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Engineering and detecting CRISPR induced genetic variants via single cell engineering

Stanford researchers have developed a new methodology called transcript-informed single-cell CRISPR sequencing (TISCC-Seq), for the direct detection and phenotyping of genetic variants in a high-throughput manner.

The characterization of phenotypes of genetic variants has remained a continued challenge. Base editors can introduce single base pair mutations directly into genomes, but in addition, can also introduce a variety of different genetic variants. The newly developed single-cell technology can i) genome engineer mutations, ii) directly identify their presence among individual cells and iii) determine each mutation's transcriptional phenotype. The multiplexed approach involves CRISPR base-editors to introduce the desired mutation into a target gene and long-read sequencing of the target gene's transcript to identify the engineered mutations. Simultaneously, the transcriptome profile can be assessed. The method allows for determination of the mutations' genotype and expression phenotype at single cell resolution via integration of the long and short read data. Additionally, the technology is not restricted to CRISPR based genome engineering since it is possible to directly genotype each single-cell independent of guide RNA. The TISCC-Seq can be applied to functionally evaluate numerous cancer mutations as one example.

Stage of Development
Proof of Concept

Applications

- Verification of CRISPR edits
- Genetic variant specific drug development

- Identification of point mutations
- Cancer

Advantages

- First single cell method for direct detection and phenotyping of a given genetic variant
- First single cell method for direct introduction of genetic variant
- Integrates short and long-read sequencing
- Compatible with any type of genome engineering method:iIndependent of guide RNA
- Allows deeper sequencing of target genes
- Low sequencing cost

Publications

- Kim, H. S., Grimes, S. M., et al. (2022). Single cell CRISPR base editor engineering and transcriptional characterization of cancer mutations. bioRxiv, 2022-10.

Patents

- Published Application: WO2024092151

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