CHEMICAL BIOLOGY

Cross-linking with SuFEx chemistry

Wang, N. et al. *J. Am. Chem. Soc.* **140**, 4995–4999 (2018).

Biocompatible, bio-orthogonal chemical reactions such as the Staudinger ligation have proven to be useful methods for biochemical and imaging studies in living cells, as well as for drug discovery. Wang et al. now add sulfur–fluoride exchange (SuFEx) chemistry to this growing toolbox. An unnatural amino acid, fluorosulfate-L-tyrosine (FSY), can be incorporated into proteins in bacterial and mammalian cells via expression of a novel, specifically evolved tRNA synthetase–tRNA pair. Incorporated FSY selectively reacts with lysine, histidine and tyrosine residues in close proximity, generating a covalent cross-link either within or between proteins. Importantly, FSY has low cytotoxicity, which the authors attribute to the low reactivity of aryl fluorosulfates inside cells. They used FSY and SuFEx chemistry to capture and analyze the protein complex between *Escherichia coli* Afb and Z protein, as well as the complex between PAPS reductase and thioredoxin. *AD*

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GENOMICS

RBP census

Huang, R. et al. *Proc. Natl. Acad. Sci. USA* **115**, E3879–E3887 (2018).

Post-transcriptional gene regulation is in large part driven by the proteins associated with RNAs, and thus it is of great interest to establish a comprehensive catalog of RNA-binding proteins (RBPs). Huang et al. developed CARIC (click chemistry–assisted RNA interactome capture) for unbiased RBP profiling. The method begins with metabolic labeling of RNA to incorporate an alkyne-containing uridine analog (EU) and a photoactivatable thio-uridine (4SU). Upon UV light exposure, proteins bound to RNAs are cross-linked to 4SU, and azide–biotin is clicked onto EU to provide a handle by which the RNA can be enriched. After digestion of the RNA and mass-spectrometry-based protein identification, the researchers obtained a list of nearly 600 RBPs from HeLa cells that included 130 proteins not known to associate with RNA. CARIC can be applied to any cell type and will enrich RBPs across all RNAs, independent of their polyadenylation status. *NR*

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IMAGING

Super-long single-molecule tracking

Tsunoyama, T. A. et al. *Nat. Chem. Biol.* **14**, 497–506 (2018).

Single-molecule tracking can provide important insight into protein dynamics, regulation and function. However, photophysical properties of fluorophores, such as bleaching and blinking, can make it challenging to track labeled molecules over extended periods. Although methods for reducing photobleaching and photoblinking are known, they can be incompatible with live imaging because of their toxicity. Tsunoyama et al. addressed this challenge by treating cells with low concentrations of dissolved oxygen along with a reducing-plus-oxidizing system to suppress both bleaching and blinking. They demonstrate that the approach works for numerous commonly used organic dyes and has only minor effects on cells. Using their approach, they extended the duration of particle tracking from ~10 seconds to ~7 minutes at video rate, while maintaining high localization precision. They used their approach to study the behavior of integrins at focal adhesions. *RS*

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GENOMICS

Tissue-specific oncogene screens

Sack, L. M. et al. *Cell* **173**, 499–514 (2018).

Some genes can lead to cancer when mutated, whereas others drive cancer as a result of copy-number increases. Sack et al. generated a library of almost 30,000 barcoded human open reading frames to screen for genes that either stimulate or suppress proliferation when overexpressed. Their lentiviral screening vectors allowed for inducible expression and tagging, as well as quantitative detection. The researchers carried out screens in mammary, fibroblast and pancreatic cell lines, and found that around 10% of genes regulate proliferation, often in a highly tissue-specific manner. Candidate genes from the screen were enriched for known oncogenes and tumor-suppressor genes, and tissue-specific drivers were typically associated with the tumor tissue of origin. Many of the candidate genes are not commonly mutated in cancers but are associated with tissue-specific focal somatic copy-number alterations. *TN*

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