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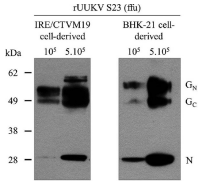
SPOTLIGHT

Articles of Significant Interest Selected from This Issue by the Editors

Insights into Tick-Borne Phlebovirus Structure and Initial Infection of Mammalian Host Cells

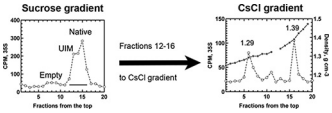
Tick-borne phleboviruses are a growing threat to humans globally. However, transmission to mammalian hosts and early steps of infection remain poorly characterized. Using the tick-borne phlebovirus Uukuniemi virus as a model, Mazelier et al. (p. 6784–6798) found that (i) the folding and *N*-glycans of the virus envelope glycoprotein G_N, (ii) the quantity of viral structural proteins per focus-forming unit, and (iii) the infectivity of virus progeny differ markedly between viruses produced in tick cells and mammalian cells. These findings shed light on specific structural properties of tick cell-derived viral progeny that may confer higher infectivity for mammalian cells.



Ratio of infectious to noninfectious particles is higher for tick cell-derived Uukuniemi viruses.

An Open and Infectious Form of Echovirus 1

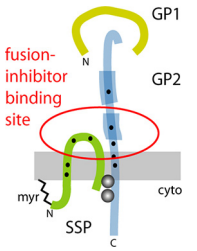
Enteroviruses cause outbreaks with severe symptoms and are associated with development of autoimmune diseases, such as type 1 diabetes. An enhanced understanding of how these viruses enter cells and uncoat may lead to development of new antiviral strategies. Myllynen et al. (p. 6759–6770) describe a form of echovirus 1 that is naturally produced from the native closed form of the capsid after uptake into cells. It is partially open but retains VP4 and is stable. This form of the virion is capable of receptor binding and infecting cells until its RNA is released from the capsid.



Two particle forms of echovirus 1, the light, native virion and the dense, open, novel virion.

Small-Molecule Fusion Inhibitors Bind the pH-Sensing Stable Signal Peptide-GP2 Subunit Interface of the Lassa Virus Envelope Glycoprotein

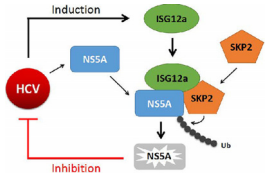
Lassa virus (LASV) is endemic in western Africa. Small-molecule compounds that antagonize pH-induced membrane fusion by the viral envelope glycoprotein (GPC) offer promise toward an effective treatment for Lassa hemorrhagic fever. Shankar et al. (p. 6799–6807) demonstrate that photoaffinity derivatives of one such fusion inhibitor specifically label both the GP2 fusion subunit and the unique stable signal peptide (SSP) in insect cell-produced LASV GPC, providing physical evidence for inhibitor binding at the pH-sensing SSP-GP2 interface. Only the mature GPC complex is labeled, suggesting that proteolytic cleavage of the GP1-GP2 precursor alters this intersubunit interface to prime for pH-dependent membrane fusion activity.



Photoaffinity mapping of the inhibitor-binding site on GPC.

ISG12a Restricts Viral Infection via a Ubiquitylation-Dependent Strategy

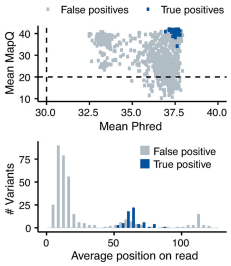
Interferon-stimulated genes (ISGs) are critical effectors of host innate immunity. However, the functions of many ISGs are poorly understood. Xue et al. (p. 6832–6845) demonstrate that ISG12a recruits an E3 ligase, S-phase kinase-associated protein 2 (SKP2), for ubiquitylation and degradation of viral proteins, which leads to restriction of viral infection. These findings provide important clues for understanding mechanisms of innate immunity.



A strategy employed by ISG12a to control viral infection.

Optimizing Variant Calling for Studies of Intrahost Diversity

Next-generation sequencing is a powerful tool for studies of intrahost viral diversity. While a large number of sequence analysis strategies have been developed to identify rare single-nucleotide variants, the accuracy of these strategies under field conditions is largely unknown. McCrone and Lauring (p. 6884–6895) used experimentally defined populations to benchmark the sensitivity and specificity of commonly used variant callers. This analysis revealed that the typical quality thresholds are unable to distinguish true mutations from false positives. The data set was used to optimize the analysis, which achieved >99.95% specificity.



Improved accuracy with more stringent quality thresholds.

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