REPRODUCTION

Unscrambling the egg–sperm divide

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An important breakthrough has been made in understanding the process that produces eggs or sperm in mammals. Contrary to previous theories that the two types of gamete are intrinsically programmed to enter meiosis, two recent papers show that levels of an external signal — retinoic acid (RA) — controls the timing of this event, and therefore the type of gamete that is produced.

Key to the production of gametes is the time at which the germ cells they are derived from enter meiosis. In mice, meiosis is initiated in females during embryonic development (at E13.5), whereas in males this occurs only after birth. This timing is crucial, as the later meiosis of male germ cells allows sperm rather than eggs to be made.

David Page and colleagues showed that an RA receptor (RAR) antagonist suppresses the expression of a pre-meiotic marker (*Stra8*) in cultured mouse embryonic ovaries. Furthermore, although *Stra8* is not normally expressed in the male gonad until after birth, addition of RA to testes in culture stimulates expression of the marker. This led

the authors to propose that RA is required for germ cells to enter meiosis, and indicates that regulated RA degradation might control the timing of this event.

In support of this, Page and colleagues showed that an inhibitor of the RA-degrading enzyme CYP26B1 induces embryonic testes to express *Stra8*. Their findings — in line with previous studies — also indicated that the *Cyp26b1* gene is expressed in embryonic testes, but not in embryonic ovaries, suggesting how the difference between the time of egg and sperm production might arise.

In a separate study, Peter Koopman and colleagues extend these findings, adding some important refinements to how the timing of meiosis induction is controlled. They carried out a screen for genes that are expressed sex-specifically during gonad development. This picked up *Cyp26b1*, which they found to be expressed initially in the developing gonads of both sexes — in contrast to the findings of Page and colleagues — but which became male-specific by E12.5.

The authors then tested for the presence of RA in the developing urogenital system. In both sexes, RA expression was detected in the mesonephros (a structure that is physically attached to the gonad). Furthermore, RA activity was found to be much higher in the developing

ovary than in the developing testis. Similar to the study by Page and colleagues, but using a wider range of meiotic markers, this study also showed that RA can induce germ-cell meiosis in cultured organs, and that this induction is inhibited by an RAR antagonist.

Koopman and colleagues also provide strong genetic evidence that CYP26B1 is responsible for controlling the timing of germ-cell meiosis in both sexes. Male *Cyp26b1*-null mice showed increased expression of meiotic markers in embryonic gonads, and germ-cell meiosis also took place earlier in female mice with the same genetic defect.

As well as revising our understanding of how sperm and eggs are produced, these results have potential practical applications. The timing mechanism provides a target for treatments to increase or suppress fertility, and understanding how it works could prove crucial in attempts to produce gametes from cultured germline stem cells.

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ORIGINAL RESEARCH PAPERS Bowles, J. et al. Retinoid signaling determines germ cell fate in mice. *Science* 30 March 2006 (doi:10.1126/science.1125691) | Koubova, J. et al. Retinoic acid regulates sex-specific timing of meiotic initiation in mice. *Proc. Natl Acad. Sci. USA* **103**, 2474–2479 (2006)

FURTHER READING Brennan, J. & Capel, B. One tissue, two fates: molecular genetic events that underlie testis versus ovary development. *Nature Rev. Genet.* **5**, 509–521 (2004)