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Emerging role of cyclophilin A in HIV-1 infection: from producer cell to the target cell nucleus

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ABSTRACT The HIV-1 genome encodes a small number of proteins with structural, enzymatic, regulatory, and accessory functions. These viral proteins interact with a number of host factors to promote the early and late stages of HIV-1 infection. During the early stages of infection, interactions between the viral proteins and host factors enable HIV-1 to enter the target cell, traverse the cytosol, dock at the nuclear pore, gain access to the nucleus, and integrate into the host genome. Similarly, the viral proteins recruit another set of host factors during the late stages of infection to orchestrate HIV-1 transcription, translation, assembly, and release of progeny virions. Among the host factors implicated in HIV-1 infection, Cyclophilin A (CypA) was identified as the first host factor to be packaged within HIV-1 particles. It is now well established that CypA promotes HIV-1 infection by directly binding to the viral capsid. Mechanistic models to pinpoint CypA's role have spanned from an effect in the producer cell to the early steps of infection in the target cell. In this review, we will describe our understanding of the role(s) of CypA in HIV-1 infection, highlight the current knowledge gaps, and discuss the potential role of this host factor in the post-nuclear entry steps of HIV-1 infection.

KEYWORDS cyclophilin A (CypA), human immunodeficiency virus (HIV), capsid, reverse transcription nuclear entry, integration

HIV-1 is a retrovirus, and the structure of the virion consists of a host-derived outer lipid membrane surrounding a conical capsid (1). The viral membrane contains approximately 7–14 envelope (Env) spikes, each composed of three heterodimers of viral gp120 and gp41 protein (2–4). The Env spike is the only known viral protein exposed on the outer surface of the virus particle (5–9) and serves as the determinant of the target cell tropism (10–12). The inner viral capsid shell is made up of ~200–250 hexamers and 12 pentamers of the capsid (CA/p24) protein (13). The capsid encases a number of viral and host factors along with two copies of the viral single stranded (ss) RNA genome (14). The HIV-1 genome encodes 15 viral proteins that perform structural, enzymatic, regulatory, and accessory functions (15, 16). These viral proteins coordinate interactions with a number of host factors to promote HIV-1 infection in a target cell.

HIV-1 replication cycle is broadly divided into early and late events/steps. The early steps begin when gp120 binds to the CD4 receptor and one of the HIV-1 co-receptors (CCR5 and CXCR4) located on the plasma membrane of a target cell (11, 17). The resulting conformational changes in Env induce the fusion of the viral and cellular membranes and the subsequent release of the viral core into the cytosol of the target cell (18). As the core is trafficked through the cytosol by the cytoskeleton network toward the nucleus (19–21), the encased reverse transcription complex (RTC)—containing the viral reverse transcriptase (RT) and other viral and host factors, begins to synthesize a double stranded (ds) DNA copy from the viral ssRNA genome (20, 22). The newly synthesized

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viral dsDNA is transported, as part of the RTC and/or preintegration complex (PIC), to the host cell nuclear pore complex (NPC). After nuclear entry, the PIC, containing the viral dsDNA, the viral integrase (IN) enzyme, and other viral/host factors, carries out integration of the viral dsDNA into active gene bodies of the host chromosomes (23). Integration of HIV-1 dsDNA completes the early steps of virus replication and establishes a provirus that persists for the life of the host cell (23). Thereafter, the late steps of the HIV-1 replication begin with the transcription of viral RNAs from the provirus. These viral RNAs are then exported from the nucleus to the host cell cytoplasm for viral protein production (24). Finally, the viral proteins and the viral ssRNA genome assemble into immature virions at the plasma membrane of the host cell, followed by budding, release, and maturation steps to produce infectious progeny virions (25, 26).

HIV-1 REPLICATION IS CRITICALLY DEPENDENT ON HOST FACTORS

Being an obligate intracellular parasite, HIV-1 is critically dependent on the host cell machinery for infection. Accordingly, after the viral core is released into the target cell cytoplasm, the viral proteins (particularly the capsid protein—CA) interact with a number of host factors to coordinate and promote early steps of virus replication (27, 28). For instance, the host kinesin adapter protein FEZ1 binds to the viral capsid and mediates trafficking of the core on microtubules to the NPCs (29, 30). Another capsid-binding host protein, Cyclophilin A (CypA) facilitates reverse transcription and nuclear import of the virus (31). The capsid also binds to host proteins including Sec24C, Nucleoporins (e.g., Nup358 and 153), Transportins (e.g., TNPO1), Bicaudal D2 (BICD2), and cleavage and polyadenylation specificity factor 6 (CPSF6) at various stages of the nuclear entry step (31–39). Furthermore, PIC-associated viral factors interact with host factors such as CPSF6 and the lens epithelium-derived growth factor (LEDGF/p75) during and/or after the nuclear entry step of virus replication (40–43) to direct the preferential integration of the viral DNA into transcriptionally active regions of the human chromosomes (23, 44–48). During the late steps of HIV-1 replication, the proviral DNA is transcribed by the cellular transcriptional machinery (49) to produce the spliced viral mRNAs and the unspliced full-length viral RNA. These viral RNAs are transported to the cytoplasm by the host exportin 1 (XPO1)-RanGTP nuclear export pathway (24). Thereafter, the viral mRNAs are translated by the host ribosomal machinery into precursor polyproteins (Pr55Gag, Pr160GagPol, and gp160), regulatory proteins (Rev and Tat), and accessory proteins (Nef, Vif, Vpu, and Vpr) (16). Next, the full-length viral ssRNA genome and the viral proteins traffic to the host cell plasma membrane, where the Gag protein coordinates the assembly of immature virus particles (25, 26, 50). Release of the non-infectious immature HIV-1 particles is coordinated by the p6Gag domain-recruited cellular endosomal sorting complexes required for transport (ESCRT) machinery (51). During the virus maturation process, the viral PR enzyme, encoded as part of the Pr160GagPol, first matures *via* auto-processing and subsequently cleaves the Pr55Gag into matrix (MA), CA, nucleocapsid (NC), and p6 and the Pr160GagPol into RT and IN proteins (52). Finally, the cell-free mature virion is ready for initiating a new infection cycle (53). Collectively, productive HIV-1 infection is critically dependent on interactions between viral and host factors at every step of the replication cycle. In this review, we will primarily focus on the tenuous, well-established, and emerging roles of the host protein CypA in HIV-1 infection.

CypA IS A UBIQUITOUSLY EXPRESSED CELLULAR PROTEIN

CypA belongs to the family of cyclophilin proteins that are ubiquitously expressed in prokaryotic and eukaryotic cells (54, 55). Cyclophilins are structurally and functionally highly conserved in both prokaryotes and eukaryotes and are part of the immunophilin superfamily. Many cyclophilins possess the peptidyl/prolyl *cis-trans* isomerase (PPIase) activity (56) that catalyzes isomerization of the peptide bond upstream of proline residues in proteins (57–59). Mammalian CypA was first identified as a cytosolic protein in bovine T cells followed by the discovery of its PPIase activity and the host cell target of the immunosuppressive drug cyclosporin A (CsA) (59–61). In humans, the *PPIA* gene

located in chromosome 7 was later identified to encode for the CypA protein (60, 62). Although CypA is an abundant cytosolic protein, there is evidence that it can be secreted in response to inflammatory stimuli (63, 64).

CypA is an 18 kDa protein with a cyclophilin-like domain (CLD) typical of all the members of the cyclophilin family (65). Structurally, CypA is a beta barrel with two alpha-helices and a beta sheet (Fig. 1A) (66, 67). Functionally, the PPIase activity of CypA is required for protein folding, protein trafficking/molecular chaperoning, cell signaling, and T cell activation (55, 57, 68–70). Thus, CypA has been implicated in a number of diseases including cardiovascular disease, type 2 diabetes, and viral infections such as influenza, hepatitis C virus, coronavirus, and HIV (71–73).

INDIRECT ROLE OF CypA IN HIV-1 REPLICATION

CypA has a high binding affinity to cyclosporin A—a calcineurin inhibitor and an immunosuppressant used in organ transplant treatment (59). CsA is a cyclic undecapeptide produced by *Trichoderma polysporum* (74, 75). CsA binds to the substrate-binding site of CypA (Fig. 1B) and inhibits its PPIase activity (69). Notably, the CsA-CypA complex binds to calcineurin and inhibits its phosphatase activity (69, 76). Evidently, inhibition of calcineurin but not CypA's PPIase activity is the molecular basis for CsA's immunosuppressive function (68, 77).

CsA played a central role in the discovery of CypA as a host factor in HIV-1 infection. In 1986, a study by Klatzman et al. was the first to report the antiviral effects of CsA against HIV-1 (78). Subsequently, a comprehensive study by Wainberg et al. (79) further clarified the inhibitory effects of CsA during acute HIV-1 infection (79). Specifically, HIV-1 infection of T cells but not monocytes was inhibited when CsA was added before or during virus inoculation. However, addition of CsA after HIV-1 inoculation had minimal inhibitory effect on viral replication or viral protein expression. Interestingly, CsA removal after HIV-1 inoculation resulted in the restoration of viral protein expression and production of progeny virions (79). Karpas et al. (80) then demonstrated that CsA treatment reduced the production of infectious HIV-1 particles from chronically infected T cells (80). These early studies established that CsA inhibited HIV-1 replication and provided a scientific basis to test this immunosuppressive drug for HIV/AIDS treatment (81–83). Unfortunately, CsA was ineffective in clinical settings and/or was toxic to HIV-1 infected individuals (81–83). Notably, non-immunosuppressive analogs of CsA also inhibited HIV-1 with equal or better potency (84, 85), suggesting that the immunosuppressive activity of CsA was dispensable for the antiviral activity. Nonetheless, these early studies of CsA pointed to a potential role of CypA in HIV-1 biology.

DIRECT ROLE OF CypA IN HIV-1 REPLICATION

In a seminal study, Luban et al. (86) discovered that CypA is a binding partner of the HIV-1 Gag polyprotein (86). It was subsequently demonstrated that CypA specifically binds to a highly conserved proline-rich region located in the N-terminal domain (NTD) of HIV-1 CA (Fig. 1B and C) (87, 88). Notably, mutation of the amino acid residue P90 or the preceding residue G89 in the proline-rich region of CA-NTD disrupted the interaction of CypA with HIV-1 Gag (87–89). Structural studies by Gamble et al. (90) identified that the proline-rich region of CA-NTD is a protruding loop and consists of the amino acid residues of ^{85}Pro-Val-His-Ala-Gly-Pro-Ile-Ala-Pro^{93} (corresponding Gag locations:^{217}Pro-Val-His-Ala-Gly-Pro-Ile-Ala-Pro^{225}) (90). They also reported that this loop, also known as the CypA binding loop, served as the primary binding interface for CypA (Fig. 1D and E) (90). The structure also revealed that the critical amino acid residues G89 and P90 of CA are located in the apex of the binding loop and are deeply buried in the CypA active site (Fig. 1E) (91, 92). The other seven amino acid residues in the CypA-binding loop of CA are involved in a hydrogen bonding network with CypA. Accordingly, it was predicted that by binding to these CA residues, CypA could accelerate isomerization of the G89-P90 peptide bond and regulate Gag conformation (93, 94). Surprisingly, the formation of a stable CypA-CA complex was found to be not a consequence of the isomerization of the

G89-P90 peptide bond by the PPIase activity of CypA (90). Therefore, it remained unclear whether the enzymatic activity of CypA is required for HIV-1 replication. Nevertheless, CypA has a higher affinity for multimeric CA relative to monomeric CA and thus has been suggested to preferentially bind assembled capsid (90, 95). Recently, a non-canonical second binding site for CypA in the viral capsid was reported (96). However, mutational analysis that disrupted this non-canonical interaction did not impair the positive effects of CypA in HIV-1 replication (97). Thus, the functional relevance of CypA binding to this second binding site during HIV-1 replication is unclear. Collectively, it appears that the replication-enhancing effects of CypA during HIV-1 infection are a consequence of its physical interaction with CA rather than its PPIase activity.

Immediately after the discovery that CypA specifically interacts with HIV-1 CA, the functional relevance of this interaction was predicted to be the incorporation of CypA from the producer cell into the budding HIV-1 particles (87, 88). This model was supported by studies showing that CypA from the producer cell is incorporated into HIV-1 particles in a CA-dependent manner (85, 88, 89). Accordingly, CypA incorporation into the virions was disrupted by mutations of the G89 or P90 residues of CA or by CsA treatment, and this disruption was associated with reduced infectivity (85, 88, 89). Most importantly, these studies identified CypA as the first cellular factor to be incorporated into budding HIV-1 particles and were instrumental in galvanizing the field to identify the exact role of this host factor during the HIV-1 replication cycle.

It is noteworthy that CypA displays distinct preferences for interacting with the CA of diverse lentiviruses (98). For instance, CypA interacts with the CA of the feline immunodeficiency virus (FIV) as well as the CA of simian immunodeficiency virus strains infecting chimpanzees (SIVcpz), African green monkeys (SIVagm), greater spot-nosed monkeys (SIVgsn), and mandrills (SIVmnd1). However, CypA does not interact with the CA of SIVs infecting sooty mangabey monkeys (SIVsmm), macaques (SIVmac), and chimpanzees originating from Gabon (SIVcpz-gab). Notably, as has been reported for HIV-1, SIVcpz virions have been shown to be able to incorporate CypA (98). Describing the function and significance of CypA-CA interactions in these viruses is beyond the scope of this review.

CypA AND HIV-1 ENTRY: A CHECKERED HISTORY

CypA was found to be incorporated into HIV-1 particles in a fixed stoichiometry to CA, and reduction in CypA incorporation correlated with reduced infectivity (87, 88). Therefore, it was hypothesized that CypA enhanced attachment/entry of the virus to the target cell and/or promoted post-cellular entry step(s) of HIV-1 replication. For cellular entry, the HIV-1 envelope glycoprotein gp120 binds to the CD4 receptor, and one of the chemokine receptors, CCR5 or CXCR4, expressed on the plasma membrane of specific immune cells (11, 17). A study by Sherry et al. (99) was the first to report a potential role of CypA in the cellular entry of HIV-1 (99). This study demonstrated that anti-CypA antibodies inhibited HIV-1 infection of the target cell by blocking viral uptake (99). Then, Saphire et al. (100) reported that the virion-associated CypA interacted with the heparan molecules of the target cell plasma membrane to promote virus attachment (100). These authors predicted that the heparan-CypA interaction was required for the initial binding of the virions to the target cell. Subsequently, Pushkarsky et al. (101) reported that the virion-associated CypA interacted with the target cell transmembrane glycoprotein CD147 to promote HIV-1 entry (101). While these studies suggested a potential role of CypA in HIV-1 cellular entry, it was unclear why only group M HIV-1 but not HIV-1 belonging to other groups required CypA for entering the target cell (102). Furthermore, this model did not explain why pseudotyping of HIV-1 particles with vesicular stomatitis virus g-protein (VSVg) in the place of HIV-1 Env relieved the requirement of CypA for cellular entry (103). Finally, it was not obvious how CypA, a cytoplasmic protein with no obvious membrane-spanning region, could promote viral entry that involves fusion of the viral membrane with the plasma membrane of the target cell. Nevertheless, studies from a number of laboratories challenged the notion of the role of producer cell CypA

by demonstrating that CypA in the target cell was functionally linked to HIV-1 infection (described in the next section). Overall, the role of virion-incorporated CypA during HIV-1 replication remains unresolved even after four decades of extensive research. Interestingly, a recent study claims that virion-associated CypA facilitates incorporation of Tat to stimulate HIV-1 infection (104).

CypA AND POST-CELLULAR ENTRY STEPS OF HIV-1 REPLICATION

There was early evidence that CypA promotes HIV-1 infection by acting at a step following target cell entry (Fig. 2). For instance, Steinkasserer et al. (105) reported that HIV-1 particles assembled in the presence of a non-immunosuppressive CsA analog (SDZ NIM 811) were less infectious (105). They reported that the CsA analog inhibited the 2-LTR circle formation and proviral DNA integration, which is suggestive of a block in the nuclear translocation of HIV-1 PICs in the infected cell (105). Thus, virion-incorporated CypA appeared to be playing a role during infection. Then, Braaten et al. (89) systematically examined the role of HIV-1 particle-associated CypA in viral infection. In their study, CypA incorporation into the virions was prevented by both CsA and CA-specific mutations G89V and P90A, which disrupt CypA-CA interaction. The resulting CypA-deficient virions were found to assemble, mature, and fuse with the target cells normally (89). Structural and biochemical studies by Weiger et al. (106) also illustrated that there was no detectable change in the morphology or yield of mature particles lacking CypA. Interestingly, the lack of virion-associated CypA led to impaired viral DNA synthesis in target cells (89). Additionally, this impairment was not a consequence of reduced endogenous reverse transcription activity of CypA-deficient virions. In a follow-up report, Braaten et al. (107) also demonstrated that HIV-1 particles produced from CypA-depleted cells showed no biochemical abnormalities, yet retained a defect at an early step of infection in the target cell. Collectively, these observations suggested that binding of target cell CypA to the incoming viral capsid is responsible for its effects on infection. Despite this, whether and how virion-associated CypA affect the early steps of HIV-1 infection are not fully understood.

The role of target cell CypA in HIV-1 infection was further strengthened by Towers et al. (116). This study reported that CypA-free virions remained as infectious as CypA-containing virions, suggesting that functional HIV-1 capsids can be assembled in the absence of a CA-CypA interaction (116). Using a clever approach of host restriction to viral infection, the authors reported that CypA-CA interaction promoted HIV-1 infection in the target cell by shielding the incoming viral capsid from the inhibitory effects of an unknown host restriction factor, now identified as TRIM5α. The requirement of CypA-CA interaction in the target cell to prevent the incoming HIV-1 from host restriction factor recognition was also reported by Berthoux et al. (117). These studies indicated that virion-associated CypA was inconsequential for HIV-1 infection of target cells. Accordingly, a comprehensive study by Hatziioannou et al. (118) confirmed that CypA-CA interaction in the producer cell during virus assembly or release has little or no effect on HIV-1 infectivity. They also reported that CsA inhibited HIV-1 infection only when CypA was expressed in the target cell. Interestingly, CA mutations A92E and G94D, located in the CypA binding loop, rendered the virus resistant to CsA and also dependent on CsA for efficient replication. However, these CA mutations did not affect virus production but affected the early steps of HIV-1 infection in the target cell (118). Collectively, these studies provided compelling evidence that the target cell CypA is important for HIV-1 replication and played an instrumental role to define the exact role of CypA in post-entry step(s) of HIV-1 infection.

There were several reasons why the role of target cell CypA in HIV-1 replication was not obvious in the early studies (119). First, CypA function was probed using a number of different experimental tools, including; (i) CA mutants with altered CypA affinity/dependence, (ii) diverse competitive inhibitors of CypA, and (iii) different methods to inhibit CypA expression. Second, it was not clear that the functional role of CypA is dependent on the cell type used for HIV-1 infection. For example, CypA promotes HIV-1

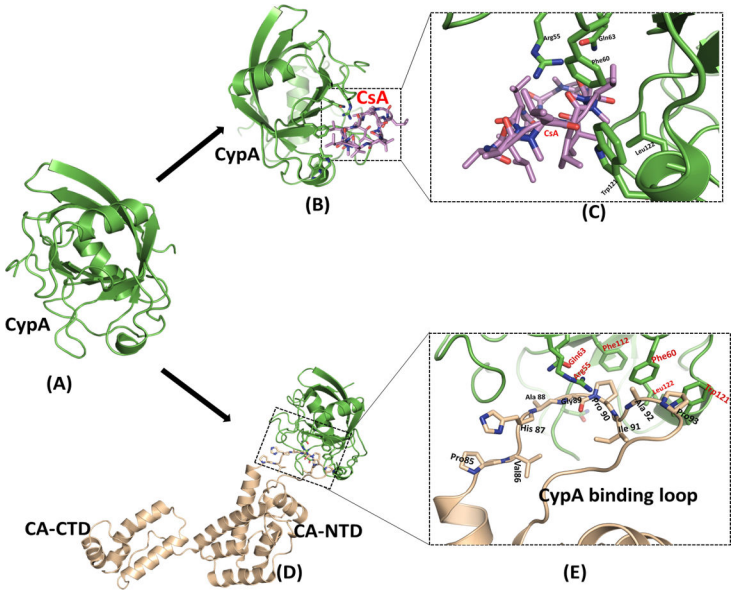

FIG 1 Structural representation of CypA complex formation with cyclosporin and HIV-1 Capsid. (A) Ribbon representation (shown in green) of Apo form of CypA (PDB ID: 1CWA). (B) The binding mode of the CypA with cyclosporin A (shown in light purple sticks; PDB ID: 1CWA). (C) A zoomed-in view (inset) of the binding mode, which shows the important active site amino acid residues (green sticks), Trp121, Leu122, Arg55, Gln63, and Phe60 of the CypA interacting with CsA. (D) CypA (green ribbons) in complex with the HIV-1 capsid (pale yellow ribbons). The structural complex (PDB ID: 5FJB) exhibits a distinct CypA-binding pattern in which CypA selectively make a contact with the loop region of HIV-1 capsid. (E) A zoomed-in view (inset) of CypA binding loop of HIV-1 capsid (pale yellow) where the important amino acid residues (His87, Ala88, Gly89, Pro90, Ile92, and Pro93) are shown in pale yellow sticks interacting with CypA key residues (Arg55, Phe60, Gln63, Phe112, Leu122, and Trp121) shown in green sticks.

infection of MT4, CEM, 293T, HOS, TE671, Jurkat T cells, and primary human CD4 +T cells (89, 102, 118, 120–123) but not in HeLa and H9 T cells (119, 120). Furthermore, HIV-1 infection of dendritic cells does not require CypA (124). Finally, it was not known then that HIV-1 infection is sensitive to CypA levels in the target cell (120, 122).

Role of CypA in HIV-1 reverse transcription

After cellular entry, HIV-1 capsid undergoes the process of uncoating, aka shedding or disassembly of the capsid, in the target cell cytoplasm (Fig. 2). Even though the exact timing, precise location, and molecular mechanism are not fully understood, uncoating is functionally linked to early steps of HIV-1 infection including reverse transcription (125–127). Notably, HIV-1 uncoating is coordinated by host factors that target two major binding interfaces on the viral capsid. CypA binds to one of these interfaces located at the CA-NTD known as the CypA-binding loop (Fig. 1) (90–92). A second binding site, formed at the interface between the NTD of one CA monomer and the CTD of an adjacent CA monomer, is targeted by nucleoporins and other host factors (35). A third interface that contributes to capsid stability is the trimeric interhexamer interface, which forms a structure that is targeted by the host restriction factor MxB (128, 129).

Braaten et al. (89) reported that point mutations in the CypA binding loop of CA-P90A or G89V/A- resulted in a significant reduction in viral DNA synthesis in the target cell . Notably, they also confirmed that reduction in viral DNA synthesis quantitatively correlated with CypA-CA binding *in vitro*. Similarly, Ackerson et al. (130) demonstrated that viral DNA synthesis was dramatically reduced in cells infected with HIV-1 P90A virions. This study was the first to measure the effects of disrupting CypA-CA binding on HIV-1 reverse transcription in human primary peripheral blood mononuclear cells (PBMCs). Subsequently, Fitzon et al. (131) reported that changing the proline residues of

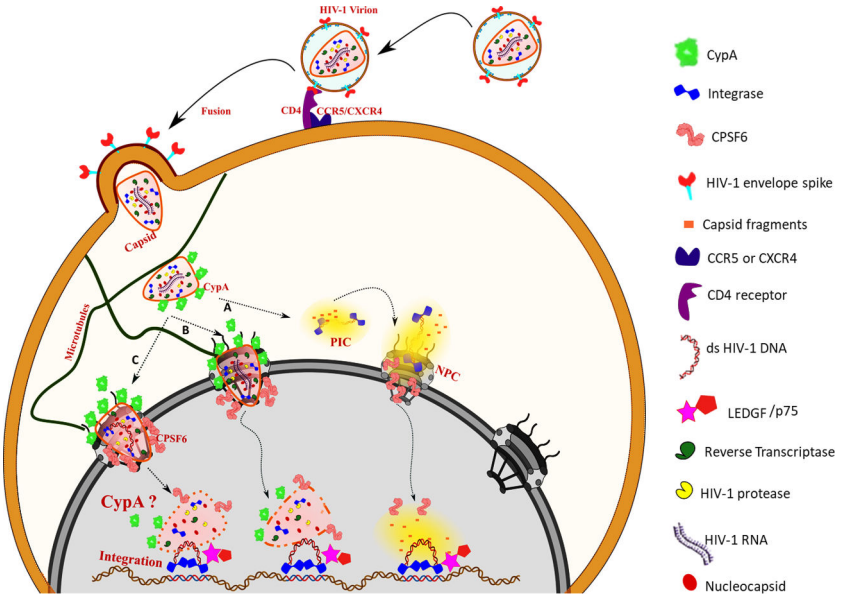

FIG 2 Schematic representation of the canonical and emerging models of the early steps in HIV-1 replication. The HIV-1 envelope spike sequentially binds to the CD4 +receptor and one of the co-receptors—CCR5 or CXCR4. This leads to the fusion of the viral and target cell membranes and the release of the capsid into the cytosol. The cytosolic CypA binds to the CypA-binding loop of the CA subunits that constitute the shell of the capsid. The CypA-bound capsid is trafficked by the cytoskeleton network toward the nucleus, and the canonical (A) and two emerging models (B-C) of the subsequent events are depicted. (A) En route to the nucleus, the RTC containing the viral RT enzyme reverse transcribes the viral ssRNA genome into a dsDNA copy. Concurrently or upon completion of reverse transcription, the intact core with the capsid disassembles/uncoats in the cytoplasm (108). The newly synthesized viral dsDNA is transported, as part of the PIC, through the NPC. The principal components of cytoplasmic PIC include viral dsDNA, viral IN, and CA. After NPC-mediated nuclear entry, the PIC-associated CA and IN interact with host factors such as CPSF6 and LEDGF/p75, respectively, thus enabling PIC-mediated integration of the viral dsDNA into active gene bodies of the host chromosomes and the canonical (A) and two emerging models (B and C) of the subsequent events are depicted. (B) Reverse transcription is completed within the intact capsid during its transport to the NPC (109), and nuclear import is facilitated by capsid remodeling/partial disassembly at the NPC (27). After nuclear entry, the PIC, still part of the partially disassembled capsid lattices, interacts with host factors that direct PIC-mediated targeted integration. (C) Reverse transcription is initiated within the intact capsid during its transport to the NPC and is only completed after the intact or almost intact capsid is imported into the nucleus (33, 45, 110–115). In the nucleus, localized disassembly of the capsid (113, 115) near or at the site of integration (110) enables interaction with host factors that direct PIC-mediated targeted integration. The representative symbols used in the schematic to depict the viral capsid contents and the host factors are shown on the right.

CA that are conserved among all HIV-1 clades caused severe defects at different stages of viral replication (131). Particularly, mutations in the proline residues in the CypA binding loop resulted in reduced levels of reverse transcription (131). In a follow-up study, Braaten et al. (107) found that CypA depletion in T cell lines resulted in a marked reduction in HIV-1 reverse transcription. Intriguingly, CypA depletion minimally altered HIV-2 DNA synthesis, suggesting that CypA's effect on HIV-1 reverse transcription is specific (107). Subsequently, a study by De Laco et al. (31) comprehensively examined CypA's effect on HIV-1 reverse transcription using 27 different human cell lines and several HIV-1 CA mutants. They reported that disruption of CypA-CA binding either by specific CA mutants, CypA-depletion, or CsA treatment decreased HIV-1 reverse transcription in all cell lines studied. Interestingly, CypA was also required for HIV-1 reverse transcription in cells in those where infection is not dependent on the CA-CypA interaction or where CypA inhibited infection (31). While these studies using immortalized

human cell lines have provided valuable insights into the role of CypA in HIV-1 reverse transcription, the advent of CRISPR-Cas gene-editing strategies finally paved the way to probe CypA's role in physiologically relevant CD4 +T cells and macrophages (132). Taking advantage of the CRISPR technology, two recent studies described CypA's positive effects on HIV-1 reverse transcription in human primary cells (133, 134). Kim et al. (133) reported that viral DNA synthesis by the CA mutant P90A is significantly lower in primary macrophages and CD4 +T cells. Similarly, Selyutina et al. (134) found that reverse transcription of HIV-1 mutants P90A and G89V is dramatically reduced in primary CD4 +T cells. These studies confirmed that CypA promotes HIV-1 reverse transcription and reported that the primary role of CypA is to protect HIV-1 from TRIM5α restriction in physiologically relevant cells.

A functional role of CypA in HIV-1 reverse transcription is also supported by studies of CsA and its analogs. For example, Song and Aiken (121) reported that CsA increased reverse transcription of CsA-dependent HIV-1 mutants A92E and G94D. Since CsA did not promote fusion of these HIV-1 mutants to target cells, these authors suggested that CsA affected HIV-1 reverse transcription (121). Another study by Ptak et al. (135) used a non-immunosuppressive CsA analog (Debio025) and probed the effect of this CypA inhibitor on HIV-1 reverse transcription. They reported that the CsA analog significantly reduced both the early and late HIV-1 reverse transcription products (135).

Collectively, these studies based on alterations in CypA expression, use of HIV-1 mutants that disrupt CypA-CA interaction, and treatment with CypA inhibitors provided strong evidence for a functional link between CypA and HIV-1 reverse transcription. The precise mechanism by which CypA promotes HIV-1 reverse transcription is not fully understood. However, the positive effects of CypA on HIV-1 infection have been linked to its ability to stabilize the viral capsid. For instance, Fitzon et al. (131) reported that specific CA mutations in the CypA binding loop alter capsid stability. Studies of CsA washout assay and core-destabilizing effects of TRIM5α have also provided evidence that CypA stabilizes the viral capsid (136–140). Notably, alterations in HIV-1 capsid stability severely impair reverse transcription in target cells (141). Even though capsid stability mutants show defects in other post-entry processes, a number of CA mutants were defective at reverse transcription, regardless of the type of changes (131, 141–144). Therefore, CypA's effect on HIV-1 reverse transcription is most likely linked to its ability to stabilize the incoming capsid (145). Presumably, a stable capsid can provide a favorable biochemical microenvironment for optimal HIV-1 reverse transcription. This model is supported by several recent studies of purified cores that are subjected to endogenous reverse transcription (146, 147). However, future studies are needed to tease out, how and whether, CypA's effect on HIV-1 reverse transcription is influenced by other capsid stabilizing host factors (148, 149). Particularly, the negatively charged metabolite Inositol hexakisphosphate (IP6), also known as Phytic acid, has emerged as a critical host factor for HIV-1 capsid stability (146, 148–151). Therefore, probing a cross-talk between CypA and IP6 in regulating HIV-1 capsid stability could provide key insights into a possible link between the cell-type dependence of CypA and differences in levels of IP6 in the target cell.

Role of CypA in HIV-1 nuclear entry

Nuclear entry of HIV-1 is coordinated and regulated by the viral capsid (Fig. 2) (152, 153). Specifically, binding of host factors NUP358 (aka RanBP2) and NUP153 to the capsid is critical for HIV-1 replication complex to gain access to the target cell nucleus (32–35, 154). The filaments of NUP358 form a ring on the cytoplasmic side of the NPC, whereas NUP153 forms a basket on the nuclear side (155–159). NUP358 binds to a hydrophobic binding pocket (N74) and the CypA binding loop (P90) of the capsid, whereas NUP153 preferentially binds to CA hexamers—to a hydrophobic pocket at the interface between two adjacent CA monomers. Particularly, NUP153 makes contacts with one of the CA monomers at helix 2 (P34, I37, P38, and S41), helix 7 (I135, L136, N139, K140, V142, and R143), helix 8 (R173, Q176, and A177), and with the adjacent

CA monomer at residues P38, Q63, R143, R173, A177, Q176, and R143. NUP358 also contains a CypA-homologous domain (34, 160) and possesses PPIase activity like CypA (161). Both NUP358 and NUP153 were initially identified as co-factors for HIV-1 infection by genome-wide screenings (160, 162). Subsequently, it was established that NUP358 promotes docking of the HIV-1 replication complex (45, 163), whereas NUP153 promotes translocation through the NPC (35, 162–165). TNPO3 was also identified as a host factor for HIV-1 nuclear import (160, 162, 166–170). However, TNPO3's effect on HIV-1 nuclear entry seems to be indirect and has been linked to its ability to transport CPSF6 into the nucleus (171–173) since the binding of cytoplasmic CPSF6 to the capsid actually inhibits HIV-1 nuclear entry. Since CPSF6 and Nup153 share the same CA binding interface, the current model is that TNPO3 facilitates binding of Nup153 by preventing premature engagement of CPSF6 to promote HIV-1 nuclear entry (35, 168).

There is strong evidence that CypA influences HIV-1 nuclear entry by coordinating binding of specific NUPs to the viral capsid (34, 162, 163, 174). Schaller et al. (34) were the first to report that CypA promotes nuclear entry of HIV-1 by coordinating with NUP358 and subsequently with NUP153. Accordingly, when the CypA-CA interaction was disrupted, utilization of these NUPs was altered during HIV-1 nuclear entry (34, 163, 164, 175, 176). For instance, CA mutations (G89V and P90A) that prevent CypA binding were less dependent on NUP358 and NUP153 expression for nuclear entry of the HIV-1 replication complex (34, 164, 175, 176). There is also evidence that CypA-CA interaction regulates the rate at which HIV-1 replication complex docks at the NPC. For instance, Dharan et al. (177) reported that the P90A mutation abolishes HIV-1 infection-induced cytoplasmic localization of NUP358. Burdick et al. (45) reported that CypA slows down nuclear import of HIV-1 replication complexes and that disrupting CypA-CA interaction resulted in a faster rate of nuclear import. For instance, compared to the wild-type HIV-1 particle the rate of nuclear import was increased for virions with a P90A mutation or with the treatment of CsA (45). Interestingly, the efficiency of nuclear import remained comparable with or without disruption of the CypA-CA interaction (45). Similarly, Zhong et al. (178) reported that G89V mutant virus has a higher rate of trafficking to the NPC compared to the wild-type virus. These observations supporting a direct role of CypA in HIV-1 nuclear import are consistent with the findings by De Laco et al. demonstrating that the infectivity defect resulting from the disruption of CypA-CA interaction correlated with a nuclear entry block (31). However, it is important to note that CypA's effect on nuclear entry is cell type dependent (31), and CypA (in conjunction with other factors) could inhibit nuclear entry of HIV-1 in old world monkey cells (179).

Interestingly, the HIV-1 CA mutant viruses defective for CypA binding (G89V and P90A) are also reported to be resistant to Myxovirus resistance B (MxB)-mediated inhibition of HIV-1 nuclear entry (180–182). Accordingly, extended passages of HIV-1 in a MxB-expressing T-cell line led to the isolation of an MxB-resistant escape virus harboring a single mutation altering the CA residue A88—a key amino acid required for CypA binding (180). Thus, MxB-mediated restriction of HIV-1 appears to require capsid binding to CypA (180, 181). Importantly, MxB resistance of certain transmitted founder HIV-1 strains mapped prevalently to mutations in the CypA-binding loop of CA (183). Remarkably and intriguingly, the addition of the A92E mutation, known to recapitulate the CypA binding-mediated effect on the CA to the P90A virus, rendered it susceptible to MxB restriction (184). Thus, the MxB restriction appears not to depend on CypA binding *per se* but rather on a specific conformational state of CA that could be conferred, for instance, by CypA binding or by a specific CA mutation that recapitulates CypA binding-mediated effect. Collectively, these studies provided strong evidence that CypA-CA interaction is necessary for the import, docking, and entry of HIV-1 replication complex through the NPC into the nucleus of an infected cell.

Role of CypA in post-nuclear entry steps of HIV-1 infection

After HIV-1 enters the nucleus of the target cell, the PIC-associated viral DNA is integrated into actively transcribing genes of the host chromosomes (Fig. 2) (23). The enzymatic

activity required for inserting the HIV-1 DNA into the host genomic DNA is provided by the PIC-associated IN (23). Accordingly, a number of PIC-associated host factors have been reported to play key roles in targeting the HIV-1 DNA into specific regions of the host chromosomes (185, 186). Interestingly, HIV-1 CA is emerging as another target for host factors in post-nuclear entry steps of infection. For instance, CPSF6 is a CA-binding host factor that plays critical roles in HIV-1 integration targeting into the gene bodies of the host chromosomes (44, 48). Interestingly, there is evidence that the CypA-CA interaction also influences HIV-1 integration targeting. For example, Schaller et al. (34) found that disrupting CypA-CA interaction altered integration targeting into host chromosomes. Surprisingly, disruption of CypA binding to CA increased targeting of HIV-1 integration into gene-dense regions (34). This contrasts with depletion of other CA-binding host factors such as CPSF6, where integration targeting is generally directed away from gene-dense regions (34, 44, 48). Although the mechanism is not fully understood, absence of CypA could increase and prolong CPSF6 binding to the capsid (178) and slow the rate of CA uncoating resulting in this unusual phenotype of integration targeting. Alternatively, disruption of CypA-CA interaction may alter the choice of optimal nuclear entry pathway(s) by the virus, thereby leading to integration into higher gene-density regions. For instance, increased integration of the P90A and G89V viruses into higher gene-density regions has been proposed to result from their impaired use of the nuclear pore complex proteins such as NUP358 and NUP153 (34). Nevertheless, the functional consequence of CypA's effect on HIV-1 integration targeting remains largely unclear.

A recent study by our group provides strong support for the potential role of CypA in HIV-1 integration (187). We reported that CypA expression regulates the integration of HIV-1 CA mutant (R264K) that evades the antiviral effects of the cytotoxic T lymphocytes (CTLs) (187). We observed that the reduced infectivity of the R264K mutant is linked to a defect at the integration step and was not a consequence of a block at reverse transcription and/or nuclear entry. Especially, several-fold increase in integration of the R264K mutant was detected in the CypA-depleted cells. Importantly, the compensatory CA mutation S173A restored the integration and infectivity defect of the R264K mutant. Although the mechanism remains unclear, these results strongly support the role of CypA in post-nuclear entry steps of HIV-1 infection, particularly in the integration step of CTL escape mutants.

The human CypA is a predominantly cytosolic protein; thus. the mechanism by which it influences post-nuclear entry steps of HIV-1 infection has been intensely debated in the field. While yeast CypA has previously been reported to localize to the nucleus of *Saccharomyces cerevisiae* (188), a recent study reported the pronounced nuclear localization of endogenous CypA in human monocyte-derived macrophages (178). Interestingly, CypA has also been reported to localize to the nucleus of Jurkat T-cells and play a novel role in the completion of cytokinesis (189). More recently, CypA has been shown to translocate to the nucleus upon stimulation of cells with stressors and play an anti-apoptotic role (190). However, despite the reported ability of CypA to localize to the nucleus independent of HIV-1 infection, the effect of CypA on post-nuclear entry steps of infection is most likely dependent on CypA's ability to bind to the HIV-1 capsid. Interestingly, a functional link between HIV-1 CA and post-nuclear entry steps of HIV-1 infection is gaining a great deal of momentum in recent years. Particularly, recent reports suggest that intact or near-intact cores can be observed inside nuclear pores and even inside the nucleus (108, 110, 191). Additionally, emerging evidence strongly suggests that HIV-1 CA regulates viral DNA integration. For instance, early biochemical studies detected CA in the viral replication complexes at/near the nuclear pores/envelope (19, 192) and transmission electron microscopy of HIV-1-infected cells revealed CA shells in close proximity to nuclear pores (193). HIV-1 CA mutants show alterations in proviral integration, PIC-mediated integration activity, and integration site selection (152, 153, 194–196). CA-binding host factor CPSF6 also regulates HIV-1 integration targeting (47, 48). Studies of small molecule inhibitors targeting CA provide further support for the

role of CA in the nucleus of HIV-1 infected cells (197–203). For example, the CA-specific inhibitor PF74 inhibits HIV-1 replication (35, 204, 205) and affects distribution of viral DNA integration into the host genome (206). Furthermore, we have provided evidence for a direct link between CA and HIV-1 integration by combining the use of PF74 as a pharmacologic probe with the measurement of the integration activity of HIV-1 PICs (207). Particularly, we have provided biochemical evidence for a direct role of CA in PIC-mediated viral DNA integration *in vitro* (207). Interestingly, and intriguingly, CypA is also necessary for the antiviral effect of PF74. For instance, Shi et al. (204) demonstrated that CsA or shRNA-mediated depletion of CypA reduced the antiviral activity of PF74 (204). Importantly, viruses harboring the CA mutation G89V or P90A were minimally affected by PF74. This finding was confirmed by Saito et al. (206) who reported that siRNA-mediated depletion of CypA reduced the antiviral activity of PF74 (206). Therefore, it is tempting to speculate that CypA could remain engaged with the CA associated with the viral replication complex (RTC/PIC) in the nucleus and influence post-nuclear entry steps. Accordingly, CypA could affect nuclear CA uncoating, engagement of the PIC with the chromatin, and integration of the viral DNA into the host DNA. However, future studies are needed to clarify these speculative models to understand CypA's role in the nucleus. Particularly, a combination of biochemical, pharmacological, genetic, structural, imaging, and molecular biology approaches is required to address the persistent and emerging knowledge gaps in the function of one of the first host factors of HIV-1 infection.

CONCLUSIONS AND FUTURE PERSPECTIVE

Tremendous progress has been made in understanding the exact role of CypA in HIV-1 infection. It is clear CypA plays important roles at various steps of HIV-1 replication cycle including uncoating, reverse transcription, nuclear import, and integration. However, the broader question of whether CypA regulates a singular molecular mechanism that drives its diverse roles or whether CypA is capable of modulating distinct partners and/or pathways at each step remains unanswered. Therefore, pinpointing the true nature of CypA during HIV infection requires a coherent model that is relevant both in laboratory models and physiologically relevant systems.

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