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Scalable pooled CRISPR screens with single cell chromatin accessibility profiling

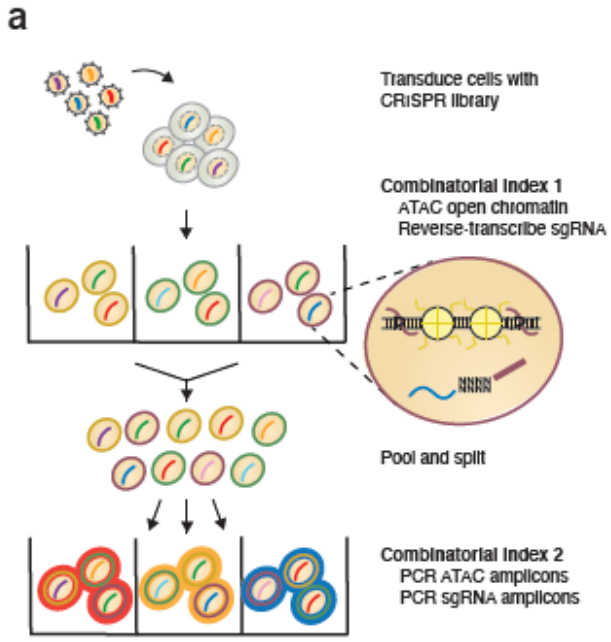

Figure 1. CRISPR-sciATAC workflow: Nuclei are split and barcoded during tagmentation and sgRNA capture, then pooled and re-split for a second barcoding step. Since CRISPR-sciATAC is plate-based and uses a unique, easy-to purify transposase, ATAC-seq libraries from thousands of single cells can be prepared in a single day.

BACKGROUND

The discovery of CRISPR and the development of pooled CRISPR mutagenesis screens has greatly propelled the identification of genes involved in a variety of phenotypic functions. Single-cell analysis/profiling has revolutionized how scientists understand and interrogate complex cell populations. CRISPR screens have been coupled to single-cell RNA-sequencing technologies linking genetic perturbations to their phenotypic outcome across the genome. Current available methods to coupling CRISPR perturbations with genomic regulatory information via ATAC-seq are time-consuming and costly.

DESCRIPTION

Scientists in the lab of Dr. Neville Sanjana at the New York Genome Center have developed a method that combines pooled CRISPR screens with single-cell chromatin accessibility ("CRISPR-sciATAC"). This method links genome-wide chromatin accessibility to genetic perturbations through simultaneous capture of ATAC-Seq fragments and CRISPR guide RNA from single cells. The method is based on a combinatorial indexing single cell ATAC-seq approach and requires no specialized equipment, rendering it a cheap and high-throughput alternative to current low throughput methods that do rely on specialized equipment like a Fluidigm device.

BENEFITS

- High throughput, high-resolution, low-cost single-cell method; CRISPR-sciATAC is 20-fold less expensive and 14-fold less time intensive than existing, low-throughput methods.
- Proof-of-concept initial study profiled genome-wide chromatin accessibility after knockout of the 20 chromatin modifying genes that are most commonly mutated across all cancers (pan-cancer), identifying even subtle changes in chromatin accessibility in cancer genes.
- Follow-up screen captured chromatin accessibility changes in over 90 chromatin remodeling genes, many of which considered novel cancer therapeutic drug targets.

APPLICATIONS

- Genome-wide screens to identify accessible chromatin regions and thus identify specific genes/loci involved in gene regulation in health or disease.
- Identification of non-coding regions that play an important role in phenotype/disease-causing (cancer-causing/cancer-related).
- Pharmacogenomics: method can be used to screen genome wide for drug response, to identify underlying regulatory networks in small molecule drug screen coupled with genetic perturbations.

PATENT INFORMATION

International Patent Publication #: WO 2021/011433

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