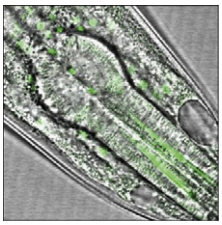
In This Issue



Probing Hydrogen Peroxide in Living Cells

PAGE 943

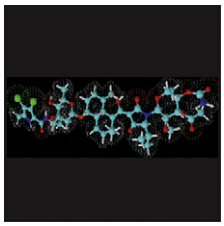
Hydrogen peroxide (H_2O_2) can act as either a beneficial signaling agent or a toxic mediator of oxidative stress depending on its location within a cell. Methods to measure H_2O_2 levels within defined regions of a cell, however, are lacking. Here, Dickinson et al. develop NucPE1, a new fluorescent dye that can detect H_2O_2 fluxes within the nuclei of live cells, an organelle particularly susceptible to oxidative stress and damage. They then apply NucPE1 to detect in vivo differences in nuclear H_2O_2 levels between normal and lifespan-enhanced *C. elegans*, suggesting a link between nuclear H_2O_2 homeostasis and aging.

Fluorine Mimicking in RNA

PAGE 949

The ability of fluorine in a C-F bond to act as a hydrogen bond acceptor is controversial. Here, Forconi et al. tested such ability in two related RNA systems, the *Tetrahymena* group I ribozyme and the ΔC209 P4-P6 RNA domain. In three cases, the introduced 2′-F mimics the native 2′-OH group, suggesting that the fluorine atom can accept a hydrogen bond. The authors show that in each of these cases, the native hydroxyl group interacts with a purine exocyclic amine.

Antibiotic Discovery: Kibdelomycin to the Rescue



PAGE 955

The emergence of resistant strains of bacteria has led to an urgent need for new antibacterial agents. To address this need, Phillips et al. applied a chemical genetic assay in the bacterial pathogen *Staphylococcus aureus* to natural products screening. Their screening resulted in the discovery of Kibdelomycin, a new class of antibiotics with broad spectrum Gram-positive antibacterial activity produced by a new member of the genus *Kibdelosporangium*. Kibdelomycin is a potent inhibitor of DNA synthesis and may be the first truly novel bacterial type-II topoisomerase inhibitor with potent antibacterial activity discovered from natural product sources in more than six decades.

Overcoming Kinase Inhibitor Resistance

PAGE 966

The emergence of resistance to protein kinase inhibitors has wide-reaching clinical and technological implications. In this paper, Balzano et al. report that mutations at two specific positions in the protein kinase scaffold have general adverse effects on inhibitor sensitivity in six distantly related kinases, typically without major deleterious consequences on kinase activity. The ability to design inhibitor-resistant mutants of protein kinases might be of significance for drug target validation and clinical practice.

Aspirin-Triggered DHA Pathway

PAGE 976

Endogenous mechanisms underlying the resolution of acute inflammation are of interest because excessive inflammation is the cause of many pathologies. Docosahexaenoic acid (DHA), an omega-3 fatty acid enriched in neural tissues, is converted into potent mediators, including resolvins and protectins, that are involved in resolving inflammatory exudates. Here, Serhan et al. describe the identification of the DHA-derived aspirin-triggered neuroprotectin D1/protectin D1, together with its stereochemistry, biosynthesis, and anti-inflammatory actions. Their results establish a new aspirin-triggered metabolome that can contribute to and enhance aspirin's anti-inflammatory and proresolving actions.

Antitumor Agents: Blocking Transcription and Breaking DNA

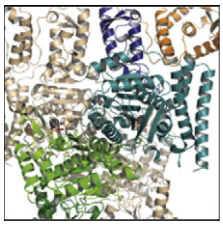
PAGE 988

Trabectedin and Zalypsis show antitumor properties against a variety of cancers. They covalently bind to the guanine located in GC-rich DNA triplets and interact with adjacent nucleotides only through Van der Waals and hydrogen bonds. Feuerhahn et al. present results that strongly suggest that Trabectedin and Zalypsis behave as interstrand cross-link lesions, although these drugs only covalently interact with one DNA strand. The drugs inhibit gene transcription by preventing the correct positioning of the transcription machinery and/or by blocking RNA Pol II elongation. Furthermore, they induce a DNA structure that protects both strands from DNase digestion and stimulates XPF/ERCC1-dependent incision.

L or D: Effect of Chirality in Peptide Cell Penetration

PAGE 1000

The use of protease-resistant D-peptides is a prominent strategy to overcome proteolytic sensitivity in the use of cell-penetrating peptides (CPPs) as delivery vectors. According to the current paradigm, chirality does not play a role in the uptake of CPPs. However, this report by Verdurmen et al. shows that cationic L-CPPs are taken up more efficiently than their D-counterparts in a cell type-dependent manner. More specifically, their results identify two key events in the uptake of CPPs: binding to heparan sulfate chains and the initiation of internalization, with only the second event depending on the chirality of the CPP.



Decarboxylase Hub Hijacked by *Mycobacterium*

PAGE 1011

The success of *Mycobacterium tuberculosis* as a human pathogen relies in part on the efficient strategies the bacillus has evolved to offset the physiological challenges caused the host organism during infection. In this work, Wagner et al. uncover the multifunctional properties and allosteric regulation mechanisms of the α-ketoglutarate dehydrogenase complex, a central metabolic hub of the tricarboxylic acid cycle, which the pathogen may use to adjust its metabolism to allow for optimal growth in different environments within the host.

Defining Polyketide Chain Length

PAGE 1021

Understanding and engineering polyketide chain length offers the opportunity to rationally manipulate the structures of many interesting antibiotics. Szu et al. have employed a variety of approaches to study the fredericamycin polyketide synthase (PKS). They show that the chain-length specificity of this PKS is considerably shorter than the backbone length of the final product. They also identified a mutant that permits chain initiation and elongation, but not termination. Further characterization of this mutant should yield fundamentally new insights into the mechanisms by which carbon chains of defined length are synthesized and released.

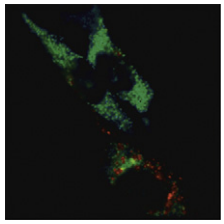
Targeting Virulence Regulation in *S. aureus*

PAGE 1032

Increasing antibiotic resistance in human pathogens necessitates the development of new approaches against infections. Targeting virulence regulation at the transcriptional level represents a promising strategy yet to be explored. A global transcriptional regulator MgrA in *Staphylococcus aureus* was identified previously as a key virulence determinant. Sun et al. used a high-throughput screen to identify 5,5-methylenedisalicylic acid (MDSA), which blocks the DNA binding of MgrA. A mouse model of infection indicated that MDSA could attenuate *S. aureus* virulence, demonstrating the utilization of small molecules to block protein-DNA interaction, thus tuning important biological regulation at the transcriptional level.

Quantifying Autophagy

PAGE 1042



Upon delivery to lysosomes, cytosolic components or organelles encapsulated inside autophagosomes are exposed to acidic pH and lysosomal proteases. Many fluorescent proteins derived from corals are tolerant of these environments. Using the coral fluorescent protein Keima, which emits differently colored signals between acidic and neutral pH, Katayama et al. have developed a probe that provides cumulative readouts of autophagic activities. They performed dual-excitation ratiometric imaging by placing Keima in the cytoplasm and the mitochondria to successfully monitor starvation-induced autophagy and membrane-depolarization-induced mitophagy, respectively. Of note is their success in the quantitative characterization of Atg5-independent autophagy.

Inhibiting Bone Degradation with Cannabinoids

PAGE 1053

Osteoporosis is a major metabolic disease affecting more than 30% of the population. Bone degeneration starts when the bone-resorbing osteoclasts become overstimulated. Recently, it was shown that the endocannabinoid system is involved in bone remodeling, but the mechanisms remain unclear. In this study, Schühly et al. show that endogenous cannabinoids are able to stimulate osteoclast formation by increasing the movement and fusion of blood-derived precursor cells. Using a novel cannabinoid receptor CB2 blocker discovered in the medicinal plant Magnolia grandiflora, they were able to generate agonists that inhibit the formation of bone-degrading cells through a CB2 receptor-dependent mechanism.

