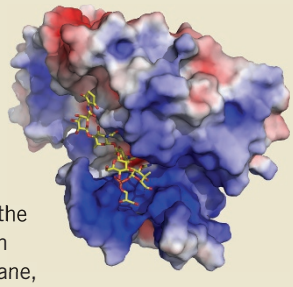
PBP complex solved



Penicillin-binding proteins (PBPs) may exist in a complex with glycosyltransferases (GTs); together they assemble the rigid peptidoglycan structure of the bacterial cell wall. Whereas PBPs, which are transpeptidases, have been well studied, attempts to solve the structure of the GT domain have been stymied by its location in the membrane, and its tendency to break down. By screening many detergents and constructs, Lovering *et al.* crystallized the PBP2 multi-functional enzyme from *Staphylococcus aureus* and have solved its structure at 2.8 Å resolution. Unique among enzymes in its class, this GT domain (GT_{51}) resembles lysozyme, which uses the same substrate (running the reverse reaction). The researchers also solve the structure of the GT in complex with the inhibitor moenomycin, and found many points of interaction, which accounts for the known low inhibitory concentration of that class of inhibitors. In addition to providing details on the enzymatic mechanism of GTs, the two structures point to potential sites for targeting new antibiotics. (*Science* **315**, 1402–1405, 2007) *LD*

MicroRNA editing

Although adenosine deaminases acting on RNAs (ADARs) have previously been proposed to increase microRNA (miRNA) diversity by converting adenosine to inosine in double-stranded primary transcripts, Kawahara *et al.* now show a physiological consequence of this phenomenon. They demonstrate the importance of such editing in controlling the activity of phosphoribosyl pyrophosphate synthetase 1 (PRPS1), a key regulator of purine metabolism and uric acid synthesis. Expression of miRNAs edited in their seed regions, but not their unedited counterparts, represses PRPS1 to prevent excessive accumulation of potentially harmful uric acid. In contrast, elevated PRPS1 levels in a mouse knockout deficient in one of the two ADAR genes causes hyperuricemia in the brain cortex but not the liver, suggesting tissue-specific regulation of the editing activity. These findings demonstrate the physiological potential of miRNA editing for alleviating or augmenting the repressive effects of miRNAs, as well as altering the target range of an miRNA. Moreover, they underscore the sensitivity of miRNAs to subtle chemical modification and give pause to those developing miRNA-based therapies. (*Science*, **315**, 1137–1140, 2007) *PH*

Polyreactive antibodies characterized

Natural antibodies, produced by V(D)J recombination in the apparent absence of antigen, may be a first line of defense against microbes and viruses. Many natural antibodies are polyreactive—that is, they bind a variety of structurally unrelated antigens with low affinity. To clarify the biological function of polyreactive antibodies, Zhou *et al.* assess their antibacterial activities. They screen monoclonal antibodies from mouse hybridomas for polyreactivity by assaying binding to single-stranded DNA, lipopolysaccharide and various proteins. One polyreactive antibody, 2E4, binds several Gram-positive and Gram-negative bacteria. It lyses the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* by fixing the third component of complement, but despite triggering the production of anaphylatoxin C5a, is unable to lyse Gram-positive bacteria. 2E4 enhances complement-dependent phagocytosis of *E. coli* and neutralizes one of the endotoxic activities of lipopolysaccharide in a complement-independent manner. Three additional antibodies that trigger complement-dependent lysis of *E. coli* are also identified. Although the *in vivo* contribution of polyreactive antibodies to innate immunity remains untested, these data suggest that passive administration of a cocktail of monoclonal polyreactive antibodies might be effective against certain infections. (*Cell Host Microbe* **1,** 51–61, 2007) *JWT*

Macromolecule separation with silicon

New ultrathin porous membranes made of nanocrystalline silicon promise to dramatically improve purification and dialysis of biological macromolecules. The membranes are ~15 nm thick—roughly the same size as proteins—and several hundred μm per side, with tunable pore sizes of 5–25 nm. These characteristics allow more precise separation between macromolecules of similar size and more than ten times faster transport of molecules below the size cut-off compared with conventional polymer membranes, which can be 10–100 times thicker and have broader pore-size distributions. Striemer *et al.* fabricate the ultrathin membranes using precision silicon deposition and etching techniques. They find that the average pore size can be varied by adjusting the temperature of the rapid thermal annealing step, which causes an amorphous silicon film to crystallize and form pores. Compared with existing ultrathin membranes, the new membranes are much stronger, supporting over one atmosphere of differential pressure. The authors demonstrate separation of two similarly sized proteins, immunoglobulin-γ (150 kDa) and bovine serum albumin (67 kDa). Moreover, they show that surface functionalization of the membranes enables separation by charge. Ultrathin nanocrystalline silicon membranes should prove useful in various contexts, including microfluidic systems, large-scale dialysis systems and micro- and macroscale pressurized filtration devices. (*Nature* **445**, 749–753, 2007) *AL*

Cracking the cancer code

'Cancer genome' projects seek to catalog the totality of somatic mutations associated with cancer. Using single-nucleotide-polymorphism arrays and genome sequencing, two groups have recently defined subsets of the cancer genome in several solid tumors and one leukemia. Starting with 210 samples from breast, lung, colorectal and other cancers, Greenman *et al.* examine 274 Mb of DNA encoding 518 protein kinase genes. They find 1,007 mutations, about two-thirds of which are novel. To distinguish mutations that contribute to the cancer and those that do not—so-called 'driver' and 'passenger' mutations—they compare the frequency of 'non-synonymous' mutations (which change the protein sequence and are subject to selection) in >600 cancer samples with that expected by chance, concluding that ~158 mutations distributed among ~66 samples are driver mutations. The second paper, by Mullighan *et al.*, concerns pediatric acute lymphoblastic leukemia (ALL). ALL is known to comprise distinct genetic subtypes defined by B-cell or T-cell origin and specific translocations, rearrangements of the *MLL* gene and aneuploid karyotypes. As these abnormalities alone are not sufficient to cause disease, the authors sought to identify cooperating oncogenic lesions for each genetic subtype. Analysis of leukemic cells from over 242 patients shows that 40% of the B-progenitor ALL samples have mutations in genes involved in B-cell differentiation. (*Nature* **446**,153–158, 2007; *Nature* doi:10.1038/nature05690 Mar 7, 2007) *KA*

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