GENE EXPRESSION

Spatial transcriptomics levels up

An improved sequential fluorescence in situ hybridization approach allows one to image the expression of 10,000 genes in single cells.

Spatial transcriptomics, the study of gene expression in biological tissues, often involves fluorescence in situ hybridization (FISH), a method to label and image mRNAs by using fluorescent oligonucleotide probes. The recent development of sequential fluorescence in situ hybridization (seqFISH) enabled the visualization of multiple transcripts in single cells in situ. In seqFISH, a series of probes are hybridized to each transcript and then removed, in sequential rounds, to generate a unique temporal barcode for each expressed gene. The number of barcodes increases with the number of fluorophores and hybridization rounds. However, mRNA molecules are so densely packed in a cell that the number of resolvable transcripts is limited by the diffraction barrier.

To overcome this limitation, Long Cai and his team at the California Institute of

Technology, in Pasadena, have improved seqFISH by developing an expanded barcode palette of 60 pseudocolors divided in three fluorescent channels. The system is based on 24 primary probes per gene, each of them bearing four overhang sequences that can hybridize with a set of fluorescent readout probes. By running sequential hybridization rounds, one can “generate a series of sparse images, which can then be resolved and combined into a super-resolution image, which then can be barcoded,” explains Cai. The method allowed them to study the subcellular localization patterns of 10,000 mRNAs in brain tissue sections, using a regular confocal microscope, and to find that certain genes are enriched in neighboring cells. “We are used to thinking about genes that are expressed in a cell-type-dependent fashion, but we found that many genes are

expressed in fashions that are dependent on neighboring cells,” says Cai.

Previous approaches “have essentially been used as a validation tool . . . because the spatial methods were limited at 100–1,000 genes,” Cai explains, so “the most important implication of this work is not just the technical achievement of getting to the transcriptome level without compromising sensitivity, but also that it enables discovery-driven research to be performed in situ.”

Alfredo Sansone

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Research papers

Eng, C. L. et al. Transcriptome-scale super-resolved imaging in tissues by RNA seqFISH. *Nature* **568**, 235–239 (2019).

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