PLASTICITY

A total makeover

The ability to generate neurons from other, easily accessible cell types from patients with a neurological or psychiatric disease is something of a holy grail for neuroscience, as such neurons would enable researchers to model the disease *in vitro* or to develop cell replacement therapies. Now, Tursun *et al.* show that germ cells can be directly converted into specific types of neuron *in vivo*.

During development, specific transcription factors induce the differentiation of cells to a particular fate, but it is thought that they can only do so in a specific cellular context. To study this context-dependence, Tursun *et al.* focused on the *Caenorhabditis elegans* transcription factor CHE-1, which is known to induce ASE neurons (a type of chemosensory neuron), and

asked whether CHE-1 is necessary and sufficient to induce an ASE cell fate. They found that, after expressing CHE-1 throughout the *C. elegans* body — both in larvae and adults — the ASE markers *gcy-5* and *ceh-36* were still only expressed in head sensory neurons.

The authors hypothesized that a factor might prevent CHE-1 from reprogramming other cells into ASE neurons, and performed an RNA interference (RNAi) library screen in which they identified LIN-53 as a potential candidate. They found that, after knockdown of *lin-53* using RNAi, CHE-1 expression could induce *gcy-5* and *ceh-36* in germ cells. Differential interference microscopy revealed that the cells now resembled neurons, even expressing axo-dendritic projections. This effect was decreased in mutant worms with a reduced mitotic pool of germ cells, but not in mutant worms in which entry into meiosis was blocked, indicating that CHE-1 can reprogramme only the mitotic pool of germ cells to a neuronal cell fate.

The newly converted cells expressed several pan-neuronal reporter genes as well as ASE-specific genes — including *gcy-7* and *eat-4* — but not genes that are normally exclusively expressed in other neuron types, suggesting that the reprogrammed cells had acquired an ASE phenotype rather than a generic neuronal phenotype.

Importantly, other neuron types could also be induced from germ cells: knockdown of *lin-53* in combination with ectopic expression of *unc-30* or *unc-3* — which are the transcription factors required for the terminal differentiation of

GABAergic and cholinergic motor neurons, respectively — reprogrammed germ cells into cells expressing the GABAergic marker *unc-47* and the cholinergic marker *arc-2*, respectively. Thus, *lin-53* loss seems to endow germ cells with the capacity to ‘redifferentiate’ into various types of neuron depending on the transcription factor that is expressed.

How does removing *lin-53* do this? LIN-53 is known to recruit histone-modifying complexes to histones H3 and H4. Two of these complexes, NURD and Sin3a, contain histone deacetylase (HDAC) components, raising the possibility that removing *lin-53* prevents HDAC activity, enabling gene transcription. Indeed, in worms treated with the HDAC inhibitors valproic acid or trichostatin A, expressing *che-1* triggered germ cells to adopt an ASE fate.

The authors speculate that LIN-53, by regulating chromatin structure, prevents transcription factors from accessing genes and inducing (re)differentiation. These findings extend a previous study showing that expressing a combination of three transcription factors could convert adult mouse fibroblasts into functional neurons *in vitro*. These studies indicate the potential of both somatic and germline cells from adult animals to convert to a distinct neuron type without having to enter a pluripotent stage.

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ORIGINAL RESEARCH PAPER Tursun, B., Patel, T., Kratsios, P. & Hobert, O. Direct conversion of *C. elegans* germ cells into specific neuron types. *Science* 9 Dec 2010 (doi: 10.1126/science.1199082)

FURTHER READING Vierbuchen, T. *et al.* Direct conversion of fibroblasts to functional neurons by defined factors. *Nature* **463**, 1035–1041 (2010)