# The origin of reproductive organs

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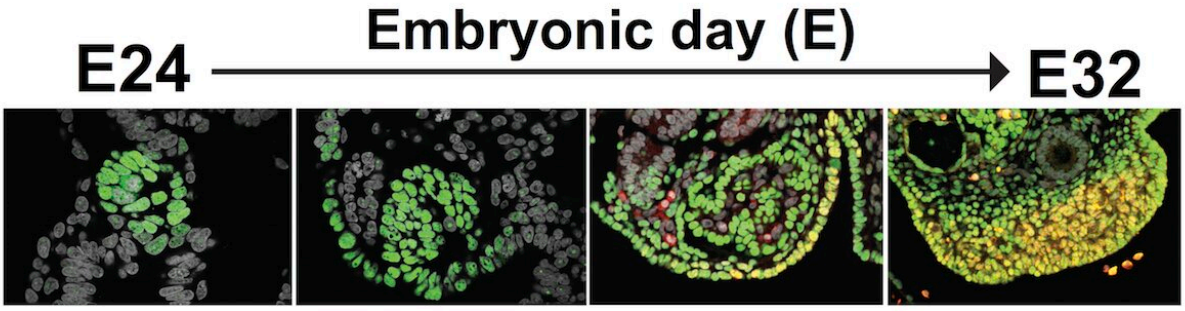


Studying embryonic development in mice and monkeys, researchers led by Kotaro Sasaki of Penn Vet discovered that a layer of cells known as the posterior intermediate mesoderm (far left) gives rise to the bipotential gonad (far right) early on in mammalian development. The bipotential gonad typically develops into either ovaries or testes. Understanding the molecular details of this process could help in intervening in disorders of sexual development. Credit: Kotaro Sasaki

Early in human development, during the first trimester of gestation, a fetus may have XX or XY chromosomes that indicate its sex. Yet at this stage a mass of cells known as the bipotential gonad that ultimately develops into either ovaries or testes has yet to commit to its final destiny.

While researchers had studied the steps that go into the later stages of this process, little has been known about the precursors of the bipotential

gonad. In a new study published in *Cell Reports* and co-led by Kotaro Sasaki of Penn's School of Veterinary Medicine, an international team lays out the detailed development of this key facet of sexual determination in two mammalian models.

"Using single-cell transcriptome data, we can get a lot of information about gene expression at each developmental stage," says Sasaki. "We can define what the default process is and how it might go awry in some cases. This has never been done in traditional developmental biology. Now we can understand development in molecular terms."

Disorders of sex development (DSD) occur when internal and external reproductive structures develop differently from what would be expected based on an individuals' genetics. For example someone with XY chromosomes might develop ovaries. These conditions often affect fertility and are associated with an increased risk of germ cell tumors.

"These disorders oftentimes create psychological and physical distress for patients," Sasaki says. "That's why understanding gonadal development is important."

To understand atypical development, Sasaki and colleagues in the current study sought to layout the steps of typical development, working with a mouse model and a monkey model.

The researchers began by examining mouse embryos throughout embryonic development, using molecular markers to track the location of different proteins suspected to be involved in the formation of reproductive structures. They noticed that by day nine of a mouse's embryonic development, a structure called the posterior intermediate mesoderm (PIM) lit up brightly with the marker for a gene critical to the development of gonads, kidneys, and the hormone-producing adrenal glands, which are located adjacent to the kidneys.

Zeroing in on the PIM and its progeny cells, the team found that, by day 10.5, these also expressed a marker known to be associated with the bipotential gonad.

"People have previously studied the origin of the urogenital organs and the kidney and based on that believed that their origins were very close," Sasaki says. "So our hypothesis was that the PIM was the origin of the gonads as well as the kidneys."

To identify the origin of the gonad, they performed lineage tracing, in which scientists label cells in order to track their descendents, which indeed supported the connection between the PIM and the gonads.

To further confirm that the PIM played a similar role in an organism closer to humans in reproductive biology, the researchers made similar observations in embryos from cynomolgus monkeys. Though the developmental timing was different from the mouse, as was expected, the PIM again appeared to give rise to the bipotential gonad.

Digging even deeper into the molecular mechanism of the transition between the PIM and bipotential gonad, the researchers used a cutting-edge technique: single-cell sequencing analysis, whereby they can identify which genes are being turned on during each developmental stage.

Not only were they able to identify genes that were turned on—many of which had never before been associated with reproductive development—but they observed a transition state between the PIM and bipotential gonad, called the coelomic epithelium. Comparing the mice and monkey embryos, the researchers came up with a group of genes that were conserved, or shared between the species. "Some of these genes are already known to be important for the development of mouse and human ovaries and testes," Sasaki says, "and some have been

implicated in the development of DSDs."

He notes that in roughly half of patients with DSDs, however, the genetic cause is unknown. "So this database we're assembling may now be used to predict some additional genes that are important in DSD and could be used for screening and diagnosis of DSDs, or even treatment and prevention."

The study also illuminated the relationship between the origin of the kidneys, adrenal glands, and gonads. "They all originate from the PIM, but the timing and positioning is different," Sasaki says.

The adrenal glands, he says, develop from the anterior portion of the PIM, or that section closer to the head and arise early, while the kidney arises later from the posterior portion of the PIM. The gonadal glands span the PIM, with some regions developing earlier and others later.

In future studies, Sasaki and colleagues would like to continue teasing out the details and stages of gonadal development. Sasaki's ultimate goal is to coax a patient's own stem cells to grow into reproductive organs in the lab.

"Some patients with DSDs don't have ovaries and testes, and some cancer patients undergo chemotherapy and completely lose their ovary function," Sasaki says. "If you could induce a stem cell to grow into an ovary in the lab, you could provide a replacement therapy for these patients, allowing them to regain normal hormone levels and even fertility. With a precise molecular map to the developing gonad in hand, we are now one step closer to the this goal."

**More information:** Kotaro Sasaki et al. The embryonic ontogeny of the gonadal somatic cells in mice and monkeys, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109075

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