GENETICS

A genetic system to study reprogramming

***Caenorhabditis elegans* can be used to probe the mechanistic basis for cell-fate conversion.**

In the flurry of excitement that now surrounds cellular reprogramming—the ability to change one differentiated cell type into another or to dedifferentiate cells to a more embryonic state—the fundamental link to developmental biology sometimes appears to have been lost.

A new study reporting a genetic system to study reprogramming, however, began with a question that is more classically ‘developmental’. Oliver Hobert and Baris Tursun at Columbia University were interested in understanding why transcription-factor activity is context-dependent. In other words, they wanted to know why a given transcription factor, when ectopically expressed in *C. elegans*, promotes a particular cell fate only in a restricted subset of cells.

“We did something rather naive to probe this,” says Tursun. “We expressed the transcription factor CHE-1 ubiquitously in the worm and then screened for mutants that would allow CHE-1 to turn other cells into neurons.” After some initial attempts with chemical mutagenesis, the researchers settled on screening an RNA interference (RNAi) library targeting about 500 candidate genes known to be involved in chromatin regulation.

CHE-1 is necessary for specifying a set of gustatory neurons, the ASE neurons, but ubiquitous ectopic expression in an otherwise wild-type worm results in fate transformation of only a few additional head neurons in the worm. When they used RNAi to knock down the histone chaperone LIN-53 in the CHE-1-expressing worms, however, Tursun and colleagues saw a dramatic increase in the number of ASE neuron-like cells in the midbodies. What is more, they could reproduce this phenotype by treating CHE-1-expressing worms with the histone deacetylase inhibitor valproic acid, suggesting that LIN-53 knockdown effects a fate change because of a role in histone function.

“We actually picked up LIN-53 in the first week of screening,” laughs Tursun, an encouraging early twist of fate in an otherwise grueling image-based screen. The reprogrammed ASE-like cells not only expressed characteristic markers of these gustatory neurons, but they also changed morphologically, growing cellular processes and acquiring a neuronal nuclear morphology. The cells that had been transformed into neurons, Tursun and colleagues found, were mitotic germ cells in the worm gonad. “Germ cells seem to have some sort of protective mechanism to prevent fate changes, so you need to know what to turn off if you want to make another cell type,” Tursun says.

What, one may well ask, is the value of a worm with its gonads full of neurons? In addition to the insight the worms provide into the function of specific factors, the overall approach presents a beautiful genetic system to study the mechanistic basis for cellular reprogramming. Screening for induction of ectopic fates can now be extended to whole-genome RNAi libraries and to chemically mutagenized worms. Screens can be carried out for factors that promote fate changes along nonneuronal lineages, using different transcription factors. And the possibility remains that cells other than germ cells, and which do not possess their unique developmental potential, may also be amenable to fate transformation and may require different perturbations, or combinations of perturbations, for this to be achieved.

It is perhaps not unexpected, given what is known about reprogramming in other systems, that proliferating germ cells are prone to undergo fate changes and that chromatin modifiers have a role in this process. But there are surely still surprises in store. Bringing the power of genetics to bear on the question of how one cell can be changed into another has as good a chance as any of uncovering hidden players in the process.

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RESEARCH PAPERS

Tursun, B. *et al.* Direct conversion of *C. elegans* germ cells into specific neuron types. *Science advance* online publication, 9 December 2010.