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DEVELOPMENT

Male versus female

In mammalian embryos the gonad can develop into either an ovary or a testis. The absence of the testis-determination gene, *Sry*, leads to ovarian development, and this has led to the assumption that the development of female traits is the default pathway. However, this view has been challenged by the demonstration that the conditional deletion of a single gene in adult mice can cause the somatic part of the ovary to develop into testicular structures, suggesting that male development is actively repressed in females.

The molecular mechanisms that drive ovary development have been unclear, but one important candidate for embryonic ovarian development is *Foxl2,* which encodes a forkhead transcription factor. During mouse development, the global deletion of *Foxl2* leads to ovarian dysfunction and infertility. By contrast, when Uhlenhaut and colleagues conditionally deleted *Foxl2* in adult mouse ovaries using a tamoxifen-inducible system, gonadal sex was reversed 3 weeks after induction. They found that ovarian granulosa cells and theca cells differentiated into testicular Sertoli and Leydig cells, respectively, and that the expression of well-characterized Sertoli and Leydig cell markers were upregulated compared with XX ovaries. Furthermore, the Leydig cells in the sex-reversed gonads produced testosterone at similar levels to a normal XY mouse.

Is the somatic reprogramming of ovary to testis in this model cell autonomous? FOXL2 expression in the conditional mutant gonads was lost 3 days after tamoxifen administration. However, *Sox9* — the target of SRY — began to be expressed in ovarian follicles 4 days after tamoxifen administration and, after a week, SOX9 was expressed in all granulosa cells, which had started to differentiate into Sertoli-like cells. This suggests that the reprogramming occurred directly within the granulosa cells. Further support for this conclusion was provided by the important finding that the granulosa cells differentiated into Sertoli cells in the presence of an oocyte, therefore challenging the hypothesis that oocytes are required for maintenance of granulosa cell fate. In addition, when the authors specifically ablated oocytes in a separate mouse model that expresses FOXL2, this did not lead to the development of male-specific cells or SOX9 expression in the ovaries of these female mice.

As *Sox9* was rapidly upregulated after loss of FOXL2, the authors suggested that FOXL2 might directly downregulate *Sox9* expression. Indeed, the *cis*-regulatory element of *Sox9* that is responsible for the gene's testis-specific expression was strongly activated after *Foxl2* deletion. They also used chromatin immunoprecipitation assays to show that FOXL2 directly binds to this element *in vivo* in wild-type female mice.

These results indicate that the establishment and maintenance of the sexual identity of the mammalian gonad are determined by the opposing actions of SOX9 and FOXL2. These findings may have important implications for patients who have premature ovarian failure or sex differentiation disorders.

Meera Swami

ORIGINAL RESEARCH PAPER Uhlenhaut, N. H. *et al.* Somatic sex reprogramming of adult ovaries to testes by FOXL2 ablation. *Cell* **139**, 1130–1142 (2009)

FURTHER READING Williams, T. W. & Carroll, S. B. Genetic and molecular insights into the development and evolution of sexual dimorphism. *Nature Rev. Genet.* **10**, 797–804 (2009)