

**Invited Review**

**The Interaction of HIV-1 with the Host Factors**

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**CONTENTS:**

- 1. Introduction
- 2. Cellular entry molecules
- 3. From the epidemiologic study
- 4. Restriction factors
- 5. Binding partners
- 6. Other cellular factors
- 7. Concluding remarks

**SUMMARY:** Human immunodeficiency virus type 1 (HIV-1) is a causative agent of acquired immunodeficiency syndrome (AIDS) in humans. In the last decade, the functions of HIV-1-encoded genes have been intensively studied. These studies have contributed to the development of the effective anti-AIDS drugs directing against the HIV-1-encoded enzymes, namely reverse transcriptase and protease. However, even the combination of these drugs is not sufficient enough to stop the progression of AIDS partly due to the emergence of drug-resistant HIV-1 mutants as well as the severe side effects. Understanding the molecular mechanisms by which cellular factors support the efficient replication of HIV-1 should contribute to develop means to control the progression of AIDS. This field is now expanding rapidly. Here we review the host factors involved in the replication of HIV-1 and highlight some findings that have a substantial impact on the retroviral research.

**1. Introduction**

After the discovery of human immunodeficiency virus type 1 (HIV-1) as the causative pathogen of acquired immunodeficiency syndrome (AIDS) in the early 1980s, thanks to the current molecular biological and virologic techniques, the development of the laboratory diagnosis, the anti-AIDS drugs, and vaccine have progressed in a substantial speed. However, the development of the effective therapeutic/preventive vaccine has been still on the struggle. Despite our efforts, the number of AIDS patients is increasing, which raises a worldwide socio-economic concern.

The hunting for the cellular factor that regulates the HIV-1 replication started soon after the characterization of the virus as summarized in Fig. 1. The molecular interaction between the host and HIV-1 is the key to understand the pathogenesis of HIV and to develop means to control HIV-1 replication. However, we still do not have the perfect picture of the precise molecular mechanisms of the life cycle of HIV-1, even it has a small genome of approximately 10 kbp encoding less than a dozen genes.

The field of the interaction between HIV-1 with host factors is currently expanding enormously (Table 1). In this review, we cast a light on some of the recently found host factors that directly or indirectly interact with HIV-1 to influ-

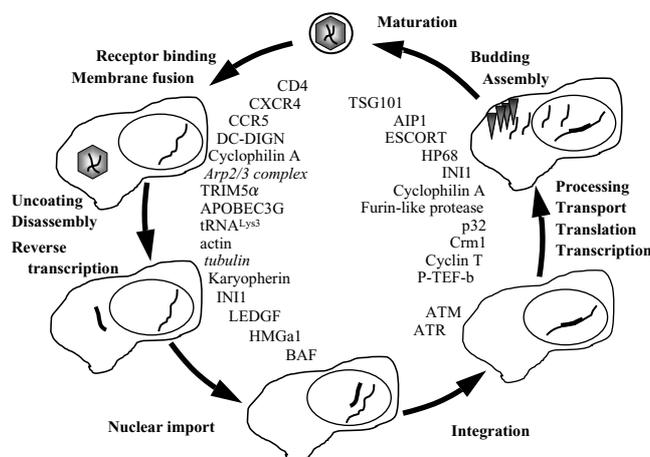


Fig. 1. The schematic representation of the replication cycle of HIV-1. Each step of the viral life cycle is indicated out of the replication circle in bold. Inside the circle, the major cellular factors involved in each step are shown. Factors affecting the HIV-1 replication via an indirect fashion are indicated in italic.

ence its replication. These factors called the attention of the general life scientists because they have deciphered the complex nature of the replication of HIV-1 as well as opened up the new research fields. To easy-to-update, it is helpful to visit the web resource NIAID HIV Protein Interaction Project that shows the comprehensive list of the cellular proteins which interact with HIV-1 (online; available from <http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/index.html>). We recommend to refer the textbooks and reviews for the further reading (1-4).

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Table 1. The major interaction between viral gene products and cellular factors

Viral protein	Cellular protein
<i>Gag</i>	
MA	Karyopherins
	Histidyl-tRNA synthetase-like (HO3)
	Calmodulin
	VAN/NAF1
CA	Cyclophilin A
	TRIM5 $\alpha$
NC	HP68/RNase L inhibitor
	Actin
p6	TSG101
	AIP1
	Nedd4
	Ubiquitin
<i>Pol</i>	
IN	INI1/hSNF5
	LEDGF/p75
	ATR
	ATM
	Karyopherins
	BAF
	XRCC5 (Ku autoantigen)
<i>Env</i>	
	CD4
	CXCR4
	CCR5
	DC-SIGN
<i>Nef</i>	
	PACS-1
	ASK1
	PAK
	PI3-kinase
	Ick
	VAN/NAF1
<i>Rev</i>	
	Crm1
	p32
<i>Tat</i>	Cyclin T1
<i>Vpr</i>	
	Karyopherins
	Uracil-DNA glycosylase
	Wee1
<i>Vif</i>	APOBEC3G

## 2. Cellular entry molecules

Until recently, the cellular entry molecules for HIV-1 were known to be the T cell surface marker CD4, one of the immunoglobulin superfamily, and the chemokine receptor CXCR4 or CCR5. More recently, a new member joined, a dendritic cell-specific ICAM-3 DC-SIGN (5,6). Not only through a cell free virus-mediated infection, HIV-1 propagates in vivo through a cell-to-cell transmission namely between the dendritic cell (DC) and CD4-positive T cell (7). HIV-1 seems to be internalized into the DC through interacting with DC-SIGN. The DC “holds” the infectious viruses in the intracellular compartment stably and, upon in contact with T cells, “passes” the viruses to T cells so that T cells are effectively infected with HIV-1. The viral transmission from DCs to T cells may partly explain the efficient and rapid establishment of HIV-1 infection upon the viral exposure. Many vaccine developers believe it unlikely that the neutralizing antibody against HIV-1 is able to perfectly protect individuals from the HIV-1 infection partly because the HIV-1’s quick hide in DCs where the antibodies can not reach the

target. Recently, the site of cell-to-cell contact, or the immunological synapse (even called the virological synapse), was visualized by the high resolution laser scanning microscopy. The detailed analysis revealed that the site of cell contact provides a unique environment where the viral receptors cluster such that the viral transmission takes place at a high efficiency (8,9). HIV-1 seems to take advantage of the immunological synapse formation between the DC and the T cell, which is crucial to maintain the immunological integrity. These findings further point the substantial significance of macrophages and DCs in the pathogenesis of AIDS (reviewed in [10]).

## 3. From the epidemiologic study

The epidemiologic observations disclosed the presence of the exposed-uninfected individuals or HIV-1-infected long-term non-progressors or slow progressors. The genetic analysis revealed that a certain genetic background seemed to confer these phenotypes (11). Through the survey of the genetic determinant that confers the resistance to the HIV-1 infection, a gene variant of CCR5 was found (12). The CCR5 $\Delta$ 32 was a truncated form of CCR5 that does not traffic to the cell surface, therefore does not serve as the viral receptor. The homozygote of CCR5 $\Delta$ 32 displays a strong resistance to HIV-1 suggesting that the functions of CCR5 are dispensable for the human well-being and, therefore, the anti-CCR5 drug is quite feasible. The presence of the HIV-1 infection-resistant individuals that are positive for the auto-antibody against CCR5 supports this idea.

The V64I polymorphism of CCR2 expresses the destabilized CCR2A isoform. It also protects cells from HIV-1 infection by interacting with and therefore downregulating expression of CCR5 at the cell surface (12,13). The V64I CCR2 variant is one of the good examples that affects the life cycle of HIV-1 negatively without binding to HIV-1 gene products directly. In contrast to the CCR5 $\Delta$ 32, the frequency of V64I CCR2 allele in Asian population is higher than Caucasians. The cohort study also revealed that the HLA A2/A28 confers the resistance to HIV-1 partly because of the efficient presentation of HIV-1 peptides on the HLA molecule to potentiate the immune response towards HIV-1 infected cells (14). On the other hand, there are some genetic backgrounds that promote the AIDS disease progression such as CCR5P1 (15). On the age of the highly active anti-retroviral therapy (HAART), it is quite helpful to conduct similar genetic analyses to provide data on the genetic variants that influence the effectiveness of anti-AIDS drugs (e.g., cytochrome P450 and P-glycoprotein). These clinico-genetic studies are very powerful, yet, need to be evaluated by independent cohort studies or laboratory studies (reviewed in [16]).

## 4. Restriction factors

Certain cell lines are hardly infected with HIV-1 even the receptors were introduced into them. This is the restriction of viral infection in the broad sense. The restriction occurs at any levels of the viral life cycle. In the field of retrovirology, the inhibition of viral entry is historically termed as the restriction of viral infection in the narrow sense (reviewed in [17,18]). It suggests either the presence of the factor that block the viral replication or the absence of the one that supports the viral replication.

*Tat*, an essential viral transcriptional activator from the viral promoter LTR, binds to the TAR element of the viral RNA and recruits the basal transcriptional machinery close to the transcription start site in order to enhance the transcription of viral RNA from LTR. The viral RNA undergoes the splicing to become mRNA for the most of the genes. However, the viral intact RNA genome has to be present in the cytoplasm to assemble a replication-competent progeny virus. HIV-1 encodes *rev* that is also essential for the viral replication, which transports the unspliced viral RNA from the nucleus to the cytoplasm by binding to the *rev*-responsive element (RRE) on the viral RNA as well as RRE-bearing singly-spliced transcripts. These systems work only when a help from the host cell is provided. The murine cells do not support HIV-1 replication because both the murine cyclin T1 and Crm1 that are unable to support *Tat* and *Rev*, respectively, to function (19,20). Surprisingly, the murine cyclin T1 differs from human's by a single amino acid. More recently, another mechanism that inhibits HIV-1 replication in the murine cells is reported in which a member of the murine spliceosome complex p32, different from the human's by a single amino acid similar to cyclin T1, is shown to be unable to support the function of *Rev* (21). However, being these factors provided, HIV-1 does not replicate fully in the transgenic mouse, suggesting that there are other points of restriction in mouse cells.

Some primate cells (i.e., cells from the rhesus macaque) are known to be resistant to the HIV-1 infection. The protection occurs mostly at the level of reverse transcription. Recently, a cellular protein TRIM5 $\alpha$  was identified as the responsible factor for this restriction (22). The human counterpart of TRIM5  $\alpha$  does not have the restriction activity towards HIV-1. The amino acid homology between human and monkey TRIM5  $\alpha$  was approximately 90%, not as high between rat and human p32. Similarly, cyclophilin A is able to modulate the cellular sensitivity toward being infected with HIV-1, suggesting that the cyclophilin A is also involved in the restriction of retroviral infection (23). Not only in the entry process, cyclophilin A also plays a role in the late phase of HIV-1's life cycle, namely the assembly.

On the virus side, the capsid (CA) is the major determinant of the susceptibility to these restriction factors although direct interaction between TRIM5 $\alpha$  and CA is not evidenced. The molecular mechanism by which these factors inhibit the reverse transcription through interacting with CA remains largely unclear. Characterizing the restriction factors and the mechanism of their actions holds the key to understand the uncoating/disassembly processes. The inter-species variation of these factors may shed lights on the theory behind the co-evolution of retrovirus and the host. In addition, it will give us some clue to build a small animal model of AIDS.

## 5. Binding partners

The hunting for the cellular protein binding to the viral gene products associates with the historically-known peculiar behaviors of HIV-1. The p6 domain within *gag* is called the late domain because the lack of p6 leads to the failure of the late step of viral life cycle – budding (Fig. 2, reviewed in [24]). A p6 binding protein, TSG-101, was found and shown to play a critical role in the budding of HIV-1 (25,26). The TSG-101 recognizes the PTAP motif within the p6 and recruits the pinch-off machinery endosome-associated complex required for transport, ESCORT, to the site of budding.

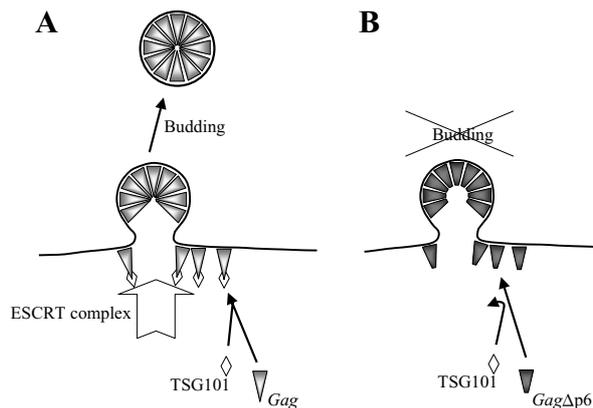


Fig. 2. The role of TSG101 in the viral budding. (A) The TSG101 (diamond) binds to the PTAP motif within the p6 domain of Gag (triangle) and recruits ESCRT complex (big arrow) to drive the budding process. (B) The Gag lacking the late domain is able to assemble at the cell surface. However, the viral particle attaches to the cell surface via a stalk-like structure and hardly buds. Expressing the wild-type Gag in conjunction with the downregulation of TSG101 by the siRNA technology or the expression of the dominant-negative TSG101 displays the similar phenotype.

The HIV-1 lacking the functional late domain shows the dramatic decrease in the viral production. The defective virus accumulates at the cell surface but seems unable to pinch-off. The isolation of TSG-101 as the p6 binder beautifully deciphers how the late domain works. Recent data further demonstrated that the multifunctional protein AIP1/ALIX also binds to p6 and plays a similar role to TSG101, recruiting the ESCORTIII complex at the cell surface to promote the pinch-off process (27,28). The ESCORT complex has been identified as the vesicular sorting machinery. The endosomal vesicle buds and fuses to the membrane organelles like the enveloped virus buds and infects cells. Since many retroviruses share the similar motifs in the late domain of *gag*, the involvement of the vesicular sorting pathway in the Gag trafficking and budding of retroviruses shall be emphasized (reviewed in [29]).

The *Vif*, a viral accessory protein, was long known to be required for virus to replicate in certain cells. The *vif*-deficient virus has a poor infectivity when the virus is produced by a "non-permissive" cell. The *Vif*-binding factor apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G (APOBEC3G) now explains how it happens (Fig. 3, reviewed in [30]). APOBEC3G was originally identified as CEM15 that was able to convert the "permissive" cells to "non-permissive" (31). APOBEC3G has an ability to deaminate the C to yield the U on the minus-strand reverse-transcribed viral genome. It ends up with the G-to-A conversion on the plus-strand of the genome. The G-to-A hypermutation damages the genomic integrity and subsequently the virus may fail to replicate. Also it may lead to the degradation of the genome by unknown mechanisms in the infected cells. The *Vif* seems to protect the viral genome by binding to APOBEC3G to induce the proteasome-dependent degradation and, therefore, blocking it from being incorporated into the viral particles in the virus producing cells. This revealed another class of the innate immunity that also works on the hepadna virus (e.g., hepatitis B virus) in which the replication depends on the reverse transcription (32).

The lentivirus can infect non-dividing cells whereas the oncoretrovirus cannot. It involves the active transport of

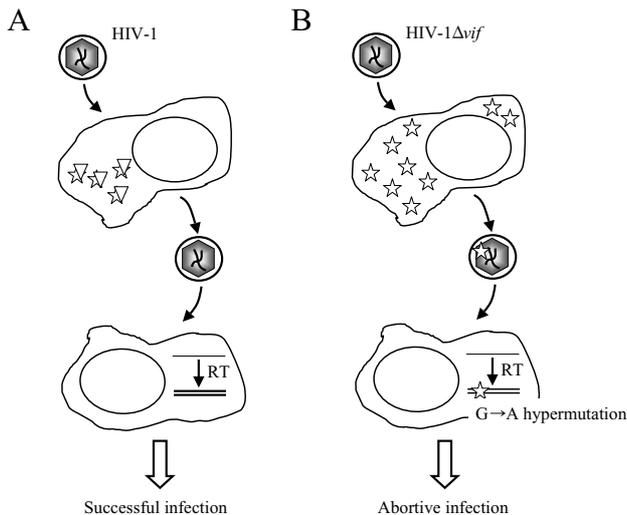


Fig. 3. The *Vif*-APOBEC3G interaction. (A) The *Vif* (triangle) binds to APOBEC3G (star) and induces the degradation of APOBEC3G that preventing APOBEC3G from being incorporated into the viral particles. (B) The *vif*-deficient virus does not block the APOBEC3G incorporation into the viral particles, which allows the C-to-U conversion on the minus-strand cDNA synthesis leading to the G-to-A hypermutation upon the plus-strand DNA synthesis by the viral reverse transcriptase. This results in the abortive infection. However, the *vif*-deficient virus is able to replicate in “permissive cells” lacking the APOBEC3G.

the genetic material from the cytoplasm to the nucleus. Viral proteins including matrix (MA), *Vpr*, and integrase play the major role in the active nuclear import of the preintegration complex (PIC). Among the binding partners to these viral proteins, the integrase interactor 1 INI1/hSNF5, a component of SNF-SWI complex, calls attention lately. INI1 was originally found by the yeast two-hybrid system (33) and was shown to facilitate the nuclear import of the PIC as well as the integration reaction *per se*. Not only the early phase of the viral life cycle, the INI1's binding to the integrase is shown to be required for late events in the viral life cycle via yet unknown mechanisms (34). It is also intriguing that a single host factor plays multiple roles in the life cycle of HIV-1. Such a protein should be the premier target for the anti-AIDS drug discovery. The human lens epithelium-derived growth factor/transcription co-activator p75 (LEDGF/p75) also binds to integrase and contributes to the nuclear import of the PIC (35). The fact that INI1 and LEDGF specifically interact with lentiviral integrases, not with oncoretroviral integrases, suggests their functional significance in the lentiviral active nuclear transport (36,37).

## 6. Other cellular factors

A cellular microenvironment seems to play a role in the life cycle of HIV-1. The detergent-insoluble membrane fraction, so called the lipid raft, is a membrane microdomain rich in cholesterol. The efficient budding of HIV-1 seems to depend on the lipid raft because the removal of cholesterol resulted in the marked reduction of viral production (38). The myristoylated proteins such as *Gag* preferentially accumulate at the lipid raft. This may help the viral assembly and budding at the lipid raft. Indeed, the lipid content of the viral envelope is reported to be similar to that of the lipid raft. Also, the lipid raft may play a role in the viral infection process. The CD4 molecule tends to localize on the lipid raft.

This may provide a microenvironment where the multiple virus-cell interaction takes place rapidly when HIV-1 encounters the target cell. It is interesting if a specific membrane lipid constituent can play an active role in the life cycle of HIV-1.

Not only the cellular proteins directly bind to HIV-1-encoded proteins, proteins incorporated into the viral particles potentially play roles in the HIV-1 replication (Table 2, reviewed in [39]). The cyclophilin A is one of the examples that was originally isolated as a *Gag* binder but later found in the virion. Some of the described factors (e.g., TSG101 and INI1) are also found in the purified viral preparations, which strengthen the idea that they are indeed the binders to the viral proteins. It is however difficult to determine the specificity and the functional significance because many of the factors (e.g., actin and EF-1a) are abundant in the cytoplasm.

The immunological interaction between HIV-1 and the host

Table 2. The major cellular proteins incorporated into the virion

In the viral particle	
Actin	
Cofilin	
Cyclophilin A	
Elongation factor 1 $\alpha$ (EF-1 $\alpha$ )	
Ezrin	
GAPDH	
Heat shock protein 70 (HSP70)	
HS-1	
INI1/hSNF5	
Lck	
Moesin	
Phosphatidylethanolamine-binding protein	
TSG-101	
Ubiquitin	
VAN/NAF1	
On the envelope	
$\beta$ 2-microglobulin	
CD molecules	
HLA class I/II molecules	
ICAM-1,2,3	
LFA-1,2	

Table 3. The major soluble factors affecting the replication of HIV-1

$\alpha$ -1-antitrypsin
$\alpha$ -defensins 1,2,3
CD8-positive cell product modifying anti-thrombin III
D Lactalbumin
Granulocyte-macrophage colony-stimulating factor (GM-CSF)
Interferon $\alpha$ , $\beta$ , $\gamma$ (IFN $\alpha$ , $\beta$ , $\gamma$ )
Interleukins (IL)
Leukemia inhibitory factor (LIF)
Lymphotoxin
Macrophage colony-stimulating factor (M-CSF)
Macrophage-derived chemokine (MDC)
Monocyte chemotactic protein-2 (MCP-2)
Natural killer cell enhancing factor A, B (NFEF)
RANTES, macrophage inflammatory protein- $\alpha$ , $\beta$ (MIP-1 $\alpha$ , $\beta$ )
RNase
Secretory leukocyte protease inhibitor (SLPI)
Stromal cell-derived factor-1 (SDF-1)
Transforming growth factor- $\beta$ (TGF- $\beta$ )
Tumor necrosis factor- $\alpha$ , $\beta$ (TNF- $\alpha$ , $\beta$ )

is another viewpoint. HIV-1 is able to escape from the host immunity because of its high self-mutagenicity. Beside that, HIV-1 targets cellular factors to protect the infected cells from the host immune system. *Nef* down-modulates expression of MHC class I molecule through interacting with PACS-1, the regulatory protein that controls the membrane protein trafficking, thereby the cellular immunity can not eliminate the HIV-1-infected cells effectively (40,41). Some cellular soluble factors are known to either positively or negatively affect the HIV-1 replication (Table 3, reviewed in [42-44]). For example, the tumor necrosis factor-alpha (TNF- $\alpha$ ) induces the HIV-1 replication. It does so via activating the nuclear factor-kappa B (NF- $\kappa$ B) that translocates into the nucleus and stimulates the transcription from HIV-1's LTR. Identifying the soluble factors and understanding how they function are also attractive subjects because the study links directly to the understanding of HIV-1 pathogenesis and the chemotherapy against AIDS.

### 7. Concluding remarks

The HAART appears successful in controlling the AIDS disease progression. However, we can not be optimistic because the drug-resistant viruses have already emerged making the HAART being ineffective and the adverse effects of anti-AIDS drugs are considerable. Because the mutation rate of cellular genome is far lower than the viral genome, developing a new class of anti-retroviral drugs that target a cellular factor is one of the options. It is no doubt that characterizing cellular factors that interact with HIV-1 contributes to not only the understanding of HIV-1 virology but also the advancement of cell biology. It ultimately provides novel targets for the antiviral intervention.

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