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<tr>
<td>Citation</td>
<td>ICR annual report (2000), 6: 42-43</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2000-03</td>
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<td>URL</td>
<td><a href="http://hdl.handle.net/2433/65228">http://hdl.handle.net/2433/65228</a></td>
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<td>Type</td>
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Nucleocytoplasmic Transport of Preintegration Complex and Viral mRNA in Retrovirus-Infected Cells

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Active transport of proteins and mRNAs between the nucleus and cytoplasm is a major process in eukaryotic cells. Recently, factors that recognize transport substrates and mediate nuclear import or export have been characterized, revealing interactions that target substrates to the nuclear pore complexes, through which translocation occurs. In the first half of the report, nuclear import of the human immunodeficiency virus 1 (HIV-1) preintegration complex (PIC) is discussed. The second half describes recent information on the mechanistic details of nuclear export of viral mRNA so-called Rev-dependent trans-activation of viral genes.

Keywords: Retrovirus / Viral integration / Rev-dependent trans-activation / Nuclear import / Nuclear export / Nucleocytoplasmic transporter

The ability of HIV-1 to transport its preintegration complex (PIC) into the nucleus of an infected cell during interphase is a unique feature (1). A basic-type nuclear localization signal (NLS) was identified in the N-terminal region of the HIV-1 matrix protein (MA) and was found to regulate viral nuclear import and infection. Genetic analysis also implicated viral protein Vpr in the process of nuclear import of the HIV-1 PIC. But this protein does not have a classical NLS, and its role in nuclear import remained unclear until recently.

Recent studies identified that Vpr controls nuclear import through an importin α-independent mechanism (1). This result was consistent with resistance of Vpr-regulated viral nuclear import to competition by NLS peptides. The binding site of Vpr on importin α does not appear to overlap with the NLS-binding sites. In fact, importin α, Vpr, and MA can assemble into a trimer. As a result of Vpr binding to importin α, the affinity of interaction between the NLS and importin α was increased approximately 10-fold. This mechanism may be instrumental in increasing the karyophilic potential of the HIV-1 PIC.

It appears, therefore, that nuclear import of the HIV-1 PIC is controlled by two viral proteins, Vpr and MA (Fig. 1). While MA contributes its NLS which connect the PIC to importin α and cellular import machinery, Vpr functions as an enhancer of the MA-importin α interaction. In addition, Vpr was found to bind nucleoporins and was suggested on these grounds to function as an importin β analog. Although this hypothesis is consistent with the role of Vpr in docking of the HIV-1 PIC to the nuclear envelope, it is hard to imagine that a small protein, such as Vpr (with a molecular mass of only 14 kDa), can perform the function of a 97-kDa importin β. We therefore favor the notion that the effects of Vpr are mediated through the importin α/β pathway. Inactivation of either partner in the HIV-1 nuclear import (i.e., MA, Vpr, or importin α/β) results in the loss of...
import function and virus inability to establish efficient infection in primary cells. These proteins, therefore, present an attractive target for development of novel anti-HIV therapeutics.

The molecular details behind CRM1-mediated Rev export are still ambiguous. Our studies have been focused on the assembly of the RRE RNA-Rev-CRM1-RanGTP complex in greater detail in vitro. CRM1 interacts directly with full-length Rev independently of the conserved leucine residues within the core of the NES and the presence of RanGTP. This Ran-independent interaction is LMB insensitive. In contrast, formation of the ternary Rev-CRM1-RanGTP complex is highly sensitive to NES mutations and is readily dissociated in vitro by LMB or by hydrolysis of Ran GTP.

Figure 1. A model of nuclear import of the HIV-1 PIC.

Figure 2. Mechanism of Rev-dependent nuclear export of viral mRNA.

References