SPOTLIGHT

Articles of Significant Interest Selected from This Issue by the Editors

Mechanism of Foot-and-Mouth Disease Virus Entry into Cells Probed

Foot-and-mouth disease is an economically devastating disease of livestock caused by foot-and-mouth disease virus (FMDV). The virus utilizes at least four members of the α subgroup of cellular integrins as receptors to infect cultured cells and is dependent on intracellular acidification for productive infection. O'Donnell et al. (p. 8506–8518) show that FMDV enters cells via a clathrin-dependent mechanism into early endosomes, where acidification probably results in release of the viral RNA. This work provides the basis for the development of potentially new antiviral chemotherapeutic targets.

Insight into Foot-and-Mouth Disease Virus Cell Entry

Foot-and-mouth disease virus (FMDV), a member of the picornavirus family, causes an extremely infectious and economically devastating vesicular disease of ruminants. Berryman et al. (p. 8519–8534) present evidence that in tissue culture cells, FMDV infection mediated by the integrin αvβ6 requires clathrin-dependent delivery from the cell surface to early/recycling endosomes and the low pH within these compartments. Evidence that integrin αvβ6 mediates virus internalization as well as attachment at the cell surface is also presented. This work provides a greater understanding of the early events of the FMDV replication cycle.

A Novel Experimental System for Studies of Hepatitis Delta Virus Replication

Hepatitis delta virus (HDV) encodes one essential protein, the small delta protein (δAg). Chang et al. (p. 8182–8188) establish a system where all δAg is provided, under tetracycline (TET) control, from a stably integrated cDNA. HDV replication using this system mimics plant viroids, which are totally dependent on host proteins. In the absence of TET, sufficient δAg is synthesized to maintain HDV genomes at about 1,000 copies per cell for at least 1 year. However, in the presence of TET, 40 times more δAg and HDV RNAs are made within 2 days, with consequent cytopathicity. Several applications of this new system are described.

Dual Role for Cell-Cell Fusion in a Nonenveloped Virus Replication Cycle

Certain species of orthoreoviruses encode a unique group of fusion-associated small transmembrane (FAST) proteins. Salsman et al. (p. 8090–8100) demonstrate that the FAST proteins are dedicated cell-cell fusion machines. These proteins mediate formation of syncytia that maintain membrane stability until extensive syncytium formation induces apoptosis. This work suggests a dual role for cell-cell fusion in the replication cycle of a nonenveloped virus. Induction of cell-cell fusion allows rapid localized transmission and replication of the virus before syncytium-induced apoptosis facilitates systemic dissemination.

Silencing Coxsackievirus B3 Infection with Short Interfering RNA

Coxsackievirus B3 (CVB3) is a major cause of many human diseases, including meningioencephalitis and myocarditis. Ahn et al. (p. 8620–8624) provide intriguing new evidence that a CVB3-specific small interfering RNA (siRNA) not only inhibits CVB3-induced cell death but also has antiviral effects on other related enteroviruses possessing sequence similarity to the targeted region. This work suggests that siRNA might be a valuable tool for treating enterovirus-related human diseases.

HCV Envelope-Receptor Interactions Induce Immunoglobulin Gene Hypermutation in B Cells

Hepatitis C virus (HCV) infection induces mutation of cellular genes, including oncogenes and immunoglobulin (Ig) genes. While the oncogene mutations are caused by HCV core and NS3 proteins, the mechanism of Ig mutation is not clear. Machida et al. (p. 8079–8089) now show that Ig mutation is induced by the binding of the viral E2 protein to the
putative viral receptor, CD81, on B cells, leading to increased expression of the activation-induced cytidine deaminase (AID). This finding has important implications for the pathogenesis of HCV infection.

**MLV Uses a Novel Mechanism To Avoid Cellular Intrinsic Immunity**

Mammalian APOBEC3 proteins can inhibit retroviral replication when packaged into virions by binding to the viral Gag protein. Complex retroviruses avoid this restriction by encoding a protein that blocks APOBEC3 function. How simple retroviruses such as murine leukemia virus (MLV) avoid inhibition has been unclear. Doehle et al. (p. 8201–8207) demonstrate that MLV Gag selectively fails to bind murine APOBEC3, although this protein inhibits HIV-1 effectively. Conversely, human APOBEC3 proteins bind MLV Gag and block MLV replication. Therefore, intrinsic immunity may be a major determinant of retroviral species tropism.

**Yellow Fever Vaccine Virus Envelope Glycoprotein Engineered To Express Foreign Epitopes**

Three-dimensional modeling of the yellow fever 17D virus envelope (E) protein suggests that it is possible to accommodate inserts of variable size and amino acid composition into the $fg$ loop. Bonaldo et al (p. 8602–8613) demonstrate that in both the dimeric and trimeric forms of E protein the insertions in the $fg$ loop are solvent exposed and do not interfere with the overall structure. Monkey neurovirulence tests suggest that insertions at this site also do not compromise the characteristic attenuated phenotype of yellow fever 17D virus. These findings further confirm the potential for the development of new live 17D-based vaccines.

**Attenuation of North American West Nile Virus Prototype Strain**

Studies using murine models have shown that the West Nile virus (WNV) strain introduced into North America in 1999 is more neuroinvasive than many related strains isolated in other parts of the world. Beasley et al. (p. 8339–8347) have demonstrated that a mutation preventing glycosylation of the envelope protein, as occurs in many attenuated WNV strains found in the Old World, reduced the neuroinvasiveness of North American WNV in mice. This finding indicates that envelope protein glycosylation is an important determinant of the enhanced virulence of WNV associated with outbreaks of severe neurological disease in North America.

**Induction of Autoimmunity by Virus-Induced Molecular Mimicry**

Virus infections are suspected of initiating various autoimmune diseases. Croxford et al. (p. 8581–8590) show that neurotropic Theiler’s virus encoding a molecular mimic of a self myelin epitope normally expressed by a *Haemophilus influenzae* protein can both induce and exacerbate CNS autoimmunity in an animal model of multiple sclerosis. The findings highlight several important requirements for infection-induced autoimmunity by showing that the disease is due to cross-reactive activation of autoreactive T cells, that the molecular mimic can be processed from the intact *Haemophilus* protein, and that autoimmune disease induction is dependent on virus-activated innate immune signals.

**Quantum Dots Used To Detect Viral Particles**

Nanometer-sized particles such as semiconductor quantum dots (QDs) have unique optical and electronic properties that are not available from either isolated molecules or bulk solids. Properties of QDs have stimulated intense interest in developing nanoparticle probes for medical diagnostics, molecular imaging, and targeted therapeutics. Agrawal et al. (p. 8625–8628) report the use of bioconjugated nanoparticles and two-color fluorescence correlation for real-time detection of virus particles in a flow channel. The results demonstrate that antibody-linked nanoparticles can rapidly and sensitively detect viral particles and can be used to estimate the relative levels of virus surface proteins. This work opens new pathways for nanotechnology applications in virology, immunology, and infectious disease detection.