MICROSCOPY

Polarized structured illumination microscopy

Nat. Commun. **10**, 4694 (2019).

Super-resolution microscopy captures detailed information on cellular structures. Zhanghao et al. describe polarization structured illumination microscopy (pSIM), which combines the benefits of structured illumination for live-cell super-resolution imaging with detailed orientation mapping, giving richer insight into the organization of labeled structures. pSIM can be carried out on commercially available structured illumination microscopes in 2D, in 3D, and in TIRF mode. It determines polarization using analysis in a spatio-angular hyperspace on the basis of the extent of a fluorophore's excitation by polarized light. The researchers demonstrated the approach by imaging filamentous structures in cells, including cytoskeletal networks and λ DNA. They also used pSIM to show the side-by-side actin ring structures in the membrane-associated periodic skeleton of hippocampal neurons. Beyond these experiments, they monitored changes in polarization in microtubules in living mammalian cells. *RS*

https://doi.org/10.1038/s41592-019-0682-6

CELL BIOLOGY

Culturing HSPCs

Nat. Med. **25**, 1566–1575 (2019).

Hematopoietic stem-cell (HSC) therapies require a reliable supply of specific types of stem cells. This supply, however, is limited by extensive differentiation of these cells when cultured. Hematopoietic stem and progenitor cells (HSPCs) are commonly cultured in hydrophobic flasks, as opposed to the hydrophilic in vivo conditions. These hydrophobic materials can lead to excessive production of reactive oxygen species (ROS), a trigger for HSPC differentiation, which may offer some explanation for the extensive ex vivo differentiation. Bai et al show that a super-hydrophilic, 3D zwitterionic matrix yields a substantial increase in self-renewal of HSPCs ex vivo by reducing excessive ROS production and precluding nonspecific differentiation. Using HSPCs derived from umbilical cord blood and bone marrow, they demonstrate a 73-fold increase in long-term HSC frequency and at least 24-week repopulating abilities in immunocompromised mice. The technique has potential to facilitate basic research on HSPCs, as well as clinical applications of HSC therapies. *AS*

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SEQUENCING

Relating anatomy to transcriptome

Cell **179**, 772–786 (2019).

Neuroanatomical methods are crucial to understanding how diverse neurons are organized. In MAPseq, a previously developed multiplexed analysis of projections by sequencing, individual neurons are labeled by random RNA barcodes that are used to reveal the projection pattern by matching target areas and source areas. However, MAPseq requires tissue homogenization for sample preparation, which discards the spatial organization of neurons. To map the somatic origin at cellular resolution, Chen et al. developed BARseq (barcoded anatomy resolved by sequencing), which employs in situ barcode sequencing at the source area and microdissection and sequencing at the target projection areas. The combination of transcriptomic and anatomical profiles can relate projection to gene expression when using marker-based Cre-labeled animals. In the mouse auditory cortex, BARseq confirmed the laminar organization of the three classes of projection neurons: intratelencephalic, pyramidal tract-like and corticothalamic. In combination with FISH, BARseq was able to map the projections of transcriptionally defined intratelencephalic subtypes in the mouse auditory cortex. *LT*

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CHEMICAL BIOLOGY

Inducing protein degradation using light

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Protein functions and cellular signaling pathways can be modulated by selectively degrading certain proteins. PROTACs, proteolysis-targeting chimeras, are molecules that recognize and bind both the protein of interest and E3 ubiquitin ligase — an enzyme that facilitates degradation of the target protein. These constructs have had considerable success, but finer control of their activity is desirable. Xue et al. have developed photo-caged (pc) PROTACs that are activated and released upon irradiation with light and can target proteins to induce desired phenotypes. The authors constructed pc-PROTACs using Brd4 protein — of interest in cancer therapy — as the target. Upon treatment, Brd4 degradation was induced successfully using photoactivation in both live Ramos cells and zebrafish embryos, with activity comparable to that of non-pc PROTACs. The added control could be helpful in both mechanistic studies and the design of localized treatment strategies. *AS*

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