Articles of Significant Interest Selected from This Issue by the Editors

Ebolavirus Requires the Endosomal Protein Acid Sphingomyelinase for Infection

Ebolavirus enters cells via macropinocytosis and can use several receptors, including endosomal protein NPC1. Miller et al. (p. 7473-7483) found that ebolavirus requires acid sphingomyelinase (ASM) and its substrate, sphingomyelin, for infection. Interestingly, like NPC1, ASM also is found in endosomes, but ebolavirus recruits it to the cell surface at the site of virus attachment. Drugs blocking ASM activity or its cell surface recruitment prevent infection. These findings highlight a new feature of the ebolavirus infection mechanism by which endosomal proteins are brought to the cell surface and suggest a treatment strategy that may apply to other pathogens that use macropinocytosis to gain cell entry.

Activation of Cap-Dependent Translation by Human Papillomavirus Type 16 E6

Expression of the human papillomavirus type 16 (HPV-16) E6 protein activates and sustains mTORC1 signaling and cap-dependent translation even under conditions of growth factor restriction. Spangle et al. (p. 7466-7472) show that this activity is shared by E6 proteins encoded by cancer-associated and non-cancer-associated mucosal HPVs. However, the cutaneous HPV E6 proteins lack this activity. This work suggests that mTORC1 inhibition may be a viable therapeutic strategy to combat lesions and cancers caused by infections with mucosal HPVs.

Human T-Lymphotropic Virus Type 1 Tax Protein Inhibits Nonsense-Mediated mRNA Decay

Some cellular and viral mRNAs are degraded by nonsense-mediated mRNA decay (NMD). By interacting with INT6/EIF3E and UPF1, which are important components of the NMD pathway, the human T-lymphotropic virus type 1 (HTLV-1) Tax protein exerts a negative effect on this process. Mocquet et al. (p. 7530-7543) determined that this activity leads to mRNA stabilization and also affects the morphology of cellular compartments concentrating factors involved in mRNA degradation. This activity of Tax may enhance viral replication efficiency and augment HTLV-1-associated leukemogenesis.

The Cornea Is a Bottleneck for Virulence of Attenuated Herpes Simplex Virus

Ocular herpes simplex virus (HSV) infections can lead to blindness. The interferon (IFN) response serves an important function in resistance against this disease. Pasieka et al. (p. 7692-7695) infected IFN-deficient mice and found that an IFN-sensitive HSV strain lacking the virion host shutoff gene remains attenuated in the cornea following ocular infection. In contrast, direct inoculation of the attenuated virus into the central nervous system bypassed the bottleneck at the cornea and displayed near wild-type virulence and replication in the brain. Together, these data demonstrate an intrinsic IFN-independent resistance to HSV infection within the cornea that can be overcome by the HSV host shutoff function.

Dominant-Negative PKR Increases Vaccine Efficacy for Rift Valley Fever

MP-12, a live-attenuated vaccine candidate for Rift Valley fever (RVF), encodes the major virulence factor NSs, which inhibits transcription of the beta interferon gene and promotes degradation of double-stranded RNA-dependent protein kinase (PKR). Lihoradova et al. (p. 7650-7661) show using a mouse model that MP-12 encoding a dominant-negative PKR in place of NSs is highly efficacious, inducing innate immunity and enhancing accumulation of viral proteins in dendritic cells at local draining lymph nodes. This study suggests a new method to improve the safety of MP-12 vaccine without decreasing its efficacy.

Endogenous Hepadnaviruses in the Budgerigar Genome

Endogenous hepadnaviruses were recently discovered in the genomes of passerine birds. Cui and Holmes (p. 7688-7691) show that endogenous hepadnaviruses also are present in the genome of the budgerigar (order *Psittaciformes*). Notably, all of the endogenous hepadnaviruses identified to date are phylogenetically distinct from their exogenous counterparts, even those sampled from the same avian order, and are more genetically diverse. These results indicate multiple integrations of hepadnaviruses into avian genomes and suggest that the evolutionary history of exogenous hepadnaviruses is likely characterized by a process of lineage birth and death.

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