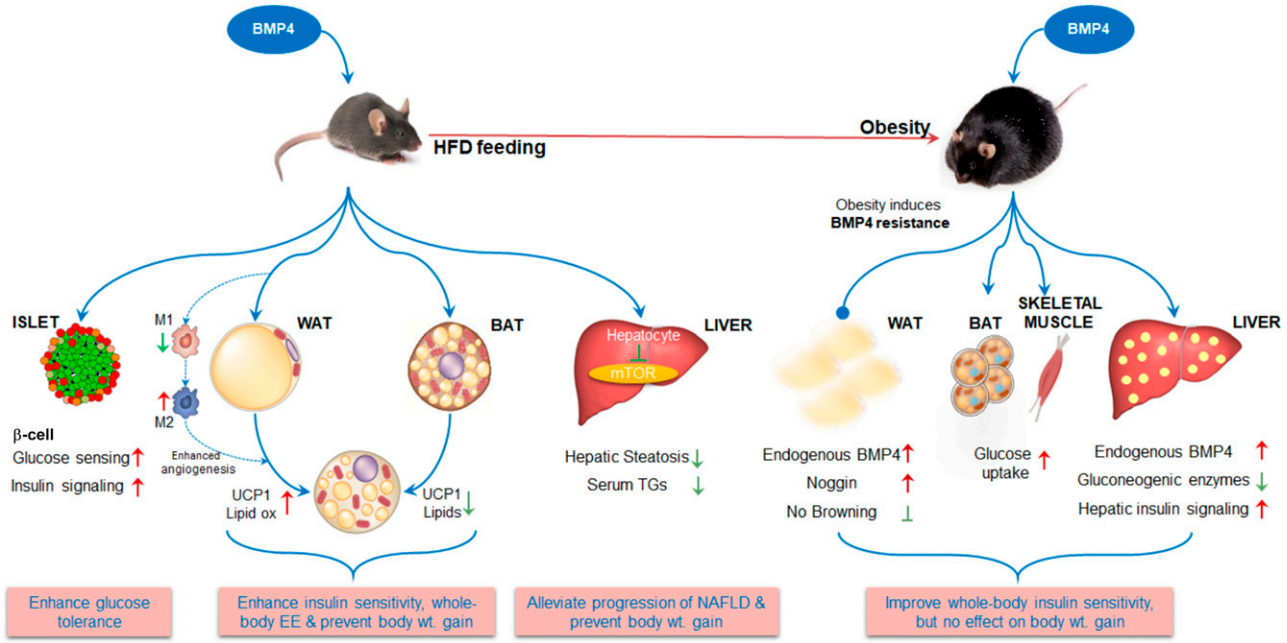

Figure 2— A schematic representation of key pathophysiological signaling pathways regulated by BMP4 in energy homeostasis and metabolism in rodent models. On the left side of the figure, target tissues/organs involved in the effects of BMP4 in lean mice as well as in HFD-fed mice have been depicted. Overexpression of BMP4 in β-cells enhances glucose sensing and ameliorates glucose tolerance. BMP4 exerts differential effects in WAT and BAT. It induces browning in WAT, whereas it impairs thermogenic capacity of BAT, but the overall combined effect results in enhanced insulin sensitivity and increased whole-body energy expenditure. Along with enhanced angiogenesis, BMP4 also reduces the proinflammatory M1 state of adipose tissue macrophages in WAT and enhances the proliferation of the anti-inflammatory M2 state. Exogenous BMP4 in liver prevents HFD-induced hepatic lipid accumulation and reduces serum triglycerides (TGs). On the right side of the figure, the effects of BMP4 in obese mice have been depicted. Obesity results in BMP4 resistance in WAT because of increased BMP antagonist levels, i.e., NOGGIN, thus inhibiting the positive effects of BMP4 on WAT browning and energy expenditure. It also improves whole-body insulin sensitivity; enhances insulin signaling in adipose cells, skeletal muscle, and liver; and reduces hepatic glucose production. Green arrows indicate downregulation or inhibition, and red arrows indicate upregulation or enhancing. Line with rounded end cap indicates BMP4 resistance in adipose tissue induced by obesity. EE, energy expenditure; ox, oxidation; UCP1, uncoupling protein 1; wt., weight.

Multiple studies using different approaches, such as transgenic mice with adipose tissue–specific BMP4 overexpression/knockout (37), adeno-associated viral vectors (AAV)-mediated BMP4 expression in BAT (11) or in liver (36), or silencing the predominant endogenous BMP4 inhibitor, GREMLIN 1, in human subcutaneous preadipocytes (9), have demonstrated that enhanced BMP4 levels and signaling induce browning of white adipocytes both in vitro and in fully mature animals in vivo (9,11,36,37).

Shao et al. (38) demonstrated that ZFP423, which activates PPARγ and adipogenesis, suppresses the thermogenic gene program through repression of the transcriptional activity of EBF2 in white adipocytes. BMP4 inhibits the interaction between ZFP423 and EBF2, allowing EBF2-mediated induction of the beige adipocyte gene program in white adipocytes. More recently, Qian et al. (39) demonstrated an additional role of BMP4 in promoting browning of white fat by regulating macrophages in SAT. Adipose tissue macrophages are numerically the dominant cells among infiltrating immune cells in human WAT (23). Moreover, the phenotypic switch from anti-inflammatory M2 phenotype to proinflammatory M1 state occurs in adipose tissue of obese individuals (40). Adipose tissue–specific BMP4 overexpression inhibited M1 macrophages, whereas it promoted M2 proliferation via enhanced p38/MAPK/STAT3/PI3K-AKT signaling pathway, resulting in enhanced thermogenic function of adipocytes along with increased angiogenesis (39). These findings highlight the potential of targeting immuno-metabolic pathways to treat obesity and associated complications.

BMP4 Effects in BAT. BMP4 exerts similar effects in the development of brown adipocytes in BAT. Similar to the induction of beige-like oxidative adipocytes in WAT, BMP4 overexpression in interscapular BAT was shown to impair the thermogenic capacity of BAT with reduced expression of genes involved in fatty acid oxidation and electron transport chains, and with increased lipid droplet size, thus promoting a white/beige-like phenotype in both SAT and BAT cells (Modica et al. [11]).

Likewise, liver-specific BMP4 overexpression leading to enhanced circulating BMP4 levels resulted in reduced UCP1 levels and impaired lipolytic activation as well as increased lipids in BAT; i.e., brown adipocytes assumed a less oxidative beige adipocyte phenotype (36). Unilocular phenotype with increased lipid droplet size and reduced expression of brown adipocyte markers were also observed in BAT of transgenic mice overexpressing BMP4 in adipose tissue (37). Thus, increased BMP4 leads to the development of a beige phenotype in both white and brown adipocytes. However, it is clear that the overall beige/browning of the large SAT depot has positive consequences for thermogenesis and fat accumulation, since it prevents the development of obesity in initially lean animal models placed on an HFD (36,37). In contrast, beiging of the cells in the small BAT seems to be less important for changing thermogenesis in vivo. However, a major limitation for this conclusion is that no studies have been performed to examine effects of increased BAT beige/browning under conditions of activated BAT such as during cold exposure or adrenergic β-3 administration.

BMP4 Antagonists. Increased endogenous BMP4 expression and secretion in hypertrophic adipocytes as well as elevated circulating levels have been observed in obesity (9,11,12). This could be a consequence of the increased cell lipid accumulation and/or a feedback mechanism to promote recruitment of new cells to compensate for expanding adipose cells. However, the effect of BMP4 is dependent not only on ambient BMP4 levels but also on levels of cellular BMP4 antagonists making the cells resistant to secreted BMP4 (9). Several antagonists, including GREMLIN 1, NOGGIN, FOLLISTATIN, CHORDIN-LIKE 1, and BMP and activin membrane-bound inhibitor (BAMBI), are expressed in adipose tissue (9). GREMLIN 1 and NOGGIN, two powerful and secreted BMP4 inhibitors, were found to be markedly increased in adipose tissue in obesity, inhibiting BMP4-induced precursor cell commitment/differentiation and white to beige/brown adipocyte conversion (9,36). Thus, WAT becomes resistant to BMP4 action in obesity due to the increased secretion of these antagonists. More specifically, adipose tissue *GREM1* is increased in man, while in mice, *NOG* is primarily upregulated (9). Silencing *GREM1* in human preadipocytes enhanced BMP4 signaling/action, resulting in upregulation of *ZNF423* and *PPARγ* as well as markers of an oxidative beige/brown adipose cell phenotype (9). *GREM1* mRNA levels in WAT were reduced following bariatric surgery in obese individuals, supporting that it is driven by obesity (41). Taken together, these findings indicate that GREMLIN 1 is a target to enhance BMP4 signaling and action in human adipose tissue and, thus, to counteract human obesity and its consequences. BMP4 is also a regulator of insulin sensitivity and action in major target tissues including WAT, liver, and skeletal muscles, independent of its effects on body weight (41). One way to enhance BMP4 action will be to antagonize the secreted endogenous BMP antagonists, and particularly GREMLIN 1 in man, to overcome the state of cellular BMP4 resistance in obesity.

T2D

T2D develops as a consequence of pancreatic β-cell dysfunction together with insulin resistance in key insulin-regulated metabolic tissues (liver, skeletal muscle, and adipocytes). TGF-β superfamily members, including TGF-β, activin, and BMPs, control several developmental processes and have been implicated in pancreatic development and disease (42–44). However, little is known about the role of BMP4 signaling in β-cell function.

Goulley et al. (45) showed that transgenic expression of BMP4 in β-cells enhanced glucose-stimulated insulin secretion and glucose clearance in adult mice. In contrast, glucose-stimulated insulin secretion was impaired in BMP4-treated rodent and human islets in vitro by inhibiting

insulin exocytosis (46,47). Perturbation of BMP signaling during embryonic development in transgenic mice could affect the developmental program for regulated insulin secretion, but further investigations are needed to understand the interplay between BMP4 and β-cell function. In our studies in mature lean and obese mice treated with BMP4 gene therapy for several months, fasting and glucose tolerance test–stimulated insulin levels were slightly lower, but this was most likely secondary to the markedly enhanced whole-body insulin sensitivity (36,41).

Interestingly, Hedjazifar et al. (48) recently illustrated that GREMLIN 1 levels are more prominently increased in T2D than in obesity alone. They further showed that GREMLIN 1 impaired insulin signaling/action, in vitro, in key human insulin target cells (i.e., adipocytes, skeletal muscle, and liver cells). Increased levels of FOLLISTATIN and FOLLISTATIN-LIKE 1, negative regulators of BMP4 signaling (49–51), have also been associated with impaired insulin signaling and glucose tolerance (52,53). However, these observations are not entirely dependent on their BMP4-antagonizing effects, as these molecules cross talk with multiple signaling pathways/processes.

NAFLD/NASH

The liver is involved in numerous critical functions in the body, and metabolic imbalance is associated with a broad range of liver diseases. In fact, the prevalence of the most common liver disorder, NAFLD, is constantly increasing worldwide (54). NAFLD is a consequence of increased hepatic lipid accumulation (steatosis) and is associated with insulin resistance and inflammation. NAFLD can progress into NASH, fibrosis, cirrhosis, or hepatocellular carcinoma, but why this only happens in certain individuals is unclear.

While increasing evidence indicates that the liver is an important target of several BMPs, very few studies have investigated the role of BMP4 in hepatic metabolism and its potential link with NAFLD/NASH. Studies have shown that hepatic BMP4 levels increase in different mouse models of NAFLD (21,55). Peng et al. (21) demonstrated that liver-specific BMP4 overexpression prevented HFD-induced lipid accumulation by regulating genes involved in lipid metabolism and alleviated the development/progression of NAFLD by suppressing mTORC1 signaling pathway. Likewise, hepatic AAV BMP4 overexpression reduced hepatic lipid accumulation in HFD-fed mice (36). Taken together, current data show that hepatic BMP4 is increased in NAFLD, which could be a compensatory mechanism to minimize liver injury. In addition, BMP4 overexpression improves hepatic insulin signaling and action in mice with already established obesity independent of changes in hepatic lipid levels (41).

Hepatic stellate cells (HSCs) have recently gained attention, as these are the main matrix-producing cells, which upon activation undergo transdifferentiation to fibrogenic myofibroblast-like cells, thereby causing fibrosis. BMP4 has been reported to activate *α-SMA* (α-smooth muscle actin), an activation marker, in cultured rat (56) and human (57) HSCs. Other studies, however, suggest that the BMP antagonist GREMLIN 1 promotes HSCs activation in HSC-T6 cells, and suppressing GREMLIN 1 in rat liver alleviates carbon tetrachloride (CCL_4)-induced hepatic fibrosis (58,59). In support of these data, transcriptional activation of *GREM1* in human liver, and adipose tissue, in a large cohort of individuals has been positively associated with degree of steatosis and ballooning, as well as inflammation and fibrosis scores (48). The intricate interplay among hepatocytes, immune cells, and HSCs further adds to the complexity of regulatory control of HSCs activation. Thus, better three-dimensional in vitro and in vivo model systems are required to understand the pathophysiology of liver fibrosis and the role of BMP4 and its antagonists with regard to their profibrotic or antifibrotic potential.

Interestingly, a recent review of the large NHANES databases in the U.S. found that obese individuals were less susceptible to development of pronounced fibrosis in the liver and had lower 15-year mortality than nonobese individuals with NAFLD (60). To what extent increased BMP4 in the liver in obesity may contribute to this is an interesting question.

BMP4 Gene Therapy Prevents Obesity and Improves Insulin Resistance

Most recent preclinical studies have used transgenic and other genetic animal models to test effects of BMP4 on obesity and metabolic traits. However, to examine potential clinical usefulness of BMP4 therapy, it is essential to examine effects, and side effects, in mature animal models. Recently, Hoffmann and colleagues (36,41) studied the effect of increasing systemic BMP4 levels by targeting the liver with AAV8 BMP4 gene therapy to increase local and systemic secretion of BMP4 in nonobese and HFD-fed obese mice. Increased BMP4 prevented obesity in initially lean mice placed on HFD due to increased energy expenditure and beige/browning of the SAT (36). In contrast, initially obese mice fed HFD for 12 weeks before adenoviral vector administration did not have reduced degree of obesity or exhibit increased energy expenditure, in spite of having high local and systemic BMP4 levels. Increased levels of the BMP4 antagonist, *NOG*, and reduced phosphorylated-SMAD signaling in WAT account for this lack of response to BMP4 therapy (41). However, several positive effects were seen in other target tissues including a clear improvement in whole-body insulin sensitivity. Insulin signaling was improved in all key metabolic tissues (WAT, liver, and skeletal muscles) along with enhanced glucose uptake in skeletal muscles and BAT as well as suppressive effects on hepatic glucose production. Cellular studies suggested this to be due to reduced gluconeogenesis in the liver and associated with increased PGC1 acetylation, while no effects were seen in kidney cells, another gluconeogenic tissue. The animals remained healthy, and no toxic or other distinct side effects were seen during the 12–16 weeks of high local and systemic BMP4 levels.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

This article summarizes recent findings regarding BMP4 signaling and actions (Fig. 1). Despite several important advances in deciphering the signaling modalities of BMP4 and its antagonists, much remains to be fully understood, in particular, the different effects observed in lean and obese animals upon increased systemic BMP4 levels. However, muscle and liver do not become resistant in the same way, and both lean and obese mice become markedly more insulin sensitive. To what extent this is due to differences in the signaling pathways and expression of BMP antagonists is still not clear.

A word of caution is warranted with regard to translating experimental studies in mice to also be relevant in man. Apart from the potential species differences, mice are also housed and studied at normal room temperature for man (around 20°C), while the thermo-neutral temperature for mice is ~30°C. This difference can influence the individual response to experimental procedures in mice, as recently shown (61).

Nevertheless, the findings summarized above reveal that BMP4 possesses novel therapeutic potential in the regulation of whole-body insulin sensitivity and hepatic glucose and lipid metabolism as well as in adipose cell browning and whole-body energy balance. The interactions between BMP4 and its antagonists present additional complexities, but identifying these interactions will increase the opportunities for better therapeutic approaches. Based on our and other animal experiments, no major side effects have been reported with long-term BMP4 treatments. However, detailed examinations of classical tissue targets such as bone mass and structure need to be performed. For the future, it is reasonable to speculate that emerging BMP4-targeting therapies will have preventive effects on both obesity and insulin resistance and may improve the clinical outcomes in metabolic disorders.

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