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Introduction to Thematic Minireview Series: Understanding Human Immunodeficiency Virus-Host Interactions at the Biochemical Level*

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HIV continues to pose major global public health challenges. An estimated 30 million of the world's population are infected with HIV, and there is not yet an effective vaccine. HIV is a member of the lentivirus genus of the Retroviridae family of viruses. HIV possesses a dimeric, positive-sense, single-stranded RNA genome of ~9700 nucleotides contained within an ~120-nm diameter enveloped virion (1). Substantial knowledge has been gained over the past 3 decades about the molecular details of how the HIV virus multiplies, the mode of viral transmission, and the disease known as AIDS caused by HIV infection. Advances in the biochemical understanding of HIV led to the combination antiretroviral chemotherapy strategy with drugs that target different steps of the virus multiplication cycle, including viral entry, synthesis and subsequent integration of the DNA provirus, and processing of viral polyprotein precursors.

The main features of the HIV multiplication cycle are summarized by the schematic shown in Fig. 1. The virion envelope includes two viral glycoproteins, the surface gp120 and the transmembrane gp41. Following virion binding to cellular receptors, including the primary receptor CD4 surface protein found on T cells and macrophages, conformational changes occur in gp120, leading to interaction with a chemokine coreceptor and subsequent membrane fusion catalyzed by gp41. The viral nucleocapsid core is then released into the cytoplasm of the infected cells, where the virion-associated reverse transcriptase (RT)[2] and RNase H catalyze the reverse transcription of the plus-strand RNA genome to produce a double-stranded linear DNA provirus flanked by LTR structures at each end. Subsequent 3′-end processing of the proviral DNA and transport to the nucleus are followed by integration of the provirus into the host chromatin catalyzed by the viral integrase (IN) protein. Synthesis of 5′-capped and 3′-polyadenylated viral RNA transcripts is catalyzed by the cellular RNA polymerase II system. Full-length viral RNAs serve as mRNA templates during translation for synthesis of the Gag polyprotein precursor and, by a ribosome frameshift mechanism, the Gag-Pol fusion precursor. Spliced transcripts encode the envelope precursor gp160 (which gives rise to the gp120 and gp41 proteins) and six accessory gene products (Vif, Vpr, Vpu, Nef, Tat, and Rev) that affect transcription and RNA processing, as well as host responses to infection. The *pol* gene encodes the viral protease (PR) in addition to the RT, IN, and RNase H enzymatic activities. The Gag precursor undergoes proteolytic processing by the viral PR to produce the matrix, capsid, and nucleocapsid proteins during the process of assembly and release of progeny virions. Assembly of budding progeny virions occurs largely at the plasma membrane.

The first four minireviews in this thematic series concern biochemical and biophysical aspects of steps in the HIV multiplication process, beginning with the initiation of infection (2), followed by stages of macromolecular synthesis and processing (3–5). The last two minireviews focus on interactions between the host and the virus and the functional roles that microRNAs (6) and cellular innate immune response components (7) play in affecting viral replication.

In the first minireview, entitled "HIV Entry and Envelope Glycoprotein-mediated Fusion," Robert Blumenthal, Stewart Durell, and Mathias Viard, at the National Cancer Institute (Frederick, MD), consider new developments in both the biochemistry and structural biology of the HIV envelope-mediated fusion process (2). The authors provide a background of the virion envelope structure, with focus on the gp120/gp41 trimer and the structural domains of the gp120 and gp41 proteins. They then discuss what is known and unknown about the HIV envelope-mediated fusion process triggered by protein interactions and conformational changes that result in lipid rearrangements and merging of the lipid envelope of the virus with the host cell membrane as part of the process of the initiation of infection.

In the second minireview in this thematic series, entitled "Human Immunodeficiency Virus Reverse Transcriptase: 25 Years of Research, Drug Discovery, and Promise," Stuart F. J. Le Grice, at the Frederick National Laboratory for Cancer Research (Frederick, MD), summarizes progress in understanding gained at the biochemical and structural levels of the process of formation of the HIV double-stranded DNA provirus from the single-stranded RNA genome template catalyzed by the viral RT DNA polymerase and RNase H activities. This first step in macromolecular synthesis during the HIV multiplication cycle has proved to be an important drug target to therapeutically reduce viral load in infected individuals. The successful targeting of RT, the development of a number of RT inhibitors approved for clinical use, and efforts toward development of RNase H inhibitors are considered, as well as the mechanisms of action of the inhibitors.

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[2] The abbreviations used are: RT, reverse transcriptase; IN, integrase; PR, protease.

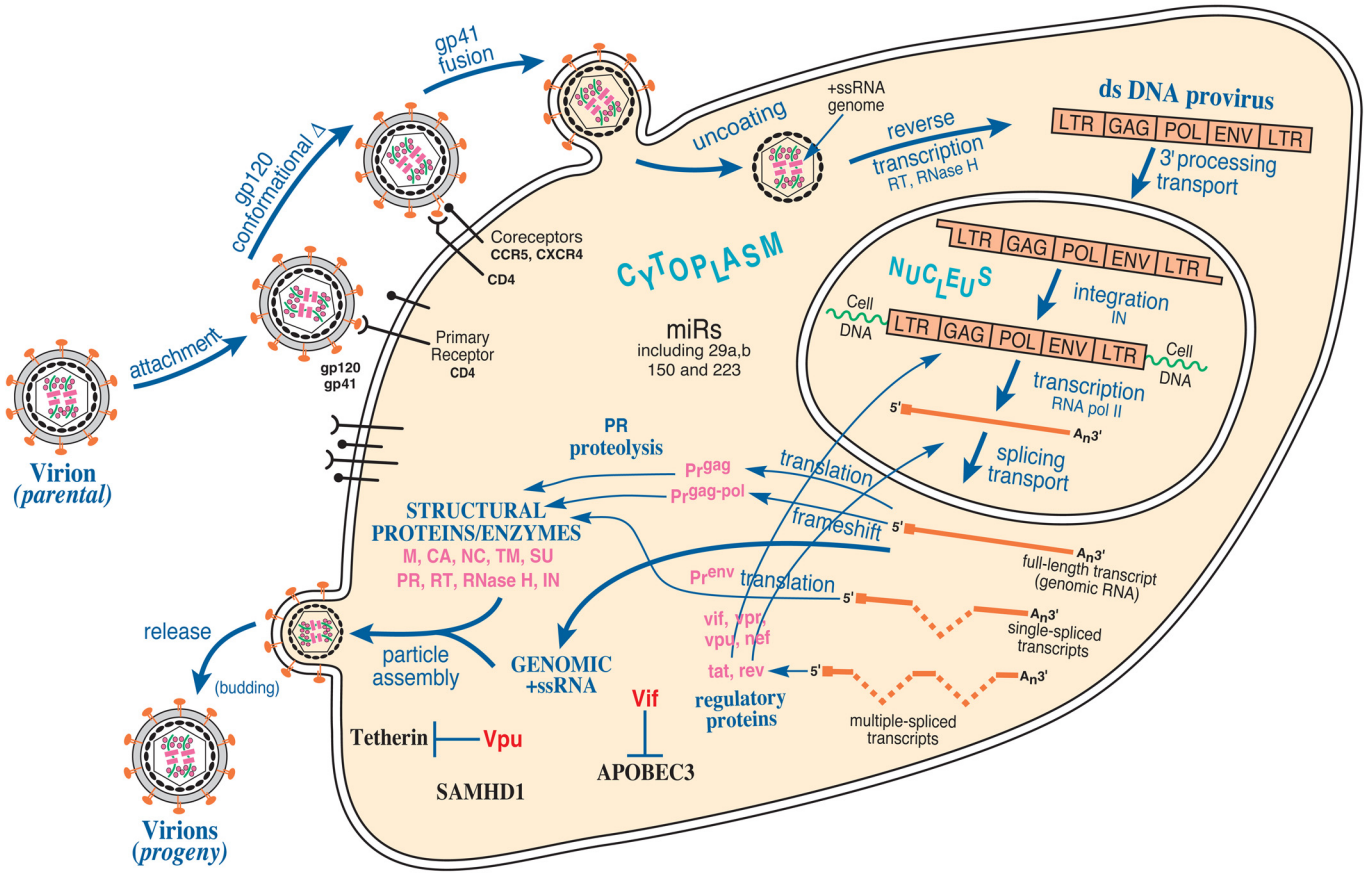

FIGURE 1. **Schematic diagram of the HIV multiplication cycle.** Enveloped HIV virion particles are depicted as *spheres*. Following entry by receptor-mediated fusion and partial uncoating of the viral nucleocapsid released into the cytoplasm, the double-stranded DNA provirus is synthesized from the positive-strand RNA genome by the virion-associated RT and RNase H activities. Proviral DNA is then imported into the nucleus and integrated into the genome of the host by a process catalyzed by the viral IN. Processed viral transcripts synthesized from the integrated proviral genome by the host RNA polymerase II system are transported to the cytoplasm, where they are translated to yield viral structural proteins and enzymes. Among the products are the polyprotein precursor that undergoes proteolytic processing, including that by the viral PR. Cellular components that affect the efficiency of production and release of infectious progeny virions from productively infected T cells include the host restriction factors APOBEC3, tetherin/BST-2, and SAMHD1, as well as microRNAs (*miRs*) including miR-29a,b, miR-150, and miR-223, implicated in the modulation of HIV replication. Accessory and regulatory viral proteins include the virion infectivity factor (Vif), which antagonizes members of the cellular APOBEC3 deaminase family, and viral protein U (Vpu), which impairs tetherin/BST-2 function. *M*, matrix; *CA*, capsid; *NC*, nucleocapsid; *TM*, transmembrane; *SU*, surface. This figure was adapted from Ref. 8.

The third minireview, written by Lavanya Krishnan and Alan Engelman at the Dana-Farber Cancer Institute and Harvard Medical School in Boston and entitled "Retroviral Integrase Proteins and HIV-1 DNA Integration," summarizes progress in understanding the mechanism of HIV DNA integration into host chromosomal DNA (4). The viral IN catalyzes both the processing of the proviral DNA to generate 3′-hydroxyl termini and the subsequent integration of the viral DNA into the cellular genome. The authors review the biochemical understanding of the nucleoprotein complexes that mediate integration, as well as progress in the development of antiviral agents that target IN-catalyzed integration.

In the fourth minireview, Sook-Kyung Lee, Marc Potempa, and Ronald Swanstrom, at the University of North Carolina in Chapel Hill, examine issues concerning the HIV protease, the role of protein processing and rearrangement in the assembly pathway of HIV virions, and the impact of protease inhibitor resistance on viral fitness and virion assembly. The Gag polyprotein precursor of virion structural proteins and the Gag-Pol precursor of the PR and the RT, RNase H, and IN enzymes are processed by a viral aspartic proteinase, which is a major target of antiviral inhibitors. What is known and what remains unresolved about proteolytic processing during the HIV particle assembly and budding process are considered, as well as the opportunity to develop inhibitors that affect these steps in multiplication.

The final two minireviews focus on the role that microRNAs and host innate immune products play in modulation of HIV infections. Zachary Klase, Laurent Houzet, and Kuan-Teh Jeang, at NIAID (Bethesda, MD), review our understanding of the functional roles of microRNAs in modulating the efficiency of HIV replication and also how HIV infection can alter the expression of cellular microRNAs. Reuben S. Harris and Judd F. Hultquist, at the University of Minnesota, and David T. Evans, at the New England Primate Research Center of Harvard Medical School, then examine mechanisms by which host innate antiviral immune responses function to modulate HIV multiplication and spread. Focus is placed on three strategies by which proteins that are inducible by interferon restrict HIV replication and the counterstrategies that HIV utilizes to impair

these innate immune restriction mechanisms. Some APOBEC3 family members, illustrated by APOBEC3G, catalyze C-to-U deamination of HIV first-strand cDNA, resulting in hypermutations, a process inhibited by the HIV Vif protein. The tetherin/BST-2 membrane protein tethers budding HIV virions to the cell surface, a process impaired by the HIV-1 Vpu protein.

Considerable progress has been made in understanding the fundamental roles that viral and cellular proteins play in determining the host susceptibility to viral infection and disease. Efforts to understand the genetic and molecular bases 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 scheme of HIV together with insights gained from atomic level structures of macromolecular components to develop new and improved antiviral treatments and preventative strategies.

REFERENCES

1. Knipe, D. M., Howley, P. M., Griffin, D. E., Lamb, R. A., Martin, M. A, Roizman, B., and Straus, S. E. (2007) *Fields Virology*, 5th Ed., Lippincott-Williams & Wilkins, Philadelphia
2. Blumenthal, R., Durell, S., and Viard, M. (2012) HIV entry and envelope glycoprotein-mediated fusion. *J. Biol. Chem.* **287,** 40841–40849
3. Le Grice, S. F. (2012) Human immunodeficiency virus reverse transcriptase: 25 years of research, drug discovery, and promise. *J. Biol. Chem.* **287,** 40850–40857
4. Krishnan, L., and Engelman, A. (2012) Retroviral integrase proteins and HIV-1 DNA integration. *J. Biol. Chem.* **287,** 40858–40866
5. Lee, S. K., Potempa, M., and Swanstrom, R. (2012) The choreography of HIV-1 proteolytic processing and virion assembly. *J. Biol. Chem.* **287,** 40867–40874
6. Klase, Z., Houzet, L., and Jeang, K. T. (2012) MicroRNAs and HIV-1: complex interactions. *J. Biol. Chem.* **287,** 40884–40890
7. Harris, R. S., Hultquist, J. F., and Evans, D. T. (2012) The restriction factors of human immunodeficiency virus. *J. Biol. Chem.* **287,** 40875–40883
8. Samuel, C. E. (2006) Virus-host interactions. *J. Biol. Chem.* **281,** 8305–8307