BMP and activin receptor membrane bound inhibitor: BAMBI has multiple roles in gene expression and diseases (Review)

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Abstract. BMP and activin membrane-bound inhibitor (BAMBI) is a transmembrane glycoprotein, known as a pseudo-receptor for TGFβ, as, while its extracellular domain is similar to that of type I TGFβ receptors, its intracellular structure is shorter and lacks a serine/threonine phosphokinase signaling motif. BAMBI can regulate numerous biological phenomena, including glucose and lipid metabolism, inflammatory responses, and cell proliferation and differentiation. Furthermore, abnormal expression of BAMBI at the mRNA and protein levels contributes to various human pathologies, including obesity and cancer. In the present review, the structure of BAMBI is briefly introduced and its associated signaling pathways and physiological functions are described. Understanding of BAMBI structure and function may contribute to knowledge regarding the occurrence of diseases, including obesity and diabetes, among others. The present review provides a theoretical foundation for the development of BAMBI as a potential biomarker or therapeutic target.

Contents

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1. Introduction

BMP and activin receptor membrane-bound inhibitor (*BAMBI*) was discovered by Onichtchouk *et al* (1) in 1999, and was considered a homologue of human non-metastatic gene A due to the strong structural similarity between the two molecules (2). *BAMBI* expression is highly conserved in chordates, from fish to humans; however, its expression patterns vary significantly among different animals. For example, the *BAMBI* gene is highly expressed in human kidney medulla, placenta and spleen tissues, but not in lung or muscle tissues (2), whereas in mice, *Bambi* is primarily expressed in heart, lung and testis tissues (3). BAMBI has a broad spectrum of effects, including effects on lipid metabolism through inhibition of adipocyte lipid deposition (4), on myogenesis through promotion of muscle stem cell proliferation and differentiation (5), on ovarian function through regulation of steroidogenesis and follicle-stimulating hormone (FSH) expression levels in porcine granulocytes (6), on inflammation through inhibition or modulation of inflammatory processes (7) and on tumor development through inhibition of tumor cell motility, invasion and survival (8). Given its important roles in physiological and pathological conditions, BAMBI has increasingly become the focus of research over the past two decades (Fig. 1).

2. Structural characteristics of BAMBI

BAMBI is a transmembrane glycoprotein comprising 260 amino acids with an N-terminal extracellular domain and a short C-terminal intracellular domain (9,10). Furthermore, *BAMBI* contains numerous important post-translational modification sites, including two protein kinase C phosphorylation sites, six casein kinase phosphorylation sites, three cAMP protein kinase sites and three N-acylation sites (11,12). The structure of the extracellular ligand-binding domain of *BAMBI* is similar to that of transforming growth factor β receptor 1 (TGFβRI)/bone morphogenetic protein receptor type 1 (BMPRI), while *BAMBI* lacks an equivalent intracellular serine/threonine kinase structural domain (9). Therefore, *BAMBI* readily forms heterodimers with *TGFβRI*/*BMPRI*, which can interfere with TGFβ or BMP pathways (10). Thus, BAMBI is considered a pseudo-receptor in the TGFβ and BMP signaling pathways (1,3). During binding of TGFβ family

members to their receptors, BAMBI can compete with type I TGFβ receptors for binding to type II TGFβ receptors. Since the serine/threonine kinase structural domain is not present in *BAMBI*, amino acid phosphorylation does not occur, thus blocking TGFβ signaling pathway transduction (Fig. 2).

3. Role of BAMBI in signal transduction

TGFβ signaling. *BAMBI*, a pseudo-receptor for TGFβ, inhibits TGFβ signaling pathway transduction, and this inhibition is mainly associated with the SMAD family molecules (13). Guillot *et al* (14) demonstrated that deletion of *BAMBI* enhances phosphorylation of the TGFβ downstream proteins, *SMAD1/5* and *ERK1/2*, thereby delineating a physiological role for *BAMBI* in endothelial environmental homeostasis and angiogenesis regulation. In addition, *BAMBI* can form a ternary complex with *SMAD7* and the *TGFβ* type I receptor, *ALK5/TGFBRI*, thus inhibiting the interaction between *ALK5/TGFBRI* and *SMAD3*, and ultimately affecting *SMAD3* activation (15). Meanwhile, *BAMBI* and *SMAD7* can inhibit *SMAD2* phosphorylation, and decreased levels of *Smad2* phosphorylation are associated with gastric cancer invasion (15-17). In addition, natural upregulation of *BAMBI* and *SMAD7* expression affects the prognosis of patients with acute myeloid leukemia (AML) (18). Hence, data published to date demonstrate that *BAMBI* can affect gastric cancer invasion, as well as serving as a novel biomarker for predicting prognosis in patients with AML. Notably, although *BAMBI* can inhibit TGFβ signaling, TGFβ can directly bind to the *BAMBI* transcriptional promoter through *SMAD3* and *SMAD4* to regulate *BAMBI* transcription, and SMAD3 and SAMD4 can synergistically enhance its transcription (19) (Fig. 3, center panel).

Toll-like receptor 4 (TLR4) signaling. TLRs are a class of pattern recognition receptors that are mainly expressed on the surface of innate immune cells (20). In 1997, the first mammalian TLR, *TLR4*, was discovered in human monocytes (21). When *TLR4* is activated, two signaling pathways are induced (22): The myeloid differentiation factor 88 (*MyD88*)-dependent pathway and the TIR domain bridging protein-dependent pathway. The two pathways require the NF-κB signaling pathway, which is a physiological regulator of the transcription and secretion of pro-inflammatory factors (23) (Fig. 3, left panel).

Lipopolysaccharide (LPS) downregulates *BAMBI* through MyD88/NF-κB-induced signaling, which in turn enhances TGFβ signaling, thereby reducing liver fibrosis in MyD88-deficient mice (24). It has been shown that the expression level of BAMBI in the livers of patients with hepatitis is significantly lower than in the livers of healthy individuals. Liu *et al* (25) found that LPS and tumor necrosis factor-α could further induce NF-κB p50-histone deacetylase 1 interaction in hepatic stellate cells (HSCs) to inhibit BAMBI transcription and ultimately enhance the TGFβ signaling pathway. In addition, LPS promotes miR-942 expression via NF-κB p50, thereby inhibiting BAMBI expression at the post-transcriptional level (26). He *et al* (27) found that the *TLR4* inhibitor, clio-095, could eliminate LPS-induced *BAMBI* downregulation, suggesting that activation of the *LPS/TLR4* axis may downregulate BAMBI expression at the mRNA and protein levels. Wanninger *et al* (28) found that inhibitors of NF-κB activation partially inhibited metformin- and lipocalin-mediated upregulation of BAMBI in human hepatocytes. In another study, it was confirmed, by meta-analysis in publicly available hepatocellular carcinoma data cohorts, that natural BAMBI overexpression was present in 78% of patients with HCC (n=803), and that it was also present and upregulated in cirrhotic samples and the tumor stroma. Furthermore, upregulated BAMBI expression was also confirmed in MDR2-KO mice (29). All these results suggest that the rise and fall of BAMBI expression levels are inextricably linked to the development of liver diseases.

LPS is also able to downregulate the expression level of BAMBI (30,31), and at the same time, the activation of bacterial autophagy is correlated with the LPS-mediated decrease in BAMBI expression, revealing a correlation between autophagy induced by bacterial infection and the expression level of BAMBI. This effect needs to be realized by the activation of the LPS/TLR4 axis (32). BAMBI may therefore be able to act as a biomarker of bacterial infection.

Wnt/β-catenin signaling. The Wnt/β-catenin pathway is a focus of intense research in the field of Wnt signaling. In humans, Wnt ligands comprise a large family of 19 glycoproteins (33). When Wnt signaling is activated, Wnt ligands first bind to the frizzled class receptor (FZD) structural domain, including the extracellular N-terminal cysteine-rich structural region of the Wnt binding domain and a single transmembrane co-receptor [low-density lipoprotein receptor-related protein 5/6 (*LRP5/LRP6*)], to form the FZD-LRP receptor complex (34,35). Subsequently, LRP6 is phosphorylated and recruits axin to the cytoplasmic tail of LRP6 (36,37). Next, LRP6 interacts with axin in the presence of scattered proteins [dishevelled protein (DVL)] (38,39), thus preventing β-catenin phosphorylation and proteasome degradation. Finally, β-catenin accumulates in the cytoplasm and translocates to the nucleus, thereby activating transcription of a series of Wnt signaling target genes (40) (Fig. 3, right panel).

BAMBI is highly expressed in melanoma tissues and may activate the Wnt signaling pathway by negatively regulating miR-708, thus accelerating melanoma development (41). In gastric cancer cells, *BAMBI* downregulation blocks translocation of β-catenin from the cytoplasm to the nucleus, thus interfering with Wnt signaling (42). Proper cellular trophoblast invasion is a prerequisite for normal pregnancy. Inadequate human trophoblast invasion leads to abnormal placental development, resulting in a variety of pregnancy-related complications such as preeclampsia and intrauterine growth restriction, all of which are detrimental to the health of both the mother and the fetus (43). Zhao *et al* (44) found that BMP2 treatment increased BAMBI mRNA levels and activated Wnt signaling in human trophoblast cells, including increasing levels of phosphorylated *GSK3β* and upregulating unphosphorylated β-catenin and downstream cytosolic cyclin D1 levels, suggesting that the upregulation of BAMBI expression levels promotes human trophoblast cell invasion and thus embryo development.

Numerous studies have linked altered Wnt signaling to tumorigenesis (e.g., rectal cancer and osteosarcoma), and *BAMBI* also plays an important role in tumorigenesis caused

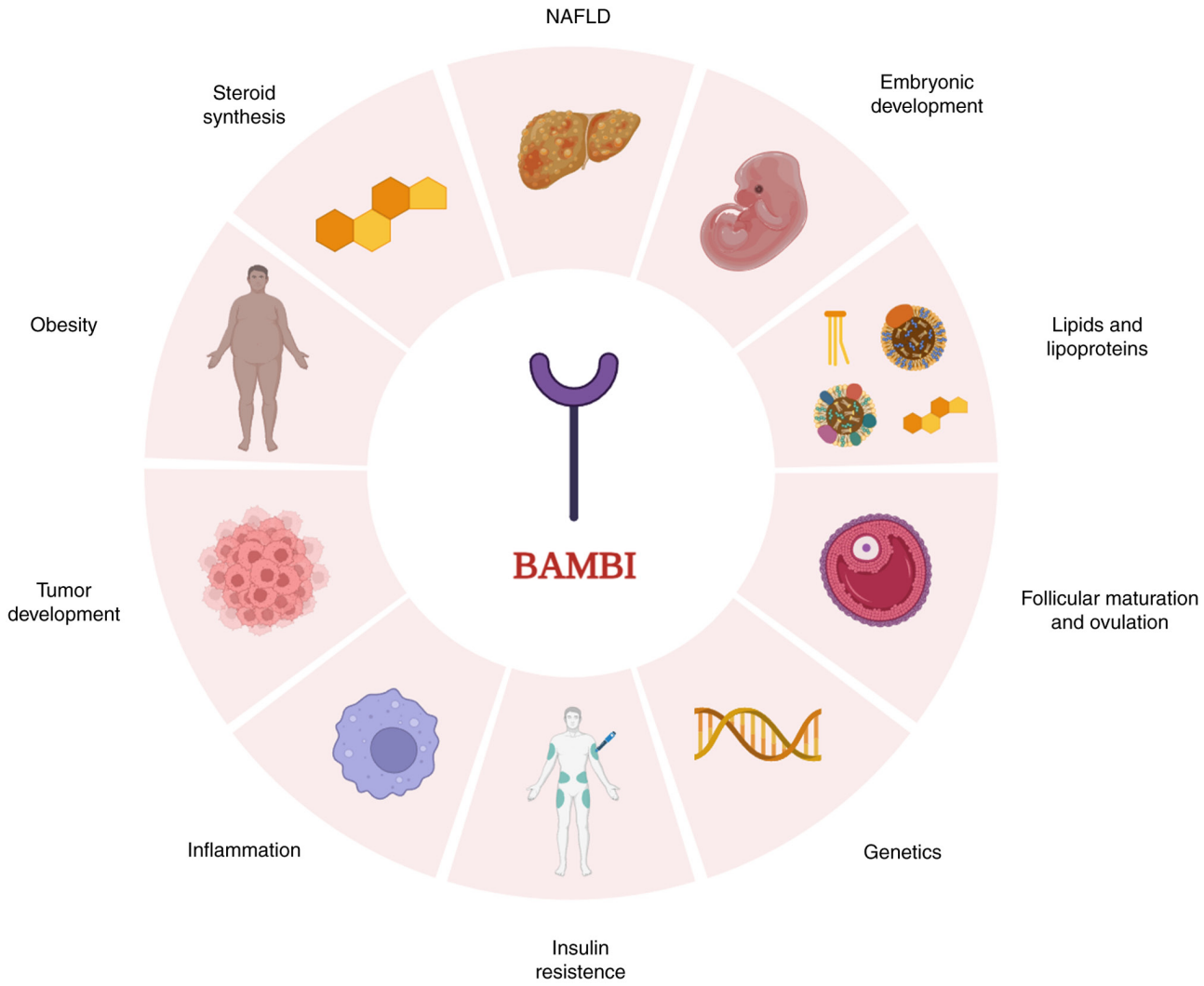

Figure 1. Diverse physiological functions of BAMBI. BAMBI is involved in a wide range of pathological processes, including inflammation, oxidative stress and adipogenesis, in diverse organs. BAMBI, BMP and activin receptor membrane-bound inhibitor; NAFLD, non-alcoholic fatty liver disease.

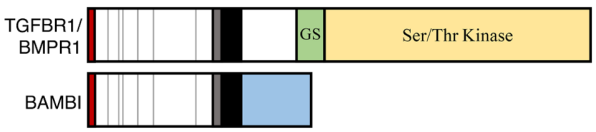

Figure 2. Schematic of BAMBI structure. BAMBI is a 261-amino acid transmembrane protein involved in the regulation of the TGFβ and Wnt signaling pathways. The structure of the extracellular ligand-binding domain of BAMBI is similar to that of TGFβRI/BMPRI, whereas BAMBI lacks an equivalent intracellular Ser/Thr kinase domain. From left to right: red box, signal sequence; white box, seven conserved cysteines (vertical lines) and the putative extracellular domain of the cysteine box (gray); black, transmembrane domain; green and yellow, GS and Ser/Thr kinase domains, respectively, of TGFBRI/BMPRI; blue, intracellular domain of BAMBI. TGFβ, transforming growth factor β; BAMBI, BMP and activin receptor membrane-bound inhibitor; BMPR1, bone morphogenetic protein receptor type 1; GS, glycine- and serine-rich sequence; Ser/Thr, serine/threonine.

by aberrant Wnt signaling activation. Fritzmann *et al* (45) found that *BAMBI* regulated metastasis in rectal cancer by linking the canonical Wnt pathway, and that Wnt/β-catenin was further activated by coactivators in the nucleus to regulate *BAMBI* expression. Sekiya *et al* (46) demonstrated that *BAMBI* expression levels in colorectal tumor cell lines were inhibited by dominant-negative mutants of T-cell factor 4 or inhibitors of β-catenin-TCF interactions. Subramaniam *et al* (47) demonstrated that *BAMBI* promotes cell proliferation and survival through the Wnt/β-catenin pathway in HSCs, as well as other cell lines. Zhou *et al* (48) found that *BAMBI* overexpression in human osteosarcoma cells strongly induced the transcription of catenin and Wnt-induced target genes, including cyclin D1 and cell cycle protein-dependent kinases, and that endogenous BAMBI knockdown by siRNA blocked the Wnt pathway. Therefore, it is evident from the aforementioned results that BAMBI is involved in the development of the aforementioned diseases through the Wnt signaling pathway, and targeted intervention of BAMBI and related factors of the Wnt signaling pathway may be a novel approach for intervention or treatment of these diseases; however, further basic and clinical experiments are needed for specific application.

Overall, BAMBI is upregulated by Wnt signaling and enhances the activity of this pathway; BAMBI overexpression upregulates levels of Wnt target genes, while silencing or deletion of BAMBI has the opposite effect.

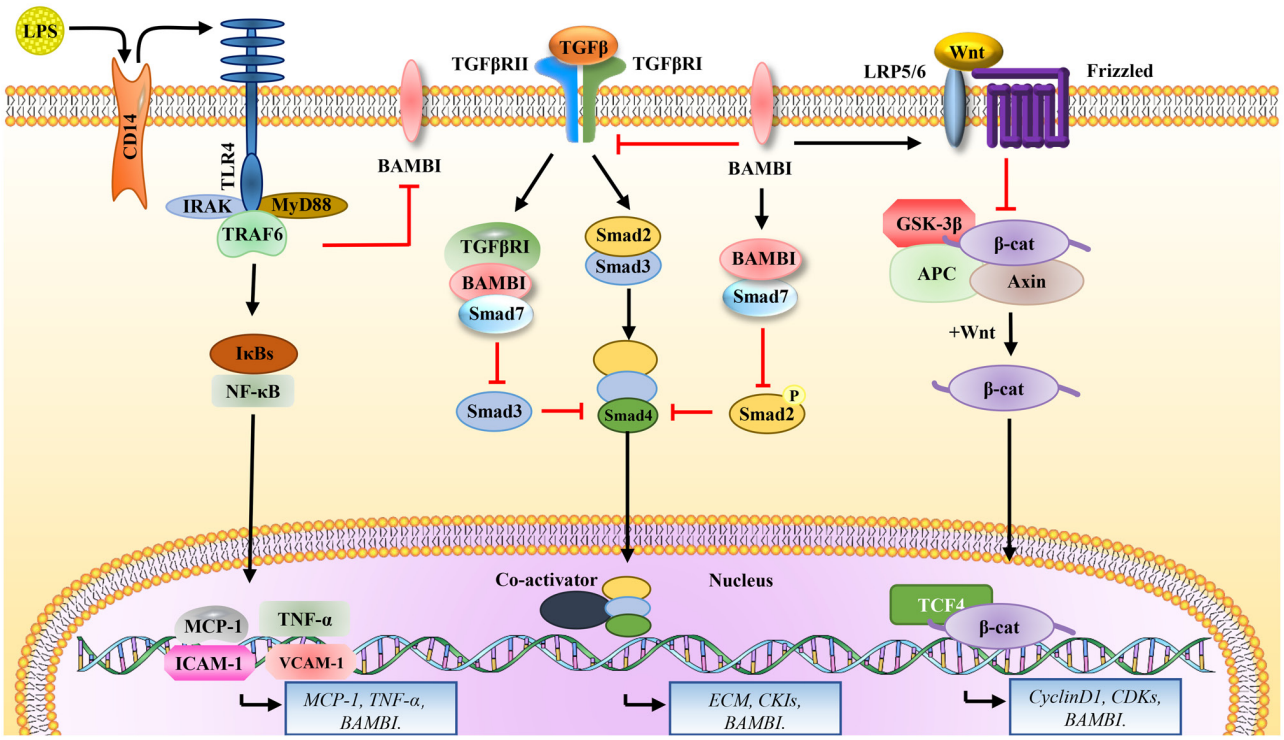

Figure 3. Signaling pathways regulated by BAMBI. BAMBI binds and affects three receptors on the cell membrane and activates downstream signaling pathways: i) LPS binds to the membrane receptor, CD14, to activate TLR4 signaling, and also downregulates BAMBI through MyD88-NF-κB-induced signaling, which in turn enhances TGFβ signaling; ii) BAMBI inhibits TGFβ signaling transduction, and this inhibition is mainly associated with the SMAD family; iii) BAMBI activates the Wnt pathway by increasing GSK3β phosphorylation and upregulating levels of unphosphorylated β-catenin and downstream cyclin D1. LPS, lipopolysaccharide; CD14, cluster of differentiation 14; TLR4, toll-like receptor 4; IRAK, interleukin 1 receptor associated kinase 1; MyD88, myeloid differentiation primary response 88; IκB, inhibitor of nuclear factor κ B kinase subunit β; NFκB, nuclear factor-kB; MCP1, C-C motif chemokine ligand 2; TNFα, tumor necrosis factor α; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; BAMBI, BMP and activin membrane-bound inhibitor; TGFβ, transforming growth factor β1; TGFβRI, TGFβ receptor 1; Smad2, SMAD family member 2; CKI, choline kinase α; LRP5, LDL receptor-related protein 5; GSK-3β, glycogen synthase kinase 3 β; APC, APC regulator of WNT signaling pathway; TCF4, transcription factor 4; CDKs, cyclin-dependent kinases; ECM, extracellular matrix.

4. Role of BAMBI in biological processes and diseases

Adipogenesis. Obesity occurs due to an increase in the ratio of caloric intake to energy expenditure, which leads to adipocyte hypertrophy (49). The role of BAMBI in lipid metabolism is relevant to research into obesity and metabolic syndrome, as there is evidence that BAMBI may be involved in regulating adipocyte differentiation and lipid metabolism pathways, affecting energy homeostasis and lipid storage (4,50). One study showed that BAMBI expression was significantly lower in adipose tissue from patients with obesity than in individuals of healthy weight, and 12 specific variant sites in *BAMBI*, including R151W and H201R, were associated with obesity, indicating a strong relationship between BAMBI and obesity (50). In this study, involving 677 children and adolescents with obesity and 529 lean control individuals, researchers conducted mutation analysis of the BAMBI coding region and intron-exon boundaries, and identified coding region variants in 21 individuals with obesity compared with 5 lean controls; the difference in variant frequency (3.1% in subjects with obesity and 0.9% in lean controls) was significant (P=0.004). However, there have been few studies on the role of BAMBI in adiposity to date, and the role of BAMBI in adipogenesis has been primarily explored at the cellular level. In 2012, Luo *et al* (51) found that BAMBI could act as a proximal effector of fibroblast growth factor 1 (*FGF1*) in human adipocytes, and was also regulated by *FGF1*, with BAMBI levels decreasing in cells that were treated with *FGF1*. In addition, PI3K and ERK signaling pathways can also regulate BAMBI expression, and TGFβ and Wnt/β-catenin signaling pathways are affected by *BAMBI*, thus inhibiting adipogenesis. In addition, Mai *et al* (52) found that *BAMBI* was downregulated during porcine preadipocyte differentiation. *BAMBI* inhibition increased adipogenesis, primarily through the Wnt/β-catenin signaling pathway. The opposite phenomenon was observed in *BAMBI* overexpressing cells, where a significant increase in nuclear translocation of β-catenin was observed, which inhibited adipogenic differentiation of adipocytes. By contrast, Huang *et al* (53) conducted dual luciferase reporter assays, which demonstrated that BAMBI was a target gene of *miR-106a* during porcine preadipocytes differentiation, and that miR-106a promotes lipogenic differentiation of porcine preadipocytes by targeting *BAMBI*. Yang *et al* (54) demonstrated that *BAMBI* gene downregulation promoted bovine preadipocyte differentiation and inhibited the myogenesis of myoblasts. In our latest study (4), adipose-specific *BAMBI* knockout mice (BAMBI AKO mice) were constructed. Phenotypically, the BAMBI AKO mice exhibited an obese phenotype after high-fat feeding, accompanied by insulin resistance and a fatty liver phenotype. In addition, *BAMBI* knockdown promotes the lipogenic differentiation of white and brown precursor adipocytes. Mechanistically, *BAMBI* deletion

caused an increased in reactive oxygen species (ROS) levels in mitochondria and promoted the mitotic clonal expansion stage of preadipocyte differentiation, which in turn increased binding of CCAAT/Enhancer-Binding Protein β (*C/EBPβ*) to downstream target genes and ultimately promoted lipogenesis, representing a possible mechanism of adipogenesis regulation through modulation of ROS levels in mice (4).

There is compelling evidence that non-alcoholic fatty liver disease (NAFLD) is more common in individuals who are overweight/obese, and the condition is closely associated with lipid metabolism dysfunction in the liver (55,56). Hepatic steatosis is a relatively benign stage of NAFLD, but can leave the liver vulnerable to further damage (57). Non-alcoholic steatohepatitis (NASH) is characterized by liver inflammation and can progress to liver fibrosis, cirrhosis and hepatocellular carcinoma (58). One study reported that BAMBI protein levels were low in human hepatic steatosis and that BAMBI levels in the liver negatively correlated with body mass index (BMI) (28). By contrast, in a high-fat diet NASH model, immunohistochemical analysis revealed a significant decrease in BAMBI protein levels in the liver (59). In addition, researchers reported a significant increase in BAMBI protein levels in experimental NAFLD, and improved hepatic oxidative stress and immune cell function after inhibition of the TLR4 signaling pathway with sparstolonin (59). Furthermore, Chen *et al* (4) showed that BAMBI gene deficiency may indirectly cause hepatic steatosis by promoting the release of fatty acids from hypertrophic adipose tissue, rather than by directly regulating adipogenesis in the liver. In conclusion, there is a large body of evidence suggesting that adipose tissue dysfunction is a key factor in NAFLD pathogenesis, and that NAFLD leads to downregulation of BAMBI, while BAMBI deficiency also causes NAFLD in high-fat diet models.

Myogenesis. BAMBI is also implicated in myogenesis, muscle tissue maintenance and repair, possibly through effects on muscle stem cell proliferation and differentiation (5,60). Numerous studies have reported that both the TGFβ and the Wnt/β-catenin pathways have regulatory roles during myogenesis, while *BAMBI* can inhibit signal transduction via these pathways in various cell types. Therefore, investigation of the contribution of BAMBI to skeletal muscle myogenesis is warranted. Zhang *et al* (60) showed that BAMBI expression levels peaked during the early differentiation stage of C2C12 myoblasts, while interfering with BAMBI expression using siRNA inhibited C2C12 myoblast differentiation and Wnt/β-catenin pathway activity. It was concluded that BAMBI is required for C2C12 myoblast differentiation and that its role in myogenesis is mediated by the Wnt/β-catenin pathway. In general, *in vivo* studies provide better evidence for the effects of genes on biological processes. Yao *et al* (5) found that *BAMBI* expression levels decreased gradually during skeletal muscle development. Moreover, *BAMBI* was generally expressed at higher levels in glycolytic muscle fibers.

Ovarian function. BAMBI may also be associated with germ cell development and normal function of ovarian tissue, and its aberrant expression can affect ovary-related reproductive physiological processes (6,61). In the context of reproduction, the results of the study by Bai *et al* (62) elegantly illustrated the role played by *BAMBI* in pig and human granulosa cells. First, the results revealed that *BAMBI* overexpression promoted the expression of aromatase and steroidogenic acute regulatory protein (*StAR*) in porcine primary granulosa cells, while mRNA and protein levels of P450scc and 3b-HSD were not significantly increased. In addition, levels of estradiol and progesterone in the culture medium were significantly increased. Meanwhile, knockdown of endogenous *BAMBI* reduced the mRNA expression levels of cytochrome P450 family 19 subfamily A member 1 (*Cyp19a1*) and StAR, as well as the estradiol and progesterone accumulation levels. In human granulosa cells, Bai *et al* (13) reported that *BMP2* activated *SMAD1/5/8* and upregulated *BAMBI* expression, suggesting that *BAMBI* is a BMP target gene in human ovarian granulosa cells that mediates negative feedback regulation of TGFβ signaling in human ovaries. In another study, Bai *et al* (63) found that stimulation of porcine granulosa cells with *FSH* reduced *BAMBI* expression levels, and concluded that *FSH* can inhibit *BAMBI* expression in porcine luteinized granulosa cells.

Studies in porcine granulosa cells suggested that *BAMBI* is involved in steroid synthesis, which is an important physiological process affecting follicular maturation and ovulation, and granulosa cells are the main cell type in follicles that produce steroid hormones in response to *FSH* and luteinizing hormone stimulation (64,65), while *TGFβ1* induces *SMAD3* phosphorylation in porcine granulosa cells (62). Pre-transfection with BAMBI-overexpression adenovirus inhibited *TGFβ1*-induced downregulation of estradiol and progesterone production, and *TGFβ1*-induced *SMAD3* phosphorylation in porcine granulosa cells (62). In cattle, *TGFβ1* concentration was negatively correlated with estradiol in follicular fluid, and *TGFβ1* decreased FSH-stimulated estradiol production in cultured granulosa cells (66). These findings revealed a potential mechanism by which BAMBI can regulate steroidogenesis in porcine granulocytes.

Pigs possess genetic and protein variants similar to those of humans, including genes associated with a number of human diseases, such as Alzheimer's disease, Parkinson's disease and obesity (67,68). In addition, pig internal organs are arranged very similarly to those of humans, and pig hearts are comparable in size and shape to those of humans. Although there are similarities between humans and pigs at the genetic level, there are also some differences (69). Overall, however, the similarities are helpful for the study of human disease models, as well as for other aspects of biomedical research, and the pig as a model animal helps to further characterize human disease and physiology (70). To conclude, the role of BAMBI in enhancing porcine reproductive performance was reviewed and, given the homology between human and porcine genes and proteins, it is hypothesized that BAMBI is a potential physiological target for enhancing female fertility and the treatment of infertility.

Inflammation. BAMBI has been found to be involved in regulating inflammatory responses. It may play a role in inhibiting or modulating inflammatory processes with potential anti-inflammatory effects. Yang *et al* (7) showed that *BAMBI* expression was significantly decreased in a rat model of spinal cord injury. Overexpression of *BAMBI* effectively reduced the expression of the mammalian target of rapamycin gene,

interleukin 1β (*IL1β*), *IL6* and *IL10*. These results suggested that *BAMBI* has neuroprotective effects in rats with spinal cord injury and can reduce the inflammatory response in rats. If these results are validated in humans, it will be a new therapeutic option to alleviate the neurological damage and inflammatory response caused by spinal cord injury. MCP1 has been recognized as a key mediator of renal fibrosis in chronic kidney diseases, including diabetic nephropathy (71). The reduction of MCP1 expression level implies that the level of inflammation as well as the level of fibrosis in the kidneys is also further reduced (72). In rat renal tubular epithelial cells, interference with *BAMBI* promoted *ERK1/2* phosphorylation and TGFβ1-induced monocyte chemotactic protein 1 (*MCP1*) expression. Conversely, *BAMBI* overexpression inhibited *ERK1/2* phosphorylation and TGFβ1-induced MCP1 upregulation. Therefore, Liang *et al* (73) suggested that in rat renal tubular epithelial cells, metformin can inhibit TGFβ1-induced MCP1 expression through a BAMBI-mediated *MEK/ERK1/2* signaling pathway. Studies have also reported on the questionable efficacy of metformin against cisplatin-induced renal cytotoxicity. The results of the study by Li *et al* (74) suggested that metformin may prevent cisplatin-induced tubular cell apoptosis and acute kidney injury by stimulating AMPKα activation and inducing tubular cell autophagy. Given this effect of metformin, the upregulation of BAMBI by metformin could also alleviate cisplatin-induced renal cytotoxicity by inhibiting the TGFβ signaling pathway. In addition, BAMBI can regulate the inflammatory responses in different tissues (e.g., glioma and lung) by directly influencing macrophage proliferation and differentiation (75,76). Furthermore, *BAMBI* overexpression reduced the expression of TGFβ, *IL1β*, *IL6* and *IL10* levels, suggesting that *BAMBI* can play a neuroprotective role by reducing inflammatory responses in rats with spinal cord injury (7).

Tumor development. Numerous studies have reported that *BAMBI* has an important regulatory role in pathological processes such as tumorigenesis and fibrogenesis, and is highly expressed in various tumor cells and tissues, including ovarian cancer cells and metastatic tumors (45,77). Human *BAMBI* gene expression is downregulated in metastatic melanoma cell lines and high-grade bladder cancer cells (2,78). Furthermore, the inhibitory effect of *BAMBI* promoter hypermethylation on *BAMBI* expression is an important epigenetic event affecting bladder cancer cell invasion (78). In this study, hypermethylation of the BAMBI promoter suppressed the expression level of BAMBI, whereas a decrease in the expression level of BAMBI activated the TGFβ pathway, which enabled the promotion of tumor cell motility, invasion and survival. In an *in vitro* study of *BAMBI*, injection of colon cancer cells transfected with *BAMBI* overexpression plasmid into the spleen tissue of nude mice resulted in rapid tumor formation and metastasis of colon cancer cells to mouse liver and lymph nodes. Further investigation of the regulatory mechanisms involved revealed that high *BAMBI* expression in colon and liver cancer cells impaired *TGFβ*-mediated inhibition of cancer cell growth (46). BAMBI has also been reported to promote the growth and invasion of human gastric cancer cells (42,79,80). Yuan *et al* (80) showed that BAMBI overexpression inhibited the TGFβ/epithelial mesenchymal transition signaling pathway and suppressed the invasiveness of gastric tumors, whereas Zhang *et al* (6) demonstrated that *BAMBI* and *SMAD7* expression levels were both significantly elevated in human gastric cancer tissues. Moreover, *BAMBI* and *SMAD7* inhibited the phosphorylation of *SMAD2*, and decreased phosphorylated *SMAD2* levels were associated with tumor invasion and poor prognosis in patients with gastric cancer (7,11,12). These findings suggested that *BAMBI* and *SMAD7* may synergistically inhibit TGFβ signaling, thereby promoting gastric cancer progression. In addition, Liu *et al* (42) found that BAMBI could also improve the prognosis of gastric cancer by regulating the classical Wnt/β-catenin pathway. To summarize, BAMBI can regulate the growth and invasion of gastric cancer cells by modulating TGFβ and Wnt/β-catenin signaling. By contrast, expression levels of the long non-coding RNA *PVT1* and *BAMBI* were significantly increased during non-small cell lung cancer development, and *PVT1* could promote cell viability, migration and invasion through miR-17-5p targeting of *BAMBI*, thus promoting non-small cell lung cancer development (81).

Besides being involved in cancer development, *BAMBI* is also associated with diseases such as liver fibrosis. A previous study reported that *BAMBI* expression was negatively correlated with donor BMI and was expressed at low levels in human fibrosis-prone fatty liver lesions (28). Furthermore, *BAMBI* was downregulated in rodent models of liver inflammation and fibrosis, and that *BAMBI* and *TLR4* were downregulated in LPS-regulated liver fibrosis; however, hepatoprotective adiponectin induced high *BAMBI* expression in human primary hepatocytes (28). *BAMBI* mRNA and protein levels were significantly reduced in patients with advanced liver fibrosis, while *BAMBI* overexpression decreased the mRNA levels of the fibrosis markers *α-SMA*, *COL1* and matrix metalloprotein in human HSCs (26). The aforementioned summarized studies suggest that *BAMBI* may contribute to inflammatory and fibrotic responses in various diseases.

Embryogenesis. Several studies have reported important regulatory roles for *BAMBI* in embryonic development and organogenesis (82-84), although a previous *BAMBI* knockout mouse study reported that *BAMBI* is not essential for embryonic development and postnatal survival (84). Onichtchouk *et al* (1) showed that *BAMBI* was closely co-expressed with *BMP4* in the early development of the African toad embryo, while another group found that *BAMBI* expression is regulated by *BMP4* in mouse embryonic fibroblasts, and that *BAMBI* spatiotemporal expression patterns are consistent with those of *BMP4* during mouse embryonic development (84).

In addition to regulating embryonic development, *BAMBI* also regulates tooth formation. Gonzales *et al* (85) reported that *BAMBI* expression is elevated during tooth formation and is involved in regulating the expression of the dental matrix proteins in the MD10-A2 cell line, which normally regulate the control of dentin mineralization (3). Furthermore, Xavier *et al* (86) found that BAMBI was expressed in kidney endothelial cells and human umbilical vein endothelial cells, and inhibited endothelial cell function. Furthermore, *BAMBI* knockdown increased capillary generation and migration, while *BAMBI* overexpression

inhibited capillary generation and migration, and an *in vivo* experiment showed that angiogenesis was increased in *BAMBI* knockout mice (14).

In conclusion, dysregulation of BAMBI affects the TGFβ pathway, which may lead to developmental disorders or diseases; however, to date, no specific syndromes or disorders have been associated with BAMBI dysregulation during embryonic development. Therefore, further basic and clinical studies are needed to determine whether any syndromes or diseases are associated with BAMBI dysregulation.

5. Conclusions and perspectives

Recent trends in molecular medicine have centered on the elaboration of the signaling pathways that control the functions of different tissues. Understanding these pathways can facilitate treatment, as well as prevention, of a wide range of pathologies arising from abnormal molecular mechanisms. Since its discovery in 1998, BAMBI has attracted considerable attention, due to its involvement in various pathophysiological processes associated with a number of diseases. In the present review, the major physiological signaling pathways involving the function of *BAMBI* and its associations with a range of diseases were evaluated. As the role of *BAMBI* in regulating lipid metabolism remains controversial, due to its inhibitory effect on TGFβ, more research is needed to determine whether BAMBI influences the development of obesity and diabetes through TGFβ signaling. Although previous studies have reported a key role for *BAMBI* in lipid metabolism, some conflicting results require further discussion and clarification. Firstly, little is known about the mechanisms that regulate *BAMBI* in various diseases. Identification of key regulators may provide new insights into the physiological functions of *BAMBI* and has potential to facilitate development of *BAMBI*-based therapeutic approaches. Secondly, the maximum dose of exogenous BAMBI recombinant protein tolerated by patients has not been studied in depth, nor has it been determined whether there are uncontrollable side effects associated with BAMBI administration.

In brief, although BAMBI can inhibit the occurrence of some tumors and provide protection for human health, at present, BAMBI is not in use as part of a specific drug treatment in clinical medicine, and more research is needed to explore this possibility. Although large, complex and accurate gene regulatory networks involving BAMBI have been discovered, further investigation is required to provide an evidence base for the application of BAMBI as a drug to treat various diseases.

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Availability of data and materials

Not applicable.

Authors' contributions

XCC, DZ and QY conceived the manuscript and summarized the contents of the manuscript. XCC, HG and LSZ were responsible for the literature search and discussion. XCC and AQX drafted the manuscript. XCC, JL and PHS wrote the revised manuscript and prepared the figures. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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