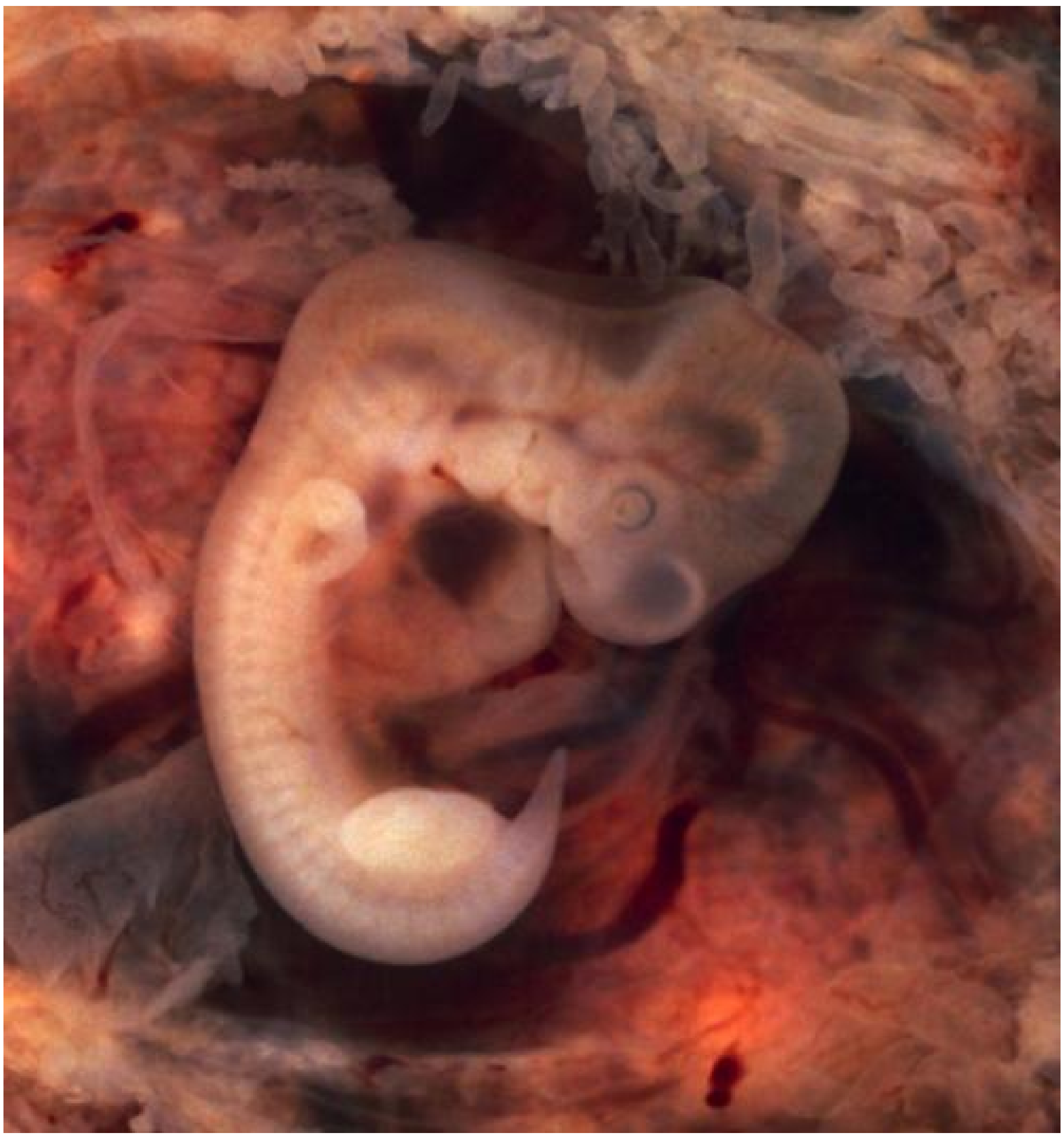
Telling left from right: Cilia as cellular force sensors during embryogenesis

January 5 2023



Human Embryo. Credit: Ed Uthman, MD/Wikipedia

Although the human body is externally symmetric across the left-right axis, there are remarkable left-right asymmetries in the shape and positioning of most internal organs, including the heart, lungs, liver, stomach, and brain.

Left-right asymmetry is known to be established during early embryogenesis by a small cluster of cells termed the left-right organizer. Within this organizer, motile cilia, hair-like structures on the cell surfaces, beat rapidly to create a leftward directional flow of extracellular fluid, which is the first outward sign of a left-right difference.

This early flow has been shown to be critical to the distinction of right from left; however, how this flow is sensed and translated into left-right asymmetry has been unknown.

A new study led by Massachusetts General Hospital (MGH) researchers now reveals that cilia in the organizer function as the creators of the flow—they also act as sensors for the biomechanical forces exerted by the flow to shape the left-right body plan of the developing embryo.

The findings were published in the journal *Science*.

"Nearly 25 years of work by numerous groups [has] shown that cilia and flow in the organizer are absolutely essential for establishing body left-right asymmetry," says Shiaulou Yuan, Ph.D., an investigator in the Cardiovascular Research Center at Massachusetts General Hospital and assistant professor of medicine at Harvard Medical School, and senior author of the study. "But we haven't had the right tools or techniques to definitively study how this all works."

To overcome this challenge, the researchers utilized zebrafish as a model for left-right development and employed a novel optical toolkit consisting of custom-built microscopy and machine learning analysis.

Their approach was unique as they developed and deployed optical tweezers—a biophysical tool that uses light to hold and move microscopic objects similar to a tractor beam—that enabled precise delivery of mechanical force onto cilia in an intact, living animal for the first time.

Utilizing these tools, the researchers discovered that cilia are cell-surface mechanosensors that are important for left-right asymmetry of the developing body and organs such as the heart.

By using optical tweezers to apply mechanical force onto cilia in the left-right organizer of zebrafish, they showed that a subset of organizer cilia sense and translate flow forces into calcium signals that control left-right development in zebrafish.

Defects in left-right asymmetry are associated with numerous human disorders, including heterotaxy syndrome, primary ciliary dyskinesia and congenital heart disease.

"The knowledge gleaned from this study not only advances our understanding of the fundamental cellular processes that govern the development of the human body, they may also open new avenues for the development of novel diagnostics of these disorders," says Yuan. "Additionally, this work may pave the way for targeted therapies on cilia signaling and mechanosensing to improve outcomes."

Yuan and his colleagues continue to investigate the molecular mechanisms that govern cilia force sensing. They also continue to develop new strategies to visualize and manipulate cilia signaling, with the long-term goal of developing novel tools for the treatment of cilia-associated disorders.

"These results, and the tools that made it possible, have provided a new window into the developmental patterning of the embryo, and also opened Pandora's box," says Scott E. Fraser, the Provost Professor of Biology and Bioengineering at the University of Southern California and a co-author on this study. "It reminds us that we have so much more to learn about how cilia signaling and mechanobiology impact development and disease."

Additional MGH and Harvard Medical School authors include Lydia Djenoune, Mohammed Mahamdeh and Christopher Nguyen. Other authors include Thai V. Truong from the University of Southern California, and Martina Brueckner and Jonathon Howard from Yale University.

More information: Lydia Djenoune et al, Cilia function as calcium-mediated mechanosensors that instruct left-right asymmetry, *Science* (2023). DOI: 10.1126/science.abq7317

Provided by Massachusetts General Hospital

Citation: Telling left from right: Cilia as cellular force sensors during embryogenesis (2023, January 5) retrieved 26 April 2024 from https://phys.org/news/2023-01-left-cilia-cellular-sensors-embryogenesis.html

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