Characterizing the host-mitochondria/virus interaction through studies of the L-A dsRNA totivirus.

Viruses and other genetic parasites are present in virtually all forms of life. This chronic condition has led to diverse host cell adaptations such as CRISPR and RNAi, whose functions attenuate these parasites. We have discovered a role for the mitochondria in viral innate immunity. Yeast are infected with a double stranded RNA (dsRNA) virus called "L-A" that is only vertically transmitted with no extracellular phase. For long thought to be a harmless commensal, we have shown that L-A accumulates to toxic levels in strains lacking the functions of the mitochondrial exoribonucleases Nuc1 and Rex2. Of note, Nuc1 is homologous to endonuclease G, a nuclease that is released from mitochondria during apoptosis in humans, and some of our studies suggest Nuc1 accumulates in the cytosol in a Por1 dependent manner to accomplish viral attenuation. The L-A RNA dependent RNA polymerase (RdRP) shows homology to those of other RNA viruses such as MERS, SARS, and SARS-Cov-2, the virus that causes the pandemic disease COVID-19. Our ongoing work is focused on the mechanisms of mitochondrial viral attenuation (1) and of RdRP inhibitory drugs such as remdesivir (2). These studies are complimented by further characterization of the L-A lifecycle using proteomic and genomic approaches to attain a comprehensive cell biological understanding of the host-virus interaction (3).