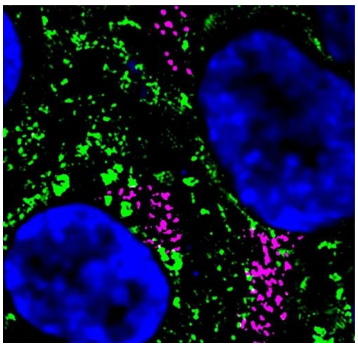
FLUORESCENT PROTEINS

All that glows is gold

Nat. Biotechnol. https://doi.org/10.1038/s41587-022-01278-2 (2022)



Credit: Nature

Researchers using fluorescent proteins to label cellular components benefit from an ever-expanding palette of available colors and properties, but increasing brightness usually comes with decreased photostability. Hirano et al. have circumvented this trend with StayGold, which is an order of magnitude more photostable than other available fluorescent proteins while maintaining optimal brightness. Rather than attempt to re-engineer an existing protein, the authors began with a naturally occurring fluorescent jellyfish protein, CU17S, whose minimal photobleaching made it ideal for development. A V168A mutation improved protein folding and chromophore maturation to create StayGold, which has brightness exceeding that of the commonly used enhanced GFP. Additional engineering created versions suitable for visualizing rearrangements of the endoplasmic reticulum at super-resolution, labeling the mitochondrial matrix and microtubule ends, and monitoring SARS-CoV-2 assembly. Although the dimeric nature of StayGold is a limitation, its fundamental photostability and brightness provides a platform for future development and exemplifies the benefits of combining natural sequence discovery with protein engineering. *CD*

https://doi.org/10.1038/s41589-022-01055-x

TRANSCRIPTIONAL REGULATION

Silenced by degradation

Nature **604**, 167–174 (2022)

Polycomb repressive complex 1 (PRC1) and PRC2 can install and read histone modifications to silence Polycomb target genes, which is thought to occur via chromatin compaction and exclusion of RNA polymerase II (Pol II). However, some contradictory evidence indicates the presence of Pol II at promoters of Polycomb target genes. Zhou et al. found that the rixosome, a complex responsible for ribosomal RNA processing and ribosome biogenesis, was recruited to Polycomb-repressed genes by PRCs, where it cleaved nascent RNAs transcribed by Pol II to contribute to the gene-silencing effect. Knocking out key components in either PRCs or the rixosome led to loss of colocalization of PRCs and the rixosome in chromatin and upregulation of a common set of genes. Both the physical interaction between PRCs and the rixosome and the RNA-degradation activity of the rixosome were required for effective gene silencing. Expression of either a PRC1 mutant subunit with impaired ability to bind the rixosome or catalytically dead rixosome subunits caused reactivation of Polycomb target genes. These findings unify apparently contradictory phenomena by revealing the role for RNA degradation in PRC-mediated gene silencing. *YS*

https://doi.org/10.1038/s41589-022-01058-8

MICROTUBULE DYNAMICS

A hidden player

Science https://doi.org/10.1126/science.abn6020 (2022)

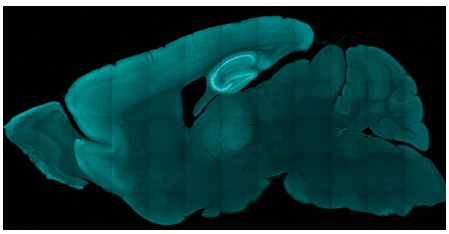
Microtubules contain a variety of post-translational modifications, including the removal and reincorporation of a tyrosine in the C terminus of α-tubulin. Recent work identified vasohibins (VASH1 and VASH2) as tubulin carboxypeptidases that mediate tubulin detyrosination. However, inactivation of vasohibin function only partially accounted for tubulin detyrosination, which suggested that additional factors may be involved. To test this possibility, Landskron et al. used gene-trap mutagenesis in a haploid human cell line deficient in both VASH1 and VASH2, and identified a previously un-annotated protein, which they called MATCAP, as a new factor in tubulin detyrosination. The combined loss of MATCAP and vasohibins blocked detyrosination, whereas over-expression of MATCAP stimulated tubulin detyrosination in cells. X-ray and cryo-electron microscopy analysis of the MATCAP structure showed it is a zinc-dependent metalloprotease that binds along microtubule protofilaments, in sharp contrast to vasohibins that are cysteine proteases that bind between adjacent microtubule protofilaments. Meanwhile, mice deficient in both enzymatic systems exhibited decreased brain volume due to impaired neurogenesis in the ventricular and subventricular zones. Overall, the findings from Landskron et al. have potentially identified all the key players in tubulin detyrosination. *GM*

https://doi.org/10.1038/s41589-022-01057-9

CELLULAR TARGET ENGAGEMENT

CATCHing drugs

Cell **185**, 1793–1805 (2022)



Credit: Li Ye

Incorporation of an alkyne or azide handle on a small molecule can enable click chemistry–based detection of covalent drug–target interactions in cell and tissue lysates, which can inform probe selectivity and pharmacokinetic properties. However, fluorescent visualization in situ and in tissues remains difficult, particularly in the brain, due to the poor signal-to-noise ratio of the probes. To improve visibility, Pang et al. developed an approach for diminishing background and enhancing clearance, called CATCH (clearing-assisted tissue click chemistry), that combines improved copper ligands with a polyacrylamide-based aqueous clearing method that removes lipids. CATCH was used on a collection of alkyne-modified analogs of covalent inhibitors of fatty acid amide hydrolase, revealing specific signals in neuronal and non-neuronal populations. CATCH was able to distinguish on-target versus off-target engagement in particular neurons through the use of competitor probes, as well as to detect dose-dependent drug–target engagement. Although its detection ability remains within covalent drugs, CATCH offers a promising first step to realizing visualization of organ or whole-animal drug–target interactions with spatial and subcellular resolution. *GM*

https://doi.org/10.1038/s41589-022-01056-w

Caitlin Deane, Grant Miura and Yiyun Song