OVARIAN FOLLICULAR GROWTH AND DIFFERENTIATION

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INTRODUCTION

The human ovaries produce a single dominant follicle that results in a single ovulation each menstrual cycle. The dominant follicle must complete all the steps in folliculogenesis in a timely manner.

FOLLICULOGENESIS

Folliculogenesis is the process in which a recruited primordial follicle grows and develops into a specialized graafian follicle with the potential to either ovulate its egg into the oviduct at mid-cycle to be fertilized or to die by atresia. In women, the process is long, requiring almost 1 year for a primordial follicle to grow and develop to the ovulatory stage. During the course of folliculogenesis, growth is achieved by cell proliferation and formation of follicular fluid, whereas development involves cytodifferentiation of all the cells and tissues in the follicle. Only a few follicles in the human ovary survive to complete the cytodifferentiation process, with 99.9% dying by a programmed cell death mechanism called apoptosis.

The mechanisms regulating follicle growth and development are under the control of changing concentrations of ligands (*i.e.* hormones and growth factors). At the endocrine level, folliculogenesis is regulated by a central nervous system, anterior pituitary, and ovary cascade mechanism. Specialized hypothalamic neurons secrete pulses of gonadotropin-releasing hormone (GnRH) into the portal blood vessels, which acts on the gonadotrophs to cause a pulsatile release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act on ovarian follicle cells to control folliculogenesis. Although GnRH, FSH, and LH are critically important in regulating folliculogenesis, hormones and growth factors, which are themselves products of the follicle, can act locally to modulate (amplify or attenuate) FSH and LH action. This is the autocrine/paracrine system of developing follicles. It is believed that this local regulatory system plays an important role in the complex mechanisms governing the timing of folliculogenesis and whether a follicle becomes dominant or atretic.

Chronology

In women, folliculogenesis is a long process. In each menstrual cycle, the dominant follicle that ovulates its egg originates from a primordial follicle that was recruited to initiate growth almost 1 year earlier. In a broad sense, there are two types of follicles: *preantral* (primordial, primary, secondary [class 1], tertiary [class 2]) and *antral* (graafian, small [class 3, 4, 5], medium [class 6], large [class 7], preovulatory [class 8]). The development of preantral and antral follicles is gonadotropin independent and gonadotropin dependent, respectively.

The rate of preantral follicle development is slow, requiring about 300 days for a recruited primordial follicle to complete the whole preantral period (Fig. 2). A long doubling time (about 10 days) for the granulosa cells is responsible for the slow growth rate. After antrum formation

The Process

Folliculogenesis occurs within the cortex of the ovary (Fig. 1). The follicles in the cortex are present in a wide range of sizes representing various stages of folliculogenesis. The goal of folliculogenesis is to produce a single dominant follicle from a pool of growing follicles. There are four major regulatory events involved in this process: recruitment, preantral follicle development, selection, and atresia.

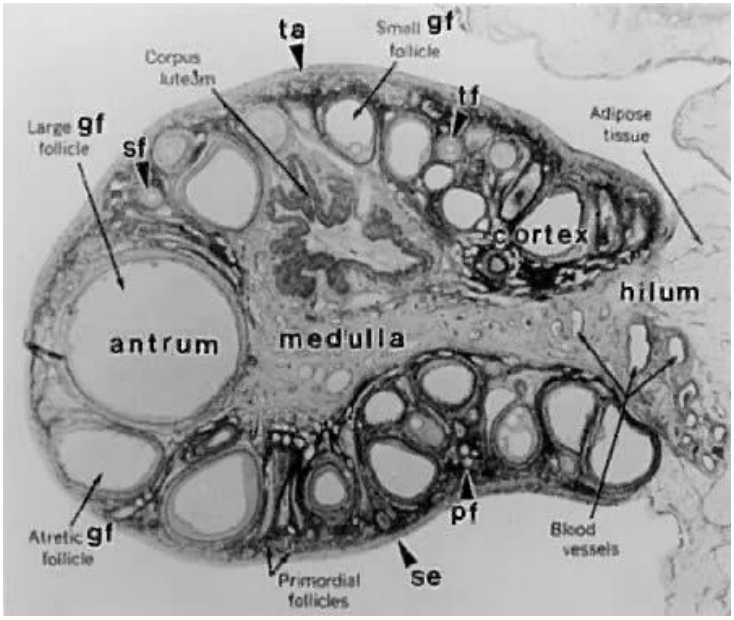

Fig. 1. An adult primate ovary. Follicular and luteal units are seen in the cortex and large blood vessels and nerves in the medulla. se, serous or surface epithelium; ta, tunica albuginea; pf, primary follicle; sf, secondary follicle; tf, tertiary follicle; gf, graafian follicle.

THE PRIMORDIAL FOLLICLE.

All primordial follicles are composed of a small primary oocyte (about 25 μm in diameter) arrested in the diplotene (or dictyate) stage of meiosis, a single layer of flattened (squamous) granulosa cells, and a basal lamina. The mean diameter of the human primordial follicle is 29 μm. By virtue of the basal lamina, the granulosa and oocyte exist within a microenvironment in which direct contact with other cells does not occur. The primordial follicles do not have an independent blood supply. It follows that primordial follicles have limited access to the endocrine system.

Recruitment.

The first major event in folliculogenesis is recruitment. Recruitment is the process by which an arrested primordial follicle is triggered to reinitiate development and enter the pool of growing follicles. All primordial follicles (oocytes) present in the human ovaries are formed in the fetus between the sixth and the ninth month of gestation. Because the entire stock of oocytes in primordial follicles is in meiotic prophase, none is capable of dividing mitotically. All oocytes (primordial follicles) capable of participating in reproduction during a woman's life are present in the ovaries at birth.

Mechanism.

The first visible sign that a primordial follicle is being recruited is that some granulosa cells begin to change from a squamous to a cuboidal shape. The first cuboidal cell is seen when the primordial follicle contains 8 granulosa cells, and the process is complete when the granulosa number reaches 19. The shape change is followed by the onset, albeit slow, of DNA synthesis and mitosis in the granulosa cells. A change in shape and acquisition of mitotic potential in the granulosa cells are the hallmarks of recruitment. Such observations suggest that the mechanisms governing recruitment may involve a regulatory response at the level of the granulosa cell. Recruitment is pituitary independent, and it probably is controlled by autocrine/paracrine mechanisms. Whether it is effected by a

stimulator or the loss of an inhibitor is uncertain; however, primordial follicles undergo rapid recruitment when removed from the ovary and cultured *in vitro*. These observations support the inhibitor idea.

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.

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.

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. The 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.

THE GRAAFIAN FOLLICLE.

A graafian follicle can be defined structurally as a heterogeneous family of relatively large follicles (0.4 to 23 mm) characterized by a cavity or antrum containing a fluid called follicular fluid or liquor folliculi. The characteristic structural unit of all graafian follicle is the antrum. For this reason, the term antral follicle is used correctly as a synonym for graafian follicle. The follicular fluid is the medium in which the granulosa cells and oocyte are found and through which regulatory molecules must pass on their way to and from this microenvironment. Surprisingly, we know almost nothing about the physiologic significance of the antrum and follicular fluid in folliculogenesis. It is clear that follicle development and ovulation occur in birds and amphibians despite the absence of an antrum and follicular fluid. Nonetheless, its presence in all mammalian species testifies to its physiologic importance.

Structure.

A graafian follicle is a three-dimensional structure with a central antrum surrounded by a variety of different cell types. There are six distinct histologic components in the graafian follicle, including the theca externa, theca interna, basal lamina, granulosa cells, oocyte, and follicular fluid (Fig. 2). A graafian follicle does not change its morphologic complexity as growth proceeds. All graafian follicles have this same basic architecture; even though there are dramatic changes in graafian follicle size, their appearance remains more or less the same.

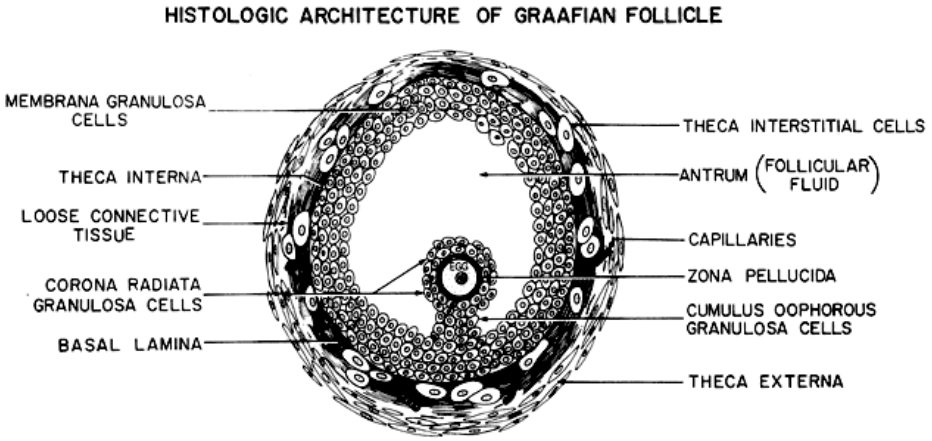

Fig. 2. Diagram of the architecture of a typical class 5 graafian follicle.

Classification.

All graafian follicles can be divided broadly into two groups: healthy and atretic (Fig. 03). The main difference between these two groups is whether apoptosis is occurring in the granulosa cells. The development of a graafian follicle (healthy or atretic) follows a progressive course over time. This implies that variability or heterogeneity is a normal consequence of folliculogenesis.

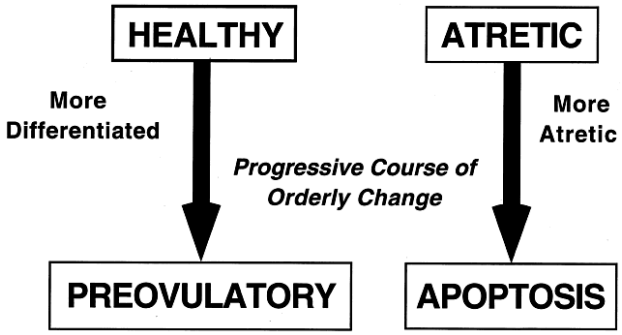

Fig. 03. The two major classes of graafian follicles: healthy and atretic.