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REVIEW

Progress on major genes for high fecundity in ewes

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Abstract The existence of major genes affecting fecundity in sheep flocks throughout the world has been demonstrated. Three major genes whose mutations can increase ovulation rate have been discovered, and all related to the transforming growth factor β (TGF-β) superfamily. The mutant *FecB* of bone morphogenetic protein receptor 1B (BMPR1B) has an additive effect on ovulation rate. Six mutations (*FecX*^{I}, *FecX*^{H}, *FecX*^{G}, *FecX*^{B}, *FecX*^{L}, *FecX*^{R}) of bone morphogenetic protein 15 (BMP15) related with fertility have been identified that share the same mechanism. All the mutants can increase ovulation rate in heterozygotes and cause complete sterility in homozygotes. Homozygous ewes with two new mutations (*FecX*^{Gr}, *FecX*^{O}) of BMP15 had increased ovulation rate without causing sterility. There are five mutations in growth differentiation factor 9 (GDF9) associated with sheep prolificacy where *FecG*^{E} and *FecG*^{F} have additive an effect on ovulation rate and litter size. The newly identified β-1,4-N-acetylgalactosaminyl-transferase 2 (*B4GALNT2*) gene of *FecL* is proposed as a new mechanism of ovulation rate regulation in sheep. *Woodlands* is an X-linked maternally imprinted gene which increases ovulation rate. In addition, several putative major genes need to be verified. This review is focused on the identification of the mutations and mechanisms whereby the major genes affecting ovulation rate.

Keywords major gene, ovulation rate, sheep, reproduction

1 Introduction

Maintenance of high levels of ovulation rate and appropriate levels of fecundity are critical for sheep production. However, genetic improvement of traits associated with reproduction (such as ovulation rate, litter size and reproductive seasonality) in sheep is challenging because these traits have low heritability, are generally not expressed until puberty, and are normally recorded only in females [1]. Fortunately, in sheep, a large range in litter size has been observed between and within breeds. These sheep breeds provide opportunities for discovery of genes that underpin improved reproductive success. Genetic studies in sheep have indicated that the ovulation rate and litter size can be regulated by the action of single genes with major effects called fecundity (*Fec*) genes [2]. To date, three of these have been shown to belong to the transforming growth factor β (TGF-β) pathway and another newly discovered candidate beyond the TGF-β superfamily, has been identified as having mutations that lead to alterations of ovulation in sheep. In addition, multiple putative major genes affecting ovulation rate in sheep have been identified in several high prolificacy sheep lines. This review is focused on the discovery of the major genes and putative major mutations affecting ovine ovulation rate and how these discoveries have provided new insights into control of ovarian function.

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2 Major genes with known mutations

2.1 *BMPR1B* and the mutation, *FecB*

In 1980, Piper and Bindon reported that the exceptional fecundity of the Booroola Merino may in part result from the action of a single major gene affecting ovulation rate according to their analysis of litter size records from Booroola Merino sheep [3]. In 1982, Davis et al. found that there was an autosomal mutation present in prolific Booroola sheep causing high ovulation of ewes [4]. The gene dosage effect of the mutation is additive for ovulation rate with an increase of 1.65 for each copy [5]. In 1989, the Sheep and Goat Genetic Nomenclature Committee assigned it *FecB* (Fecundity Booroola). By 2001, three groups found that the mutation is located in the *BMPR1B* gene [6–8]. This point mutation, which can significantly increase the ovulation rate of ewes [8,9], is at base 746 of the coding region (746 A → G) in the highly conserved intracellular kinase signaling domain of the *BMPR1B*

which causes a glutamine to arginine amino acid substitution [7].

BMPR1B, which belongs to the TGF-β receptor family, takes part in signal transduction of many factors, such as BMP15, BMP2, BMP4, BMP6, BMP7, growth differentiation factor 5 (GDF5) and mullerian inhibiting substance/anti-mullerian hormone (MIS/AMH) [10]. It mainly occurs in ovaries of sheep [11], but is also widely expressed in other tissues (ear, spinal cord, pituitary, bone, uterus, hypothalamus, kidney, skeletal muscle and fallopian tubes) [12] and is important in follicle development [13]. *BMPR1B* knockout mice were found to be infertile due to defects in the cumulus expansion and fertilization [14].

The *FecB* mutation is found in various sheep breeds, such as Booroola Merino sheep (Australia) [6–8], Garole sheep (India) [15,16], Javanese sheep (Indonesia) [15], Kendrapada sheep (India) [17], Bonpala sheep (India) [18], Kalehkoohi sheep (Iran) [19], Small Tail Han sheep (China) [20–28], Hu sheep (China) [20,23,28–31], Duolang (China) [32], Cele (China) [33], Wadi sheep (China) [34], Altay sheep (China) [35], and Bayanbulak sheep (China) [36].

Although the *FecB* gene has been widely used for sheep breeding improvement, it remains unclear how this mutation affects the receptor to cause changes in ovarian function. Although it has been reported that homozygous ewes have higher plasma FSH concentration, more granulosa cells and smaller diameter preovulatory follicles compared to wild-type [37,38], there were no changes in the ovarian secretion rates of steroid or inhibin during either the follicular or luteal phases of the estrous cycle [39]. It has also been reported that the mutated *BMPR1B* is associated with decreased responsiveness of ovine granulosa cells to the action of BMPR1B ligands such as GDF5, BMP4 [9]. Unfortunately, it remains to be determined which specific ligands act on BMPR1B and how the downstream signaling pathways influence cell functionality in Booroola sheep.

2.2 *BMP15* and the mutations $FecX^{I}$, $FecX^{H}$, $FecX^{G}$, $FecX^{B}$, $FecX^{L}$, $FecX^{R}$, $FecX^{Gr}$ and $FecX^{O}$

BMP15, a member of the TGF-β superfamily located on the X chromosome, has a 1182 bp CDS mainly present in the ovaries [11]. To date, six mutations ($FecX^{I}$, $FecX^{H}$, $FecX^{G}$, $FecX^{B}$, $FecX^{L}$ and $FecX^{R}$) related with fertility have been identified in sheep, as shown in Table 1. These included three substituted mutations, two non-sense mutations, and one deletion mutation. All of these spontaneous mutations increased the ovulation rate in heterozygotes and caused complete sterility in homozygotes due to primary ovarian failure [40–44]. The effects of these mutations in various sheep are summarized in Table 1.

Biological activities of BMP15 on prolificacy in sheep have been reported. First, granulosa cell proliferation and mitosis can be stimulated by the expression of BMP15. Secondly, BMP15 stimulates the expression of granulosa cells kit-ligand that is required for the early development of the follicle. Thirdly, BMP15 can inhibit FSH receptor expression, as a result, the FSH-induced expression of steroidogenic acute regulatory protein (StAR), P450 side-chain cleavage enzyme (P450scc), 3β-hydroxy-steroid dehydrogenase (3β-HSD), LH receptor, and inhibin/activin subunits (α, βA, and βB) were all inhibited by BMP15 [10]. Finally, BMP15 and GDF9 proteins showed synergistic action in the process of oocyte maturation, ovarian cumulus expansion and ovulation due to the similar structure of the heterodimer formed when they are co-expressed.

In the Inverdale ewes, compared with wild-type ewes, $FecX^{I}$ heterozygotes have some distinctive characteristics such as more differentiated follicles in the ovary, fewer granulosa cell in these follicles, increased sensitivity of granulosa cells to LH in the early stage of follicle and smaller corpus luteum [57]. Further research found that $FecX^{H}$, $FecX^{G}$ and $FecX^{B}$ have similar characteristics to $FecX^{I}$. This indicated that all four mutations may have the same action mechanism [41,58]. It was considered that granulosa cells in heterozygous ewes with mutations in *BMP15* may develop an earlier responsiveness to LH for most of the follicles, increasing ovulation rate in sheep [59].

In general, heterozygous ewes with mutations in both *BMP15* and *GDF9* exhibited higher fertility than those having a mutation in only one of these genes. Liao et al. found that when mutant *GDF9* was co-expressed with mutant *BMP15*, the secretion levels of both proteins were significantly lower than those of cells co-expressing wild-type *GDF9* and mutant *BMP15*, suggesting a possible mechanism for the extreme fertility observed in the compound heterozygous mutant sheep [60].

Recently, two novel non-conservative mutations of *BMP15* called $FecX^{Gr}$ and $FecX^{O}$, which lead to hyper prolificacy, have been identified in the French Grivette and the Polish Olkuska breeds through genome-wide association studies. It is noteworthy that the homozygous ewes of these mutations also had an increased ovulation rate without becoming sterile [45]. Their findings suggest an additional role of the BMP15 protein in ovarian folliculogenesis.

2.3 *GDF9* and the *FecG* mutants

Studies on mice showed that GDF9, a member of the TGF-β superfamily, is required for ovarian folliculogenesis [61]. *GDF9*, being an oocyte-specific expressed gene, is essential for normal follicular development from the early stage in sheep and has been mapped on ovine chromosome 5 [62,63]. After these findings were published, mutations in *GDF9* were identified in some high-

Table 1 Known mutations of major genes and the effects or their encoded proteins on ovulation rate of ewes heterozygous and homozygous for these mutations

Gene	Line/breed	Allele	Coding residue	Chromosome	Change in ovulation rate		Change in litter size		Reference
					1 copy	2 copy	1 copy	2 copy	
BMPR1B	Hu, Small Tail Han, Booroola, Garole, Javanese	*Booroola* (*FecB*)	Q249R	6	+ 1.50	+ 3.00	+ 1.00	+ 1.50	[6–8]
BMP15	Romney, Inverdale	*Inverdale*($FecX^I$)	V299D	X	+ 1.00	POF	+ 0.60	POF	[40]
	Romney, Hanna	*Hanna* ($FecX^H$)	Q291Ter	X	+ 1.00	POF	+ 0.60	POF	[40]
	Belclare	*Belclare* ($FecX^B$)	S367I	X	+ 1.00	POF	/	POF	[41]
	Belclare, Cambridge	*Galway* ($FecX^G$)	Q239Ter	X	+ 0.70	POF	/	POF	[41]
	Lacaune	*Lacaune* ($FecX^L$)	C321Y	X	+ 1.50	POF	/	POF	[42]
	Rasa Aragonesa	*Rasa* ($FecX^R$)	154-159 delWVQKSP	X	/	POF	+ 1.30	POF	[43,44]
	Grivette	$FecX^{Gr}$	T317I	X	0.41	2.05	/	/	[45]
	Olkuska	$FecX^O$	N337H	X	/	/	0.62	1.21	[45]
GDF9	Belclare, Cambridge	*High Fertility* ($FecG^H$)	S395F	5	+ 1.40	POF	/	/	[41]
	Icelandic Thoka	*Thoka* ($FecG^T$)	S427R	5	+ 1.20	POF	+ 0.70	POF	[46]
	Embrapa	*Embrapa* ($FecG^E$)	F345C	5	+ 0	+ 0.82	+ 0	+ 0.58	[47,48]
	Finnish Landrace, Belclare, Norwegian White Sheep	$FecG^F$	V371M	5	+ 0.17	/	/	/	[49,50]
	Ile-de-France sheep	$FecG^V$	R315C	5	/	POF	/	POF	[51]
Woodlands	Coopworth	*Coopworth* ($FecX2^W$)	/	X	+ 0.39	≥W +	+ 0.25	≥W +	[2,52]
B4GALNT2	Lacaune	*FecL*	/	11	+ 1.50	+ 3.00	0.50	/	[53,54]
OLKUSKA	Olkuska	/	/	/	+ 1.00	/	+ 0.60	/	[2,55]
BELLE-ILE	Belle-Ile	/	/	/	/	/	/	/	[2]
Unknown	Romeny	*FecW*	/	/	+ 0.80–1.00	/	/	/	[56]

Note: POF, primary ovarian failure; /, no or unclear.

fecundity sheep breeds around the world [64]. To date, the five mutations in *GDF9*, High Fertility ($FecG^H$) [41], Thoka ($FecG^T$) [46], Embrapa ($FecG^E$) [47], G7 ($FecG^F$) [49,50] and Vacaria ($FecG^V$) [51], which introduce a non-conservative amino acid change, have been reported to be associated with the sheep prolificacy (Table 1). The peculiarity of the polymorphisms in *GDF9* is that $FecG^E$ and $FecG^F$ have additive effects on ovulation rate and litter size, whereas $FecG^H$, $FecG^T$ and $FecG^V$ cause increased ovulation rate and litter size in the heterozygotes and sterility in the homozygous carriers [51].

The mutation $FecG^H$, which introduces serine to phenylalanine change at residue 395, was first identified and associated with sterility or increased ovulation rate in the Belclare and Cambridge sheep breeds. It was thought to disrupt the interaction with the type 1 TGF-β family [65]. One copy of $FecG^H$ was estimated to increase the ovulation rate by 1.4 in the Belclare and Cambridge breeds [2].

$FecG^T$, which was characterized in Icelandic Thoka sheep, has a single base change (A1279C) resulting in a non-conservative amino acid change (S109R) in the C terminus of the mature GDF9 protein, predicted to disrupt binding to the type 2 receptor [46,65].

The mutant found in the Brazilian Santa Ines sheep is called $FecG^E$. This mutation leads to a substitution of a phenylalanine with a cysteine in the mature peptide, which was predicted to be involved in dimer formation. The ewes of the $FecG^E$ allele homozygote carriers showed an increase in their ovulation rate (82%) and prolificacy (58%) and the heterozygous ewes had no change in ovulation rate compared to wild-types [47,48,65].

Recently, a point mutation (c.943C > T) of *GDF9* was identified in Brazilian Ile de France ewes, resulting in an amino acid change (p.Arg315Cys) in the cleavage site of

the propeptide called $FecG^V$ [49]. The SNP (c.1111G > A), responsible for a Val to Met substitution at position 371, which has previously been identified and not found to be associated with fertility in Belclare and Cambridge sheep, was shown to have strong association with litter size in Norwegian White Sheep [51].

2.4 *FecL* mutant

During the first 20 years of its operation the artificial insemination co-operative (OVI-TEST) implemented an on-farm selection scheme in France and the selection response for prolificacy in Lacaune sheep breed has been significant since 1975 [66]. In 1998, a major fecundity gene *FecL*, which genetically determined large variation in litter size, was initially described in the meat strain of the French Lacaune sheep breed [53]. In a previous study, *FecL* had been identified to be an autosomal major gene by a statistical approach and had been localized on sheep chromosome 11 (OAR11) by a full genome scan. Recently, fine mapping research reduced the interval between two SNP markers on OAR11 g.36910171T > C and g.37107627G > C. This interval was estimated at 197 kb based on ovine genome OARv3.1 and it was proposed that *B4GALNT2*, encoding the glycosylation enzyme β-1,4-N-acetyl-galactosaminyltransferase 2, was the best positional and expressional candidate for *FecL*. Within this interval of localization, SNP g.36938224T > A and SNP g.37034573A > G have been found to be fully associated with the $FecL^L$ mutation. These two SNPs, which were non-coding SNPs close or within the *B4GALNT2* gene, caused ectopic expression in the ovarian follicles and overexpression of this protein in granulosa cells induced atypical glycosylation of follicular target proteins in granulosa cells [54,67]. Therefore, the fecundity gene *FecL* in sheep affected the ovulation rate in a different way compared to the *TGF-B/BMP* signaling genes. In the Lacaune meat breed population, the influence of $FecL^L$ on inheritance of ovulation rate is additive as one copy increases ovulation rate (ova) by approximately 1.5 ova, and litter size by 0.5 lambs compared to the wild-type allele [53].

3 Inheritable major gene with unknown mutation (*Woodlands*)

Davis et al. studied the inheritance of ovulation rate which was recorded from a screened high prolificacy Coopworth sheep flock [52]. Breeding values for ovulation rate suggested that a major gene (*Woodlands* gene) for ovulation rate with a non-Mendelian inheritance pattern was segregating in this family line. Ovulation rate data indicated that it was expressed where females inherit a paternal allele but was silenced when they inherited a maternal allele. Also it was unlike either *Inverdale* or *Hanna*, thus this gene is on the X chromosome which is maternally imprinted. The locus *FecX2* and the allele symbol $FecX2^W$ have been assigned to this mutation. This was the first reported imprinted gene that can affect ovulation rate in sheep [2]. The increase in ovulation rate observed in the heterozygous sheep with the *Woodlands* mutation was 0.39. One copy of the *Woodlands* gene increases litter size by about 0.25 extra lambs per lambing ewe while the effect on litter size when homozygous has not been determined [2]. In 2002, Davis and Juengel et al. also identified another line of sheep (Metherell line) with the same inheritance pattern as the *Woodlands* gene [68]. At present, the mechanism by which the *Woodlands* gene is affecting ovulation rate is unknown [65]. The inheritance pattern of the *Woodlands* gene appears not to be that of the previously described mutations in *BMP15* or *GDF9*. It is expected that new further studies may reveal a new pathway, other than the TGF-β family, that can control ovulation rate in sheep.

4 Putative major genes need to be verified

4.1 Olkuska

About 100 years ago, Olkuska sheep were bred by crossing long-wool Polish sheep with Friesian, Pomeranian, and Holstein sheep. In 1991, on the basis of ovulation rate records, Martyniuk and Radomska assigned Olkuska ewes a genotype and proposed that a major gene for prolificacy may exist in the Olkuska sheep, which is similar to the Booroola gene. They found that at least one record of ovulation rate of heterozygous ewes was ≥3, while it was ≥5 in homozygous ewes. They also estimated that one ewe may ovulate one extra egg per copy of the putative gene [2]. However, no significant relationships between the putative Olkuska genotype and blood protein polymorphisms were found by previous study. In 2002, from the result of DNA tests of a highly prolific Olkuska ewe, Davis et al. declared that there was no *FecB* mutant like *BMPR1B* in Booroola sheep and no $FecX^I$ mutation like *BMP*15 in Inverdale sheep or in Olkuska sheep [15,65]. Progress in elucidating the inheritance of prolificacy in Olkuska sheep was slow. The putative major gene is still unknown. One of the reasons for this is that the Olkuska is an endangered breed with small population and flock sizes. This study reported that there were only 58 registered ewes in five flocks in 2000, and the endangered status of Olkuska was listed as “critical-maintained” [2]. Nevertheless, it would be potentially useful to identify the putative major gene in Olkuska.

4.2 Belle-Ile

Belle-Ile sheep in France have high average ovulation rate (2.54) and high average litter size (2.23). The variation in

ovulation rate ranges from 1 to 8, while the variation in litter size ranges from 1 to 7. Belle-Ile sheep also have high repeatability of ovulation rate, 0.8 compared to 0.6 in Javanese sheep, 0.6–0.7 in Booroola sheep, 0.7 in Cambridge sheep and 0.6–0.8 in Icelandic sheep. All these breeds have segregating major genes for prolificacy. This implied that a major gene is segregating in Belle-Ile. Malher and Le Chere hypothesized that an autosomal major gene for prolificacy is segregating in Belle-Ile with evidence of Mendelian inheritance of prolificacy in progeny of this breed. However, the putative major gene has yet to be found. Belle-Ile sheep are also classified as an endangered breed, with small remaining flocks, like Olkuska [2]. More sheep and bigger flock sizes are needed to quantify the size of the effect on ovulation rate and to study the mode of inheritance of this putative major gene, thus research progress has been slow.

4.3 NZ Longwool

Davis et al. found the evidence of segregating major genes in commercial flocks of Perendale, Romney and Border Leicester × Romney sheep in New Zealand. In these flocks the *Booroola BMPR1B* mutation was not found by DNA testing. Although it was found that one flock of Border Leicester × Romney had the *Inverdale BMP15* mutation ($FecX^I$), this does not explain all the highly prolific sheep in these flocks. From the pedigree information, the imprinted *Woodlands FecX2* prolificacy gene is not present in any of these flocks [55]. In 2006, Davis et al. measured the ovulation rates in 547 Romney ewes with high prolificacy. They suggested that a segregating major gene (*FecW*) was increasing prolificacy of this flock. One copy of the putative gene increased ovulation rate by 0.8–1.0 eggs per ovulating ewe, which showed autosomal inheritance [56]. Further research on the mode of inheritance of these genes and the genetic basis of the prolificacy in these flocks is needed.

5 Gene interaction effects between mutants

Ewes carrying mutations in more than one major gene have also been identified and the combination of mutants has been found to produce synergistic effects, with higher ovulation rates than in animals with a single mutation.

Interactions between different mutations in the *BMP15* gene can lead to sterility. The crossbred females with $FecX^I$ and $FecX^H$ mutations had stripy ovaries and were sterile [58]. Hanrahan et al. reported that the crossbred Belclare females with $FecX^G$ and $FecX^B$ mutations also had stripy and sterile ovaries [41].

The crossbred females with $FecX^I$ and $FecB^B$ mutations exhibited higher ovulation rate than wild-types or those with an individual mutation [2,27]. The combined effect of $FecX^I$ and $FecB^B$ appeared to be multiplicative, suggesting that there is a functional interaction between BMP15 and BMPR1B [69,70]. Interactions among these genes, and other mutations yet to be identified, have also been demonstrated. Ewes that carry mutations in both the *BMPR1B* and *BMP15* genes, as well as the *Woodlands* allele, have very high ovulation rates, and the effects of the genes appear synergistic [55,71]. Analysis of another putative gene, the Davisdale, segregated in the AgResearch Fertility flock, also indicates an additive effect with the *Inverdale* mutation [72].

One copy of the *BMP15* mutation together with one copy of the *GDF9* mutation had an additive effect on ovulation rate [2,41,73,74]. Active immunisation of ewes with BMP15 and/or GDF9 peptides affected ovarian follicular development and ovulation rate [75]. Moreover, the analysis of GDF9 and BMP15 in oocyte lysate suggested that GDF9 and BMP15 may be secreted as a complex mix of forms by follicular fluid and from cell lines expressing GDF9 or BMP15 [60,75–78]. Lacaune ewes carrying mutations in both *FecL* and *FecX* loci had a greater ovulation rate than those with either mutation alone [42,66,79].

6 Genetic mutations and their association with high prolificacy in sheep native to China

China has a long history of sheep breeding and there are 42 native sheep breeds reared in China [80]. Most of these have only single births, while some of them have high prolificacy, for example, Small Tail Han (STH) sheep and Hu sheep [81].

It has been shown that the *FecB* mutation, found in Booroola Merino ewes, occurs in many Chinese sheep breeds. The procedure to identify the ovine fecundity gene *FecB* has now been established in China [82]. Chinese farmers gain considerable benefit from improving flock prolificacy or breeding prolific strains through cross-breeding. *FecB* can be used to breed prolific sheep, for example, the Chinese Merino prolific strain and STH super high prolificacy strain. Since the 1990s, Hu sheep germplasm was introduced into Chinese Merino (Xinjiang type) though reciprocal crossing and phenotype selection [83]. Now, STH sheep have been widely introduced into several sheep breeds to breed prolific strains or to improve the fecundity of different breeds for mutton or wool production in China.

Our group also found that STH sheep carry the same $FecX^G$ mutation of the *BMP*15 gene as do Belclare and Cambridge ewes [84–87]. Ewes with the heterozygous mutant had 0.55 ($P < 0.01$) more lambs than wild-type ewes. After comprehensive analysis, the STH ewes carrying both mutations in *BMPR1B* and *BMP15* genes had greater litter size than those with either mutation alone [27].

In addition, one novel single nucleotide mutation (G729T) in exon 2 of the *GDF9* gene in the CD genotype that resulted in an amino acid change (Gln243His) was identified in STH sheep. The ewes with heterozygous mutant CD genotype had 0.77 ($P < 0.01$) more lambs than those with wild-type CC genotype [86,88].

7 Conclusions and future directions

Implementation of effective programs of reproductive management involving synchronization of genetic potentials for reproductive ability with the production environment could maximize profitability of sheep production [1]. The use of selected prolific ewes with genetic mutation affecting ovulation rate has proven to be an exceptional tool to detect major genes. The incorporation of a major gene for prolificacy into flocks by using marker-assisted selection (MAS) could substantially enhance selection pressure on other traits leading to genetic improvement. As shown above, the TGF-β superfamily now represents a key system in the control of ovulation rate and ovarian folliculogenesis in sheep. Also *B4GALNT2* being the *FecL* fecundity gene opens new lines of investigation regarding ovarian glycosylation. However, there is still considerable knowledge required to be gained regarding the regulation and function of these identified major genes.

This includes, but is not limited to, a better understanding of the mechanism of *BMPR1B* in ovulation. As stated above, neither physiology nor protein interaction can illustrate how *FecB* mutation affects the receptors to cause changes in ovulation. Researchers did not observe similar effects when *FecB* was introduced into the mouse *BMPR1B* gene, suggesting this mutation has a species-specific function [89]. Thus a more appropriate animal model is needed to perform functional analysis. In addition, due to extreme difficulties in obtaining the crystal structure, the effect of the Booroola mutation on the kinase activity of ovine BMPR1B has not been verified [65]. Currently it is likely that more information on *BMPR1B* and related pathways can be obtained by the help of high-seq technologies with elaborate design.

GDF9 and BMP15 may be secreted as a complex mix of forms to regulate ovarian follicular development [76,78]. Unfortunately, the biological activity of the complex formed from GDF9 and BMP15 and the interaction with receptors are all unclear. The close interactions between GDF9 and BMP15, therefore, are likely to have a critical biological impact that should be taken into account in future studies [90].

Several approaches and new methods can be used to study the high prolificacy trait in sheep native to China. Most previous studies carried out by researchers regarding to Chinese native sheep breeds were by genetic association analysis at the single gene level. There was no genome wide association study (GWAS) performed based on pedigree records. Thus GWAS conducted in sheep breeds with different prolificacy is needed. Also, knockout sheep models will be vital for future understanding of how oocyte-derived growth factors regulate ovarian functions.

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