HIV-1 assembly and maturation

Brief Review

A. G. Bukrinskaya

University Massachusetts Medical School, Program in Molecular Medicine, Worcester, Massachusetts, U.S.A.

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Summary. HIV-1 particles have been studied by structural and chemical approaches, however, the processes of assembly, budding and maturation are just beginning to be characterized, and molecular details of these processes remain poorly defined. This brief review summarizes some recent findings on the final steps of the HIV-1 life cycle and touches upon some unanswered questions, particularly regarding the processes involved in virus maturation and infectivity.

Introduction

The life cycle of Human immunodeficiency virus 1 (HIV-1) consists of sequential events which are regulated by both viral and cellular proteins. The late phase in the HIV-1 morphogenesis includes assembly of new viral particles, their release from the plasma membrane of the host cell and maturation coupled with infectious activity.

The Gag p55 precursor plays a central role in virus assembly. This protein is sufficient for production of viral particles in the absence of the other viral proteins [35], it is involved in the recruitment of viral proteins including Pol and Env and some cellular proteins involved in assembly and budding processes. Gag also interacts with viral genomic RNA forming intermediate assembly complexes and transports them to plasma membrane for encapsidation into viral particles [26, 30, 31, 98], most probably through interaction with the cytoskeleton of infected cells [7].

The structure of Gag p55 precursor

Gag p55 precursor is proteolytically cleaved by the virus-encoded protease, a product of the pol gene, leading to the production of mature Gag proteins.
The cleavage products from the N terminus are matrix p17, which coats the inner leaflet of the viral membrane; capsid p24, which forms a cone-shaped core that contains two copies of genomic viral RNA; p2 spacer protein followed by nucleocapsid p7, which is bound to genomic RNA; a spacer protein p1 and p6 (Fig. 1). Gag p55 contains three distinct functional protein domains involved in virus morphogenesis: the membrane-binding domain (M), the Gag-Gag interaction domain (I) and the late domain (L).

The M domain is located at the N terminus of MA and consists of a covalently attached myristic acid added posttranslationally to the amino terminus of the matrix sequence, as well as a number of basic residues. The myristic acid anchors Gag into the lipid bilayer while basic residues further stabilize Gag-membrane association through electrostatic interactions with the negatively charged phosphate groups.

The I domain is at the C terminus of CA and N terminus of NC, it contains multiple basic residues within the NC sequences. This portion of p55 is involved in multiple functions including Gag multimerization, RNA binding, reverse transcription and formation of preassembled virion complexes. The presence of two zinc binding motifs and a high content of basic residues in NC are important for RNA binding by this protein. This domain promotes Gag-Gag interaction followed by Gag multimerization [13, 16, 25, 78, 82]. The C terminal domain of CA (amino acids 150–231) is important for virus assembly and budding. A major homology region (MHR) within this domain is highly conserved among retroviral Gag proteins. Mutations in this region block virus assembly by preventing CA-CA interaction [76, 113].

The L domain is on the N terminus of p6 and assists in virus detachment from the cell surface by recruiting the cellular protein Tsg101 [15, 26, 27, 32].

**Virus assembly**

An essential function during viral assembly is to organize the viral RNA and associated enzymes for ordered disassembly and reverse transcription upon entry of host cell. The most important regions involved in assembly are the C terminal domain of CA as well as p1 and NC within the I domain [26, 37, 85, 105, 115].

The precise ordering of assembly steps has not been definitively determined, and multiple steps are likely to occur simultaneously. The assembly process can be artificially divided into the following steps: (1) Formation of Gag p55 complexes (Gag multimerization). (2) Binding of Gag p55 complexes to genomic viral RNA.