MINI REVIEW

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The role of pituitary gonadotropins and intraovarian regulators in follicle development: A mini-review

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Abstract

Background: The process of follicle development is tightly regulated by pituitary gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) and intraovarian regulators (eg, steroids, growth factors, and cytokines).

Methods: This review outlines recent findings on the mechanisms of human follicle development, based on the research on animal models such as mice, rats, cows, and sheep.

Main findings: Phosphatidylinositol 3-kinase/protein kinase B signaling pathway and anti-Müllerian hormone are involved in primordial follicle activation during the gonadotropin-independent phase. The intraovarian regulators, such as androgen, insulin-like growth factor system, activin, oocyte-derived factors (growth differentiation factor-9 and bone morphogenetic protein 15), and gap junction membrane channel protein (connexin), play a central role in the acquisition of FSH dependence in preantral follicles during the gonadotropin-responsive phase. Antral follicle development can be divided into FSH-dependent growth and LH-dependent maturation. The indispensable tetralogy for follicle selection and final maturation of antral follicles involves (a) acquisition of LH dependence, (b) greater capacity for E2 production, (c) activation of the IGF system, and (d) an antiapoptotic follicular microenvironment.

Conclusion: We reproductive endocrinologists should accumulate further knowledge from animal model studies to develop methods that promote early folliculogenesis and connect to subsequent gonadotropin therapy in infertile women.

KEYWORDS
follicle development, follicle-stimulating hormone, growth factor, luteinizing hormone, steroid

1 | INTRODUCTION

The ovarian follicle, consisting of an oocyte surrounded by two types of somatic cells (granulosa cells and thecal cells), represents the basic functional unit of the ovary. Follicle development involves activation of primordial follicles, continual growth through primary, secondary, preantral, and antral follicles, selection and maturation of a single dominant follicle, and ovulation (Figure 1). The process of follicle development is tightly regulated by pituitary gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) and intraovarian regulators (eg, steroids, growth factors, and cytokines).[1] This review outlines recent findings on human follicle development mechanisms, based on research on animal models such as mice, rats, cows, and sheep.[2]

2 | FOLLICULAR DEVELOPMENT STAGES

Follicle development can be classified into the following three phases according to their developmental stage and gonadotropin dependence[1,3]: (a) follicle growth through the primordial, primary, and secondary stages, which is entirely independent of FSH and LH (gonadotropin-independent phase); (b) follicle transition from the preantral stage to the early antral stage, which, although primarily controlled by intraovarian regulators,[4] can be stimulated by FSH (gonadotropin-responsive phase)[3]; and (c) follicle growth and maturation beyond the early antral stage, which includes follicle recruitment, selection, and ovulation, and is dependent on FSH and LH (gonadotropin-dependent phase).[5]

3 | GONADOTROPIN-INDEPENDENT PHASE: ACTIVATION OF PRIMORDIAL FOLLICLES

Females are born with approximately 2 million primordial follicles in their ovaries. After birth, primordial follicles are dormant in the ovaries for a long time; however, eventually, a group of them begin to grow into primary follicles (primordial follicle activation). Although the activation mechanism of primordial follicles has not been clarified thus far, it has been suggested that some primordial follicles may proceed with growth by exiting from the inhibition of primordial follicle activation in the ovary.[2] According to recent animal studies, activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway[6-13] and inhibition of anti-Müllerian hormone (AMH)[14-17] have been implicated in the activation of primordial follicles.

The PI3K/Akt pathway is an intracellular signal transduction system that induces proliferation and survival of various cells and is believed to be involved in primordial follicle activation in the ovary. Phosphatase and tensin homolog (PTEN) deleted on chromosome 10 is an enzyme that suppresses the PI3k/Akt pathway. The inhibitory effect of PTEN maintains the dormancy of the primordial follicles in the ovary for a long time.[2,6] When the inhibitory effect of PTEN is removed and the PI3K/Akt pathway is activated in several primordial follicles, the oocyte transcription factor forkhead box O3 (FOXO3) is phosphorylated and exported from the nucleus and is degraded in the cytoplasm.[7] This loss of transcriptional activity of FOXO3 in oocytes possibly turns on the switch of primordial follicle activation (Figure 1).[2,6] In PTEN[10] and FOXO3[8] knockout (KO) mice, primordial
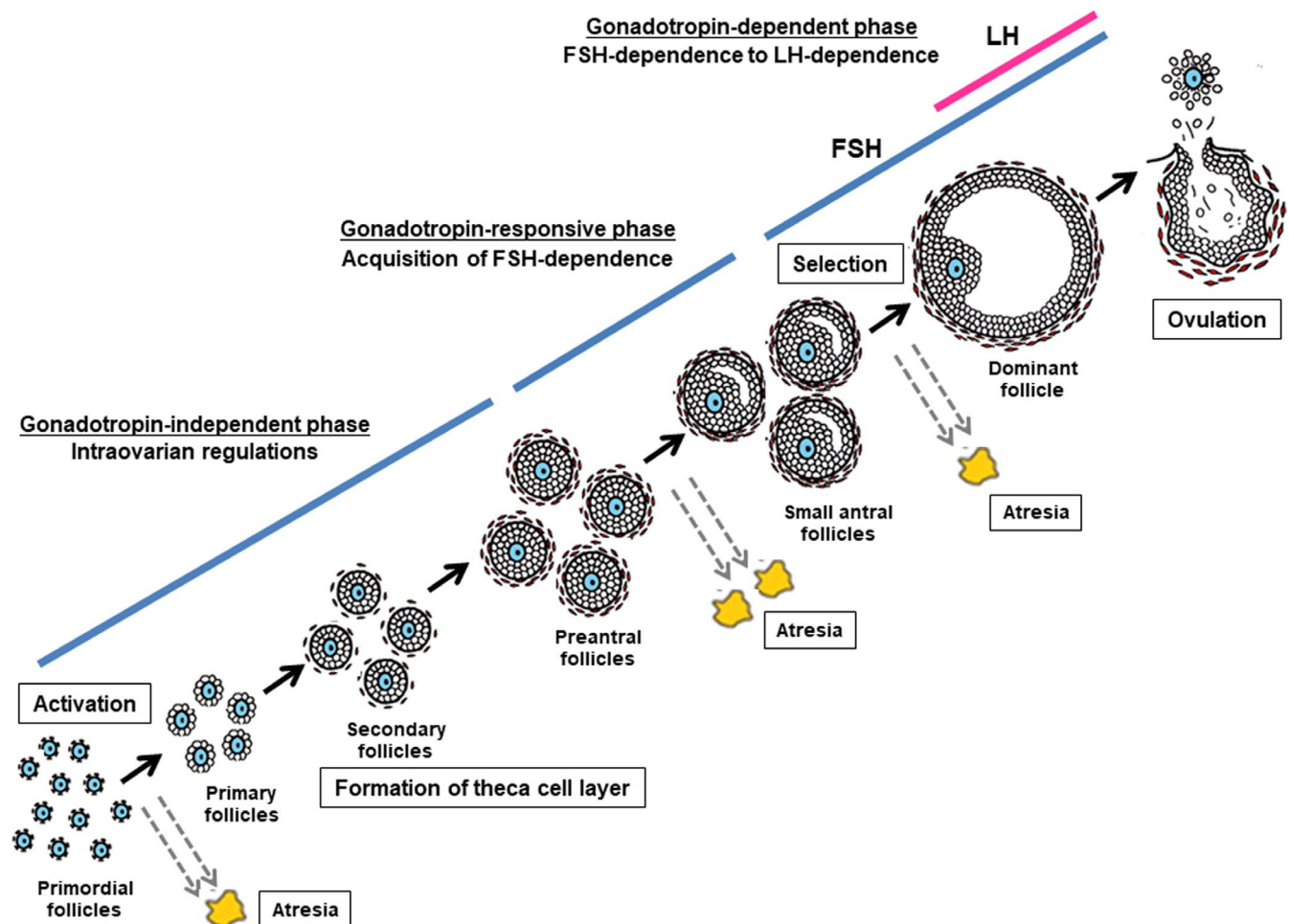

FIGURE 1 Follicle development, selection, and ovulation. FSH, follicle-stimulating hormone; LH, luteinizing hormone [Colour figure can be viewed at wileyonlinelibrary.com]

follicles were activated globally and began to grow simultaneously, which resulted in early depletion of ovarian follicles. Although the exact mechanism of external stimulation that releases the inhibitory effect of PTEN and activates the PI3K/Akt pathway in the ovary has not been clarified, the involvement of the Kit ligand (KL) and its receptor c-Kit has been speculated.[6,18,19]

Anti-Mullerian hormone is a growth factor belonging to the transforming growth factor-β (TGF-β) superfamily. In humans, AMH is expressed in the granulosa cells of preantral follicles and small antral follicles (~6 mm in diameter). However, its expression was not observed in large antral and preovulatory follicles.[20-22] In AMH KO mice, primordial follicles began to grow globally and were depleted faster, suggesting that AMH inhibited primordial follicle activation.[14] However, the exact mechanism of removing the inhibitory effect of AMH in the ovary to activate primordial follicles remains unclear.[2] Serum AMH levels reflect the number of preantral and small antral follicles and are used clinically to assess ovarian reserve and function.

Forkhead box L2 (FOXL2) is a granulosa-specific transcription factor, and its expression begins in pregranulosa cells (granulosa progenitor cells) around the primordial follicles.[23] In FOXL2 KO mice, follicle growth was arrested between the primordial and primary stages,[24,25] and granulosa cells were transdifferentiated into Sertoli-like cells,[26] suggesting that FOXL2 was involved in the activation of primordial follicles and maintenance of granulosa cell function.

4 | GONADOTROPIN-RESPONSIVE PHASE: ACQUISITION OF FSH DEPENDENCE IN PREANTRAL FOLLICLES

The developmental process of primordial, primary, and secondary follicles is not dependent on pituitary gonadotropins and is controlled by intraovarian regulators. Follicles acquire FSH dependence during the transitional stage from preantral to antral follicles, and the developmental mechanism begins to switch from intraovarian regulators to FSH.[1,3] Acquisition of FSH dependence is crucial in determining follicular fate (growth vs. atresia) beyond the preantral stage.

Follicle-stimulating hormone is a glycoprotein hormone composed of heterodimers of α- and β-subunits, and the β-subunit characterizes the physiologic function of FSH. The specific receptor for FSH (FSHR) is expressed in granulosa cells of secondary and preantral follicles.[2] In KO mice of the FSHβ subunit or FSHR, primordial follicle activation and subsequent growth to preantral follicles were observed. Nevertheless, follicle growth was arrested at the preantral stage, and no antral follicles were formed in these KO mice.[5,27] These findings indicate that FSH is indispensable for follicle growth and antral formation during the preantral-to-antral transition.

Intraovarian regulators that play a central role in the acquisition of FSH dependence at the preantral stage include androgen, insulin-like growth factor (IGF) system, activin, oocyte-derived factors (growth differentiation factor-9 [GDF-9] and bone morphogenetic
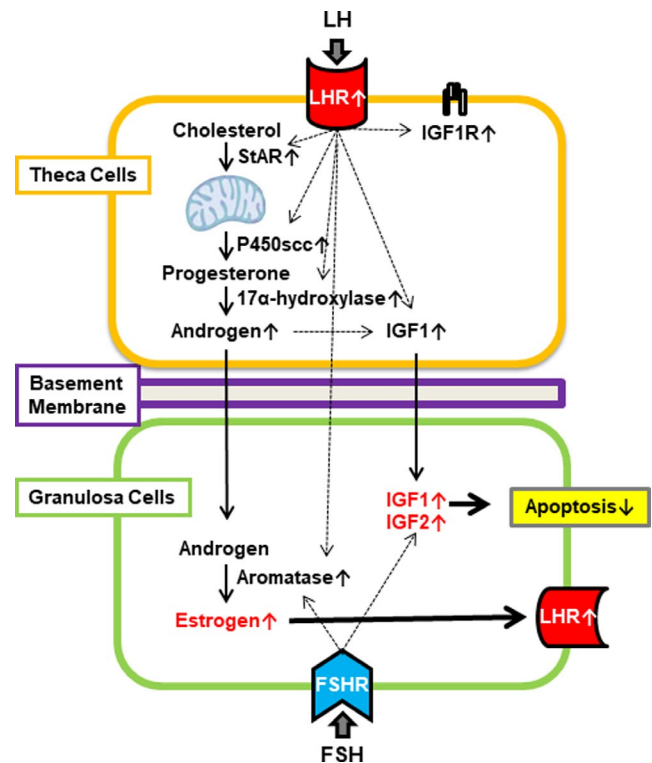

FIGURE 2 A hypothetical model illustrating a 2-cell 2-gonadotropin system around follicle selection.[76] FSH, follicle-stimulating hormone; LH, luteinizing hormone; FSHR, FSH receptor; LHR, LH receptor; IGF, insulin-like growth factor; IGF1R, IGF1 receptor [Colour figure can be viewed at wileyonlinelibrary.com]

protein 15 [BMP 15]), and gap junction membrane channel protein (connexin).[2]

Formation of the theca cell layer at the secondary and preantral stages is one of the key events for acquiring FSH dependence in preantral follicles (Figure 1).[1] The theca cell layers not only provide blood supply to follicles but also sensitize the follicles to gonadotropins. Granulosa cell factors (eg, IGF1 and KL) stimulate the recruitment of theca cells from ovarian cortical stromal cells,[28-30] whereas oocyte-derived GDF-9 is involved in the differentiation of theca cells during early follicle development.[31-34] When preantral follicles were formed, granulosa cells expressed FSHR and theca cells expressed LH receptor (LHR), thereby presenting the prototype of "2-cell 2-gonadotropin theory" (Figure 2).[1]

Theca-derived androgens bind to androgen receptors (ARs) in granulosa cells,[35] thereby inducing FSHR expression and follicle growth during the preantral-to-antral transition.[34,36-38] AR deficiency in the mice ovary induces granulosa cell apoptosis, arrests antral follicle growth, and results in premature ovarian failure.[39-42] Thus, androgens play an important role in the growth, survival, and acquisition of FSH dependence in preantral follicles.[1,2]

The IGF system includes two ligands (IGF1 and IGF2), two receptors (IGF1R and IGF2R), and some binding proteins (IGFBPs) that regulate IGF action in various cells.[43] IGF1 induces the expression of FSHR and aromatase (an enzyme that converts androgen to estrogen) in granulosa cells during the preantral-to-antral

transition.[44] IGF1 KO mice exhibited preantral follicle blockage, suggesting that the activation of the IGF system in the ovary was essential for follicle growth beyond the preantral stage.[45] In the human ovary, IGF2 may be more functionally important than IGF1.[46]

Activin, a growth factor of the TGF-β superfamily, promotes FSH production and secretion in the pituitary gland.[47-51] Additionally, it induces the expression of FSHR and aromatase in granulosa cells.[52-55] In activin receptor KO mice, follicle growth was arrested at the early antral stage.[56]

Both GDF-9 and BMP 15 are oocyte-derived growth factors belonging to the TGF-β superfamily. GDF-9 promotes androgen production in theca cells, and the androgen produced induces FSHR expression and proliferation of granulosa cells, thereby promoting follicle growth and acquisition of FSH dependence in rat preantral follicles.[34,57] In GDF-9 KO mice, follicle growth was arrested at the secondary stage, and the theca cell layer was not formed.[31,58] Thus, GDF-9 plays a central role in the crosstalk between oocyte-granulosa-theca cells during the preantral-to-antral transition.[1]

Although GDF-9 is involved in the early folliculogenesis of poly-ovulatory animals (eg, mice and rats), BMP 15 may be more important in mono-ovulatory animals (eg, sheep and humans).[2] In BMP 15 mutant sheep, follicle growth was arrested at the primary stage, similar to that in GDF9 KO mice.[59-61] Human BMP 15 mutations exhibited ovarian dysgenesis, early blockage in folliculogenesis, and premature ovarian failure.[62-64] Therefore, oocyte-derived GDF-9 and BMP 15 lead follicle development during the preantral-to-antral transition in both mono-ovulatory and poly-ovulatory animals.

The transmembrane protein, connexin, forms intercellular membrane channels of gap junctions that allow the exchange of ions, metabolites, and signaling molecules between adjacent cells. Connexin 37 KO mice exhibited follicle arrest during the preantral-to-antral transition, suggesting that the crosstalk between oocyte-granulosa-theca cells was essential for follicle growth beyond the transitional stage.[65]

5 | GONADOTROPIN-DEPENDENT PHASE: FSH-DEPENDENT GROWTH AND LH-DEPENDENT MATURATION OF ANTRAL FOLLICLES

In humans, when antral follicles reach a diameter of 2-5 mm, they are subjected to cyclic control by circulating FSH and LH (Figure 3). Approximately 5-15 antral follicles begin FSH-dependent growth each month, but only a single dominant follicle is selected and can eventually ovulate (Figure 1).[46] The primary function of follicles is to support the development of competent, mature oocytes. As antral follicles grow and mature, oocytes also grow, mature, and acquire capacitation.

Follicle-stimulating hormone stimulates the proliferation and differentiation of granulosa cells of antral follicles through the induction of numerous genes via activation of the cyclic adenosine
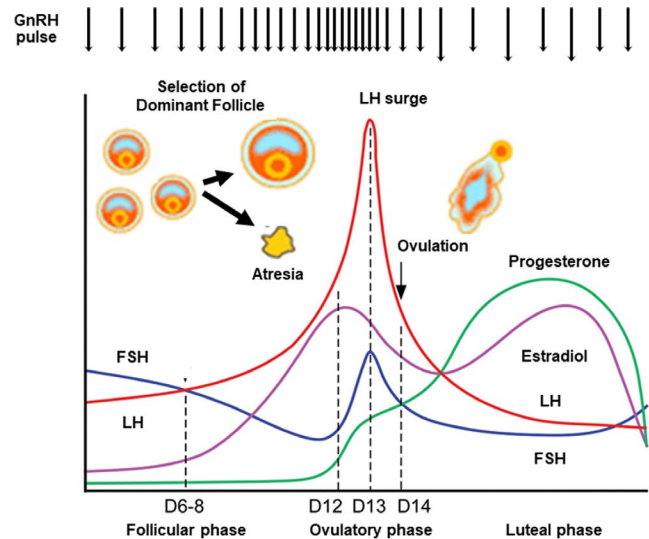

FIGURE 3 Hormonal dynamics of the hypothalamic-pituitary-ovarian axis during the menstrual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone; D, cycle date [Colour figure can be viewed at wileyonlinelibrary.com]

monophosphate/protein kinase A (cAMP/PKA) pathway, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, and PI3K/Akt pathway.[66] FSH also strongly suppresses granulosa cell apoptosis of antral follicles by activating the PI3K-Akt pathway.[66] In the absence of FSH, follicle atresia occurs through granulosa cell apoptosis.[3]

In humans, FSH plays a central role in the regulation of follicle recruitment and growth, whereas LH is mandatory for further follicular growth (beyond 10 mm in diameter) and estradiol (E2) production in the antral stage.[67,68] FSHR expression is highest in granulosa cells of small antral follicles (2-5 mm in diameter); however, its expression is strongly suppressed in granulosa cells during follicle selection (7-9 mm in diameter). Conversely, LHR expression is significantly induced in granulosa cells during follicle selection.[69] Thus, antral follicle development can be classified into FSH-dependent growth and LH-dependent maturation (Figure 1).[70]

6 | GONADOTROPIN-DEPENDENT PHASE: SELECTION OF A SINGLE DOMINANT FOLLICLE

The indispensable tetralogy for follicle selection and final maturation of antral follicles in bovine follicles involves (a) acquisition of LH dependence, (b) greater capacity for E2 production, (c) activation of the IGF system, and (d) an antiapoptotic follicular microenvironment.[71-76]

In antral follicles, LHR is expressed only in theca cells and mural granulosa cells (outermost layer of granulosa cells lying next to the basal lamina) but not in cumulus cells (granulosa cells surrounding oocyte) nor oocytes.[77] LHR expression in mural granulosa cells is induced by FSH with various intraovarian factors (eg, E2, IGF1).[78]

Conversely, LHR expression in cumulus cells is suppressed by oocyte-derived factors (such as GDF-9).[79-81] In KO mice of the LHβ subunit or LHR, antral follicle growth was arrested, and no preovulatory follicles or corpora lutea were found, indicating that LH was essential for antral follicle maturation and ovulation.[82-84]

E2 stimulates proliferation, induces the expression of FSHR, LHR, aromatase, and IGF1, and suppresses cell apoptosis in granulosa cells.[2] In KO mice of estrogen receptor and aromatase, antral follicles could not reach the preovulatory stage and failed to ovulate. This resulted in atresia, suggesting that estrogen was necessary for follicle maturation, survival, and ovulation.[85-89]

In humans, the traditional theory for follicle selection has been explained by the FSH-E2-inhibin axis.[72,90] E2 and inhibin-B, secreted from granulosa cells of developing follicles, reduces circulating FSH levels during the early/mid-follicular phase, which is essential in the orchestration of mono-ovulation in women (Figure 3).[91,92] Only follicles with the highest FSH sensitivity (ie, the highest FSHR expression in granulosa cells) can survive and continue to develop as a single dominant follicle, even at reduced FSH levels. On the other hand, follicles with low-FSH sensitivity (ie, lower FSHR expression in granulosa cells) cannot fully receive the antiapoptotic effect of FSH and induce granulosa cell apoptosis and follicle atresia under low-FSH conditions.[75,90]

Another recent theory for follicle selection is the acquisition of LH dependence in antral follicles. It is hypothesized that the first follicle that expresses LHR in mural granulosa cells and acquires LH dependence can survive and mature as a dominant follicle.[71,72,76] In bovine antral follicles, LH has been shown to induce LHR and aromatase expression, activate the IGF system, and suppress cell apoptosis in mural granulosa cells (tetralogy for follicle selection) via paracrine action from theca cells.[76] Thus, LH plays an important role in follicle selection and final maturation of antral follicles and preparation for subsequent ovulation (Figure 2).

7 | CONCLUSION

Women are responsible for species conservation and are destined to explore the possibility of pregnancy through follicle development and ovulation every month. The selection of a single dominant follicle and massive oocyte loss by follicle atresia in each cycle may be a biological intent to inherit the best genomic information within the selected oocytes to the next generation. On the other hand, infertility treatment requires as many oocytes as possible to increase pregnancy rates, and increasing the number of developing follicles by ovarian stimulation is one of the most important starting points of treatment. However, we can currently control only gonadotropin-dependent antral follicle growth; the activation of primordial follicles; and gonadotropin-independent growth until preantral follicles remain uncontrollable. We should study these aspects further from animal model studies to develop methods that promote early folliculogenesis, as well as subsequent gonadotropin therapy in infertile women.

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