HAEMATOPOIESIS

Instructing fate

CORBIS

“G-CSF and M-CSF can instruct the lineage fate of genetically unmanipulated GMPs.”

Do cell-extrinsic cytokines provide the necessary signals that instruct the lineage fate of haematopoietic progenitor cells (HPCs) (instructive model) or do they simply select HPCs that are already committed to a specific lineage by providing survival and proliferation signals (selective model)? Schroeder and colleagues provide an answer to this long-debated question and show that granulocyte colony-stimulating factor (G-CSF) and macrophage CSF (M-CSF) instruct the lineage

choice of granulocyte-macrophage progenitors (GMPs).

Cytokines are necessary and sufficient for the generation of mature blood cells but, owing to technical limitations, it has not been possible to show that they can actually instruct the lineage choice of unmanipulated HPCs under physiological conditions. Continuous single-cell tracking is required to determine the exact kinship, lineage commitment and cell death of all individual cells in HPC colonies, and only then can the instructive model be reliably proved. So, the authors used transgenic mice in which the expression of enhanced green fluorescent protein (EGFP) is under the control of the lysozyme M gene locus (*LysM*), which is expressed specifically by myelomonocytic cells. They showed that undifferentiated GMPs express very low levels of *LysM*-EGFP; however, following culture with either G-CSF or M-CSF the expression of *LysM*-EGFP is upregulated in differentiating GMPs, their colony-forming potential is lost and they become mature neutrophil granulocytic or monocytic cells, respectively. Therefore, *LysM*-EGFP can be used as a marker for single-lineage-restricted cells.

Next, the authors continuously monitored hundreds of GMPs and all their progeny at the single-cell

level throughout their development *in vitro* (4 days and 4 hours) in the presence of either G-CSF or M-CSF by time-lapse microscopy. They found that ~90% of GMPs differentiated exclusively into a single lineage in the presence of either cytokine alone, indicating that GMPs are bipotent. In addition, no cell death occurred in ~88% of GMP pedigrees that were generated in the presence of either G-CSF or M-CSF and resulted in exclusively single-lineage progeny. The lack of cell death excludes the possibility that single-lineage progeny were generated owing to selection and indicates that the cytokine present in the culture provided the essential lineage choice instruction to bipotent GMPs. As well as determining lineage choice, G-CSF and M-CSF were shown to accelerate the differentiation of GMPs compared with interleukin-3, interleukin-6 and stem-cell factor.

This study describes a new method for cell fate analysis and shows that G-CSF and M-CSF can instruct the lineage fate of genetically unmanipulated GMPs.

Olive Leavy

ORIGINAL RESEARCH PAPER Rieger, M. A., Hoppe, P. S., Smejkal, B. M., Eitelhuber, A. C. & Schroeder, T. Hematopoietic cytokines can instruct lineage choice. *Science* **325**, 217–218 (2009)