Journal club

HETEROGENEITY OF SISTER CELL FATES

Multipotent stem and progenitor cells can differentiate into multiple cell types. How lineage choice is controlled is a central question in stem cell research, but little is known about the underlying molecular mechanisms. The main difficulty in understanding this process is due to a feature of stem and progenitor cells — heterogeneity between cells — which was accurately described three decades ago by Suda, Suda and Ogawa. Cells within a population not only differ in their commitment to specific fates but also in their timing of making such a decision.

The authors analysed lineage choices of hundreds of mouse haematopoietic progenitor cells by manually separating their daughter cells and quantifying their lineage output. Both the lineage choice and the timing of lineage commitment varied vastly between daughter cells. By combining these results with those of a follow up study, it became clear that commitment to a single lineage could either occur slowly and in a stepwise manner over generations, or within just one generation. Importantly, different behaviours could be observed even between sister cells, excluding potential differences in starting cells as a reason for variable lineage output and speed at which commitment occurs.

This study highlights the importance of analysing the behaviour of single cells over time. It also illustrates a major challenge for unravelling the molecular control of stem and progenitor cell fate decisions: it requires studying cells undergoing the same fate decision precisely at the time when the cells commit. For this, homogeneous cell populations in which individual cells have identical and synchronized behaviour should be available. However, as demonstrated by the authors, stem and progenitor cell fate decisions are heterogeneous and non-synchronized.

Experimental procedures such as stem and progenitor cell purification were not as refined then as they are today. However, even using the most recent enrichment protocols, individual stem and progenitor cells generate progeny of unpredictable lineage composition and with different kinetics. Ultimately, continuous single-cell analysis, combining live non-invasive quantification of regulatory molecules and their networks together with knowledge of future cell fates, will be necessary to overcome this problem.

However, this remains technically challenging, and the molecular control of stem and progenitor cell fates and their heterogeneity remains almost as puzzling as 30 years ago.

Timm Schroeder
Department of Biosystems Science and Engineering (D-BSSE), Eidgenössische Technische Hochschule (ETH) Zürich, 4058 Basel, Switzerland.
e-mail: timm.schroeder@bsse.ethz.ch

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