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Cellular and molecular pathways associated with ovarian physiology and estrus cycle in buffaloes

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Abstract
Buffaloes contribute greatly to the rural livestock economy of developing countries by providing milk, meat and draught power. Improving reproductive efficiency of buffaloes can help in exploiting their productive potential. Ovary is the functional unit of female reproductive system and understanding the cellular functions of the ovary and the molecular pathways associated with ovarian physiology of buffaloes may help in identifying intricate molecules involved in estrus cyclicity and estrus behavior. Review of literature revealed a paucity of information on signaling pathways associated with ovarian physiology and estrus cycle in buffaloes. Efforts need to be directed towards the studies on ovarian follicular dynamics and estrus cycle in buffaloes in the context of the role of signaling molecules involved in ovarian cyclicity and various factors affecting the estrus cycle. The data obtained from such kind of basic studies may aid in enhancing reproductive efficiency of buffaloes.

Keywords: ovary, buffalo, estrus, folliculogenesis, pathways

Introduction
Buffalo is considered as the dairy animal for 21st century due to its higher adaptability and productivity in the changing climatic conditions (Paul *et al*., 2003; Siddiky and Faruque, 2018) [78, 93]. Buffalo milk has higher protein content, lower amounts of somatic cells and a lower cholesterol content and its meat has important human health benefits than beef *Bos Taurus* (Ahmad *et al*., 2008) [2]. Though buffalo farming is advantageous in many ways, the major constraint to the full exploitation of the productive potential of the buffaloes is the overall low reproductive efficiency as reflected by late maturity, poor manifestation of estrus signs, silent estrus and seasonality in breeding (Ravinder *et al.*, 2016; Selvam *et al*., 2017) [83, 91]. Buffaloes reach puberty at around 24 months of age (10-36mn on average).

The ovary performs important functions including the oocyte and follicle formation and storage, development of follicles and oocyte culminating in ovulation and the production of reproductive hormones (Verhoeven and Lambalk, 2018) [107]. Based on the physiological and endocrinological events, the estrus cycle is divided into four phases namely estrus (day 0), metestrus (day 1–4), diestrus (day 5–18) and proestrus (day 19 to estrus) (Ramadan, 2017). The estrus cycle is a dynamic process and is approximately 21 days in length, ranging from 17 to 24 days and the duration of estrus varies from 5 to 27 hours, (20 hours on average). The length of estrus cycle in buffalo may vary which can be attributed to various factors including adverse environmental conditions, nutrition and irregularities in secretion of ovarian steroid hormones (Kaur and Arora, 1984; Nanda *et al*., 2003) [53, 66].

Buffaloes are negatively photoperiodic showing a natural increase in estrus cyclicity during decreasing day length, expressing estrus behavior during September to January with the signs intensifying from October to November (Singh and Nanda, 1993; Sane *et al*., 1994) [97, 90]. As per the reports of D' Occhio *et al*. (2020) [31], seasonal breeding in buffalo is being influenced by exogenous (photoperiod, climate, nutrition, management) and endogenous (hormones, genotype) factors. Having an insight into the cellular and molecular pathways associated with ovarian physiology and estrus cycle in buffaloes will greatly help in understanding the role of intricate molecules in ovarian cyclicity and reproduction. Such understanding can in turn have clinical implications in *in vitro* fertilization (IVF) (Nandi *et al*., 2002) [67] and embryo transfer technology (ETT) (Baruselli *et al*., 2020) [8]. This review aims to focus on the cellular and molecular pathways associated with ovarian function and reproductive cycles in buffaloes.

Folliculogenesis and ovarian follicular dynamics

The ovarian physiology and its follicular dynamics leading to the estrus cycle is associated with intricate molecular pathways involving various genes, gene transcripts, proteins and small molecules. These pathways and the factors (intrinsic and extrinsic factors) influencing them can contribute to the animal in exhibiting the various signs of estrus/heat.

The processes of oogenesis and folliculogenesis are dependent on each other which ultimately influence the reproductive cycle of mammalian females. Oocytes are developed from primordial germ cells. Normal development of mammalian oocytes depends on a complex and developmentally-regulated series of events occurring within the follicle. The development of oocyte gets arrested in the ovary at the primordial follicle stage, and thereafter continues throughout the reproductive life once the folliculogenesis begins.

Folliculogenesis involves development of the ovarian follicles that includes primordial (resting follicles), primary (follicles activated for development or atresia), secondary (large-sized follicles) and tertiary follicles (antral and preovulatory follicles) (Fortune *et al*., 2000; Suh *et al*., 2002) [35, 100]. The process of folliculogenesis commences with the recruitment of the primordial follicles and ends with either ovulation or death by atresia. Multidirectional interactions between the oocyte, granulosa cells (GCs), theca cells, and the hypothalamic-pituitary axis (HPA) of the endocrine system are crucial for all of the complex developmental transitions of folliculogenesis which actually occurs in three phases (Macklon and Fauser, 2001; Hillier, 2001) [61, 42].

Endocrine control of developmental transitions of folliculogenesis

The phase from primordial follicle initiation to the late preantral phase in which follicle development appears to be controlled by expression of a range of local factors is gonadotrophin-independent phase. The intermediate phase in which follicles will respond to the actions of gonadotrophins but do not require them for normal growth and development is gonadotrophin-responsive phase. And the phase from the antral stage to preovulatory stage is termed gonadotrophin dependent where follicles increase in size and develop further only in the presence of critical threshold concentrations of the luteinising hormone (LH) and follicle stimulating hormone (FSH).

Gonadotrophin-independent phase of folliculogenesis

Formation of primordial follicles: Role of oocyte derived and germ cell specific transcription factors (TFs)

Formation of primordial follicles is dependent upon the expression of the oocyte-derived transcription factor, folliculogenesis-specific basic helix-loop-helix, also called as factor in the germline alpha FIGa (Soyal *et al*., 2000) [98] and the production of a somatic cell-derived factor WNT4 (Vainio *et al*., 1999) [105]. The interaction between the oocytes and granulosa cells continues throughout the folliculogenesis (Cecconi *et al*., 2004) [21]. During the early stage of folliculogenesis, dynamic alterations occur in the oocyte resulting in the expression of various genes, which are regulated by germ-cell specific transcription factors (TFs)-factor in the germline alpha (FIGLA) (Huntriss *et al*., 2002; Bayne *et al*., 2004) [46, 10], newborn ovary homeobox protein (NOBOX) (Rajkovic *et al*., 2004; Choi *et al*., 2007; Lechowska *et al*., 2011) [81, 22, 56], LIM-homeobox protein 8 (LHX8), spermatogenesis and oogenesis specific basic helix-loop-helix transcription factor 1 (SOHLH1), and SOHLH2 (Choi and Rajkovic, 2006) [23]. These TFs were found to play an important role in the maintenance, survival and assembly of primordial follicles (Lim and Choi, 2012) [59].

Factors regulating the fate of primordial follicles

An intricate coordination between the stimulatory and inhibitory substances determines a primordial follicle's fate of survival, quiescence, or recruitment (Reddy *et al*., 2010) [87]. The phosphatase and tensin homolog (PTEN) signalling pathway is believed to be critical for germ cell quiescence due to premature primordial follicle activation in mice and includes genes like Forkhead box O3, Foxo3a, (Castrillon *et al*., 2003; Reddy *et al*., 2008) [19, 85]. 3-phosphoinositide-dependent protein kinase-1 (PDK1) (Reddy *et al*., 2009) [84] and other factors are connected to PTEN pathway and are found to promote primordial follicle survival. (Reddy *et al*., 2009) [84]. Many inhibitory factors repress the activation of the primordial follicle from entering folliculogenesis and survival factors prevent primordial follicle loss via apoptosis (Reddy *et al*., 2010) [87]. Upon selection, primordial follicles become primary follicles by initial recruitment, where in the cells within the follicle produce growth and signalling factors that act in an autocrine and paracrine manner regulating the initial recruitment process (Gura and Freiman, 2018) [39]. Initial recruitment in turn is a complex, multidirectional process involving several cell types and signalling molecules that converge on multiple signalling pathways (Adhikari and Liu, 2009) [1].

The phosphatidylinositol 3-kinase (PI3K) signalling pathway is a regulatory pathway that controls not only initial recruitment, but also cell proliferation, survival, migration, metabolism associated with ovarian folliculogenesis. The various proteins that favour PI3K signalling include 3-phosphoinositide dependent protein kinase-1 (PDPK1), mammalian target of rapamycin complex 1 (mTORC1), protein kinase B (AKT) (Reddy *et al*., 2005) [86], and ribosomal protein S6 (rpS6) (Engelman *et al*., 2006; Stokoe, 2005; Cantley, 2002; Yang and Guan, 2007) [33, 99, 17, 108]. The proteins that inhibit PI3K signalling (Simpson and Parsons, 2001) [94] include forkhead box O3 (FOXO3), PTEN, and tuberous sclerosis 1 and 2 (TSC1 and TSC2).

A basal level of PI3K signaling is needed for oocyte survival. Certain factors like basic fibroblast growth factor (bFGF) (Nilsson *et al*., 2001; Nilsson and Skinner, 2004) [70, 72], leukemia inhibitory factor (LIF) (Morita *et al*., 1999; Nilsson *et al*., 2002) [63, 69], keratinocyte growth factor (KGF), bone morphogenetic proteins 4 and 7 (BMP4) (Nilsson and Skinner, 2003) [71] and BMP7 (Lee *et al*., 2004) [55], and platelet-derived growth factor (PDGF) (Kezele *et al*., 2005) [54] (Nilsson *et al*., 2006; Hutt *et al*., 2006) [68, 48] were found to exhibit a dramatic increase in initial recruitment. LIF produced by granulosa cells induces these cells to express the kit ligand (KL) (Parrott and Skinner, 1999) [76] that binds to its cognate receptor c-kit on the oocyte surface and regulates the expression of bone morphogenetic protein (BMP)-15 gene (BMP-15). On the other hand, inhibiting factors include anti-Mullerian hormone (AMH) (Durlinger *et al*., 2002) [32], FOXO3 (Castrillon *et al*., 2003) [19]. FOXO3 is a downstream effector of the PTEN/PI3K/AKT signalling pathway of cell proliferation and survival (Cantley and Neel, 1999; Li *et al*., 2010) [16, 57] and the chemokine, SDF-I and its receptor

(CXCR4) (Holt *et al*., 2006) [43]. nil

Gonadotropin-independent phase of folliculogenesis

In the gonadotropin-independent phase of folliculogenesis, the locally produced regulatory factors support the physiological development of germ and somatic cell components via granulosa cell-oocyte interactions which occurs through gap junctions and paracrine factors (Buccione *et al*., 1990; Cecconi *et al*., 1996) [14, 20]. The primary follicles continue to develop to become secondary and tertiary follicles (also known as preantral follicles). The stages of development involving transitions from the primary stage to the early antral stage are mostly driven by the above described intraovarian factors and signaling pathways. The various intrinsic ovarian factors involved in pre-antral/antral follicle development are given in table 1 (Modified from Gura and Freiman, 2018) [39].

Gonadotropin-responsive phase of folliculogenesis

The middle transitions of folliculogenesis are gonadotropin-responsive as theca cells contain luteinizing hormone (LH) receptors, and granulosa cells contain follicle-stimulating hormone (FSH) receptors at early stages of development. Preantral follicles then develop into antral follicles. Most early antral follicles undergo atresia, which is a controlled apoptosis-mediated process of follicle death.

It is during the follicular phase of a female's reproductive cycle, a small cohort of antral follicles are rescued from atresia and selected to develop further into preovulatory follicles (also known as Graafian follicles) by cyclic recruitment which is largely driven by FSH signalling (Zeleznik, 2001; Richards, 1980) [109, 88].

Hormones secreted from the hypothalamic-pituitary-ovarian axis act in an endocrine manner to coordinate the later stages of cyclic recruitment (Mc Gee and Hsueh, 2000) [62]. These preovulatory follicles are the major producers of estrogens and are the only follicle type that is capable of ovulation. Estradiol production is largely driven by FSH signaling, as FSH increases the levels of aromatase in granulosa cells. Increasing FSH levels give rise to maturing antral follicles, and thus increasing estradiol levels. Insulin-like growth factors (IGFs) and activin A also facilitate the increase in estradiol levels during this period (Ginther *et al*., 2002; Bashir *et al*., 2016) [37, 9]. Estradiol, in turn, negatively feeds back to the HPA causing a decrease in FSH levels. This is also accomplished by the action of inhibin B, which is a granulosa cell-produced peptide hormone that inhibits the anterior pituitary from producing and secreting FSH. The dominant antral follicle then produces threshold levels of estradiol that positively feedback to the HPA initiating the ovulatory LH surge and thereby the ovulation.

The extra-cellular matrix (ECM) surrounding follicular cells of the ovary also influence regulatory process involved in follicular growth and development. This is by means of producing proteases like plasminogen-plasmin system, matrix metalloproteinases (MMPs) (collagenase, gelatinase and stromelysin) (Salamonsen, 1996) [89] and specific protease inhibitors, such as plasminogen activator inhibitor (Liu *et al*., 1991) [60], tissue inhibitors of metalloproteinases-l and -2 (Smith *et al*., 1999) [96] which are involved in the binding and the release of growth factors and act as key components of the intraovarian mechanisms controlling folliculogenesis and the development of the dominance mechanism.

Ovarian granulosa cells (GCs) play an important physiological role in supporting the development and selection of the dominant follicle by controlling oocyte maturation and by producing the steroid hormones, estrogen (E2) and progesterone (P4) that are critical for maintenance of the ovarian cycle. In turn, the mammalian ovarian follicular development is tightly regulated by crosstalk between cell death, survival and differentiation signals (Chowdhary *et al*., 2012) [24].

Follicular development in buffaloes occurs in wave like pattern with two waves (Baruselli *et al*., 1997) [7] or three waves (Barkaw *et al*., 2009) [6] as the most common pattern and reflects a genetic and/ environmental influence (Murphy *et al*., 1991) [65]. Follicular size and circulating concentration of estrogen were found to play an important role in controlling follicular development and in determining the number of waves in the estrus cycle. When both are attained (follicular size of > 10mm and estradiol concentration > 5.0 pg/ ml) after the emergence of the 2nd wave, the cycle will be 2 wave cycle, and when not attained the cycle continues to be 3 wave cycle (Nosier, 2003) [73]. During the reproductive season, the number of waves in an estrus cycle in buffaloes is found to be associated with the luteal phase and with estrous cycle length (Baruselli *et al*., 1997) [7].

In the follicle, an oocyte and surrounding granulosa cells communicate by means of the oocyte-derived factors, growth differentiation factor 9(GDF9), and bone morphogenetic protein15 (BMP15), which ensures the coordinated oocyte growth and follicular development. Granulosa cells supply nutrients and metabolites through gap junctions to oocytes and secrete paracrine signals to regulate oocytes. Oocytes in turn regulate granulosa cell proliferation and differentiation and induce antrum formation via GDF9 and BMP15. The oocyte-derived factors also were found affect cAMP and cGMP production in granulosa cells which will inturn induce GDF9 and BMP15 synthesis by the oocytes (Alam and Miyano, 2019) [3].

In the gonadotrophin dependent phase, oocyte and granulosa cells produce a variety of growth factors (GFs) that act broadly to influence gonadotropin action in positive and negative ways (Erickson and Shimasaki, 2001) [34]. The activation of WNT/CTNNB1/ β-catenin signaling pathway by R-spondin2 (RSPO2) whose expression is restricted to the oocyte of developing follicles has been found to be essential for oocyte-granulosa cell interactions that drive maturation of the ovarian follicles. RSPO2 also acts in a paracrine manner to sustain granulosa cell proliferation in early developing follicles (Cian *et al*., 2020) [26].

Mammalian target of rapamycin (mTOR) is an integrator of pathways important for cellular metabolism, proliferation, and differentiation, is expressed at all stages of oocyte development and is also essential for cyclic recruitment by linking extra- and intracellular cues from nutrients, stress, growth factors, and hormones. MTOR-dependent pathways in primordial or growing oocytes were found to differentially affect downstream processes including follicular development, sex-specific identity of early granulosa cells, maintenance of oocyte genome integrity, oocyte gene expression, meiosis, and preimplantation developmental competence. This is possible by controlling the expression of genes, Gja4 and Oosp1, -2, -3 (involved in oocyte–granulosa communication), Aldh1a2 (essential for development and survival of oocytes), Ythdf2 and Lsm1 (implicated in the control of oocyte maturation processes (Guo *et al*., 2018) [38].

Hence, folliculogenesis is a complex and dynamic ovarian process involving multiple ovarian and endocrine cells and

numerous signals (Jones and Shikanov, 2019) [51]. Both primordial follicle assembly and the ability to remain quiescent are vulnerable to errors in development and environmental insult (Hannon and Curry, 2018) [40].

Estrogen disrupting chemicals (EDCs) (Chen *et al*., 2007) [25], bisphenol A (BPA) (Zhang *et al*., 2012; Hunt *et al*., 2012) [111, 45] were found to disrupt various aspects of early primordial follicle development. Embryonic exposure to the phytoestrogen genistein was also found to disrupt primordial follicle assembly (Jefferson *et al*., 2006; Cimafranca *et al*., 2010; Patel *et al*., 2017) [50, 27, 77]. Also, the prenatal exposure to plasticizers like phthalates were also found to have effects on female reproduction (Zhou *et al*., 2017) [112]. Embryonic exposure of the herbicide atrazine resulted in the early demise of the primordial follicle pool (Gely-Pernot *et al*., 2017) [36].

The reproductive potential of a female buffalo thus is dependent upon the population of properly developed primordial follicles during fetal ovarian development. During folliculogenesis, only less than 1% of ovarian follicles which are present at birth will gain the capacity to ovulate. Oocytes and granulosa cells generally undergo apoptosis during fetal life and adult life respectively. The equilibrium between the prosurvival molecules (Bcl-2, Bcl-x, TRAIL, TVB) and the pro-apoptotic molecules (Bax, Bok, Bad, and Bak) contributes to the regulation of the apoptosis. Follicular atresia is mediated by apoptosis, which initially starts in the GCs layer (Bettegowda *et al*., 2008; Dhali *et al*., 2017) [11, 30], followed by apoptosis of the theca cells (Uri-Belapolsky *et al*., 2014) [104].

Ovarian follicular atresia is induced by activation of both the extrinsic (death receptor) and intrinsic (mitochondrial) pathways in GCs (Uri-Belapolsky *et al*., 2014) [104]. Stem cell factor ligand and c-KIT receptors, Kit and Mgf gene encode KIT receptor and ligand respectively. KIT–KIT ligand interaction has been found to have pro-survival effects in the oocytes, primordial, primary and antral follicles.

Apoptosis is central to many aspects of the ovary (Zhang *et al*., 2014; Jones and Pepling, 2013) [110, 52]. It is carried out by several molecular pathways, of which Bcl-2 family, TNF, caspases and TGF-β proteins appear to be the major players. The molecules involved in these pathways can be categorized into four classes: (i) molecules involved in the follicular survival, including Bcl-2, TGF-b, c-Kit, NOBOX, NTS, survivin, XIAP, AHR, BMP, GATA-4, SCF, integrin and GnRH; (ii) molecules involved in the follicular atresia, including Fas, caspases, TNF, TVB, Par-4, p53, prohibitin, c-Myc, interferon and ET; (iii) molecules involved in follicular selection/loss, including Bcl-2, Bax, FSH, inhibin, Fas ligand and caspases; and (iv) molecules involved in luteogenesis, including Fas/Fas ligand, caspase 3, Bax, prohibitin, BMP ligands and receptors (BMPR receptors) and PGF2 (Hussein *et al*., 2005) [47]. Prohibitins also influence the action of various gene products function that act as a "molecular switch" by controlling cellular fate (favours survival of the GCs) and thereby determine the progress of follicular development by regulating the expression of anti-apoptotic genes (Bcl2, Bclxl) in ovarian preantral GCs (Chowdhury *et al*., 2012) [24]. Factors like AMH, BMP-15, GDF-9 have major regulatory roles during both the gonadotrophin-independent and dependent stages of follicle development.

A very recent study conducted by Capra *et al* (2020) [18] to understand the changes in the oocyte molecular status in relation to season in buffalo clearly revealed the influence of season on oocyte competence and in turn transcription of genes in the oocyte related to folliculogenesis. The study of microRNA (miRNA) and transcriptomic profiles of oocytes (OOs) and corresponding follicular cells (FCs) from buffalo ovaries collected in the breeding (BS) and non-breeding (NBS) seasons revealed differential expression (DE) of 13 miRNAs, 2 mRNAs and 22 genes in FCs. DE- miRNAs in the two seasons for both OOs and FCs are found to be involved in follicular maturation and development regulation. Seasonal changes modified the expression of miR-143, miR-25, miR-222 and miR-199a in buffalo OOs. DE-miRNAs target gene analysis uncovered pathways associated with transforming growth factor β (TGFβ) and circadian clock photoperiod. Co-expression analysis of miRNAs and mRNAs revealed a positive correlation between miR-296-3p and genes related to metabolism and hormone regulation. Gene Ontology (GO) analysis of miRNA target genes and differentially expressed genes (DEGs) in OOs highlighted pathways related to triglyceride and sterol biosynthesis and storage crucial for folliculogenesis and acquisition of oocyte competence. The decreased oocyte competence in the NBS was in turn found to be associated with the change in the expression of secreted phosphoprotein 1 (SPP1), RUNX family transcription factor 2 (RUNX2) and Cathepsin K (CTSK) (Munakata *et al*., 2016; Sugimura *et al*., 2017; Papamentzelopoulou *et al*., 2012; Boone *et al*., 1997) [64, 101, 75, 12] decreased expression of heat shock protein family A (Hsp70) member 1A (HSPA1A) (Palumbo and Yeh, 1994) [74] (related to oocyte survival and apoptosis), down regulation of interleukin-1 beta (IL-1β) (involved in ovulation-associated events such as prostaglandin production and steroidogenesis) (Tilly *et al*., 1991; Caillaud *et al*., 2005; Lima *et al*., 2018; Dang *et al*., 2017) [103, 15, 58, 28] in the oocytes and also downregulation of genes related to gonadotropic hormone synthesis and metabolism. Apolipoprotein E (APOE) is found to be expressed in cultured ovarian granulosa cells, and is also present in human follicular fluid where the relative levels are correlated with serum E_2 concentration (Brown *et al*., 1989) [13] indicating the molecules associated with signalling pathways for the production of E_2 and also the influence of season on miRNA and transcriptomic profile of oocytes and follicular cells in buffalo.

Factors affecting estrus in buffaloes

The estrus behaviour in buffaloes is found to vary with the breed (Purohit and Rao, 2018) [79], external factors like temperature and humidity (Dash *et al*., 2016; Tailor and Nagda, 2005) [29, 102], season and length of the day (Hozyen *et al*., 2016; Hassan *et al*., 2007) [44, 41], body condition score (BCS) (Anitha *et al*., 2011) [4], management factors like nutrition (Vale, 2007) [106] and housing system (Sharma *et al*., 2010) [92], age and body weight (Qureshi, 2009) [80], conditions like post-partum anestrus (Arya and Madan, 2001; Singh and Brar, 2008) [5, 95] and genetic makeup of the animal (Imran *et al*., 2018) [49].

Conclusions

The process of development of dominant ovarian follicle is dependent and controlled by the oocyte and oocyte in turn acquires developmental competence during its growth within the follicle. And this bidirectional communication ensures that the cyclicity of the estrus is maintained. The cyclicity of estrus and the associated estrus behaviour may be controlled by the molecular/ signalling pathways associated with folliculogenesis. The estrus behaviour of an individual can

again be a determinant of genetic makeup of an individual animal controlled by exogenous factors like climate, photoperiod, nutrition and environmental insults. Hence, studies on molecular pathways associated with folliculogenesis in the context of estrus behaviour in buffaloes considering the factors affecting the estrus cycle may help in identifying reproductive biomarkers and thereby improving the reproductive efficiency in buffaloes.

Table 1: Intrinsic ovarian factors involved in the pre antral follicle development (Modified from Gura and Freiman, 2018)

Factor	Source	Action
Activins	Granulosa cells	Stimulate granulosa cell proliferation
AMH	Granulosa cells	Inhibitory factor on small follicle development
BMP15	Oocyte	Stimulate granulosa cell proliferation
BMP4/7	Theca cells	Modulate FSH signaling to increase estradiol levels, prevent premature luteinization
Connexins 37 and 43	Granulosa cells and granulosa-oocyte junction	Communication between granulosa cells to granulosa cells and oocyte to granulosa cells. Knockouts have inhibited development beyond primary stage
Cyclin D2	Granulosa cells	FSH stimulated factor that controls granulosa cell proliferation
GDF9	Oocyte	Theca cell recruitment. Knockouts have inhibited development beyond primary stage
Hedgehog signaling members	Granulosa cells and theca cells	Proper theca cell function
IGF1/IGFR	Granulosa cells	Enhance granulosa cell responsivness to FSH
KGF	Theca cells	Modulating communication between theca cells and granulosa cells
Kit/kit ligand	Granulosa cells and oocyte	Continued follicle development, oocyte growth, and theca cell organization
NTF5/BDNF/NTRK2	Granulosa cells and oocyte	Knockouts have impaired development beyond primary stage
WT1	Granulosa cells	Inhibitory factor on small follicle development

IGFI, insulin-like growth factor 1; IGFR, insulin-like growth factor receptor; NTF5, neurotrophin 5; BDNF, brain-derived neurotrophic factor; NTRK2, neurotrophic tyrosine kinase receptor type 2; WT1, Wilms tumor 1.

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