A Unique Umbravirus with an Exoribonuclease-Resistant, Translated Subgenomic RNA

*Opium poppy mosaic virus* (OPMV) is a single-stranded plus-sense RNA virus that does not encode a capsid protein and requires a helper virus. Ilyas et al. (e02109-20) found that OPMV generates two similarly sized subgenomic RNAs (sgRNAs), one of which is synthesized by the replicase and is the template for translation of viral movement proteins. The other is generated by an exoribonuclease-resistant sequence, a mechanism that normally produces small, noncoding sgRNAs. However, this sgRNA codes for a 30-kDa protein with a functional role in OPMV accumulation. The authors also determined that OPMV uses a *Barley yellow dwarf virus*-like translation element (BTE) as one of its 3’ cap-independent translation enhancers. While BTEs were thought to have little in common beyond a 17-nucleotide conserved sequence, analysis of the 14 known BTE structures showed that BTEs contain additional, strongly conserved sequences and structural features that include residues known to interact with translation initiation factor eIF4G.

**GPCR and Ion Channel Genes Exploited by Influenza Viruses**

Influenza A and B viruses exploit host genes and their pathways for replication and egress. Anti-influenza drugs target viral proteins for inhibition, but often have reduced efficacy due to antigenic shift and drift in the virus proteins. Therapeutics targeting host genes and associated pathways necessary for virus replication offer a refractory approach toward drug resistance while potentially providing broad efficacy. Using RNA interference (RNAi), Orr-Burks et al. (e02410-20) identified 16 pro-influenza virus G-protein-coupled receptors (GPCR) and 5 pro-influenza virus ion channel genes using A/WSN/33-, A/CA/04/09-, and B/Yamagata/16/1988-infected A549 cells, providing targets for host-directed therapeutic strategies.

**Nucleoprotein Availability Defines both Virus and Host Biology**

Negative-sense RNA viruses form viral replication complexes where polymerase-bound viral RNA genomes are packaged around helical nucleoprotein scaffolds. Nilsson-Payant et al. (e02274-20) used diverse RNA viruses to demonstrate that limiting nucleoprotein availability results in replicative catastrophe characterized by a loss of polymerase processivity and a dramatic shift from full-length to aberrant genome production. Furthermore, limited nucleoprotein availability also results in a robust induction of the antiviral host response. This study describes the key role viral nucleoprotein levels play in maintaining the balance between negative-sense RNA virus replication and cellular host detection.
The Dr. Jekyll/Mr. Hyde Nature of IRF-3 during Gammaherpesvirus Infection

Interferon regulatory factor 3 (IRF-3) is classically perceived as an innate immune factor that promotes type I interferon expression and therefore attenuates acute replication of diverse viruses, including murine gammaherpesvirus 68 (MHV68). Johnson et al. (e02208-20) originally aimed to define the extent to which IRF-3 attenuates chronic MHV68 infection, as the antiviral role of IRF-3 has been exclusively defined during acute infection. Surprisingly, and in contrast to its antiviral role during acute MHV68 replication, IRF-3 expression promoted the establishment of latent MHV68 infection in splenic B cells. This observation emphasizes an underappreciated concept that traditional innate immune factors are likely to moonlight during chronic virus infections, with potentially unanticipated novel phenotypes.

SARS-CoV-2 Entry and Type I Interferons

The presence of a furin cleavage site in the spike protein of SARS-CoV-2 is a feature that distinguishes it from the phylogenetically related bat sarbecoviruses. This site has been proposed to be a determinant of the higher transmissibility between individuals of SARS-CoV-2 than of SARS-CoV-1. Winstone et al. (e02422-20) demonstrate that the sensitivity of SARS-CoV-2 to inhibition of cell entry by interferon-induced transmembrane protein 2 (IFITM2), which is known as an entry inhibitor of diverse enveloped viruses, is reduced by the presence of the furin cleavage site, suggesting that proteolytic processing of SARS CoV-2 spike may represent a potential therapeutic target for COVID-19.