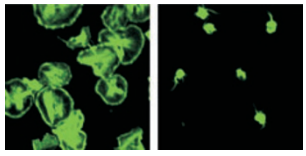
TRAPPING TUBULIN

Blocking the mitotic spindle has been an effective strategy in clinical treatment of cancer by paclitaxel, a drug which stabilizes preassembled tubulin through reversible binding and prevents dissociation of αβ-tubulin into protein dimers. Paclitaxel was believed to bind to a luminal site, but it was unclear how the compound reached the relatively inaccessible interior wall. Buey *et al.* predicted that paclitaxel binds to an exposed site on the exterior of the microtubule before translocation to its luminal site. The authors tested the paclitaxel-mimetic cyclostreptin from the bacterium *Streptomyces* sp. and found that unlike paclitaxel, which binds reversibly, cyclostreptin binds irreversibly, through covalent modification of two distinct β-tubulin residues. Using molecular modeling, they showed that these sites are labeled sequentially by cyclostreptin, which agrees with the prediction that microtubule stabilizing agents first bind a low-affinity site and then relocate to the inner wall. Because of the irreversible nature of its mechanism, cyclostreptin escapes ejection from the cell and therefore has the potential to overcome the clinical toxicity and resistance characteristic of paclitaxel treatment. [**Articles, p. 117; News & Views, p. 81**] *MB*

Playing with platelet peptides



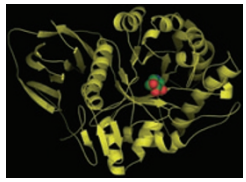
Peptide sequences within proteins are known to play important roles in mediating protein-protein interactions. However, it can be difficult to identify these short motifs. To identify peptide sequences involved in platelet biology, Edwards *et al.* developed a bioinformatic method to search for ten-residue peptide motifs from human transmembrane platelet proteins. In order to identify regions likely to have functional importance, they specifically focused on peptide sequences that are conserved in related proteins from different species but that are distinct from homologous human proteins. Approximately half of the sequences identified had activity as either agonists or antagonists of platelet aggregation, and one sequence was shown to inhibit a specific platelet signaling pathway. [**Letters, p. 108; News & Views, p. 83**] *JK*

Regulating death in Huntington disease

Huntington disease is caused by polyglutamine expansions in the huntingtin protein, but mechanistic information as to how these glutamine expansions cause neurodegeneration is lacking. Previous research has shown that prevention of cell death can prevent the disease phenotype, which suggests that insight into the mechanism of cell death in cells expressing mutant huntingtin may provide insight into the disease as a whole. Varma *et al.* screened an expansive chemical library to identify molecules that rescue cells expressing mutant huntingtin, but not normal cells, from death. Four compounds demonstrated efficacy in a variety of Huntington model systems and inhibited cleavage of caspase-3 in mutant but not normal cells or in a yeast model system, which indicates that these models may probe different aspects of the mutant huntingtin phenotype. [**Brief Communications, p. 99**] *CG*

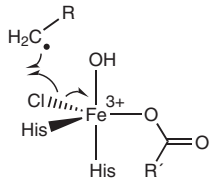
In This Issue written by Mirella Bucci, Catherine Goodman and Joanne Kotz

Isofagamine to the rescue



Gaucher disease is caused by mutations to acid β-glucosidase, an enzyme that hydrolyzes glucosylceramide to β-glucose and ceramide. Several treatments have been developed for this disorder, but they are limited by inconvenient drug delivery or adverse side effects. One emerging therapeutic strategy is to identify chemical or pharmacological chaperones that can assist the mutated sequence to fold and function normally. Pharmacological chaperones have previously been found for acid β-glucosidase, but their mechanism of action is not understood. Lieberman *et al.* explored the role of one such chaperone, isofagamine, by demonstrating its ability to rescue lysosomal trafficking of the enzyme. They further used isofagamine to discover a new conformation of the protein active site. The cocrystal structure not only allowed docking of the native substrate, which was not possible with previously solved structures, but also provided key insight into the molecular interactions of Asn370, mutations of which are prevalent in Gaucher disease. [Letters, p. 101; News & Views, p. 84] *CG*

Radical rebound revealed



Many natural products contain halogen atoms, but the mechanisms for introduction of these unusual substituents can vary greatly across substrates and biosynthetic pathways. Galonić *et al.* investigated the mechanism of CytC3, the iron halogenase that chlorinates the γ-carbon of L-2-aminobutyric acid in the construction of cytotrienin. This enzyme shares features with a class of hydroxylases, but whether CytC3 also shares the general catalytic mechanism of these hydroxylases has remained unclear. By reconstituting a consecutive three-enzyme series from the biosynthetic pathway to load and modify the substrate, the authors provided spectroscopic evidence for the key Fe(IV) intermediate in the postulated reaction mechanism, simultaneously confirming the enzyme activity and expanding the breadth of reactions known to be catalyzed by this iron-oxo species. Further studies with a deuterated substrate demonstrated that the enzyme is extremely efficient at suppressing side reactions. [**Letters, p. 113; News & Views, p. 86**] *CG*

Membranes light up

Signaling to the interior of the cell originates on cellular membrane scaffolds. Although ensemble measurements are important for identifying cell surface signaling molecules and mechanisms, they do not allow for both spatial and temporal resolution of signaling activity. In a Review article, Jaiswal and Simon examine optical imaging strategies that allow dynamic visualization of events over the entire cell surface. The authors review the advances in laser scanning microscopy, fluorescence correlation spectroscopy and total internal reflection fluorescence microscopy, and in approaches that allow for imaging below the diffraction limit of visible light. Combined with new probes for fluorescent labeling, these tools allow for the imaging of single cell surface events and shed new light on the role of membranes in signaling. [Review, p. 92] *MB*

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