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Review

Newly identified host factors modulate HIV replication

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Contents

Just when basic research in HIV seemed to have ebbed, exciting new discoveries at steps of viral post-entry and exit from infected cells provide fundamental new insights into eukaryotic biology and innate antiviral defense mechanisms. These studies reveal an unexpected role for TRIM5α, new functions for RNA editing enzymes APOBEC3G and APOBEC3F as well as interesting twists in the formation of multivesicular bodies by Tsg101 and AIP1. By highlighting these steps, this review also describes blocks that restrict HIV replication in other species and prevent the development of new animal models of AIDS.

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The human immunodeficiency virus type 1 (HIV) is a lentivirus and is an example of "complex" retroviruses [1]. Compared to "simple" retroviruses, whose genomes encode only three polyprotein precursors, namely the group-specific antigen (Gag), polymerase (Pol), and envelope (Env), the HIV genome encodes several additional open reading frames (ORFs). They code for two regulatory proteins, the transcriptional transactivator (Tat) and the regulator of virion gene expression (Rev), as well as four accessory proteins, the "negative effector" (Nef), viral infectivity factor (Vif), and the viral proteins r (Vpr) and u (Vpu) [2].

Like other viruses, HIV must replicate by hijacking the cellular machinery to synthesize and assemble new virions. For example, for its exit from the cell, HIV has usurped the cellular endosomal sorting complexes required for transport (ESCRT) machinery, which is recruited by Gag and results in the exocytosis of virions from multivesicular bodies (MVBs) [3,4]. In addition, it must also counteract rather sophisticated host defense mechanisms. The identification of these factors has been long in coming. Recently, substantial post-entry blocks have been revealed. One of these blocks is caused by tripartite motif protein 5α (TRIM5α), which is overcome by Gag [5], and the other is caused by apolipoprotein B mRNA-editing enzyme catalytic-polypeptides 3G and 3F (APOBEC3G and APOBEC3F) [6–8], which are neutralized by Vif. What follows is a brief review of the viral replicative cycle, followed by highlights of these recent new developments.

1. Overview of HIV replicative cycle

HIV is an enveloped virus that enters the organism via mucous membranes or intravenously. Env consists of gp120 (SU, surface subunit) and gp41 (TM, transmembrane subunit). Dendritic cells play an important role in capturing and transporting the virus to lymphoid organs. They express dendritic cell-specific intracellular adhesion molecule 3 (ICAM-3)-grabbing integrin (DC-SIGN), which binds gp120 and stores viral particles in an infectious form [9]. gp120 then binds CD4 on the surface of macrophages and T lymphocytes [10], which is one of the receptors for HIV [11] (Fig. 1). Upon a conformational change in gp120 [12,13], Env interacts with the CC chemokine receptor 5 (CCR5: R5, macrophage tropic or non-syncytium inducing (NSI) strains) [14], or CxC chemokine receptor 4 (CXCR4: X4, T cell tropic or syncytium inducing (SI) strains) [15]. These interactions prompt a conformational change in gp41, which mediates the fusion between the virus and the host cell (reviewed in [16]). Once internalized, HIV is uncoated, and viral reverse transcriptase (RT) copies the genomic RNA into the double stranded cDNA. During this stage, HIV has to counteract two types of host factors that block retroviral infection: TRIM5α and APOBEC family members (see below). The completion of reverse transcription gives rise to the HIV pre-integration complex (PIC), which is composed of double-stranded viral cDNA, integrase (IN), matrix (MA), Vpr, RT, and the high-mobility group DNA-binding protein, HMGI(Y) [17]. The

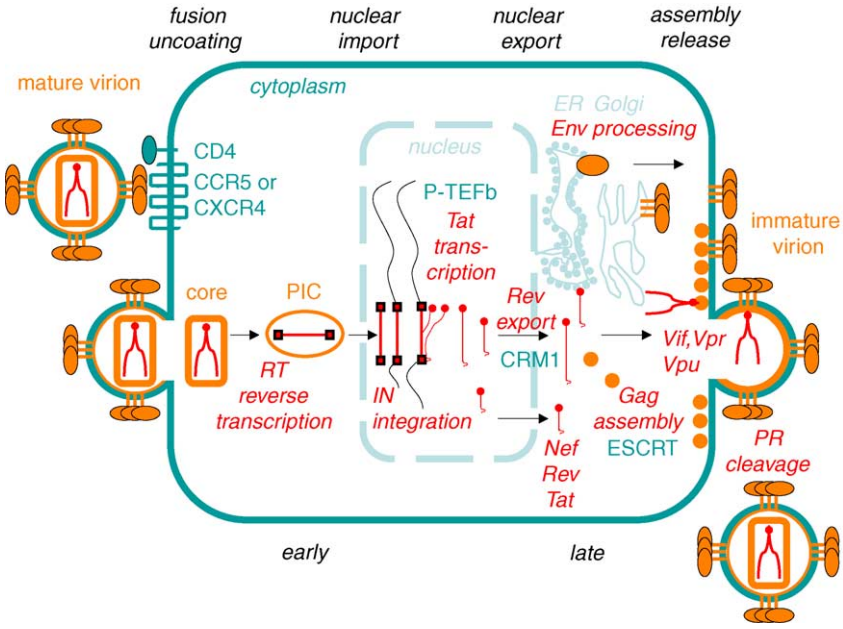

Fig. 1. The replicative cycle of HIV. Viral structural components, nucleic acids, RNA and DNA, and cellular components are represented in brown, red and green colors, respectively. Viral steps are described with red letters. Below or above them are presented cellular targets for these processes. Early and late phases denote steps before and after viral transcription, respectively. They are further subdivided into cytoplasmic and nuclear phases, as denoted above the schematic of the cell. Of viral transcripts, only unspliced genomic and singly spliced mRNA species require Rev, CRM1 and RanGTP for their export from the nucleus. These transcripts code for Gag, Pol and Env polyprotein precursors as well as Vif, Vpr and Vpu. Multiply spliced viral transcripts encoding Nef, Rev and Tat do not require Rev and appear early. After immature virions are released, PR cuts Gag and GagPol polyprotein precursors into their structural and enzymatic subunits.