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CELL SIGNALLING

A fertility network

Mammalian fertility depends on luteinizing hormone (LH)-induced changes in ovarian follicular growth. A new study now reveals some of the signalling components that effect these changes.

As oocytes mature and follicles grow, the somatic granulosa cells (GCs) in the ovarian follicle terminally differentiate into luteal cells, constituting the corpus luteum that forms after ovulation. LH induces the expression of epidermal growth factor (EGF)-like proteins, but the roles of the EGF network in LH-induced follicular changes remain undefined.

To investigate, Fan *et al.* created a mouse model in which the network components extracellular signal-regulated kinase 1 (ERK1) and ERK2 were depleted in GCs. These *Erk1/2*$^{gc-/-}$ mice were infertile because ovulation and the differentiation of GCs failed, although expression of positive cell cycle regulators and proliferation of GCs continued. Furthermore, whereas serum oestradiol levels rose in these mice, progesterone levels did not, because corpora lutea could not form. Therefore, GC fate decisions depend on the activation of ERK1 and ERK2 by LH and the EGF-like factors.

Of the 563 LH target genes identified in GCs of ovulating follicles, the effects of 77% were impaired in *Erk1/2*$^{gc-/-}$ cells, including those that regulate oestradiol biosynthesis. Mice with GCs that lack C/EBPβ have an ovarian phenotype similar to *Erk1/2*$^{gc-/-}$ mice, and point mutations show that C/EBPβ is a substrate of ERK1 and ERK2. These components therefore form a key signalling network in GCs, in which LH-induced signalling through EGF-like proteins activates ERK1 and ERK2 and their substrates, leading to reprogramming and terminal differentiation.

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ORIGINAL RESEARCH PAPER Fan, H.-Y. *et al.* MAPK3/1 (ERK1/2) in ovarian granulosa cells are essential for female fertility. *Science* **324**, 938–941 (2009)