A111 · Spatial transcriptome and whole genome characterization of single nuclei in human tissues

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Session: Day 1 · Thu Oct 1, 2026 · 9:45–10:45 AM

Recent studies have portrayed human tissues as mosaics of mutant clones that continuously evolve, interact with their microenvironment, and pave the road to disease. However, current technologies are often only compatible with specific cell types or clonal structures, lose information about the spatial context, lack single cell resolution or have limited capacity to facilitate joint multi-omic readouts. Therefore, they preclude a high-resolution interrogation of somatic mutation profiles linked with single cell phenotypes within human tissues. Here, building on the Slide-tags technology, we developed a robust multi-omic assay, Slide-tags DNA, to simultaneously profile genome-wide somatic variants, transcriptional state and spatial location at single-nucleus resolution. We performed single-nucleus whole genome sequencing at 10-15X depth on cancer and normal tissues, achieving uniform genome capture (Gini coefficient ≤ 0.1, ~93% of the genome with at least 1X coverage) while retaining standard quality snRNAseq readouts and accurate spatial positioning. Using somatic variants called from Slide-tags DNA genomes, we reconstructed cell phylogenies to study the transcriptional states and spatial growth patterns of subclones in colorectal metastasis and normal human tissues. As the field continues to chart the somatic mutation landscape of the human body, Slide-tags DNA will be a crucial tool to understand the spatial and phenotypic context in which these mutations arise and contribute to normal and diseased tissue development.

Spatial transcriptome and whole genome characterization of single nuclei in human tissues

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Recent studies have portrayed human tissues as mosaics of mutant clones that continuously evolve, interact with their microenvironment, and pave the road to disease. However, current technologies are often only compatible with specific cell types or clonal structures, lose information about the spatial context, lack single cell resolution or have limited capacity to facilitate joint multi-omic readouts. Therefore, they preclude a high-resolution, unbiased interrogation of somatic mutation profiles linked with single cell phenotypes within human tissues. Here, building on the Slide-tags technology, we developed a robust multi-omic assay, Slide-tags DNA, to simultaneously profile genome-wide somatic variants, transcriptional state and spatial location at single-nucleus resolution. We applied the assay to a human colorectal metastasis and normal tissues, generating over 500 single-nucleus whole genomes at 10-15X depth with uniform genome capture (Gini coefficient ≤ 0.1, ~93% of the genome with at least 1X coverage) while retaining standard quality snRNAseq readouts and accurate spatial positioning. We developed custom bioinformatics strategies to reconstruct high-quality single nucleus phylogenies from Slide-tags DNA genomes and to study the corresponding transcriptional states and spatial growth patterns of the inferred subclones in our cancer and normal tissue samples. As the field continues to chart the somatic mutation landscape of the human body, Slide-tags DNA will be a crucial tool to understand the spatial and phenotypic context in which these mutations arise and contribute to normal and diseased tissue development.

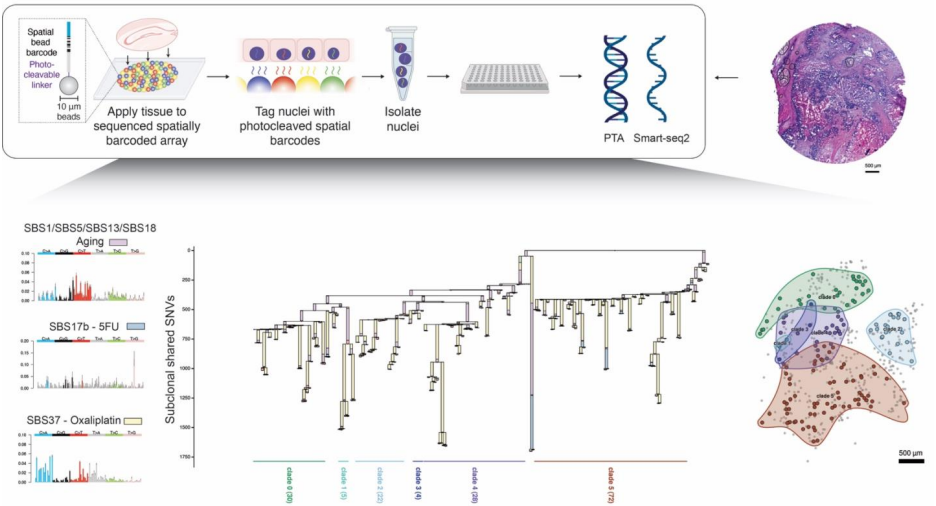

Figure 1. Slide-tags DNA generates spatially-resolved transcriptomes and whole genomes at single nucleus resolution. A colorectal metastasis liver metastasis section was processed with Slide-tags DNA. 221 nuclei were sequenced at ~10-15X depth to generate a single nuclei lineage tree and to discover mutational signatures. Early mutational events were associated with aging, while later events were associated with genotoxic chemotherapy. Nuclei were spatially mapped, revealing subclone spatial localization and enabling association of subclone genomic and transcriptomic features with histology.