In This Issue

Antagonistic Retinoids: "Rebels" with a Cause

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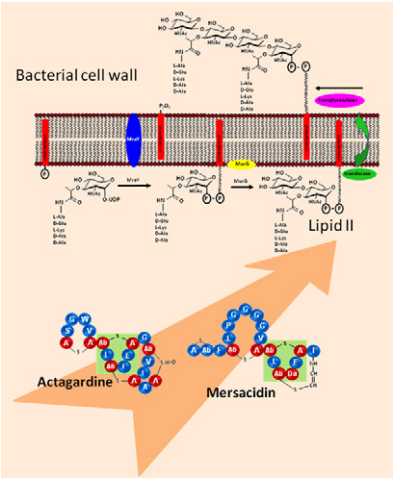
The nuclear hormone receptors are attractive drug targets because they regulate major (patho)physiological processes and their ligands are convenient for chemical synthesis. Importantly, subtle changes in the structure of a ligand can direct the activity towards a particular receptor subtype and various types of functional specifications, such as agonism/antagonism, (hetero)dimer selectivity, or cell/pathway selectivity. Germain et al. reveal here structural insight into the differential interaction with coregulators, which accounts for very different functionalities of several antagonistic retinoids. As coregulators act as platforms to assemble complexes with epigenetic activities, such ligands can be used to differentially regulate RAR-mediated gene programs.

Lantibiotic Mersacidin under Scalpel



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Lantibiotics are a class of antibacterial compounds with activity against Gram-positive pathogens. Due to the biosynthetic origin of lantibiotics, the manipulation of the peptide backbone in this class is particularly amenable to engineering. Appleyard et al. show that it is possible to develop efficient systems for manipulation of this type of molecule. A library of Mersacidin variants was generated and compounds with improved antibacterial potency were obtained, opening up the possibility of using this type of methodology for further improvements in the properties of this class of compounds and providing useful information regarding the flexibility of this biosynthetic pathway. (Figure credits: Appleyard et al.)

Magic Bullet Hits Multiple Targets

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Mycobacterium tuberculosis remains a major global health problem increasingly characterized by antibiotic resistance. In this work, Barkan et al. identify and validate a new target for antimicrobial development in *M. tuberculosis*. The major lipids of the cell wall, mycolic acids, are modified with cyclopropane rings by a family of methyltransferases. Barkan et al. show here that inhibition of this entire methyltransferase family by a single compound produces cell death and synergy with existing antimycobacterials. In addition to identifying a new antibiotic strategy for *M. tuberculosis*, these findings establish that a family of homologous enzymes can be targeted by a single compound, expanding the common conception of the inhibitor-target relationship.

New Functions for Old Enzymes

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Mycolic acids are major and specific lipids of the *Mycobacterium tuberculosis* cell envelope. Understanding the biosynthesis of these critical components is an important goal toward the design of new antituberculosis therapetutics. FadD32, a fatty acyl-AMP ligase (FAAL), activates C_{50}-C_{60} fatty acids to be condensed with C_{22}-C_{26} acids to yield mycolic acids. The present work by Léger et al. reveals the acyl-ACP ligase function of FadD32, in addition to its recognized FAAL activity. FadD32 may thus be the prototype of a group of *M. tuberculosis* polyketide-synthase-associated adenylation enzymes possessing such activity. A FadD32 substrate analog inhibited the enzyme activity, mycolic acid synthesis, and mycobacterial growth.

ΔF508-CFTR Getting Sorted Out

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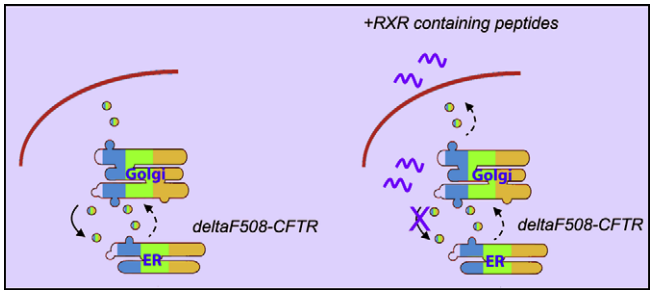
The major cystic-fibrosis-causing mutation deltaF508-CFTR leads to misfolding and mistrafficking of the protein with retention in the endoplasmic reticulum (ER). In the current study, Kim Chiaw et al. introduce a peptide-based approach that targets an endogenous di-arginine ER retention motif that becomes aberrantly exposed in ΔF508-CFTR. Our results suggest that a particular di-arginine motif proximal to the signature motif in NBD1 may contribute to retention of ΔF508-CFTR. More importantly, the retention conferred by this particular motif in situ can be overcome using a peptide-based approach. This structural feature may thus comprise a molecular target for effective cystic fibrosis therapies.

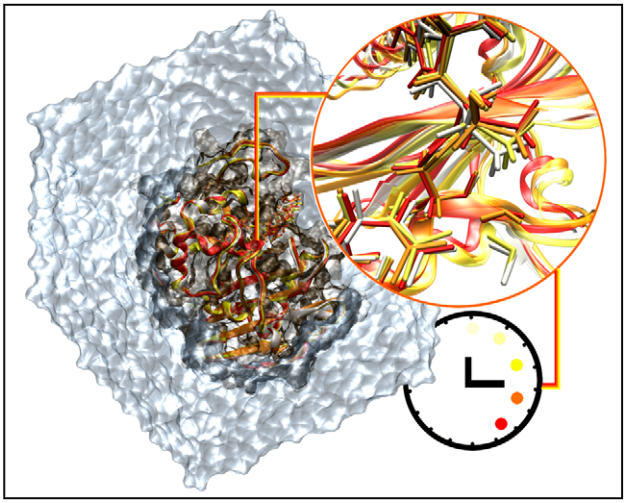


Cytokine Activities of Human Tyrosyl-tRNA Synthetase

PAGE 531

Heritable mutations in tRNA synthetases are causally linked to disease. While aminoacyl-tRNA synthetases are universal proteins known for catalysis of aminoacylation, the later-developed expanded functions of many mammalian synthetases in cytokine signaling and regulatory pathways are considered to be the main connection with diseases. The work by Kapoor et al. shows that the ancient conserved architecture of tRNA synthetases can protect the essential aminoacylation function when new cell-signaling epitopes are introduced near the catalytic site. Consequently, because of the protective isolation of the active site, disease-causing mutations that affect only cell signaling can arise and be transmitted.

Mechanistic Diversity of Class D Carbapenemases



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Class D carbapenemases hydrolyze last-generation β-lactam antibiotics, the carbapenems. Docquier et al. compared the crystal structure of OXA-48 with available β-lactamase structures. Surprisingly, the structure of OXA-48 was similar to that of OXA-10, an enzyme devoid of carbapenemase activity, indicating that the hydrolysis of these compounds could depend on subtle changes in the active-site region. Moreover, the active-site groove of OXA-48 was different from that of OXA-24 (another carbapenemase). Molecular dynamics pointed to the functional relevance of residues located in or close to the β5-β6 loop and allowed the authors to propose a mechanism for carbapenem hydrolysis by OXA-48. (Figure-credit: Docquier et al.)

Bacterial Cell Wall Crumbling Down

PAGE 548

This report by D'Elia et al. describes surprising genetic connectivity among three vital processes in Gram-positive bacteria, namely isoprenoid, peptidoglycan, and wall teichoic acid biogenesis. This connectivity was revealed with a library of small-molecule probes of bacterial physiology and follows in the wake of recent studies revealing a paradox in teichoic acid synthesis. Enzymes acting early in teichoic acid synthesis are now understood to be dispensable for cell viability, suggesting that the polymer itself is expendable, while the loss of late-acting pathway enzymes is lethal. These latest findings open the door for strategies to exploit these complex genetic interactions for new antibiotic discovery.

Tau Pre-mRNA SRE in the Grips of Mitoxantrone

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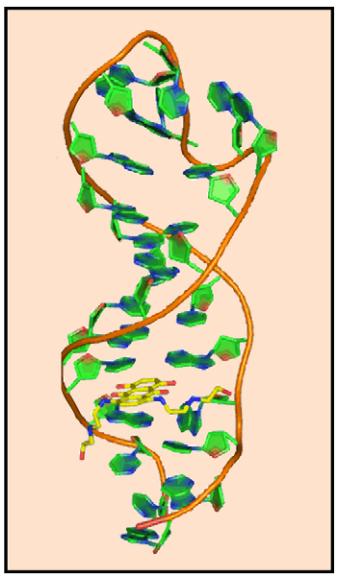
Destabilization of an RNA regulatory element by mutations observed in patients alters pre-mRNA splicing of tau protein and causes familiar forms of neurodegenerative diseases. Since stabilizing the RNA by single-nucleotide changes reverses the splicing pattern, a small molecule that stabilizes this RNA could potentially be a drug candidate. Here, Zheng et al. report the structure of the RNA-splicing regulatory element bound to such a stabilizing molecule, the anticancer drug mitoxantrone. This structure provides a rationale to optimize the activity of this class of compounds and sheds light on the general mechanism of the interaction of mitoxantrone with nucleic acids.



Alternative Epimerization Catalyzed by a Member of VOC Superfamily

PAGE 567

Exemplified by antidiabetic acarbose and antifungal validamycin, C_7N-aminocyclitols all share a valienamine moiety, which is essential for the biological activities and whose biosynthesis requires an epimerization reaction. In this issue, Xu et al. characterized an epimerase ValD genetically and biochemically from a validamycin biosynthetic pathway. ValD converted 2-*epi*-5-*epi*-valiolone to 5-*epi*-valiolone, representing an alternative epimerization for C_7N-aminocyclitol biosynthesis. It is also confirmed to be a giant dimeric metalloenzyme of the vicinal oxygen chelate (VOC) superfamily, with strong metal-binding capacity. The data presented here intensified the diversity of C_7N-aminocyclitol biosynthesis and displayed pathway engineering potential for generating improved C_7N-aminocyclitol derivatives.

