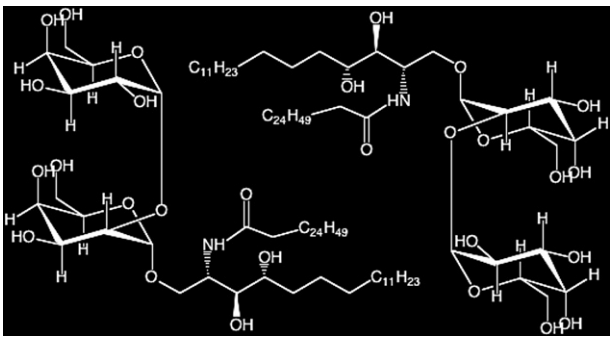
In This Issue

Ferristatin Engages Lipid Rafts

PAGE 647

Iron is an essential nutrient required for numerous cellular process and its homeostasis is a tightly regulated. In plasma, iron exists bound to transferrin. Upon transferrin binding to its cognate receptor, it is internalized through clathrin-mediated endocytic process. Ferristatin is a small molecule inhibitor previously shown to block iron assimilation from transferrin. Now, Horonchik and Wessling-Resnick demonstrate that ferristatin induces internalization and degradation of transferrin receptors by a lipid-raft-mediated pathway. Internalization promoted by ferristatin is independent of clathrin and dynamin and is blocked by the cholesterol-depleting agents fillipin and nystatin. The degradation of transferrin receptors by this novel pathway is sensitive to both proteosomal and lysosomal inhibitors and ultimately accounts for ferristatin's ability to block transferrin-mediated iron uptake.

Glycosphingilipids/Natural Killer T-Cells Face Off



PAGE 654

Natural killer T (NKT) cells have been shown to recognize glycosphingolipids (GSLs) from sphingomonas bacteria. The antigens previously tested contain a monosaccharide and a C18:0 sphingosine lipid. These bacteria, however, also have oligosaccharides containing GSLs and GSLs with different sphingosines, including a C21:0 sphingosine with a cyclopropyl ring (C21cycl). Kinjo et al. studied the stimulation of NKT cells with synthetic GSLs containing natural tetrasaccharide sugars or the C21cyclo sphingosine. The results indicate variability in the antigenic potency of different sphingomonas GSLs, with the C21cyclo sphingosine having intermediate potency, and the oligosaccharide-containing antigens exhibiting limited or no stimulatory capacity.

Targerting Prostate-Specific Antigen

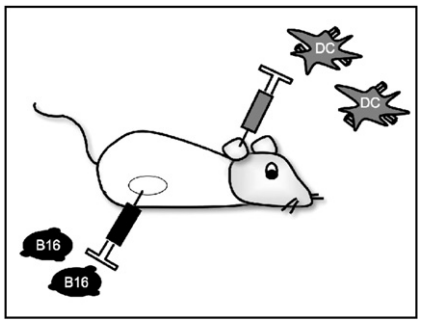
PAGE 665

Prostate cancer cells exclusively produce high levels of prostate-specific antigen (PSA) and, for this reason, PSA is the biomarker used to detect prostate cancer and monitor therapeutic response. Functionally, PSA is a serine protease. Emerging evidence suggests that PSA's proteolytic activity plays a role in the pathobiology of prostate cancer. To better understand this role and to potentially develop targeted imaging and therapeutic agents, LeBeau et al. have used an iterative approach to identify potent and selective peptidyl boronic acid PSA inhibitors. The application of these peptidyl inhibitors towards the therapy and imaging of human prostate cancer is currently under evaluation.

OX40 Receptor-Activating Aptamer

PAGE 675

Therapeutic manipulation of immune responses for the treatment of diseases including cancer has become an important focus of biomedical research. Many receptors are activated by multimerization on the cell surface. Molecular scaffolds have been utilized to assemble multiple receptor-binding peptide ligands to induce receptor multimerization and activation. Dollins et al. demonstrate that a flexible molecular scaffold can be used to convert an RNA ligand (aptamer) that recognizes OX40, a member of the tumor necrosis factor receptor superfamily, into a receptor agonist. Such OX40 receptor-activating aptamers can induce receptor function and enhance the potency of tumor vaccines in mice. (Figure adopted from Dollins et al.)



Protein Kinase CK2 – get the POM-POMs

PAGE 683

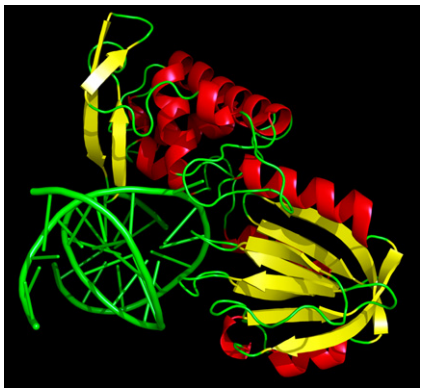
Protein kinase CK2 is disregulated in number of cancers and is now considered to be a highly relevant pathophysiological target, thus creating a need for the identification of the appropriate chemical inhibitors. Prudent et al. present the identification and the characterization of the unique class of non-ATP-competitive CK2 inhibitors, polyoxometalates (POMs). POMs are *inorganic* complexes formed between early transition metal ions (V^{V}, Mo^{VI}, or W^{VI}) and oxo ligands. As inhibitors, POMs exhibit a remarkable activity and a striking specificity for CK2, targeting a domain outside the ATP- and peptide substrate-binding sites. Thus, these compounds represent nonclassical kinase inhibitors interacting with CK2 in a unique way.

A Different Iterative Type I PKS

PAGE 693

Azinomycin B is a complex natural product with potent antitumor activity. To produce the highly diverse functionalities present in its final structure, azinomycin B biosynthetic machinery had to evolve different strategies, including (1) incorporation of unusual building blocks into the nonribosomal peptide synthetase (NRPS) assembly line, (2) NRPS on line modification, (3) reductive release of the assembled intermediate as an aldehyde, and (4) NRPS-post modifications. Zhao et al. now characterize AziB and demonstrate that AziB is a 5-methyl-naphthoic acid (NPA) synthase. AziB is a new member to bacterial iterative type I polyketide synthases (PKSs) and shows the fourth selective reductive pattern in aromatic polyketide biosynthesis governed by this family.

Bulky Lesion Not a Problem



PAGE 706

The challenge for DNA glycosylases, enzymes involved in the base excision repair pathway, such Fpg and hOgg1, is to identify and remove one lesion among millions of undamaged bases by not only identifying small lesions that didn't cause large disruptions of local DNA structures, but also by accommodating and processing bulky lesions using the same active site. Combining chemical synthesis of derivatized DNA molecules, designed to mimic small and large lesions, with comparative structural analysis of Fpg bound to damaged DNA, Coste et al. established the molecular basis for formation of an unproductive but stable complex between Fpg and the bulky DNA lesion. The authors suggest that formation of this unproductive complex inhibits DNA repair processes, thus explaining the long persistence of these lesions observed in vivo.

CFTR Takes Double Punch

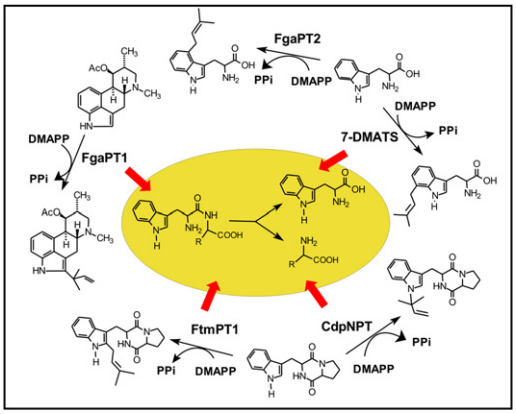
PAGE 718

Secretory diarrheas such as cholera and Traveler's diarrhea are major health problems in developing countries. The CFTR chloride channel provides the main pathway for fluid secretion into the intestine in secretory diarrheas. Sonawane et al. synthesized a series of polyethylene glycol-conjugated CFTR inhibitors that block CFTR by occluding its external pore. A substantially higher potency of divalent versus monovalent conjugates was found, which appears to result from a cooperative binding mechanism. Good potency, chemical stability, and membrane impermeability of the compounds developed in this study make them highly attractive candidates for further preclinical development.

Indole Prenyltransferases Now in the Role of Aminopeptidase

PAGE 729

Prenyltransferases catalyze the transfer of allylic prenyl groups to acceptor molecules. Kremer and Li now show that four recently identified indole prenyltransferases form *Aspergillus fumigatus* AF293 also exhibit tryptophan aminopeptidase activities. This unique catalytic promiscuity of prenyltransferases is readily distinguishable from prenyltransferase reaction. For example, aminopeptidase activities could be inhibited by addition of EDTA, in contrast to the prenyltransfer reactions catalyzed by the same enzymes, which are independent of the metal ions' presence. The results described here provide further supports for the hypothesis that the indole prenyltransferases from fungi have evolved directly from a common ancestor. (Figure credits: Kremer and Li)



Macrolides Inhibit Glycosidase

PAGE 739

Macrolides are a large class of clinically relevant drugs, mostly known for their antibiotic activity due to their ability to affect bacterial protein biosynthesis through interaction with ribosome. Sadeghi-Khomami et al. now report that macrolides act as competitive inhibitors of glycosidases by binding directly to the active site. The work highlights the value of saturation transfer difference nuclear magnetic resonance (STD-NMR) spectroscopy that enabled the authors to monitor binding of substrates to inactive enzyme variants, providing insight into the enzyme active site structure and recognition of nonphysiological substrates and inhibitors. Whether there is any clinical significance to the inhibition of glycosidases by macrolide antibiotics remains to be determined.

