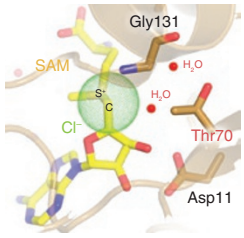
BMP ironed out

Bone morphogenetic protein (BMP) signaling is important in various developmental processes, including specification of the dorsoventral axis during zebrafish embryogenesis. As with many signaling pathways that invoke kinases, it has been difficult to identify compounds specifically targeted against the BMP pathway. Here, Yu *et al.* screened 7,500 compounds for those that could dorsalize zebrafish embryos, with the idea that such compounds would be BMP antagonists. One compound, dorsomorphin, blocks the expression of the peptide hormone hepcidin, linking this critical iron balance regulator with BMP signaling. [**Articles, p. 33; News & Views, p. 15**] *MB*

Image-based SARs

Advances in automated microscopy have enabled image-based high-throughput screens, but making sense of the large amount of resulting information is still challenging. Young *et al.* have now applied 'factor analysis', a method for analyzing complex datasets, to reduce the complexity of screening data while maintaining the biological information. The authors screened approximately 6,500 small molecules for their effects on cell cycle state. Then, using the derived 'factors', hits could be grouped into biologically interpretable phenotypes. By comparing this phenotypic data with measures of chemical similarity and predictions of the small-molecule targets, the authors obtained meaningful structure-activity relationships from the cell-based screening data. [**Articles, p. 59; News & Views, p. 18**] *JK*

Nucleophilic chlorination

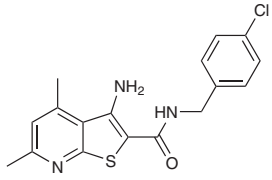


The natural product salinosporamide A is a 20S proteasome inhibitor that requires a chlorine atom for potent activity. Eustaquio *et al.* found that *salL*, a gene in the *sal* biosynthetic cluster, is required for *in vivo* chlorination of salinosporamide A. Unlike the oxidative mechanism that predominates in biological chlorination, SalL chlorinates *S*-adenosyl-L-methionine by a nucleophilic substitution reaction with mechanistic similarities to a known fluorinase. Although SalL did not accept fluoride as a substrate, the enzyme could catalyze iodination or bromination. Through its use of an orthogonal biological chlorination mechanism, SalL could prove valuable for the biosynthesis of halogenated small molecules. [Articles, p. 69] *JK*

Defining docking

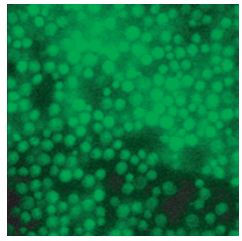
Biosynthetic pathways use modular, multidomain protein machinery to iteratively construct peptides and polyketides. In nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) systems, these domains interact via portable recognition sequences at the ends of each module. Recent discoveries of hybrid NRPS-PKS systems suggest that these proteins may also be governed by recognition sequences, but the precise nature of these contacts was unknown. Richter *et al.* have now determined the structure of the TubC docking domain from the tubulysin biosynthetic pathway. The dimeric αββαα fold presents a patch of positively charged amino acids that serves as a docking code for the partner domain. Mutation of three key arginines confirmed that these residues have an important role in binding, thus defining a new type of protein-protein interface. [**Articles, p. 75**] *CG*

Dialing in M_4



Cholinergic pathways, which use acetylcholine as the primary neurotransmitter, have been implicated in critical central nervous system (CNS) functions and can be modulated to treat CNS diseases. Muscarinic acetylcholine receptors (mAChRs) are mediators of cholinergic transmission. However, selectively modulating the five subtypes of mAChRs has been difficult. Shirey *et al.* now report a highly selective potentiator that binds to an allosteric site of the M_4 mAChR. Using this compound, the authors found that M_4 is involved in excitatory, but not inhibitory, synaptic transmissions in the hippocampus. This selective small-molecule modulator will be important for further investigating the biological roles of M_4 and may provide a basis for developing therapeutics. [Articles, p. 42] *JK*

Second guessing second messengers



The endogenous phosphate metabolism of budding yeast cells is modulated based on phosphate levels in the environment. Phosphate metabolism genes are regulated by the PHO system, including the kinase complex Pho80-Pho85 and the inhibitor Pho81. In order to inhibit the kinase activity of Pho80-Pho85, Pho81 requires the inositol pyrophosphate IP_7. Lee *et al.* now show that IP_7 effects this inhibition through reversible binding to the Pho80-Pho85-Pho81 complex. This noncovalent binding induces a conformational change in the complex that prevents substrate binding. IP_7 therefore acts in a manner characteristic of classical second messengers, rather than through covalent modification. [**Articles, p. 25; News & Views, p. 16**] *MB*

Damage be gone

DNA glycosylases such as *Escherichia coli* adenine glycosylase MutY search for and remove damaged DNA bases. However, the relative importance of the various steps of base pair recognition and base removal, collectively known as base excision repair, are unknown. Using *in vitro* adenine glycosylase and binding assays, along with an *in vivo* cellular repair assay, Livingson *et al.* have now begun to translate *in vitro* enzyme kinetics into *in vivo* functional parameters that define how MutY recognizes DNA lesions. By testing oxidatively damaged guanine residues that incorrectly pair with adenine residues, they found a correlation between mismatch affinity and *in vivo* excision by MutY, which suggests that high-affinity binding is the rate-limiting step for repair. [Articles, p. 51] *MB*

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