Poster 11: How studying cell-to-cell gene expression variability could help deciphering endothelial-to-hematopoietic transition

Bérénice Dugué 1, Geoffrey Garcia 1, Olivier Mansier 1.2, Chloé James 1.2, Charles Dussiau 1.2
1 - University of Bordeaux, UMRl034, Inserm, Biology of Cardiovascular Diseases, 33600, Pessac, France
2 - CHU de Bordeaux, Laboratoire d'Hématologie, 33600, Pessac, France

Introduction: Differentiation is often conceptualized as a biological process resulting from the deterministic execution of programs encoded in the genome. According to this theory, ail cells committed to a specific cellular fate follow the same instructions and therefore should exhibit minimal cell-to-cell gene expression variability. However, the importance of stochasticity in differentiation is increasingly recognized. It has recently been demonstrated that a peak of cell-to-cell gene expression variability occurs during avian erythropoiesis in vitro [1] and during adult human hematopoiesis in-vivo [2]. In this context, we aimed at demonstrating the importance of stochasticity in gene expression during another biological process: the endothelial-to-hematopoietic transition (EHT) (the process that allows generation of hematopoietic stem cells (HSC) during embryogenesis from specific endothelial cells of the dorsal aorta). **Methods**: Public Single-cell RNA-seq data from murine and human cells undergoing EHT were analyzed in order to assess cell-to-cell gene expression variability during the transition. We first reconstructed the differentiation trajectory of the cells and then measured cell-to-cell gene expression variability along the differentiation trajectory using Shannon Entropy as previously described [2].

Results: An increase in cell-to-cell gene expression variability is observed during EHT. Interestingly, this variability does not decrease after the transition, contrary to what was observed in adult hematopoiesis. Moreover, the genes whose cell-to-cell variation of expression increases the most over the course of EHT are enriched in transcription factors; some were already known to be involved in this process, but we also found ones that may be of interest for EHT.

Conclusion: Our analysis confirms previous studies on the role of cell-to-cell gene expression variability during differentiation processes [1,2] and supports the stochastic view of differentiation. The cell-to-cell gene expression variability remains high at the end of EHT, suggesting that cells emerging from EHT are notas homogeneous as previously thought, which is in line with the study of Guibentif et al [3]. Sorne of the transcription factors with the biggest cell-to-cell variation of expression during EHT had not yet been described as having a role in this specific process ; therefore, it may be of interest to study the potential raie of these transcription factors in experimental models of EHT.

[1]: Richard, Angélique, et al. « Single-Cell-Based Analysis Highlights a Surge in Cell-to-Cell Molecular Variability Preceding Irreversible Commitment in a Differentiation Process ». PLOS Biology, vol. 14, no 12, déc 2016, p. e1002585, https://doi.org/l0.1371/journal.pbio.1002585.
[2]: Dussiau, Charles, et al.« Hematopoietic differentiation is characterized by a transient peak of entropy at a single-cell level ». BMC Biology, vol. 20, no 1, mars 2022, p. 60, https://doi.org/10.1186/sl2915-022-01264-9.
[3] : Guibentif, Carolina, et al. « Single-Cell Analysis Identifies Distinct Stages of Human Endothelial-to-Hematopoietic Transition ». Cell Reports, vol. 19, no 1, avril 2017, p. 10-19, https:/ /doi.org/10.1016/j.celrep.2017 .03.023