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Sister Cells in Harmony: Experimental and Mathematical Evidence of Homogeneity in Hematopoietic Human Stem and Progenitor Cells

Alessandro Donada[1], **Gurvan Hermange**[2], Idan Milo[1], Jacques Vargaftig[3], Christophe Willekens[4], David Michonneau[5], Paul-Henry Cournède[2], Leïla Perié[1]

1 Institut Curie, Paris, France
2 Université Paris-Saclay, CentraleSupélec, Gif-sur-Yvette, France
3 Institut Curie, Saint-Cloud, France
4 Gustave Roussy, Villejuif, France
5 Saint-Louis Hospital, Paris, France

Given the growing understanding of the heterogeneity of human hematopoietic stem and progenitor cells (HSPC), investigating the factors contributing to this heterogeneity at the single-cell level has become crucial.

In this study, we combine experimental and mathematical methods to explore the question of the homogeneity inside families of human HSPC, defined as cells that share a common ancestor.

For that purpose, we developed two distinct experimental assays. In the first one, we followed the first divisions of HSPC by live-cell imaging. We found sister cells to be synchronous, i.e., dividing almost simultaneously (independently from the division time of the mother cell). In the second assay, we cultured HSPC at single-cell level for three or four days, and analyzed the resulting offspring by flow cytometry, for their division properties (number of divisions encountered and cell types). We found that cells originating from a common ancestor are concordant in fate and homogeneous in division, meaning that they tend to be of the same cell type and to have encountered the same number of divisions. Therefore, our experimental results suggest that human hematopoiesis is formed by homogeneous cell families and that this homogeneity would result from two distinct properties: synchronicity and concordance.

To validate our results, eliminate potential biases, and verify that our experimental observations could not be obtained by alternative hypotheses, we developed a mathematical approach, modelling the HSPC short-term proliferation and differentiation process and calibrating this model from our experimental data using a statistical inference method. Among the 18 hypotheses we implemented, the most likely is the one where sister cells are concordant and synchronous. Interestingly, more complex models proposing different properties for non-same-type sister cells were rejected, suggesting that the concordance and synchronicity properties would not depend on the sister cell types but be inherited from the mother cell. We performed additional single-cell transcriptomics that confirmed this hypothesis.

Overall, our study unveils the first evidence, in humans, of intrinsic cellular memory transmitted from mother to daughter HSPC, establishing a hematopoietic system with homogenous cell families and heterogeneous inter-familial structure.