Research internship project (Master): Unravelling sex-specific polarization and functions of human macrophages

Project background

Macrophages are specialised white blood cells equipped with a range of scavenger, pattern recognition and phagocytic receptors, which enable them to sense and respond to foreign invaders and tissue injury. They play a key role in the first line of defence against infection and are crucial for the maintenance of tissue homeostasis. Based on signals from their microenvironment, they polarize towards pro-inflammatory M1 or anti-inflammatory M2 macrophages. Using computational approaches, we identified a novel transcription factor implicated in M1 macrophage polarization. This transcription factor resists X-chromosome inactivation and remains biallelically expressed in female cells, presumably leading to higher dosage in females (XX) compared to males (XY). Females generally develop stronger immune responses than males, resulting in a better response against pathogens. On the flip side, females are more prone to develop autoimmune disease. We hypothesize that our novel transcription factor candidate contributes to these sex-based immunological biases in females through the skewing of macrophages towards the pro-inflammatory M1 phenotype.

In this project, we aim to get a better understanding of sex-based differences in the immune response, and potentially identify new targets for the treatment of infectious- and autoimmune diseases. We will compare male versus female macrophages for their polarization potential and their ability to control infection. We will also mechanistically investigate the role of our transcription factor of interest in this process using CRISPR based approaches.

About the Zaugg group

The Zaugg Group at EMBL Heidelberg (https://www.embl.org/groups/zaugg/) investigates the variation of molecular phenotypes among individuals along with their genetic and epigenetic variation with the aim of better understanding the molecular basis of complex genetic traits and diseases. We have a long-standing expertise in computational biology, epigenetics and gene regulation, and we are particularly interested in studying the interaction of cells – including immune cells – with their microenvironments, and how extrinsic signals interact with the cell-intrinsic signalling-regulatory networks. This particular project is a wet lab project funded by the Infection Biology transversal theme at EMBL (https://www.embl.org/about/programme/research-plans/infection-biology/), in collaboration with the Heard group at EMBL Heidelberg. The project is led by Nila Servaas, a postdoc in the group who has a strong background in molecular immunology.

Project activities

The following laboratory assays will be involved in the internship:
Genome engineering using the CRISPR-Cas9 system; Flow cytometry; RT-qPCR; RNA-fluorescence in situ hybridization (FISH); Microscopy, Phagocytosis and chemotaxis assays; RNA- and ATAC sequencing; Generation of iPSC-derived macrophages; Cell culture.

Required skills / interests

Eager to learn; Able to work in a team but not scared to work independently; Good communication skills (in English); Affinity with immunology; Prior experience in a molecular biology lab (especially cell culture) is a plus.

Duration

At least 6 months, starting summer 2023

Contact

If you are interested in the project, send an email to Judith Zaugg (judith.zaugg@embl.de) and Nila Servaas (nila.servaas@embl.de) with a short motivation and your CV.

Research internship project (Master): Unravelling stem cell niche compositional changes upon hematological malignancies in the bone

Project background

The human bone marrow (BM) niche is an intricate organ system, composed of hematopoietic stem cells (HSCs), immune cells, and rare stromal components including endothelium, smooth muscles, mesenchymal stromal cells (MSCs), including osteoblasts and adipocytes. As individuals age, HSCs may acquire somatic mutations that can lead to expansion of mutation-carrying clones (CHIP), which in some progress into myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). The transformation of the BM niche into a neoplasm-supporting state by malignant cells is not fully understand, especially on the gene regulatory level. Our group has generated several single cell sequencing data sets of the BM niche (stroma, endothelium, T cells, HSCs) from AML mouse models and human BM aspirates of healthy, CHIP, MDS and AML patients. We observe significant differences in the abundance of various niche cell types and see particular inflammatory and stress-induced gene signatures upregulated.

The goal of this project is to enhance our understanding of how the BM niche is transformed by malignant cells by translating our single cell data into the spatial context. We have fixed bones from AML mice and human FFPE bone fragments matching to our single cell data. We will apply and further optimize antibody panels for multiplexed imaging (immuno-SABER (*Saka et al., Nat. Bio. 2019*)) to characterize multiple cell types at the same time in tissue sections. We will then compare their organization and abundance in correlation to malignant cells. Moreover, we will apply (targeted) spatial transcriptomics methods (10X Visium, Light-seq (*Kishi et al., Nat. Meth. 2022*)) to profile the more sensitive cell types (for example endothelial cells), which we could barely recover from our single cell data.

About the Zaugg group

The Zaugg Group at EMBL Heidelberg is dedicated to explore the relationship between molecular phenotypes, genetic and epigenetic variation among individuals to better understand the molecular basis of complex genetic traits, and diseases. We have a long-standing expertise in computational biology, epigenetics, and gene regulation. We are particularly interested in studying the interaction of cells with their microenvironment and how extrinsic signals interact with the cell-intrinsic signalling-regulatory networks. This project is in collaboration with the Saka group (EMBL Heidelberg), whose expertise lies in developing tools and methods for immunofluorescence and spatial transcriptomics. This project will be primarily wet lab, led by Karin Prummel, a postdoc with a strong background in stem cell biology, omics technologies and microscopy, and working with the Zaugg and Saka groups.

Project activities

The following laboratory assays will be involved in the internship: microscopy, (multiplexed) immunofluorescence (Immuno-SABER), spatial transcriptomics (Light-Seq, 10X Visium, etc.), tissue handling, fluorescence ISH. Also possibility to gain experience in computational analysis: image analysis (Fiji/Python/R), (bulk) RNA-seq (R), spatial transcriptomics (R)

Required skills / interests

Eager to learn, able to work in a team but also independently, good communication skills (in English), affinity with cancer and stem cell biology, prior experience in a molecular biology lab (especially microscopy, immunofluorescence, RNA work)

Duration

At least 6 months, start possible from summer 2023

Contact

If you are interested in the project, send an email to Judith Zaugg (judith.zaugg@embl.de) and Karin Prummel (karin.prummel@embl.de) with a short motivation and your CV.