Ovarian Follicular Development: Atresia or Ovulation

Sang-Young Chun

Hormone Research Center College of Natural Sciences, Chonnam National University, Kwangju 500-757, Republic of Korea

The development of ovarian follicles involves several sequential stages: initiation, growth, selection, and ovulation. Although the factors that initiate the growth of "resting" primordial follicles remain elusive, the key endocrine events controlling follicle growth in mammals have been known for many years. Once follicles have begun to grow, basal levels of LH/FSH maintain growth up until the small antral stage. Small antral follicles are selected to continue growth by subtle increases in basal levels of LH/FSH. Once selected, the growing of dominant follicles acquires specific functional characteristics that permit them to differentiate to the preovulatory stage and synthesize estradiol. Increased serum estradiol triggers the surge of gonadotropins that, in turn, stimulates the preovulatory follicles to ovulate and lutenize. Follicles that are not selected or fail to ovulate become atretic.

Once a follicle begins to grow, growth seems to be continuous until the follicles meets one of two fates - ovulation or atresia. The growth of follicles is controlled not only by the pituitary hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH), but also by local intraovarian factors such as IGF-I, EGF, bFGF, activin/inhibin, Il-1, and TNF. Less than 1% of ovarian follicles endowed at birth are normally ovulated during female reproductive life of which those follicles are capable of responding to all necessary hormones. The vast majority of follicles are eliminated by a degenerative process known as atresia. It has become clear that atresia is a normal physiological process of cell death necessary for ovarian homeostasis resulting in removal of excess cells. Recent biochemical analysis has revealed the occurrence of internucleosomal DNA fragmentation, a hallmark of apoptosis, in atretic follicles and has facilitated the investigation into the hormonal regulation of follicle atresia. Based on our studies using cultured rat follicles, it becomes clear that the regulation of follicle apoptosis involves redundant intraovarian hormonal control mechanisms which are dependent upon the stage of follicle development. Multiple growth factors play an important role as intrafollicular survival factors. In contrast, TNF-α, androgen, GnRH, and Il-6 appear to be intraovarian atretogenic factors. Thus, particular stage of follicles requires certain set of intraovarian survival factors to continue to grow. If the follicle loses the capability to respond to any one of survival factors, intraovarian atretogenic factors will be activated to remove the follicle.

The preovulatory surge of LH induces ovulation with a series of changes in various follicular compartments that culminate in the resumption of oocyte maturation, the rupture of the follicle

wall, and the transformation of the follicle into a corpus luteum. the second messenger cAMP has been implicated in the regulation of oocyte maturation. Although a decrease in intraoocyte levels of cAMP precedes oocyte maturation, LH induction of follicle rupture and oocyte maturation is associated with major increases of cAMP in ovarian follicles. We have recently demonstrated that phosphodiesterase (PDE) 3B isozyme mRNA is specifically concentrated in oocytes while PDE 4D isozyme mRNA is expressed in granulosa cells of follicles. Moreover, specific inhibitor of PDE 3 suppresses oocyte maturation, suggesting that selective regulation and expression of PDEs may be involved in the regulation of cAMP levels and control of oocyte maturation in the preovulatory mammalian follicle.

Other event following the LH surge is the rupture of follicle wall and release of a fertilizable ovum into the fallopian tube. The most prominent changes leading to follicle rupture include the dissolution of the follicle extracellular matrix and the dissociation of a dense collagen fibers in follicle wall. Therefore, we have investigated the role of proteolytic processes in follicle rupture. It has been demonstrated that LH stimulates ovarian coexpression of both tissue-type plasminogen activator (PA) and collagenase, and their respective inhibitors PA inhibitor-1 and tissue inhibitor of metalloproteinase-1. These proteolytic enzymes are expressed time- and cell-specific manner, ensuring that only the preovulatory follicle wall is dissociated. These results suggest that the highly localized and precisely balanced remodeling of perifollicular extracellular matrix is necessary for the fine-tune control of action of proteolytic enzymes during follicle rupture.

The analysis of follicle apoptosis should lead to better treatment modalities for ovulation induction as well as a better understanding of the mechanisms underlying premature ovarian failure, menopause, and polycystic ovarian syndrome. In addition, understanding of mechanisms of oocyte maturation and follicle rupture will provide a new avenue to develop the next generation of 'designer' contraceptive pills.

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