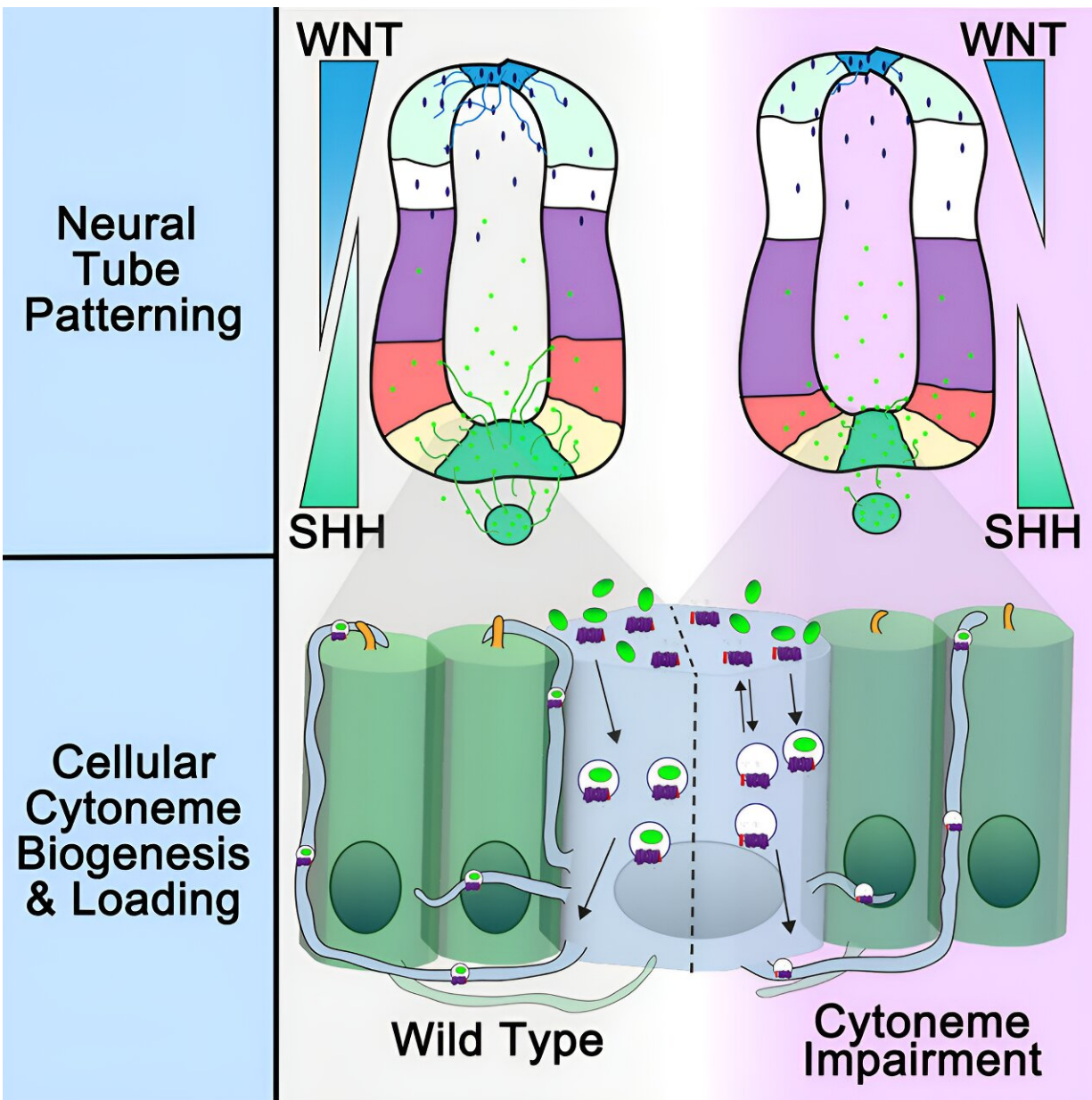


Elusive cytonemes guide neural development, provide signaling 'express route'

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Graphical Abstract. Credit: *Cell* (2024). DOI: 10.1016/j.cell.2023.12.003

St. Jude Children's Research Hospital scientists found that cytonemes (thin, long, hair-like projections on cells) are important during neural development. Cytonemes connect cells communicating across vast distances but are difficult to capture with microscopy in developing vertebrate tissues.

The researchers are the first to find a way to visualize how cytonemes transport signaling molecules during mammalian nervous system development. The findings were [published](#) in *Cell*.

"We showed cytonemes are a direct express route for signal transport," said corresponding author Stacey Ogden, Ph.D., St. Jude Department of Cell and Molecular Biology.

"Cells need to communicate with each other during development and tissue homeostasis and be able to reach more than just their neighbors. We've identified one way that signals are loaded into cytonemes for transport to responding [cell populations](#) and demonstrated that tissue patterning does not happen properly when this mode of signal dispersion is compromised."

Express signal delivery sets up the nervous system for success

Researchers in Ogden's lab were the first to visualize mammalian cytonemes in the developing nervous system by combining modern microscopy techniques with optimized sample preparations.

"For a long time, visualizing these structures in developing mammalian tissue has been challenging," Ogden said. "But we've finally found a way."

Using their new methods, the scientists captured images of how cytonemes act as an "express" system that can skip over intervening cells to directly deliver signals to more distant ones, similar to an express subway that only stops at major stations. One of the major stations is the notochord, which produces a signal that plays a crucial role in organizing the developing spinal cord. Ogden's team captured images of the transport process happening in the cytonemes originating from the notochord.

When the researchers prevented signaling proteins from entering cytonemes, [neural development](#) was disrupted in mouse models, causing major neurological defects.

"This is the first demonstration of these cytoneme-based transport processes occurring during the development of a complex mammalian tissue such as the neural tube," Ogden said. "Then we showed that when we reduce cytoneme numbers or decrease the ability of cells to load signaling proteins into these structures, we get developmental defects."

Cytoneme transport helps establish the gradient

Mammalian development is a carefully guided process that must be coordinated for all organs and tissues to form correctly. One way cells know when to adopt a specific fate is by responding to distinct thresholds of signaling proteins called morphogens.

Cells will respond differently to these signals across a signaling gradient, taking on different characteristics in response to high and low concentrations of a particular morphogen. A good gradient is necessary

for development; a bad gradient can spell disaster.

Despite their importance, how these patterns of morphogens are created across fields of organizing cells has remained a mystery. Simple diffusion can explain some, but not all, of these gradients. The neurological deficits created when the scientists blocked signals from entering cytonemes provide evidence that supports a key role for cytoneme signaling during morphogen patterning.

"These deficits are really the first direct evidence that cytoneme-based signaling plays a key role during neural tube patterning," Ogden said.

Transporting 'sonic hedgehog' through cytonemes

The St. Jude group clarified one way that a gradient of the sonic hedgehog morphogen is formed in the neural tube. Sonic hedgehog was already known as a critical signaling molecule in neural development, but its route to reach its target cells has been difficult to ascertain. The study identified cytonemes as key contributors to a solution that creates the sonic hedgehog signaling gradient. Correspondingly, when sonic hedgehog could not be loaded in cytonemes, its signaling function was compromised.

"In the morphogen signaling research field, we've always wanted to know how a signal gets from one population of cells to spread across a receiving cell population to make a gradient," Odgen said. "It's really exciting to show that [cells](#) that are producing morphogen signals are playing an active role in getting them to where they need to go through cytonemes. The signaling cell is not only making the morphogen, but it's also helping to physically deliver the signal."

What remains unclear is how widespread cytoneme express transport of signaling proteins is in development.

"Here, we've used [sonic hedgehog](#) as a model," Ogden said. "But we also have evidence that these structures may be important for transporting other signals that are crucial during neural tube development. Now that we've developed a system to visualize these cytonemes, we can begin to uncover the true breadth of their function."

More information: Eric T. Hall et al, Cytoneme signaling provides essential contributions to mammalian tissue patterning, *Cell* (2024). [DOI: 10.1016/j.cell.2023.12.003](#)

Provided by St. Jude Children's Research Hospital

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