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How the optic tectum stacks up

Sticky proteins help create distinctive pattern in visual center of the zebrafish brain.

FOCAL POINT

PHOTOS COURTESY OF JAMES JONTES

(Left to right) James Jontes, Marc Wolman, Sharon Cooper, and colleagues showed that δ-protocadherins help create the cellular columns in the fish's optic tectum. The researchers determined that different δ-protocadherins are expressed in distinct bands. In the optic tectum of a zebrafish embryo (far right), the bands expressing *pcdh7* (green) and *pcdh19* (purple) show little overlap.

δ-Protocadherins promote family get-togethers in the developing zebrafish brain. These adhesion proteins help related cells stack up to form columns that are essential for responding to visual stimuli, Cooper et al. reveal (1).

In human brains, the visual cortex parses the information streaming in from our eyes. The structure is organized as a series of repeating columns of neurons that radiate through the layers of the cortex (2). In zebrafish the optic tectum performs the same job as the visual cortex, but researchers haven't worked out how the different cell types in the optic tectum are arranged and what controls its development. Cooper et al. wondered whether δ-protocadherins help organize the optic tectum. This family of proteins helps fasten adjacent cells together and is abundant in the optic tectum (3). In addition, the proteins are essential for the formation of normal brain circuits in humans. Mutations in one δ-protocadherin gene, *PCDH19*, trigger a type of epilepsy (4).

When Cooper et al. analyzed the expression of δ-protocadherins in the brains of 4-day-old zebrafish larvae, they noted a striped pattern in the optic tectum. The scientists saw a similar picture in transgenic fish engineered to express GFP in cells that normally express one of the δ-protocadherins, pcdh19. When the researchers added labels for pcdh19 and pcdh7a, they observed little overlap between bands of cells producing each type of protein. The researchers hypothesized that differential expression of δ-protocadherins parcels out the tectum into distinct domains.

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But how do δ-protocadherin–expressing cells organize into columns? A clue came from the observation that neuroepithelial cells that express *pcdh19* already form a striped pattern in 1-day-old embryos. Neuroepithelial cells are the stem cells of the early brain, so proliferation of *pcdh19*-expressing cells would result in columns. By following transgenic embryos over the first few days of development, the researchers found that they could trace the columns in 4-day-old larvae to labeled neuroepithelial cells that were present earlier in development.

Transplantation experiments provided further evidence that columns arose from individual epithelial cells. Typically, cells inserted into a blastula will scatter, and only one or a few will settle in the optic tectum. When the team transferred cells engineered to produce GFP if they expressed *pcdh19* into unlabeled blastulas, these cells gave rise to columns in 4-day-old embryos.

However, it wasn't clear whether the δ-protocadherins merely marked the columns or helped orchestrate their formation. To address this question, the researchers used transcriptional activator-like effector nucleases (TALENs) to snip and inactivate the zebrafish *pcdh19* gene. They then crossed these mutants with the transgenic, GFP-expressing fish. Less than half of the offspring of these crosses had columns in the optic tectum. The cells in these fish were less sticky, which may have allowed them to disperse and eliminate the columns.

The scientists next asked whether the loss of pcdh19 caused visual defects. Zebrafish larvae normally swim toward a bright light. Cooper et al. determined that mutant fish lacking *pcdh19* were less likely to move toward a light. And if they swam toward it, they took longer to reach their target than did control fish. Turning off the lights causes the fish to perform a distinctive maneuver, known as an O-bend, that enables them to escape what could be a dangerous situation. Larvae missing *pcdh19* were less likely to perform O-bends, the team found.

The team's findings indicate that δ-protocadherins help arrange related neurons into columns in the developing optic tectum. "They are acting at a much earlier stage of development than we would have imagined," says senior author James Jontes. The similarity of the columns in the fish's optic tectum and the mammalian visual cortex suggests that δ-protocadherins might perform a similar role in mammals. One question researchers now need to answer, says Jontes, is how these columns help process input from the eyes and enable the fish to react to their surroundings.

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3. Blevins, C.J., et al. 2011. *Neuroscience.* 199:523–534.
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