THE MECHANISM OF HUMAN OVARIAN PRIMORDIAL FOLLICULAR ASSEMBLY AND DEVELOPMENT

Yosep Sutandar[1], Suryono S.I. Santoso[2]

ABSTRAK

Latar Belakang: Pembentukan dan perkembangan folikel primordial merupakan aspek yang penting pada sistem reproduksi perempuan, tetapi mekanismenya masih kurang dipahami. Pembentukan folikel primordial adalah proses dimana folikel primordial ovarium terbentuk. Sebuah folikel primordial terdiri dari oosit yang berada di profase jika pembelahan meiosis yang pertama dan dikelilingi oleh satu lapisan sel-sel pra-granulosa. Proses ini secara langsung memengaruhi jumlah oosit yang tersedia bagi seorang wanita sepanjang usia reproduksinya. Kelainan pada perkembangan folikel primordial menyebabkan sejumlah patofisiologi, tetapi mekanisme terjadi masih belum dapat dipahami.
Tujuan: Untuk memahami mekanisme perakitan dan pengembangan manusia ovarium folikel primordial.
Metode: Review artikel
Kesimpulan: Pembentukan folikel primordial adalah proses dimana folikel primordial ovarium terbentuk. Pembentukan folikel primordial dihambat oleh progesteron untuk tingkat yang lebih besar daripada estrogen, namun kedua steroid tersebut menghambat proses pembentukan. Proses apoptosis oosit secara acak dalam sarang oosit diperlukan untuk pembentukan folikel dan tumor necrosis factor-alpha (TNF) tampaknya juga terlibat dalam proses ini. Baru-baru ini, penelitian telah menunjukkan bahwa KL, basic fibroblast growth factor (bFGF), leukemia inhibitory factor (LIF), KGF, dan bone morphogenic protein -4 (BMP-4) dapat memengaruhi perkembangan folikel primordial.

Kata kunci: folikel, primordial, pembentukan, perkembangan.

ABSTRACT

Backgrounds: primordial follicle assembly and development is a critical aspect of female reproduction, but poorly understood process on mechanistic level. Primordial follicle assembly is the process by which ovarian primordial follicles are formed. A primordial follicle is composed of an oocyte arrested in prophase if the first meiotic division and surrounded by a single layer of pre-granulosa cells. These processes directly affect the number of oocytes available to a female throughout her reproductive life. Abnormalities in primordial follicle development lead to a number of pathologies, but the mechanism are poorly understood.
Objective: To understand the mechanism of assembly and development of human ovarian primordial follicle.
Method: Literature review
Conclusion: Primordial follicle assembly is the process by which ovarian primordial follicles are formed. Primordial follicle assembly was inhibited by progesterone to a greater degree than estrogen, but both steroids inhibited the assembly process. The apoptosis of random oocytes in the oocyte nests is required for primordial follicle assembly and tumor necrosis factor-alpha (TNFβ) appears to be involved in this process. More recently, studies have demonstrated that KL, basic fibroblast growth factor (bFGF), leukemia inhibitory factor (LIF), KGF, and bone morphogenic protein-4 (BMP-4) can influence primordial follicle development.

Key words: follicle, primordial, assembly, development

[1,2] Division of Reproductive Medicine, Department of Obstetrics and Gynecology
Faculty of Medicine University of Indonesia, National Center Hospital Dr. Cipto Mangunkusumo
Telephone: 081294037518. Email: yosep.sutandar@gmail.com

INTRODUCTION

Primordial follicle assembly and development is a critical aspect of female reproduction, but poorly understood process on a mechanistic level. The assembly of primordial follicles that occurs in the later stages of fetal development for a human and in the early postnatal period for the rodent is a distinct process from the induction of primordial follicle development involving the primordial to primary follicle transition.[1] Primordial follicle assembly is the process by which ovarian primordial follicles are formed. A primordial follicle is composed of an oocyte arrested in prophase if the first meiotic division and surrounded by a single layer of pregranulosa cells.[2] Follicle assembly in humans occur during gestation. The pool of assembled primordial follicle is the source of oocytes for follicle growth and ovulation over the course of a female's reproductive life.[1] Abnormalities in primordial follicle development lead to a number of pathologies (premature ovarian failure (POF) and female infertility).

At 18-20 weeks of gestation, the highly cellular cortex is gradually perforated by vascular channels originating in the deeper medullary areas. This marks the beginning of follicle formation.[3] As the finger-like vascular projections enter the cortex, it takes on the appearance of secondary sex cords. As blood vessels invade and penetrate, the divide the previously solid cortical cell mass into smaller and smaller segments. Drawn in with the blood vessels are perivascular cells that originate in the mesonephros or in the coelomic epithelium. Some believe that the coelomic epithelium is the origin of all ovarian somatic cells; others favor a mesenchymal or dual origin.[4, 5] These cells give rise to the preganulosa cells that surround the oocytes, which have completed the first stage of meiosis. The resulting unit is the primordial follicle—an oocyte arrested in prophase of meiosis, enveloped by a single layer of spindle-shaped preganulosa cells, surrounded by a basement membrane. Residual mesenchyme not utilized in primordial follicle formation is noted in the interstices between follicles, forming the primitive ovarian stroma. This process of primordial follicular development continues until all oocytes in the diplotene stage can be found in the follicles, sometime shortly after birth.[6] Primordial follicle development refers to both the assembly process and primordial to primary follicle transition process. Nest of germ cells (i.e. oogonia) develop in the embryonic period and have been also referred to as clusters or cysts. The assembly of primordial follicles requires a transition from nests to primordial follicles. The follicle does not exist until the primordial follicle assembles. The subsequent development of the primordial follicle involves the primordial to primary follicle transition.

The formation of primary follicle is marked by a change of the preganulosa layer to a cuboid layer of granulosa cells. This change is associated with proliferation. In the human it is estimated that about 13 preganulosa cells surround the oocyte and with the change to a primary follicle, the number increase to about 76 granulosa cells.[6] A later and perhaps more accurate study concluded that the primary follicle contains about 105 granulosa cells, associated with an increase in average diameter from 40 to 54 um.[7]

Primordial Follicle Assembly

The assembly or formation of the primordial follicles requires individual oocytes to segregate and associate with squamous granulosa cells. Nests of associated oocytes undergo random apoptosis of individual oocytes to derive isolated oocytes that then associate with precursor squamous granulosa cells.

An interesting observation from the in vitro culture of 0-day-old rat ovaries was that the majority of primordial follicles that assembled continued to develop spontaneously into primary follicles.[8] An inhibitory mechanism appears to be established in vivo that was not established in the 0-day-old ovary cultures that allowed spontaneous primordial follicle

development. To investigate what factors may influence or inhibit this development, the cultures were treated with several agents.[8] Both estrogen at a 10^{-6} M concentration and progesterone at a 10^{-6} M concentration dramatically inhibited the primordial to primary follicle development. Primordial follicle assembly was inhibited by progesterone to a greater degree than estrogen, but both steroids inhibited the assembly process.

This previous study also demonstrated that the ability of progesterone to inhibit the assembly of primordial follicle is in part mediated through a reduction in oocyte apoptosis. Previously it has been shown that oocytes exist unassembled in nests and that apoptosis of surrounding oocytes causes isolated oocytes to develop and assemble with precursor granulosa cells to form primordial follicles.[9] The apoptosis of random oocytes in the oocyte nests is required for primordial follicle assembly[9, 10] and tumor necrosis factor-alpha (TNFá) appears to be involved in this process. TNFá appears to promote this random oocyte apoptosis to allow primordial follicle assembly.[11]

From the previous research. Progesterone (P4) has been shown to inhibit follicle assembly, while tumor necrosis factor-alpha (TNFá has been shown to promote the apoptosis that is necessary for follicle assembly. The present study examines how TNFá and progesterone interact to regulate primordial follicle assembly. The progesterone receptors expressed at the time of follicle assembly included the surface membrane progesterone receptors PGRMC1, PGRMC2, and RDA288. Progesterone increased the expression of several genes (TANK, NFkB, Bcl2l1, and Bcl2l2) involved in a signaling pathway that promotes cell survival and inhibits apoptosis. Observation indicate that P4 acts through the surface membrane progesterone receptors to regulate primordial follicle assembly, and that TNFα can override the inhibitory actions of P4 on follicle assembly.[12]

The current study utilized a systems approach to detect all genes that are differentially expressed in response to seven different growth factor and hormone treatments known to influence (increase or decrease) primordial follicle assembly. One novel factor, basic fibroblast growth factor (FGF2), was experimentally determined to inhibit follicle assembly. A gene bionetwork analysis identified gene modules of coordinately expressed inter-connected genes and it was found that different gene modules appear to accomplish distinct tasks during primordial follicle assembly. Prediction of physiological pathways important to follicle assembly were validated using ovary culture experiments in which ERK1/2 (MAPK1) activity was increased.[13]

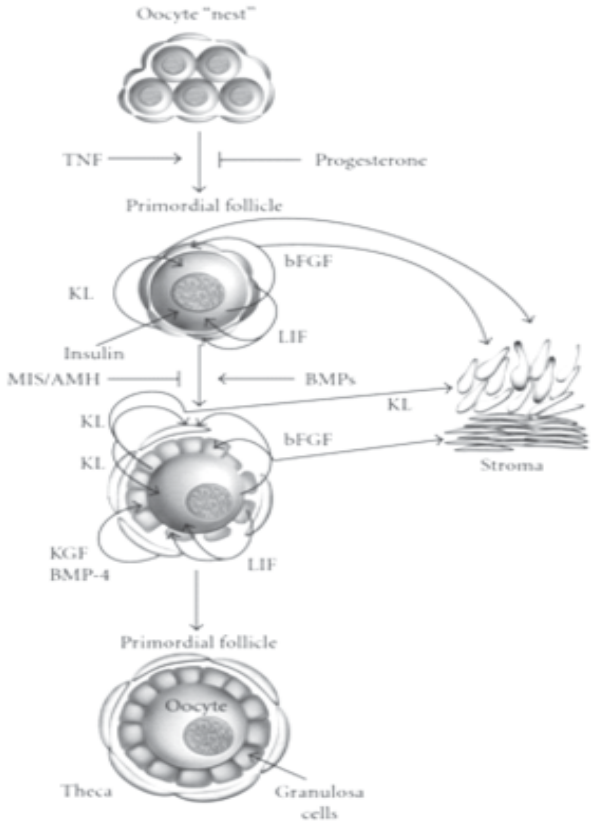

Figure 1. Cellular Interaction in Follicular Assembly and Development.[1]

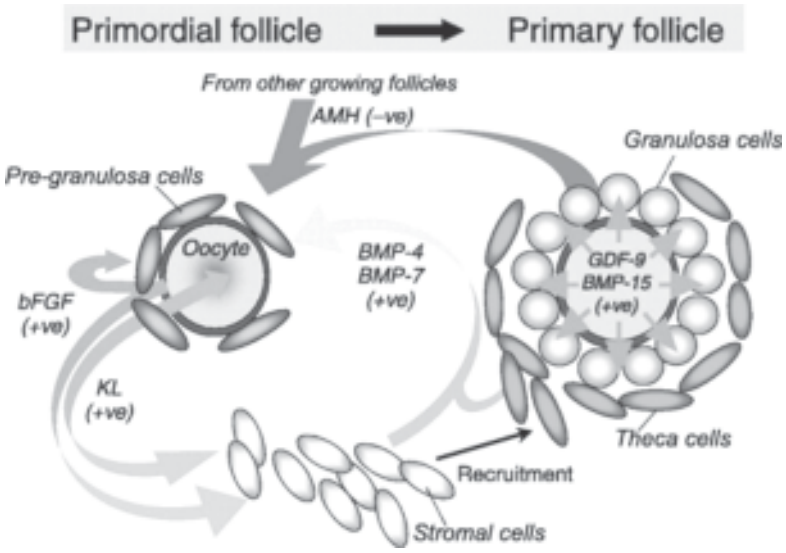

Figure 2. Transition from Primordial Follicle to Primary Follicle[14]

Primordial to Primary Follicle Transition

Previous observation have demonstrated that theca cells produce transforming growth factor (TGF) á, keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) that regulate granulose cells, whereas granulose cells produce kit ligand (KL) that can influence theca cells and the oocyte. More recently, studies have demonstrated that KL, basic fibroblast growth factor (bFGF), leukemia inhibitory factor (LIF), KGF, and bone morphogenic protein-4 (BMP-4) can influence primordial follicle development.

Kit Ligand

The KL (also termed stem cell factor, multipotent growth factor) is a growth factor with both soluble and membrane bound forms that have a wide range of effects on various cell types.[15] KL was found to induce the primordial to primary follicle transition. [16] KL produced by granulosa cells appears to act on oocyte to stimulate it to enlarge and initiate development. KL was found to stimulate stromal cell and theca cell growth. KL stimulates theca cell androgen production, but has no effect on stromal cell steroidogenesis. KL also was found to stimulate KGF and HGF mRNA levels in theca cells. KL expression was stimulated by gonadotropins, KGF, and HGF. Therefore, KL appears to be a critical factor in primordial to primary follicle transition.[17]

Basic Fibroblast Growth Factor

bFGF has been localized to the oocytes of primordial and primary follicles of several species. The bFGF is localized to granulosa cells of developing preantral follicles, but not to granulosa cells of human primordial follicles. bFGF is important in regulating a wide range of ovarian functions including granulosa cell mitosis[18], steroidogenesis[19], differentiation[20], and apoptosis[21]. Therefore, bFGF, like KL, appears to be a primordial follicle inducing factor. bFGF was found to be primarily localized to the oocyte of the primordial and early stages follicles. bFGF was found to stimulate both theca cells and stromal cell growth.[12] Therefore, bFGF influence primordial follicle development.

Leukemia Inhibitory Factor

LIF is a factor that acts at a specific GP130 transducing receptor involving the JAK-STAT pathway to influence a number of developmental systems.[22] Like KL, LIF has been shown to influence primordial germ cells in vitro and in vivo, but its role in oocyte development remains to be elucidated.[23] Therefore, LIF can promote primordial follicle development, and LIF neutralizing antibody can partially inhibit spontaneous follicle development.

Keratinocyte Growth Factor

A mesenchymal-derived growth factor that mediates mesenchymal-epithelial interactions is KGF. KGF is a fibroblast growth factor (FGF7), related molecule found to stimulate epithelial cell proliferation.[24] Previous studies have documented the production of KGF by theca cells from antral follicles and its potential to influence granulosa cell growth.[25]

KGF has also been found to stimulate the primordial to primary follicle transition. KGF is localized to the newly recruited precursor theca cells in contact with the layer of developing granulosa cells. This suggest that the KGF is produced by the recruited precursor theca cells and acts on the adjacent granulosa cell.[12] This is one of the first specific markers for this developing precursor theca cell population and supports the concept that precursor theca cells are an integral part of primordial follicle development.

Bone Morphogenic Proteins

The BMP family of growth factors is in the TGFâ superfamily. The first BMP shown to be associated with primordial follicle development was BMP-15. BMP-7 appears to have a role in early follicle development and involves a stromal cell interaction with the primordial follicle.[26, 27]

BMP-4 has been shown to promote the primordial to primary follicle transition and appears to be essential for oocyte survival.[12] That suggest BMP-4 is required for primordial follicle.

CONCLUSION

Primordial follicle assembly is the process by which ovarian primordial follicles are formed. The cell-cell interaction required during follicle development are speculated to be mediated in part through the local production and actions of a variety of factors. Primordial follicle assembly was inhibited by progesterone to a greater degree than estrogen, but both steroids inhibited the assembly process. The apoptosis of random oocytes in the oocyte nests is required for primordial follicle assembly and tumor necrosis factor-alpha (TNFá) appears to be involved in this process. TNFá appears to promote this random oocyte apoptosis to allow primordial follicle assembly. Observation from previous research indicate that P4 acts through the surface membrane progesterone receptors to regulate primordial follicle assembly, and that TNFá can override the inhibitory actions of P4 on follicle assembly.

The primordial to primary transition is distinct from subsequent follicle development because of hormone independence and less differentiated cell population. Recently, studies have demonstrated that KL, basic fibroblast growth factor (bFGF), leukemia inhibitory factor (LIF), KGF, and bone morphogenic protein-4 (BMP-4) influence primordial follicle development.

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