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Association Of the BMP4 Genes Polymorphism with Physiological Traits

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ABSTRACT

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β family of proteins that have been implicated in the paracrine regulation of granulosa cell (GC) function , The growth and development of follicles within the ovary are highly dependent on autocrine and paracrine signaling involving growth factors from granulosa cells, theca cells, stromal interstitial cells, and the oocytes, The growth factor bone morphogenetic protein-4 (BMP-4) and its receptor (BMPR-IB) have been detected in ovaries, The objective of the current study was designed to Association of the BMP4 genes polymorphism with physiological traits in Iraqi cattle. So far, more than 30 members have been identified in the BMP family of which BMP4 is the most important one. BMP4 can inhibit progesterone production by granulosa cells and decrease basal granulosa cells progesterone secretion and totally abolish FSH-stimulating action both in cattle and sheep. BMP-4 promotes primordial follicle development and the primordial-to-primary follicle transition, BMP-4 plays an important role in promoting the survival and development of primordial follicles in the neonatal ovary. The expression and function of bone morphogenetic protein 4 (BMP4) gene in bovine cumulus cells (CCs) was investigated to reveal the mechanisms by which it regulated cell apoptosis and proliferation. BMPs are intra-ovarian factors expressed in mammalian ovaries by oocytes, granulosa and theca cells.

Keyword: *Bone morphogenetic proteins (BMPs), cumulus cells (CCs), cattle, granulosa and theca cells*

1. INTRODUCTION

BMP4 mRNA in cattle is localized in both granulosa cellS [GCs] and theca(Glister *et al*., 2011) cells whereas BMP4 protein is primarily localized in theca cells(Díaz *et al*., 2016), BMP4 has been shown inhibit both estradiol and progesterone production by bovine GCs, Previously, BMP4 has been shown to stimulate estradiol production but inhibit progesterone production by rat GCs inhibit both estradiol and progesterone production by bovine GCs(Yamashita *et al*., 2011) inhibit progesterone production by ovine and either increase proliferation of ovine GCs or have no effect on bovine or human GC proliferation (Spicer, L. J *et al* .,2021). Thus, species differences may exist in terms of the GC response to BMP4 whereas elevated BMP4 exposure increases the proportion of growing follicles.

During development the level of exposure to spec), BMProwth factors regulates cell differentiation For example, in *Xenopus* and *Drosophila* embryos, ectoderm cells require BMP signaling for their maintenance, but differentiation of these cells to become dorsal or ventral structures is mainly determined by the presence of extracellular BMP antagonists or binding proteins, which modify local concentrations of biologically active BMP(Zakin, L *et al*.,2010) .The paracrine growth factors bone morphogenetic protein-4 (BMP-4) and BMP-7, and their receptors, BMPR-II, BMPR-IB, and BMPR-IA, have been detected in ovaries A mutation in BMPR-IB has been associated with an increased ovulation rate in ewes , BMP-4 and BMP-7 have been shown to inhibit progesterone and promote estrogen secretion (Eric E. Nilsson *et al*., 2003) ,BMP4 is a key growth factor well known in promoting bone regeneration and has been reported to be able to regulate T cell development in the thymus

1.1 Definition Bone morphogenetic protein:

Bone morphogenetic proteins (BMPs) are a group of growth factors also known as cytokines and as metabologens (Reddi AH *et al* .,2009). Originally discovered by their ability to induce the formation of bone and cartilage, BMPs are now considered to constitute a group of pivotal morphogenetic signals, orchestrating tissue architecture throughout the body.(Bleuming S A *et al*/., 2007) The important functioning of BMP signals in physiology is emphasized by the multitude of roles for dysregulated BMP signalling in pathological processes. The bone morphogenetic protein (BMP) family of ligands plays important roles in a multitude of processes during embryonic development and adult homeostasis by regulating cellular lineage commitment, morphogenesis, differentiation, proliferation, and apoptosis of various types of cells throughout the body (Andrews, M. G *et al*.,2017). In this review, we describe biochemical properties and biological activities of BMP family members in development and diseases.BMP family represents a functionally diverse group of proteins. There are fifteen BMP isoforms (BMP1-15) sub-divided into distinct subgroups based on their sequence homology (Chen, D *et al*.,2004).

1.2 Bone Morphogenetic Protein types:

About 15 members (BMP1–BMP15) of the BMP family have been identified in mammalian species (Wang, *et al*., 2014). These BMP members belong to the transforming growth factor-β (TGFβ) superfamily. Several members of the BMP family (BMP2, BMP4, BMP6, BMP7, and BMP15) act as an autocrine / paracrine regulator of the ovarian follicular development and ovulation through BMP/SMAD signaling pathway (Kumar, *et al*., 2006). Reproductive performance is a key factor determining the efficiency of flock production, especially in the developing countries of Africa and Asia where the sheep industry is significant (Mazinani, *et al*.,2020).

BMP	Known functions	Gene Locus
BMP1	**BMP1 does not belong to the TGF-β family of proteins*. It is a metalloprotease that acts on procollagen I, II, and III. It is involved in cartilage development.	Chromosome: 8; Location: 8p21
BMP2	Acts as a disulfide-linked homodimer and induces bone and cartilage formation. It is a candidate as a retinoid mediator. Plays a key role in osteoblast differentiation.	Chromosome: 20; Location: 20p12
BMP3	Induces bone formation.	Chromosome: 14; Location: 14p22
BMP4	Regulates the formation of teeth, limbs and bone from mesoderm. It also plays a role in fracture repair, epidermis formation, dorsal-ventral axis formation, and ovarian follical development.	Chromosome: 14; Location: 14q22-q23
BMP5	Performs functions in cartilage development.	Chromosome: 6; Location: 6p12.1
BMP6	Plays a role in joint integrity in adults. Controls iron homeostasis via regulation of hepcidin.	Chromosome: 6; Location: 6p12.1
BMP7	Plays a key role in osteoblast differentiation. It also induces the production of SMAD1. Also key in renal development and repair.	Chromosome: 20; Location: 20q13
BMP8a	Involved in bone and cartilage development.	Chromosome: 1; Location: 1p35–p32
BMP8b	Expressed in the hippocampus.	Chromosome: 1; Location: 1p35–p32
BMP10	May play a role in the trabeculation of the embryonic heart.	Chromosome: 2;

		Location: 2p14
BMP11	Controls anterior-posterior patterning.	Chromosome: 12; Location: 12p
BMP15	May play a role in oocyte and follicular development.	Chromosome: X; Location: Xp11.2

1.3 Association of BMP4 gene polymorphic variants with growth traits.

It has been reported that morphogenetic proteins (BMPs) have multiple roles in skeletal development, homeostasis and regeneration in mammals and livestock, but very few traceable information are available regarding the association of BMP4 gene variants with body weight of indigenous livestock types (Khare *et al*., 2022). BMP2 and BMP4 are closely related proteins and are thought to be the mammalian homologs of dpp, which is known to specify the dorsoventral patterning in the Drosophila embryo. It has been reported that BMP4 induces ventroposterior mesoderm in Xenopus.

Moreover, BMP4 acts as a dorsalizing signal from the epidermal ectoderm in the vertebrate. We hypothesized that BMP4 could be a candidate for the signaling molecule which acts early in axial skeletogenesis (Akira Nifuji *et al.,* 2009). Bone Morphogenetic Proteins (BMPs) play an important role in the fusion of the upper lip, main palate, and craniofacial growth, primarily expressed in palatal shelf epithelial and mesenchymal cells (Avasthi, K. K *et al*.,2022).

Bone morphogenetic protein 4 (BMP4) is a BMP family member. This protein has anabolic and pleiotropic functions that are assumed to play crucial roles in skeletal development, bone formation, and white beige and brown adipogenesis regulation During development (KHARE, V *et al*.,2022). Bmp-4 has a role in lung development. During embryogenesis, BMP4 is involved in specifying the ventral foregut endoderm that gives rise to the respiratory system. It participates in the formation of the primitive lung bud, which eventually develops into the lungs. (Guan, R., Yuan, L *et al*.,2022)

BMP4 signaling influences cell fate decisions, including the differentiation of alveolar epithelial cells, smooth muscle cells, and endothelial cells within the developing lung.

1.4 The role of BMPs system in ovarian follicle growth and differentiation

In livestock ovaries, the expression pattern of BMPs ligands and receptors indicates that the BMPs system and GDF9 form a vital part of this intra-follicular network (Rossi *et al*., 2015). The BMPs system and GDF9 regulate granulosa cell proliferation, differentiation, and apoptosis during follicle formation through autocrine/ paracrine action in the ovary (Ajafar *et al*., 2023). bone morphogenetic proteins (BMPs), growth differentiation factors (GDFs), TGF-βs, activins and inhibins, and anti-Müllerian hormone (AMH), are expressed in the ovary and play essential roles in the regulation of folliculogenesis, oogenesis and ovarian functions (Chang, H. M *et al*.,2016).

BMP are produced by oocytes which in turn not only influence normal follicular development but also play a key role in regulating the number of follicles ovulating at each cycle (ovulation rate), (Juengel, J. L *et al*.,2005). BMPs play an important role in the control of primordial germ cell formation, oocyte growth and maturation (Rossi *et al*., 2015). BMP15 and GDF9 are released by ovarian follicles, leading to the transformation of primary follicles to the basal form and involved in follicular and oocyte maturation, proliferation/atresia of granulosa and theca cells, steroidogenesis, ovulation, and corpus luteum formation (Ajafar *et al*., 2023).

1.5 Bone morphogenetic proteins and ovarian function in farm animals

The BMPs system in the ovary plays a vital role in regulating granulosa cell proliferation, differentiation, and their responsiveness to follicle stimulating hormone (FSH) (Chu et al., 2018). BMPs in sheep and cattle control granulosa cells proliferation by suppressing the FSH receptors expression (Haas *et al*., 2019). During follicle and oocyte maturation in farm animals, BMPs signaling affects animal fertility by regulating sex hormone secretion, gene expression of gonadotropin receptors, and oocyte quality (Figure 1) (Sanfins *et al*., 2018). BMPs signaling is also related to ovulation rate and estrus cycle (Lochab & Extavour, 2017). BMP15 (also known as GDF9b) has been shown to be essential for normal follicular growth and regulating ovulation rate in sheep.

The BMP subfamily members, BMP2, 4, 6 and 7 have been shown to be expressed by follicular cells in several species such as mice, rats, chickens and cows. BMP15 and GDF9 in regulation of follicular growth and ovulation rate as well as the known effect of mutations in the BMPRIB gene on ovarian activity in sheep. (Juengel, J. L *et al*.,2006). BMP-15 is produced in the largest quantities in the ovary. ovine and bovine. caprine species, BMP-15 has been found in the oocytes and granulosa cells of all types of follicles but not in granulosa cells of primordial folliclesand suggested to be required for the follicular development up to the ovulatory stage (Celestino, J. J *et al*.,2011)

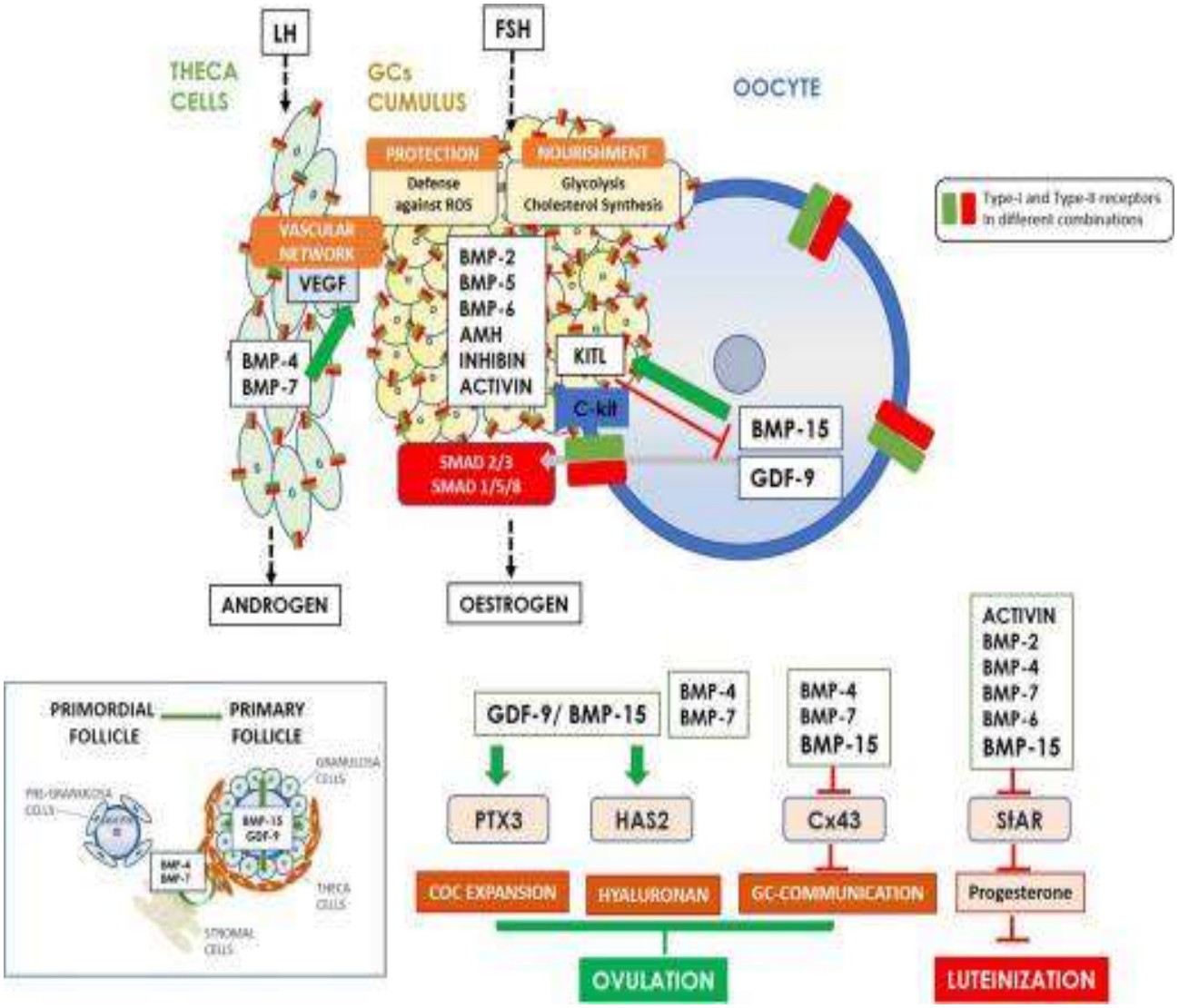

Figure 1. The main bone morphogenetic proteins (BMPs) members and the functional roles in regulating ovarian physiology. Source: Adapted from Sanfins et al. (2018).

1.6 Evolutionary divergence of BMP4 gene

Bone morphogenetic protein 4 (BMP4) regulates skeletogenesis, osteoblastic differentiation, and the induction of hair follicles. Its protein-coding region contains a signal peptide, prodomain (which regulates post-translational synthesis), and a mature domain (which mediates gene function). (Zhang, D. J *et al*.,2014).

Bone morphogenetic protein 4 (bmp4) has long been of interest to geneticists due to its role in the development and diversification of cranial morphologies in a wide range of organisms. In particular, the clear correlation of bmp4 expression levels to the incredible range of jaw morphology in African cichlids as well as beak biodiversity in Darwin's finches is well established .to have crucial roles in the development of the head, teeth, and jaws. (Charlene L. McCord *et al* ., 2016). Moreover, compared to the mature domain, the signal peptide and pro-domain have experienced dramatic variation in all vertebrates. Six amino acid sites in the pro-domain were identified to be under diversifying Darwinian selection in mammals. These results indicate that the signal peptide and pro-domain of BMP2 may be involved in skeletal poly-morphology during mammal evolution and the mature domain may also contribute to this function in non-mammals. This supports the hypothesis that morphological variations in mammals result mainly from a change in post-translational control of synthesis, whereas in non-mammals they result mainly from gene functional change (Wang, Z., Yuan, L *et al*.,2009).

1.7 Bone morphogenetic proteins (BMPs) activins

BMPs are secreted growth factors with diverse functions in regulating developmental processes such as ectopic bone formation, embryogenesis, and neurogenesis (Wagner, D. O *et al*.,2010). BMPs are highly conserved and morphologically

similar ligands, but they are sub-categorized into at least four classes based on receptor specificity: BMP2/4, BMP5 /6 / 7/8a/8b, BMP9/10, and BMP12/13/14 (Bragdon, *et al*., 2011, Ganjoo *et al*., 2022). Activins and bone morphogenetic proteins (BMPs) belong to the transforming growth factor-β (TGF-β) superfamily and have critical roles in multiple physiological and pathological processes (Szilágyi, S.S *et al*.,2022). Activins are homo-dimeric or hetero-dimeric proteins consisting of two cross-linked β subunits. The three mains bioactive activin dimers include activin A (βAβA), B (βBβB) and AB (βAβB) (). The three mains bioactive activin dimers include activin A (βAβA), B (βBβB) and AB (βAβB). Activins are generally involved in development and tissue homeostasis/repair, as evidenced by their roles in wound healing and scar formation. activins, and growth and differentiation factors (GDFs), which are other key TGF-β superfamily members that immunologically affect cancer progression, BMPs, activins, and GDFs are also similar to TGF-β in their having context-dependent effects on tumor progression; however, targeting certain ligands from these superfamily members has proven to be aviable treatment strategy in several cancer models (Ganjoo *et al*., 2022).

The activins and inhibins are among the 33 members of the TGF-β family and were first described as regulators of follicle-stimulating hormone (FSH) secretion and erythropoiesis. It has biological processes, ranging from the early stages of embryonic development to highly specialized functions in terminally differentiated cells and tissues. gonadotropin-releasing hormone (GnRH)-mediated release of FSH and were named “activins” because their effects were functionally opposite to those of inhibin in this context (Namwanje, M *et al*.,2016).

2. LITERATURE REVIEW

2.1 Role of Bone Morphogenetic Protein4 (BMP4) in ovary:

The growth and development of follicles within the ovary are highly dependent on autocrine and paracrine signaling involving growth factors from granulosa cells, theca cells, stromal interstitial cells, and the oocytes (Parrott JA *et al*.,1994)

Sheep have the BMP15 gene on their X chromosome, GC demonstrated that BMP15 inhibits progesterone production induced by FSH without affecting estradiol BMP15 polymorphism has on ovarian function, litter size, and reproduction in livestock, BMP15 is regarded as one of the crucial genes that influence reproduction in livestock. Mutations in the sheep breeds have been attributed to defects in the ovarian BMP system, which lead to an increased ovulation rate (Eric & Michael *et al*., 2003)

Granulosa cells (GCs), cumulus cells (CCs) surrounding oocytes play an essential role in oocyte maturation, follicle growth and maturation, ovulation and embryo development. Oocyte and CCs form cumulus-oocyte complex (COCs) and maintain an intense bidirectional communication. It has been shown that BMPs regulate mammalian folliculogenesis (Tian, Y. Q *et al*., 2022). BMPs are important due to their crucial role in follicular growth and differentiation, cumulus expansion and ovulation (L Sarma *et al*., 2019). The proliferation and apoptosis of granulosa cells or cumulus cells are closely related to follicle growth and development.

The BMP family is the largest one among the TGF-β superfamily of growth factors and has multifaceted functions in modulating cell proliferation, differentiation and viability. Initially, BMP4 was identified for its function in promoting the formation of cartilage and bone tissue, but now BMPs have been shown to regulate the development of teeth, kidneys, skin and muscle (Tian, Y. Q *et al.* 2022). And the growth and development of the ovarian follicle are regulated by BMPs with the spatial and tissue-specific pattern. Of these, BMP2, BMP5 and BMP6 are expressed in GCs, BMP6 and BMP15 are expressed in oocytes and BMP2, BMP4 and BMP7 are expressed in theca cells. The expression of BMP4 mRNA has been examined in the ovarian follicular cells of cattle, sheep, mice, rats and geese. For bovine secondary follicles, the supplementation of BMP4 in culture medium improved the follicle growth and antrum formation (Tian, Y. Q *et al.* 2022).

n human preimplantation embryos cultured in vitro, BMP4 addition compromised the rate of blastocyst formation and induced cell apoptosis in the blastocyst. Overall, BMP4 participates in the follicle development and female fertility (Tian, Y. Q *et al.* 2022)

2.2 The relationship between BMPs and follicle stimulated hormone (FSH)

It was found that BMP4 and BMP7 regulated GC function as paracrine factors in different species in different ways, by promoting follicle stimulating hormone (FSH) -stimulated estradiol secretion, decreasing FSH-stimulated progesterone and they did not affect GC proliferation in the rats. In cattle, they improved basal and IGF-stimulated estradiol and follistatin secretion, increased granulosa cell numbers, but attenuated progesterone secretion. In sheep, BMP4 weakened FSH-stimulated progesterone and in mouse, the BMP4 gene inhibited oocyte apoptosis and reduced the rate of primordial follicle atresia. (Tian, Y. Q *et al*. 2022)

Ovarian growth factors, such as members of the transforming growth factor β (TGFβ) family, play important roles in follicle recruitment, follicle selection, and FSH responsiveness. Bone morphogenetic protein 4 expression is extremely high in healthy follicles, which can operate directly on the granulosa and result in a significant alteration in the follicle-stimulating hormone (FSH) activity. This may prevent progesterone production and secretion and thereby eliminate FSH stimulating

action either in cattle or sheep (Cheng, H *et al*., 2022). Studies performed predominantly in rodents showed that the various Bone Morphogenetic Proteins (BMPs) are expressed in a cell-specific manner in the ovary and display spatial and temporal changes in expression depending on the stage of follicular development. BMP15 is specifically expressed by oocytes, also in oven, bovine and human, whereas BMP6 has an oocyte/granulosa cell expression pattern in various species. BMP2 is expressed by granulosa cells in rodents and bovine, while BMP4 and BMP7 are theca cells derived growth factors with mRNA expression detectable from the small preantral stage onwards in rats. However, in mice, human and bovine ovaries also granulosa cell expression of BMP4 mRNA has been reported. (van *et al*., 2013).

The folliculogenesis is a continuous process regulated by a variety of endocrine and intraovarian factors. One of these factors is the bone morphogenetic protein (BMP) that belongs to TGF-β superfamily. Until now, 15 BMPs were described, and only seven (BMP-2, -3, -3b, -4, -6, -7 and 15) expressed in mammalian ovaries. Although BMPs were originally named for their ability to induce bone formation, they are pleiotropic proteins that regulate cell fate determination, proliferation, apoptosis, and differentiation during both embryogenesis and adulthood. Several BMPs have been suggested as autocrine/ paracrine regulators of bovine ovarian follicular development, demonstrated by the expression of BMP4 and BMP7 in granulosa and theca cells (aloza, S *et al*., 2017). BMP 4 expression is very high in healthy follicles but rarely detectable in follicles undergoing atresia, which can act directly on granulosa cells and cause important changes in FSH (follicle stimulating hormone) action (Baloza, S *et al*., 2017). So, BMP 4 could have relation to reproductive functions in mammals- (L Sarma *et al* .,2019)

Bone Morphogenetic Proteins (BMPs) are candidate genes belonging to the member of the TGF-β (Transforming Growth Factor-beta) super family. BMPs play a major role in embryonic development, homeostasis, repairing of various tissue patterning, cell differentiation and apoptosis (L Sarma *et al*.,2019), which may contribute through molecular breeding to increased productivity in the goats. The transforming growth factor beta (TGF-β) superfamily contains 30 members known as BMP members, with the bone morphogenetic protein 4 (BMP4) gene being the most crucial of these. It has been demonstrated that the BMP4 gene plays a vital role in cumulus expansion, ovulation, follicular growth, and differentiation., BMP4 is involved in many important processes, such as mesoderm progenitor and endothelial induction, mesodermal differentiation, somite formation, ectodermal differentiation, and myogenesis induction (VAISHALI KHARE1 *et al* .,2022). BMP4 normally plays a key role in lung development. Epithelial-mesenchymal interactions and branching mor-phogenesis in the lung are likely to involve polypeptide signalling molecules and transmembrane receptors known to be required for the development of other organ systems. Potentially important secreted growth and differentiation factors include members of the fibroblast growth factor (FGF), trans-forming growth factor-beta (TGF-β), bone morphogenetic protein (BMP), and epidermal growth factor (EGF) families, (Nasri, A *et al*., 2021).

2.3 Associated BMPs with different pathways

Many studies were found that bone morphogenetic proteins (BMPs) could promote the proliferation of granular cells and secretion of steroids, and then regulate the growth of follicles through BMPs/SMAD pathway. So far, there were 8 SMADs have been found, of which SMAD1, 2,3, 5, and 9 are receptor activated. The BMPs could phosphorylate the receptor activated SMAD1, 5 and 9 through binding and phosphorylating its receptors The activated SMADs then binding to SMAD4 to form heterodimer and transfers into nucleus as transcriptional factor to activate the expression of related genes. The SMAD4 could initiate the transcription of frizzled homolog 4 (FZD4), and then activate the FZD4-dependent Wnt signal to prohibit the apoptosis of granular cells indicating that SMAD4 promotes follicle development through the regulation of granular cells proliferation (Wei *et al*.,2023)

Previous experiments demonstrated that BMP4 acts through BMP receptors on enteric neural crest-derived cells [ENCDCs] and regulates cell migration (Faure, C *et al* .,2007) and differentiation of enteric neurons and glial cells. BMP proteins also play an important role in determining the neuronal-to-glial cell ratio in the ENS, with Noggin-mediated inhibition of BMP increasing the total number of neurons (Chalazonitis, A *et al*., 2008), while decreasing the proportion of glia. BMPs also promote gangliogenesis when ENCDCs aggregate, which is associated with changes in the expression of neural cell adhesion molecule (NCAM). Blocking BMP signaling in the mesenchymal layer of the intestine inhibited the development of smooth muscle and resulted in abnormal patterning of the ENS. BMP4 misexpression in the chicken gizzard mesenchyme leads to hypertrophic ectopically positioned ganglia. (Fu, M *et al*.,2006)

Finally, exposure of rat ENCDC cultures to GDNF in combination with high levels of BMP2 or BMP4 leads to significantly more neurons.(Chalazonitis, A *et al*.,2004) BMP4 overexpression leads to large and ectopic enteric ganglia, while its inhibition with Noggin leads to hypoganglionosis; (BMP4 promotes enteric [ganglion formation; GDNF inhibits the response to BMP4, suggesting interactions between these signaling pathways in the regulation of distal ENS formation (Kovács *et al*.,2023). Studies showed that some BMPs may regulate early thymocyte differentiation and inhibit early T cell development, and also may inhibit T cell activation and differentiation. However, the mechanism behind this pathway is still unknown (Huang *et al*.,2021).

3. CONCLUSION

The present review provides valuable information on the association of BMP4 was designed to Association of the BMP4 genes polymorphism with physiological traits in Iraqi cattle. BMP-4 promotes primordial follicle development and the primordial-to-primary follicle transition, BMP-4 plays an important role in promoting the survival and development of primordial follicles in the neonatal ovary. Breeders need to pay attention to the importance of BMP4 as fertility markers since abnormalities in their expression may result in animal infertility

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