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How meiotic arrest happens

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The mystery of how meiotic arrest is maintained in mouse oocytes is revealed this week in Science by Lisa M. Mehlmann and colleagues at the University of Connecticut Health Center. The team reports that meiotic arrest requires the presence of a G-protein-coupled receptor in the oocyte that elevates cAMP, which has been previously shown to be critical for preventing completion of meiosis (*Science* 2004, **306:**1947-1950).

Meiosis begins when oocytes are still very small cells, but it then arrests for a long period after the oocyte has reached its full size, according to co-author Laurinda A. Jaffe, and depends on signals from the follicle. In a previous study, the team had found that the heterotrimeric G protein, Gs, in the oocyte is required to maintain meiotic arrest; Gs activates adenylyl cyclase to keep cyclic AMP elevated.

Jaffe looked for the means by which Gs is stimulated. "If there's an oocyte adenylyl cyclase that is [maintaining cAMP levels], then these are usually activated by a receptor, said Richard M. Schultz, of the University of Pennsylvania, so that is where Jaffe began. Using a "really cool bioinformatic approach that identified the receptors that are out there, they kind of homed in on a couple," said Schultz, who was not involved in the study. One of these was the G-protein-coupled receptor GPR3, for which a knockout mouse was available commercially.

Although the GPR3 receptor maintains meiotic arrest with constant signals from the follicle, gonadotropins produced by the pituitary will set off resumption of meiosis prior to oocyte maturation and ovulation. So, according to Schultz, two signals must control the receptor - one from the follicle cells to maintain arrest and one from the pituitary gland to release the arrest. The previous observation that removing an oocyte in meiotic arrest from its follicle results in spontaneous resumption of meiosis would be explained by the removal of the signal from the follicle. In addition, then, "somehow the gonadotropin would result in the cessation of the production of that ligand," he said.

"So from my perspective, this is major conceptual breakthrough," Schultz said. "This is moving back up now and saying, this may be a receptor-mediated process. And it's almost looking like Xenopus, where there's a stimulus coming in from the somatic cells - and in this case it's probably a steroid hormone."

Throughout evolution, steroids have been conserved as activators of oocyte maturation, according to Khaled Machaca of the University of Arkansas for Medical Sciences, who also speculated that meiotic arrest pathways might be conserved across species. "There's all this going on now with G-protein-coupled receptors being the key signaling pathways for oocyte maturation in zebrafish and trout," said Machaca, who was not involved in the study.

Jaffe said that in principle, understanding meiotic maturation is applicable to either infertility treatments or contraception - ;but first it would have to be investigated whether humans have the same system or not. "It might be possible to use that knowledge to think about ways to control maturation of oocytes in vitro," he said.

"Likewise, in the same sense that birth control pills work on hormonal regulation at one level, this is another level of control which - way down the road - someone could potentially exploit as a way of regulating fertility," said Jaffe.

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