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DIGITAL VISION

DEVELOPMENT

Many roads lead to commitment

The molecular events that govern the transition of a multipotent cell to a state in which it is committed to a specific lineage are poorly characterized, at least partly because of the difficulty in following individual cells through this process. Using single-cell analyses in a well-characterized mouse haematopoietic cell line, a recent paper suggests that there are multiple entry points to lineage commitment through sporadic expression of lineage regulators.

The multipotent haematopoietic cell line EML can give rise to cells of the myeloid or erythroid lineages. Previous work had separated populations of EML cells with a global erythroid transcriptional signature or with a global myeloid transcriptional signature (termed the SCA1^{low} population and SCA1^{hi} population, respectively). Analysis at the population level had suggested that cells could fluctuate between these transcriptional programmes while retaining self-renewal potential. That is, multipotent cells could 'sample' different global transcriptional programmes before becoming committed to a particular lineage. Under this model, lineage-biased gene expression and self-renewal capacity exist in the same cells (this modified an earlier model in which multipotent cells are 'primed' for alternative potential fates).

In this work, Pina *et al.* analysed the SCA1^{low} population at a single-cell level. They found that this population is heterogeneous for expression of the key erythroid transcription factor *Gata1* and for self-renewal capacity. Indeed, they were able to separate the SCA1^{low} population into two distinct subpopulations: one contained all of the self-renewal capacity that was seen in the SCA1^{low} population; the other contained almost all of the GATA1 protein that was seen in SCA1^{low} population, but it lacked self-renewal capacity and was committed to the erythroid lineage (this is referred to as the erythroid-committed population (EryCP)). Therefore, their work does not support the model in which multipotent cells sample global lineage-specific programmes.

EryCP cells represent a group of cells that have just crossed the boundary from multipotency to lineage commitment. Although the EryCP cells have irreversibly committed to becoming erythroid cells, their transcriptional programme is closer to that of self-renewing cells in the EML cultures than to cells that have undergone erythroid differentiation. That is, they are committed without expressing a complete erythroid transcriptome. Pina *et al.* also performed quantitative analyses in single EryCP cells of the expression of a panel of genes that are known to be expressed in multipotent, erythroid or myeloid cells. They found substantial cell-to-cell variation and, intriguingly, they found that erythroid commitment in some cells could occur without expression of some erythroid factors (including *Gata1*) or without silencing some markers of other lineages. The heterogeneity suggests that commitment does not require a coordinated gene-expression programme but rather that it is triggered by sporadic expression of lineage factors and then later consolidated into a coherent transcriptional programme.

This model is supported by evidence that haematopoietic stem cells that are isolated from bone marrow show low-frequency expression of lineage-associated genes. A similar model has been proposed for a granulocyte cell line based on population studies, suggesting that it may be more broadly applicable.

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ORIGINAL RESEARCH PAPER Pina, C. *et al.* Inferring rules of lineage commitment in haematopoiesis. *Nature Cell Biol.* 19 Feb 2012 (doi:10.1038/ncb2442)