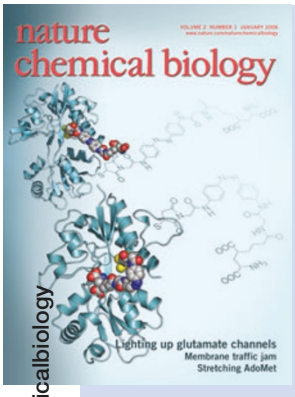
IN THIS ISSUE



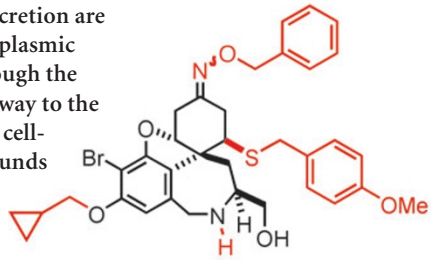
COVER STORY

Glutamate is the principal excitatory neurotransmitter of the mammalian central nervous system and can act through a ligand-gated ion channel, the ionotropic glutamate receptor (iGluR). Trauner, Isacoff and colleagues have developed a synthetic optical switch for activating iGluRs in which an agonist is tethered to the receptor by an azobenzene chemical linker. Light triggers the isomerization of the azobenzene, and thus reversibly induces agonist binding to the receptor. Upon activation, agonist binding induces functioning of the ion channel. These light-activated channels can now be used to probe the neurobiology of iGluR and to develop nanoscale devices.
[Articles, p. 47; News & Views, p. 11] *JK*

How to activate Hedgehog?

A purine derivative called purmorphamine induces the differentiation of progenitor stem cells to osteoblasts, or bone-producing cells. Although purmorphamine had been found to target the Hedgehog signaling pathway, the precise molecular target was unknown. Sinha and Chen have now shown that purmorphamine is an agonist of Smoothened. Smoothened is a transmembrane protein that transmits an intracellular signal following Hedgehog binding to its receptor. The authors show that Smoothened is regulated by direct binding of purmorphamine to the transmembrane region. Identification of the target is an important step forward for using this compound as a drug lead for stem cell and cancer diseases in which Hedgehog signaling is misregulated.
[Brief Communications, p. 29; News & Views, p. 10] *JK*

Small molecule stops secretion



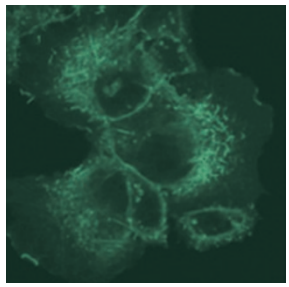
Proteins destined for secretion are synthesized in the endoplasmic reticulum and pass through the Golgi apparatus on the way to the plasma membrane. In a cell-based screen for compounds that inhibit protein trafficking from the Golgi to the plasma membrane, Kirchhausen, Shair and coworkers identified a compound called secramine that inhibited transport out of the Golgi. The authors pinpointed Cdc42, a member of the Rho GTPase family known to be involved in the secretory pathway, as the target of secramine. Inhibition of Cdc42 required the presence of RhoGDI, a protein that is involved in targeting Cdc42 to membranes. The authors propose a model in which secramine stabilizes the interaction between Cdc42 and RhoGDI and as a result prevents translocation of Cdc42 to the Golgi membrane. Secramine provides a new tool for investigating Cdc42 function in diverse cellular pathways.
[Articles, p. 39; News & Views, p. 7] *JK*

In This Issue written by Joanne Kotz and Terry L. Sheppard.

Adding on to AdoMet

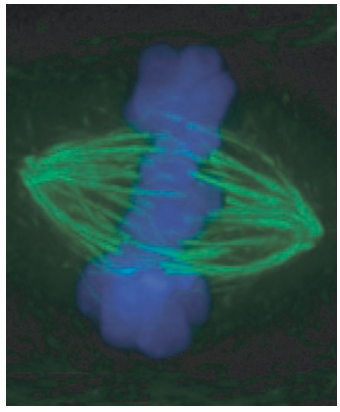
S-Adenosyl-L-methionine (AdoMet) provides the methyl group for biological methylation of biomolecules, including DNA, RNA and proteins. Such methylation is involved in important biological processes including chromatin regulation and gene silencing. The functional roles of methylation could be precisely probed by replacing methyl groups with longer alkane chains. However, the enzymatic transfer of these analogs has been difficult. Klimašauskas, Weinhold and colleagues chemically synthesized AdoMet analogs with extended carbon chains. Analogs with double or triple bonds adjacent to the site of nucleophilic attack were efficiently enzymatically transferred to DNA. These DNA modifications can now be used to probe the biology of methylation.
[Brief Communications, p. 31; News & Views, p. 8] *JK*

A withering cytoskeleton



Withaferin A is a steroidal lactone natural product found in the desert plant *Withania somnifera*. Extracts from these plants have been used in traditional medicine, but the molecular mechanisms of the active components have not been fully elucidated. Whitesell and coworkers now show that withaferin A targets cells through regulation of the cytoskeleton. The authors synthesized a biotinylated withaferin A analog and identified annexin II as its major target. Withaferin A forms a covalent cross-link with annexin II, which enhances the protein's ability to aggregate F-actin. These studies suggest that annexin II offers a viable therapeutic target and provide mechanistic insight into how withaferin A and related withanolide compounds exert their effects on cells.
[Letters, p. 33] ***TLS***

Small molecules inform cell division



In eukaryotes, inheritance of genetic information requires the precise transfer of replicated chromosomes from parental to progeny cells during cell division. Because cell division is a complex process that includes mitosis and cytokinesis, dissecting the molecular choreography of each step of the process remains an important goal of cell biology research. Over the years, small-molecule inhibitors, such as colchicine (see also **Commentary, p. 3**), that target specific components of the cell division machinery have served as tools to understand key steps in cell division. In a review article in this issue, Lampson and Kapoor discuss several unresolved biological questions about cell division that are being brought into focus through the use of selective small-molecule probes.
[Review, p. 19] ***TLS***