CLINICAL IMPLICATIONS OF BASIC RESEARCH

Master Regulators of Female Fertility

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Ovulation, initiated by the proestrus surge of the pituitary luteinizing hormone, culminates in the rupture of the ovarian follicle and is followed by the delivery of a mature oocyte. This event, an essential prelude to fertilization, has long piqued curiosity and is a focus of research in reproduction. Fan et al.[1] recently found that two signaling molecules — extracellular signal–regulated kinases 1 and 2 (Erk1 and Erk2) — are critical to luteinizing hormone–induced ovulation in mice.

The ovulatory response in mammals represents a complex series of events consisting of at least four distinct components: the resumption of meiosis (also known as oocyte maturation), the expansion and mucification of the cumulus oophorus, a shift from the production of follicular estrogen to the production of progesterone (with luteinization of the granulosa cells), and the disintegration of the follicle wall, which allows the release of the oocyte (Fig. 1). It has previously been shown that Erk1 and Erk2 mediate the effect of luteinizing hormone on both cumulus expansion and oocyte maturation (as established in vitro, with the use of cumulus-oocyte cultures and isolated intact ovarian follicles[2,3]). Moreover, a study of primary granulosa cell culture suggests that Erk1 and Erk2 mediate the luteinizing hormone–induced breakdown of cell-to-cell communication, a prerequisite of oocyte maturation (Fig. 1).[3] However, through their recent study, Fan et al. have found that Erk1 and Erk2 are essential to the entire repertoire of ovarian responses that result in ovulation.

Central to their study is a mouse model of female infertility; they engineered a mouse that did not produce Erk1 or Erk2, specifically, in the granulosa cells (and thus also in the cumulus cells, which are derived from the granulosa cells). The sexually mature mutant female mice did not ovulate and were completely infertile. The ovaries of these mice contained preovulatory follicles but not corpora lutea; accordingly, concentrations of serum estradiol in the mice were elevated, whereas progesterone concentrations remained low. The lack of response to luteinizing hormone was also observed in sexually immature mutant mice treated with exogenous hormones; their oocytes remained meiotically arrested, and the cumulus oophorus did not expand. Neither luteinization nor follicle rupture occurred in these animals.

This study defines Erk1 and Erk2 as master regulators of fertility that mediate the effect of luteinizing hormone on all components of the ovulatory response: oocyte maturation, cumulus expansion, luteinization, and follicle rupture. These findings seem to suggest that any defect in the signal-transduction pathway of Erk1 or Erk2 inevitably results in a global fertility failure that cannot be treated with exogenous hormones. However, as shown by Fan et al., if the molecular pathology is restricted to the somatic cells of the ovarian follicle, the oocyte is fully able to resume meiotic maturation: when the authors physically isolated oocytes from the ovarian follicle, the oocytes spontaneously matured, arresting in metaphase II.

Fan et al. intended the engineered mouse to be lacking Erk1 and Erk2 only in the somatic cells of the ovarian follicle. The oocytes of these mutant mice would be expected to express *Erk1* and *Erk2*, leading to the question of whether such a strategy to "rescue" fertility would work in women who are infertile because of an aberration in this signaling pathway. Such aberration would presumably affect all cell types, including the oocyte. However, Erk1 and Erk2 signaling in the oocyte is not known to be involved in the first meiotic division; rather, it regulates arrest of the metaphase in the second meiotic division.

One can thus envisage a strategy to extricate fertility — by aspirating the oocyte from the ovarian follicle — which would presumably result in the spontaneous resumption of meiosis. Oocytes that undergo in vitro maturation are identified by the presence of the first polar body. These oocytes would then be subjected to in vitro fertilization, followed by embryo transfer. The absence of a corpus luteum would necessitate a

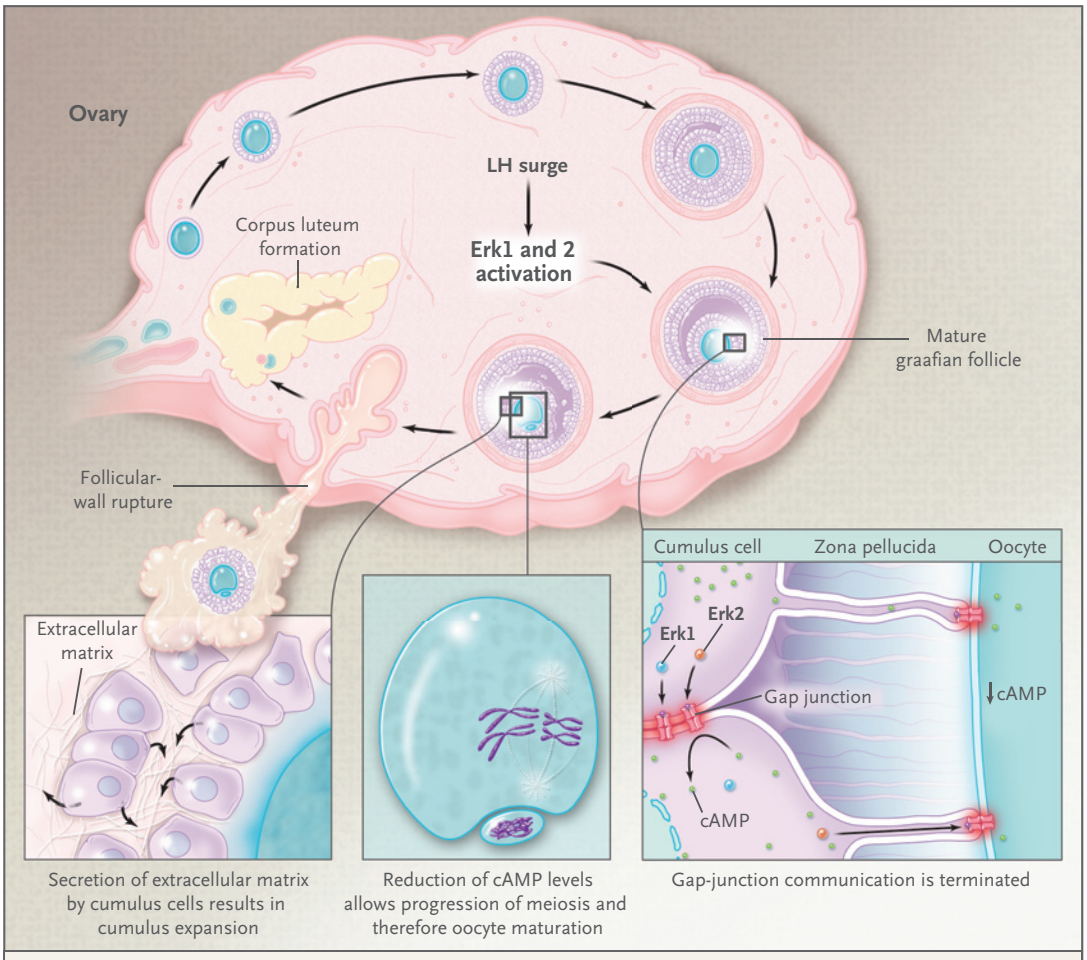

Figure 1. Luteinizing Hormone, Signaling, and Ovulation.

Fan et al.[1] found that luteinizing hormone (LH) induces the ovulatory response in the mouse through the extracellular signal–regulated kinases 1 and 2 (Erk1 and Erk2). This study, together with others,[2,3] suggests a scenario in which Erk1 and Erk2, in response to follicular exposure to LH, phosphorylate the gap-junction proteins in the granulosa and cumulus cells, leading to a diminution in the flow of molecules, such as cyclic AMP (cAMP), both between these cells and between the cumulus cells and the oocyte. In the oocyte, cAMP represses the resumption of meiosis and thus maturation; a reduction of cAMP in the oocyte (brought about through diminished contact between the oocyte and cumulus cells) results in a resumption of meiosis and thus oocyte maturation. The mucification of cells around the oocyte also depends on Erk1 and Erk2. These proteins also mediate LH-induced rupture of the follicular wall and the formation of the corpus luteum.

progesterone supplement to maintain pregnancy throughout the first trimester. Of course, the success of such a strategy depends on many factors not yet established, such as the extent to which *ERK1* and *ERK2* in women mimic their orthologous genes in the mouse and whether inactivation of the ERK1 and ERK2 pathways (for example, by mutation) causes infertility in humans. The work by Fan et al. calls for further research that will address such issues.

No potential conflict of interest relevant to this article was reported.

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1. Fan HY, Liu Z, Shimada M, et al. MAPK3/1 (ERK1/2) in ovarian granulosa cells are essential for female fertility. Science 2009;324:938-41.
2. Su Y-Q, Wigglesworth K, Pendola FL, O'Brien MJ, Eppig JJ. Mitogen-activated protein kinase activity in cumulus cells is essential for gonadotropin-induced oocyte meiotic resumption and cumulus expansion in the mouse. Endocrinology 2002;143:2221-32.
3. Sela-Abramovich S, Chorev E, Galiani D, Dekel N. Mitogen-activated protein kinase mediates luteinizing hormone-induced breakdown of communication and oocyte maturation in rat ovarian follicles. Endocrinology 2005;146:1236-44.