In This Issue

Transcriptional Switch: To Bio or Not To Bio

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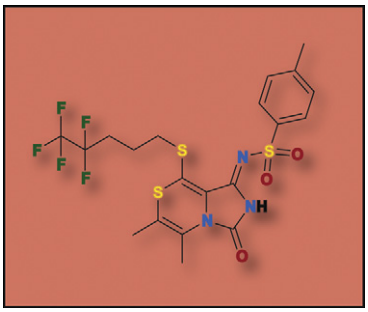
BirA is a bifunctional *E. coli* protein that acts as a repressor of biotin (bio) operon expression and as an enzyme that covalently attaches biotin to its cognate acceptor proteins. The mechanism of operon repression requires BirA dimerization triggered by BirA-catalyzed synthesis of biotinoyl-adenylate (bio-AMP). The postulated model suggests that an unmodified acceptor protein binds the monomeric BirA:bio-AMP complex and thereby blocks assembly (dimerization) of the form of BirA that binds DNA. Here, Solbiati and Cronan test this proposal and, based on their findings, argue that the regulatory switch does not require the extensive protein-protein interactions proposed to play a critical role in the current model.

A Client-Selective Hsp90 Inhibitor



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Hsp90 has pivotal roles in multi-organ physiology and pathology. So far, almost all known Hsp90 inhibitors are known to bind to the Hsp90′s N-terminal ATP-binding site and simultaneously induce degradation/activation of its multiple client proteins. Here, Kimura et al. describe the characterization of ITZ-1, a small molecule inhibitor of Hsp90 with client selective property. Within the Hsp90 client proteins, ITZ-1 strongly induced heat shock factor-1 (HSF1) activation and caused mild Raf-1 degradation, but scarcely induced degradation of a broad range of Hsp90 client proteins by binding to the Hsp90 C terminus. ITZ-1 may be useful as a cytoprotective agent.

Antifungal Phosphonate Oligopeptides Biosynthesis

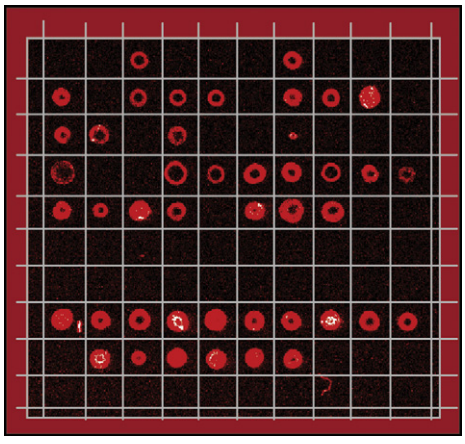
PAGE 28

The gene cluster from *Bacillus subtilis* ATCC6633 responsible for biosynthesis of the phosphonate antibiotic rhizocticin was identified and characterized by Borisova et al. using a combination of biochemistry, genetics, and molecular biology. Expression of these genes in a heterologous host led to production of the desired antibiotic. In vitro biochemical experiments showed that an early step in the biosynthetic pathway involves an unusual aldol reaction between phosphonoacetaldehyde and oxaloacetate catalyzed by an aldolase homolog, RhiG. This transformation provides a new biosynthetic route to structurally diverse phosphonate natural products.

The Microarray Bead Game

PAGE 38

Several approaches have been developed for screening combinatorial libraries or collections of synthetic molecules for agonists or antagonists of protein function, each with its own advantages and limitations. In this report, Astle et al. describe an experimental platform that seamlessly couples massively parallel bead-based screening of one bead–one compound combinatorial libraries with microarray-based quantitative comparisons of the binding affinities of the many hits isolated from the bead library. Combined with other technical improvements, this technique allows the rapid identification of the best protein ligands in combinatorial libraries containing millions of compounds without the need for labor-intensive resynthesis of the hits.



Small Molecules to the Rescue: Oncogenic p53 Mutant

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Small molecules that bind to and rescue the function of mutant p53 have broad implications as anticancer therapeutics. The p53 cancer mutation Y220C presents a unique opportunity to target mutant p53 due to the mutation-induced formation of a surface cavity that can accommodate stabilizing small molecules. Results obtained by Basse et al. paint a clear picture of how a drug-like molecule could dock within the mutational cavity of the Y220C mutant. In this way, the findings provide the framework for the rational design of lead ligands that rescue the transcriptional activity of the oncogenic p53-Y220C by selectively targeting the mutation site.

Late Biosynthetic Steps of FR-900098

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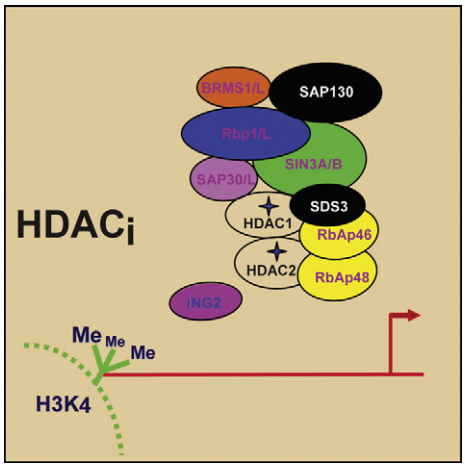
FR-900098 is a potent chemotherapeutic agent for the treatment of malaria. Here, Johannes et al. produced this compound in a recombinant *E. coli* strain and elucidated the biosynthetic mechanisms. The authors uncovered an unprecedented functional role of nucleotide conjugation in natural product biosynthesis. In addition, they discovered that the biosynthetic route for phosphonic acid antibiotic, FR-33289, is embedded in the FR-900098 biosynthetic route. These studies now open the possibilities for metabolic engineering in *E. coli* to increase production of the antimalarial antibiotic and combinatorial biosynthesis to generate novel derivatives of FR-900098 with more potent antimalarial activity.

Inhibit"ING" Deacetylases



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Deacetylase inhibitors are promising therapeutics for several diseases, including cancers and neurodegenerative diseases. These drugs are known to inhibit deacetylase activity by targeting the catalytic site. Here, Smith et al. find that these small molecule inhibitors can also disrupt critical protein-protein interactions within multisubunit deacetylase complexes and, through this, alter chromatin targeting of the deacetylases. This suggests that deacetylase inhibitors use multiple avenues to disrupt deacetylase activity.

Heavy Metals in NRF2 Signaling Pathway

PAGE 75

Transcription factor NF-E2 p45-related factor 2 (Nrf2) mediates adaptation to oxidants and electrophiles through upregulating genes that contain antioxidant response elements (ARE) in their promoters. Using the stably transfected human AREc32 reporter cell line, Wang et al. found that copper and other transition metals enhanced induction of ARE-driven luciferase by 2-tert-butyl-1,4-hydroquinone (tBHQ) due to increased oxidation to 2-tert-butyl-1,4-benzoquinone (tBQ). Compounds which share para- or ortho-hydroquinone structure, such as catechol estrogens, dopamine, and L-DOPA, also induce ARE-driven luciferase in a Cu^{2+}-dependent manner. Thus, the oxidation of para- and ortho-hydroquinones to quinones represents the rate-limiting step in the activation of Nrf2 and may account for a significant portion of their biological effects.

TB: Seeking Help!

PAGE 86

Methionine aminopeptidase (MetAP) is a metalloprotease that removes the N-terminal methionine during protein synthesis. To assess the importance of the two MetAPs in *M. tuberculosis*, Olaleye et al. overexpressed and purified each of the MetAPs to near homogeneity and characterized them in vitro. The authors screened a library of 175,000 compounds against MtMetAP1c and identified inhibitors of both MtMetAPs. It was found that the MtMetAP inhibitors were active against *M. tuberculosis*. Knockdown of MtMetAP1a, but not MtMetAP1c, resulted in decreased viability of *M. tuberculosis*. These results suggest that MtMetAP1a is a promising target for developing antituberculosis agents.

