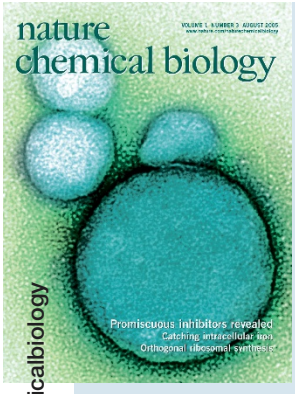
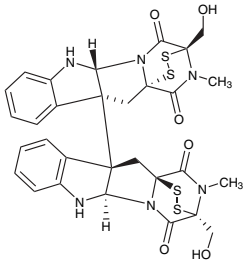
IN THIS ISSUE



COVER STORY

New drug leads are often identified by screening small-molecule libraries for inhibitors of a specific enzyme activity or protein-protein interaction. Although some of the inhibitors identified in these screens will be the desired specific inhibitors, other compounds inhibit nonspecifically because of aggregation. Distinguishing between the specific and nonspecific inhibitors is important for deciding which leads to pursue. Shoichet, Guy and colleagues report that a surprisingly large percentage of 1,000 'drug-like' small molecules showed nonspecific or promiscuous inhibition in enzyme assays. The authors developed rapid assays, one based on detergent sensitivity and the other on light scattering, that enabled identification of these aggregation-based inhibitors. They also used this information to refine a computational program for identification of promiscuous inhibitors. The combination of these biochemical assays and *in silico* methods provides an opportunity to more efficiently identify drug lead candidates. **[Letters, p. 146; News & Views, p. 125]** *JK*

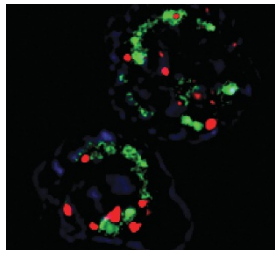
Inhibiting histone methylation



Post-translational modifications of histone proteins play important roles in regulating gene expression. For example, histone methylation is known to maintain stable gene expression during cellular differentiation. The methylation of lysine 9 within the tail of histone 3 is catalyzed by a specific histone methyltransferase and has been shown to invoke heterochromatin-mediated gene repression. To find an inhibitor of this enzyme, Imhof and coworkers screened a library of compounds against methyltransferase, SU(VAR) 3-9. They identified a fungal metabolite, chaetocin, that selectively inhibits lysine-specific methyltransferases, both *in vitro* and *in vivo*. To date, no specific small-molecule inhibitor of this enzyme class exists, and chaetocin may provide an invaluable tool for gene repression studies. **[Brief Communications, p. 143]** *GW*

Catching Intracellular Iron

Bacteria secrete hydrophilic siderophores to chelate extracellular iron. However, *Mycobacterium tuberculosis* resides within macrophages and little is known about its mechanisms for obtaining intracellular iron. Groves and colleagues investigated the function of a lipophilic siderophore from mycobacteria called mycobactin J, and found that it could capture intracellular iron. In contrast to the diffuse localization of metal-free mycobactin, the mycobactin J–metal complex concentrated in lipid-sorting domains called lipid droplets. These lipid droplets accumulated adjacent to phagosomes,

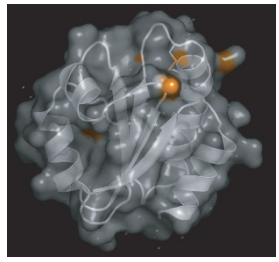


endocytic vesicles in which mycobacteria multiply, suggesting that mycobacteria co-opt endogenous host lipid-trafficking mechanisms to obtain iron. Identification of this pathway suggests a new route for developing antibiotics targeting tuberculosis. [Letters, p. 149; News & Views, p. 127] *JK*

New cellular building blocks

Engineering cells to perform expanded functions is one focus of synthetic biology. Developing non-native components is an important step toward programming new cellular pathways. Chin and colleagues developed a selection method for generating ribosome-mRNA pairs that recognize each other but do not interact with endogenous ribosomes or mRNA. Using a combination of positive and negative selection, the authors generated multiple orthogonal ribosome-mRNA combinations. Attaching one fragment of β-galactosidase onto a selected mRNA and the other fragment onto a native mRNA generated a system in which both endogenous and designed ribosome-mRNA pairs are required to functionally reconstitute β-galactosidase activity. This demonstration of a Boolean logic function suggests that these new cellular pieces will be useful for reprogramming cells. **[Articles, p. 159]** *JK*

NO controls caspase activity



Although the *in vivo* importance of protein S-nitrosation for regulating cellular signaling pathways is well established, protein-assisted mechanisms for site-specific cysteine nitrosation have not been determined. Nitrosation of the active site cysteine of caspase-3 inactivates the enzyme and is known to be important for regulating cellular apoptosis. However, a solution reaction with nitric oxide (NO) does not have the necessary specificity for the catalytic cysteine. Mitchell and Marletta found that thioredoxin can catalyze the specific transnitrosation and denitrosation of the caspase-3 active site cysteine and a unique cysteine on thioredoxin. This study suggests that thioredoxin may be a new player in the *in vivo* modulation of caspase-3 activity. [Letters, p. 154; News & Views, p. 126] *JK*

Profiling proteomics

Ongoing DNA mapping and sequencing efforts have generated a wealth of information about the organization and evolution of genomes, but they have also shown us how far we are from understanding the workings of the proteome. The review article by Saghatelian and Cravatt illustrates how chemical and biological tools, when combined in thoughtful ways, have built upon our knowledge of genome sequences to profile protein activity and modification chemistry, engineer new specificities into proteins and begin to illuminate the complex relationships of small-molecule metabolites. **[Review Articles, p. 130]** *TLS*

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