Heat Shocking the KEAP1/NRF2/ARE Pathway

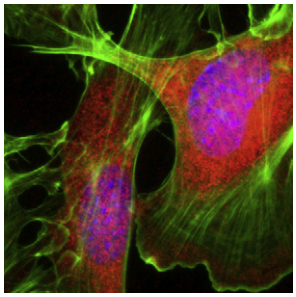
PAGE 1355

The heat shock response and the KEAP1/NRF2/ARE pathway are inducible defense systems that allow the cell to adapt and survive under stress conditions. Zhang et al. found that structurally diverse inducers of the KEAP1/NRF2/ARE pathway, all of which react with sulfhydryl groups, have a dual cytoprotective role by also activating the heat shock response, thus implicating the heat shock response as a target for Nrf2 inducers. This newly uncovered duality contributes to the cytoprotective effects of such molecules in models of carcinogenesis, cardiovascular disease, and neurodegeneration.

Aminoacylated tRNAs Hijackers

PAGE 1362

Cyclodipeptide synthases (CDPSs) are small enzymes structurally related to class-I aminoacyl-tRNA synthetases that hijack aminoacylated tRNAs from their canonical role in ribosomal protein synthesis and use them for cyclodipeptide formation. Seguin et al. show that a predicted protein identified in the sea anemone *Nematostella vectensis*, *Nvec*-CDPS2, is an active CDPS catalyzing the formation of various cyclodipeptides, thus representing the first enzyme involved in nonribosomal peptide synthesis to be identified in animals.



Arginylation and Methylation Go Hand in Hand

PAGE 1369

Protein arginylation and arginine methylation are two posttranslational modifications of emerging importance that involve Arg. Saha et al. demonstrate that posttranslationally added arginines can be further modified by methylation and that this double modification can regulate nuclear architecture. This is exciting evidence that posttranslationally modified sites of proteins can undergo subsequent posttranslational modifications, establishing a functional link between protein arginylation and Arg-methylation. It is likely that such double modifications can increase the complexity of the signaling, exert many regulatory functions through a limited number of protein sites, and even provide a unique type of protein code.

Synergizing with β-Lactam Antibiotics

PAGE 1379

A chemical-genetic strategy was utilized to identify essential genes of methicillin resistant *Staphylococcus aureus* (MRSA) required for antibiotic resistance. Lee et al. describe key chemical genetic interacting networks that restore antibiotic susceptibility to hospital- and community-acquired MRSA. The authors provide a rational framework for developing inhibitors of targets within this chemical genetic interaction network, which if paired with existing β-lactam antibiotics would display synergistic antibacterial activity and offer a combination agent strategy to restore the efficacy of this important antibiotic drug class.

Reverse Cisplatin Resistance

PAGE 1390

Deubiquitinases (DUBs) represent a promising family of targets for new therapies of human cancers and neurological diseases. Chen et al. discovered selective and cell-active inhibitors against human USP1/UAF1, a DUB complex involved in translesion synthesis and DNA interstrand crosslink repair. The inhibitors reverse the chemoresistance of non-small cell lung cancer (NSCLC) cells to cancer drug, cisplatin.

Accelerating Inhibitor Development for DUBs

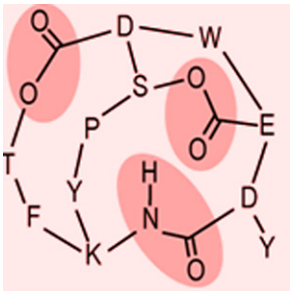
PAGE 1401

Converting lead compounds into drug candidates is a crucial step in drug development, requiring early assessment of potency, selectivity, and off-target effects. Altun et al. use activity-based chemical proteomics to determine the potency and selectivity of deubiquitylating enzyme (DUB) inhibitors in cell culture models. The mass spectrometry based approach described here allows direct target discovery of small molecular compounds in a cellular environment, providing important information on their mechanism of action.

Leader Peptide Guiding the Biosynthesis

PAGE 1413

Microviridins are ribosomally produced unique protease inhibitors from bloom-forming cyanobacteria that have both ecological and pharmacological relevance. Two ATP grasp ligases introduce ω-ester and ω-amide bonds into the peptide backbone to yield rare cage-like structures. Weiz et al. report the establishment of a minimal expression system for microviridins, characterize the MdnA leader peptide, and identify a strictly conserved binding motif that is specific for microviridin ligases. They further unveil that the ABC transporter MdnE is crucial for cyclization and processing of microviridins and is essential for stability of the microviridin biosynthesis complex.



In This Issue

Prion Protein Embraces the Lipid

PAGE 1422

Prion diseases are neurodegenerative disorders characterized by the prion protein (PrP) misfolding and accumulation in the brain. PrP-lipid interactions play a role during the misfolding process, and Sangher et al. now provide an atomic-level view of the complex between the neuronal ganglioside GM1 and PrP. The GM1 binding epitope on PrP involves amino acids previously suggested to modulate prion protein misfolding and the new structural information will be useful for targeting of the complex by small molecule inhibitors.

Bisubstrate Adenylation Inhibitors of Biotin Protein Ligase

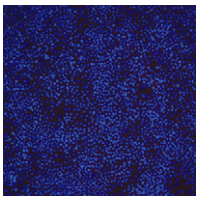
PAGE 1432

The mycobacterial biotin protein ligase (*Mt*BPL) regulates lipid metabolism in *Mt*b. Duckworth et al. have rationally designed a bisubstrate inhibitor of *Mt*BPL, which displays potent subnanomolar enzyme inhibition and antitubercular activity. This inhibitor decreases in vivo protein biotinylation of key enzymes involved in fatty acid biosynthesis and exhibits *Mt*BPL-dependent antibacterial activity. Collectively, the data suggest that *Mt*BPL is a promising target for further antitubercular therapeutic development.

From Natural Product Extracts to Active Compounds

PAGE 1442

The chemical diversity of nature has tremendous potential for discovery of new medicinal agents. However, the crude extracts containing these molecules derived from plants and microorganisms can be difficult to test in current day drug discovery programs due to accompanying pigments, salts, and polymers that interfere with sensitive biological assays. Furthermore, the concentration of a particular chemical component may vary greatly, thus easily going undetected if tested below its effective concentration or appearing overtly toxic if tested at high concentration. Cruz et al. now describe a method that avoids these pitfalls and rapidly identifies natural products with promising activity.



Self-Assembling Peptide Nanotubes Against HCV

PAGE 1453

An estimated 180 million people worldwide are infected with hepatitis C. No vaccine against hepatitis C is currently available; therefore, there is an urgent need for new classes of anti-HCV drugs. In this study, Montero et al. report a class of supramolecular agents specifically targeting HCV entry at a postbinding step. The results suggest that these antiviral peptides can efficiently control viral spread in cell culture, making them potential candidates for controlling spread of the infection in vivo, including restricting the spread of emerging drug-resistant virus variants in combination therapy.

Allosteric Regulation of PKCζ

PAGE 1463

Enzymes transmit information that turns cellular functions ON and OFF. Is it possible to use the mechanisms of regulation of enzymes for the development of medicines to turn enzymes ON or OFF for treatment of human diseases? Lopez-Garcia et al. build on previously developed small compounds that target a site (termed "PIF-pocket") on a protein kinase and activate the enzyme, and describe reversible compounds that binding to the PIF-pocket of PKCζ inhibit the enzymatic activity. Thus, the PIF-pocket is a switch that can be targeted with drugs to turn these enzymes ON or OFF.

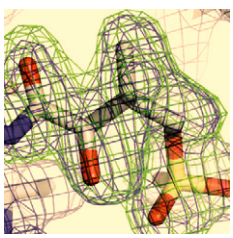
Inhibit Autophagy by Breaking the Mitochondrial Chain

PAGE 1474

Autophagy is a cellular lysosome-dependent catabolic mechanism mediating the turnover of intracellular organelles and long-lived proteins. Here Ma et al. show that antimycin A, a known inhibitor of mitochondrial electron transport chain (mETC) complex III, can inhibit autophagy through its inhibitory activity on mETC complex III. Therefore, mETC complex III may have a role in mediating autophagy induction.

Take a Look at the Carrier

PAGE 1482



The common metabolites, fatty acids, polyketides, and nonribosomal peptides, are all synthesized by complex enzyme machines using small carrier domains to traffic and activate building blocks. The carrier domain is a dynamic component of the process, shuttling pathway intermediates to enzyme active sites. Here Liu et al. report an approach to structurally fix carrier domains suitable for structural analysis. As an example, the structure of a two-domain construct was determined with a mechanism-based inhibitor.

Allosteric Antagonists of GPRC6A Receptor

PAGE 1489

Gloriam et al. describe a pioneering chemogenomic ligand inference between families of G protein-coupled receptors, a major drug target class. This proof-of-concept expands the prospects of successful drug design and discovery. It resulted in the discovery of ligands with allosteric antagonistic activity at GPRC6A, a receptor recently indicated to have a role in metabolism. These ligands constitute useful research tools towards investigating the signaling mechanism of the GPRC6A receptor at the cellular level and serve as initial lead compounds for further optimization of potency and selectivity enabling future ex vivo/in vivo pharmacological studies.

Single Cluster, Two Natural Products

PAGE 1499

Indole alkaloid cluster in *P. chrysogenum* is responsible for the production of roquefortine C, glandicolines, and meleagrin, all derived from cyclo-L-His-L-Trp by modification reactions. Now, Garcia-Estrada et al. deduce the functions of the modifying enzymes using knockdown mutants; for example, they show that a prenyltransferase catalyses the reverse prenylation in R-configuration in carbon 3-position of the diketopiperazine, followed by ring closure between C2 and N12. Two oxidoreductases and one cytochrome P450 oxygenase are involved in hydroxylations and dehydrations of the pathway intermediates, and one N-OH methyltransferase leads to meleagrin.

