

Minireview Prologue

**VIRUS-HOST INTERACTION MINIREVIEW SERIES – HUMAN
IMMUNODEFICIENCY VIRUS, HEPATITIS C VIRUS, AND INFLUENZA VIRUS**

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Running title: Virus-Host Interactions.

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Viral agents of infectious disease such as human immunodeficiency virus (HIV), influenza virus and hepatitis C virus (HCV) continue to pose daunting public health challenges. Substantial information is known about the multiplication cycles, the means of transmission and the diseases caused by these three viruses, all of which are human pathogens that possess RNA genomes (1). Efforts to understand their viral multiplication schemes at the molecular level, and to elucidate the interactions that occur between viral and cellular gene products that together determine the host's susceptibility to infection and disease, have shed significant new insights about HIV, influenza and HCV viruses. The first two minireviews in this issue concern HIV and influenza virus. They focus on the genetic and biochemical aspects of two viral proteins, the Vif protein of HIV (2) and the M2 protein of influenza virus (3), and the functional roles that they play during establishment of productive viral infections. The third minireview focuses on the structure and function of the viral proteins involved in the replication of HCV RNA (4).

In the first minireview, Ya-Lin Chiu and Warner Greene at the University of California, San Francisco in their article entitled "The APOBEC3 Cytidine Deaminases: Distinct Antiviral Actions Along the Retroviral Life Cycle" consider new developments in both the biochemistry and biology of the cellular APOBEC3 family of cytidine deaminases in the context of retroviral infections (2). They discuss the antiviral activity that APOBEC3 proteins display against HIV and other retroviruses, and also the counter measures used

by the viruses to antagonize APOBEC3-mediated retroviral genome editing. The principal features of the HIV multiplication cycle are summarized in Figure 1. 3G is one of the APOBEC3 cellular cytidine deaminases that when encapsidated in budding HIV progeny virions, subsequently inhibits HIV in newly infected cells by causing genome editing (dG-to-dA transitions) of the viral single-stranded DNA intermediate. Lentiviruses like HIV and primate foamy viruses have acquired accessory viral proteins, Vif and Bet respectively, that impair the genome editing activity of APOBEC3. In the case of HIV, the virion infectivity factor (Vif) protein targets the APOBEC3 protein for proteasomal degradation in productively infected activated CD4 T cells and macrophages. The ability of HIV to antagonize APOBEC3 is reminiscent of the ability of several other viral gene products to antagonize the actions of IFN (5). Recent advances in the understanding of the lethal editing of viral genomes by the virion-incorporated APOBEC3 observed in the absence of Vif, and the discovery that a form of the APOBEC3G protein restricts HIV post entry in resting CD4 cells by a mechanism that is not antagonized by Vif, are described. Finally, APOBEC3 as a promising new therapeutic target for anti-HIV drug development is considered by Chiu and Greene (2).

The second minireview of the series, by Lawrence Pinto and Robert Lamb at Northwestern University entitled "The M2 Proton Channels of Influenza A and B Viruses," summarizes progress in understanding the M2 ion channel proteins of the influenza A and B viruses. Influenza viruses, members of the

Orthomyxoviridae, are enveloped viruses with segmented, negative-stranded RNA genomes (1). The principal features of the influenza multiplication cycle are summarized in Figure 2. The M2 proton channel functions firstly at the initiation stage of infection, where during virus entry acidification plays an important role in the release of partially uncoated nucleocapsids, a step necessary for viral transcription to occur. Pinto and Lamb review recent insights into the biochemical properties of the viral M2 ion channel proteins, how these proteins function in proton transport, and the molecular basis of the actions of the antiviral therapeutics amantadine and rimantadine (Flumadine) that inhibit influenza A viruses by impairment of the A/M2 ion channel activity. Influenza A viruses are important pathogens that pose a continuing threat. Avian influenza strains (H5N1, H7N7) are highly pathogenic and problematic in poultry. While the number of human H5N1 cases resulting from bird transmission to humans so far is low, human disease caused by avian influenza H5N1 virus provides an example of a newly emerging infectious agent with a high mortality rate of infected individuals. Adaptation of highly pathogenic avian influenza strains to humans, with the acquired ability to undergo efficient human to human transmission, could yield viruses with pandemic potential. Thus, understanding the structural basis for the function of influenza virus proteins such as M2 may provide an opportunity, through rational drug design, to devise new inhibitors that act broadly against different influenza virus strains without impairing essential cellular functions.

Hepatitis C virus (HCV), a member of the *Flaviviridae*, is an enveloped virus with a positive-sense single-stranded RNA genome (1). The principal features of the HCV multiplication cycle presumed to take place in infected liver cells are summarized in Figure 3. Much of our understanding derives from study of the HCV replicon system. In the third

minireview of the series, Nicole Appel, Torsten Schaller, Francois Penin and Ralf Bartenschlager at the University of Heidelberg and University of Lyon describe new structural and biochemical sights into the hepatitis C virus replication complex (4). Resolution of the 3D-structures of some of the HCV proteins, together with cell biological studies, is discussed. These studies provide important new insights into HCV RNA replication, the viral proteins and cellular machinery required, and how the virus counters some of the host innate immune responses. HCV infects more than 150 million of the world's population, with infection often leading to persistent viremia and progressive liver disease (1). Chronic liver disease caused by HCV, including liver cirrhosis and hepatocellular carcinoma, is a major global problem. Current therapy for HCV, pegylated interferon alpha and ribavirin, shows response rates of 40-80% depending upon HCV genotype. A system for production of infectious HCV in cell culture was described in 2005. The availability of a cell culture system, together with knowledge that has been gained about the structure and function of HCV proteins (4), provides opportunities to target viral enzymes involved in RNA replication in the search for new avenues of antiviral therapy.

Considerable progress has been made in understanding the fundamental roles that viral and cellular proteins, acting together, play in determining the host susceptibility to viral infection and disease. Efforts to understand the genetic and molecular basis of virus-host interactions have led to the identification of specific gene products that play key roles in determining the outcome of infections. Some of the immediate challenges, and opportunities, in the field of biochemical virology involve using knowledge of the replication schemes of HIV, HCV and influenza virus to develop new and improved antiviral treatment and preventative strategies for these viral infections.

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FOOTNOTES

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¹Abbreviations used: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; Vif, virion infectivity factor.

FIGURE LEGENDS

FIGURE 1. Schematic diagram of the human immunodeficiency virus multiplication cycle. Enveloped HIV virion particles are depicted as spheres. Following entry by receptor-mediated fusion and partial uncoating of the viral nucleocapsid, the DNA provirus is synthesized from the positive-strand RNA genome by virion-associated reverse transcriptase (RT) and RNase H activities. Proviral DNA then is imported into the nucleus and integrated into the genome of the host. Processed transcripts synthesized from the integrated proviral genome by host RNA polymerase II are transported to the cytoplasm where they are translated to yield viral structural proteins following proteolytic processing by viral protease (PR). Accessory and regulatory proteins are produced from spliced transcripts, including the virion infectivity factor (Vif) protein. Vif antagonizes the function of members of the cellular APOBEC3 cytidine deaminase family including 3G, thereby permitting the production of infectious progeny virions from activated CD4-T cells. In the absence of Vif, APOBEC3G is packaged in the budding particle and subsequently inhibits HIV in newly infected cells by causing genome editing and hypermutation.

FIGURE 2. Schematic diagram of the influenza virus multiplication cycle. Enveloped influenza virion particles are depicted as spheres, in which the viral HA integral membrane glycoprotein mediates binding to the cellular receptor. Partial uncoating and release of the viral nucleocapsid into the cytoplasm follow penetration via receptor-mediated endocytosis. The viral envelope also contains a small amount of the M2 ion channel protein essential for virion uncoating. M2 is the target of the antiviral drug, amantadine. The eight negative-sense single-stranded RNA genome segments are shown as wavy lines in nucleocapsid structures. The parental nucleocapsid is imported into the nucleus, where the virion-associated polymerase complex catalyzes primary transcription. Influenza virus transcripts are processed and transported to the cytoplasm where they are translated by the host cell protein-synthesizing machinery. Newly synthesized progeny nucleocapsids may participate in further secondary transcription or may be exported to the cytoplasm where particle assembly occurs at the plasma membrane. The NA protein, which possesses neuraminidase activity (and is the target of Tamiflu), is the third viral integral membrane glycoprotein component of the influenza virion envelope. Adapted from (5) with permission.

FIGURE 3. Schematic diagram of the hepatitis C virus multiplication cycle. Enveloped HCV virion particles are depicted as spheres. Following entry most probably by receptor-mediated endocytosis, uncoating results in the release of the positive-sense single-stranded RNA genome. The 5'-untranslated region includes an internal ribosome entry site (IRES) that directs cap-independent synthesis at the endoplasmic reticulum of a polyprotein of about 3000 amino acids that undergoes proteolytic processing to produce 10 viral proteins, some structural (core C, E1, E2, p7) and others nonstructural (NS2, NS3, NS4A, NS4B, NS5A, NS5B). In addition to its role as

mRNA, the positive-sense genome RNA also serves as the template for RNA replication in association with intracellular membranes catalyzed by viral RNA-dependent RNA polymerase (NS5B). Other components of the HCV replication complex include both viral proteins and cellular factors (4). The complementary minus-sense RNA produced then serves as the template for synthesis of positive-sense RNA that fulfills three functions, mRNA for translation, template for RNA replication, or progeny genome that undergoes encapsidation into new virions. Adapted from (6) with permission.





