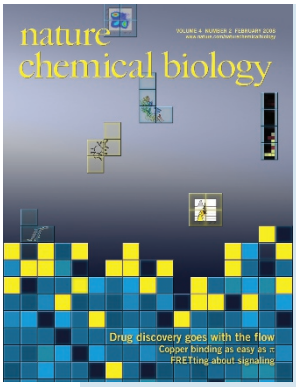
IN THIS ISSUE



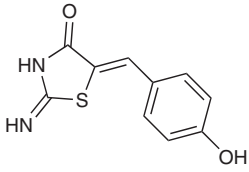
Compound screening gets more specific

Flow cytometry is a useful tool for whole-cell screening in that multiple proteins in multiple cell types can be monitored in a single experiment or in a high-throughput setting. Krutzik *et al.* use a specific flow cytometry technique they call phospho-flow, which allows for quantitative measurement of the phosphorylation levels of intracellular signaling proteins in whole cells, to show that single drug effects can be extended to large-scale screening efforts. They identified several compounds that selectivity inhibit only the Jak-Stat signaling pathway of B cells from among all of the cell types found in whole blood. The new drug screening platform can be used through the various testing and monitoring stages of the drug discovery process where the desired target is a network of proteins in populations of single physiologically and disease-relevant cells. [**Articles, p. 132**] *MB*

Coordinated GPCRs

Ligand-mediated G protein–coupled receptors (GPCRs) transmit information into the cell via G protein–linked signaling pathways. The way in which extracellular ligands initiate signaling, however, is not completely clear. Now Vilardaga *et al.* provide insight into the signaling of a GPCR heterodimer composed of morphine and norepinephrine receptors. The authors use fluorescence resonance energy transfer to demonstrate that the proteins undergo conformational changes that cause ligand binding at one receptor to inhibit signaling by the other. In addition, they found that morphine-induced inhibition of norepinephrine-mediated signaling is distinct from the opposite process, which suggests these effects are agonist-dependent. Further work will be needed to precisely elucidate the conformational changes that govern these effects, but these results demonstrate that unlocking intracellular signaling is more complex than previously anticipated. [**Articles, p. 126**] *CG*

Small molecules in ATM transactions

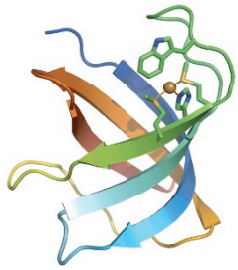


MRN is a protein megacomplex that senses DNA double-strand breaks (DSBs) and recruits and activates the ATM kinase pathway for DSB correction. Functional studies of MRN are limited because genetic inactivation of MRN components such as Mre11 is lethal. Using a forward genetic chemical screen, Dupré *et al.* identified an MRN inhibitor called mirin that acts specifically on the ATM-activating step of the repair pathway by binding to Mre11 and disrupting its exonuclease activity, which serves to excise broken DNA ends. Because it is not lethal, mirin should prove useful in further studies of the MRN-ATM pathway and also represents a potential strategy for sensitizing tumors to agents that induce DNA breaks. [Articles, p. 119; News & Views, p. 86] *MB*

Written by Mirella Bucci, Catherine Goodman & Joanne Kotz

Corrected after print 13 February 2009.

Copper binding: it's a Trp

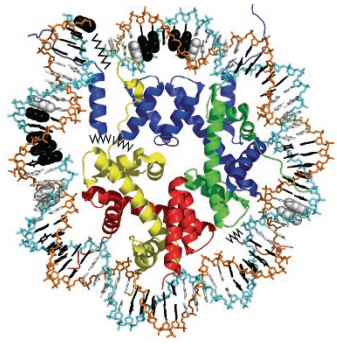


In biological systems, cations such as Na^+ and K^+ can be bound through noncovalent cation-π interactions with aromatic amino acids. In contrast, these interactions have not been reported to play a role in cellular recognition of transition metals. Xue *et al.* now report the crystal structure of CusF, a periplasmic copper trafficking protein, with Cu(I) bound and find a tryptophan 3.3 Å from the metal site. Resonance Raman spectroscopy demonstrates that there is a cation-π interaction between the Cu(I) and the tryptophan, thus revealing a new mode for transition metal binding. [**Brief Communications, p. 107; News & Views, p. 85**] *JK*

Thiamine diphosphate without its Glu

Thiamine diphosphate functions as an enzymatic cofactor in a variety of reactions, including decarboxylations and transketolations. A key step in catalysis is the deprotonation of the C2 carbon of the cofactor. A conserved active site glutamate is believed to play an essential role in stabilizing the formation of the resulting carbanion. Kaplun *et al.* have solved the structure of glyoxylate carboligase, which reveals a valine in place of the conserved glutamate. Replacing the glyoxylate carboligase valine with an aspartate or glutamate resulted in an increased rate of C2 deprotonation; however, the rate of product release and the overall reaction rate were decreased. Thus, glyoxylate carboligase appears to sacrifice the rate of initial thiamine diphosphate activation in order to maximize the overall rate of reaction. [Articles, p. 113] *JK*

Platinum drugs at the core



Cisplatin and related complexes have proven to be important anticancer drugs despite the significant toxicity associated with their use. Development of a new generation of platinum-containing drugs would benefit from an increased understanding of the mechanism of action of these compounds. Through crystallography and biochemical analysis, Wu *et al.* have now determined the sites of cisplatin- and oxaliplatin-induced cross-links in both naked DNA and nucleosome core particles (NCPs). The results revealed important differences in reactivity between the two; for instance, the centers of the NCPs were 'hot spots' for adduct formation despite the fact that some of these same stretches of sequence were not targeted in naked DNA. This is particularly surprising because NCP centers are relatively inaccessible to most proteins and small molecules. Future studies can now begin to unravel the mechanism for this NCP core selectivity. [**Brief Communications, p. 110**] *JK*

Corrigendum: In this issue

Mirella Bucci

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In the initially published version, the chemical structure of mirin displayed in the section entitled "Small molecules in ATM transactions" was incorrect. The corrected structure of mirin is now provided in the HTML and PDF versions of this 'In this issue' section.