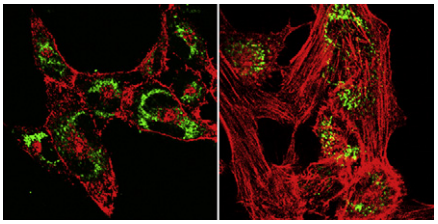
Cell

Virus-Host Interactions

Viruses display remarkable specificity in both the host species and the cell types that they infect. Understanding this specificity reveals insight into the basic host components that are required for the viral life cycle and host restriction factors that limit the virus. This issue's Select takes a closer look at some of the limitations to virus replication, including a report identifying an unexpected origin of a controversial retrovirus.



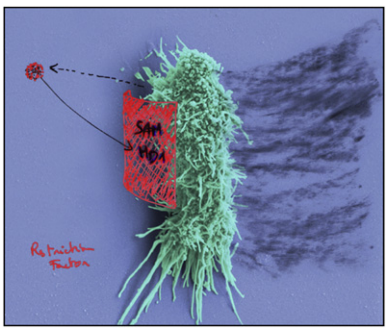
In wild-type (left) and viperin knockdown (right) fibroblasts that are infected by human cytomegalovirus, viperin is induced only in the wild-type cells. The viral vMIA protein (green) is present in mitochondria in both, but the actin cytoskeleton (red) is disrupted only in the viperin-expressing cells. Image courtesy of J.-Y. Seo and P. Cresswell.

HCMV Turns Defense into Offense

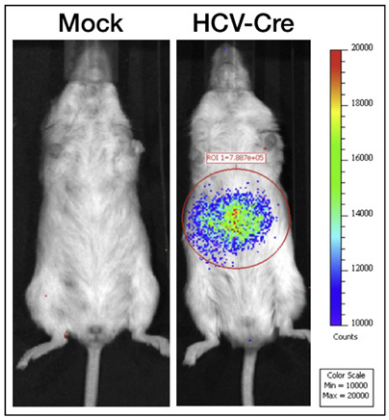
Given that viruses have evolved many mechanisms of counteracting host immune systems, it seems counterintuitive at first that human cytomegalovirus (HCMV) would specifically induce expression of an antiviral host protein called viperin. Seo et al. (2011) now resolve this conundrum by deciphering the activities of viperin and of a viral protein, viral mitochondria inhibitor of apoptosis (vMIA). They show that the direct binding of vMIA to viperin and the resulting relocalization of viperin to mitochondria turn viperin into a weapon not against its intended target, but against the host. By adding a mitochondrial localization sequence to viperin, the authors provide evidence that many of the effects previously attributed to vMIA are, in fact, due to mislocalized viperin. These effects include decreasing ATP availability leading to abnormal cell enlargement (cytomegaly) and cytoskeletal disruption, which facilitates infection. To elicit the reduction in ATP, viperin binds the HADHB subunit of the mitochondrial trifunctional protein (TFP), an enzyme that catalyzes multiple steps in mitochondrial fatty acid β oxidation. How viperin limits TFP function remains to be elucidated. Also, given that other mechanisms of ATP generation presumably remain intact, it is not known how the activity of vMIA-bound viperin is precisely controlled to reduce the level of ATP to a level that induces cytoskeletal disruption and cytomegaly, but not below a threshold that would trigger apoptosis. What is clear is that vMIA-induced relocalization of viperin has a double advantage for the virus, reducing its antiviral activity but also turning the cell's defense against itself, inducing a cellular energy crisis that facilitates viral infection.
Seo, J.-Y. et al. (2011). Science 332, 1093–1097.

Protecting Dendritic Cells from HIV-1 Infection

Three cellular proteins—APOBEC3G, TRIM5α, and tetherin—have been characterized as HIV-1 restriction factors. Although potent under certain conditions, each of these HIV-1 restriction factors has limited activity in humans due to a variety of evolutionary adaptations of the virus. Now, Laguette et al. (2011) identify a new HIV-1 restriction factor, SAMHD1, that is highly active against HIV-1 in human cells because the virus has evolved no means to counteract this protein. SAMHD1 is highly expressed in dendritic and myeloid cells that are previously known to be nonpermissive to HIV-1 infection. They show that high-level expression of SAMHD1 is sufficient to block HIV-1 infection in cells otherwise permissive to HIV-1 infection, and its removal in dendritic cell subsets significantly increases HIV-1 infection. To identify this factor, Laguette et al. used the knowledge that certain nonpermissive cell types could be infected when forced to express the HIV-2/SIV accessory protein Vpx, hypothesizing that Vpx binds and degrades an HIV-1 restriction factor. Pull-down of Vpx-binding proteins in nonpermissive cell lines identified SAMHD1, an interferon-γ-inducible factor that is sensitive to Vpx-mediated degradation. This data helps to explain why certain primary dendritic and myeloid cells that express the receptor and coreceptor for HIV-1 entry remain refractory to infection. Further studies are needed to determine the mechanism of SAMHD1 inhibition of HIV-1 infection and the role of SAMHD1 in HIV-2/SIV pathogenesis. This finding will help our understanding of retrovirus pathogenesis and may open up new avenues for vaccine development.
Laguette, N., et al. (2011). Nature. Published online May 25, 2011. 10.1038/nature10188.



Human dendritic cells (blue pseudocoloring). Dendritic cells are largely refractory to HIV-1 infection due to the expression of the newly identified SAMHD1 protein. The photographs were decorated by the French artist Fabrice Hyber. The EM image was obtained from Olivier Schwartz, Stéphanie Guadagnini, and Marie-Christine Prevost (Electron Microscopy Core Facility, Institut Pasteur).



Visualization of hepatitis C virus infection in the liver of mice expressing human entry factors. Image courtesy of A. Ploss.

Breaking the Species Barrier

Developing model systems and methods to study human viral infections is typically difficult because cell lines and animal systems can lack the expression of key host proteins that are necessary for viral replication and may contain cellular restriction factors that limit virus spread. Two groups present new experimental models of hepatitis C virus (HCV) infection that overcome major hurdles for its study. Triyatni et al. (2011) developed a method to produce infectious HCV particles of theoretically any genotype in mammalian cells without using the error-prone HCV replication machinery. Interestingly, they find that expressing a subgenomic replicon of West Nile virus (a flavivirus in the same family as HCV) makes cells capable of HCV assembly and release. The HCV genome and proteins could then be supplied as plasmids along with a plasmid-encoded bacteriophage RNA polymerase that drives cytoplasmic transcription. This method is a major advance over current HCV culture systems because it avoids the viral adaptive mutations that typically accompany HCV replication in tissue culture and facilitates studies on an array of infectious primary viral variants.

Existing mouse models for HCV infection are useful but limited and involve transplantation of human hepatocytes into immunocompromised mice. Dorner et al. (2011) have now taken an important step forward with the development of a more tractable mouse model for HCV infection. The researchers expressed each of the previously identified human HCV entry factors (CD81, claudin 1, occludin, and scavenger receptor type B class I) in mouse hepatocytes. Using recombinant HCV-expressing CRE recombinase to infect mice that contain CRE-activated luciferase or GFP/β-galactosidase reporters, HCV uptake could be detected in cells expressing CD81 and occludin or all four factors. Because these animals are immunocompetent, Dorner et al. are also able to determine the efficacy of various vaccine vectors against a variety of HCV genotypes, demonstrating the usefulness of this mouse model to the study of future HCV vaccines.

Triyatni, M., et al. (2011). PLoS Pathog. 7, e1001333.
Dorner, M., et al. (2011). Nature 474, 208–211.

Viral Detectives Uncover the Origins of XMRV

Scientists delve into the mystery of XMRV. Image courtesy of K. Delviks-Frankenberry and V. Pathak.

Since the first report of a gammaretrovirus termed xenotropic murine leukemia virus-related virus (XMRV) in 2006, numerous studies have debated its origins, as well as its link to disease. Reports previously suggested that XMRV may be an artifact—a PCR contaminant—and others affirmed that it was an infectious human pathogen. What is XMRV's true identity? According to Paprotka et al. (2011), it accidentally arose through chance recombination events in a laboratory. The virus was originally discovered in human prostate tumors, but an identical virus was later found in a prostate cancer cell line. Researchers looked at the genesis of these cell lines for clues to the origin of the virus. Nearly two decades ago, human prostate tumors, which grow poorly in culture, were shown to grow well when serially passaged through nude mice, a method used to generate a number of the widely used prostate cancer cell lines. Paprotka et al. isolated genomic DNA from a number of different passages of the prostate cancer cells, as well as from the original tumor, and showed that none of the samples prior to 1993 contained XMRV DNA. Early xenografts and some mouse lines did, however, contain two replication-defective viruses, each highly homologous to XMRV on opposite ends of their genome, termed PreXMRV-1 and PreXMRV-2. Phylogenetic analysis of these two viral sequences suggested that PreXMRV-1 and PreXMRV-2 recombined when coexpressed in the same cell to generate XMRV during the passage of prostate tumor xenografts in mice that harbored these endogenous precursor viruses. Thus, the short but tumultuous history of XMRV provides a cautionary tale of the awesome capacity of viruses, even those considered defective, to adapt and thrive in unexpected ways.

Paprotka, T., et al. (2011). Science. Published online June 2, 2011. 10.1126/science.1205292.

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