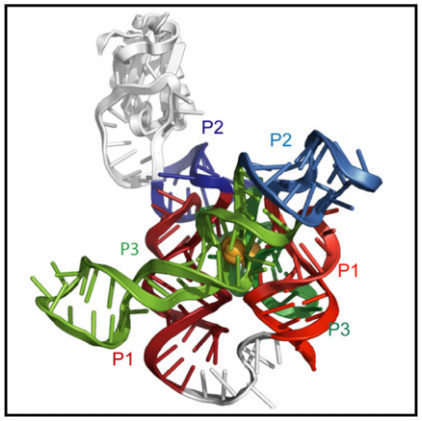
In This Issue

Lipidomics and Systems Biology

PAGE 284

Lipidomics is the large-scale identification and quantitation of structurally distinct lipids in biologic systems. Recent developments in mass spectrometry have allowed the facile assessment of alterations in the composition and content of multiple lipid molecular species during numerous biologic processes. Shotgun lipidomics can determine the structure and quantity of diverse lipids directly from extracts of biological tissues providing a facile approach to understanding the pleiotropic roles of lipids on cellular function. Here, Gross and Han comment on these recent developments and on integrating lipidomics into the systems biology to achieve comprehensive understanding of cellular function and regulatory mechanisms.



Glycine Riboswitch: Two Ligands Are Better Than One

PAGE 293

The glycine riboswitch regulates gene expression through the cooperative recognition of its amino acid ligand by a tandem pair of aptamers. A three-dimensional model of the tandem riboswitch from the glycine permease operon of *Fusobacterium nucleatum*, reported by Butler et al., reveals the glycine binding sites and an extensive network of interactions, largely mediated by asymmetric A-minor contacts, that serve to communicate ligand binding status between the aptamers. This provides a structural basis for how RNA can cooperatively respond to a small molecule for the regulation of gene expression.

Bridge Built of Unnatural Amino Acids

PAGE 299

Hutchins et al. report a strategy for synthesizing heterodimeric antibody conjugates using an unnatural amino acid with orthogonal reactivity. As proof of concept, authors have generated anti-Her2 Fab-Saporin conjugates that demonstrate excellent potency in vitro. This methodology should be useful for site-specifically conjugating antibodies to other proteins, synthetic toxins, imaging agents, and radioisotopes.

Synthetic Biology Yields New Antibiotics

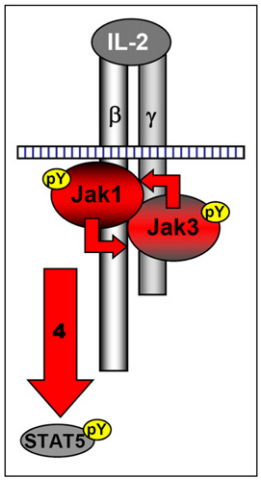
PAGE 304

Synthetic biology approach can be applied to rational modification of the structure of an antibiotic, as demonstrated by Alt et al. The authors introduced a structural moiety that could serve as an "import handle," facilitating the import of the antibiotic into the bacterial cell. The study builds on earlier results showing that catechol siderophore transporters can be used in a Trojan horse approach for the active import of antibiotics. The incorporation of the import handle moiety into the antibiotic structure was achieved through a synthetic biology strategy. Such strategies are promising for the generation of new bioactive molecules in future.

Jak1 Trumps Jak3

PAGE 314

Jak1 cooperates with Jak3 in signaling through γc-containing receptors. Haan et al. show that a Jak3-selective inhibitor was less efficient in abolishing STAT5 phosphorylation than pan-Jak inhibitors. The authors therefore explored the roles of Jak1 and Jak3 kinase functionality in signaling using a reconstituted system and kinase-inactive and "analogue-sensitive" mutants of Jak1 and Jak3 and found that Jak1 plays a dominant role over Jak3. These data challenge the notion that selective ATP-competitive Jak3 kinase inhibitors will be effective immune suppressive agents.



RNA-Ligand Docking Hits a Spot

PAGE 324

The increasing number of RNA crystal structures enables a structure-based approach to the discovery of new RNA-binding ligands. To develop the area of RNA-ligand docking, Daldrop et al. have conducted a virtual screening exercise for a purine riboswitch to probe the strengths and weaknesses of RNA-ligand docking. Using a protein-ligand docking program with minor modifications, new ligands with binding affinities in the micromolar range were identified, including compounds based on molecular scaffolds not resembling known ligands. RNA-ligand docking performed comparably to protein-ligand docking, indicating that this approach is a promising option to explore the wealth of RNA structures for structure-based ligand design.

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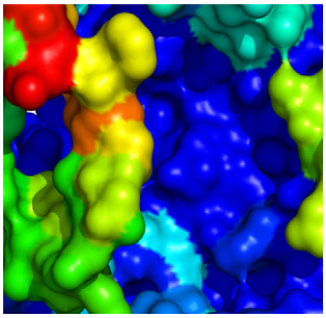
Peptide Hormone with Iron Fist

PAGE 336

The peptide hormone hepcidin is a key homeostatic regulator of iron metabolism and acts by binding to the iron exporter ferroportin. In this study, Clark et al. determine the key residues within the N-terminal region of hepcidin that influence its interaction with ferroportin and explore the structure/function relationships at these positions. In addition, the authors investigate the effect of replacing the disulfide bonds in hepcidin with diselenide bonds on structure and biological activity. The results provide mechanistic insight into the interaction between hepcidin and ferroportin.



Hot-Spots and iPred

PAGE 344

Geppert et al. present "iPred," an alignment-free computational method for prediction of protein-protein interface residues. Prediction robustness was assessed on more than 1500 proteins and data show that functional "hot-spot" residues are enriched among the predicted interface residues. iPred is based on a knowledge-based scoring function and does not rely on sequence conservation, so that rapid interface identification is possible even for proteins for which homologs are unknown.

A News Spin on Quinone Synthetases

PAGE 354

The biochemical and genetic basis of secondary metabolism in the plant pathogen *Ralstonia solanacearum* was investigated by Wackler et al. Although similar to fungal quinone synthetases and, more distantly, to nonribosomal peptide synthetases, the tridomain enzyme RalA was identified as a furanone synthetase. The findings imply a dissimilar mechanism and new biochemistry for quinone synthetases. The results also help annotate orphan natural product genes, discovered during genome sequencing, more accurately; predict biosynthetic capacities more precisely; and make "mining" for new bioactive compounds more effective.

Eph Receptor Tyrosine Kinase, Semisynthetic and Active

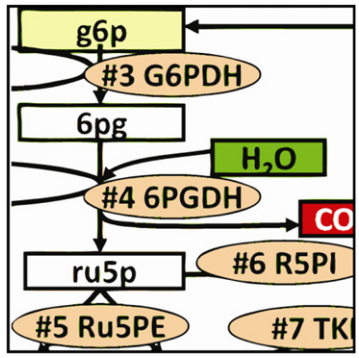
PAGE 361

Singla et al. describe a chemical biology approach for generating milligram amounts of highly pure and biologically active Eph tyrosine kinase receptors that are ideal for structural and functional analysis. Phosphoproteomics-based characterization of the semisynthetic Eph receptor provides novel insight into the sequential order of phosphorylation of individual tyrosine residues in the ligand-induced kinase activation mechanism. The reported method should be general enough to be easily applicable to many other multidomain single-pass transmembrane receptors, allowing the production of large amounts of various functional cell-surface proteins for structural studies using X-ray crystallography and cryoelectron microscopy.

Synthetic Enzymatic Pathways for Jet Fuel

PAGE 372

In microbial fermentations, only a small fraction of glucose is allocated to NAD(P)H generation. Now, Wang et al. use 12 enzymes in one pot to self-assemble a synthetic pathway for low-cost biohydrogenation; that is, desired biological reactions work without the other complex interactions that take place within a cell. This cell-free synthetic pathway process both increases product yield and reaction rate. The hybrid of biocatalysis and catalysis would produce sulfur-free jet fuel with an unprecedented high energy conversion efficiency, much higher than those of fatty acid esters and bioalkanes by aerobic fermentations.



When Bacteria Get Hormonal

PAGE 381

Hormaomycin is a structurally highly unusual peptide hormone that induces morphological differentiation and the production of secondary metabolites in various bacteria. Now, Höfer et al. reveal insights into how the producer organism *Streptomyces griseoflavus* assembles this unique natural product.

Protease Beacons for Endogenous MT1-MMP Activity Detection

PAGE 392

Directed evolution was applied by Jabaiah and Daugherty to identify peptide substrates with enhanced hydrolysis rates by MT1-MMP suitable for protease beacon development. Screening of a random pentapeptide library, using two-color CLiPS, yielded several substrates identical to motifs in distinct collagens. To identify substrates with enhanced cleavage rates, a second-generation decapeptide library incorporating the consensus was screened under stringent conditions. These substrates are hydrolyzed by human-MT1-MMP at a faster rate than reported peptide substrates. Finally, incubation of soluble protease beacons incorporating the optimized substrates, but not previous substrates, enabled direct detection of endogenous MT1-MMP activity of human-fibrosarcoma (HT-1080) cells.

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