Key regulator of nervous system development works by blocking signaling protein

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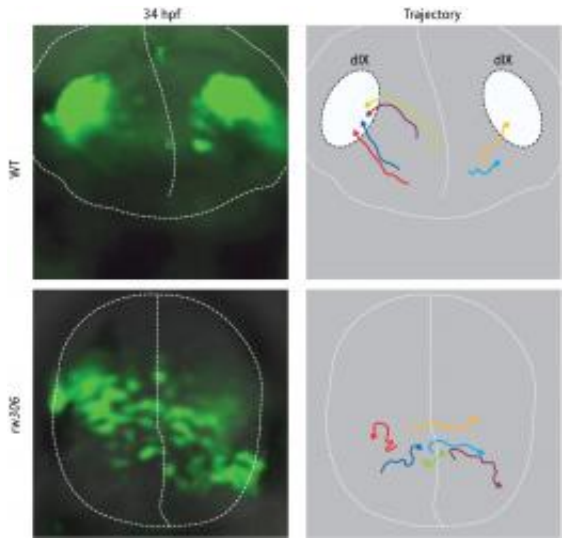

Figure 1: Thirty-four hours after fertilization, motor neuron precursors (green) in wild-type zebrafish embryos (top) show clear organization, relative to the disrupted migration apparent in the moerw306 mutant fish (bottom). Right panels illustrate the trajectories of selected neuronal precursors over the course of development. Credit: Reproduced, with permission, from Ref. 1 2011 Elsevier Inc

Neuroepithelial stem cells, the early progenitors for much of the nervous system, need to maintain a keen sense of direction in order to properly manage replication, migration and maturation. These cells are highly polarized, and exclusively initiate cell division at their apical (top) end rather than at their basal (bottom) end, although it has remained a

mystery how they determine which way is up.

By studying a zebrafish mutant with defective migration in a subset of motor neurons (Fig. 1), a team led by Shinya Ohata and Hitoshi Okamoto at the RIKEN Brain Science Institute in Wako has now uncovered valuable details about how polarity is managed. The linchpin in this process is Notch, a membrane-spanning signaling factor; when activated, Notch sheds its intracellular portion, which enters the nucleus and switches on genes that prevent neuroepithelial cells from differentiating into neurons. The researchers determined that their mutant fish contained an alteration in the gene encoding the Mosaic eyes (Moe) protein, which stimulates Notch signaling by blocking one of its inhibitors, the Crumbs (Crb) protein, and thereby maintains cells in an undifferentiated state.

Moe also proved to be an important regulator of cell migration and apico–basal polarity, although Ohata and Okamoto were surprised to learn that these effects are mediated by a poorly characterized secondary Notch-mediated signaling mechanism. In this 'non-canonical' pathway, the intracellular domain of Notch does not need to enter the nucleus to achieve an effect, but instead transmits instructions via another protein, R-Ras. The data suggest that these effects are further promoted by a positive feedback loop in which R-Ras activation stimulates Moe activity.

By acting as a high-level regulator for these various pathways, Moe serves a crucial role in ensuring that neuroepithelial cells preserve proper directionality during division and maintain their stem cell state until they arrive at the appropriate position within the embryo. "Immature status and apico–basal polarity of neuroepithelial cells, which are critical for apically restricted cell division, are both maintained by a single signaling pathway: the Crb/Moe complex-Notch pathway," says Ohata. "This could be a key link [in understanding] the fundamental properties of

neuroepithelial cells."

The researchers are now examining their favored model for Moe function, in which this protein inhibits Crb by physically sequestering it from the Notch receptor. "We are testing this hypothesis by investigating the dynamics of Crb, Moe and Notch using in vivo time-lapse imaging, which is a great advantage of doing experiments in zebrafish," says Ohata.

More information: Ohata, S., et al. Dual roles of Notch in regulation of apically restricted mitosis and apicobasal polarity of neuroepithelial cells. *Neuron* 69, 215–230 (2011). www.cell.com/neuron/abstract/S0896-6273(10)01074-3

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