PHARMACOLOGICAL CHAPERONES

α-Helical masquerade

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Finding compounds that can modulate protein-protein interactions (PPIs) or protein misfolding defects is challenging owing in part to the large, featureless surfaces that need to be targeted. Several strategies exist—for example, using peptidic or nonpeptidic α-helix mimics to modulate PPIs—but the solubility and synthetic methods for these molecules have limited their utility. To overcome some of these barriers, Oh *et al*. developed a synthetic strategy to generate a one-bead one-compound library of nonpeptidic α-helix mimics based on a triazine-piperazine-triazine scaffold whose side chains could be modified to promote better hydrophilicity. Specifically, the authors first added a peptoid-encoding component to the beads and subsequently performed high-throughput screens against MCL-1, an antiapoptotic member of the BCL-2 family of proteins that has been implicated in various cancers, and against α-synuclein, whose misfolding is implicated in Parkinson's disease. The MCL-1 screen found several compounds that bind MCL-1 and inhibit its known functional interaction with a BH3 helical peptide *in vitro* and its interaction with BAK *in vivo*. One of these compounds was predicted by *in silico* docking to mimic the binding mode of the BH3 peptide. The α-synuclein screen found two hit compounds that bind α-synuclein and decrease its aggregation propensity. These results suggest that PPI inhibitors and protein folding modulators (collectively, 'pharmacological chaperones') against different helical proteins can be identified from α-helix mimic libraries. *MB*

CARBOHYDRATES

Xylan feels the pinch

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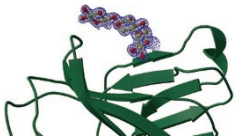

SATISH NAIR

Human gut commensal bacteria are required for digestion of carbohydrates such as xylan, but the specific enzymes involved in these processes are not fully characterized. To gain insights into xylan degradation, Zhang *et al*. examined two *Bacterioides* strains that are particularly enriched in genes that encode carbohydrate-active enzymes. Transcriptional analysis of bacterial cells exposed to xylan demonstrated that the genes encoding the putative proteins BiXyn10A and BACOVA_04390 from the glycoside hydrolase 10 (GH10) family were the most upregulated in the two strains; biochemical analysis of purified BiXyn10A showed that it degrades two common xylan substrates. Bioinformatics analysis identified an unusual 250-amino-acid insertion within the GH10 sequence of BiXyn10A that was suspected to encode tandem carbohydrate-binding modules (CBMs), though it had low homology to known CBMs. Isothermal titration calorimetry of the two isolated CBMs demonstrated that they bind wheat arabinoxylan and related substrates with slightly different specificity, and mutational analysis confirmed the importance of these modules for xylan degradation by the GH10 enzyme. Biochemical characterization of additional homologs of the tandem CBMs from BiXyn10A homologs confirmed binding to xylohexaose. A co-crystal structure of this interaction suggests that these new CBMs are specific for xylan because of the unusual orthogonal placement of aromatic residues within the binding site that pinch the xylan substrate, inducing a kink in the backbone. *CG*

BIOSYNTHESIS

All together now

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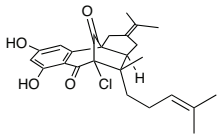

Merochlorins A and B are natural products that contain complex ring structures and carbon–chlorine bonds. Teufel *et al.* now report the reconstitution of the merochlorin biosynthetic pathway *in vitro*, which generates these two terpenoids from dimethylallyl diphosphate (DMAPP), geranyldiphosphate (GPP) and malonyl–CoA. The authors first showed that Mcl17, which is homologous to type III polyketide synthases, could produce the tetrahydroxynapthalene ring from five molecules of malonyl–CoA. They then determined that Mcl22 joined GPP and DMAPP via a highly unusual 'head-to-torso' coupling reaction, thereby forming a branched sesquiterpene diphosphate. Mcl23 was shown to mediate the coupling of this sesquiterpene diphosphate to the tetrahydroxynaphthalene ring *in vitro*. As the authors were not able to generate sufficient pre-merochlorin via enzymatic synthesis to carry out additional experiments, they chemically synthesized this molecule. Addition of this compound to a Δ*mcl23* strain of *Streptomyces* led to the production of both merochlorins, indicating that pre-merochlorin was an intermediate in the biosynthetic pathway. In a companion paper, Diethelm *et al.* showed that the vanadium-dependent haloperoxidase Mcl24 catalyzed the site-specific chlorination of the naphthalene ring and the subsequent oxidative dearomatization-cyclization reaction cascade to ultimately generate merochlorins A and B. These results provide a compelling example of how architecturally complex natural products can be generated from three simple building blocks using just four enzymes. *JMF*

TRANSPORTERS

Death by ions

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The maintenance of ion homeostasis is crucial to ensure cell viability. Disrupting this balance through increased ion flux into cells triggers programed cell death, a process known as apoptosis. Prodigiosin is a natural product that promotes cancer cell death by allowing the influx of HCl into cells across what are normally impermeable membranes. Many groups have synthesized similar ion transporters, but few have been successful in mimicking the biological effects of prodigiosin. Ko *et al*. synthesized pyridine diamide–strapped calixpyrroles, which transport chloride and sodium ions across lipophilic membranes. Using ion-specific fluorescent probes, the authors observed an increase in the intracellular levels of chloride and sodium in mammalian cells when the small-molecule transporter was present. These cell lines exhibited reduced cellular viability features consistent with caspase-mediated apoptosis, including increased reactive oxygen species, mitochondrial cytochrome *c* release and activation of caspases. The authors verified the requirement of sodium and chloride for promoting apoptosis. For instance, they showed that the frequency of cell death decreased when the transporter was added to cells cultured in a chloride- or sodium-free medium. Finally, the authors found that sodium chloride influx and ROS production occurred earlier than the first indication of cell death, confirming that the influx of ions into cells promotes apoptosis. *GM*

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