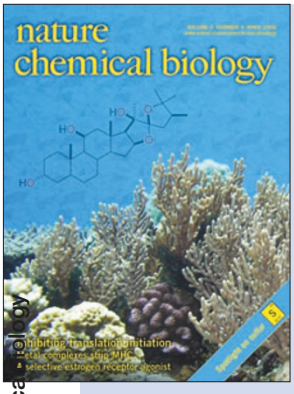
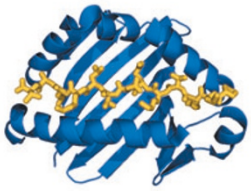
IN THIS ISSUE



COVER STORY

For eukaryotic ribosomes to bind and translate mRNAs, the messages must first be primed by initiation factors (eIFs) that include a DEAD-box RNA helicase, eIF4A. Pelletier and colleagues purified hippuristanol, a polyoxygenated steroid, from extracts of the coral *Isis hippuris* and found that it can inhibit translation by blocking the ATPase activity of eIF4A, which is required for eIF4A-mRNA binding. They were also able to use hippuristanol to help define the requirements for the replication of various viruses. Generally, mRNAs that have internal ribosomal entry sites (IRESs) can bypass the need for eIFs or require only a subset of them. However, hippuristanol could inhibit initiation on poliovirus IRESs, so it was then used to delay the replication of this virus. Because it can act reversibly, hippuristanol offers unique control over eIF4A-dependent initiation.
[Articles, p. 213; News & Views, p. 176] *MB*

Metals break apart MHC molecules

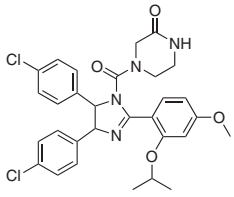


In the immune system, class II major histocompatibility complex (MHC) proteins display peptides on antigen-presenting cells (APCs). These peptides can then be recognized by T cells to trigger an immune response. DeDecker and colleagues conducted high-throughput screening and found that the Pt(II) complexes cisplatin and carboplatin, as well as Pd(II) and Au(III) complexes, inhibited peptide-MHC interactions—even those of high affinity. The inhibition occurred by an allosteric mechanism. The metal complexes could block APC activation of T cells *in vivo*, suggesting that noble metal complexes are promising leads for treatment of autoimmune diseases. Au(I) complexes are a traditional treatment for rheumatoid arthritis for which the mechanism of action had been unknown. The new observation that Au(III) can disrupt peptide-MHC interactions, along with the known *in vivo* oxidation of Au(I) to Au(III), may now provide a molecular basis for the therapeutic effects of gold therapy.
[Letters, p. 197; News & Views, p. 178] *JK*

Heparin biosynthesis step-by-step

Despite its widespread use as an anticoagulant, the physiological role of heparin is still not fully known. Heparin is biosynthesized solely inside connective-tissue mast cells, where it is stored in secretory granules and released during immune and allergic responses. Heparin consists of a proteoglycan core that undergoes subsequent enzymatic modifications. A key step in heparin biosynthesis is the conversion of D-glucuronic acid (GlcA) to L-iduronic acid (IdoA). It was suspected that the *Hsepi* gene product catalyzed this transformation, but the neonatal lethality of *Hsepi* -deficient mice had prevented the testing of this idea. Rodewald and coworkers generated *Hsepi*-deficient mast cells and showed that *Hsepi* is exclusively responsible for the conversion of GlcA to IdoA in heparin biosynthesis, and also that this conversion is necessary for subsequent sulfation.
[Brief Communications, p. 195] *JK*

Nutlin-3 and damage control



Mutations in the p53 tumor-suppressor protein are found in approximately half of human cancers. Thus, therapeutic agents that modulate p53 activity offer potential for cancer treatment. Nutlin-3 is a known small-molecule antagonist of MDM2, a protein that binds p53 and negatively regulates its activity. In mice, nutlin-3 has a potent antitumor effect, with virtually no toxicity to normal cells. Now, Bernards, Beijerberger and colleagues suggest how nutlin-3 may display this selectivity. Using an RNA interference barcode screen, the authors searched for proteins involved in the cellular response to nutlin-3. Although several known downstream components of p53 signaling were affected by nutlin-3 treatment, the screen showed that 53BP1, a protein involved in the ATM-CHK-53BP1 DNA damage checkpoint pathway, is an important mediator of nutlin-3 cellular toxicity. Induction of DNA damage signaling in cells improved the ability of nutlin-3 to block p53 activation. On the basis of these results, the authors suggested that MDM-2 inhibitors offer excellent therapeutic potential for cancers with wild-type p53 and activated DNA damage signaling.
[**Letters, p. 202**] *TLS*

A third way for estrogen signaling

Canonical estrogen signaling proceeds through two intracellular estrogen receptors (ERα and ERβ). However, the recent discovery of a third estrogen-responsive G protein–coupled receptor, GPR30, in the endoplasmic reticulum of cells raises questions about estrogen signaling. In this issue, Prossnitz, Oprea and coworkers identify a small-molecule agonist of GPR30. Through virtual screening of a library of 10,000 GPCR-privileged structures, the authors identified 100 candidate compounds, which were screened for selective GPR30 binding activity in cells. One compound, G-1, bound GPR30 1,000 times more selectively than ERα and ERβ and induced physiological responses consistent with GPR30 agonism. This nonsteroidal compound offers a useful probe of *in vivo* estrogen signaling and also demonstrates the utility of virtual screening to refine compound libraries for biomolecular screening.
[Letters, p. 207; News & Views, p. 175] *TLS*

Spotlight on sulfur

Sulfur is an essential element. Although some organisms use it as an energy source [**Research Highlights, p. 184**], sulfur is more commonly seen as a structural element in amino acids, vitamin cofactors, ribonucleotides and iron-sulfur clusters. In this issue, we examine sulfur's role in biology. Marc Fontecave discusses advances and challenges in our understanding of iron-sulfur clusters. [**Commentary, p. 171**] The pathways for incorporation of sulfur atoms into biomolecules have remained obscure. Eugene Mueller reviews how recent studies have illuminated our understanding of sulfur trafficking, using thiolated ribonucleotides as a case study. [**Review, p. 185**] Charles Lauhon provides additional insight into the complexity of sulfur transfer chemistry through a discussion of a recent paper on the biosynthesis of 2-thiouridine. [**News & Views, p. 182**] *TLS*

In This Issue written by Mirella Bucci, Joanne Kotz and Terry L. Sheppard.