Follicular Growth and Development--2

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THE PREANTRAL FOLLICLE.

The early stages of folliculogenesis can be divided into three classes based on the number of layers of granulosa cells, the development of theca tissue, and the expression of a small cavity or antrum.

The classes are the primary, secondary, and early tertiary follicles . As the morphologic complexity increases, important cellular and physiologic changes occur in the follicle that render it competent to respond to gonadotropins. The following sections examine the structure and function changes that accompany preantral follicle growth and development.

Primary Follicle.

A primary follicle consists of one or more cuboidal granulosa cells that are arranged in a single layer surrounding the oocyte . Simultaneous with the shape change and mitotic activities that accompany recruitment , the cuboidal granulosa cells begin to express FSH receptors.. Although the granulosa cells express FSH receptors at this very early stage in folliculogenesis, it is believed that the physiologic levels of plasma FSH during the normal menstrual cycle do not influence granulosa responses because primary follicles lack an independent vascular system. FSH-induced changes in primary follicle function may occur in response to abnormally high levels of plasma FSH, such as those that occur during ovulation induction or aging.

Beginning approximately at the time of recruitment, the oocyte begins to grow and differentiate. This period is marked by a progressive increase in the level of oocyte RNA synthesis.[1]A number of important oocyte genes are turned on at this time. For example, the genes encoding the zona pellucida (ZP) proteins (*i.e.* ZP-1, ZP-2, and ZP-3) are transcribed and translated.[17] The secreted ZP proteins begin to polymerize near the oocyte surface, forming an extracellular matrix coat (the zona pellucida) that eventually encapsulates the egg. The importance of the zona pellucida is emphasized by the fact that the carbohydrate moiety of ZP-3 is the species-specific sperm-binding molecule.It is responsible for initiating the acrosome reaction in capacitated sperm.[19]

During primary follicle development, the granulosa cells send processes through the zona layer, where they form gap junctions with the oocyte cell membrane, or oolemma . Gap junctions are intercellular channels composed of proteins called connexins . This communication between the granulosa and oocyte remains throughout folliculogenesis and is responsible for the synchronous expression of important activities (positive and negative).

Secondary Follicle.

A secondary follicle is a preantral follicle with 2 to 10 layers of cuboidal or low columnar cells that form a stratified epithelium . the transition from a primary to a secondary follicle involves the acquisition of a second layer of granulosa cells. This transition is accomplished by the continuing division of the granulosa cells. The mechanisms regulating granulosa mitosis are poorly understood A fundamental concept that emerges from this work is that the oocyte plays a pivotal role in regulating folliculogenesis through its ability to produce novel regulatory ligands (*e.g.* GDF-9), which are crucial for folliculogenesis.

One of the most important changes that occur in the development of a secondary follicle is the acquisition of a theca layer. This tissue, which consists of a layer of stroma-like cells around the basal lamina, subsequently differentiates into the inner theca interna and outer theca externa . Theca development is accompanied by the neoformation of numerous small vessels, presumably through angiogenesis . This is a critical event because blood circulates around the follicle, bringing nutrients and hormones (*e.g.* FSH, LH) to and waste and secretory products from the secondary follicle. In this regard, some stromal cells in the inner layer express LH receptors. These cells subsequently differentiate into steroidogenic cells called theca interstitial cells (TICs), most likely in response to the plasma LH delivered by the theca vascular system.All the granulosa cells in secondary follicles express FSH receptors. It seems likely that diffusion of plasma FSH into the secondary follicle may evoke FSH-dependent granulosa responses. The outer layer of stroma cells subsequently differentiates into smooth muscle cells called the theca externa. These smooth muscle cells are innervated by the autonomic nervous system.

In the secondary follicle, the oocyte completes its growth. When the follicle is about 200 μm in diameter, the oocyte has attained its maximum size and grows no more, despite the fact that the human follicle enlarges to a diameter of 2 cm or more An important differentiation event that occurs when the oocyte completes its growth is acquisition of the capacity to resume meiosis. Oocytes normally do not resume meiosis during folliculogenesis, and a mechanism must operate to inhibit this process (*i.e.* germinal vesicle breakdown [GVBD]) and the resumption of meiosis. The underlying mechanism for the inhibition remains unknown; however, there is evidence to support the concept that granulosa derived cAMP may play an important role in inhibiting the resumption of meiosis.In such a mechanism, FSH-induces cAMP in the granulosa cells, which diffuses into the oocyte through the C×37 gap junction, where it proceeds to inhibit GVBD .

Tertiary Follicle.

When a preantral follicle completes the secondary stage in development, it contains five distinct structural units: a fully grown oocyte surrounded by a zona pellucida, six to nine layers of granulosa cells, a basal lamina, a theca interna, and a theca externa . The first indication of the onset of tertiary follicle development is the appearance of a cavity in the granulosa cells. In response to an intrinsic stimulus, a cavity begins to form at one pole of the oocyte. This process, called cavitation or beginning antrum formation, is characterized by the accumulation of fluid between the granulosa cells that in time results in the formation of an internal cavity . At completion of cavitation, the basic plan of the graafian follicle is established, and all the various cell

types are in their proper position awaiting the stimuli that will shift them along paths of differentiation and proliferation .