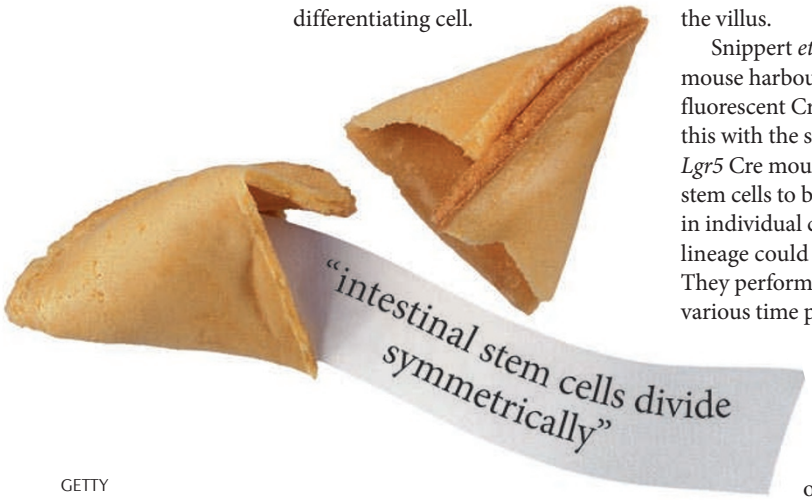
STEM CELLS

Dividing with symmetry

Stem cell population homeostasis, which ensures that stem cells divide to produce a differentiating cell and a new stem cell, is widely thought to be achieved through asymmetric cell division, whereby each division generates a cell of each fate. In this scenario, fate asymmetry is an 'invariant' result of division (whether it is determined by external factors or the segregation of internal factors). Alternatively, the two daughter cells generated by division may not have intrinsically divergent fates and could potentially become two stem cells, two differentiating cells or one differentiating and one stem cell. If this is the case then stem cell homeostasis would be regulated at the population level so that, on average, each stem cell division results in one stem cell and one differentiating cell.



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These theoretical alternative models have been difficult to observe in mammalian tissues owing to the size of tissues and the difficulty of identifying individual stem cells *in vivo*. Now, in *Cell* and *Science*, two studies show that mouse intestinal stem cells divide symmetrically and adopt stem or differentiating states in a stochastic manner.

These studies used the intestinal epithelium as a model for mammalian adult stem cells, as it is a rapidly self-renewing tissue and is known to have a simple layout — it is a sheet of cells that bends in space to form the crypts and villi of the intestine. Stem cells locate at the crypt base and feed daughter cells into the compartment above (the transit-amplifying compartment), the cells of which divide and differentiate, moving upwards in the villus.

Snippert *et al*. generated a mouse harbouring a four-colour fluorescent Cre-reporter and crossed this with the stem cell-specific *Lgr5* Cre mouse. This enabled crypt stem cells to be fluorescently labelled in individual colours so that their lineage could be traced *in vivo*. They performed clonal analyses at various time points. In the short term (up to 14 days) they found that single stem cells generated different numbers of daughter stem cells or none, showing that intestinal stem cells follow divergent fates, some differentiating and some remaining pluripotent. However, stem cell numbers were maintained on average across different clones, indicating that stem cell loss in a clone is compensated for by expansion of adjacent clones.

Lopez-Garcia *et al*. used an inducible system that labels proliferative cells in the crypts of the small intestinal epithelium and the colon. By performing long-term lineage tracing (across 30 weeks), both sets of authors showed that crypts gradually become monoclonal, whereby all stem cells of the crypt are derived from a single precursor stem cell. Both groups used a novel quantitative analysis of the clonal fate data to show that stem cells are equipotent. Their turnover follows a pattern of neutral drift dynamics, in which stochastic stem cell loss through differentiation is compensated for by symmetric self-renewal of neighbouring stem cells.

Whether homeostasis is achieved at the population level in other stem cell types remains to be determined.

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ORIGINAL RESEARCH PAPERS Snippert, H. J. *et al*. Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. *Cell* **143**, 134–144 (2010) | Lopez-Garcia, C., Klein, A. M., Simons, B. D. & Winton, D. J. Intestinal stem cell replacement follows a pattern of neutral drift. *Science* 23 Sep 2010 (doi:10.1126/science.1196236)