BMPR-1B in Livestock Reproduction: Protein and Genetic Regulation, Molecular Signaling, and Implications for Breeding

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Abstract

Bmpr-1b gene encodes a serine/threonine kinase receptor which is involved in the bone morphogenic protein signaling and playing essential roles in various biological processes particularly reproductive performance. This narrative review summarises findings of BMPR-1B protein and its signaling component, such as phosphorylation, glycosylation, ubiquitination, and sumoylation, as well as the genetic and epigenetic mechanisms that regulate *Bmpr-1b* expression, and evaluates their relevance to livestock reproduction. The study of PTMs in BMPR-1B creates new possibilities for advancing animal genetics and improving livestock reproduction. The interaction of BMPR-1B with pathways like Wnt, Hedgehog, and Notch, exhibiting its broader regulatory effect. The *FecB* mutation (Q249R substitution) in *Bmpr-1b* is a prominent fecundity-associated variant that, through its effects on SMAD phosphorylation in granulosa cells, provides a potential mechanistic basis for the increased ovulation rate and litter size observed in carrier ewes, with an approximately additive effect of 1.0–1.5 additional

ova per allele copy. Integrating genomic, proteomic, and PTM data provide interesting opportunities for improving livestock fertility and developing targeted therapeutic strategies. Future studies will be necessary to elucidate predicted modifications and broader metabolic interactions of BMPR-IB to enhance reproductive health and production efficiency.

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Keywords: BMP signaling, *FecB* mutation, Molecular breeding, Productivity, PTM

Abbreviations

BMPR-1B: Bone Morphogenetic Protein Receptor Type IB

PTMs: Post-translational modifications

FecB/ booroola: The allele of *Bmpr-1b*

Hsd3b1: Hydroxysteroid dehydrogenase isoforms

CYP19 : Aromatase cytochrome P450 family 19

SNPs: Single nucleotide polymorphisms

SMAD: Suppressor of mothers against decapentaplegic homolog

SMURF1*:* Smad ubiquitin regulatory factor 1

H3K9: Histone H3 Lys9

PCAF: p300/CBP-associated factor

TAK1: Transforming growth factor beta-activated kinase 1

MAPK: Mitogen-activated protein kinase

PI3k: Phosphatidylinositol 3-kinases

JNK: c-Jun N-terminal kinase

QTL: Quantitative Trait Loci

GDF5: Growth Differentiation Factor 5

GDF9: Growth Differentiation Factor 9

HSP10: Heat Shock Protein

MAS: Marker-Assisted Selection

TGFβ: Transforming Growth Factor β

PDGFs*:* Platelet-Derived Growth Factors

FGF: Fibroblast Growth Factor

IHH: Indian hedgehog signaling

Background

The *Bmpr-1b* gene encodes a transmembrane serine/threonine kinase receptor that is essential in the bone morphogenetic protein (BMP) signaling pathway which is a subset of the TGF-beta superfamily. BMP signaling pathway is important in various cellular processes like the cellular response to growth factor, apoptosis, proliferation, and differentiation. Actually, Bone Morphogenetic Protein Receptor Type IB (BMPR-1B) has significant function in various tissues including bone mineralization [1], cartilage development [2], muscle homeostasis [3], neural crest cell migration and differentiation [4] the ovulation cycle [5], and retina development in the eye [6]. However, primary focus of this review is BMPR-1B role in reproduction, particularly ovulation and ovarian function

Post-translational modifications (PTMs) are critical biochemical processes that modify proteins after translation and influence their function and activity. The activity, localization, and stability of BMPR-1B are regulated by PTMs. Furthermore, BMPR-1B signaling activity is affected by PTMs including phosphorylation, glycosylation, and ubiquitination in various tissues [7]. Signal transduction cascade is initiated by phosphorylation of BMPR-1B. Upon binding to BMP receptors, the receptor becomes activated via phosphorylation and subsequently phosphorylates SMAD transcriptional regulators, thereby upregulating the BMP signaling pathway [8]. Additionally, sumoylation of SMAD4 enhances its localization in the nucleus which lead to further influencing gene expression [9]. Although most PTM studies are conducted in rodents or humans, *BMPR-1B*'s conserved role across mammals suggests that similar regulatory mechanisms are likely operational in livestock species

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PTMs in animal science provide an insight into the aspects of underlying key regulatory mechanisms involved in productivity traits. The *Booroola* gene, a key element in reproductive biology, associated with higher ovulation rates, making it the most promising candidate for PTM studies. The BMP receptor, considered as a potential important receptor in ovarian folliculogenesis. A prominent mutation in *BMPR-1B* (*FecB*, Q249R substitution) enhances SMAD phosphorylation producing the Booroola phenotype characterized by premature development of numerous small antral follicles and a consequently higher ovulation rate. Booroola Merino ewes exhibit average 3–5 ovulations per cycle compared to 1–2 in their wild-type equivalents [10].

Genetic diversity among breeds and their variations influence the PTM patterns. Comparative proteomic analysis (via mass spectrometry) of Booroola and Lacaune (high-fertility breeds), indicated different glycosylation profiles in BMPR-1B, where ovarian tissue sialylation which is statistically associated with litter size [11,12]. These findings suggest that glycosylation contributes to ligand-receptor interactions and may enhance reproductive efficiency. It has been shown that environmental factors can affects PTM pattern. Protein suplemented diet in rams improved semen quality and fertility and was associated with altered *Bmpr-1b* expression [13]. Predicting PTMs enhance our understanding of its role in reproductive biology and its interactions with other pathways. This would be applied to advance breeding strategies in desirable traits in livestock, such as increased fertility and reproductive efficiency. In this study, we summarized current knowledge of PTM of BMPR-1B and it's application in animal science. This field of study can aiding breeders in the development of targeted breeding programs.

Methods

This is a narrative review with a structured literature search. We searched PubMed, Scopus, Web of Science, and Google Scholar combinations of ("BMPR-1B" or BMPR1B or "*FecB*") and ("post-translational modifications" or phosphorylation or glycosylation or ubiquitination

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or sumoylation, or “litter size” or “reproduction” or “ovulation” or “granulosa cells”) and (“sheep” or “ovine” or “goat” or “caprine” or “cattle” or “bovine” or “livestock” or “human” or “rodent” or “*in vivo*”), in the last 26 years (2000–2026). This study included all studies (case-control and cross-sectional studies, original articles, review articles, animal studies) investigating BMPR1B/BMPR-1B, FecB, PTMs, or reproductive traits. After screening title and abstract irrelevance articles were excluded. Italicized *BMPR-1B* refers to the human gene, italicized *Bmpr-1b* refers to the animal gene, and non-italicized BMPR-1B refers to the encoded protein.

BMPR-IB role in livestock reproductive biology

Recent studies focused on BMPR-IB role in reproductive biology, in livestock species, particularly sheep. *Bmpr-1b* gene polymorphisms have been associated with litter size among the Chinese Hu sheep which exhibit its role in fecundity regulation. *Bmpr-1b* expression in the ovaries of the prolific sheep significantly was higher which supporting its regulatory functions in reproductive performance [14]. Further studies on *Bmpr-Ib* gene revealed that its significantly correlated with multiple births in Suffolk sheep [15]. Rodent models also demonstrated that BMPR-1B influence male reproductive development through testosterone production [16]. Knock-down of cathepsin D leading to upregulation of *Bmpr-1b* in granulosa cells of goats, consequently affected cell proliferation and apoptosis, which are critical for ovulation and fertility [17]. Another study on Awassi sheep revealed that reproductive charachters affected by specific polymorphisms in *Bmpr-1b* gene which suggesting its potential application in selective breeding strategies as a genetic marker for improving fertility [18].

Regulatory role of BMPR-IB in testicular function

Testicular function and steroidogenesis, like testoestrone production, through multiple mechanisms affected by BMPR-IB. In Leydig cells BMPR-IB is involved in the expression of

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key steroidogenic enzymes which are essential for testosterone synthesis. Knockingdown of *BMPR-IB* in male mice upregulated of hydroxysteroid dehydrogenase isoforms (*Hsd3b1*), which is associated with testosterone production, while downregulated Hsd3b6 and Cyp19 enzymes which involved in conversion of androgens to estrogens [16]. These findings highlits BMPR-IB role in maintaining the balance between androgen and estrogen production. Growing evidence suggests that, BMPR-IB activity is regulated by hormons, particularly in response to gonadotropins which stimulate the testes function. The administration of gonadotropins, BMPR-IB antagonisms, increased testosterone levels, it means that BMPR-IB may exert an inhibitory effect under certain hormonal conditions. BMPR-IB is also contributed in the developmental regulation of testosterone production. *BMPR-IB* expression is detrimental during puberty through affecting of the seminal vesicles growth and reproductive maturity [16,19].

Conserved role of BMPR-IB in ovarian function of various species

BMPR-IB appears to be important role in ovarian function in multiple species, notably in Ovis aries and rodents. Various breeds of sheep such as Small Tailed Han sheep and Booroola merino benefits of *Bmpr-1b* mutation, which is associated with higher rate of ovulation and litter sizes. This mutation enhances granulosa cell differentiation and follicle maturation, which leads to hyperprolificacy [20,21]. In neonatal rats, BMP-4 as an upstream ligand of BMPR-IB signaling, promotes the development of primordial follicles. BMP-4 treatment increased proportion of developing primary follicles, which representing its essential role in early ovarian development [22]. Similarly, immunohistochemical studies in pigs show that *Bmpr-1b* is expressed in different ovarian cell types, thereby receptor may have functions in the regulation of follicular growth and ovulation rates [23].

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Bmpr-1b gene variant effects in ovulation rate

The *FecB* mutation in the *Bmpr-1b* gene implicating functional role of genetic variation on ovulation and fertility. This mutation is found in the *Bmpr-1b* gene which belongs to TGF-β superfamily [24,25]. It has a functional additive effect on ovulation rate with an increase in the number of corpora lutea per cycle by approximately 1.6 for each gene copy [26]. The mutation affects follicular development through regulating ovarian follicle maturation and subcequent increase in ovulation rates and litter sizes [10]. It has been suggested that the altered kinase domain of the BMPR-1B receptor through influencing SMAD protein expression and phosphorylation regulats follicular development [20]. The genetic variaty can be serve as an effective tool for studying molecular mechanisms of ovulation and improving reproductive performance through specific breeding strategies [27]. Single nucleotide polymorphisms (SNPs) in the *Booroola* gene are concentrated in regions related to reproductive traits. These SNPs can utilized as an effective genetic markers for selecting animals with optimal fertility phenotype [20].

BMPR-1B signaling pathways

BMPR-1B is regulating BMP signaling pathway. Upon BMP ligands binding, it triggers both SMAD-dependent (canonical) and SMAD-independent (non-canonical) pathways. Consequently, regulatinon of gene expresion, cell growth, cell differentiation, and cell death which are essential in tissue development and homeostasis. As shown at Fig. 1 in the canonical signaling pathway, upon BMP ligands (e.g., BMP2, BMP4, and BMP7) binding to BMPR-1B, forming a heterotetrameric complex. The type II receptor that possessing constitutive kinase activity phosphorylates the glycine-serine domain and leading to BMPR-1B activation. Activated BMPR-1B phosphorylates receptor-regulated SMADs (SMAD1/5/8), which subsequently form a complex with SMAD4 and translocate to the nucleus lead to transcriptional regulation of targeted genes [28]. This process can be negatively regulated by

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SMAD6. Furthermore, the signaling cascade is optimized by various PTMs. For example, SMAD6 can facilitate the ubiquitination and degradation of BMPR-1B, thereby modulate the signal. However, by ubiquitination of SMAD6, its inhibitory effect is lost, resulting in promoted BMP signaling [9]. In contrast in non-canonical pathways, BMPR-1B interact with other signaling cascades such as TAK1, MAPK, PI3k, and JNK to intermediates regulation of various cellular process based on tissue specifeic functions [29].

BMPR-IB interactions with other signaling pathways

BMPR-IB involved in various biological process via cell communication that interfering in several signaling pathways. Although most pathway interaction studies have been conducted in rodents or humans, the highly conserved role of *BMPR-1B* across mammals strongly suggests that similar mechanisms operate in livestock species. It is demonstrated that BMPR-IB interact with Notch signaling through modulating Notch ligands and receptors interactions, as well as regulating downstream Notch target genes [30] potentially influencing follicular development and ovulation in ovarian follicles. BMPR-IB also engages in Hedgehog signaling particularly in Sonic Hedgehog signaling by regulating the activity of Gli transcription factors [31], which may impact oocyte maturation and granulosa cell function. BMPR-1B also interacts with Wnt signaling by modulating the expression of Wnt ligands and receptors, or by regulating β-catenin activity [32], which are essential for follicular growth and ovulation. While direct livestock-specific studies remain limited, the expression of *BMPR-1B* in ovarian cells and its established role in granulosa cell proliferation provide strong evidence for its involvement in these pathways. To further elucidate the reproductive relevance of these interactions, future research should focus on sheep, cattle, and goats, thereby confirming their applicability to livestock reproduction.

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PTMs influence on reproductive traits

PTMs by various mechanisms including gene expression, chromatin dynamics, and hormonal signaling influence reproductive performance. In meiosis, histone modification, such as phosphorylation and methylation, affecting chromatin structure and function, which allows the proper meiotic divisions. These modifications are essential for haploid gametes formation and consequently, for successful sexual reproduction [33]. It has been suggested that epigenetic modifications, including DNA methylation and histone modifications, are associated with reproductive disorders such as infertility and pregnancy problems. Environmental factors induces advers effect through epigenetic modifications and consequently, affecting gene expression related to reproductive functions [34]. Transcriptional activities of steroidal hormone receptors, such as estrogen and progesterone, have been regulated by PTMs. These modifications influence the stability, localization and functioning of receptors and consequently, regulating key reproductive events in the early stages of pregnancy [35].

Protein PTMs and signalling precision

PTMs after transcription regulate BMPR-1B activity and, consequently, determine receptor localisation, half-life and signaling output. The PTMs considerd as a molecular switches that refine the receptor dynamic based on cellular context. Actually, receptors activity are sensitive to PTMs and can be utilized as a programmable control points. Duo to Smurf1 inhibition without genotype modification receptor half-life is increased, and consequently, enhanced the litter size. However, modifing receptor glycosylation may enhance their performance by transgenic aproch. Integrating PTM with additive quantitative trait loci (QTL) and epigenetic modifications allows a structured breeding program [36,37,38]. This aproch combines favourable alleles, epigenetic regulation of gene expression, and PTMs optimize receptor signalling (Table 1).

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Table 1. PTMs that regulates BMPR-1B signaling activity, localization, and stability, and subsequent functions in major tissues.

PTM	Substrate	Site	Species	Effect	Ref.
Ser/Thr phosphorylation (GS domain)	BMPR-1B	GS domain	mammalian cell models	kinase activation by type II receptor	[8,28]
SMAD1/5/8 C-terminal phosphorylation	SMAD1/5/8	SSXS motif	ovine granulosa cells (FecB context)	pathway output increased in carriers	[20,24]
N-/O-glycosylation	BMPR-1B ectodomain		in silico	ligand–receptor interaction (proposed)	[36]
Ubiquitination	BMPR-1B	—	non-livestock	receptor turnover (proposed for BMPR-1B; Smurf1 demonstrated for MEKK2)	[36,37]
Ubiquitination	SMAD6	—	non-livestock	loss of inhibitory function → enhanced BMP signaling	[36,37]
Sumoylation	**SMAD4** (not BMPR-1B)	—	human/rodent cell lines	nuclear localization, transcriptional activity	[9]
Clathrin-dependent internalization	BMP receptors	—	non-livestock	trafficking/signal duration (general BMP-receptor mechanism)	[38]

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Potential targeting PTMs for infertility treatment

Recent studies focused on potential targeting of PTMs for therapeutic programs of male infertility. Sperm proteome analysis showed that sperm function are regulated by PTMs like

phosphorylation and glycosylation. Understanding molecular mechanisms advances our Knowledge of sperm biology, in turn, identifying of biomarkers for diagnosing and treating male infertility [39]. Its well known that normal spermatogenesis are regulated by epigenetic modifications such as histone modifications and DNA methylation. Investigatin of these modifications could provide new therapeutic tools for male infertility driven by epigenetic abnormality [40]. For example, Sialylation as a specific type of PTM plays an important role in sperm development and fertilization. Therby, investigation of sialylation mechanisms may lead to clinical indicators for infertility detection and consequently potential treatments [41]. These approaches indicating the potential of targeting PTMs as a fertility therapeutic strategy, particularly in male reproductive health. Further research is needed to elucidate practical utilize of these findings.

Cross-talk between pathways

The *Booroola* is involved in the molecular cross-talk between reproductive and metabolic pathways. This cross-talk is important for orcestration of homeostasis with reproductive efficiency. Hormonal signaling pathways also affected by the gen activity, consequently influencing fertility and metabolic health in livestock [24]. It has been shown that in granulosa cells the *FecB* mutation affects the abundance of proteins contributed to cholesterol metabolism, carbohydrate metabolism, amino acid biosynthesis, and glutathione metabolism [24]. Proteotranscriptomic analysis of hypothalamic tissue in different stages of estrous cycle revealed that homozygous *FecB* mutant sheep have an increase in GnRH secretion pathways like, GABAergic synapse**,** neuroactive ligand–receptor interactions**,** and MAPK and estrogen signaling compared to wild type. These findings highlits the interaction between the BMPR-1B signaling and other parts of reproductive regulatores [24]. *FecB* has been correlated with BMP2 and BMP4 signaling through interacting with downstream proteins. In addition, the intraction of *FecB* with other target proteins including GDF5, GDF9, RhoD, and HSP10 has

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been reported [42]. Rodent modeles showed that BMP pathways negatively influences fibroblast growth factor (FGF) signaling through downregulating *Fgfr1* expression and subsequently inhibiting downstream STAT and ERK1/2 MAPK activation. This is indicating a complex regulatory network involvement in balancing follicular development.

BMPR-1B gene/protein investigation in production efficiency

Bmpr-1b gene has been found to play an important role in the bone and cartilage development in sheep, however its role in bone-related traits has been less studied compared to its reproductive functions. It has been reported that mutation of *Bmpr-1b* gene is associated with some skeletal disorders. Analysis of BMPR-1B gene/protein interactions with other signaling pathways can provide valuable information in breeding and management of sheep to avoid of skeletal defects and improve overall health and efficiency [20,43]. The bioinformatics studies of BMPR-1B elucidating its role in skeletal fitness, and this will provide essential insights into advancing therapeutic procedure to manage bone and cartilage malformations. Bioinformatics tools can identify genetic mutations or regulatory changes in the *BMPR-1B* gene that modulating protein expression and functional activity. These information enable to the development of diagnostic tools to identify predispositions to skeletal disorders such as osteoporosis and osteoarthritis. Additionally, application of computational models to mapping the protein interaction networks and downstream signaling pathways may provide key molecular mechanisms to skeletal improvement. This findings could facilitate the design of therapeutics that will target these pathways [44]. Analyzing large datasets of genetic and proteomic information related to *BMPR-1B* could reveal specific molecular directs that correlate with disease progression, allowing earlier detection with more targeted interventions. *BMPR-1B* variations in sheep could serve to improving breeding programs to minimize the occurrence of inherited bone disorders in livestock.

Structural data for the BMPR-1B extracellular and kinase domains enable in silico screening of receptor modulators. As proof of concept in a cancer context, N9-aryl-N6-ureidoadenine

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derivatives were docked into the BMPR-1B ATP-binding site and showed antiproliferative activity in cell assays. These data do not establish therapeutic efficacy and derive from a non-livestock context; their relevance to reproduction is hypothetical. Validation in ovine granulosa-cell systems would be required before ligand-based modulation of BMPR-1B could complement genetic approaches in livestock [45-49].

Link between PTMs and reproductive performance

Association between the *Booroola* gene and prolificacy in sheep have been well established and its proteins effect on fertility is triggered by PTMs. PTMs such as phosphorylation and glycosylation are essential in regulating protein functions which is ensuring proper regulation of reproductive processes. PTMs of proteins in male fertility involved in spermatogenesis which affect sperm quality and motility. Disruption of PTMs process may impair sperm function and consequently, male infertility [12]. It has been suggested that the *Booroola* gene expression regulated by epigenetic mechanisms, including histone modifications and DNA methylation. Normal spermatogenesis and fertilization processes can affected by epigenetic modifications and consequently influence fertility [40]. Studing the PTMs association with the BMPR-1B may provide reliable biomarkers for male infertility assay, as specific PTMs can dysrupt sperm development and maturation process [50].

Methods for PTM prediction

Advancements in bioinformatics have lead to the development of computational tools for PTM prediction. Techniques using deep learning, such as MusiteDeep and DEEPPTM, are being developed to predict PTM sites through protein sequences, which provides a high-throughput alternative to experimental approaches. These tools analyze protein sequences to identify potential modification sites, providing information in regulatory mechanisms. Mass-spectrometry has mapped the BMPR-1B pinteraction network in mammalian cells, and

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CRISPR/Cas9 disruption of *Bmpr-1b* in in-vitro-produced sheep embryos has validated the early developmental roles of this gene, offering the probability of precision editing at this locus in livestock [42,51]. Integrating PTM profiles and genomic data leading to increase fertility predictions, as combining the *FecB* genotype with phosphorylation status increases ovulation rate prediction accuracy which highlites the interplay between genetic variation, PTM dynamics, and environmental factors, providing a mechanistic basis for optimizing reproductive traits through targeted genetic selection.

Bmpr1b-associated QTLs and reproductive eficiency

The *Bmpr-1b* gene, commonly recognized by the *FecB* mutation which is a well-established QTL with an important role in regulating ovulation rate and litter size in sheep. It is a single nucleotide substitution (A746G) which leads to a Q249R amino acid change, in the intracellular kinase domain of the BMPR-1B receptor [20,26]. Functionally, amino acid substitution enhances receptor activity, resulted in stimulating follicular development and suppressing granulosa cell apoptosis [48].

Quantitative genetics represents that the *FecB* QTL exhibits a dose-dependent, largely additive effect with partial dominance inheritance pattern. Each copy of the *FecB* allele increasing ovulation rate per estrous cycle by about 1.5 to 2.0 ova and it has been found that this effect is cumulative [20,26]. Homozygous ewes (BB) produce more ova than heterozygotes (B+), and both genotypes ovulation number are higher than those of their wild-type conterparts (++). Notably, the difference between BB and B+ is less than between B+ and ++, which suggests that it is dose-dependent, largely additive effect with partial dominance genetic effects [52]. The partialy dominant genetic effects of *Bmpr-1b* make it a perfect candidate for marker-assisted selection (MAS). Selection for heterozygotes animals can subsequently increase prolificacy without causing overprolificacy that is often achived with homozygous carriers, which may increase management challenges or elevate the risk of dystocia. Beyond its

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established role as a reproductive QTL, *Bmpr-1b* has also been found to have an association with growth rate and body weight, although it seems that these associations are less consistent across breeds. Genome-wide association studies (GWAS) and QTL mapping in Chinese Hu sheep have found *Bmpr-1b*-linked loci, which affecting weaning weight and postnatal growth, again with approximately additive genetic contributions [52]. These findings support a pleiotropic effect of *Bmpr-1b* to considering it as a multi-trait genetic marker. On the other hand, its effects be able to increase with generations under positive selection because of the approximately additive behavior of *Bmpr-1b* QTLs.

Implications of *Bmpr-1b* polymorphisms on reproductiveperformance

Specific polymorphisms in *Bmpr-1b* gene, notably *FecB*, exhibit a significant positive correlation with litter sizes in prolific breeds such as Small Tailed Han and Hu sheep and Booroola merino sheep [14,53]. The *Bmpr-1b* polymorphisms can serve as a tool for MAS, enabling breeders to select genotypes associated with higher fecundity, consequently, improved production efficiency in livestock [54,21]. Moreover, production efficiency economicaly can improved by utilizing these genetic markers [55,56].

Specific breeds which benefit from *Bmpr-1b* polymorphisms

The Booroola Merino sheep is characterized by specific mutations at *Bmpr-1b* gene, which play a key role in its high fecundity. The key mutation is Q249R substitution that occurs in the intracellular kinase domain of the *Bmpr-1b* receptor. This non-conservative change is linked to higher rate of ovulation and litter sizes [26,20]. A746G mutation results in replacment of glutamine to arginine at position 249 in the protein sequence. It is identified with hyperprolificacy phenotype of Booroola ewes and is not found in other sheep breeds which not derived from the Booroola strain [25,57]. The *FecB* variant exhibit sustained phosphorylation and increased ligand responsiveness to GDF5. There are several breeds which exhibit

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significant benefit from *Bmpr-1b* polymorphisms. For instance, researches on Small Tailed Han Sheep revealed a significant association between *Bmpr-1b* polymorphisms and higher litter size. Ewes with this genotypes, *FecB* variant, produced more lambs than their counterparts [53,55,58]. Among them Booroola Merino sheep known as exceptional prolific breed due to carring specific mutations in the *Bmpr-1b* gene that enhance its reproductive traits [59]. Meanwhile, Kalehkoohi Sheep, an Iranian breed, also showed a significant association between *Bmpr-1b* polymorphisms and litter size, that indicats its potential for genetic improvement [60]. Even in cases where specific *Bmpr-1b* mutations were not found such as Egyptian Breeds (Barki and Rahmani), the potential for appling *Bmpr-1b* polymorphisms to improving litter size remains [56]. These breeds exemplify the *Bmpr-1b* polymorphisms application for economic and reproductive advantages in livestock breeding. Table 2 highlights the genetic polymorphisms in *Bmpr-1b*.

Table 2. *Bmpr-1b* polymorphisms, QTLs, and breed-specific effects on reproductive traits

Polymorphism	Mutation	Breed	Trait Impact	Reference
FecB	A746G (Q249R)	Booroola Merino	↑ Ovulation (1.5–2.0 ova/copy), ↑ Litter size	[20, 26]
FecB	A746G (Q249R)	Small Tailed Han	↑ Litter size	[21, 52]
FecB	A746G (Q249R)	Hu Sheep	↑ Litter size	[14]
FecB	A746G (Q249R)	Kalehkoohi (Iranian)	↑ Litter size	[59]
***Bmpr-1b* SNPs**	Multiple	Suffolk Sheep	↑ Multiple births	[15]
***Bmpr-1b* SNPs**	Multiple	Awassi Sheep	↑ Reproductive traits	[18]

Epigenetic regulation of *Bmpr-1b* gene

Epigenetic factors are affected *Bmpr-1b* expression during development, differentiation, and pathologic processes. It has been shown that CpG islands of *BMPR-1B* promoter was

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hypermethylated in the glioblastoma tumor-initiating cells which silencing its expression. Polycomb Repressive Complex 2 (PRC2) regulated this silencing by recruiting DNMT1, resulting in stable gene silencing. EZH2 knockingdown or demethylating lead to *BMPR-1B* expression and induced astroglial differentiation [61]. Similar DNA methylation patterns between placental tissue and fetus suggest that *BMPR-1B* may also influence long-term developmental traits through fetal programming and metabolic disease. *BMPR-1B* also regulated in histone modification level. It has been reported that H3K9 acetylation at the *BMPR-1B* promoter in osteogenic differentiation of mesenchymal stem cells is upregulated by histone acetyltransferase p300/CBP-associated factor (PCAF), resulted in enhanced transcription and bone formation [62]. In addition to, chromatin remodeling is evidenced by *BMPR-1B* gene silencing in cancer which driven by EZH2/PRC2-mediated deposition of repressive H3K27me3 marks [61].

Non-coding RNAs (ncRNAs) are one of the post transcriptional mediator which involved in BMPR-1B transcription. It has been demonstrated that MicroRNAs (miRNA) such as miR-125b and miR-1306 through binding to the 3′ untranslated region of BMPR-1B mRNA, inhibiting its translation and inducing granulosa apoptosis, thereby affecting ovarian follicle health and fecundity in sheep [48,63]. Beside miRNAs, long non-coding RNAs also contribute to the ncRNAs regulatory network. For example, BMPR1B-AS1 can be considered a competiting endogenous RNA that bind miR-7-2-3p to upregulat BMPR-1B indirectly and activate the PI3K/Akt/NF-κB signaling pathway in endometrial cancer cells [64]. *BMPR-1B* expression is additionaly regulated by epitranscriptomic mechanisms such as N6-methyladenosine modification which make its regulation more complex. LINC00657/miR-144-3p/BMPR1B axis are regulated by methyltransferase-like 3 which promotes osteogenic differentiation of mesenchymal stem cells [65].

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Applications in animal science

BMPR-1B is the key regulatory element within BMP signaling pathway. The *BMPR-1B* gene (Gene ID: 658) is located on the chromosome 4q22.3, between base pair positions 94,757,955 to 95,158,448 in the human reference genome (GRCh38/hg38). The BMPR-1B belongs to transmembrane serine/threonine kinases family consists of 502 amino acids. Ligand binding to the BMPR-1B leads to formation of the complex with type I and type II receptors, subsequently activation of SMAD transcription factors. It is a single-pass type I membrane protein and is predominantly expressed in tissues such as skeletal muscle, proximal tubular cells, immune system cells, and reproductive organs which indicats its functional relevance across diverse physiological process [66]. The *Bmpr-1b* gene in sheep is a orthologue of the human *BMPR-1B* gene which shows significant structural and functional conservation. It is located on the *Ovis aries* genome chromosome 6 (OAR6), aligning with syntenic region of human chromosome 4q22.3, establising its evolutionary conservation among mammals [18].

Bmpr-1b gene mutation or dysfunction may cause pathological conditions. For instance, Loss-of-function or hypomorphic *BMPR-1B* variants cause in human leads to acromesomelic dysplasia, which is a rare skeletal disorder involved in disproportionate short stature and limb malformations along with genital anomalies [67,68]; and brachydactyly type A1D, characterized by shortened fingers [69].

In the last decades, genome-editing technology such as CRISPR/Cas9 was applied to Bmpr-1b editing in sheep, as well as validating its roles in fertility and development, which represent a progressive in precision breeding approaches in livestock [51]. Addditional genomic data of NCBI gene database and the Animal QTLdb offer comprehensive details of *Bmpr-1b*-linked QTLs related to reproduction and growth traits in sheep.

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Conclusion and perspective

BMPR-1B not only affected reproduction but also plays a part in balancing metabolic and reproductive processes, which are important for animals health and fertility. The development of computational tools has led to the discovery of key PTM sites, providing information that extend beyond traditional genetic approaches. These findings are applicable as growing evidence to reflect the practical value of smarter breeding strategies that can enhance fertility in livestock. Identifying and analyzing PTMs will also open up the path to discovering biomarkers for reproductive health and developing novel infertility treatments. Prospectively, it will be important to ensure that the role of the predicted PTM sites is substanted by apparent research. The combination of data sets of various analysis such as gene expression and protein results will more thoroughly explain these complex systems. This approach can help create more sustainable and efficient farming activity which in the end is benefitial to both producers and animals. The accuracy of PTM predictions depends on the quality and quantity of available data. Integrating multi-omics data could enhance prediction models. Moreover, predicted PTM sites needs to be validate experimentaly for their biological relevance and impact on protein function. Further research is needed to elucidate cross-talk between the *Bmpr-1b* alleles and other metabolic pathways and introducing novel strategies for managing reproductive health in livestock.

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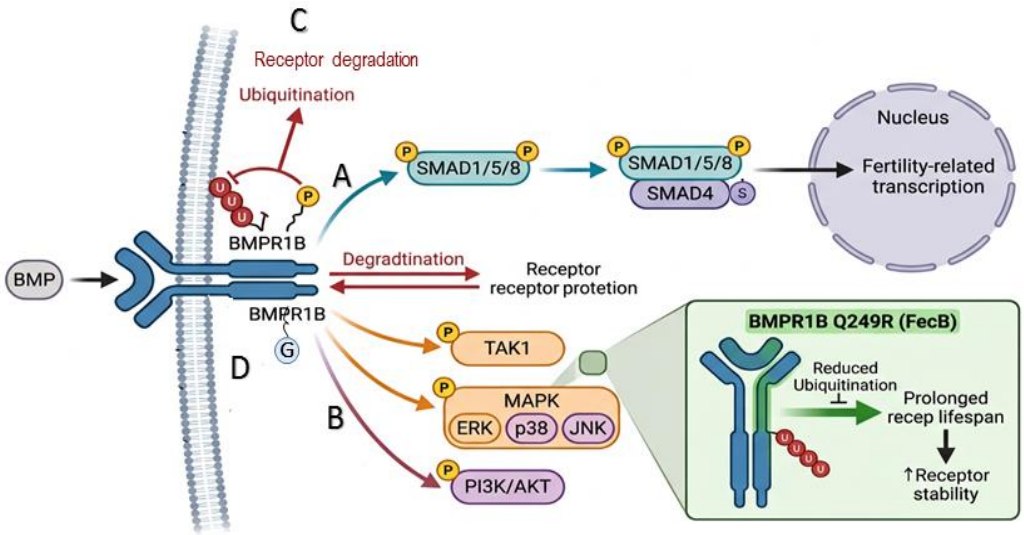
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Figure legends

Figure 1. an overview of BMPR-1B in both canonical (Smad-dependent) and non-canonical (Smad-independent) signaling pathways. It also highlights key PTMs (phosphorylation, sumoylation, ubiquitination) that modulate BMPR-1B signaling dynamics. A: Phosphorylation through canonical pathway activates SMAD signaling finally SMAD4 sumoylation involved in nuclear translocation triggers the transcriptional regulation of target genes. B: phosphorylation of TAK1, MAPK, PI3K activates through non-canonical signaling pathways in turn receptor stability. C: Ubiquitination mediated by SMAD6 degrades BMPR-1B, reduced receptor lifespan. D: Glycosylation enhances ligand-receptor interactions. The figure was produced with help of Noah, an AI tool.

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عنوان مقاله: مطالعه ژن BMPR-1B در تولیدمثل حیوانات مزرعه‌ای: تنظیمات ژن و پروتئین، سیگنالینگ مولکولی و کاربرد آن در برنامه بهبود نژادی

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چکیده فارسی:

ژن *Bmpr-1b* کدکننده ی یک گیرنده‌ی سرین/ترئونین کیناز است که در مسیر پیام‌رسانی پروتئین مورفوژنتیک استخوان (BMP) مشارکت دارد و نقش‌های بنیادینی در فرآیندهای زیستی به ویژه عملکرد تولیدمثلی بر عهده دارد. هدف از انجام این مطالعه مروری گردآوری یافته های پروتئین BMPR-1B و مولکول های سیگنالینگ آن نظیر فسفریلاسیون، گلایکولیزاسیون و یوبیکوئیتیناسیون، و نیز سازوکارهای تنظیمی ژنتیکی و اپی‌ژنتیکی این ژن و اهمیت آن در تولیدمثل حیوانات مزرعه‌ای است. مطالعه الگوهای تغییرات پساترجمه ای افق‌های نوینی برای ارتقای ژنتیک حیوانات و بهبود بازده تولیدمثلی فراهم می‌آورد. یکی از شناخته شده‌ترین موتاسیون‌ها ی این ژن *FecB* بوده که از طریق فسفوریلاسیون پروتئین‌های SMAD در سلول‌های گرانولوزا سبب افزایش نرخ تخمک‌ریزی و در نتیجه افزایش دوقلوزایی در میش‌های حامل این آلل می‌شود. همگرایی داده‌های ژنومیک، پروتئومیک و تغییرات پساترجمه ای فرصتی فراهم می‌آورد تا بتوان عملکرد مولکولی ژن‌ها را پیش‌بینی کرد، اهداف درمانی جدید کشف نمود و باروری دام را بهبود بخشید. در نهایت، انجام مطالعات آینده‌نگر با تمرکز بر تأیید تغییرات پیش‌بینی‌شده، شناسایی تعاملات متابولیکی گسترده‌تر و روشنگری مکانیسم‌های تنظیمیBMPR-1B ، می‌تواند در ارتقای سلامت تولیدمثلی و افزایش بهره‌وری تولید در دامداری‌ها نقش تعیین‌کننده‌ای ایفا نماید.

واژگان کلیدی:

مسیر سیگنالینگ BMP، موتاسیون *FecB*، بهبود ژنتیکی، بازدهی تولید مثل