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ADVANCEMENT IN MOLECULAR GENETICS TO UNDERSTAND THE MOLECULAR REPRODUCTION OF LIVESTOCK - FOLLICULAR DEVELOPMENT

Md Mahmodul Hasan Sohel* and Mehmet Ulas Cinar

Department of Animal Science, Faculty of Agriculture, Erciyes University
38039 Kayseri, Turkiye

***Corresponding author:** Md Mahmodul Hasan Sohel, E-mail: sohel.mmh@gmail.com

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ABSTRACT

Follicular development in the mammalian ovary is a complex process which is potentially regulated by an orchestrated action of the pituitary gonadotropins, e.g., follicle stimulating hormone (FSH) and luteinizing hormone (LH), and local ovarian factors, such as peptide growth factors and steroids. Along with hormonal activation it is necessary to have tight coordination of expression of genes during follicular development. This review highlights the structure and function of ovary, follicle and follicular development. This review also confirms the temporal and spatial expression of the specific genes and miRNAs and their involvement in different modulators, the synthesis of active factors, their interactions, and the dynamics of their receptors on the follicular cell surface may be the ultimate determinants of cellular events which are crucial to coordinated growth and differentiation of follicular cells leading to folliculogenesis and ovulation.

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INTRODUCTION

Typically, the ovaries produce a single dominant follicle that results in a single ovulation each estrus cycle. In any given cycle, the dominant follicle must complete all the steps in follicular development in a timely manner. In this capacity, it survives the negative events that operate to destroy the other follicles by atresia. Recognition that only a few follicles become dominant beautifully demonstrates the fundamental principle that folliculogenesis in mammals is a highly selective process. In this review we will focus on what is known about the process underlying the expression of the structural and functional organization of developing follicles and how their growth and developments are controlled genetic materials.

The ovary

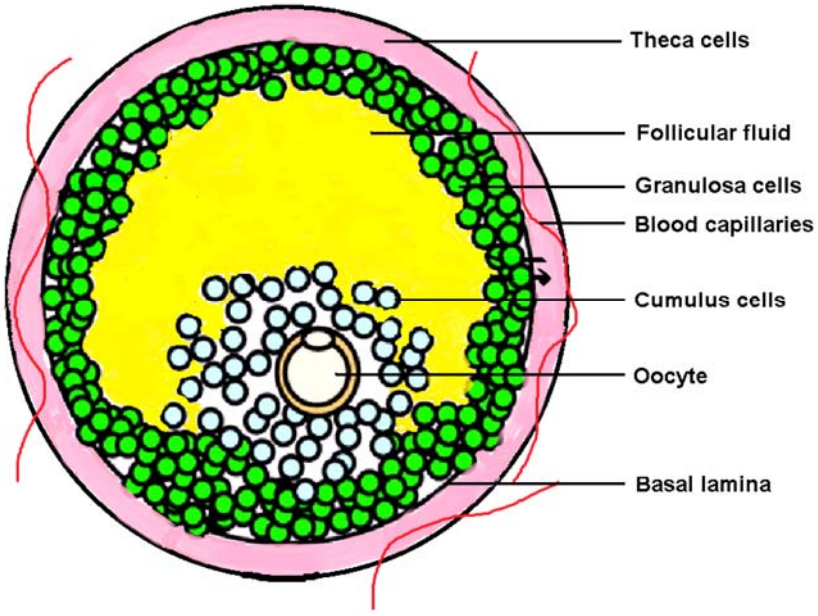
The ovary, the primary organ of female reproductive system, is the only source of female germ cells called oocyte which is pre-requisite for sexual reproduction. The ovarian follicle is the fundamental unit of the ovary which contains the oocyte that may eventually ovulate, undergo fertilization and sustain embryo development. It also provides the essential steroids and protein hormones which are crucial for maintenance of the ovarian cycle, follicular development, the secondary sex characteristics and preparation of the uterus for implantation, and after ovulation, the corpus luteum provides the hormones essential for establishment and maintenance of pregnancy (Pohler et al., 2012). Follicle formation and follicular development have been well documented for many mammalian species including cattle (Adams, 1999; van Wezel and Rodgers, 1996), sheep (Evans et al., 2000; Seekallu et al., 2010), pig (Schwarz et al., 2008) and human (Gougeon, 1996; van Dessel et al., 1996). However, the control of follicular reserves (Tilly and Rueda, 2008) and entry of follicles into the growth path towards atresia or ovulation (Findlay et al., 2002) are not well understood.

The follicle and its molecular structure

The adult ovary contains a reserve of inactive primordial follicles. Each contains a small non growing oocyte and a layer of non-dividing pre-granulosa cells encapsulated by the follicular basal lamina (Irving-Rodgers et al., 2009). Number of primordial follicles are selected and become active every day, and the oocyte commences growing while the granulosa cells start to divide. As the granulosa cells divide, the number of layers of cells (called the membrana granulosa or follicular epithelium) around the oocyte increases, and the follicular basal lamina expands (Cox, 1997). Later in development, a fluid filled cavity or antrum forms and specialized stromal layers, the theca interna and externa, develop. Only follicles that reach the stage of having a large antrum, and in the follicular wave following regression of corpora lutea, can ovulate an oocyte in response to the surge release of LH (Rodgers and Irving-Rodgers, 2010). Following ovulation, the granulosa cells and thecal cells differentiate into the large and small luteal cells of the corpus luteum, and the vascular supply of the corpus luteum is derived from the capillaries of the theca interna. All non-ovulating follicles undergo atresia and regression (Rodgers and Irving-Rodgers, 2010).

Ideally a fully grown follicle (graafian follicle) is a three-dimensional structure with an antrum in centre and surrounded by a variety of different cell types (**Figure 1**). There are at least six distinct histologic components in the mature follicle, including the theca externa, theca interna, basal lamina, granulosa cells, oocyte, and follicular fluid (O'Shea, 1981). Following paragraphs highlight the different components of a follicle and their functions. The remarkable characteristics of theca externa is the presence of smooth muscle cells (Amsterdam et al., 1977), which are innervated by autonomic nerves (Erickson et al., 1985). Although the physiologic significance of the theca externa remains unclear, there is evidence that it has certain function during ovulation and atresia (Moley and Schreiber, 1995). The theca interna is composed of differentiated TICs located within a matrix

of loose connective tissue and blood vessels. In all graafian follicle, LH is a key regulatory hormone for TIC function, and its importance in regulating TIC androgen production *in vivo* and *in vitro* has been established (Erickson et al., 1985). Beginning at the very early stages of graafian follicle development, the TICs express their differentiated state as androgen (*i.e.* androstenedione-producing cells) (Erickson et al., 1985). The theca interna is richly vascularized and serves to deliver hormones (*e.g.* FSH, LH), nutrient molecules, vitamins, and cofactors required for the growth and differentiation of the oocyte and granulosa cells. The theca compartments (*i.e.* theca externa and interna) express their differentiated functions at the beginning of graafian follicle development (at cavitation) and appear to constitutively express a mature phenotype throughout



the life and death of the graafian follicle.

Figure 1. Schematic presentation of a fully grown follicle indicating different components.

Basal lamina is a specialized extracellular matrix sheets that provide mechanical support and important signals for growth and differentiation to cells with which they are associated (Yurchenco and Schittny, 1990). It separates the granulosa cells from the surrounding stromal elements in primordial and pre-antral follicles, or from the specialized stromal theca layers in antral follicles (Irving-Rodgers and Rodgers, 2006). Basal laminas are generally observed as a single layer aligned to the cell surface. However, a number of physiological and pathological conditions lead to different morphological appearances of basal laminas (Irving-Rodgers et al., 2009). The follicular basal lamina is believed to play a role in influencing granulosa cell proliferation and differentiation (Irving-Rodgers and Rodgers, 2006). Additionally, it has been well documented that the components of basal lamina/basement membrane obtained from non-ovarian sources regulated the morphology and steroidogenesis in granulosa cells from rat and human ovaries (Furman et al., 1986).

In the antral follicle, granulosa cells represent the major category of follicular cells. The granulosa cells and oocyte exist as a mass of perfectly shaped and precisely positioned cells. The positional variation of granulosa cells creates at least four different cell layers or domains. These are the outermost domain is known as membrana granulosa, the inner most domain is the periantral, the intermediate domain is the cumulus oophorus, and the domain close together to the oocyte is the corona radiata (Amsterdam and Rotmensch, 1987). A characteristic histologic

property of the membrana domain is that it is composed of a pseudostratified epithelium of tall columnar granulosa cells, all of which are anchored to the basal lamina (Rodgers and Irving-Rodgers, 2010). The differentiation of a granulosa cell can be traced to its position within the cellular mass. For example, cells in the membrana domain stop proliferating before those in central domain (Hirshfield, 1989). The ability of the granulosa cells to continue dividing in the inner domains of a follicle throughout graafian follicle development leads to conclude that they might be precursor cells (Hirshfield, 1989). Cumulus oophorus may be defined as those granulose cells which are closely associated with oocyte (Tanghe et al., 2002). The fully developed cumulus oophorus perform three important biological functionsfirstly, before ovulation it supports during oocyte maturation (Tanghe et al., 2002), secondly during ovulation it conducts the oocyte in to the oviduct (Mahi-Brown and Yanagimachi, 1983) and finally shortly after ovulation it participate in the complex mechanisms that controlling the access of spermatozoa in to the oocyte (Tanghe et al., 2002).

In mammals, several studies have demonstrated that steroidal and nonsteroidal factors produced by granulosa and theca cells together influence proliferation and differentiation of both cell types on opposite sides of a basal membrane during folliculogenesis (Driancourt et al., 2000; Gougeon, 1996; Monget et al., 2002). During preantral follicle development, LH receptors are found exclusively on theca cells and FSH receptors exclusively on granulosa cells. It has been well documented that LH stimulates theca cell androgen and growth factor production, while FSH induces aromatase expression and increases the conversion of theca cell androgen to estrogen, which is commonly known as two-cell two-gonadotropin theory (Hillier et al., 1980). Androgens also enhance FSH action in the follicles by increasing FSH receptor expression, FSH-induced granulosa cell aromatase activity and proliferation, and follicular growth (Pakarainen et al., 2005).

Follicular development

In present most widely accepted hypothesis of follicular reserve is “at birth the ovaries of primates and most domesticated animal species contain a finite number of primordial follicles whereas in rodents this ovarian reserve develops in the first few days postpartum” (Fortune, 2003). In contrast, Johnaon *et al.* demonstrated the existence of mitotically active germ cells in juvenile and adult mouse ovaries, and claim stem cellbased renewal of follicle reserve in postnatal mammalian ovaries (Johnson et al., 2004). Although some studies reported the presence of mitotically active germ cells in ovaries of some species of prosimian primate adults (*Loris tardigradus lydekkerianus* and *Nycticebus coucang*) (David et al., 1974; Duke, 1967), to date the presence of germline stem cells in other mammalian species remains to be proven (Telfer, 2004).

Follicular development within the ovary is a dynamic process which occurs throughout the estrous cycle and involves recruitment of follicles into the growing pool, physiological and morphological changes in the follicular cells, physiologic selection of an ovulatory follicle and ovulation or regression (Araki et al., 1996). Since it is a continuous process, therefore throughout the reproductive life, the mammalian ovary contains a mixed population of follicles in different stages of development. There is a large pool of primordial follicles in the bovine ovary (~150,000) in a resting phase, some of them are released in each estrous cycle and this process continues throughout the reproductive life and the number of follicles decrease to about 3,000 by the age of 15-20 years (Hunter et al., 2004). Sequential recruitment, selection and growth of the follicles, atresia, ovulation and luteolysis these processes are repeated on a cyclical order within the ovary and resulting in the development of a number of ovulatory follicles (Hunter et al., 2004). All follicles start as a primordial follicle, among them some will eventually develop to the preovulatory stage. Morphologic studies of ovaries have shown that during ovarian follicular developmental process a primordial follicle continuously grow into primary follicles, preantral and antral follicles (van Wezel and Rodgers, 1996). Only antral follicles are capable of releasing oocytes at a stage when the

oocyte can be fertilized (Tomic et al., 2004). Thus, the continuous growth of primordial follicles to the antral stage is essential for female fertility. The development of a follicle begins with the transformation of the flattened pre-granulosa cells of the primordial follicle to cuboidal granulosa (follicular) cells, after which a follicle with a single layer of granulosa cells is termed a primary follicle (Eppig, 2001). The granulosa cells in primary follicles undergo continuous proliferation, the oocyte enlarges and becomes surrounded by a zona pellucida. Gradually the follicles changes to secondary follicles and, when fibroblast cells in the inner thecal layer differentiate, the secondary follicle is defined as a preantral follicle. The early growth phase of a follicle is considered to be independent of gonadotropin stimulation (Braw-Tal and Roth, 2005; Palma et al., 2012), nevertheless some studies has reported that the presence of FSH receptors in these immature follicles (Ranta et al., 1984). It is poorly understood, why a few primordial follicles start to grow and how they are selected, but paracrine factors within the ovary such as cytokines and epidermal growth factor has shown to be involved in this process. In the early luteal phase of each menstrual cycle, cohorts of preantral follicles undergo further growth into antral follicles (Nussey and Whitehead, 2001). At this time, the follicles enlarge, the thecal cells become richly supplied with blood vessels and a fluid-filled cavity (the antrum) forms (Fraser, 2006). The oocyte itself becomes surrounded by several layers of granulosa cells known as the cumulus oophorus (Khamsi, 2001).

In bovine and several other mammalian species, the pattern of follicular development during the terminal stages of folliculogenesis (follicles ≥4 mm) has been characterized as wave-like pattern that include 2 or 3 consecutive waves, which refers to the periodic and synchronous growth of a group of follicles (Adams, 1999; Hunter et al., 2004). The wave-like pattern of follicular development in heifers was first proposed more than 50 years ago by Rajakoski using the histological data of ovaries collected from different heifers on different days of the estrous cycle (RAJAKOSKI, 1960). However, the proposed wave-like developmental pattern of follicles was validated using ultrasonographic realtime follicular images, collected over a time-period on the same follicles from the same set of animals (Pierson and Ginther, 1986, 1984; Sirois and Fortune, 1988). During each wave of follicular growth, a group (normally 1 to 6) of follicles (primordial) 4 to 5 mm in diameter emerge and begin to grow, this phase is termed as recruitment. Initiation of each wave of follicular growth is preceded by a transient increase in FSH that begins about 2.5 day before initiation of the new wave of follicular growth and starts to decline about the time of appearance of the group of follicles in the wave. This subsequent decrease of circulating FSH is temporally associated with the selection of the dominant follicle (Adams, 1999).

The group of recruited follicles grow over the next 36 to 48 h, after which one follicle (8 to 9 mm in diameter) is selected (selection) for further growth to become larger than the others, where as others stop growing and undergo atresia (Adams et al. 1992). The selected follicle achieves dominance over the other follicles in the cohort, which regress while the dominant follicle continues to increase in size. During this stage of follicular development, granulosa cells of large healthy, estrogensecreting follicles also acquire LH receptors (Ireland and Roche, 1983). It has been shown that the granulosa cells of large healthy antral follicles possess more LH receptors than smaller atretic follicles (Ireland and Roche, 1983; Spicer et al., 1986) and the levels of mRNA for LH receptor in granulosa cells of a dominant follicles increase as follicular development advances. When the dominant follicle reaches its maximum size, it maintains that size for 3 to 6 day before regressing if the animal is in the luteal phase of the estrous cycle (Ginther et al., 1996). The fate of the dominant follicle that reaches maximum size during the luteal phase of the estrous cycle and of subordinate follicles that enter as cohorts during the initiation of each wave of follicular growth is atresia. If luteal regression occurs during the growing phase of the dominant follicle, the fate of dominant follicle follicle is ovulation (Kastelic et al., 1990).

Cell-cell communication during follicular development

Oocyte growth and follicular development occurs in an ovarian follicular microenvironment characterized by extensive cell-cell interaction mediated by gap junctional communication, as well as autocrine, paracrine and endocrine signaling. Gap junctions coupling between surface membranes of oocytes and their surrounding granulosa cells has been reported from the primordial stage in mice (Mitchell and Burghardt, 1986) and secondary follicle stage in cattle (Fair et al., 1997). Gap junctions are specialized structures occurring between very close cell-cell contact; facilitate the transfer of amino acids, glucose metabolites and nucleotides to the growing oocyte (Eppig, 1991). The proteins connexins is the principle component of gap junction. It has been demonstrated that connexins 32, 37, 43, 45 and 57 have been detected within growing and mature mouse follicles (Wright et al., 2001). However, in cattle, connexin expression shows in a stage specific manner; for instance, Cx26 is expressed in oocytes of primordial, primary and secondary follicles and in the granulosa of healthy antral follicles (Johnson et al., 1999). Furthermore, expression of Cx37 in preantral follicles is high, but expression decreases significantly at the onset of antral formation (Nuttinck et al., 2000). However, the reverse is true of Cx43, which is weakly expressed, in preantral follicles but increased significantly at the onset of antral cavity formation and become more intense with increase in follicular size in healthy antral follicle (Nuttinck et al., 2000). These collective data provides a plausible suggestion of differential regulation of Cx37 and Cx43 throughout folliculogenesis. Studies in mice (Wright et al., 2001), and pig (Itahana et al., 1996) indicating the expression of connexins is associated with granulosa cell proliferation. Connexin KO mice exhibit infertility due to failure of follicle growth past the late preantral stage. Furthermore, gonadotropin stimulation could not induce ovulation in these mice (Carabatsos et al., 2000). Studies has revealed that smaller gonads appear on Cx43 deficient mice in the neonates and impaired post natal folliclulogenesis; indicating the importance of requirement of Cx43 for both germ line development and early folliculogenesis (Juneja et al., 1999).

During follicular development, mesenchymal-derived thecal cells produce a number of growth factors that include KGF (keratinocyte growth factor) and HGF (hepatocyte growth factor) (Parrott and Skinner, 1998a). Both KGF and HGF are mesenchymalderived growth factors that act on adjacent epithelial cells in a number of tissues (Parrott and Skinner, 1998a). During follicular development gene expression of KGF and HGF is developmentally and hormonally regulated in thecal cells (Parrott and Skinner, 1998a, 1998b). Thecal cells have been shown to produce and secrete these growth factors (Parrott et al., 1994), furthermore, granulosa cells have also been shown to proliferate in response to KGF and HGF *in vitro* (Parrott et al., 1994). These observations strongly suggest that KGF and HGF may be important mediators of ovarian mesenchymal-epithelial cell interactions that promote folliculogenesis. Moreover, later investigations demonstrate that thecal cell-derived KGF and HGF also stimulate KL expression in granulosa cells (Parrott and Skinner, 1998a). The actions of KGF and HGF on granulosa cell KL expression indicate that these growth factors also alter cellular parameters other than cell growth (Parrott and Skinner 1998c). As granulosa cell-derived KL is important for oocyte maturation, thecal cells may indirectly regulate oocyte function by influencing granulosa cell production of KL (Parrott and Skinner, 1998a).

Several studies have demonstrated the importance of the gap junction network during oocyte growth, development and meiotic maturation (Simon et al., 1997; Vozzi et al., 2001). Denudation of preantral mouse oocytes prior to in vitro culture inhibits their growth, alone or in co-culture with granulosa cells (Eppig, 1979). In addition, the growth rate of oocyte is directly correlated to the number of granulosa cells coupled to the oocyte (Herlands and Schultz, 1984). It has been well documented that granulosa cells play a crucial role in oocyte development (Buccione et al., 1987), affecting the pattern of protein phosphorylation in oocytes in a stage specific manner (Cecconi et al., 1991). In mice, the network facilitates the transport of a paracrine factor which is commonly known as ‘Cumulus expansion enabling factor’ (Eppig et al., 1993). In addition, this paracrine factor appears to be essential for bringing about gonadotropin induced production of hyaluronic acid and

cumulus expansion just before ovulation (Salustri et al., 1990). Gene targeting ablation of Cx37 resulted in the removal of all gap junctions from the mouse oocyte surface and compromised oocyte meiotic maturation (Simon et al., 1997). Similarly, exposition of bovine COCs to gap junction uncoupling agents during routine in vitro maturation reversibly blocked the resumption of meiotic maturation and anti-sense silencing of Cx43 expression in COCs with a recombinant adenovirus resulted in the inhibition of GVBD in 50% of the COCs (Vozzi et al., 2001).

Recent studies suggested that cell secreted vesicles play an important role to perform cell to cell communication during follicular development (da Silveira et al., 2012; Sohel et al., 2013). These studies confirm that vesicles including microvesicels and exosomes are present in both equine and bovine follicular fluid and they may contain information that can be transported to recipient cells. Proteomics and real-time PCR expression analysis indicate that proteins and miRNAs are present within microvesicles and exosomes isolated from follicular fluid of equine. Moreover, the same miRNAs also are found to be present in surrounding follicular cells which actually indicating the origin of miRNAs in follicular fluid. Importantly, using both in vitro and in vivo approaches, it has been demonstrated that microvesicles isolated from ovarian follicular fluid could be taken up by surrounding granulosa cells (da Silveira et al., 2012). Using a similar approach we demonstrated that miRNAs are also present in not only exosome but also non exosomal fraction of follicular fluid of bovine. Moreover, we showed that these miRNAs have different expression pattern in follicular fractions (exosomal and non exosomal) based on their oocyte competency. Furthermore, using in vitro approach we demonstrated that these exosomes are taken up by the surrounding granulosa cells which increase the level of endogenous miRNA level and subsequent alteration of mRNA levels in follicular cells (Sohel et al., 2013).

Involvement of mRNAs in follicular development

Ovarian follicle development is a highly complex coordinated process that requires coordination among the hypothalamus, the anterior pituitary, and the ovary, as well as bidirectional communication between the different cellular compartments within the follicle itself (Albertini et al., 2001). Paracrine and autocrine signaling mechanisms, for instance members of the transforming growth factor β (TGFB) family, insulin-like growth factor (IGF), kit ligand, and anti-Mullerian hormone, derived from the follicular somatic cells and the oocyte, communicate bidirectionally between the cellular compartments and direct follicle development (Dong et al., 1996; Erickson and Shimasaki, 2000; Kreeger et al., 2005). Finally, oocyte-specific gene products such as the zona pellucida proteins, factor in the germline alpha, and NLRP5 (MATER) have different expression pattern throughout the development phase and impact follicle and oocyte maturation. Working together, genes from these diverse categories form a communication network that results in the growth and development of the follicle and the oocyte, and most importantly the formation of a healthy and fertilizable egg (Parrish et al., 2011).

Early follicular development requires the appropriate expression of many genes at different developmental stages. Recent studies on natural mutations in sheep and on mutant mouse models demonstrated that the expression of different oocyte-specific genes is essential during early follicular development in a stage specific expression pattern (Choi and Rajkovic, 2006). *Figla*, *Nobox*, *Pten*, *Foxo3A* and nerve growth factor genes are involved in the formation of primordial follicles, whereas genes such as *βFGF*, *GDF 9* and *BMP 4* are involved in the transition from primordial to primary follicles. Other genes such as *BMP15* are not expressed in the oocyte until the primary follicle stage and are involved in the transition from primary to secondary follicles, as shown in sheep (Monget et al., 2012). Although some large scale expression studies have been conducted on rodent and human oocytes (Grøndahl et al., 2013; Pangas et al., 2006; Yoon et al., 2006), expression profiling of different follicular components appeared very difficult due to the very small size of the follicles and the mixture of preantral stages in the ovary. Two studies, in particular,

identified the specific transcriptome of human oocytes in the quiescent state (Grøndahl et al., 2013; Markholt et al., 2012). These studies highlighted enriched functions (transcription, RNA post transcriptional modifications) and molecular mechanisms (cell cycle, androgen signaling) in human oocytes, which were also identified in the only preliminary analysis conducted in sheep species to date (Bonnet et al., 2013). Using a laser capture microdissection method combined with RNA-seq technology to explore the transcriptome in oocytes and granulosa cells (GCs) during development of the sheep ovarian follicle they first documented the expression profile of 15 349 genes, then focused on the 5 129 genes showing differential expression between oocytes and GCs. Enriched functional categories such as oocyte meiotic arrest and GC steroid synthesis reflect two distinct cell fates. It has been identified that the implication of GC signals transduction pathways such as SHH, WNT and RHO GTPase. In addition, signaling pathways (VEGF, NOTCH, IGF1, etc.) and GC transzonal projections suggest the existence of complex cell-cell interactions. Finally, they highlighted several transcription regulators and specifically expressed genes that likely play an important role in early folliculogenesis (Bonnet et al., 2013).

Sma-and Mad-related protein 4 (SMAD4) is the central mediator of the transforming growth factor beta signaling pathway and is closely related to mammalian reproductive ability and the development of ovarian follicles. Liu and his colleagues found that the porcine SMAD4 protein was expressed at high levels in GCs and oocytes from primary, preantral, and antral follicles, and only slightly expressed in theca cells; its expression level was down-regulated in apoptotic ovarian GCs, suggesting that SMAD4 may be involved in ovary development and selection (Liu et al., 2014). In another study, it has been documented that microarray analysis performed on GCs revealed that 450 and 111 genes were differentially expressed at 1 and 22 h post peak LH surge, respectively. Further, to understand the molecular functions and genetic networks, authors analyzed microarray data using Ingenuity Pathway Analysis and revealed majority of the differentially expressed genes to cluster within processes like steroidogenesis, cell survival and cell differentiation (Rao et al., 2011). Form these studies it is clearly evident that some mRNAs critically play an important role during follicular development.

Involvement of miRNAs in follicular development

The mammalian ovary is an extremely dynamic organ within which sequential waves of follicular growth and regression, rupture of mature follicles and the adjacent ovarian wall during ovulation, repair of the ovulation wound and the formation of fully functional corpora lutea followed by its demise a few days later occur within relatively short cycles and under tight transcriptional regulation throughout a female's reproductive life (Hawkins and Matzuk, 2010). Cyclic ovarian activity is key to reproductive success and the profound changes in tissue composition and function involved require exquisite spatio-temporal co-ordination of proliferation, apoptosis and differentiation of many different cell types within follicles (McBride et al., 2012). Recruitment of growing follicles, atresia, ovulation, and luteal tissue formation and regression are dynamically regulated events that regenerate on a cyclical basis in the ovary. These events involve dynamic changes in cellular growth, angiogenesis, steroidogenesis, cell cycle, and apoptosis and are accurately regulated at the endocrine and tissue levels (Carletti and Christenson, 2009). Deregulation in the regulatory network results in ovarian failure such as premature ovarian failure (POF) due to disruption of folliculogenesis, blockage of ovulation, and loss of oocytes *via* apoptosis (Yang et al., 2012). Small RNA populations have been identified by cloning-based or next-generation sequencing of normal ovarian tissues from human (Landgraf et al., 2007), cattle (Hossain et al., 2009; Huang et al., 2011; Tripurani et al., 2010), mice (Ahn et al., 2010; Mishima et al., 2008), pigs (Li et al., 2011), and sheep (McBride et al., 2012). Most of those studies involved analyses on whole ovaries rather than on specific ovarian tissue components, an approach that, although very useful for comprehensive identification of miRNA sequences, provides very limited

insight into their functional relevance (McBride et al., 2012). For many miRNAs, cloning frequencies changed across developmental stages, and some miRNAs were clearly expressed differentially between follicular and luteal stages, this data suggests the involvement of miRNAs in the follicular–luteal transition period (McBride et al., 2012). Several studies have been precisely examined the involvement of specific miRNAs in different aspects of follicle development. Dynamic changes in the levels of different miRNAs have been reported during follicle development in mice (Lei et al., 2010; Yao et al., 2009), pigs (Xu et al., 2011) and sheep (McBride et al., 2012) and also in response to stimulation of murine follicular cells with gonadotropins (Yin et al., 2012) or growth factors (Yao et al., 2010). Treatment of granulosa cells from mouse pre-antral follicles with TGFβ1 in culture resulted in the upregulation of three miRNAs and downregulation of 13 miRNAs (Yao et al., 2010). A subsequent study (Yin et al., 2012) showed that miR-383, a miRNA downregulated by TGFβ1, positively regulated aromatase expression and oestradiol production by mouse granulosa cells in culture. These observations, together with the finding that miR-383 levels increased *in vivo* during equine chorionic gonadotropin (eCG)-induced follicle growth and decreased following administration of hCG, provide strong support for a role for miR-383 in physiologically regulating changes in oestradiol production during follicle development. Three recent *in vitro* studies have also proposed roles of miRNAs in regulating granulosa cell proliferation and apoptosis. First Yan *et al.* Reported attenuation of activin-induced proliferation of mouse granulosa cells by miR-145 targeting of both activin receptor 1B and cyclin D2 (Yin et al., 2012).

In another study, showed that miR-23a was pro-apoptotic in cultured human luteinised granulosa cells presumably by decreasing the levels of X-linked inhibitor of apoptosis protein (XIAP) and increasing caspase-3 cleavage, although it was not clarified whether these were actually direct targets of miR-23a in granulosa cells (Yang et al., 2012). Using a microarray approach in porcine ovarian follicles, another study demonstrated that miR-26b expression increased during follicular atresia and further showed that this miRNA could induce granulosa cell death by directly targeting ataxia telangiectasia mutated (ATM), a gene involved in DNA repair (Liu et al., 2014). Overall, these studies illustrate how a key follicular function, oestradiol production, can be distinctly regulated, directly or indirectly, by different miRNAs.

CONCLUSION

Although the full extent to which mRNAs and miRNAs are involved in mammalian ovarian function remains unknown, important steps are being made to understand how miRNAs regulate follicular and luteal development. Studies have already identified genome-wide mRNA and miRNA populations putatively involved in follicular atresia, ovulation and the follicular– luteal transition. Further, despite generic challenges in identifying physiologically relevant roles of miRNAs in animal tissues, miRNA regulation of aromatase expression has already been described with some detail, and progress is also being made in other aspect to understand the mechanism and involvement of mRNA and miRNA in follicular development.

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