DEVELOPMENT

Terminal differentiation

The identity of a neuron is determined by the so-called terminal differentiation genes (TDGs), which are activated by specific transcription factors. It is largely unknown how the TDGs are selected during developmental processes. Bertrand and Hobert now show how specific cues are integrated into the neuronal lineage to initiate the expression of TDGs in the cholinergic interneuron AIY of *Caenorhabditis elegans*, uncovering potentially general concepts of neuronal lineage specification.

During early blastomere cell divisions the transcription factor POP-1 is asymmetrically localized between daughter cells, and this asymmetry is regulated by the Wnt–β-catenin signalling pathway. The ratio of POP-1 to its co-activator SYS-1 determines whether a gene is expressed or repressed. At later stages, terminal division of the mother cell generates the AIY and SMDD sister neurons. The ~40 TDGs of the AIY neuron are under the control of two transcription factors, TTX-3 and CEH-10, that form a complex. The authors used a combination of forward and reverse genetic approaches to investigate how asymmetric divisions in the AIY cell lineage contribute to the terminal differentiation programme of AIY interneurons and whether the Wnt–β-catenin pathway is also involved.

STOCKBYTE

First, the authors showed that *C. elegans* carrying mutations of the transcription factor REF-2 lacked TTX-3 and CEH-10, and also lacked AIY interneurons. Analysis of the time window of REF-2 expression showed that REF-2 was transiently expressed in the mother cell but no longer expressed after the terminal division. Deletion analysis revealed a putative binding site for REF-2 in the *ttx-3* promoter region, suggesting that REF-2 might participate in the initiation of TTX-3 expression and AIY differentiation. After terminal division, TTX-3 levels persist in the AIY neuron and disappear in the SMDD sister, accompanied by onset of CEH-10 expression in only the AIY cell.

Next the authors investigated whether the differential activity of TTX-3 in AIY and SMDD sister neurons depends on the Wnt–β-catenin signalling pathway and POP-1. They established that in the newly generated AIY neurons the POP-1/SYS-1 ratio is low, favouring the expression of CEH-10, whereas in the newly generated SMDD cells the POP-1/SYS-1 ratio is high; these differences are generated through asymmetric Wnt signalling. In temperature-sensitive mutants in which the Wnt–β-catenin signalling pathway was impaired just before cleavage of the mother cell, the AIY and SMDD cells lacked differential expression of TTX-3 and CEH-10, suggesting that Wnt–β-catenin signalling is required for establishing the differential identities of AIY and SMDD neurons during terminal division. Furthermore, the authors found that in the final stage of development POP-1 is no longer expressed in the AIY neuron and that TTX-3 and CEH-10 maintain their own expression and directly activate the terminal differentiation genes.

It remains to be shown whether the progressive regulation of neuronal differentiation during development through asymmetric divisions and integration of the Wnt–β-catenin signalling pathway is generally applicable to neuronal lineage determination. As a step in this direction, the authors showed that the system also seems to operate in several other lineages.

Claudia Wiedemann

ORIGINAL RESEARCH PAPER Bertrand, V. & Hobert, O. Linking asymmetric cell division to the terminal differentiation program of postmitotic neurons in *C. elegans*. *Dev. Cell* **16**, 563–575 (2009)