Modeling HSC aging with single cell approaches to decipher myeloproliferation onset

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Abstract (10 lines)

Hematopoietic stem cells (HSCs) represent a rare population of cells residing in the Bone Marrow at the top of hematopoietic hierarchy. The hematopoietic system declines with age and this age-related alteration is associated to defects in HSC function and an increase of myeloid-derived hematological disorders such as myeloproliferative neoplasms (MPNs). However, the effect of the biological parameters of HSC aging on MPN remains poorly understood. The PhD project will be dedicated to develop single-cell transcriptomic data analyses and network modeling to unveil how aged-related HSC decline is orchestrated during aging and is linked to MPN development. We will build on previously generated scRNA-seq data from aging mutant mouse models, which exhibit an accelerated HSC aging phenotype and increased susceptibility to hematological malignancies. We will apply computational methods recovering complex trajectories from transcriptomic data to define dynamic changes in HSC potential through comparative analysis of young, old and mutant mouse models. The reconstructed trajectories will be validated by examining variation in known marker genes and then exploited to build a mathematical model of relevant transcriptional pathways and regulators in different lineages to unveil the molecular mechanisms promoting MPN development in aged HSCs.

Keywords Regulatory networks, mathematical and logical modelling, HSC aging, Myeloproliferative neoplasms, data integration, transcriptional regulation

Objectives (5 lines)

In this project, we aim to decipher transcriptional networks in the context of aged-related myeloproliferation. To this purpose, we propose to use a combination of data analysis and network modelling approaches to identify key regulatory mechanisms and target molecules which lead to blood disease and aging. Our study will result in a molecular characterization of HSC aging processes, a better understanding of their association to MPNs and the discovery of potential new critical events for monitoring MPN onset.

Proposed approach (experimental / theoretical / computational) (10 lines)

This thesis project will combine two approaches: 1) Identifying and characterizing cell populations that are responsible to MPN development based on their transcriptional profiles. Relying on existing multi-omics data

(bulk and single-cell RNA-seq and ATAC-seq), the student will use data integration approaches, and then use network inference methods to decipher the underlying regulatory mechanisms. The results will then be combined with cis-regulatory motif analysis to predict novel transcriptional and epigenetic regulatory interactions associated with specific populations. 2) Developing a mechanistic model for the transcriptional, signaling and epigenetic network associated with age related disease. Building on pre-existing models, the student will progressively introduce newly inferred regulatory interactions into a comprehensive logical model, perform dynamical analyses, compare the results with existing data, and finally predict novel intervention points to slowdown the deterious effect of aging.

Interdisciplinarity (10 lines)

This is a collaborative project between a mathematical team and a biological team. MABioS (Mathematics and Algorithms for Systems Biology) team is located at Luminy, in the Mathematical Institute of Marseille (I2M) and gathers expertise in discrete mathematics, graph theory and combinatorics to model and analyze gene regulatory networks. The research team " Epigenetics in normal and malignant hematopoiesis » led by Estelle Duprez is hosted in the Marseille Cancer Research Center. The team is specialized in epigenetic aging and leukemia and develops sc-omics projects to understand the development of age-related hematopoietic diseases and resistance to treatments. Both teams have recently generated single-cell omics data related to HSC aging that led to the construction of a logic model of HSC differentiation and the prediction of important events in HSC aging. To be successful, the PhD student will need to integrate biology, bioinformatics and mathematics. tools and will benefit from the expertise of the two teams, from experimental biologists to computer scientists and mathematicians.

Expected profile (5 lines)

The proposed project can be tackled from mathematical or computational biology perspectives. We hence seek for PhD student with either: i) A master degree in mathematics and interest in discrete dynamical systems, combinatorics and graph theory, or ii) A master degree in an area related to Computational Biology with interest in data analysis, genetics and single-cell multiomics . The candidate should have a broad interest in cellular biology and be willing to cross discipline.

Is this project the continuation of an existing project or an entirely new one?
In the case of an existing project, please explain the links between the two projects (5 lines)

The two teams have been collaborating on aging mechanisms of the hematopoietic stem cell. This PhD proposition is a continuation of that project that has focused on age-related HSC alteration but will develop a new aspect as it will be related to age-related disease development

2 to 5 references related to the project

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Hao, Y., Hao, S., Andersen-Nissen, E., Mauck, W.M., 3rd, Zheng, S., Butler, A., Lee, M.J., Wilk, A.J., Darby, C., Zager, M., et al. (2021). Integrated analysis of multimodal single-cell data. Cell *184*, 3573-3587 e3529. 10.1016/j.cell.2021.04.048.

Naldi A, Hernandez C, Levy N, *et al*. (2018). The CoLoMoTo Interactive Notebook: Accessible and Reproducible Computational Analyses for Qualitative Biological Networks. *Front Physiol* 9: 680.

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Caiado F, Pietras EM, Manz MG. (2021) Inflammation as a regulator of hematopoietic stem cell function in disease, aging, and clonal selection. *J Exp Med,* 218(7):e20201541. doi: 10.1084/jem.20201541.

3 main publications from each PI over the last 5 years

**: Common publications between the two teams.*

- * Hérault, L., Poplineau, M., **Duprez, E**., **Remy, E**. A novel Boolean network inference strategy to model early hematopoiesis aging, *in press Computational and Structural Biotechnology Journal***.** bioRxiv 2022.02.08.479548; https://doi.org/10.1101/2022.02.08.479548

- Cantini L, *et al*. **Remy, E** Baudot A (2020). Benchmarking joint multi-omics dimensionality reduction approaches for the study of cancer. *Nat Commun* 12(1): 124.

- * Hérault L, Poplineau M, Mazuel A, Platet N, **Remy É**, **Duprez E** Single-cell RNA-seq reveals a concomitant delay in differentiation and cell cycle of aged hematopoietic stem cells. *BMC Biol*. 2021 Feb 1;19(1):19. doi: 10.1186/s12915-021-00955-z. PMID: 33526011

- Poplineau M, Platet N, Mazuel A, Hérault L, N'Guyen L, Koide S, Nakajima-Takagi Y, Kuribayashi W, Carbuccia N, Haboub L, Vernerey J, Oshima M, Birnbaum D, Iwama A, **Duprez E**. Noncanonical EZH2 drives retinoic acid resistance of variant acute promyelocytic leukemias. *Blood*. 2022 Dec 1;140(22):2358-2370. doi: 10.1182/blood.2022015668.

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- Koubi, M., Poplineau M., Vernerey, J., N'Guyen L., El-Kaoutari, A., Garciaz, S., Tiberi, G., Maqbool, MA, Andrau, JC, Guillouf, C., Saurin, A., **Duprez E**. Regulation of the positive transcriptional effect of PLZF through a non-canonical EZH2 activity. *Nucleic Acids Research*, 46: 3339-3350. (2018) PMID: 29425303