17652 Helical structure of Streptococcus virulence factor
17717 Hepatitis C virus evades immunity
17786 Mouse model of pneumonic plague progression
17846 Understanding cerebellar long-term potentiation
17852 Probe identifies endocannabinoid transporter

BIOPHYSICS

Helical structure of Streptococcus virulence factor

According to Nicola Smith et al., the bacteriophage-encoded hyaluronidase, HylP1, of Streptococcus pyogenes contains a catalytically active triple-stranded β-helix that functions as a hyaluronan (HA) lyase. S. pyogenes causes a wide range of invasive infections such as necrotizing fasciitis and toxic septicemia. Previous research has shown that several of the bacteria’s virulence factors, including HylP1, are encoded by bacteriophage, but the events that induce S. pyogenes toxigenesis have not been well understood. Smith et al. expressed recombinant HylP1 and found that the enzyme cleaved HA into long oligosaccharide chains, an activity believed to allow HylP1 to reduce the viscosity of HA during phage penetration of the cell wall of S. pyogenes. The authors resolved the structure of HylP1 at 1.8 Å resolution and showed that the central core is a single, right-handed, triple-stranded β-helix in the form of an irregular triangular tube. Each surface of the triangular tube contains a groove lined with positively charged arginine or lysine amino acid residues spaced so that they can bind the negatively charged glucuronic acid of HA. Although the triple β-helix exists in other viral tail proteins, those helices have not been shown to be catalytically active. — F.A.

“Structure of a group A streptococcal phage-encoded virulence factor reveals a catalytically active triple-stranded β-helix” by Nicola L. Smith, Edward J. Taylor, Anna-Marie Lindsay, Simon J. Charnock, Johan P. Turkenburg, Eleanor J. Dodson, Gideon J. Davies, and Gary W. Black (see pages 17652–17657)

IMMUNOLOGY

Hepatitis C virus evades immunity

Xiao-Dong Li et al. report that NS3/4A, the serine protease of the hepatitis C virus, cleaves the mitochondrial antiviral signaling protein (MAVS), allowing the virus to evade immunity. Previous research has shown that MAVS is targeted to the mitochondrial outer membrane and induces IFN-β, and though NS3/4A has been shown to inhibit interferon production, the target of the protease in the viral pathway had not been identified. Li et al. cotransfected expression vectors encoding NS3/4A and MAVS into human embryonic kidney cells together with a reporter driven by the IFN-β promoter. NS3/4A inhibited the induction of IFN-β, whereas a mutant NS3/4A lacking the protease ability did not. The protease cleaved MAVS at cysteine 508, and substituting an arginine at this residue resulted in the inability of NS3/4A to cleave the mitochondrial protein. NS3/4A and protease-resistant MAVS colocalized to the mitochondrial membrane and bound together in a coimmunoprecipitation experiment. Using a hepatitis C virus replicon cell culture system, protease-resistant MAVS was found to induce IFN-β in the presence of NS3/4A, whereas the protease cleaved wild-type MAVS, which did not provoke the immune response. — F.A.

“Hepatitis C virus protease NS3/4A cleaves mitochondrial antiviral signaling protein off the mitochondria to evade innate immunity” by Xiao-Dong Li, Lijun Sun, Rashu B. Seth, Gabriel Pineda, and Zhijian J. Chen (see pages 17717–17722)

MICROBIOLOGY

Mouse model of pneumonic plague progression

Wyndham Latham et al. use a mouse model of Yersinia pestis infection to characterize the interactions between bacterium and host and elucidate the progression of pneumonic plague. Latham et al. intranasally administered Y. pestis strain CO92, isolated from a fatal case of human plague, to mice. The animals subsequently succumbed to severe bronchopneumonia closely resembling the human disease. A strikingly biphasic mode of infection was observed, beginning with an anti-inflammatory state in the first 24–36 h and rapid progression...
to a proinflammatory state by 48 h, with death following within 3 days. Through DNA microarray analysis, ~10% of the Y. pestis genome was found to be differentially regulated in the mouse lung 48 h after infection, compared with bacteria grown in broth. Many of the highly up-regulated genes included known virulence factors, such as 33 genes associated with CD-1 plasmid-based type III secretion system. The findings may validate the use of DNA microarray technology to identify essential virulence loci and suggest that at least part of Y. pestis’s infection success is derived from its ability to multiply rapidly during the early stages of infection, essentially unchecked by the host immune system. — B.T.

“Progression of primary pneumonic plague: A mouse model of infection, pathology, and bacterial transcriptional activity” by Wyndham W. Lathem, Seth D. Crosby, Virginia L. Miller, and William E. Goldman (see pages 17786–17791)

NEUROSCIENCE

Understanding cerebellar long-term potentiation

According to Wataru Kakegawa and Michisuke Yuzaki, a mode of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking may help explain postsynaptic long-term potentiation (LTP) in the cerebellum. LTP and long-term depression (LTD), the long-lasting changes in synaptic strength thought to underlie learning and memory, involve the trafficking of AMPA receptors to and from the synaptic membranes. Although LTD in the cerebellum occurs in postsynaptic sites and has been widely studied, cerebellar LTP of postsynaptic origin has only recently been elucidated, and its molecular mechanisms remain uncharacterized. Kakegawa and Yuzaki used whole-cell patch clamp recordings from Purkinje cells of mouse cerebellar slices to identify a mechanism underlying postsynaptic LTP at parallel fiber–Purkinje cell synapses. Nitric oxide-induced LTP was found to be modulated by factors known to induce the exocytosis of GluR2, a subunit once thought to be constitutively delivered to synapses. The authors suggest that this mechanism may be the reverse process of parallel fiber-LTD and might underlie the extinction phase of motor learning. — M.M.

“Mechanism underlying AMPA receptor trafficking during cerebellar long-term potentiation” by Wataru Kakegawa and Michisuke Yuzaki (see pages 17846–17851)

Cerebellar LTP occurs at the postsynaptic site.

PHARMACOLOGY

Probe identifies endocannabinoid transporter

S. A. Moore et al. used a radioactive ligand and its parent molecule to identify a putative transport protein of anandamide, an endogenous cannabinoid. Endogenous cannabinoids are released in both central and peripheral tissues. Although much is known about the release of anandamide and its hydrolysis by the enzyme fatty acid amide hydrolase (FAAH), proving the existence of a specific anandamide transport protein has been elusive. Moore et al. found that the radioactive ligand binds to a plasma membrane protein distinct from FAAH, and that both molecules competitively inhibit anandamide uptake. Intraperitoneal administration of the ligand’s parent molecule caused anandamide levels to rise in the rat brain, suggesting that the ligand blocks anandamide transport. The parent molecule reduced paw-licking pain responses in rats in a dose-dependent manner, without inducing motor deficits. The authors suggest that the physiological effects and specific binding site characteristics observed using the ligand support the existence of an anandamide transport protein. Manipulating endocannabinoid signaling via synthetic anandamide transport antagonists may provide therapeutic benefits similar to those of medicinal marijuana without the adverse effects associated with its use. — B.T.


Probe identifies endocannabinoid transporter

S. A. Moore et al. used a radioactive ligand and its parent molecule to identify a putative transport protein of anandamide, an endogenous cannabinoid. Endogenous cannabinoids are released in both central and peripheral tissues. Although much is known about the release of anandamide and its hydrolysis by the enzyme fatty acid amide hydrolase (FAAH), proving the existence of a specific anandamide transport protein has been elusive. Moore et al. found that the radioactive ligand binds to a plasma membrane protein distinct from FAAH, and that both molecules competitively inhibit anandamide uptake. Intraperitoneal administration of the ligand’s parent molecule caused anandamide levels to rise in the rat brain, suggesting that the ligand blocks anandamide transport. The parent molecule reduced paw-licking pain responses in rats in a dose-dependent manner, without inducing motor deficits. The authors suggest that the physiological effects and specific binding site characteristics observed using the ligand support the existence of an anandamide transport protein. Manipulating endocannabinoid signaling via synthetic anandamide transport antagonists may provide therapeutic benefits similar to those of medicinal marijuana without the adverse effects associated with its use. — B.T.