

DEVELOPMENT

How deep are your cells?



The depth of cells — the number of cell divisions since the zygote — can be assessed by eye in *Caenorhabditis elegans*, but has been difficult to estimate accurately in humans and in mice. A new study has developed a non-invasive, accurate and systematic way to quantitatively estimate cell depth on the basis of the number of mutations in microsatellites (repetitive DNA sequences), and has applied it to several cell lineages in mice. This new method provides the key to understanding whether neurons can regenerate and whether adult females can create new oocytes, as well as shedding light on the dynamics of stem cells.

Each time a cell divides, somatic mutations are introduced — this means that the number of mutations can be used as a measure of the depth of a cell. Owing to the high abundance of microsatellites in humans and mice, and because slippage mutation — which is coupled to cell division — occurs at a relatively high rate in microsatellites, the authors

analysed approximately 100 microsatellites and used them to estimate cell depth.

Previous estimates were based on theoretical calculations, which incorporated assumptions of proliferation kinetics and cell number, and were calculated only for oocytes and sperm cells. The authors derived a simple linear correlation between the depth of a cell and its genetic drift from the zygote using an *ex vivo* calibration set-up. They used this correlation to provide the first precise estimates of the depth of a range of cell types in mice. They found that the average depth of oocytes is 29 cell divisions, which is consistent with previous estimates. The average depth of B cells ranges from 34 to 79; this was linearly related to age, suggesting that B cells undergo one division per day.

The quiescent nature of adult stem cells was confirmed in this study: the depth of four types of adult stem cell was found to range from 24 to 40 divisions, values that are generally lower than the differentiated cells in this

study. In addition, the average depth of satellite cells (adult stem cells under the basal lamina of muscle fibres) was similar across a range of ages, suggesting that they too have a low turnover.

The authors concede that their estimates might be imprecise to some extent owing to the variable nature of mutations, differences in mutation rates *ex vivo* and *in vivo*, and differences between various tissues. However, the future development of a compensation step would be likely to overcome these limitations. This method for the accurate estimation of cell depth will allow tissue-turnover rates to be determined in various animals and, importantly, in humans. This will provide a way to address fundamental questions about the behaviour of the body under physiological and pathological conditions.

Elizabeth Neame

ORIGINAL RESEARCH PAPER

Wasserstrom, A. *et al.* Estimating cell depth from somatic mutations. *PLoS Comput. Biol.* **4**, e1000058 (2008)