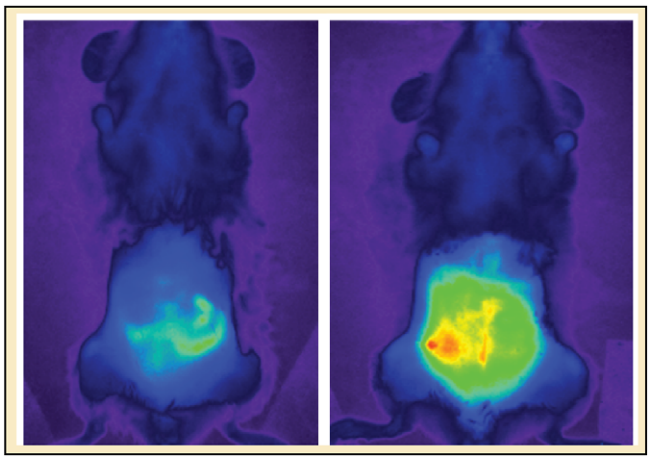
In This Issue

Visualizing Myeloperoxidase Activity in Atherosclerosis-Associated Macrophages



PAGE 1221

The myeloperoxidase-derived oxidant hypochlorous acid (HOCl/OCl^-) is implicated in the pathogenesis of atherosclerosis and other inflammatory states. Shepherd et al. have synthesized sulfonaphthoaminophenyl fluorescein (SNAPF), a new far-red, fluorgenic probe for imaging HOCl. SNAPF displays selective activation in the presence of HOCl, whereas little or no signal increase is observed upon exposure of the probe to other biologically relevant oxidants. The long wavelength absorption and emission of SNAPF minimize the effects of tissue autofluorescence and facilitate imaging through tissue. Application of SNAPF led to successful imaging of HOCl in human atherosclerotic plaque and in an experimental murine peritonitis model (figure adapted from Shepherd et al.).

Synthetic Mycoketide Antigens for T Cells

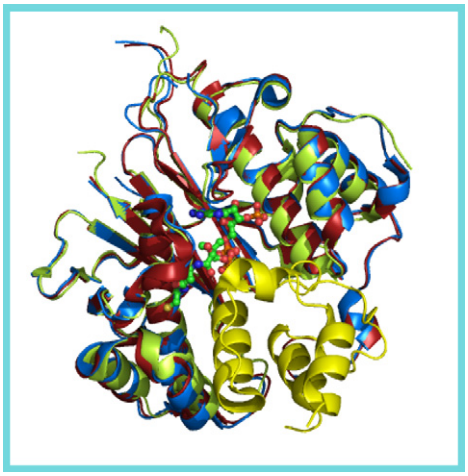
PAGE 1232

Whereas αβ T cells were previously thought to solely recognize peptide antigens, the discovery of CD1 antigen-presenting molecules show how lipid antigens stimulate T cell responses. Here, de Jong et al. finds that synthetic lipids that mimic the structure of mycobacterial mannosyl phosphomycoketide antigens potently activate a T cell line, and that compounds with lipid-branching patterns found in mammalian or bacterial species do not. These studies show how lipid structure can influence T cell responses to promote recognition of pathogens and provide synthetic compounds that can be used to modulate human T cell responses.

Human Holo ACP Synthase Mechanistic Details

PAGE 1243

The paper by Bunkoczi et al. describes the crystal structure of the human phosphopantetheinyl transferase (holo ACP synthase) complexed with CoA and Mg^{2+} and in ternary complex with CoA and ACP. The enzyme exhibits an α/β fold and 2-fold pseudosymmetry similar to the Sfp phosphopantetheinyl transferase from *Bacillus subtilis*. Although the bound ACP exhibits a typical four-helix structure, its binding compared to other ACP acceptor domains is unusual in that it is facilitated predominantly by hydrophobic interactions. Furthermore, a detailed mechanism is proposed describing the substrate binding and catalytic process.



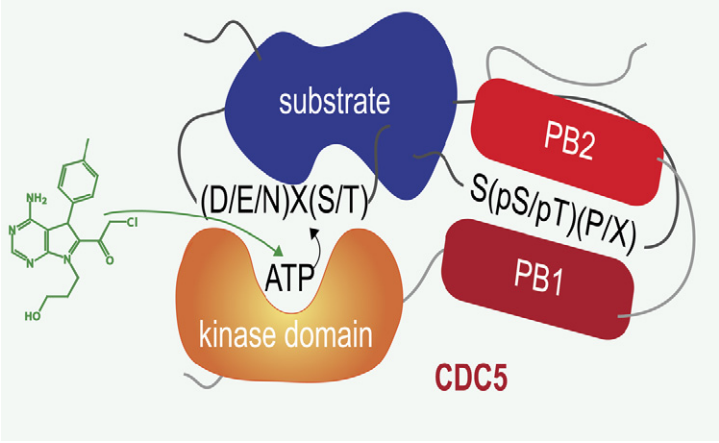
Visual Snapshots of Kinase Activity at the Onset of Mitosis

PAGE 1254

A key characteristic that distinguishes intracellular biochemistry from test tube enzymology is that the cell, and not the investigator, controls the temporal and spatial elements of enzyme-catalyzed reactions. Bresnick, Lawrence, and their colleagues employed a light-activatable sensor to interrogate intracellular protein kinase activity at the onset of mitosis. This investigator-controlled bioreagent furnished visual snapshots of kinase action at distinct mitotic stages. In combination with protein kinase C (PKC) isoform selective inhibitors, these investigators found that PKC ß activity is essential for nuclear envelope breakdown, but it is abruptly switched off upon entry into metaphase.

In This Issue

Chemical Genetic and Bioinformatic Exploration of Polo-like Kinase Pathway



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Polo-like kinases are critical cell cycle regulators. To uncover new aspects of their function, Snead et al. employed chemical genetics to develop the first specific inhibitor of Cdc5, the budding yeast Polo-like kinase. Cdc5 required a new approach, extending our chemical genetic method to kinases with atypical active sites. Pharmacological Cdc5 inhibition resulted in a pluripotent phenotype, confirming known Cdc5 functions and newly ascribing a role in mitotic spindle positioning, a process critical for proper genetic inheritance. Screening bioinformatics-informed candidates in vivo using a cell-permeable inhibitor to regulate endogenous kinase activity enabled identification of the novel, low-abundance Cdc5 substrate Spc72 (Figure adapted from Snead et al.).

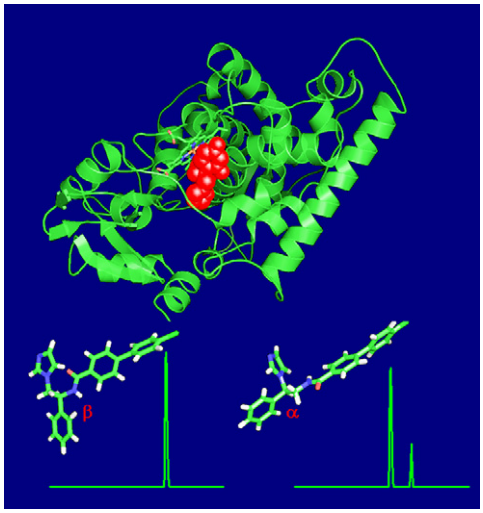
Combating *Candida* by Disrupting Cdc42/Effectors Binding

PAGE 1273

The morphologic transition *of Candida albicans* from yeast to hyphae is pathogenesis relevant. This transition is regulated by multiple cellular signaling pathways, one of which involves *C. albicans* Cdc42 (CaCdc42), a small GTPase, interacting specifically with the extended CRIB (eCRIB) domains of effectors. Here, Su et al. report that in vivo inhibition of CaCdc42 by peptide-mediated transduction of the eCRIB peptides can inactivate and even reverse this morphologic transition. The work provides a promising strategy for disease intervention through disrupting aberrant protein-protein interactions in diseases and brings the concept of signal transduction therapy into the front line of drug target discovery.

Sterol 14α-Demethylase Targeted Antitrypanosomal Therapy

PAGE 1283



Human infections with pathogenic protozoa are often deadly and yet there are practically no drugs to assure a cure. In this work, Lepesheva et al. have shown that specific inhibition of protozoan CYP51 can provide treatment for African and American trypanosomiases. Correlation between the potency of the compounds to inhibit CYP51 from *Trypanosoma brucei* and antiparasitic effect in human stages of the *TB* life cycle suggests that, similar to plants, *TB* species require functional sterols for their growth and development. In *Trypanosoma cruzi*, the effect of the inhibitors is even more pronounced, suggesting a potential lead structure for antitrypanosomal therapy (Figure by Lepesheva et al.).

Dimeric Positive Modulators of AMPA Receptor

PAGE 1294

Dimeric positive allosteric modulators of ionotropic glutamate receptors have been designed, synthesized, and characterized pharmacologically. These compounds, designed by Kaae et al., are dimers of arylpropylsulfonamides and target the cyclothiazide-binding site at AMPA receptors. The dimers have dramatically increased potencies, more than three orders of magnitude higher than the corresponding monomers. One dimer was cocrystallized with the GluR2-S1S2J construct, and an X-ray crystallographic analysis showed the dimer to bridge two identical binding pockets on two neighboring GluR2 subunits. Thus, this represents an amazing structural evidence of a homomeric dimer bridging two identical receptor binding sites.