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The interactions between virus proteins and host cells are intricate and impact diverse processes. Recent papers explored in this issue’s Microbiology Select reveal unexpected mechanisms by which viruses interact with host cells to facilitate infection, promote replication of their genomes, and foster horizontal gene transfer.

**HIV Tat Tweaks P-TEFb**

The Tat (transactivator of transcription) protein of the human immunodeficiency virus (HIV) hijacks host P-TEFb (positive transcription elongation factor b) to promote HIV transcription. A recently published structure by Tahirov et al. (2010) provides insight into how this interaction shapes the function of P-TEFb. P-TEFb is a complex consisting of human cyclin-dependent kinase 9 (Cdk9) and cyclin T1, and the structure provides an explanation for more than 1100 tolerated mutations in Tat. It also reveals that although the major interface of Tat is with cyclin T1, it also interacts with the regulatory T loop of Cdk9. The work shows that Tat affects the conformation of P-TEFb, including a change in the substrate-binding surface of the kinase. The authors propose that the unfolding of the α helix HC of cyclin T1 observed with Tat binding could contribute to the release of P-TEFb from HEXIM, a protein that maintains P-TEFb in an inactive form. In addition to this key mechanistic insight into Tat function, the structure opens a window on possible therapeutic strategies that would seek to block activity or formation of the complex. On this point the authors raise the appealing prospect that the conformational change exhibited upon Tat binding could be advantageous for the design of inhibitors that only interfere with the function of the Tat·P-TEFb complex, leaving the native function of P-TEFb unimpaired.

T.H. Tahirov et al. (2010). *Nature*. Published online June 10, 2010. 10.1038/nature09131.

**ERADicating Doubt about Membrane Origin**

During infection of host cells, coronaviruses induce the formation of double-membrane vesicles that are thought to be the location of virus genome replication. Despite the importance of this step in the coronavirus life cycle, it remains uncertain precisely where this membrane comes from. Findings by Reggiori et al. (2010) now provide evidence that the virus commandeers an element of the endoplasmic reticulum (ER) quality-control machinery in the formation of the double-membrane vesicles. They demonstrate that double-membrane vesicles induced by mouse hepatitis virus (MHV) are characterized by the presence of short-lived ER chaperones, such as EDEM1 (ER degradation-enhancing alpha-mannosidase-like 1) and OS-9, which recognize misfolded proteins as part of ER-associated protein degradation (ERAD). Prior work has shown that EDEM1 is removed from the ER in a process called ERAD tuning, and the authors show that ERAD tuning is impaired in MHV-infected cells. They further show that the double-membrane vesicles are characterized by the presence of LC3, a protein that when lipidated is targeted to autophagosomal membranes. However, this pool of LC3 is not lipidated, and the authors demonstrate that an intact autophagy machinery is not needed for MHV infection. Further work is needed to characterize the role of nonlipidated LC3 in MHV infection. In the current study, the authors demonstrate that decreasing its expression protects cells against MHV infection, suggesting that LC3 may be a useful therapeutic target for the treatment of coronavirus infections.

F. Reggiori et al. (2010). *Cell Host Microbe* 7, 500–508.
Catching a Glimpse of Infection's Opening Act

Cryo-electron microscopy (cryo-EM) had provided stunning images of nonenveloped viruses, revealing their exquisite organization and inner workings. Advancing this field of study, a recent report by Liu et al. (2010) provides a view of the structural changes in a marine podovirus, cyanophage P-SSP7, that accompany release of its double-stranded DNA genome. P-SSP7 and related phages infect one of the world’s most abundant organisms, Prochlorococcus marinus, a marine photosynthetic cyanobacterium that collectively account for a sizeable proportion of ocean photosynthesis. The authors use single-particle cryo-EM to analyze the virus structure both with and without packaged DNA and establish clear differences at the portal vertex, including alterations at the nozzle tip and in the position of the tail fibers. From this analysis it appears that the position of the tail fibers relative to an adapter protein determines whether the nozzle valve will be open to allow release of the genomic contents of the phage. The authors then examine by cryo-electron tomography P-SSP7 in the process of infecting Prochlorococcus cells and provide evidence that the tail fibers are positioned in an orientation similar to that observed in empty phage. This observation supports the view that a change in tail fiber position, likely upon interaction with a suitable host cell-binding site, precedes a series of conformational changes that trigger nozzle opening. These findings establish a framework for future efforts to assess in detail the cascade of molecular events that ultimately leads to the transfer of phage DNA into infected cells.

X. Liu et al. (2010). Nat. Struct. Mol. Biol. Published online June 13, 2010. 10.1038/nsmb.1823.

Trade Secrets of Pathogens Exposed

Bacterial pathogenicity islands encode virulence proteins and have the capacity to spread disease-causing genes between bacterial species through horizontal gene transfer. Recent findings by Tormo-Más et al. (2010) reveal a clever mechanism by which pathogenicity islands are mobilized in the bacterium Staphlococcus aureus. Among the factors that can be found on staphlococcal superantigen-carrying pathogenicity islands (SaPIs) is the toxin responsible for toxic shock syndrome. SaPIs are typically quiescent due to repression mediated by the protein Stl. However, when the bacterium is infected by a helper phage, SaPIs become mobilized and packaged into virus-like particles by proteins supplied by the infecting bacteriophage. The work of Tormo-Más et al. reveals that this quiescent state is disrupted by the binding of Stl to a bacteriophage-encoded protein, which interferes with the binding of Stl to DNA thereby permitting SaPI expression, excision, and replication. Surprisingly, in analyzing a number of different SaPIs, the authors show that derepression is not always mediated by the same phage protein in each case, but instead different SaPIs rely upon different phage proteins. In part, such a mechanism is possible because each SaPI encodes its own Stl protein, and Stl proteins are not highly conserved. Regardless, this remarkable feat of molecular adaptability should encourage future efforts to determine how Stl proteins interact with their phage-binding partners and how binding then leads to SaPI derepression.

M.A. Tormo-Más et al. (2010). Nature 465, 779–782.

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