Analysis of genomics and epigenomics data to clarify the identity and functions of plasmacytoid dendritic cells

Degree : M2

Expected start date : 01/01/2024

Expected duration (in weeks) : 32

Research area : Computational biology, Genomics

Application deadline : 03/10/2023

Type of internship : Academic

Project description

Plasmacytoid dendritic cells (pDCs) are hematopoietic cells characterized by high and rapid production of type I and III interferons in response to viral-type stimuli (ref.1). However, the identity of pDCs is ambiguous. Whether pDCs belong to the family of dendritic cells (DCs) or innate lymphoid cells (ILCs) is currently debated (ref.2). Indeed, pDCs are characterized by 3 identity components : (i) a specific molecular identity conserved between mice and humans (ref.3), (ii) shared characteristics with classical DCs (cDCs), including a specific transcriptomic module (ref.3), and (iii) a transcriptomic module and signaling pathways common with lymphocytes, in particular B cells (ref.1).

The aim of the project will be to elucidate the ambiguous identity of pDCs, relative to other immune cell types, in particular cDCs and ILCs, by assessing the proximity of their transcriptomic and epigenetic programs. In other words, the main objective will be to determine the positioning of pDCs in an atlas of immune cells, on the basis of their genomic information, via 5 tasks.

Task1. Create 2 atlases of mouse immune cells, each including pDCs, different types of ILCs, T and B lymphocytes, cDCs and myeloid cells, using public data and data from the Dalod laboratory. Atlas1. Transcriptomic profiling catalogue (scRNAseq). Atlas2 : Epigenetic profiling catalogue (ATACseq). Method. Validated analysis pipelines will be used to integrate data from different mouse studies to generate atlases (ref.4). Clusters of different immune cell types will be generated by using dimension reduction and clustering algorithms, and annotated with gene signature enrichment statistical tests.

Task2. Measure the distances between pDCs and other immune cell types in the Atlases. Method. Robust gene expression profiling data for each immune cell type will be generated in silico by aggregating data from single cells within each of the homogeneous clusters obtained (ref.5), to then perform clustering analyses (PCA, hierarchical) in a manner allowing to calculate the distance between immune cell types.

Task3. Define the gene modules specific to pDCs (Gene Module 1), shared with cDCs (Gene Module 2) or with ILCs (Gene Module 3) in Atlas1. Task4. Define the areas of open chromatin specific to pDCs (Epigenetic module peak 1), shared with cDCs (Epigenetic module peak 2) or with ILCs (Epigenetic

module peak 3) in Atlas2. Method. Differential expression analyses and enrichment statistical tests will be performed between cell types.

Task5 : Infer the molecular mechanisms regulating the identity of pDCs. Method. Statistical tests for enrichment of transcription factor binding sites, of annotations associated with genes (e.g. EnrichR), for each gene or epigenetic module identified, and high-throughput application of gene set enrichment analysis (GSEA, BubbleGUM) across cell types.

Profile sought : The student must be interested in the application of bioinformatics to immunology, motivated by new omics technologies and their computational processing, and enjoy learning and developing in a dynamic and constantly changing environment, have good organizational skills and ability to summarize scientific results, good communication skills with biological researchers, ability to work as part of a team.

Skills required : Good knowledge of the R language, knowledge of transcriptomic data analysis methods (bulk RNAseq or single cell RNAseq), knowledge of mathematical methods for analyzing multidimensional data (PCA, UMAP, etc.), good written and spoken scientific English, knowledge of system administration under Linux.

The environment : The internship will take place under the responsibility of Dr. Dalod, at the CIML, an internationally renowned immunology center located on the Luminy university campus, south of Marseille. You will be working as part of a multidisciplinary collaboration between the team of Dr Dalod, Dr Aïtor Gonzalez, an expert in data analysis from the TAGC laboratory located on the same campus, and the CB2M group (Computational Biology, Biostatistics & Modeling) that organizes and federates the CIML's bioinformaticians (around 20 people). At CB2M, you will benefit from existing expertise in single-cell and spatial transcriptomics analysis methods, and in the tools used to ensure reproducibility of results (Open Science, FAIR data). In a dedicated room, you will be surrounded by the majority of the CIML bioinformaticians on a daily basis and will play an active role in the dynamism of this community. This internship is designed to be pursued as a thesis project. The student will be offered supervision and preparation for competing for a PhD salary from ED62 (Life and Health Sciences Doctoral School).

Contact details : Please e-mail Dr. Marc Dalod (dalod@ciml.univ-mrs.fr) with your CV, a motivation letter and the contact information of two referees.

Project references

1. Reizis B. Plasmacytoid Dendritic Cells : Development, Regulation, and Function. Immunity. 2019. PMID : 30650380.
2. Ziegler Heitbrock L, Ohteki T, Ginhoux F, Shortman K, Spits H. Reclassifying plasmacytoid dendritic cells as innate lymphocytes. Nat Rev Immunol. 2023. PMID : 36380022.
3. Robbins SH, Walzer T, Dembélé D, Thibault C, Defays A, Bessou G, Xu H, Vivier E, Sellars M, Pierre P, Sharp FR, Chan S, Kastner P, Dalod M. Novel insights into the relationships between dendritic cell subsets in human and mouse revealed by genome-wide expression profiling. Genome Biol. 2008. PMID : 18218067.

4. Stuart T, Butler A, Hoffman P, Hafemeister C, Papalexi E, Mauck WM, Hao Y, Stoeckius M, Smibert P, Satija R. Comprehensive Integration of Single-Cell Data. Cell. 2019. PMID : 18218067.

5. Elahi Z, Angel PW, Butcher SK, Rajab N, Choi J, Deng Y, Mintern JD, Radford K, Wells CA. The Human Dendritic Cell Atlas : An Integrated Transcriptional Tool to Study Human Dendritic Cell Biology. J Immunol. 2022. PMID : 36427009.

Information about team

Host structure

Host structure name : Centre d'Immunologie de Marseille-Luminy (CIML)

Tutelage name list : CNRS, Inserm, AMU

Host structure address : 163 avenue de Luminy, 13288 Marseille Cedex 09

Name of the host structure director : Marc DALOD

Doctoral School team affiliation : ED62

Team

Team leader name : Marc DALOD

Team leader email : dalod@ciml.univ-mrs.fr

Internship supervisor name : Marc DALOD

Internship supervisor position : Researcher (DR)

Internship supervisor email : dalod@ciml.univ-mrs.fr

Team publication(s)

1. Valente M, Collinet N, Vu Manh TP, Popoff D, Rahmani K, Naciri K, Bessou G, Rua R, Gil L, Mionnet C, Milpied P, Tomasello E**, Dalod M**. Novel mouse models based on intersectional genetics to identify and characterize plasmacytoid dendritic cells. Nat Immunol. 2023. PMID : 36928414. **Co-senior authors.

2. Abbas A*, Vu Manh TP*, Valente M, Collinet N, Attaf N, Dong C, Naciri K, Chelbi R, Brelurut G, Cervera-Marzal I, Rauwel B, Davignon JL, Bessou G, Thomas-Chollier M, Thieffry D, Villani AC, Milpied P, Dalod M**, Tomasello E**. The activation trajectory of plasmacytoid dendritic cells in vivo during a viral infection. Nat Immunol. 2020. PMID : 32690951. *Co-first authros **Co-senior authors.

3. Reizis B, Idoyaga J, Dalod M, Barrat F, Naik S, Trinchieri G, Tussiwand R, Cella M, Colonna M. Reclassification of plasmacytoid dendritic cells as innate lymphocytes is premature. Nat Rev Immunol. 2023. PMID : 36959479.
4. Cheema AS, Duan K, Dalod M, Vu Manh TP. Harnessing Single-Cell RNA Sequencing to Identify Dendritic Cell Types, Characterize Their Biological States, and Infer Their Activation Trajectory. Methods Mol Biol. 2023. PMID : 36905526.
5. Robbins SH, Walzer T, Dembélé D, Thibault C, Defays A, Bessou G, Xu H, Vivier E, Sellars M, Pierre P, Sharp FR, Chan S, Kastner P, Dalod M. Novel insights into the relationships between dendritic cell subsets in human and mouse revealed by genome-wide expression profiling. Genome Biol. 2008. PMID : 18218067.

Team composition

Number of researchers : 3

Number of researchers with habilitations : 2

Number of university teachers : 0

Number of university teachers with habilitations : 0

Number of engineers or technicians : 1

Number of ATER : 0

Number of first year Master : 0

Number of second year Master : 0

Number of PhD students : 4

Number of first year PhD students : 2

Number of second year PhD students : 2

Number of third year PhD students : 0

Number of fourth year PhD students : 0

Potential PhD recruitment : Yes