IMAGING

A window into the dynamic world of mouse reproduction

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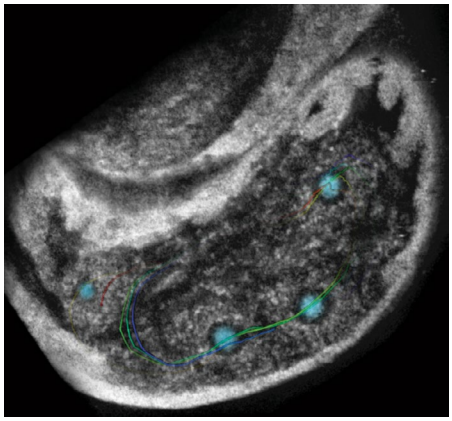
It all started with a picture. Richard Behringer, a developmental biologist at the University of Texas MD Anderson Cancer Center in Houston, was writing a book about reproduction and was looking for a more modern impression of the mouse reproductive system than previous pictures captured under a simple microscope, recalls Irina Larina. Across the street at Baylor College of Medicine, Larina – whose biophotonics lab builds tools to help capture developmental events – recorded an image with their optical coherence tomography (OCT) machine. This non-invasive imaging approach, common in optometry clinics, uses light to generate an image, similar to how ultrasound uses sound waves, and can penetrate about a millimeter into tissue, which is deeper than fluorescence-based microscopy can reach.

Her picture didn't make the cut, but Larina saw a new opportunity. At the time, her lab was focused on the developing heart. After seeing that image, which captured an embryo in motion, she shifted their focus to the reproductive system.

Catching the reproductive journey of an egg is no small feat – "this is a process happening deep within the body, and on such a small spatial scale," says Larina. Ova and sperm are tiny indeed, measured in microns; once they meet, that little fertilized egg must make its way through its mother's oviduct to the uterus, where it implants and begins to grow, within a designated timeframe. The journey, which takes about four days in humans and three in mice, was long thought by many in the reproductive field to be relatively simple and straightforward. The field envision that the cilia that line the oviduct gently and steadily ferry the embryo towards its destination as they rhythmically beat, Larina says; as ciliopathies are commonly linked to fertility issues, it seemed like a reasonable assumption.

"What we uncovered turns out to be enormously more complicated than anyone expected," Larina says. She and her former post-doc, Shang Wang (now with his own lab at the Stevens Institute of Technology in New Jersey), detail the dynamic journey of an egg in a recent publication in *Cell Reports*.



Embryos (blue) in motion in the mouse oviduct. Credit: Shang Wang & Irina Larina

In previous work published in *Scientific Reports*, Larina and colleagues used OCT to capture cilia dynamics in mouse oviducts that had been surgically exposed in pregnant mice; this approach however limits the experimental time available. To better capture details in vivo, they added a window. This technique, adapted from a similar implant designed at the Weizmann Institute for imaging mouse ovaries, eliminates the otherwise light-scattering effect of skin and muscle while allowing the animal to behave and mate normally.

Through the window onto the mouse oviduct, Wang and Larina saw movement – *a lot* of movement. In the upper portion of the oviduct, the embryos moved in quick circles as they waited for a luminal constriction to ease up; after a few hours, this 'gate' opened and allowed the embryos to continue on their way. Past the gate, the embryos were accompanied by periodic contractions of the lumen that acted like a suction pump and pulled them onward. In the final section of the oviduct, known as the isthmus, embryos "flew" rapidly back and forth until they reached the utero-tubal junction, where another luminal 'gate' is likely to be present, says Larina. These observations suggest there are novel spatially and temporally defined roles for smooth muscle in the embryo transfer process, in addition to beating cilia. "There's a lot to explore," Larina says. "Now we have tools to investigate these processes properly."

There are more images to come. Behringer, who collaborated with Larina on the cilia paper and who Larina acknowledges for reviewing the current manuscript, appreciates her results. "Every time Irina shows me another movie of some aspect of mouse reproduction that she has generated I feel so privileged to be seeing something that has never been seen before and is revising our thoughts on reproductive biological processes," he commented via email.

From here, Larina plans to explore what genes, hormones, and other potential mechanisms control embryo transfer to the uterus. This, she says, has implications for treating pathologies as well as for developing novel contraception methods. She also hopes to push OCT technology to capture other details about reproduction in vivo, including a big piece of the puzzle: fertilization itself. She has been working on a means to track the trajectories of sperm but as they close in on an oocyte, cumulous cells that surround the egg begin to obscure things. "We are still on the way," she says, but an increasingly dynamic view of reproduction is quickly coming into view.

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