GENETICS

Optically measuring barcodes

Askary, A. et al. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-019-0299-4 (2019).

DNA barcoding technologies have been applied in profiling cell identities and recording dynamic biological information. In the developmental system, the continuous editing of barcodes can be used as a unique identifier for reconstructing developmental lineage. However, in situ readout of barcode edits with spatial information remains challenging. Askary et al. introduce Zombie, an approach that enables in situ imaging-based readout of DNA barcodes with sensitivity comparable to that of sequencing approaches. Zombie uses phage RNA polymerases to transcribe a DNA barcode that is downstream of a phage promoter and integrated in the genome of fixed cells. They then use single-molecule FISH or hybridization chain reaction to detect the amplified RNA products as an optical measurement of the DNA barcodes. Zombie can resolve single nucleotide differences and has been applied in chick embryos and adult mouse brain tissues for SNV detection. *LT*

https://doi.org/10.1038/s41592-019-0716-0

GENOMICS

Genomic variation in non-tumor cells

Jakubek, Y. A. et al. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-019-0297-6 (2019).

Many cancer cells harbor high levels of genomic variation. While some of these somatic mutations are likely to drive oncogenesis, a comprehensive picture of their origin, prevalence and role in tumor and non-tumor cells is still under investigation. Jakubek et al. analyzed SNP array genotype data from 1,708 normal-appearing adjacent-to-tumor (NAT) tissue samples (27 cancer sites) and 7,149 blood samples from The Cancer Genome Atlas (TCGA) dataset. By focusing on megabase-scale somatic copy number alterations (sCNAs), they identified widespread sCNAs in different NAT and blood samples. More sCNAs were detected in NAT samples than in blood samples, and there is heterogeneity in rate and genomic distribution among cancer sites. Although some NAT tissues share sCNAs with adjacent tumor, others independently accumulate their own set of sCNAs, even targeting the same oncogenes. This framework and analysis deepen our understanding of genomic variation in tissues appearing normal upon pathology examination and their role in tumor origin. *LT**

https://doi.org/10.1038/s41592-019-0717-z

GENETICS

Reconstituting selectable markers

Jillette, N. et al. *Nat. Commun.* **10**, 4968 (2019).

Selectable markers such as antibiotic resistance genes are important tools for cell genotype screening. Yet it is not easy to select for multiple transgenes because of the limited number of selectable markers. Jillette et al. have developed a system that splits marker genes into different transgenic vectors. In a two-split system, the coding sequence of, for example, an antibiotic resistance gene is split into two fragments. One fragment is cloned upstream of an N-terminal split intein in a vector carrying one transgene and the other fragment is cloned downstream of a C-terminal split intein in the second transgenic vector. Upon delivery of the vectors, only cells expressing both intein-split markers can reconstitute the antibiotic resistance marker via protein trans-splicing. They further demonstrate the approach by sequential selection with two-split markers by reconstituting a six-split hygromycin resistance marker. *LT*

https://doi.org/10.1038/s41592-019-0713-3

NEUROSCIENCE

Finding exciting inputs

Walker, E. Y. et al. *Nat. Neurosci.* **22**, 2060–2065 (2019).

Identifying the sensory stimuli that optimally excite neurons in sensory pathways is important for understanding information processing. However, the stimulus space in, for example, the visual system is vast, and identifying optimal stimuli is not straightforward. Walker et al. devised 'inception loops', which combine in vivo recordings of neuronal activity with in silico modeling. The researchers performed calcium imaging in layer 2/3 of the mouse primary visual cortex while showing the mice images of natural scenes. They then trained a deep convolutional network to predict neuronal responses from the images shown. Using the trained network, the researchers could identify images that excited individual neurons best. The researchers call these stimuli the most exciting inputs (MEIs). When presented to the mice, these MEIs indeed elicited strong responses in the neurons they were designed for. Inception loops may be particularly useful for studying neural computation in higher order brain areas, where optimal stimuli are even more elusive. *NV*

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