IN BRIEF

NEUROSCIENCE

Mapping spatial diversity

Bayraktar, O. E. et al. *Nat. Neurosci.* **23**, 500–509 (2020).

The layered organization of the cortex is well established for mammalian brains, but whether astrocytes exhibit spatial heterogeneity has been unclear. To assess spatial diversity, Bayraktar et al. have established a pipeline consisting of multiplexed single-molecule fluorescence in situ hybridization, high-resolution imaging, cell segmentation and quantification. To analyze astrocyte diversity in the mouse cortex, the researchers first identified candidate genes by dissecting the upper and lower cortex, purifying astrocytes and performing transcriptomic analysis. Using their pipeline, the authors then established that astrocytes formed three layers that were not congruent with neuronal layers. Furthermore, the researchers observed differences in layered gene expression in different cortical areas. *NV*

https://doi.org/10.1038/s41592-020-0838-4

GENE EXPRESSION

Guiding Cas13 for RNA knockdown

Wessels, H.-H. et al. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-020-0456-9 (2020).

Cas13, guided by a single CRIPSR RNA, is known to target RNA and has shown activities in targeted knockdown, RNA editing and RNA imaging without mutating the genome. Cas13d, a subtype of Cas13, has been used for efficient RNA knockdown in mammalian cells. Yet little is known about the design rules of guide RNA (gRNA) for optimal Cas13d activity. To learn more about Cas13d activity, Wessels et al. performed knockdown tiling screens targeting a GFP transgene, as well as endogenous transcripts including cell-surface proteins, in human cells. The researchers evaluated the knockdown efficacy of 24,460 gRNAs and found that both gRNA sequence and target site features affect knockdown efficacy. On the basis of the screen results, they establish an on-target model to predict gRNA knockdown efficacy, which successfully sorted high-activity gRNAs from poorly performing ones. In addition, they provide a resource for optimized gRNAs that target protein-coding transcripts in the human genome. *LT*

https://doi.org/10.1038/s41592-020-0841-9

CHEMICAL BIOLOGY

Noncanonical amino acids on display

Tharp, J. M. et al. *Nat. Commun.* **11**, 1392 (2020).

Noncanonical amino acids can be used to expand the chemical space of peptides and proteins. However, their use in phage display has been limited by the fact that *Escherichia coli* harboring clones with nonsense codons do not grow as well as those with only sense codons. Tharp et al. have developed an approach to bypass this limitation. Their approach exploits a phenomenon called superinfection immunity, in which an infected bacterium becomes resistant to further infection by the same type of phage. After library preparation intended to introduce one amber codon per clone, the library was expressed in cells. Cells harboring clones without an amber codon were able to express an additional surface protein that prevented them from being superinfected with a second phage used for selection, allowing those harboring in-frame amber codons to be further enriched. The researchers used their approach to develop peptides containing butyryllysine that bind and inhibit the protein SIRT2. *RS*

https://doi.org/10.1038/s41592-020-0839-3

GENOMICS

Diverse human genomes

Bergström, A. et al. *Science* **367**, eaay5012 (2020).

Despite decades of exploration of human genetic variation, more data is still needed for a more complete and in-depth picture. Compared to genotyping arrays, whole-genome sequencing has the potential to avoid ascertainment biases and identify rare variants. Bergström et al. sequenced 929 human genomes to an average of 35× coverage from 54 populations that are geographically, linguistically and culturally diverse. Hundreds of thousands of previously undocumented variants were found to be common in one or more population, highlighting the value of sequencing diverse populations. Demographic analysis showed different population size histories and modes of population separation, reflecting the effects of migration and gene flow. Archaic introgression from Neanderthal and Denisovan groups were detected to various degrees. While Neanderthal ancestry was more likely to have resulted from one major episode of admixture, the history of Denisovan introgression appeared to be more complicated. *LT**

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