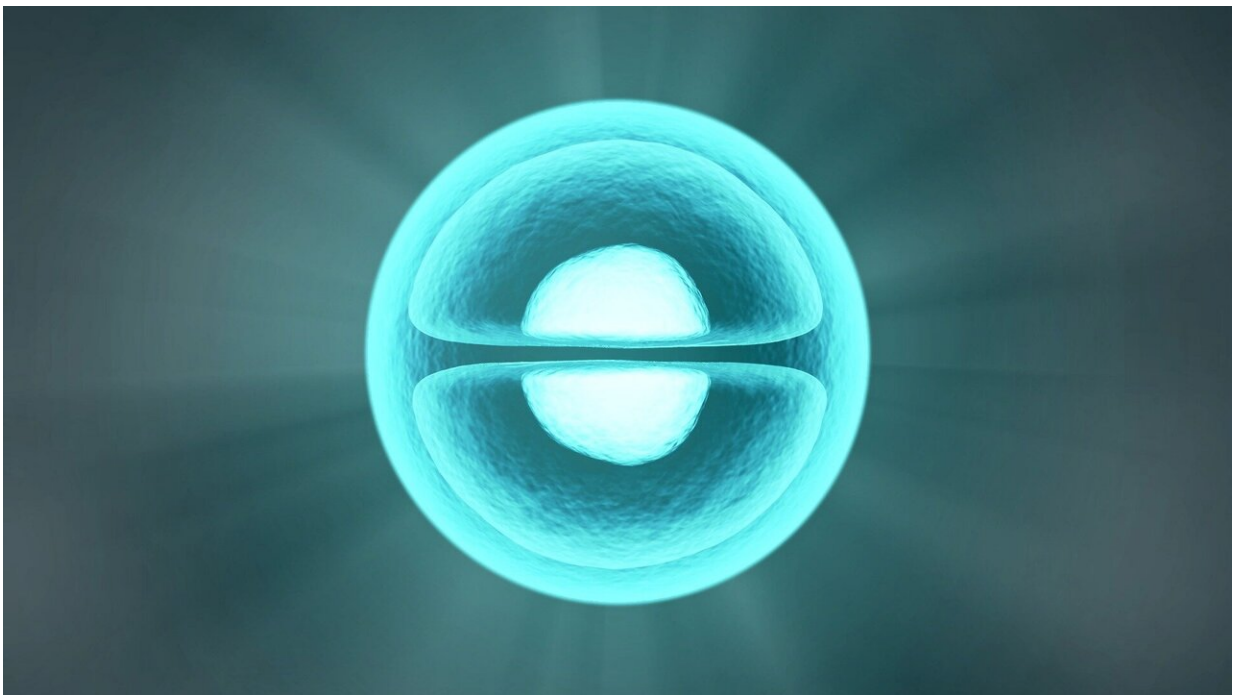


# Researchers identify mechanism that explains how tissues form complex shapes that enable organ function

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From the smooth tubes of our arteries and veins to the textured pockets of our internal organs, our bodies are made of tissues arranged in complex shapes that aid in performing specific functions.

But how do cells fold themselves so precisely into such complicated configurations during development? What are the [fundamental forces](#) driving this process?

Now, researchers at Harvard Medical School have discovered a mechanical process by which sheets of cells morph into the delicate, looping semicircular canals of the inner ear.

Published Dec. 22 in *Cell*, the research, done in zebrafish, reveals that the process involves a combination of [hyaluronic acid](#), produced by cells, that swells with water, and thin connectors between cells that direct the force of this swelling to shape the tissue.

Although conducted in zebrafish, the work reveals a basic mechanism for how tissues take on shapes—one that is likely to be conserved across vertebrates, the researchers say, and may also have implications for bioengineering.

## **A Model of Transparency**

Study senior author Sean Megason, professor of systems biology in the Blavatnik Institute at HMS, and his team study how cells develop into complex, three-dimensional structures. To address this question, they turned to a classic—and ideal—model organism: zebrafish.

"They're transparent, so we just stick them under a microscope and look at this entire process from a single cell to a larva that can swim and has all its parts," explained study first author Akankshi Munjal, who conducted the research as a postdoctoral researcher at HMS and is now an assistant professor of cell biology at Duke University.

These parts include the semicircular canals, three fluid-filled tubes in the inner ear that are needed for balance and orienting in space. Little is

known about how the semicircular canals form, in part because in many species they are obscured by the middle and outer ear. In zebrafish, however, the canals sit close to the surface, allowing researchers to watch them develop under a microscope.

"This was an exciting opportunity for us to look at how a three-dimensional organ forms from a simple sheet of cells," Munjal said. "We could look at the inner ear in the embryo with complete accessibility."

"The inner ear is a model for how cells work together to make complex structures that are needed for organisms to function," Megason added. "We went into it thinking it was a beautiful structure, but not knowing what we would find."

What they did find surprised them.

The conventional thinking is that the proteins actin and myosin act as tiny motors inside cells, pushing and pulling them in different directions to fold a tissue into a specific shape. However, the researchers discovered that zebrafish semicircular canals form through a markedly different process. During development, the cells produce hyaluronic acid, which is perhaps most well known as an antiwrinkle agent in beauty products. Once in the extracellular matrix the acid swells up, not unlike a diaper in a swimming pool. This swelling creates enough force to physically move nearby cells, but since the pressure is the same in all directions, the researchers wondered how the tissue ends up stretching in one direction and not another to form an elongated shape. The team found that this is accomplished by thin connectors between cells—dubbed cytocinches—that constrain the force.

"It's like if you were to put a corset on a water balloon and deform it into an oblong structure," Munjal said. This combination of swelling and cinching progressively shapes an initially flat sheet of cells into tubes.

"Our work shows a new way of doing things," Megason said, adding that he hopes it will encourage people to consider additional mechanisms that may be involved in shaping tissues. "Cells have to use many different forces in order to accomplish what they need to, and time will tell exactly what the balance is between the molecular approaches of actin and myosin and the more physical approaches of pressure."

Their discovery likely has broader implications, Megason and Munjal added.

The genes that control hyaluronic acid production in zebrafish semicircular canals are also present in the [semicircular canals](#) of mammals, suggesting that a similar process may be occurring. Moreover, hyaluronic acid is found in multiple parts of the human body, including skin and joints, indicating that it may play a role in shaping many tissues and organs—an avenue for future research.

If that does turn out to be the case, then studying the genes involved in hyaluronic acid production could help researchers understand congenital defects in organs where hyaluronic acid drives development.

"This is likely to be a widespread, conserved mechanism across species and organs," Munjal said.

The mechanism could also be applied to bioengineering, where researchers are attempting to prod stem cells into forming buds, tubes, and other complicated shapes, with the ultimate goal of culturing organs in the lab.

Lab-grown organs are still a work in progress, Megason noted, but a key step will be parsing how organs form inside an organism. "We're trying to dissect the steps of how a complex organ such as the inner ear is made in vivo, and then quantitatively understand those steps," Megason said.

"We hope this will set the foundational groundwork for having [cells](#) grow into whatever pattern and shape we want."

**More information:** Sean G. Megason, Extracellular hyaluronate pressure shaped by cellular tethers drives tissue morphogenesis, *Cell* (2021). [DOI: 10.1016/j.cell.2021.11.025](https://doi.org/10.1016/j.cell.2021.11.025).  
[www.cell.com/cell/fulltext/S0092-8674\(21\)01373-8](https://www.cell.com/cell/fulltext/S0092-8674(21)01373-8)

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