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Combination Nucleic Acid Cytometry with Single Cell Genomics for the Study of Rare Cell Populations

Stanford researchers have developed a scalable assay that combines single-molecule nucleic acid imaging with single-cell sequencing, enabling the enrichment and detailed study of rare cell populations in complex biological samples.

Single-cell genomics technologies have proven critical for understanding cellular diversity and function, enabling precise mapping of genetic and transcriptomic information at the level of individual cells. While single-cell genomics can identify cell types based on marker transcripts, there are no methods for isolating these populations for further downstream analysis. This is a particular challenge for studying rare cell types, including many involved in disease.

Stanford researchers therefore developed a scalable assay that enables single-cell RNA sequencing profiles from complex subcellular mixtures defined by the presence or absence of RNA transcripts. This new strategy integrates single-molecule nucleic acid imaging (e.g., smFISH) with single-cell sequencing. Researchers were able to enrich and study rare cell populations from immune populations as well as fixed brain tissue. Overall, this innovative approach not only expands the applicability of single-cell genomics but also enhances our ability to explore cellular heterogeneity in greater detail, providing a powerful tool for both basic research and clinical applications.

Stage of Development
Proof of concept: researchers isolated and analyzed rare cell populations from a mixture of immune cells and from frozen and fixed brain tissue.

Applications

- Study of rare cell types/states, including those not defined by cell surface markers
- Basic research including pathology, genomics, infectious disease, cancer, and immunology
- Study of gene edited cell therapy/gene therapy products

Advantages

- No available methods for integrating single-molecule transcript imaging with single-cell genomics
- Enrichment prior to single-cell sequencing maximizes sample utility and minimizes costs
- No sample loss compared to standard single-cell sample preparation
- Higher power for downstream analysis of rare cell types
- Takes advantage of existing, commercially available kits
- Protocol compatible with frozen or FFPE samples
- Not reliant on antibody staining
- Enables sophisticated AND/NOT/OR logic gating of populations for profiling

Publications

- Abay, T., Stickels, R.R., Takizawa, M.T. et al. Transcript-specific enrichment enables profiling of rare cell states via single-cell RNA sequencing. *Nat Genet* (2025).

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