Project abstract

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PROJECT PROPOSAL

Title: Profiling DNA methylation patterns at single-cell resolution in Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is an aggressive hematological malignancy with poor prognosis driven by the differentiation arrest of blood cells (blasts). Single-cell transcriptomic analysis has contributed to the detailed characterization of leukemic blast cells[1], yet their epigenetic alterations are poorly understood on the single-cell level. This is especially true for DNA methylation, since an appropriate single-cell technology has not been available. We recently developed scTAM-seq[2]; a single-cell method profiling up to 1,000 CpG methylation states in up to 10,000 cells per experiment. Profiling DNA methylation patterns in AML is especially crucial, since common leukemic mutations occur in modifiers of DNA methylation such as DNMT3A, TET2, or IDH1/2.

Within this project, we will leverage scTAM-seq to describe the DNA methylation landscape of AML, especially with respect to DNMT3A/TET2 mutations. Since scTAM-seq is based on the Mission Bio Tapestri technology, DNA methylation can be read out together with somatic mutations in DNMT3A/TET2 and the expression of surface proteins at the single-cell level. The selection of CpGs to be profiled with scTAM-seq has already been conducted. The resulting data will provide a high-resolution map of the differentiation state of the cells. The scientist can work both in the wet-lab to perform scTAM-seq together with an experienced technician from the division together with support by the scOpen-lab, as well as on data analysis. Current data analysis shows that scTAM-seq data provides a map of hematopoietic differentiation at a similar resolution compared to scRNA-seq. Additionally, clonal information is present in scTAM-seq data, such that the clonal hierarchy of cancer evolution can be profiled with already developed computational methods. Ultimately, we aim at understanding which of the clones drives a potential relapse, or whether there are therapy-induced changes in the DNA methylation state.

The project offers the unique opportunity to profile an epigenetic modification in single-cells and to understand individual clonal evolution.

References

1. Beneyto-Calabuig, S. *et al.* Clonally resolved single-cell multi-omics identifies routes of cellular differentiation in acute myeloid leukemia. *Cell Stem Cell* **30**, 706-721.e8 (2023).
2. Bianchi, A. *et al.* scTAM-seq enables targeted high-confidence analysis of DNA methylation in single cells. *Genome Biol* **23**, 229 (2022).