



Role of certain growth factors and hormones in folliculogenesis

SURESH DINKAR KHARCHE¹, DAYANIDHI JENA², CHETNA GANGWAR³, AMIT KHATTI⁴ and
B BALAMURUGAN⁵

ICAR-Central Institute for Research on Goats, Makhdoom, Uttar Pradesh 281 122 India

Received: 22 January 2019; Accepted: 9 April 2019

ABSTRACT

Folliculogenesis is an inextricable process associated with female fertility and infertility cases. This process involves many events at cellular and molecular level in a highly orchestrated fashion which culminates with ovulation. Various factors like hormonal factors, growth factors, role of ovarian micro environment, diseases of reproductive tract etc. influence the process of folliculogenesis in systematic manner. The function and mechano-biology of these growth factors and hormones have been studied by many researchers. This review discusses about those hormonal and growth factors which are involved in folliculogenesis process.

Key words: Estrus synchronization, Folliculogenesis, Growth factors, Hormones, Superovulation

Folliculogenesis is one of the most fascinating physiological phenomena which involves the development of a pre-ovulatory size follicle from an activated primordial follicle following the growth and differentiation of oocyte and its surrounding granulosa cells. This follicular development is regulated by many intrinsic and extrinsic factors like increasing steroidogenesis in ovarian compartments, up and down regulation of certain genes, secretion of growth factors from ovarian compartment and so on (Kharche *et al.* 2008). In a broad sense this whole process can be categorised into two distinct stages, the gonadotropin-independent (preantral) and gonadotropin dependent (antral or Graafian) stage (Erickson 2000). The three phases of folliculogenesis are recruitment, selection and dominance. During this whole process, a follicle can be categorised into a primordial, primary, secondary and tertiary (antral) follicle based on the number and morphology of granulosa cell layers and size of the oocyte. It is well established that folliculogenesis and oogenesis are associated with many morphological, molecular, and metabolic changes within growing ovarian follicles and cumulus oocyte complexes from C-Kit and stem cell factor (McNatty *et al.* 2000, Park *et al.* 2005, Zama *et al.* 2005, Antosik *et al.* 2016) to uterine bacterial load (Sheldon *et al.* 2002). After the establishment of follicular wave theory,

many mysteries revolving around the folliculogenesis were unfolded. Simultaneously, it also squashed many earlier concepts regarding the folliculogenesis. The process of follicle selection, recruitment and finally ovulation from a single follicle in monovular species like cattle and buffalo from one follicle is slowly unfolding. The study on folliculogenesis helps to solve many issues regarding infertility, estrus synchronization, superovulation and IVF (Kharche *et al.* 1996, Driancourt 2001, Atanasov *et al.* 2015). The detailed study of folliculogenesis and its related events have been carried out in many species like cattle (Rawlings *et al.* 2003), buffalo (Azawi *et al.* 2009), goat (Rawlings *et al.* 2003) sheep (Evans 2003, Vinnoles *et al.* 2014) and pig (Antosik *et al.* 2016). It is now well established that the ovaries of these animals contain two different pools of follicles which ultimately decide the fate of the reproductive life of the animal. The two groups are the non-growing pool and the growing pool. The non-growing pool contains the primordial follicles, whereas the growing pool contains the primary, secondary and tertiary follicles (Wilhelm 2003). The primordial follicles from the non-growing pool enter into the growth phase throughout the reproductive life. They embark on a long journey from the arrested pool to growing pool to transform themselves into primary, secondary and tertiary follicles. The transformation of flattened pre-granulosa cells of the primordial cells to cuboidal cells triggers the much needed step to kick-start the development of the follicle. The development process involves increase in size of oocyte and transformation of surrounding squamous pre-granulosa cells to cuboidal cells.

Recruitment phase involves assignment of a rapidly growing cohort of follicles for the process that culminates

Present address: ¹Principal Scientist (kharche62@gmail.com), ³Scientist (chetnaom82@gmail.com), Animal Physiology and Reproduction Division, ^{2,4,5}PhD Scholar (krishna5dj@gmail.com, amitkhatti@gmail.com, balavet07@gmail.com), Division of Animal Reproduction, Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh.

with ovulation. Selection process is whereby one or more of the recruited follicles are selected to develop further. The dominance phase is the cornerstone of folliculogenesis which involves the dominance of one or few follicle(s), depending upon different species, from a cohort of follicles. Among the pool of follicles, the one which is destined to grow further and establish dominance over other follicles (Ireland and Roche 1987) occurs only after dominance and is established by the deviation process. In a nutshell, a follicle does not represent dominance over other follicles before the deviation process. The follicular dominance phase is where the follicles are functionally dominant and capable of ovulating after luteal regression while they are still growing (Wilhelm 2003). The beginning of deviation is manifested by continued growth rate of the future dominant follicle (DF) and a decrease in growth rate of the future largest subordinate follicle when the largest follicle is about 8.5 mm (Ginther 2016, Ginther *et al.* 2016).

Role of primordial follicle pool: The mammalian ovary has many functions to discharge starting from steroidogenesis, release of ova to maintenance of reproductive tract. All this happens in a well synchronised and coordinated manner involving neural, endocrinological and hormonal systems. In a nutshell, the functions of the mammalian ovary are integrated into the continuous repetitive process of follicular development, ovulation, CL formation, and regression (McGee and Hsueh 2000, Richards *et al.* 2002, Vanderhyden B 2002, Gougeon A 2004). Primordial follicles are first origin follicles among all follicles which are surrounded by layers of flattened pregranulosa cells arrested at the diplotene stage of meiosis I (Nilsson *et al.* 2007, Adhikari and Liu 2009). Their activation from resting stage 1 is inevitable for the process of folliculogenesis. The mechanisms underlying the activation of primordial follicles involve: (i) the PI3K signalling pathway in oocytes which communicates between the oocytes and the surrounding granulosa cells (also involves receptor protein tyrosine kinase (RPTK) Kit and its ligand, Kit ligand) (Driancourt *et al.* 2000, Liu *et al.* 2006, Adhikari and Liu 2009), (ii) regulation of Cdk-p27 complex (p27 inhibits the cell cycle and found in high amount in quiescent cells whereas Cdk complexes are thought to promote the transitions between the different phases of the cell cycle) (Kaldis 2007, Adhikari and Liu 2009) (iii) action of hormones, growth factors and cytokines like IGF, b-FGF and neurotrophins (Massague *et al.* 2000, Nilsson *et al.* 2001, Adhikari and Liu 2009).

Role of hormones and growth factors vis-à-vis folliculogenesis: Many earlier studies as well as recent advances discovered the very pertinent actions of specific hormones, growth factors and other active biomolecules role in the process of entire folliculogenesis. The five growth factors which are central to the folliculogenesis are growth differentiation factor-9 (GDF-9), bone morphogenetic protein-15 (BMP-15/GDF-9B), bone morphogenetic protein-6 (BMP-6), transforming growth factor-2-(TGF-2), and fibroblast growth factor-8 (FGF-8). It must be noted

that ovary is the only organ which expresses GDF-9 and BMP-15 (Erickson and Shimasaki 2001).

Role of hormonal factors

Action of FSH and LH: Gonadotrophins are fundamental to the mechanisms regulating follicle status and development (Vegetti and Alagna 2006). Follicles in the ovary are either quiescent or committed to one of two pathways: growth or atresia. The hormone that is primarily responsible for the onset of ovarian activity, and hence puberty, is luteinising hormone (LH). FSH is the cornerstone of the establishment of dominant follicle formation and physiology of granulosa cells. These two hormones play crucial role in the event of folliculogenesis. In domestic animals the secretion of FSH and LH is controlled by two functionally separate, but superimposable systems. These are the episodic/tonic system, which are responsible for the continuous basal secretion of gonadotrophins and stimulates the growth of both germinal and endocrine components of the ovary, and the surge system, which controls the short-lived massive secretion of gonadotrophins, particularly LH, responsible for ovulation (Jennifer *et al.* 2005). In granulosa cells, FSH has been shown to stimulate low-density lipoprotein receptors (LDLr) concentrations, P450_{scc} and P450_{arom} activity. During the follicular phase, LH increases the theca cell expression of LH receptors, steroid acute regulatory protein (StAR), P450_{scc}, 3 β -HSD-II and P450_{c17}, whereas FSH increases granulosa cell expression of aromatase and 17 β -HSD-I. As a consequence, LH stimulates progesterone secretion from luteal cells and androgen secretion from theca cells; whereas FSH stimulates progesterone and oestradiol secretion from granulosa cells (Palemo 2007). It also plays a key role in follicular fluid formation, cell proliferation, E2 production, and LH receptor expression. FSH also regulated the upregulation of LH receptors in granulosa cells. The expression of CYP19 mRNA, which is critical in the biosynthesis of estrogen, is stimulated by follicle stimulating hormone (FSH) in rats, humans and ruminants (Monga *et al.* 2011). Both FSH and estradiol are critical regulators of folliculogenesis. Thus, the growing follicle produces an increasing amount of 17 β -estradiol under the influence of FSH and growth factors.

Action of estrogen: Estrogen has a well-established role as a feed backregulator of gonadotrophins secretion but it also has an acknowledged pivotal role as an intra-follicular modulator. The principal estrogen is estradiol 17 β (E2), a product of androgen aromatisation which occurs in a cooperative process between theca cells and granulosa cells. Estrogen stimulates the proliferation of granulosa cells in follicles and serves to facilitate the actions of FSH and LH (Grzesiak *et al.* 2012). Estrogens act via specific receptors (ER α and ER β), which function as nuclear transcription factors. Within the ovary, there is a strong consensus that both ER α and ER β are expressed in granulosa cells of preantral and antral follicles. In a nutshell, there is an obligatory role for estrogen in follicle development with

the critical period evident prior to ovulation, but not including early follicle development up to the antral stage. Apart from that, it also plays facilitatory role of during preantral growth and differentiation phase (Drummond 2006, Ginther 2018).

Action of Androgen: It is a well-established fact that Androgens have significant role in male reproduction; however, its function in female reproduction is not explored much. Androgen receptors are expressed in many female tissues, including the reproductive organs. After the biosynthesis of androgens in theca cells, they are transported to granulosa cells where they are converted to most active form of estrogen, 17β -estradiol by aromatase. The converting p450 enzyme aromatase is induced by FSH (Simpson 2000). In theca cells, androstenedione is converted to testosterone by 17β hydroxysteroid dehydrogenase (17β -HSD), following conversion of testosterone to dihydrotestosterone (DHT) by 5α -reductase in granulosa cells (Kimura *et al.* 2007). The biological action of androgen in ovary is depicted in Fig 1.

Androgens involves in early stages of folliculogenesis, augments development of the pre-antral follicle. In exclusion to that, it also regulates the expression of granulosa FSH receptor, insulin-like growth factor(IGF-1) and IGF-1 receptor at the mRNA level.

Role of growth factors

Role of transforming growth factor β superfamily: The TGF- β superfamily is made up of a number of proteins with the potential to act as intra-ovarian regulators of ovarian function (Knight and Glistler 2006). TGF- β s are released from cells in a latent form that does not bind to the high affinity TGF- β receptor (Harpel *et al.* 1992) and the critical step in the regulation of TGF- β activity appears to

be its conversion into the active form. TGF- β s act synergistically with gonadotrophins to control the differentiation of follicular cells.

Growth factors like GDF-9, AMP-6, BMP-15 and IGF I (Selvaraju *et al.* 2001, Selvaraju *et al.* 2001a, Kharche *et al.* 2003) play critical roles in follicle development and female fertility. In the absence of GDF-9, folliculogenesis is blocked at the primary preantral stage resulting in infertility. GDF-9 stimulates the expression of hyaluronansynthase 2 (HAS2), cyclo-oxygenase 2 (COX-2), and steroid acute regulatory protein (StAR) which are essential for cumulus expansion and progesterone production (Erickson and Shimasaki 2001). These growth factors also have stimulatory effect on FSH. They also play pivotal roles in specifying ovulation rate and litter size in domestic animals. Recent studies have identified a number of mutations in these genes that cause increased fertility and infertility in heterozygous or homozygous ewes carrying the mutations, respectively. Genetic studies have identified causal point mutations in the GDF-9 and BMP-15 genes in sheep which resulted in large litters (Moore *et al.* 2004). Interestingly, heterozygous ewes with mutation in both BMP-15 and GDF-9 exhibit higher fertility as compare to those having mutation in only one of the genes (Liao *et al.* 2004).

Role of Vascular endothelial growth factors: Vascular endothelial growth factor (VEGF) or vascular permeability factor (VPF) is a member of cystine-knot growth factors responsible for signal transduction in the formation of blood vessels. They are important signalling proteins involved in both vasculogenesis (the de novo formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature). It plays critical role in restoring the oxygen supply to tissues when

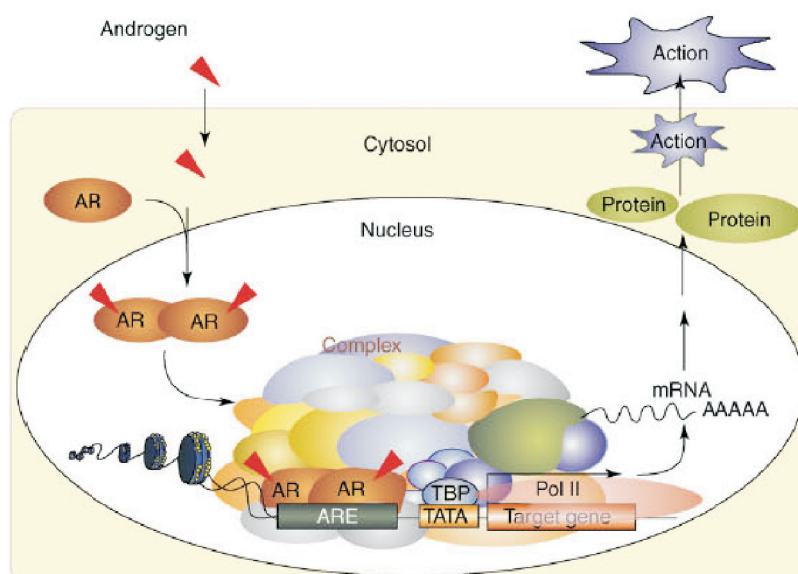


Fig. 1. Action of androgen in ovary. (AR, Androgen Receptor; TBP, TATA-box-binding protein; TATA, TATA box; Pol II, RNA polymerase II; Adapted from Kimura *et al.* 2007).

blood circulation is inadequate such as in hypoxic conditions (Palmer and Clegg 2014).

The functional role of vascular endothelial growth factor (VEGF) is imperative for follicular development owing to its significant role in angiogenesis. By this action it helps in the proliferation and survival of granulosa cells. The biological effects of VEGF are regulated by two membrane receptors, VEGFR1 and VEGFR2, and two soluble receptors, sVEGFR1 and sVEGFR2, which play an antagonistic role (Serrano *et al.* 2016). These 5 genes, i.e. VEGF, VEGFR1, VEGFR2, sVEGFR1 and sVEGFR2 expresses their action in granulosa cells and theca cells. The expression of VEGF is related to granulosa cells whereas theca cells express the receptors. The follicle meant to be dominant, reduces the mRNA expression of sVEGFR1 and sVEGFR2 (as they play antagonist role in development process), favouring VEGF binding with VEGFR2 and, hence, improve the follicular health and development.

Role of brain ribonuclease messenger RNA in granulosa cells of dominant follicle

Another protagonist player in the folliculogenesis is the Brain ribonuclease (BRB). It is a member of the Ribonuclease A superfamily having molecular weight of 10–28 kDa proteins. The angiogenin(RNase5) is a ribonucleaseA superfamily member and it has been found that it has potential linking with the morphologic changes and angiogenesis in the ovary. It is less expressed in the E2-active dominant follicles as compared to the E2-inactive subordinate follicles and is positively regulated by IGF1 (Kharche *et al.* 2003, Fortune *et al.* 2001), T4, and LH and negatively regulated by PGE2 and TNF-developing follicles (Martinez *et al.* 2018, Dentis *et al.* 2016).

Role of gene associated with the three stages of follicular growth

In ruminants the number of follicles recruited in a wave varies from species to species and selection of dominant

follicle occurs roughly 3 days after rise of FSH (Krishan *et al.* 2016). After that the FSH levels drop and subordinate follicles slow their growth and undergo atresia, while the dominant follicle enters a phase of LH-dependent growth. During all these critical period the developmental competence of the oocyte determines the fate of would be dominant follicle. All these events are governed by a number of genes, the expression of some are up-regulated and some are downregulated, to pave the way for growth and further development of dominant follicle (Fig 2).

Among all these, few genes which plays protagonist role in the growth and atresia phase are Angiopoietin 2(ANGPT2), Ankyrin (ANK3), CD36 and vnnin (VNN1) which continuously up-regulated from growing to plateau and atretic phase whereas budding uninhibited by benzimidazoles 1 (BUB1), cyclin B1 (CCNB1), cyclin dependent kinase regulatory subunit(CKS2) and pituitary tumor-transforming 1 (PTTG1) expressed more in growing phase but less in plateau and atretic phase signifying their role in growing phase. The other genes like tubulin beta 6 (TUBB6), tyrosine-protein kinase receptor (TYRO3) are downregulated during the dominance phase but up-regulated during the growing and atretic phase (Girard *et al.* 2015).

Application of complementary DNA microarray (DNA chip) technology for study of folliculogenesis: A number of methods have been applied to study folliculogenesis like reverse transcription–polymerase chain reaction (RT-PCR) but each carries its own disadvantage. However, recent advances in the field of molecular biology have given edge to study folliculogenesis. The DNA chip technology is one such method where folliculogenesis can be studied in a better way (Liu *et al.* 2001). Microarrays are simply a surface onto which DNA fragments, oligonucleotides, or other substrates are placed in a grid pattern so that each sample in the array has a specific coordinate. Both glass chips and nylon membranes have served as support surfaces enabling the hybridization of either DNA or cRNA probes to both qualitatively and quantitatively assess the DNA or RNA content of the sample. Using this technique, both determinations are possible (Reid *et al.* 2001). It provides a potential tool for study of complex phenomenon which is associated with gene expression in a wider range. It can be applied to study the mechanisms and regulation of folliculogenesis at the genetic level (Yoon *et al.* 2005, Liu *et al.* 2001). This oligonucleotide microarray-based (DNAchip) hybridization analysis allows rapid detection of gene expression profiles of hundreds to thousands of genes simultaneously.

Ovarian folliculo genesis has to pass through various physiological events like morphological, endocrinological, molecular and cellular to produce preovulatory follicle and culminating with ovulation. Although there are many factors which are responsible for these pathways have been well explained but there are many to be explored. With the advent of newer techniques the detailed architecture and

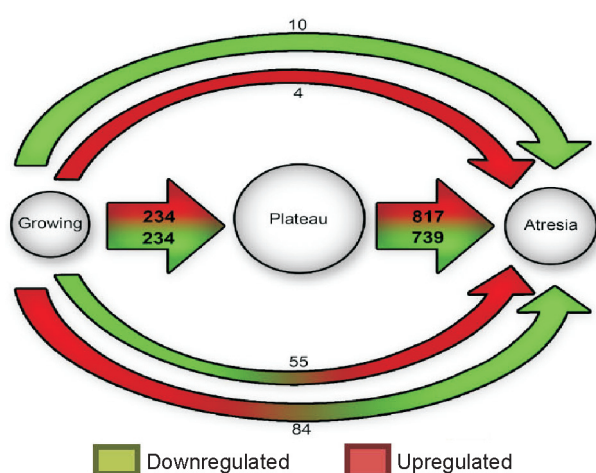


Fig. 2. The number of genes modulated between different growth stages (Girard *et al.* 2015).

programming of folliculogenesis can be studied at a more molecular level. The genetic pathways, the trophic factors involved during all these processes and their regulations at cellular and molecular level determine the microenvironment of folliculogenesis.

REFERENCES

- Adhikari D and Liu K. 2009. Molecular mechanisms underlying the activation of mammalian primordial follicles. *Endocrine Reviews* **30**(5): 438–64.
- Antosik Pawe, Jeseta Michal, Kranc Wiesawa, Chachua Adrian, Bryja Artur, Joanna Budna, Sylwia Ciesióka, Katarzyna Wojtanowicz-Markiewicz, Dorota Bukowska, Klaus-Peter Brüssow, Magorzata Bruska, Micha Nowicki, Pavlina Hulinska, Marie Machatkova and Bartosz Kempisty. 2016. Expression of integrins and GDF9 mRNAs is associated with ovarian follicle size and donor puberty status in pigs. *Medycyna Weterynaryjna* **72**(12): 750–54.
- Atanasov B, De Koster J, Bommelé L, Dovenski T and Opsomer G. 2015. Pathways of the dominant follicle after exposure to sub-luteal circulating progesterone concentrations are different in lactating dairy cows versus non-lactating heifers. *Animal Reproduction Science* **154**: 8–15.
- Azawi O I, Ali A J and Noaman U T. 2009. A study on the ovarian follicular dynamic in Iraqi Northern Buffaloes. *Tropical Animal Health Production* **41**: 79–83.
- Dentis J L, Schreiber N B, Gilliam J N, Schutz L F and Spicer L J. 2016. Changes in brain ribonuclease (BRB) messenger RNA in granulosa cells (GCs) of dominant vs subordinate ovarian follicles of cattle and the regulation of BRB gene expression in bovine GCs. *Domestic Animal Endocrinology* **55**: 32–40.
- Driancourt M A. 2001. Regulation of ovarian follicular dynamics in farm animals: implications for manipulation of reproduction. *Theriogenology* **55**: 1211–39.
- Driancourt M A, Reynaud K, Cortvrindt R and Smits J. 2000. Roles of KIT and KIT LIGAND in ovarian function. *Reviews of Reproduction* **5**: 143–52.
- Drummond A E. 2006. The role of steroids in follicular growth. *Reproduction Biology and Endocrinology* **4**: 16.
- Erickson G F and Shimasaki S. 2001. The physiology of folliculogenesis: the role of novel growth factors. *Fertility and Sterility* **76**(5): 943–349.
- Erickson G F. 2000. *The Graafian follicle: a functional definition* pp. 31–48. *Ovulation: evolving scientific and clinical concepts*. (Ed) Adashi E Y. New York: Springer-Verlaag.
- Evans A C O. 2003. Ovarian follicle growth and consequences for fertility in sheep. *Animal Reproduction Science* **78**: 289–306.
- Fortune J E, Rivera G M, Evans A C O and Turzillo A M. 2001. Differentiation of dominant versus subordinate follicles in cattle. *Biology of Reproduction* **65**: 648–54.
- Ginther O J, Baldrighi J M, Siddiqui M A R and Araujo E R. 2016. Complexities of follicle deviation during selection of a dominant follicle in *Bostaurus* heifers. *Theriogenology* **86**: 2012–19.
- Ginther O J. 2018. Variations in follicle-diameter deviation and a growth spurt in the dominant follicle at deviation in *Bos taurus* heifers. *Animal Reproduction Science* **188**: 155–64.
- Ginther O J. 2016. The theory of follicle selection in cattle. *Domestic Animal Endocrinology* **57**: 85–99.
- Girard A, Dufort I, Douville, G and Sirard M A. 2015. Global gene expression in granulosa cells of growing, plateau and atretic dominant follicles in cattle. *Reproductive Biology and Endocrinology* **13**: 17.
- Gougeon A. 2004. Dynamics for human follicular growth: morphologic, dynamic, and functional aspects, pp. 25–43. *The ovary*. 2nd ed. (Eds) Leung P C K and Adashi E Y. San Diego: Elsevier Academic Press.
- Grzesiak M, Knapczyk-Stwora K, Duda M and Slomczynska M. 2012. Elevated level of 17-estradiol is associated with overexpression of FSHR, CYP19A1, and CTNNB1 genes in porcine ovarian follicles after prenatal and neonatal flutamide exposure. *Theriogenology* **78**: 2050–60.
- Harpel J G, Metz C N, Kojimi S and Rifkin D. 1992. Control of transforming growth factor-b activity: Latency versus activation. *Progress in Growth Factor Research* **4**: 321–35.
- Ireland J J and Roche J F. 1987. Hypotheses regarding development of dominant follicles during the estrous cycle. (Eds) Roche J F and O'Callaghan D. *Follicular Growth and Ovulation Rate in Farm Animals*. Martinus Nijhoff Publishers, Dordrecht, p. 1.
- Jennifer L J, Heywood R S, Peter R S, Laurel D Q, Derek A H, Stan Lun, St. John Wakefield and Kenneth P M. 2005. Origins of follicular cells and ontogeny of steroidogenesis in ovine fetal ovaries. *Molecular and Cellular Endocrinology* **191**: 1–10.
- Kaldis P. 2007. Another piece of the p27 Kip1 puzzle. *Cell* **128**: 241–44.
- Kharche S D, Majumdar A C and Srivastava S K. 2003. Effect of insulin administration at oestrus on fertility of crossbred cattle. *Indian Journal of Animal Science* **73**(8): 888–89.
- Kharche S D, Majumdar A C and Srivastava S K. 2003a. Influence of exogenous insulin before breeding on conception rate in crossbred cattle. *Indian Journal of Animal Science* **73**(8): 890–91.
- Kharche S D, Majumdar A C, Agrawal S K and Sharma G Taru. 2008. Superovulatory response and embryo production efficiency in goats following pre-treatment with hCG and oestradiol-17 β . *Indian Journal of Animal Science* **78**(2): 150–53.
- Kharche S D, Sharma G T, Agarwal S K, Majumdar A C, Sanwal P C and Sharma N C. 2001. Pretreatment effect of human chorionic gonadotropin and estradiol-17 β on ovarian response, embryo quality and endocrine profile in cattle superovulated with FSH-P. *Indian Journal of Animal Science* **71**(7): 644–49.
- Kharche S D, Dutta T K, Dutt T, Ansari M R and Taneja V K. 1996. Effect of once or twice daily injection of FSH-P on superovulatory response, embryo recovery and their quality in crossbred cattle. *Indian Journal of Animal Science* **66**(4): 363–65.
- Kimura S, Matsumoto T, Matsuyama R, Shiina H, Sat T, Takeyama K and Kato S. 2007. Androgen receptor functions in folliculogenesis and its clinical implication in premature ovarian failure. *Trends in Endocrinology and Metabolism* **18**(5): 183–89.
- Knight Phil G and Glister Claire. 2006. TGF-b superfamily members and ovarian follicle development. *Reproduction* **132**: 191–206.
- Krishan J, Surbhi Agarwal, Juhipathak, Rakesh Kaushik, Mehtab S Parmar, Sriti Pandey, Mukesh K Bharti, Vikash Chandra, S K Jindal, S.D. Kharche, P K Rout G and Taru Sharma. 2016. Influence of follicular fluid and gonadotropin supplementation on the expression of germ cell marker genes during in-vitro maturation of caprine (*Capra hircus*) oocytes. *Small Ruminant Research* **144**: 41–47.

- Liao W X, Moore R K and Shimasaki S. 2004. Functional and molecular characterization of naturally occurring mutations in the oocyte-secreted factors bone morphogenetic protein-15 and growth and differentiation factor-9. *The Journal of Biological Chemistry* **279**(17): 17391–96.
- Liu Hung-Ching, Zhiming He and Rosenwaks Zev. 2001. Application of complementary DNA microarray (DNA chip) technology in the study of gene expression profiles during folliculogenesis. *Fertility and Sterility* **75**(5): 947–55.
- Liu K, Rajareddy S, Liu L, Jagarlamudi K, Boman K, Selstam G and Reddy P. 2006. Control of mammalian oocyte growth and early follicular development by the oocyte PI3 kinase pathway: new roles for an old timer. *Developmental Biology* **299**: 1–11.
- Martinez I Y H, Santos A P C, Bottino M P, Orlandi R E, Santos G, Simoes L M S, Souza J C, Díaz A M G, Binellie M and Sales J N S. 2018. Molecular and endocrine factors involved in future dominant follicle dynamics during the induction of luteolysis in *Bos indicus* cows. *Theriogenology* **111**: 78–83.
- Massague J and Chen Y G. 2000. Controlling TGF-signaling. *Genes and Development* **14**: 627–44.
- McGee E A and Hsueh A J. 2000. Initial and cyclic recruitment of ovarian follicles. *Endocrine Reviews* **21**: 200–14.
- McNatty K P, Fidler A E, Juengel J L, Quirke L D, Smith P R, Heath D A, Lundy T, Connell A O and Tisdall D J. 2000. Growth and paracrine factors regulating follicular formation and cellular function. *Molecular and Cellular Endocrinology* **163**: 11–20.
- Monga R, Ghai S, Datta T K and Singh D. 2011. Tissue-specific promoter methylation and histone modification regulate CYP19 gene expression during folliculogenesis and luteinisation in buffalo ovary. *General and Comparative Endocrinology* **173**: 205–15.
- Moore R K, Erickson G F and Shimasaki S. 2004. Are BMP-15 and GDF-9 primary determinants of ovulation quota in mammals? *Trends in Endocrinology and Metabolism* **15**(8): 356–61.
- Nilsson E, Parrott J A and Skinner M K. 2001 Basic fibroblast growth factor induces primordial follicle development and initiates folliculogenesis. *Molecular and Cellular Endocrinology* **175**: 123–30.
- Nilsson Eric, Rogers Natalie and Skinner M K. 2007. Actions of anti-Mullerian hormone on the ovarian Transcriptome to inhibit primordial to primary follicle transition. *Reproduction* **134**: 209–21.
- Palemo R. 2007. Differential action of FSH and LH during folliculogenesis. *Reproductive BioMedicine* **15**(3): 326–37.
- Palmer B F and Clegg D J. 2014. Oxygen sensing and metabolic homeostasis. *Molecular and Cellular Endocrinology* **397**: 51–57.
- Park Chang-Eun, Kwang-Yul Cha, Kyungjin Kim and Kyung-Ah Lee. 2005. Expression of cell cycle regulatory genes during primordial-primary follicle transition in the mouse ovary. *Fertility and Sterility* **83**(2): 410–18.
- Rawlings N C, Evans A C O, Honaramooz A and Bartlewski P M. 2003. Antral follicle growth and endocrine changes in pre-pubertal cattle, sheep and goats. *Animal Reproduction Science* **78**: 259–70.
- Reid R, Dix D J, David Miller and Stephen A. Krawetz. 2001. Recovering filter-based microarray data for pathways analysis using a multipoint alignment strategy. *BioTechniques* **30**(4): 762–67.
- Richards J S, Russell D L, Ochsner S, Hsieh M, Doyle K H, Falender A E, Lo Y K and Sharma S C. 2002. Novel signalling pathways that control ovarian follicular development, ovulation, and luteinization. *Recent Progress in Hormone Research* **57**: 195–220.
- Selvaraju S, Agarwal S K, Kharche S D, Majumdar A C and Shanker U. 2001. Ovarian response, embryo production and hormonal profile in superovulated goats treated with insulin. *Theriogenology* **59**: 1459–68.
- Selvaraju S, Agarwal S K, Kharche S D, Srivastava S K, Majumdar A C and Shanker U. 2001. Fertility response and hormonal profile in repeat breeding cows treated with insulin. *Animal Reproduction Science* **73**: 141–49.
- Serrano P V O, Guzmán A, Hernández-Coronado, C G, Castillo-Juárez, H and Rosales-Torres, A M. 2016. Reduction in the mRNA expression of sVEGFR1 and sVEGFR2 is associated with the selection of dominant follicle in cows. *Reproduction in Domestic Animals* **51**: 985–91.
- Sheldon I M, Noakes D E, Rycroft A N, Pfeiffer D U and H. Dobson. 2002. Influence of uterine bacterial contamination after parturition on ovarian dominant follicle selection and follicle growth and function in cattle. *Reproduction* **123**: 837–45.
- Simpson E R. 2000. Role of aromatase in sex steroid action. *Journal of Molecular Endocrinology* **25**: 149–56.
- Vanderhyden B. 2002. Molecular basis of ovarian development and function. *Frontiers in Bioscience* **7**: 2006–22.
- Vegetti W and Alagna F. 2006. FSH and folliculogenesis: from physiology to ovarian stimulation. *Reproductive BioMedicine* **12**(6): 684–94.
- Vinnoles C, Paganoni B L, McNatty K P, Heath D A, Thompson A N, Glover K M M, Milton J T B and Martin G B. 2014. Follicle development, endocrine profiles and ovulation rate in adult Merino ewes: effects of early nutrition (pre- and post-natal) and supplementation with lupin grain. *Reproduction* **147**: 101–10.
- Wilhelm K. 2003. Follicular dynamic and ovulation in cattle—a review. *Archives of Animal Breeding* **46**(2): 187–98.
- Yoon Se-Jin, Kyeoung-Hwa Kim, Hyung-Min Chung, Dong-Hee Choi, Woo-Sik Lee, Kwang-Yul Cha and Kyung-Ah Lee. 2005. Gene expression profiling of early follicular development in primordial, primary, and secondary follicles. *Fertility and Sterility* **85**(1): 193–203.
- Zama A M, Hudson III F P and Bedell M A. 2005. Analysis of hypomorphickitlsl mutants suggests different requirements for kitl in proliferation and migration of mouse primordial germ cells. *Biology of Reproduction* **73**: 639–47.