In This Issue

Glycan-Binding Proteins Identified by HTS

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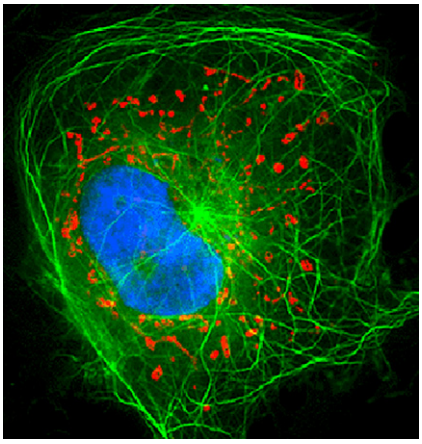
A variety of cellular processes, like cell-cell interactions and immune regulation, are mediated by glycan-binding proteins (GBPs). GBPs bind specific glycans with affinity in the micromolar to millimolar range. The low binding affinity and the lack of well-characterized glycan libraries have hindered development of efficient analytical methods for GBP/glycan-motif-binding screen. Kim et al. developed a rapid glycan immobilization technique via 4-hydrazinobenzoic acid (HBA)-functionalized beads that allows GBPs screening in high-throughput manner. The screen was followed by high-accuracy mass spectrometry and allowed detection of GBPs with low abundance in biological samples.

Venturing into the Far-Red



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The development of fluorescent proteins for the use in life sciences provided scientists with remarkable tools to visualize and monitor biological processes in the living systems. Fluorescent proteins with red-shifted emission are highly desirable for tissue and whole-body imaging. Kredel et al. engineered a red fluorescent protein, eqFP611, and obtained folding-optimized, red-shifted variants with superior stability and brightness. In addition to demonstrating the application potential of eqFP611 variants in cellular assays, the authors show that the red shift is caused by a *trans-cis* isomerization of the chromophore. Curiously, the present case is a rare example of green fluorescent protein (GFP)-like protein in which both *cis* and *trans* isomers are brightly fluorescent. (Figure adopted from Kredel et al.)

Oncogenic-RAS Signaling Turns Rusty

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Synthetic lethal screening is a strategy used to discover small molecules with increased activity in cancer cells harboring a specific mutation. Yang and Stockwell screened small molecules for synthetic lethal interactions with oncogenic RAS, which resulted in the identification of RSL3 and RSL5. Counterscreening with bioactive compounds gave insights into the mechanism of action for RSL3 and RSL5, including the involvements of MEK, reactive oxygen species, and cellular iron. Probing aspects of oncogenic-RAS signaling with small molecules identified in this study revealed that this signaling enriches the cellular iron pool by modulating the iron metabolism network.

Dynamics of Large Protein Assemblies Monitored in Real Time

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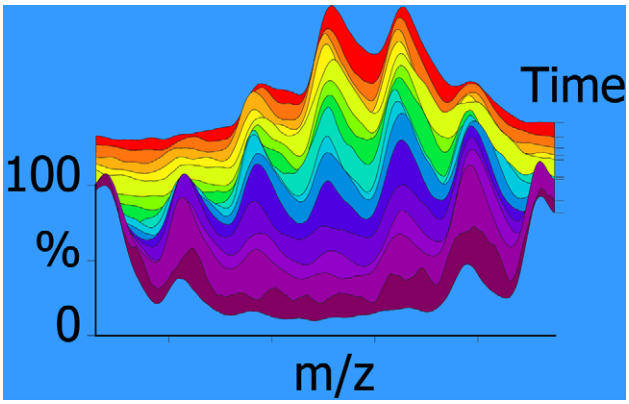
The function of protein complexes is governed by their structure and associated dynamics. Many structural biology techniques, however, provide only a static picture and are not suited to the study of nonequilibrium states. This article by Painter et al. describes a real-time mass spectrometry approach which enables the simultaneous determination of the organization and dynamics of large protein assemblies. The authors show how two related, small heat-shock proteins from *Arabidopsis* coassemble to form heterododecamers by exchange of dimeric units. This implies that these proteins function as part of dynamic chaperone network capable of modulating substrate specificity within the cell. (Figure adopted from Painter et al.)



Coupled Dynamic Structure of Polypurine Tracts

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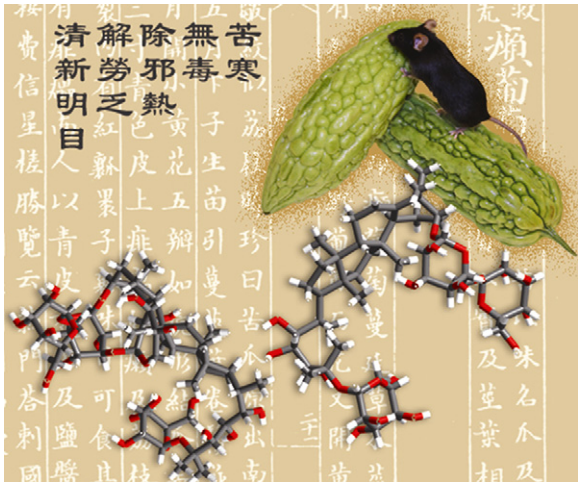
A purine rich region of the (+) RNA genome of retroviruses and retrotransposons, the polypurine-tract (PPT), is resistant to hydrolysis by the RNase H subdomain of reverse transcriptase (RT) and ultimately serves as a primer for (+)-strand DNA synthesis. Here, Yi-Brunozzi et al. applied NMR spectroscopy to search for pre-existing structural features in RNA/DNA PPT-containing hybrids, derived from HIV-1 and Ty3, in the absence of RT. While both hybrids were found to adopt global A-form-like helical geometries, observed structural perturbations in hybrids modified through base-pair changes or by incorporation of a thymine isostere, 2,4-difluoro-5-methylbenzene, suggest that PPTs may function as structurally coupled domains.

Dispelling Evil Heat and Regulating Glucose Metabolism



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Bitter melon, *Momordica charantia*, is one of the traditional Chinese herbal medicines, described as "Bitter, cool, non-toxic, dispelling evil heat, relieving fatigue, refreshing and illuminating" by Li Shizhen, famous botanist and pharmacologist from the Ming Dynasty. Tan et al. now identify the active compounds responsible for the reported antidiabetic properties of this medicinal vegetable. Authors show that isolated cucurbitane triterpenoids potently stimulate translocation of the insulin-responsive glucose transporter GLUT4 to the cell membrane and activate AMP-activated protein kinase (AMPK). Consistent with these findings, acute administration in mice resulted in a significant enhancement of glucose disposal and increases in fatty acid oxidation. (Figure, Chinese text interpretation, and source information courtesy of Tan et al.)

The World of Inositol Pyrophosphates

PAGE 274

Inositol pyrophosphates (PP-IPs) are signaling molecules linked to a wide range of cellular functions. A study by Draškovič et al. suggests that inositol hexakisphosphate kinase (IP6K) converts the natural substrates inositol pentakisphosphate and inositol hexakisphosphate to several products with an increasing number of phospho-anhydride bonds, resulting in formation of pyrophosphate and/or triphosphate groups. All three mammalian IP6K isoforms appear to share similar activities both in vitro and in vivo, and promiscuous activity of mammalian IP6Ks leads to products of diverse yet specific stereochemistry.

Reidispongiolide Wags its Tail

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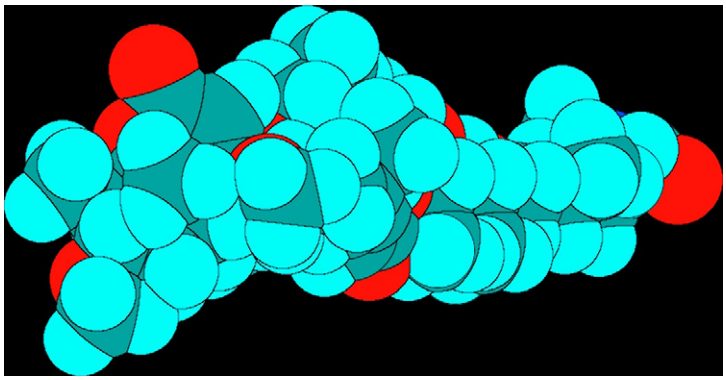
Drugs that block the regulation of actin filament dynamics have substantial therapeutic interest. One such class of compounds includes synthetic mimetics of reidispongiolide A, composed of a tail and a macrolide ring. Perrins et al. now show that the tail accounts for all of the actin-binding and cytotoxic activities of reidispongiolide. Small hydrophobic groups attached to the tail increased the binding affinity for actin and cytotoxicity, suggesting that the role of the ring is to stabilize the actin-tail complex. The authors propose that the incorporation of other hydrophobic groups to the tail could improve targeted delivery of these synthetic mimetics of reidispongiolide to specific tumor cells, for example.



Argifin Sheds Most of Its Structure, Remains Active

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Chitin is a polysaccharide built from N-acetylglucosamine units, found as the main component of the fungal cell walls and insects' exoskeleton. Chitin is digested and degraded by a family of glycoside hydrolases, chitinases. Previous studies have established that a natural product, argifin (cyclopentapeptide), can inhibit chitinase activity by mimicking protein/carbohydrate interactions. Andersen et al. now show, using cumulative truncation of the argifin peptide, that most of the activity of the peptide resides in a dimethylguanylurea that binds deep in the emzyme active site. Dimethylguanylurea has the largest binding-efficiency index and satisfies all the requirements for an excellent fragment for drug design efforts.

