



REVIEW [REVISIÓN]

FOLLICULAR DEVELOPMENT IN DOMESTIC RUMINANTS
[DESARROLLO FOLICULAR EN RUMIANTES DOMÉSTICOS]

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SUMMARY

Knowledge on the physiological processes that control follicular development may allow for the development of strategies to increase reproductive efficiency in domestic ruminants. Follicle development depends on the balance between survival factors, proliferation and cell death, which determine whether the follicle starts and continues to grow or is removed from the ovary. During fetal development of the female, primordial germinal cells proliferate by mitosis to reach the gonadal ridge, where the oogonia are surrounded by flattened cells to assemble the primordial follicles. Kit ligand, BMP-15 and GDF-9 stimulates a group of primordial follicles to begin their growth until they reach preantral development. The growth to the antral stage seems to be independent of gonadotrophins and promoted by growth factors. In gonadotrophin suppressed animals follicles will grow up to a diameter of 2 mm in sheep and 4mm in cattle. The cyclic secretion of FSH and LH promotes the recruitment and growth to the large antral stage and the eventual ovulation if luteolysis occurs. Follicular development in cows, sheep and goats during the estrous cycle occurs in a pattern like-wave, where groups of follicles begin their growth in response to an increase of FSH, but only some (sheep and goats) or one (cows) is selected as the dominant, and ovulates if its dominance coincides with the lysis of the CL and the reduction of progesterone. Among the factors that determine whether a large antral follicle starts, continues and completes its development are its responsiveness to gonadotrophins, its steroidogenic capability and the presence of survival and proliferating factors such as IGF-I and VEGF.

Key words: cell death factors, domestic ruminants, follicular development, survival and proliferation factors.

RESUMEN

El conocimiento de los procesos fisiológicos que controlan el desarrollo folicular puede permitir desarrollar estrategias para incrementar la eficiencia reproductiva en rumiantes domésticos. El desarrollo del folículo depende del balance entre factores de sobrevivencia, proliferación y muerte celular, los cuales determinan si el folículo inicia y continúa su crecimiento o es eliminado del ovario. Durante el desarrollo embrionario y fetal de la hembra las células germinales primordiales proliferan por mitosis hasta alcanzar la cresta gonadal, donde la ovogonia es rodeada por células aplanadas para ensamblar a los folículos primordiales. El ligando de Kit, BMP-15 y GDF-9 estimulan a grupos de folículos primordiales para que inician su crecimiento hasta alcanzar el desarrollo preantral grande. El crecimiento hasta la etapa antral parece ser independiente de gonadotropinas y promovida por factores de crecimiento. En ovinos y bovinos cuya secreción de gonadotropinas está suprimida experimentalmente, los folículos antrales alcanzan hasta 2 y 4 mm respectivamente. La secreción cíclica de FSH y LH promueve el reclutamiento y permite que subgrupos de folículos antrales grandes continúen su crecimiento y probablemente ovulen, si coinciden con la luteolisis. El desarrollo folicular en vacas, borregas y cabras durante el ciclo estral, se da en un patrón de olas foliculares en las que grupos de folículos inician su crecimiento en respuesta a la elevación de FSH, pero solo algunos (borregas y cabras) o uno (vacas) será seleccionado como dominante y ovulara si su dominancia coincide con la lisis del CL y la reducción de progesterona. Dentro de los factores que determinan si un folículo antral pequeño inicia, continua y termina su desarrollo destacan, su capacidad de respuesta a gonadotropinas, su capacidad esteroidogénica y la presencia de factores de

sobrevivencia y proliferación celular tales como IGF-I y VEGF.

INTRODUCTION

Follicular development can be divided into two phases: an gonadotropin independent (FSH and LH) phase, where the follicle grows from primordial to large antral follicle, and another phase FSH- and LH-dependent (Webb et al., 2004) where the follicle will reach the preovulatory status and if there is an adequate frequency and amplitude of LH pulses, will ovulate (Webb et al., 2004).

In domestic ruminants, the number of follicles ovulated during a female's reproductive life is minimal compared to the number of follicles she is born with (Aerts and Bols, 2010). Then, it seems that the main fate of the follicle, is not the ovulation but degeneration or atresia. This seems to follow a selection process to ensure ovulation of only those follicles with oocytes that optimize the fertilization odds (Hsueh et al., 1994).

This review focuses on the origin of primordial follicles, their morphological classification, the cellular mechanisms that determine the follicle fate and the characteristics of follicular development in domestic ruminants.

ORIGIN OF PRIMORDIAL FOLLICLES

The origin of oocytes and primordial follicles during early embryonic development has been extensively reviewed (Smitz and Cortvrindt, 2002; Skinner, 2005; Adams et al. 2008; Aerts and Bols, 2010). After fertilization, once the endoderm, mesoderm and ectoderm have been formed, a group of cells derived from the endoderm differentiate to give rise to primordial germinal cells (PGC) from which, in the case of a female embryo, oocytes will develop (Adams et al., 2008; Mollgard et al., 2010). Around day 30 of embryonic development in cattle (Aerts and Bols, 2010), day 28 in humans (Smitz and Cortvrindt, 2002) and day 22 in sheep (McNatty et al., 1995), the gonadal ridges develop to later be colonized by the PGC. By day 35 in cattle, day 41 in humans and day 23 in sheep, the PGC begin to migrate through the dorsal mesentery to the gonadal ridges (McNatty et al., 1995; Smitz and Cortvrindt, 2002; Aerts and Bols, 2010). During their journey, the PGC continue to multiply by mitosis (Aerts and Bols, 2010) to several thousand cells (Tam and Snow, 1981). When the PGC are internalized in the gonadal ridge, mitotic activity ceases and they become embedded in the germinal

Palabra clave: Desarrollo folicular, factores de sobrevivencia y proliferación células, factores de muerte celular, Rumiantes domésticos.

cords. From this stage forward, the PGC are called oogonia. The gonadal cords are composed of germinal epithelial cells, mesenchymal and basal lamina (Adams et al., 2008). The maximum number of PGC in humans by the fifth month of fetal life is approximately 7 million of which only 2 million will remain until birth (Pepling and Spradling, 2001); while in cattle, the maximum number of PGC is 2,100,000 which decreases to 130,000 at birth (Aert and Bols, 2010a). Meiosis of oogonia in cattle begins between 75 and 80 days of embryonic life and arrested in prophase I (diplotene). At this stage, the chromosome are de-condensed and surrounded by the nuclear membrane forming a germinal vesicle (Smitz and Cortvrindt, 2002). Until then, the oogonia are grouped into structures called nests or cysts of primordial cells (Figure 1) kept in contact through gap junctions (Pepling, 2006). Subsequently, the oocytes are separated from the nest and surrounded by a layer of flattened epithelial cells (pregranulosa cells) derived from the germinal cord. A basal lamina is deposited on the surface of the pregranulosa (Figure 1) to isolate the primordial follicle to the ovarian stroma (Adams et al., 2008; Aerts and Bols, 2010). In the ovaries of bovine embryos, primordial follicles can be detected at day 90 of gestation (Yang and Fortune, 2008), while in sheep, these type of follicles can be observed from day 75 of fetal life (McNatty et al., 1995).

MORPHOLOGICAL CLASSIFICATION OF THE FOLLICLES

The growth and development of primordial follicles to ovulatory follicles involves the differentiation and proliferation of follicular cells, as well as an increase in the oocyte diameter. Follicles have been classified based on morphological characteristics acquired during its development (Figure 2). It is worth noting that this classification system may vary according to species and authors (Braw-Tal and Yossefi, 1997; McNatty et al., 1999). In embryonic folliculogenesis, the primordial follicles constitute the oocyte which is surrounded by at least 10 flattened cells known as pregranulosa cells (Fair et al., 1997) and a basement membrane (Aerts and Bols, 2010). Depending on the degree of development, the primordial follicles are classified into primordial follicles surrounded only by flat pregranulosa cells and intermediate follicles which are surrounded by pregranulosa cells and some cubic granulosa cells (Gougeon and Busso, 2000). The differentiation of all pregranulosa to granulosa cells transform the primordial follicle into a primary

follicle, which is formed by the oocyte and 10 to 40 granulosa cells. In cattle, the diameter of the follicle and oocyte at this stage of development is 40 to 80 μm and $0.42 \pm 31.12 \mu\text{m}$ respectively (Braw-Tal and Yossefi, 1997). The proliferation of granulosa cells increases the number of layers (> 2) and cells (40-100) surrounding the oocyte to give rise to a secondary follicle (Fair, 2003) or small preantral follicle (Braw-Tal and Yossefi, 1997). At this stage of development, the zona pellucida has not developed and the theca interna cells begin to differentiate (Aerts and Bols, 2010). The secondary follicle continues to increase the number of granulosa cells and the deposit of the components that form the zona pellucida, as well as the total differentiation of the theca interna, forming large preantral follicles (Braw-Tal and Yossefi, 1997; Aerts and Bols, 2010). The theca cells differentiate from the interstitial stromal cells and appear as single cells on the basal lamina from the primary follicle (Hirshfield, 1991). The beginning of the formation of the antrum, the formation of the totality of the zona pellucida and the differentiation of the theca externa marks a tertiary follicle (Aerts and Bols, 2010). The tertiary follicles may be subdivided into small antral follicles which contain more than 6 layers and over 250 granulosa cells (Braw-Tal and Yossefi, 1997) or large antrals follicles that contain many layers of granulosa cells. During all of these stages of development, both the follicle and oocyte diameters increase (Figure 2). The large antral follicles, also known as de Graaf follicles, have a well-formed follicular antrum, as well as a group of granulosa cells (called cummulus cells) surrounding the oocyte (Aerts and Bols, 2010). The number of follicles reaching this developmental stage depends on the species, and the development of a large antral follicle to an ovulatory follicle will depend on the endocrine milieu in which antral follicles develop (Fortune et al., 2001).

DEVELOPMENT OF PRIMORDIAL AND EARLY ANTRAL FOLLICLES

The development of the primordial follicle to a preantral follicle basically involves cellular growth, proliferation and differentiation (Braw-Tal, 2002). Even when, the mechanisms that control the differentiation of pregranulosa to granulosa cells during activation of the primordial follicles and the subsequent proliferation of the granulosa are unknown, molecules like kit ligand (KL) and its receptor (c-Kit), Growth differentiation factor 9 (DGF-9) and bone morphogenetic protein 15 (BMP-15) are involved (Oktem and Oktay 2008; Fortune, 2003; Moniruzzaman and Miyano, 2010).

Kit Ligand (KL) and its receptor (c-Kit)

The KL or stem cell factor exists as both soluble (KL-1) and membrane-spanning proteins, which are synthesized from two alternatively spliced forms of the messenger RNA (Skinner, 2005; Hutt et al., 2006a). In mice, KL-1 is a 248 aa polypeptide that is initially anchored to the membrane, but due to enzymatic cleavage in the region coded by the exon 6 it releases a soluble polypeptide (AA 164-165) (Roskoski, 2005). The KL receptor is a type III tyrosine kinase receptor called c-Kit. This receptor has 5 extracellular immunoglobulin-like domains, of which 1 and 3 are the ligand binding sites, while 4 is the site of dimerization, moreover the receptor has a hydrophobic transmembranal domain and intracellular tyrosine kinase domains (Roskoski, 2005).

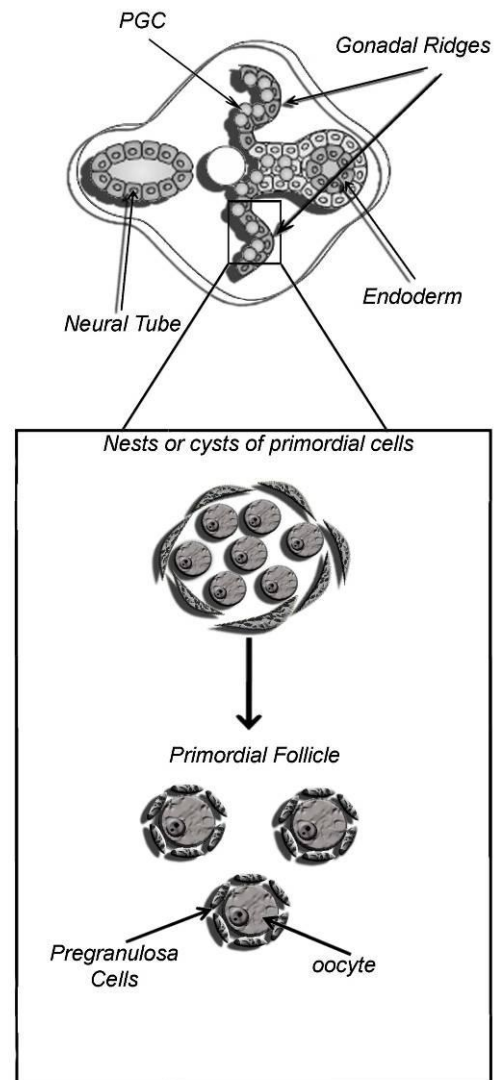


Figure 1. Origin of oocyte and primordial follicles during embryo development (adapted from Pepling, 2006)







	Follicle Type	No. of GC**	Diameter **	
			Follicle	Oocyte
	Primordial	<10 *	< 40 um	29.7 um
	Primary	From 10 to 40	40 to 80 um	31.1 um
	Small Preantral	40 to 100	81 to 130 um	49.5 um
	Large Preantral	101 to 250	131 to 250 um	68.6 um
	Small Antral	> 250	0.25 to 0.5 mm	92.9 um
	Large Antral		0.6 a 20 mm cows 0.5 a 9 mm sheep and goat	

Figure 2. Classifications of follicle type according to granulosa cell (GC) number and diameter of follicle and oocyte during follicular development (adapted from Braw-Tal and Yossefi 1997 and Aerts y Bols, 2011).

* Pregranulosa cells

** Values in cows

The KL protein and its mRNA are present in pregranulosa cells, whereas c-Kit is only found in the oocyte (Hutt et al., 2006a). This indicates that KL may regulate germinal cell survival. For instance in cultured rat ovaries, the addition of 100 ng/mL of KL into the culture medium reduces the percentage of apoptotic oocytes compared to the controls (Jin et al., 2005). In the same experiment, KL interacting with c-Kit activated the mitogen-activated protein kinase pathway (MAPK) and the phosphatidylinocytol-3-kinase (PI3K) pathways. The MAPK activation promotes the oocyte growth whereas the PI3K activation increases the expression of Bcl-2 and Bcl-xL lowering Bax expression to prevent oocyte apoptosis (Jin et al., 2005). Similar studies in rat ovarian cultures have shown that 50 to 150 ng/mL KL added to the culture medium increases the diameter of the oocyte but does not increase the diameter of primary follicles (Hutt et al., 2006b). Recent findings show that inactivation of the PI3K signaling pathway of KL reduces the survival of primordial follicles and causes an abnormal accumulation of ovarian follicles

arrested in the early stage of development (John et al., 2009). This evidence suggests that KL promotes the survival of the oocyte. However, the differentiation and proliferation of granulosa cells must be mediated by other factors since these cells do not express c-Kit.

GDF-9 and BMP-15

Growth differentiation factor 9 and BMP-15 are members of the transforming growth factor β (TGF- β) superfamily of proteins expressed by several cell types including the oocyte (Sun et al., 2010; Otsuka et al., 2011). Like most members of TGF- β , GDF-9 and BMP-15 are composed of two β subunits and a α -helix stabilized by disulfide bridges forming a cysteine knot-like structure (Laissue et al., 2008). Both GDF-9 and BMP-15 are synthesized as preproteins containing a signal peptide, a N-terminal domain and a mature carboxyl terminal. Bioactive molecules are released through post-transcriptional processes that consist in removing the signal peptide, dimerization and breaks in preserved dibasic proteolytic sites (Laissue et al., 2008). The GDF-9 and BMP-15 bind to its specific serine/threonine kinase type II receptors to form a complex with the type I receptor that catalyzes the phosphorylation of Smad transcription factors (Laissue et al., 2008; Sasseville et al., 2010; Sun et al., 2010).

As stated before, GDF-9 and BMP-15 are synthesized primarily in the oocyte and are implicated in controlling the proliferation and survival of granulosa cells (Su et al., 2009; Moniruzzaman and Miyano, 2010). Moniruzzaman and Miyano (2010) concluded that in mammals, GDF-9 and BMP-15 regulate follicular development from primary follicles, but are not involved in the activation of primordial follicles. These findings are supported in goat ovaries where the expression of BMP-15 is higher in secondary follicles than in primary or primordial follicles (Celestino et al., 2011). Seemingly, the addition of GDF-9 to goat ovarian tissue cultures decreased the population of primordial follicles and increased the number of intermediate and primary follicles (Martins et al., 2010), indicating that GDF-9 promotes both differentiation and proliferation of pregranulosa and granulosa cells.

Inhibitors of early follicular growth

In addition to the factors mentioned previously, the oocyte and the granulosa cells also produce proteins that inhibit follicular development. The Forkhead transcription factor 3a (FOXO3a) halts the transition from primordial to primary follicle in rodents (Reddy et al., 2005), by inhibiting cyclin-dependent kinases, thus decreasing proliferation (Kops et al., 2002) and stimulating apoptosis of the oocyte and follicular cells (Liu et al., 2009). FOXO3a is phosphorylated by KL

(Liu et al., 2009) and testosterone (Yang et al., 2010) inactivating the protein and preventing cell apoptosis allowing the transition from primary to secondary follicle. The anti-Müllerian hormone (AMH), synthesized by granulosa cells (Sadeu et al., 2008), is another member of the TGF- β family known to inhibit the development of primordial follicles (Moniruzzaman and Miyano, 2010): for example, in rat ovarian cultures, the addition of AMH reduces the transition from primordial to primary follicles even in the presence of KL (Nilsson et al., 2007).

Thus the follicle fate is marked by the balance of inhibitor and promoter factors. Kit-ligand, GDF-15 and BMP-9 stimulate primordial follicle growth and development up to the preantral stage, while the increased expression of FOXO3a and AMH induces oocyte apoptosis and follicle atresia (Figure 3).

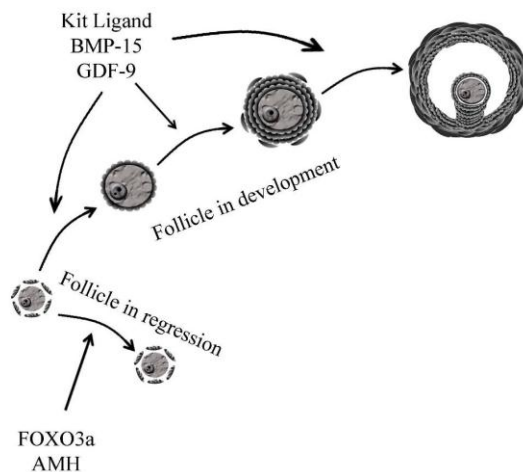


Figure 3. Molecules involved in activation, development or regression of preantral follicle (adapted from Moniruzzaman and Miyano, 2010)

FINAL DEVELOPMENT OF ANTRAL FOLLICLES

The final development of large antral follicles occurs in a wavelike pattern, where a cohort of follicles of similar size, continue their growth in response to an increase in FSH (Ginther et al., 1989; Rathbone et al., 2001). In cattle, each wave of follicular growth lasts between 7 to 9 days (Mihm et al., 2000), during which there is a transient peak of FSH, a selection phase that results in reducing the number of growing follicles and a decline in the concentration of circulating FSH. This coincide with the onset of atresia of most follicles (subordinate follicles), however, follicle with diameters equal to or larger than 8 mm may remain dominant (Mihm et al., 2000) and ovulate if animal hormonal milieu is adequate. If the dominant follicle coincides with the lysis of the CL and the subsequent

fall of P_4 , the inhibitory effect exerted by P_4 on GnRH is eliminated and an LH preovulatory peak is reached, which leads to the ovulation of the follicle (Fortune et al., 2001).

In order to better understand the mechanisms that control the final development of antral follicles, its process has been divided into three phases: cyclical recruitment, selection and dominance.

Cyclic recruitment

Cyclic recruitment refers to the initiation of the growth of a group of large antral follicles in response to increasing FSH concentrations (McGee and Hsueh, 2000; Webb et al., 2003). Each wave of follicular growth is preceded by a transient peak of FSH that lasts 1 to 2 days (Adams, 1999, Mihm et al., 2000) and if this peak is experimentally blocked, the wave of growth does not occur or is delayed (Quirk et al., 2004). However, only few follicles respond to the FSH surge. It has been reported that the expression of mRNA for gonadotropin receptors, cytochrome P450 17 α hydroxylase (P_{450c17}) and 3 β hydroxysteroid dehydrogenase (3 β -HSD) is not different between recruited and not recruited follicles. In contrast, the expression of P_{450scc} (side-chain cleavage) enzyme complex and $P_{450arom}$ (aromatase) is higher in recruited than undrafted follicles (Bao and Garverick, 1998; Webb et al., 1999). This suggests that the ability of a follicle to produce E_2 determines its capacity to respond to the FSH surge during recruited.

Selection

Follicular selection is the process by which one or more recruited follicles are selected to continue its growth in each wave (Webb et al., 1999). It has been suggested that the production of E_2 and the ability to respond to gonadotropins are important characteristics that the follicle must have to be selected and escape atresia (Fortune et al., 2001). *In situ* hybridization studies reported increased expression of mRNA for FSH receptors in the bovine granulosa cells of selected follicles in comparison to follicles that were only recruited. Likewise, the dominant follicles selected have greater expression of LH receptor in theca and granulosa cells (Bao and Garverick, 1998, Webb et al., 1999). Thus, selected follicles will be those that survive with low levels of FSH and respond to the LH ovulatory stimulus (Spicer et al. 1986; Jolly et al. 1994; Xu et al., 1995).

The selected follicle or follicles must be able to produce large amounts of E_2 , to trigger the preovulatory surge of LH and induce ovulation (Fortune et al., 2001). The expression of mRNA for P_{450scc} is higher in theca and granulosa cells of selected

follicles than those only recruited (Bao and Garverick, 1998). Similarly, the expression of P_{450c17} and 3 β -HSD in theca cells and P_{450arom} in granulosa cells increases in the selection (Bao and Garverick, 1998). The concentration of E₂ in bovine dominant follicles reaches its maximum on day 4 and gradually decreases on days 6, 8 and 10 (Xu et al., 1995). In cattle, the concentration of E₂ in the follicular fluid is higher in selected follicles (follicles collected on day 4 and 6 of the cycle), than in those only recruited (day 0 and 2 of the cycle). In sheep, healthy follicles of 3 to 6 mm and larger than 6 mm have a higher E₂ concentration in follicular fluid than follicles in early or advanced atresia (Alonso-Pozos et al., 2003; Valdez et al., 2005). Although, responsiveness to gonadotrophins and the ability to produce E₂ are important factors in the selection of the dominant follicle, there are other molecules that regulate this process.

In cattle, the concentration of free IGF-I in follicular fluid and the rate of degradation of binding proteins, IGFBP-4 and IGFBP-5 is higher in selected follicles compared to those not selected (Rivera and Fortune, 2003). Furthermore, these authors hypothesized that during selection of dominant follicles the degradation of IGFBPs increases the free IGF-I in the follicular fluid to promote the synthesis of E₂ and the proliferation of granulosa cells (Rivera and Fortune 2003). Recently, it has been shown that the addition of 50 ng/mL of IGF-I, increases cell proliferation, the expression of P_{450scc}, 3 β HSD and P_{450arom}, IGF-I type 1 receptor and the proapoptotic gene *bax* in cattle granulosa cells *in vitro* (Mani et al., 2010). Granulosa cells of selected follicles, have higher expression of GDF and BMP receptors than pre-selected follicles (Jayawardana et al., 2006). Other important molecules involved in follicle selection and dominance are the vascular endothelial growth factor (VEGF) and its membrane receptors, VEGFR1 and VEGFR2 (Rosales-Torres and Guzmán, in press). In ovine preovulatory (> 6mm) and large follicles (4 to 6 mm) the expression of VEGF164 and VEGF120 in granulosa cells is reduced with advancing degree of atresia, without major changes in theca cell expression (Rosales-Torres et al., 2010). In cultured bovine granulosa cells, 1 ng/ml VEGF increased cell proliferation in a similar way as 10 ng/ml FSH, while the combination of VEGF and FSH exacerbates the proliferation of granulosa cells (Doyle et al., 2010). In selected follicles, the expression of VEGF120, VEGF164 and VEGFR2 is higher in comparison to non-selected follicles (Shimizu et al., 2007). Additionally, VEGF has also been shown to have cytoprotective and proliferative effects on granulosa cells (Greenaway et al., 2004; Irusta et al., 2010).

Dominance

Dominance can be seen as the mechanism by which one or more follicles, depending on the species, reach a rapid development in an endocrine environment where growth of other follicles is suppressed (Webb et al., 1999).

The dominant follicle is selected because it has a molecular machinery that allows it to produce large amounts of E₂, respond to low levels of FSH and the preovulatory LH and present changes in the bioactivity of growth factors such as IGF-I, GDF-9 and VEGF. Follicular dominance in cows is established once the selected follicle reaches 8 to 8.5 mm in diameter and produces high amounts of E₂ and inhibin, which cause a decrease in serum FSH concentration (Campbell et al., 1995; Kulick et al., 1999).

Inhibins are dimeric glycoproteins, linked by disulfide groups, which belong to the TGF- β superfamily (de Kretser et al., 2002). In the follicles, inhibin is produced by the granulosa cells (Findlay et al., 2001) and suppresses both the synthesis and release of FSH in the gonadotrophs of the adeno-hypophysis, and thus can be considered as the main regulator of secretion of FSH (Arai et al., 1996). In rats, passive immunization against inhibin increases FSH concentrations (Arai et al., 1996), whereas in prepubertal rats there is a negative correlation between plasma concentrations of inhibin and FSH between days 5 and 15 after birth (Herath et al., 2001). Studies show that when steroid-free bovine follicular fluid is administered during the emergence of the first follicular wave in heifers, the growth of the dominant follicle is blocked, coinciding with the reduction in FSH serum concentrations (Bleach et al., 2001). In pituitary cell cultures, the use of bovine or porcine follicular fluid, or human recombinant inhibin, reduced FSH secretion without affecting LH secretion (Gregg et al., 1991). Moreover, the use of anti-inhibin in guinea pigs, increases FSH levels (Shi et al., 1999).

Two mechanisms are proposed to explain how inhibin blocks FSH synthesis and release. Inhibin can bind and block the action of activin (Knight and Glister, 2001). Activin binds to receptor type I and type II. The binding of activin to the type II receptor (a receptor with serine-threonine kinase domain) promotes dimerization and phosphorylation of type I activin receptor. This subsequently phosphorylates nuclear activating factors Smads (Robertson et al., 2000; Cook et al., 2004) that stimulates FSH synthesis. Therefore, binding of inhibin to activin type II receptor prevents the formation of the activin-receptor complex and thus blocking the activation of Smads. Alternatively, inhibin may binds to an specific receptors to directly act on the gonadotroph to block the activation of

Smads or activate inhibitors of these proteins (Robertson et al., 2000; Cook et al., 2004)

As was mentioned, E₂ is also involved in follicular dominance (Kaneko et al., 1995). In cycling heifers, CL lysis results in an increased of E₂ serum concentrations and a reduction in the concentration of FSH from the application to the preovulatory peak of LH (Bleach et al., 2001). In sheep, the continuous infusion of GnRH and the intramuscular application of 25 micrograms of E₂ (12 hr before hypophysectomy) significantly decrease the expression of mRNA for the β subunit of FSH (Turzillo et al., 1998). In contrast, there is evidence in cows, the use of an anti-estradiol had no effect on the FSH levels at any stage of the estrous cycle (Kaneko et al., 1995).

The role of E₂ on GnRH and LH secretion is well documented (Looper et al., 2003). The E₂ exerts a dose-dependent effect on GnRH release and produces a biphasic secretion pattern, reducing the pulse size but increasing the pulse frequency (Evans et al., 1994). The expression of GnRH receptors is regulated by the hormone itself and by E₂ concentrations. In addition, the amount of LH released by gonadotrophs depends of the concentration of GnRH receptors (Turzillo et al., 1998; Looper et al., 2003), so we may assume that E₂ rather than directly inhibiting FSH synthesis or release, changes the pattern secretion and pituitary sensitivity to GnRH to increase LH and reduce FSH secretion.

Although the dominant follicle may continue its growth in an environment containing low concentrations of FSH, LH responsiveness is essential for growth to continue (Webb et al., 2004). This idea is supported by evidence showing the appearance of mRNA for LH receptor in granulosa cells of dominant follicles between 8 and 9 mm in diameter (Bao and Garverick, 1998, Webb et al., 1999). It has been suggested that a characteristic pattern of LH pulses, added to the presence of LH receptors on granulosa cells is required to maintain the ovulatory ability of dominant the follicle (Webb et al., 2004).

Figure 4 shows the main changes in the expression of genes involved in the recruitment, selection and dominance during the development of antral follicles.

WAVES OF FOLLICULAR GROWTH

Cattle

In cattle, the growth of a follicle from primordial to ovulatory can take 3 to 4 months with a growth phase gonadotropin independent and other gonadotropins dependent phase (Webb et al., 2004). During the gonadotropin-independent growth, groups of follicles

grow from primordial to antral follicles (McNatty et al., 1999). In cattle the gonadotropin-dependent follicular growth occurs in pattern like-waves, during which sub-groups of large antral follicles continue growing. During the estrous cycle there are two to three waves of follicular growth (Forde et al., 2010). The waves start approximately on days 2, 9 and 16 of the cycle (Adams, 1999; Webb et al., 1999) in cycles with three waves of growth or on days 2 and 11 in cycles with two waves (Sirois and Fortune, 1988). Each wave of follicular growth lasts from 7 to 9 days (Mihm et al., 2000). It is reported that during each wave of follicular development a group of about 24 follicles with a diameter of 3 mm begin their growth during the transient peak of FSH (Ginther et al., 1996; Mihm et al., 2000), but other authors report that in each follicular wave only 5 to 10 follicles with a diameter of 4 to 5 mm, are those that are initiating growth in response to the transient FSH peak (Hamilton et al., 1995; Driancourt, 2001). From this group, only one follicle is selected to continue to grow and exert dominance over the rest of contemporary follicles that have started to grow together (Webb et al., 1999, Fortune et al., 2001, Webb et al., 2004). Fortune et al. (2001) reports that in *Bos taurus* cattle, dominant follicle selection occurs when the follicle reaches a diameter of 8 mm while subordinates only reach 7 mm. This deviation or selection occurs approximately at day 2 after onset of follicular wave (Fortune et al., 2001). In *Bos indicus*, the results reviewed by Sartori and Barros (2011) show that selection of dominant follicle of the first follicular wave, occurs at 2.6 ± 0.18 days after ovulation while the diameter of the dominant follicle and subordinate follicle is 5.9 ± 0.4 mm and 5.5 ± 0.3 mm, respectively. The dominant follicle of each wave of growth continues to grow at an accelerated rate (1.6 mm/day, Sirois and Fortune, 1988) and if its development coincides with CL lysis and the decrease of P₄, it may ovulate with a diameter between 12 to 20 mm in *Bos taurus* (Adams, 1999; Evans, 2003) or 7 mm in *Bos indicus* (Gimenes et al., 2008).

Sheep

The number of waves of follicular growth in sheep is highly variable. Results reviewed by Adams (1999) report that 8 to 29% of the animals have three waves of growth, while 60 to 80% have 4 waves, and even until 34% may have 5 waves (Adams, 1999). Other reports suggest that most of the animals have 2 to 4 follicular waves (Noel et al., 1993; Evans, 2003). The duration of growth of each follicular wave in Suffolk sheep with three waves was 6 days and these were observed in both the reproductive period as well as in the seasonal anestrus period (Noel et al., 1993). Likewise in Merino sheep, during the non-breeding season, there were 1.5 ± 0.5 waves of follicular

development during a period of 10 days, with an average duration of 7.1 ± 0.2 days (Souza et al., 1996). In sheep with three waves of follicular development during autumn and winter, the wave emergencies usually occur on days 0, 6 and 12 of the interovulatory period (Ali et al., 2006). In animals with more waves, the length of each wave is shortened, but the ovulatory wave begins around day 12 of the estrous cycle (Bartlewski et al., 1999). In this specie, in each follicular wave a group of follicles with a diameter of 1 (Duggavathi et al., 2003) to 2 mm (Noel et al., 1993) begin their growth in response to FSH. As in other species, one or two follicles (depending on the breed) are selected as dominant and continue to grow at a rate of 1 to 1.2 mm/day (Bartlewski et al., 1999). The diameter of the non-ovulatory and ovulatory dominant follicle is similar (5 to 7 mm and 6 to 7 mm, respectively; Evans, 2003).

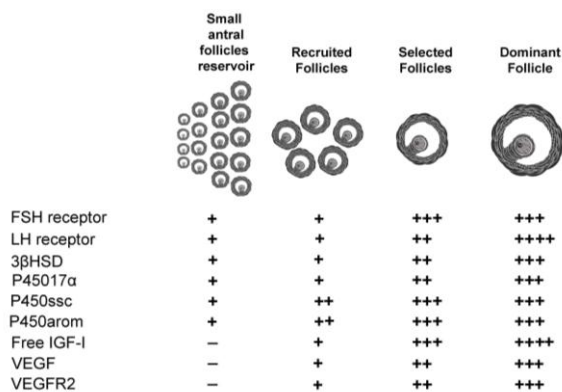


Figure 4. Molecules related with the recruitment, selection and follicular dominance during the development of antral follicles (adapted from Bao and Garverick, 1998; Rivera and Fortune, 2003; Shimizu et al., 2007 and Rosales-Torres et al., 2010).

Goats

In goats, the number of waves of follicular growth prevailing is 2 to 4 during the estrous cycle (de Castro et al., 1999; Adams, 1999, Medan et al. 2005; Simoes et al., 2006), although depending on the breed, up to 6 waves of growth have been reported (Evans, 2003; Berlinguer et al., 2009). Due to the large variation in the number of waves, the onset of each one is highly variable, as well as the interval between waves (de Castro et al., 1999, Medan et al., 2003, Medan et al., 2005). The number of follicles that start growing in each wave is not well established, however it is reported that about 4 follicles with a diameter >3 mm begin their growth in response to transient peak of FSH (Berlinguer et al., 2009). On the other hand, the diameter of the dominant follicle in the same wave is similar regardless of the number of waves that the

animal has (de Castro et al., 1999; Medan et al., 2003; Medan et al., 2005). Finally, in Shiba goats the diameter of the dominant follicle in anovulatory waves ranges from 6 to 6.7 mm, while the ovulatory follicle can reach up to 8.2 mm in diameter (Medan et al., 2003 and 2005). However, Evans (2003) reports that the diameter of the non-ovulatory dominant follicle and ovulatory follicle is similar.

CONCLUSIONS

The fate of ovarian follicles during follicular development depends on the action of survival factors that allow the follicle cells to proliferate and grow. The absence of survival factors coupled with the action of death-related factors will prevent the follicle from developing. The growth and development of primordial follicle to a antral follicle is stimulated by kit ligand, GDF-9 and BMP-15, while the presence or action of AMH and FOXO3a inhibit the follicular development in these stages. The last development of antral follicles depends on the action of gonadotropins. In addition to the action of these hormones, other factors as well as the presence of FSH and LH receptors, the steroidogenic capacity of follicle, and the IGF-I and VEGF action are essential for that one or more antral follicles could be recruited, selected, achieve dominance and if is possibly ovulated.

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