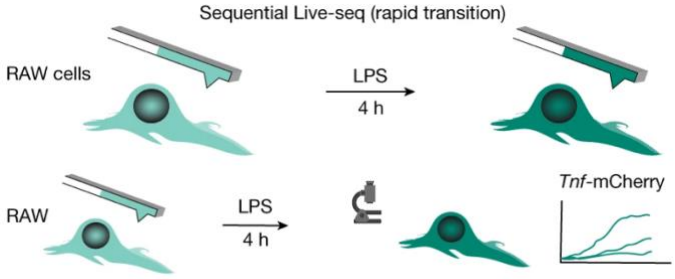
Single Cell Transcriptomics

Newsletter September 2022

Paper 1

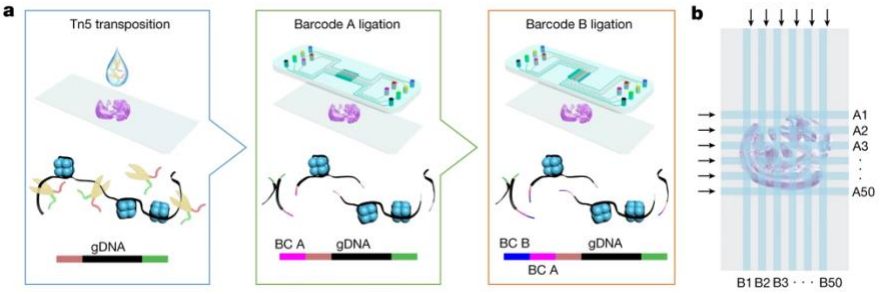
Chen, W *et al.* [Live-seq enables temporal transcriptomic recording of single cells](), *Nature*, 2022



Chen, W et al. from EPFL and ETH Zurich established Live-seq, a single-cell transcriptome profiling approach which preserves cell viability during RNA extraction using a cytoplasmic biopsy. The technology is based on fluidic force microscopy (FluidFM), which coupls force control with volume control and was previously shown to allow single-cell extractions. By optimizing both FluidFM procedure and Smart-seq2 and combining them, the authors showed that high-quality, cytoplasmic mRNA can be withdrawn from live, single cells in an amount that was compatible with transcriptome profiling. This procedure allows to directly couple the current state of a cell to its downstream molecular and phenotypic properties. The authors demonstrated how Live-seq could be used to perform sequential molecular profiling of the same cells. In addition, Live-seq could function as a transcriptomic recorder by preregistering the transcriptomes of individual macrophages to subsequently identify factors underlying macrophage lipopolysaccharide (LPS) response heterogeneity, uncovering basal *Nfkbia* expression level and cell cycle state as important phenotypic determinants.

Paper 2

Deng, Y *et al.* [Spatial profiling of chromatin accessibility in mouse and human tissues](), *Nature*, 2022

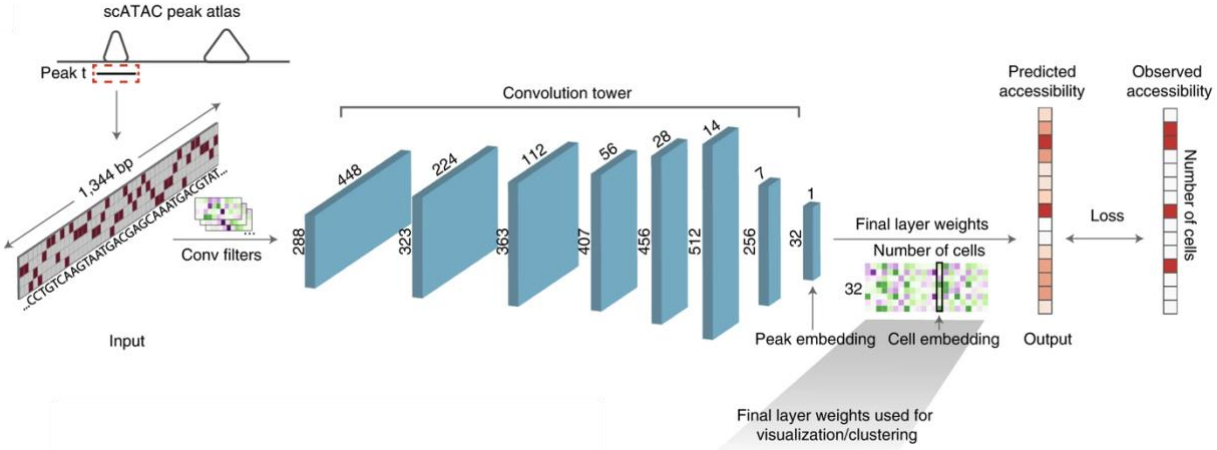


The emergence of spatial transcriptomics has enabled genome-scale gene expression mapping, but the ability to capture spatial epigenetic information of tissue at the cellular level and genome scale is lacking. The authors of this paper described a method for spatially resolved chromatin accessibility profiling of tissue sections using next-generation sequencing (spatial-ATAC-seq) by combining in situ Tn5 transposition chemistry and microfluidic deterministic barcoding. By profiling mouse embryos using spatial-ATAC-seq, they delinaeated tissue-region-specific epigenetic landscapes and identified gene regulations involved in the development of the central nervous system. They also applied spatial epigenomics to human tissues, including tonsils and the hippocampus. Spatial-ATAC-seq revealed a spatially distinct organization of immune cell types and states in relation to lymphoid follicles and extrafollicular zones. This technology adds a new dimension to spatial biology by bring spatial chromatin accessibility to the field and may offer a wide range of applications in normal development and pathogenesis study.

Paper 3

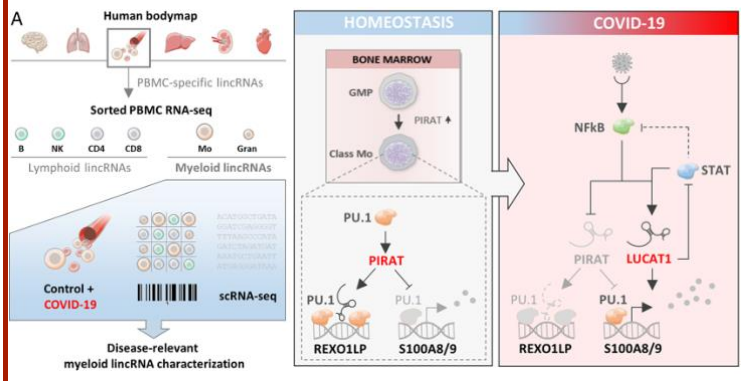
Yuan, H. & Kelley, D. R. [scBasset: sequence-based modeling of single-cell ATAC-seq using convolutional neural networks], *Nature Methods*, 2022

Single-cell assay for transposase-accessible chromatin using sequencing (scATAC-seq) shows great promise for studying cellular heterogeneity in epigenetic landscapes, but there remain important challenges in the scATAC-seq data analysis due to the inherent high dimensionality and sparsity. Yuan, H and Kelley, D proposed a more expressive sequence-dependent model for scATAC-seq based on deep convolutional neural networks (CNNs) appied to DNA sequences. In these models, the initial convolutional layer learns transcription factor (TF) motifs and other sequence factors. Subsequent layers compute nonlinear combinations of these features, to produce an explicit embedding of the sequence. When trained on multiple tasks, the final linear layer transforms the sequence embedding to predict accessibility for each task (sequencing experiments).Its parameters implicitly embed the multiple tasks based on how they make use of the latent variables in the sequence embedding. The authors showed that these cell embeddings outperformed state-of-the-art methods for clustering and cell-state representation in multiome data. By making use of sequence information in a deep learning framework, they also achieved improved scATAC-seq denoising, integration with scRNA-seq and TF activity inference over alternative methods.



Paper 4

Aznaourova, M *et al.* [Single-cell RNA sequencing uncovers the nuclear decoy lincRNA PIRAT as a regulator of systemic monocyte immunity during COVID-19], *Proceedings of the National Academy of Sciences*, 2022



The systemic immune response to viral infection is shaped by TFs, such as NF-κB, STAT1, or PU.1. Although long noncoding RNAs (lncRNAs) have been suggested as important regulators of TF activity, their contributions to the systemic immunopathologies observed during SARS-CoV-2 infection have remained unknown. Aznaourova, M *et al.* employed a targeted scRNA-seq approach to reveal lncRNAs differentially expressed in blood leukocytes during severe COVID-19. These results uncovered the lncRNA PIRAT (PU.1-induced regulator of alarmin transcription) as a major PU.1 feedback-regulator in monocytes, governing the production of the alarmins S100A8/A9, key drivers of COVID-19 pathogenesis. Knockout and transgene expression, combined with chromatin-occupancy profiling, characterized PIRAT as a nuclear decoy RNA, keeping PU.1 from binding to alarmin promoters and promoting its binding to pseudogenes in naïve monocytes. NF-κB–dependent PIRAT down-regulation during COVID-19 consequently releases a transcriptional brake, fueling alarmin production. Alarmin expression is additionally enhanced by the up-regulation of the lncRNA LUCAT1, which

promotes NF-κB–dependent gene expression at the expense of targets of the JAK-STAT pathway. These results suggested a major role of nuclear noncoding RNA networks in systemic antiviral responses to SARS-CoV-2 in humans.

New papers from Danish researchers

Dworkin, L. A *et al*. **Applying transcriptomics to study glycosylation at the cell type level**, *iScience*, 2022

Kim, D *et al*. **Systemic approaches using single cell transcriptome reveal that C/EBPγ regulates autophagy under amino acid starved condition**, *Nucleic Acids Research*, 2022

Kohler, K. T *et al*. **Ductal keratin 15+ luminal progenitors in normal breast exhibit a basal-like breast cancer transcriptomic signature**, *NPJ breast cancer*, 2022

Koutrouli, M *et al*. **U-CIE [/juː ‘siː/]: Color encoding of high-dimensional data**, *Protein Science*, 2022

Perera, M *et al*. **Transcriptional heterogeneity and cell cycle regulation as central determinants of primitive endoderm priming**, *Elife*, 2022

Rothová, M. M *et al*. **Identification of the central intermediate in the extra-embryonic to embryonic endoderm transition through single-cell transcriptomics**, *Nature Cell Biology*, 2022

Wang, F *et al*. **Endothelial cell heterogeneity and microglia regulons revealed by a pig cell landscape at single-cell level**, *Nature communications*, 2022

Next Single Cell Seminar

Date: TBA

If you would like to announce anything single cell related, being it job announcement, event, your published paper, technology development etc., please contact us.

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