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Molecular Crosstalk between HIV-1 Integration and Host Proteins – Implications for Therapeutics

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1. Introduction

The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS), which is one of the leading causes of infectious disease-related mortality worldwide (UNAIDS, 2010). An HIV infection is a chronic disease. While there is no regimen to eradicate the HIV from an infected person, there are more than 20 drugs approved for the treatment of HIV infection, the majority of which target viral reverse transcriptase (RT) and protease (PR). In addition to the development of chemotherapeutic agents such as RT and PR inhibitors (RTI and PI), the advent of the combination therapy of different classes of antiviral drugs, the highly active antiretroviral therapy (HAART), has brought a significant decrease in the morbidity and mortality associated with HIV infections for over a decade. Nowadays, HAART is a standard treatment for HIV infection and AIDS (Palella et al., 1998). However, despite the successful suppression of HIV RNA detected in plasma over prolonged periods of time and a dramatic decrease in patient mortality, HAART is still facing problems, including the emergence of drug resistant viruses and serious side effects in treated individuals. In addition, current treatments only suppress the HIV replication, and eradication of virus from the body cannot be achieved. Therefore, considerable efforts have been made to develop novel anti-HIV drugs that exhibit entirely distinct mechanisms of action. To date, three additional classes of inhibitors have been approved by the US Food and Drug Administration (FDA) as oral anti-HIV agents: a fusion inhibitor blocking the fusion step of the viral and cellular membranes, an entry inhibitor targeting coreceptor binding by the virus, and an integrase (IN) inhibitor blocking the integration step of viral DNA.

Although many promising inhibitors against HIV replication have arisen over recent years, the current approach in anti-HIV chemotherapy is mostly based on competitive agents targeting the active sites of viral enzymes or the binding pockets of cellular receptors. One of the drawbacks of existing drugs, particularly the antivirals exhibiting allosteric effects, is the rapid emergence of mutant HIV strains resistant to the drugs due to the innately high mutational rate in of viral enzymes. On the other hand, it is becoming increasingly clear that protein-protein interactions (PPIs) could also serve as attractive targets of drugs for human

therapeutics (Cochran, 2001; Arkin & Wells, 2004; Pagliaro et al., 2004; Ryan & Matthews, 2005). PPIs are central to most biological processes including virus infection and many human diseases are attributed to aberrant PPIs in cells. Not surprisingly, there are a number of interactions between viral and cellular proteins involved in all stages of HIV replication (Goff, 2007; Arhel & Kirchhoff, 2010) and recent evidence demonstrates that these PPIs can be potential targets for the development of a novel class of anti-HIV drugs termed small molecule protein-protein interaction inhibitors (SMPPIIs) (Busschots et al., 2009; Christ et al., 2010). Although a challenging approach, an advantage of SMPPIIs in HIV chemotherapy is that the mutation rate in the PPI interface is considerably low compared to the mutation rate in the active sites of viral enzymes, particularly for the host proteins. Therefore, SMPPIIs targeting HIV and cellular proteins hold great promise with regards to preventing the emergence of drug resistant viruses in administrated persons. Thus, understanding the molecular basis of virus-host interactions should provide new insights into alternative strategies for the treatment of HIV infection and AIDS. In this chapter, we focus our attention on integration, an essential step in the HIV replication cycle catalyzed by IN, and review the current knowledge of molecular interactions between IN and cellular cofactors.

2. HIV infection - from cell entry to integration

HIV belongs to lentivirus, a separate genus of the *Retroviridae* family, and it can be further divided into antigenically distinct members, HIV-1 and HIV-2 (Levy, 2009). In the case of HIV-1, the enveloped viral particle contains two copies of positive sense RNA of 9.7-kb in length which encode two regulatory (*tat* and *rev*) and four accessory (*vpr*, *vif*, *vpu*, and *nef*) genes in addition to the characteristic retroviral *gag*, *pol*, and *env* genes. These protein-coding regions are flanked by the 5′ and 3′ long terminal repeat (LTR) sequences that are required for reverse transcription, integration, and gene expression steps.

HIV-1 infection begins with the specific binding of the viral envelope (Env) glycoprotein gp120 to the CD4 receptor molecule on the surface of target cells. This interaction triggers a conformational change in the gp120 that facilitates subsequent binding to a coreceptor. As for the coreceptor, most of HIV-1 strains use either the α-chemokine receptor CXCR4 or the β-chemokine receptor CCR5. The formation of the gp120, CD4, and coreceptor complex then induces refolding of the gp41 subunit of Env, allowing the fusion of the HIV-1 and cell membranes.

After penetrating the cell membrane, the HIV-1 core particle, which contains genomic RNA and the proteins needed to establish an infection, is first released into the cytoplasm where it then undergoes the uncoating process. Although this uncoating is defined as the loss of HIV-1 capsid (CA) protein after the entry step, the nature and timing of the uncoating process is poorly understood (Arhel, 2010). The formation of the reverse transcription complex (RTC), in which reverse transcription from viral RNA to DNA takes place, accompanies the uncoating of infecting virion core (Warrilow et al., 2009; Arhel, 2010). Currently, little is known about the components of the RTC, although several studies have shown that matrix (MA), Vpr, RT, and IN are contained in the HIV-1 RTC (Fassati & Goff, 2001; McDonald et al., 2002; Iordanskiy et al., 2006). CA is only found in the HIV-1 RTC very early after cell entry but it becomes barely detectable at later times (Fassati & Goff, 2001). Interestingly, in the case of the Moloney murine leukemia virus (MoMLV), CA has shown to be stably associated with the RTC even at the later stages (Fassati & Goff, 1999). These pieces

of evidence suggest that dissociation of CA from the HIV-1 core proceeds rapidly as compared to other retroviruses.

The newly synthesized full-length viral DNA remains associated with viral and cellular proteins in a high molecular weight nucleoprotein complex. This integration-competent nucleoprotein complex is called the preintegration complex (PIC) (Goff, 2001; Suzuki & Craigie, 2007). Although the structure of the PIC is also poorly understood, a number of studies using immunoprecipitation assays have revealed that HIV-1 PICs retain many components of the RTC (Farnet & Haseltine, 1990, 1991; Bukrinsky et al., 1993; Gallay et al., 1995; Farnet & Bushman, 1997; Miller et al., 1997; Iordanskiy et al., 2006). Additionally, several cellular proteins have been shown to associate with the HIV-1 PIC (Farnet & Bushman, 1997; Li et al., 2001; Lin & Engelman, 2003; Llano et al., 2004). A defining characteristic of the PIC is its full fidelity to the authentic integration reaction. When purified IN alone is used for an *in vitro* integration reaction, most of the products are the result of the integration of only a single viral DNA end into one strand of target DNA (Bushman & Craigie, 1991; Turlure et al., 2004). In contrast, a PIC isolated from virus-infected cells is able to efficiently insert both viral DNA ends into the target DNA in a pairwise manner *in vitro*, and this is a hallmark of the integration reaction *in vivo* (Farnet & Haseltine, 1990; Chen & Engelman, 2001). Another striking feature of PICs is that suicidal intramolecular integration into its own viral DNA, a reaction termed autointegration, is precluded and it has been reported that cellular proteins are implicated in this barrier to autointegration in HIV-1 PICs (Yan et al., 2009).

The PIC formed in the cytoplasm also serves as the vehicle for the translocation of its genetic cargo (i.e. viral DNA) into the nucleus. Once the PIC reaches the nuclear periphery it must gain entry into the nucleus for integration. In non-dividing cells such as macrophages, the PIC must permeate the barrier of an intact nuclear envelope. This is particularly important as macrophages are a major target of HIV-1 infection. How is the PIC to cross the nuclear envelope? Passive diffusion cannot explain the translocation because the size of the HIV-1 PIC exceeds the allowances of a nuclear pore. Molecules up to 9 nm in diameter can pass through the nuclear pore complex by diffusion (Mattaj & Englmeier, 1998), but the HIV-1 PIC is estimated to be more than 50 nm in diameter (Miller et al., 1997; McDonald et al., 2002; Nermut & Fassati, 2003). Thus, active transport mechanisms are necessary for this task; one widely accepted model is that the HIV-1 PIC possesses karyophilic signals and many viral and cellular proteins have been proposed as the karyophilic proteins that cause the nucleoprotein complex to be imported into the nucleus (Fouchier & Malim, 1999; Fassati, 2006; Luban, 2008). Although the actual participation of these proteins in the nuclear import of HIV-1 PICs is a matter of debate (Fassati, 2006; Suzuki & Craigie, 2007), this property is important in the pathogenesis of HIV-1 (Blankson et al., 2002). Additionally, the ability of HIV-1 to infect non-dividing cells makes the virus an attractive candidate for a gene transfer vector (Verma & Somia, 1997).

In the nucleus, chromosomal DNA serves as the target for integration. Integration is essential in the replication of all retroviruses including HIV-1, and this step as well as reverse transcription are hallmarks of retroviral infection. The integration process occurs in three well-characterized reactions referred to as 3'-end processing, DNA strand transfer and gap repair (described below). IN catalyzes the first two reactions whereas the last reaction is likely carried out by yet-to-be identified cellular enzymes (Turlure et al., 2004). Once integrated, the viral DNA, called the provirus, is acted upon by cellular transcription factors to express viral genes and can persist indefinitely in the host cell genome (Fig. 1).

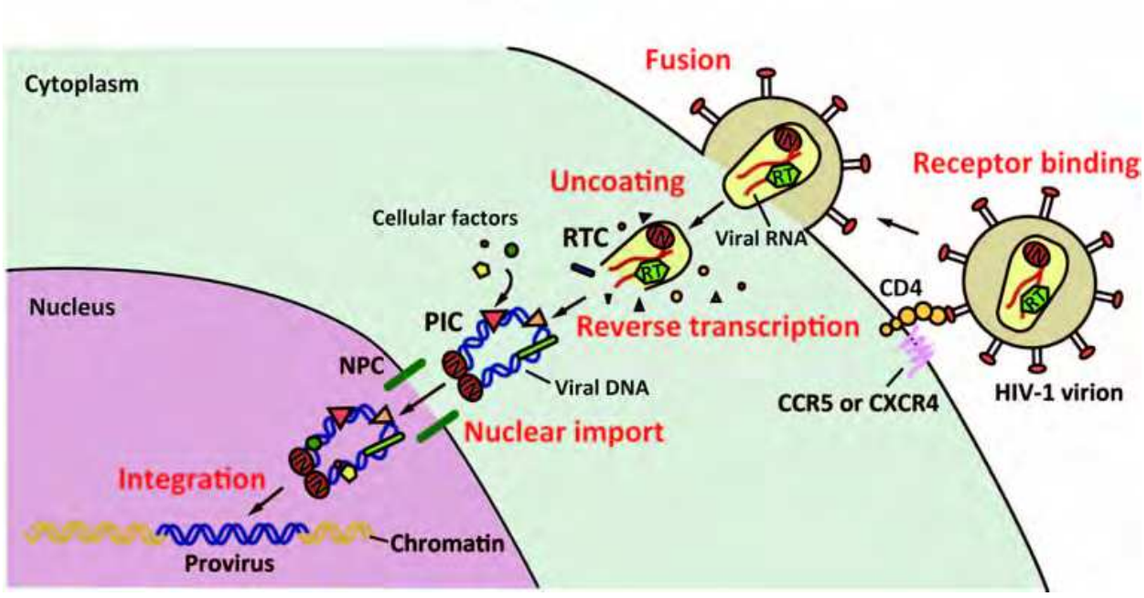

Fig. 1. Early stages of HIV-1 replication. HIV-1 infection begins with the binding of Env to the CD4 receptor and a coreceptor (CCR5 or CXCR4), allowing fusion between the cellular and viral membranes. After entry, the viral nucleoprotein core containing the genomic RNA is released into cytoplasm and reverse transcription takes place in a nucleoprotein complex called the RTC. The resulting full-length viral DNA remains associated with viral and cellular proteins in an integration-competent nucleoprotein complex termed the PIC. This PIC mediates integration of viral DNA into chromatin. Integrated viral DNA, called the provirus, then acts as a transcription template for the synthesis of viral RNAs.

3. HIV-1 IN and the mechanism of integration

3.1 IN structure

During HIV-1 replication, IN is expressed from the provirus as the C-terminal part of a 160-kDa Gag-Pol polyprotein and it is incorporated into nascent virions. Following the budding and release of viral particles from infected cells, viral PR cleaves the Gag-Pol precursor protein to generate the mature form of IN (Swanstrom & Wills, 1997). In the HIV-1 genome, Gag (a precursor for structural proteins such as MA, CA and nucleocapsid [NC]) and Pol (a precursor for enzymes such as PR, RT and IN) are encoded by overlapping open reading frames (ORFs), and the Gag-Pol precursor is generated by ribosomal frameshifting during translation of the *gag* gene. This translation mechanism results in the synthesis of Gag-Pol at a 20-fold lower level than Gag's in HIV-1 infected cells (Jacks et al., 1988). Consequently, only 50 to 100 molecules of IN are contained in a viral particle. Although the production of Gag protein has been reported to suffice for generation of virus-like particles (VLP) (Mergener et al., 1992), incorporation and processing of the Gag-Pol protein is required for the formation of infectious HIV-1 virions (Swanstrom & Wills, 1997; Wu et al., 1997).

HIV-1 IN is a 32-kDa protein that consists of three structurally and functionally distinct domains called the N-terminal domain (NTD), the catalytic core domain (CCD), and the C-terminal domain (CTD) (Fig. 2A) (Lewinski & Bushman, 2005). The structures of these individual domains have been determined by X-ray crystallography or NMR (Craigie, 2001; Vandegraaff & Engelman, 2007). The CCD is highly conserved amongst retroviral INs and

contains a triad of conserved amino acids comprising of Asp64, Asp116, and Glu152 and this is termed the D,D-35-E motif. By coordinating divalent metal ions such as Mg^{2+} to this motif, the CCD domain plays a key role during the integration reaction (Lewinski & Bushman, 2005). This domain is dimeric in solution and the crystal structure of the dimer shows that the CCD domain consists of a five-stranded β-sheet and six α-helices. This structure is also found in many nucleotidyl transferases including RNase H, bacterial Mu, and the Argonaute protein of the RNA-induced silencing complex (RISC). Hence, IN belongs to the superfamily of polynucleotidyltransferases (Vandegraaff & Engelman, 2007).
A well-conserved motif is also found in the NTD, which comprises two His and two Cys residues (HHCC motif). This domain contains a bundle of three α-helices, and the HHCC motif stabilizes the helices by coordinating Zn^{2+}. Mutation studies of the NTD have indicated that the HHCC motif contributes to the multimerization and catalytic function of HIV-1 IN (Lewinski & Bushman, 2005).
In contrast to the NTD and CCD, the CTD is the least conserved domain of retroviral INs. Although the functional role of the CTD for catalysis is less clear, this domain exhibits strong and non-specific DNA-binding activity *in vitro*. The isolated CTD forms dimers in solution, and its monomer has an all β-strand SH3-type fold (Lewinski & Bushman, 2005).

3.2 Integration reaction

The chemical mechanism of the integration catalyzed by HIV-1 IN has been elucidated by *in vitro* biochemical studies using recombinant IN protein and oligonucleotide DNA substrates (Craigie, 2001; Lewinski & Bushman, 2005; Vandegraaff & Engelman, 2007). This reaction proceeds with well-defined 3′ processing and strand transfer steps (Fig. 2B). In the 3′ processing step, IN specifically recognizes the viral attachment (*att*) sites on the 5′ and 3′ LTRs where it removes two nucleotides from each of the 3′ ends of the viral DNA to expose a recessed hydroxyl immediately following a CA dinucleotide that is conserved among retroviruses and many transposons. Water serves as the nucleophile this cleavage of viral DNA. Next, in the strand transfer step, the exposed hydroxyl groups attack a pair of phosphodiester bonds on opposite strands of the target DNA, causing the viral DNA termini to be covalently linked to the protruding 5′ phosphoryl ends of the target DNA. Since the cleavage sites on the opposite strands of target DNA are separated by 5 bp, HIV-1 integration generates a five-base duplication flanking the provirus. Stereochemical analysis has revealed that these reactions occur by single-step transesterification mechanism (Engelman et al., 1991).
The 3′ processing and strand transfer steps are reproducible *in vitro* using recombinant IN and DNA substrates, indicating that IN alone is sufficient to carry out the DNA breakage and joining reactions. However, these events yield short staggered DNA breaks at the points of joining, and so in virus-infected cells the mispaired 5′ viral DNA ends must be excised and the resulting nicks filled in order to produce the provirus (gap repair step). However, this final step is likely carried out by yet-to-be identified cellular enzymes and the molecular mechanisms involved in this reaction have not yet been elucidated (Smith & Daniel, 2006; Yoder et al., 2006; Turlure et al., 2004).

4. Cellular proteins interacting with HIV-1 IN

Although the enzymatic activities of HIV-1 IN in the integration reaction have been clearly defined by *in vitro* biochemical studies, numerous genetic analysis of HIV-1 DNA have

demonstrated that mutations in the *IN* gene, including deletion mutants, influence many other stages of viral replication in addition to integration. This pleiotropic effect of IN is characterized by defects in uncoating, reverse transcription, nuclear import, viral gene expression, virion precursor protein processing, and virion morphology (Shin et al., 1994; Engelman et al., 1995; Masuda et al., 1995; Bukovsky & Gottlinger, 1996; Leavitt et al., 1996; Nakamura et al., 1997; Engelman, 1999; Tsurutani et al., 2000; Lu et al., 2004; Dar et al., 2009; Briones et al., 2010). However, the mechanisms for these pleiotropic effects of the *IN* gene are still poorly understood.

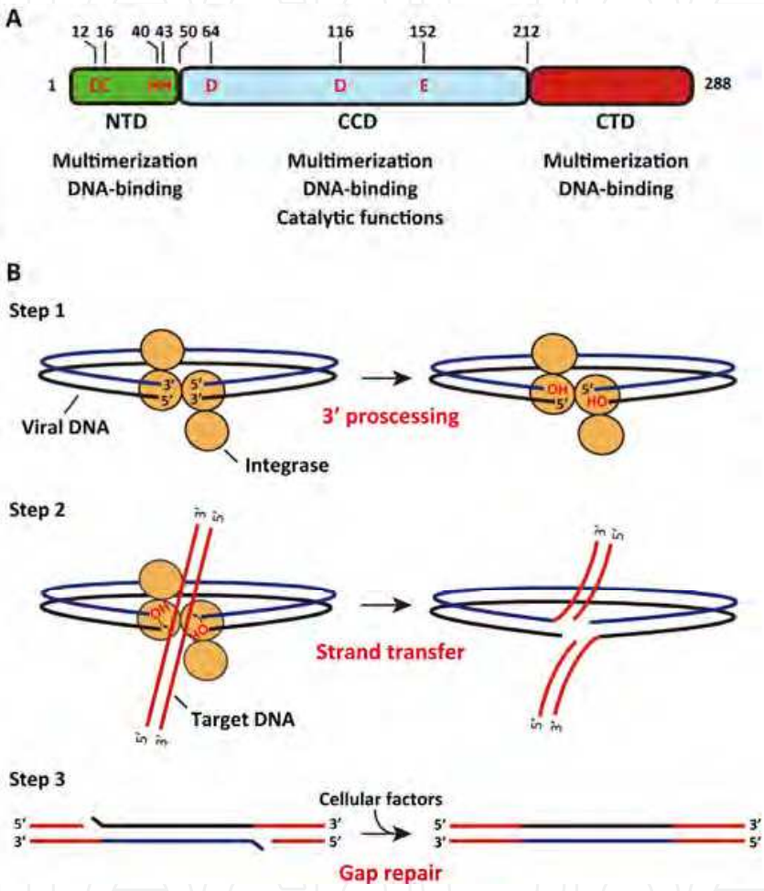

Fig. 2. HIV-1 integration reaction. (A) Domain organization of HIV-1 IN. Retroviral IN , including HIV-1 IN, consists of the N-terminal domain (NTD), catalytic core domain (CCD), and C-terminal domain (CTD). Highly concerved aspartic (D) and glutamic acid (E) residues are found in the CCD, forming the catalytic centre in IN (D,D-35-E motif). Likewise, the NTD contains a well-conserved motif that is formed from two histidine and two cystein residues (HHCC motif) while the CTD is the least conserved of the retroviral INs domains. (B) Mechanism of DNA integration. IN recognizes both ends of the viral DNA and removes two nucleotides from each of the ends (3' processing). This reaction takes place in the cytoplasm. After entering the nucleus and binding to chromosomal DNA, IN cleaves the target DNA in a staggered fashion via the exposed hydroxyl groups (OH) on the viral DNA ends, the viral DNA termini are then joined to the cuts (strand transfer step). Finally, the resulting nicks at the viral-target DNA junction are repaired by cellular enzymes to complete the integration process (gap repair step).

Meanwhile, a number of cellular proteins have been identified as binding partners for HIV-1 IN (Turlure et al., 2004; Al-Mawsawi & Neamati, 2007; Ao et al., 2007; Christ et al., 2008; Woodward et al., 2009; Ao et al., 2010). Some of these cellular interactors have been reported to assist in HIV-1 integration in infected cells (Turlure et al., 2004). However, other cellular partners for HIV-1 IN appear to have functional roles in steps other than the integration process including reverse transcription, nuclear import, and infectious particle production (Yung et al., 2001; Hamamoto et al., 2006; Al-Mawsawi & Ao et al., 2007; Mousnier et al., 2007; Neamati, 2007; Christ et al., 2008; Ao et al., 2010). These pieces of evidence suggests that PPIs between IN and its cellular partner could be the molecular basis for the pleiotropic effects that have been observed in genetic studies using HIV-1 with mutant IN.
Below, we summarize the current knowledge of the HIV-1 IN-binding cellular proteins and their possible roles in virus replication.

4.1 Cellular interactors affecting on integration step

So far, identification of HIV-1 IN cofactors has mostly been conducted by using yeast two-hybrid screenings or co-immunoprecipitation assays (Turlure et al., 2004). Integrase interactor 1 (INI1) was the first IN-binding protein identified by the yeast two-hybrid screening (Kalpana et al., 1994). INI1 is the human homologue of yeast SNF5, a core subunit of the ATP-dependent SWI/SNF chromatin-remodeling complex (Wang et al., 1996). Thus, INI1 is also known as hSNF5. By exposing transcriptionally active regions of chromatin, SNF5 regulates the expression of numerous genes in eukaryotic cells (Carlson & Laurent, 1994). INI1/hSNF5 is a 385 amino acid protein that is composed of three conserved domains including two direct imperfect repeat (Rpt) regions (Rpt1 and Rpt2) and a C-terminal coiled-coil domain referred to as the homology region III (HRIII) (Morozov et al., 1998). A yeast two-hybrid assay has revealed that the Rpt1 is necessary for binding to HIV-1 IN (Morozov et al., 1998).
In an early study using recombinant HIV-1 IN, INI1/hSNF5 was found to stimulate the integration reaction *in vitro* (Kalpana et al., 1994). However, when the minimal IN-binding domain of INI1/hSNF5, including the Rpt1 region (residues 183-294) termed S6, was co-transfected with HIV-1 proviral DNA in HEK293 cells, a 10,000-fold reduction in virus production from the transfected cells was observed (Yung et al., 2001). Moreover, expression of the S6 fragment in Jurkat T cells protected the cells against HIV-1 replication (Yung et al., 2001). Although this inhibitory effect was not detected in full-length INI1/hSNF5, the WT INI1/hSNF5 has been shown to be incorporated into virions during virus production (Yung et al., 2001; Yung et al., 2004). Given the recent report that depletion of endogenous INI1/hSNF5 did not affect the transduction efficiency of an HIV-1-based vector, this suggests that INI1/hSNF5 is likely implicated in post-integration steps, rather than the integration step as we shall see below, particularly in HIV-1 production (Ariumi et al., 2006).
In terms of integration cofactors, lens epithelium-derived growth factor (LEDGF) is the first host protein whose role has been most clearly elucidated (Engelman & Cherepanov, 2008). LEDGF, a transcriptional regulator that belongs to the hepatoma-derived growth factor (HDGF) related protein (HRP) family, was identified as an IN-binding protein as a result of co-immunoprecipitation analysis using FLAG-tagged HIV-1 IN (Cherepanov et al., 2003). LEDGF is a 530 amino acid protein that consists of several functional domains (Fig. 3A) (Engelman & Cherepanov, 2008). The N-terminal 92 amino acid region is termed the PWWP (Pro-Trp-Trp-Pro) domain. The PWWP domain is conserved amongst the HRP family

proteins and is thought to function as a protein-protein interaction domain and/or DNA-binding domain (Stec et al., 2000; Qiu et al., 2002). LEDGF also includes three segments of polar amino acids called CR (charged region) domains, and a putative nuclear localization signal (NLS) and dual copies of the AT-hook DNA-binding motif can be identified in the N-terminal half of the protein. In addition, a limited proteolysis analysis of recombinant LEGFP has revealed an evolutionarily conserved domain at the C terminus, which mediates the interaction with HIV-1 IN (integrase-binding domain: IBD) (Cherepanov et al., 2004). The IBD is a compact right-handed bundle composed of five α helices (Cherepanov et al., 2005b). As for HIV-1 IN, CCD has been identified as the main determinant for interactions with LEDGF (Fig. 3A) (Maertens et al., 2003; Cherepanov et al., 2005a).

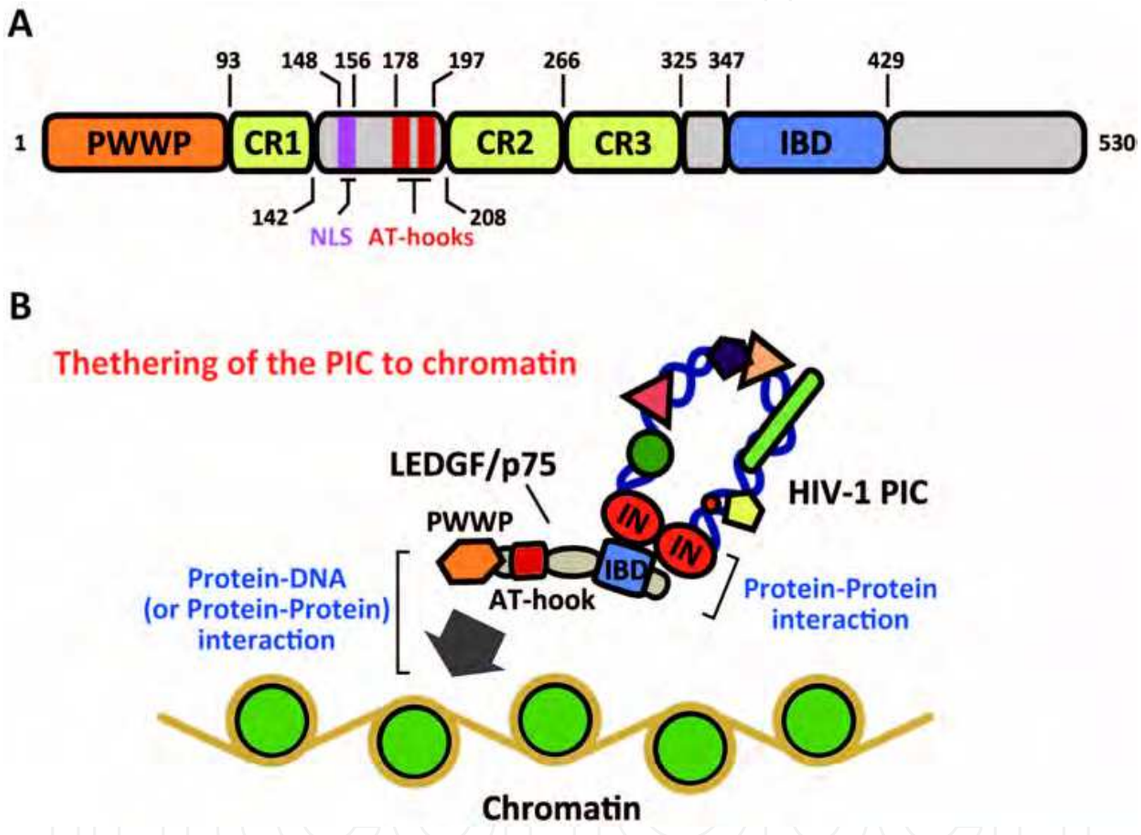

Fig. 3. Function of LEDGF in HIV-1 integration. (A) Domain structure of LEDGF. LEDGF is a 530 amino acid protein containing the PWWP domain, CR domains, a putative NLS, and dual copies of the AT-hook DNA-binding motif. Interaction of HIV-1 IN and LEDGF occurs between the CCD of IN and the C-terminal IBD of LEDGF, and this has been demonstrated to be critical for enhancement of the intgration reaction *in vitro* and *in vivo*. (B) LEDGF-mediated tethering of the HIV-1 PIC to chromain. The most widely accepted model of LEDGF function in HIV-1 infection is that LEDGF serves as an adaptor molecule to anchor the PIC to chromain via i) protein-protein interaction between IN and LEDGF and ii) subsequent protein-DNA interaction between LEDGF and chromatin. This thethering function may also regulate integraton-site selection of the HIV-1 PICs in virus-infected cells.

Early works using recombinant proteins have shown that LEDGF is able to stimulate the integration activity of the HIV-1 IN *in vitro* (Cherepanov et al., 2003, 2004). Furthermore, LEDGF associates with HIV-1 PICs (Llano et al., 2004). While these studies have raised the possibility that LEDGF might be implicated in the integration reaction of HIV-1 infection, subsequent *in vivo* studies using RNA interference reported that depletion of endogenous LEDGF resulted in only a modest effect or none at all on the replication efficiency of HIV-1 (Llano et al., 2004; Vandegraaff et al., 2006; Zielske & Stevenson, 2006). However, if residual expression of LEDGF is sufficient to complement the activity of HIV-1 IN in virus-infected cells, the results obtained by experiments using RNA interference-based knockdown assays might downplay the contribution of LEDGF to HIV-1 replication. Indeed, a significant reduction of HIV-1 infection was observed in human $CD4^+$ T cells in which there was a more complete knockdown of endogenous LEDGF (Llano et al., 2006a), and in mouse embryo fibroblasts (MEFs) derived from LEDGF knockout mice (Marshall et al., 2007; Shun et al., 2007), indicating a crucial role of LEDGF in virus replication. These genetic knockdown and knockout studies have revealed that the defect in HIV-1 replication in the absence of LEDGF clearly occurred at the DNA integration step (Llano et al., 2006a; Marshall et al., 2007; Shun et al., 2007). How is LEDGF involved in the integration process of HIV-1? Several lines of evidence have demonstrated that although *in vitro* integration by recombinant IN or PIC derived from HIV-1-infected cells occurs almost randomly, *in vivo* integration sites of HIV-1 are enriched with active transcription units (TUs) (Bushman et al., 2005). Considering the fact that the N-terminal PWWP domain/AT-hook motifs mediate chromatin-binding of LEDGF (Llano et al., 2006b; Turlure et al., 2006) and are also required for HIV-1 infection as much as the IBD (Llano et al., 2006a; Shun et al., 2007), the simplest model would be that LEDGF functions as a molecular adaptor for tethering HIV-1 IN within the PIC to chromatin, thereby promoting the integration process (Fig. 3B). Since LEDGF is a transcriptional coactivator, it would be plausible that the distribution of LEDGF on certain regions of chromatin is a primary determinant for the integration site specificity of HIV-1 (De Rijck et al., 2010). Indeed, genome-wide studies analyzing integration sites in HIV-1-infected cells have shown that a significant reduction in the frequency of integration into TUs was observed in LEDGF knockdown and knockout cells (Ciuffi et al., 2005; Marshall et al., 2007; Shun et al., 2007).

Posttranslational modifications of HIV-1 IN by cellular enzymes have also been reported to be implicated in integration. p300, a histone acetyltransferase (HAT), was first identified as a cellular protein that directly binds to HIV-1 IN *in vitro* and in human cells (Cereseto et al., 2005). HATs are known as enzymes that catalyze the transfer of acetyl groups from acetyl coenzyme A (acetyl-CoA) to specific lysine residues within the N-terminal tails of nucleosomal histones. This histone acetylation leads to chromatin decondensation and transcriptional activation (Roth et al., 2001). In addition to histones, HATs are able to acetylate other proteins including transcription factors. *In vitro* analysis using recombinant proteins showed that p300 can also acetylate three specific lysines (Lys264, Lys266, and Lys273) in the C-terminus of HIV-1 IN (Cereseto et al., 2005). Interestingly, the acetylation increased IN binding to LTR DNA its catalysis of the strand transfer reaction *in vitro* (Cereseto et al., 2005). Because HIV-1 harbouring mutations in the Lys264, Lys266, and Lys273 of IN exhibited replication defect at the integration step, these results suggest that acetylation of IN is important for efficient integration during HIV-1 infection (Cereseto et al., 2005). A recent study from the same group showed that another HAT, GCN5, was also able to mediate the acetylation of HIV-1 IN, and provirus formation was inefficient in GCN5-

depleted cells (Terreni et al., 2010). However, it should be noted that the role of acetylation of IN in HIV-1 replication remains controversial (Topper et al., 2007; Vandegraaff & Engelman, 2007).

Another type of posttranslational modification of IN that regulates HIV-1 infection has also been demonstrated. The c-Jun NH_2-terminal kinase (JNK), a member of mitogen-activated protein kinase (MAPK) family, is reported to phosphorylate a highly conserved serine residue (Ser57) in the CCD of HIV-1 IN. This phosphorylated IN is, in turn, recognized by the cellular peptidyl-prolyl *cis-trans* isomerase Pin1, and this association with Pin1 induces a conformational change in HIV-1 IN, eventually resulting in an increase in IN stability (Manganaro et al., 2010). Intriguingly, expression of JNK is very low in resting $CD4^+$ T cells, which are resistant to the establishment of productive infection by HIV-1, but not in activated cells permissive to HIV-1 infection. Hence, JNK and Pin1 may collaborate to increase the permissivity of T lymphocytes to HIV-1 via the phosphorylation and subsequent stabilization of IN (Manganaro et al., 2010).

Several other cellular proteins including uracil DNA glycosylase (UDG), heat-shock protein (HSP) 60, Rad18, and *Polycomb* group protein EED (embryonic ectoderm development) have also been found to interact with HIV-1 IN (Willetts et al., 1999; Parissi et al., 2001; Mulder et al., 2002; Violot et al., 2003), and some of them have been shown to stimulate *in vitro* integration activity of recombinant IN (Parissi et al., 2001; Violot et al., 2003). Yet, the contributions of these cellular interactors in HIV-1 integration and infection remain unclear (Turlure et al., 2004).

4.2 Cellular interactor affecting on reverse transcription step

It has been demonstrated that a specific interaction occurs between the HIV-1 IN and RT (Wu et al., 1999; Zhu et al., 2004), and that IN stimulates RT-catalyzed early synthesis of viral DNA *in vitro* (Dobard et al., 2007). This suggests that interaction between IN and RT has a functional consequence during the reverse transcription step of HIV-1 infection. Supporting the role of IN in viral DNA synthesis, a cellular binding protein for IN has been implicated in the reverse transcription of HIV-1. Gemin2 is a component of the survival of motor neurons (SMN) complex that is essential for the biogenesis of spliceosomal small nuclear ribonucleoproteins (snRNPs). The SMN complex, which is composed of an SMN protein and 7 additional proteins (Gemin2-8), recognizes specific sequences and structures of small nuclear RNAs and serves as an assembly complex for snRNP formation (Paushkin et al., 2002). A yeast two-hybrid screening identified Gemin2 as a novel interactor of HIV-1 IN (Hamamoto et al., 2006). This interaction involves the CTD alongside partial contribution from the CCD of HIV-1 IN (Hamamoto et al., 2006). Although Gemin2 was found in the HIV-1 PIC, knockdown experiments using small interfering RNA (siRNA) revealed that depletion of endogenous Gemin2 significantly reduced HIV-1 infectivity in human primary monocyte-derived macrophage (MDM), and importantly, the replication defect was observed at the early reverse transcription step during virus replication (Hamamoto et al., 2006). Moreover, a recent study shows that viral DNA synthesis by RT is augmented by IN in a Gemin2-dependent manner *in vitro* (Nishitsuji et al., 2009). These results suggest that the concerted action of IN and Gemin2 enhances the RT-catalyzed reverse transcription step in HIV-1 infection.

4.3 Cellular interactors affecting on nuclear import step

As mentioned above, a striking feature of HIV-1 is its ability to infect non-dividing cells. The nuclear envelope is intact in the non-dividing cells, and the HIV-1 PIC must cross this

nuclear envelope to integrate viral DNA into chromosomal DNA. Therefore, it is believed that the HIV-1 PIC carries karyophilic signals that cause it to be transported into the nucleus through nuclear pore complexes (NPCs) (Suzuki & Craigie, 2007). HIV-1 IN has been implicated as a karyophilic protein that facilitates the nuclear import of the PICs (Ikeda et al., 2004). Although many studies using reporter proteins have shown that HIV-1 IN accumulates in the nucleus (Petit et al., 1999; Pluymers et al., 1999; Ikeda et al., 2004), recent evidences suggest that IN may lack a transferable NLS and that the accumulation of HIV-1 IN may be attributed to its interactions with the cellular karyophilic protein(s) (Devroe et al., 2003; Llano et al., 2004).

Shortly after its identification as an interactor of HIV-1 IN, LEDGF was proposed as the karyophilic factor (Maertens et al., 2003). A siRNA-mediated knockdown experiment showed that depletion of endogenous LEDGF abolished nuclear accumulation of HIV-1 IN in HeLa cells (Maertens et al., 2003). Because the LEDGF is the cellular component of HIV-1 PICs (Llano et al., 2004), this suggests that LEDGF is the nuclear import factor directing IN and viral DNA into the nucleus (Maertens et al., 2003). However, this overplays the role of LEDGF in HIV-1 replication; replication defect of HIV-1 in LEDGF knockdown and knockout cells was not observed at the step of nuclear import of the PIC, as measured by the formation of a circular ligation product of viral DNA in the nucleus (Llano et al., 2006a; Shun et al., 2007). Thus, LEDGF should contribute to the stable tethering of IN and viral DNA (i.e. the PIC) to chromatin, thereby regulating integration efficiency and integration-site selection of HIV-1 (Fig. 3B) (Engelman & Cherepanov, 2008).

Translocation of proteins (cargo molecule) across the NPC requires specific transport receptors. Importin is one of the best-studied receptors for nuclear translocation. Importin contains two subunits, importin α and importin β. The NLS of a cargo molecule is first recognized by importin α, and after binding to importin β, the cargo-receptor complex is targeted to the NPC via direct association of importin β with components of the NPC called nucleoporin (NUP) (Mattaj & Englmeier, 1998). To date, several importins have been reported to interact with HIV-1 IN (Krishnan et al., 2010). By employing the *in vitro* nuclear import assay, importin 7, a member of importin β family acting as an import receptor for ribosomal proteins and histone H1, was shown to mediate nuclear import of the HIV-1 PICs (Fassati et al., 2003). Although HIV-1 IN was found to interact with importin 7 through the CTD (Ao et al., 2007), the functional role of this cellular protein in the nuclear entry of the PIC remains a matter of debate (Zielske & Stevenson, 2005).

Another member of the importin β family, transportin 3 (TNPO3/transportin-SR2), has also been identified by yeast two-hybrid screening as an HIV-1 IN-binding protein that directs the PICs to the nucleus (Christ et al., 2008). The requirement of TNPO3 in HIV-1 replication was confirmed by studies using siRNA-mediated knockdown (Brass et al., 2008; Konig et al., 2008; Krishnan et al., 2010). However, a recent study reveals that CA, but not IN, determines the TNPO3 dependency during HIV-1 replication (Krishnan et al., 2010). Additionally, later studies disclosed that the different cellular proteins regulating nucleocytoplasmic trafficking, importin α3 and NUP153, also interact with HIV-1 IN (Woodward et al., 2009; Ao et al., 2010). Understanding how the HIV-1 PIC crosses the intact nuclear envelope in non-dividing cells is one of the most fascinating areas in retroviral research. Further experiments will be therefore required to unveil the role of IN and its cellular cofactors in the active transport of the HIV-1 PIC into the nucleus (Suzuki & Craigie 2007).

4.4 Cellular interactors affecting on postintegration steps

Following integration, the provirus serves as a template for viral gene expression. During this postintegration process, disassembly of IN from the integrated viral DNA is a prerequisite for efficient transcription (Yoder & Bushman, 2000). It is well known that when HIV-1 IN is solely expressed in mammalian cells it undergoes proteasome-mediated degradation via ubiquitination (Mulder & Muesing, 2000). Although the function of this ubiquitin-mediated degradation of IN in HIV-1 replication remains unclear, one ubiquitination pathway has been suggested to participate in the gene expression step of HIV-1 replication through the degradation of IN (Mousnier et al., 2007). von Hippel-Lindau-binding protein 1 (VBP1) was identified as a cellular partner for HIV-1 IN by yeast two-hybrid screening. VBP1, also known as a subunit of the prefoldin chaperone, associates with the substrate recognition component of the cullin2-based von Hippel-Lindau (Cul2/VHL) ubiquitin ligase complex. Co-immunoprecipitation assays showed that HIV-1 IN bound both VBP1 and pVHL, and this IN-pVHL interaction was reduced by siRNA-mediated knockdown of endogenous VBP1 expression (Mousnier et al., 2007). Intriguingly, the depletion of VBP1 by siRNA had a negative impact on the transcriptional activity of integrated HIV-1 DNA without affecting provirus formation. Additionally, the specific knockdown of components of the Cul2/VHL ubiquitin ligase complex, including VBP1, resulted in a slower degradation and a decreased ubiquitination of HIV-1 IN as observed in pVHL deficient cells, indicating that Cul2/VHL ubiquitin ligase is responsible for the proteasomal degradation of IN (Mousnier et al., 2007). This study suggests that the recruitment of Cul2/VHL ubiquitin ligation complex by VBP1-IN interaction may play a pivotal role in degradation of IN, leading to efficient transition from integration to viral gene expression during HIV-1 infection.

Recently, a different class of ubiquitin ligase was found to interact with HIV-1 IN (Yamamoto et al., 2011). By employing a tandem affinity purification (TAP) procedure combined with mass spectrometry (MS) analysis, we have identified Huwe1 (HECT, UBA, and WWE domain containing 1), a HECT (homologous to E6-AP carboxyl terminus)-type E3 ubiquitin ligase, as a novel cellular interactor of MoMLV IN. Interestingly, Huwe1 also interacts with HIV-1 IN, and the binding was mediated through the CCD of IN and a wide-segment of Huwe1 (Fig. 4A). Because Huwe1 was associated with the PICs in immunoprecipitation assays, this ubiquitin ligase was expected to have a role in the integration process. However, when endogenous Huwe1 was depleted from a human T cell line by RNA interference technique, comparable levels of reverse transcription, integration, and gene expression were observed in HIV-1-infected knockdown and control cells. On the other hand, the knockdown experiment revealed that the infectivity of HIV-1 virions released from Huwe1-depleted T cells was significantly augmented compared to the virions produced from control cells, suggesting that Huwe1 has a negative impact on the production of infectious virions during HIV-1 replication (Yamamoto et al., 2011).

One question to be pondered is how the IN-binding protein Huwe1 modulates HIV-1 infectivity. IN is expressed as the C-terminal part of the Gag-Pol protein that is required for the formation of infectious virions during retroviral replication (Swanstrom & Wills, 1997). Further analysis showed that Huwe1 also associates with the HIV-1 Gag-Pol polyprotein in a C-terminal IN domain dependent manner (Yamamoto et al., 2011). Given that incorporation of Huwe1 into HIV-1 virions was not detected, one possibility would be that Huwe1 blocks the proper intracellular localization of the Gag-Pol precursor. It has been well demonstrated that during HIV-1 particle assembly, viral structural proteins, including Gag-

Pol, are taken up by the detergent-resistant membrane (DRM) fraction, the so called lipid raft, which is characterized by its insolubility against non-ionic detergents such as NP-40 (Halwani et al., 2003; Ono, 2010). In contrast, Huwe1 was distributed in a NP-40-soluble (non-DRM) fraction (Yamamoto et al., 2011). Thus, Gag-Pol precursor protein may be sequestered by Huwe1 present in the non-DRM domains of the cytoplasm through the IN region, resulting in interference of proper localization of Gag-Pol to the lipid raft where assembly of infectious virions is meant to take place (Fig. 4B, left).

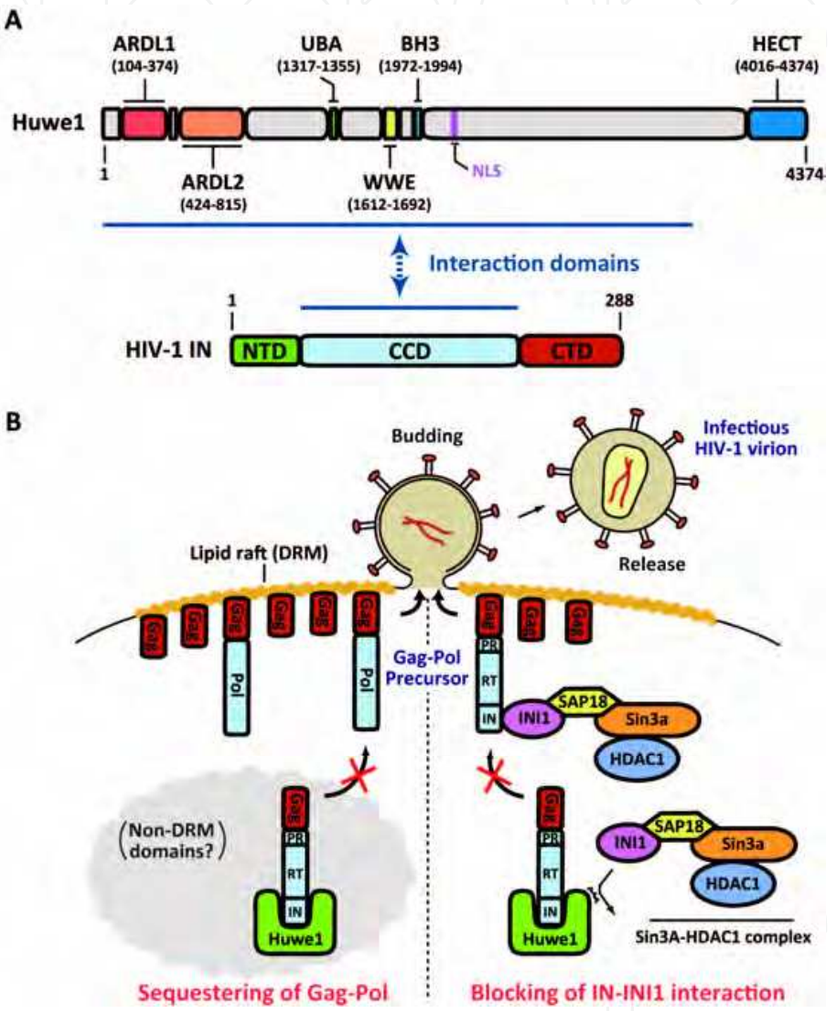

Fig. 4. A novel HIV-1 IN-binding protein, Huwe1. (A) Interacting domains between Huwe1 and HIV-1 IN. Huwe1 is a HECT-type E3 ubiquitin ligase which possesses several recognizable domains; ARLD (Armadillo [ARM] repeat like domain) 1 and 2 in the N-terminus, UBA (ubiquitin-associated), WWE, and the well-conserved BH3 domain in the middle, and a HECT domain in the C-terminus. Our study shows that Huwe1 interacts with the CCD of HIV-1 IN through a broad region spanning 3,500 amino acids (Yamamoto et al., 2011). (B) Possible mechanisms by which Huwe1 hampers the formation of infectious HIV-1. In virus producing cells, Huwe1 may act as a scaffolding modulator that reduces infectivity of virions by interfering with the proper localization (left) or function (right) of HIV-1 Gag-Pol precursor through interactions with IN.

Another possible mechanism for the Huwe1-mediated negative modulation of HIV-1 infectivity is that Huwe1 could mask the IN region of Gag-Pol, thereby blocking the incorporation of INI1/hSNF5 and its associated cellular factors into HIV-1 virions (Fig. 4B, right). As described above, INI1/hSNF5 has been shown to be specifically encapsidated into HIV-1 virions, probably through the IN region of Gag-Pol (Yung et al., 2001, 2004). In addition, a recent study demonstrates that the IN-INI1/hSNF1 interaction selectively recruits SAP18 and HDAC1, components of the Sin3a-HDAC complex, into the HIV-1 virion, increasing the infectivity of the virions (Sorin et al., 2009). Although Huwe1 is an E3 ubiquitin ligase, our study suggests that enzymatic activity of Huwe1 is not involved in the ubiquitination and subsequent proteasomal-degradation of IN and Gag-Pol (Yamamoto et al., 2011). Therefore, in HIV-1 producer cells, Huwe1 may function as a scaffolding modulator that hampers proper localization or function of the Gag-Pol precursor protein via interaction with IN region (Fig. 4B).

5. Conclusion and implications for future treatment of HIV infection

This chapter highlights the functional role of PPIs between HIV-1 IN and its cellular cofactors for virus replication. Although the indispensability of these IN interactors in the HIV-1 infection cycle requires further validation, research into intracellular binding proteins of IN provide an important insight for the development of novel classes of anti-HIV drugs: inhibitors blocking IN-cellular protein interactions that can act synergistically with existing drugs. The design of this class of inhibitors (i.e. SMPPIIs) is an emerging field in retroviral research, but the rationale for their availability in blocking HIV-1 replication has been demonstrated in SMPPIIs against IN-LEDGF interaction (Christ et al., 2010). One impact on the pharmacological aspect is that, because cellular interactors for IN appear to be implicated in steps other than the integration process, SMPPIIs targeting IN could block HIV-1 replication at multiple steps. Therefore, further analysis of the mechanism by which the IN interactors regulate virus infection can be the basis of a promising new strategy for the treatment of HIV-1 infection and AIDS.

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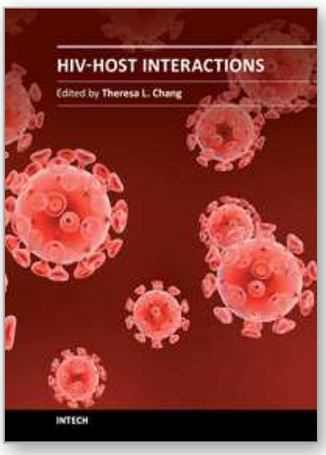

HIV-Host Interactions

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HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and Trichomonas vaginalis on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

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