In This Issue

Ethylene Receptors Sense More than Strain

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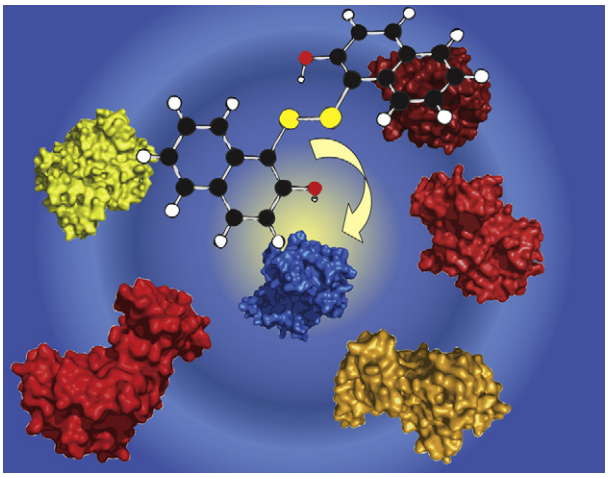
Ethylene, the simplest alkene, is a plant hormone that influences fruit ripening, developmental processes, stress response, and senescence. Initial hormone perception requires presence of ethylene receptors, such as ETR1, where ethylene binds to a copper(I) cofactor located in the receptor's sensor domain. Although ethylene is a molecule of high symmetry, Pirrung et al. now show that its receptor exhibits selectivity for asymmetric ligands. The finding is surprising but consistent with an asymmetric, protein-based receptor. The authors also shed new light on the mechanism of action of 1-methylcyclopropene, an ETR1 antagonist that involves unexpected chemical modification of the receptor. Furthermore, the study defines the molecular basis of the high binding affinities of alkene ligands for the copper-containing ethylene receptors in higher plants.

Selected from the Pak



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Lack of target specificity is a common drawback of kinase inhibitors that target the conserved ATP-binding pocket. Nonconserved regulatory elements found in some kinases may offer alternative targets for more selective kinase inhibition. Deacon et al. report the identification of IPA-3, a highly selective small-molecule inhibitor that targets the Pak kinase autoregulatory mechanism. Biochemical studies suggest that IPA-3 may trap a transient intermediate step in Pak activation, and cell-based experiments demonstrate selective inhibition of Pak in live cells. These results suggest that screening assays that recapitulate biologically important regulatory mechanisms may reveal novel opportunities for kinase inhibition.

Hammerhead Ribozyme: Just Add Water

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Hammerhead ribozymes catalyze the RNA phosphodiester isomerization reaction, leading to an RNA self-cleavage. The molecular mechanism of the catalysis has been extensively debated. The structure of the full-length ribozyme confirmed the role of two invariant nucleotides, G12 and G8, as the general base and the general acid, but did not address the role of solvent molecules and divalent ions. Martick et al. now present new structural data on the full-length hammerhead ribozyme in the presence of manganese ions, Mn^{2+}, which led to improved resolution and solvent ordering, thus revealing the presence of potentially catalytically important water molecules in the active site. The authors suggest that the ordered solvent molecules might participate in a proton transfer relay or assist in activating the general acid and base.

Breaking the Aminergic GPCRs Drug Design Code

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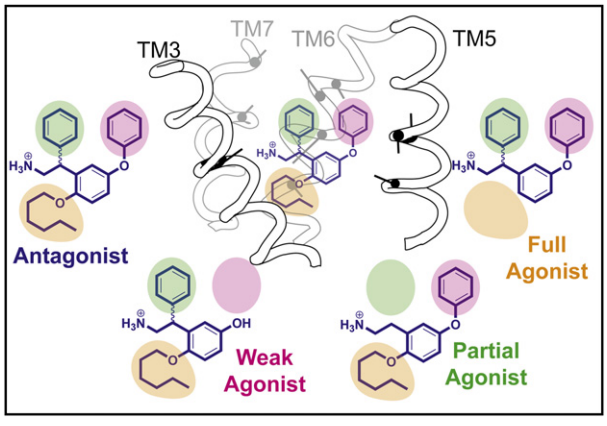
Despite the successful development of numerous drugs that can regulate the activity of aminergic G-protein coupled receptors (GPCRs), the underlying principles for developing activators and/or inhibitors are not well understood. Tan et al. applied the rotamer toggle switch model of GPCR activation toward a design of agonists and antagonists of TAAR1, an orphan GPCR. This approach proved fruitful and resulted in rational design and synthesis of rTAAR1 superagonists and lead antagonists. The strategy might be generally useful for deciphering the code to aminergic GPCR drug design by providing a conceptual framework for understanding the relationship between the molecular structure of a drug and its pharmacological properties. (Figure adopted from file provided by Tan et al.)



Mimicking Host Defense Peptides

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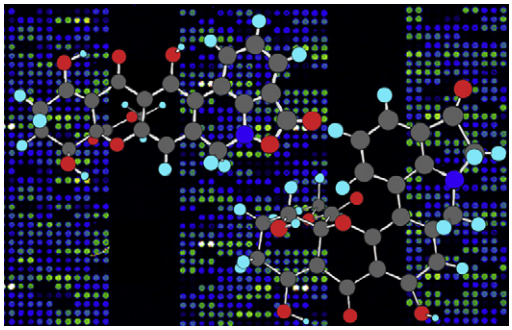
In the era of increasing antibacterial resistance and "super bugs," low molecular weight peptide-based compounds, termed host defense peptides (HDPs) are increasingly recognized as a potential source for new antimicrobial agents. Radzishevsky et al. now describe biophysical properties of a library of 103 HDP mimics, oligo-acyl-lysines (OAKs). OAKs present an innovative intercalation of polar and hydrophobic residues, with a sequence that can be varied to produce quasi-unlimited alternatives. Therefore, OAKs design provides an efficient tool for dissecting the parameters believed to be crucial for HDPs activity. The work provides a robust basis for future investigations and contains a library with a wealth of bioactive HDP-mimetics.

Halting *Candida*'s Poly(A) Polymerase



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Using a *C. albicans*-based chemogenomics approach, Jiang et al. have screened collections of crude natural product extracts and identified a novel antifungal compound, parnafungin, which disrupts 3′ mRNA processing by specifically inhibiting the poly(A) polymerase activity. Parnafungin displays potent and broad-spectrum activity against diverse clinically relevant fungal pathogens and in vivo efficacy in a murine model of candidiasis. This work demonstrates how functional genomics and chemical-genetic strategies can be applied directly in a fungal pathogen and used to efficiently exploit the potential of natural products for antifungal lead discovery. (Figure adopted from file provided by Jiang et al.)

Mitochondria Ahoy!

PAGE 375

Mitochondria are important targets for cancer chemotherapy and other disease treatments. Gaining access to this organelle is not trivial. The inner mitochondrial space is separated from the cytoplasm by a system of two membranes: outer and inner mitochondrial membrane (OMM and IMM, respectively). OMM is similar to the plasma membrane, and it can be expected that compounds that can penetrate plasma membrane can also penetrate OMM. However, IMM is notoriously impenetrable and posses a serious challenge for the design and development of mitochondria-specific therapeutics. Here, Horton et al. report a rational development of mitochondrial transporters: synthetic cell-permeable peptides that are able to enter mitochondria. These mitochondria-penetrating peptides (MPPs) exhibit efficient cellular uptake and specific localization to the mitochondria of living cells.

Vitamin D Receptor Agonist Go Super

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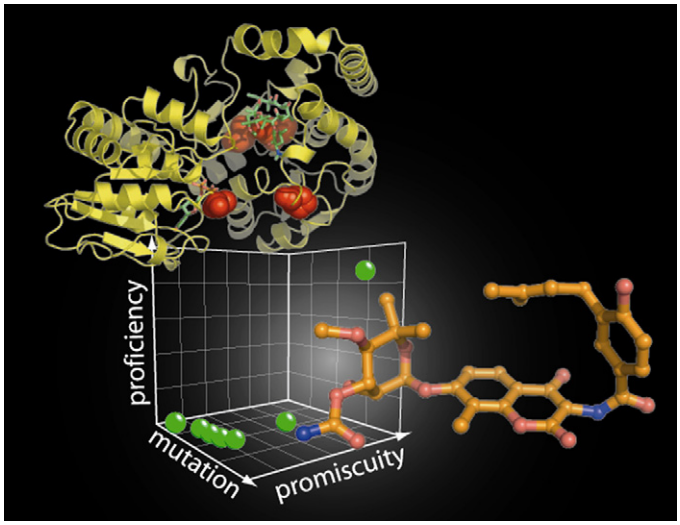
Vitamin D nuclear receptor (VDR) belongs to a superfamily of steroid/thyroid hormone/retinoid nuclear receptors and acts as a ligand-dependent transcription factor to control multiple biological responses. Its malfunction leads to a number of disease states. Although available, 1α,25-dihydroxyvitamin D_3 analogs don't have significant clinical relevance. Therefore, Hourai et al. set out to generate new VDR ligands using the knowledge of the crystal structure of VDR bound to its natural ligand. They present synthesis, in vitro, and in vivo characterization of designed VDR superagonist ligands and demonstarate that one of the new compounds exhibits improved properties and activity in mice. The two crystal structures of VDR with newly produced ligands provide an explanation for the observed transactivation potency.

"Hot Spot" Gets it Done



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Williams et al. applied a two-phase "hot spot" saturation mutagenesis strategy to rapidly evolve the specificity of the macrolide glycosyltransferase OleD toward a nonnatural coumarin antibiotic acceptor, novobiocic acid. Incredibly, even in the absence of a high-throughput screen for glycosylation of novobiocic acid, this approach led to the rapid identification of a variant glycosyltransferase with a several-hundred fold improvement in catalytic activity, which was mirrored by an improvement in promiscuity toward glycosyl donor substrates. The work highlights the potential for developing "designer: glycosyltransferases for a wide range of drugs and drug leads. (Figure credits: Williams et al.)

FabH Posts Clear Enter and Exit Signs

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Mycobacterium tuberculosis is the causative agent of tuberculosis, one of the deadliest contemporary infectious diseases. Long fatty acids, mycolic acids, are abundant cell wall components of *M. tuberculosis* and their biosynthesis represents an attractive drug target. A key step in this process is catalyzed by an enzyme, FabH, and involves sequestering a long carbon chain deep within the binding pocket. The available FabH structure suggests that the binding necessitates chain threading through a long and twisted passageway. Now Sachdeva et al. demonstrate that the FabH exists in an open form which permits binding and release of long carbon chain substrates, inhibitors, and product without laborious twisting and threading. The authors predicted similar large-scale movements for other enzymes involved in mycolic acid biosynthesis.

