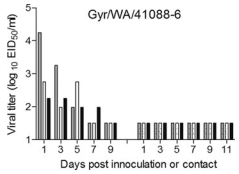
Articles of Significant Interest Selected from This Issue by the Editors

North American H5 Avian Influenza Viruses: Risk Assessment for Human Infection

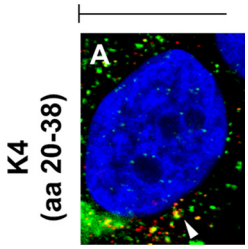
Outbreaks of novel highly pathogenic H5Nx avian influenza viruses have resulted in the loss of nearly 50 million chickens and turkeys in the United States since these viruses were first identified in December 2014. Pulit-Penaloza et al. (p. 10286–10293) showed that H5N2 and H5N8 viruses isolated from birds display moderate pathogenicity in mammalian models and lack the capacity to transmit between ferrets in a direct contact setting. These findings suggest that the new avian viruses currently pose a low risk to humans and would need to acquire additional changes to become a pandemic threat.



Transmissibility of influenza viruses in ferrets.

L2 Minor Capsid Protein Becomes Transmembranous during Human Papillomavirus Entry

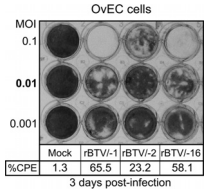
The nonenveloped human papillomavirus (HPV) interacts with cytosolic host cell factors, such as retromer complexes and dynein, for transport to the nucleus. Using accessibility of antibodies to specific epitopes in differentially permeabilized cells, DiGiuseppe et al. (p. 10442–10452) provide evidence that the minor capsid protein L2 penetrates intracellular membranes after viral capsid uncoating. C-terminal and N-terminal sequences of a putative transmembrane domain (residues 45 to 65) are accessible and inaccessible to antibody binding, respectively, under conditions that selectively permeabilize the plasma but not intracellular membranes. These data suggest that L2 facilitates HPV trafficking by temporarily becoming transmembranous.



Accessibility of L2 epitopes.

Host-Specific Effect of NS3 Proteins on the Biological Properties of Bluetongue Virus

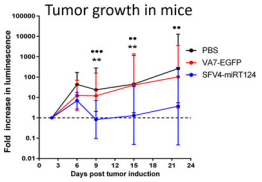
Bluetongue virus (BTV) is transmitted by *Culicoides* biting midges and causes severe disease in ruminants. The viral NS3 proteins play key roles in BTV infection. Ftaich et al. (p. 10467–10481) report that in mammals, unlike in *Culicoides*, sequence variability of these proteins is associated with alteration in BTV replication kinetics and virulence. Notably, a single amino acid polymorphism can lead to a host-specific variation in the NS3 turnover rate. These findings shed light on the influence of NS3 proteins during BTV infection and may help to predict the disease potential of circulating BTVs during outbreaks.



NS3 proteins modulate BTV replication kinetics in ovine cells.

MicroRNA-Regulated Alphavirus with Increased Oncolytic Potency

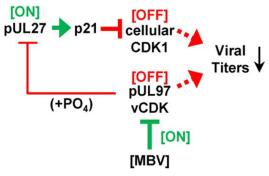
The type I interferon response limits the oncolytic potency of nonvirulent alphaviruses, but several potential strains have not been tested due to their neurotoxicity. Martikainen et al. (p. 10637–10647) showed that a miR-124-targeted virulent Semliki Forest virus, SFV4-miRT124, fails to replicate in neurons. However, this virus retains its natural tolerance to type I interferons in cultured glioma cells and infects orthotopic tumors in mice, resulting in significant tumor growth retardation and improved survival. These results suggest that new viral RNA-based approaches can lead to development of potent oncolytic vectors for cancer therapy.



SFV4-miRT124 diminishes tumor growth in mice.

Antagonistic Protein Activities in Human Cytomegalovirus Antiviral Therapy

Human cytomegalovirus (HCMV) encodes a diverse repertoire of proteins, with some regulating the activities of others during the long replication cycle. Bigley and colleagues (p. 10230–10246) demonstrate an antagonistic relationship between HCMV proteins pUL27 and pUL97. The pUL97 kinase promotes pUL27 phosphorylation and is inhibited by the antiviral agent maribavir (MBV). Inhibiting the kinase allows prolonged pUL27-dependent expression of a cyclin-dependent kinase (CDK) inhibitor, $p21^{Cip1}$, which disrupts virus production. These findings define an underlying mechanism of MBV antiviral activity and provide another example of coordinated viral protein functions.



Model of MBV antiviral activity involving antagonistic protein activities.

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