Current Research in Structural Biology 2 (2020) 222–228

Contents lists available at ScienceDirect

Current Research in Structural Biology

journal homepage: www.journals.elsevier.com/current-research-in-structural-biology

Graphical Review

A snapshot of HIV-1 capsid–host interactions

Joshua Temple [1], Therese N. Tripler [1], Qi Shen [1], Yong Xiong [*]

Department of Molecular Biophysics and Biochemistry, Yale University, 266 Whitney Avenue, New Haven, CT, 06511, USA

ARTICLE INFO

Keywords:
HIV-1
Capsid
Viral–host interaction
Nuclear import
Restriction factor

ABSTRACT

From cellular deposition of the HIV-1 capsid to integration of the viral genome, the capsid constitutes a primary target of a variety of host proteins that work to either promote or inhibit HIV-1 infection. Successful progression of HIV-1 infection depends on interactions between the capsid and host factors involved in stability, cellular transport, nuclear import, and genome integration. The virus must also guard its reverse-transcribing genome inside the capsid from host restriction factors that bind the capsid and suppress infection. Understanding the structure and dynamics of the capsid protein (CA) component and the assembled capsid sheds light on the molecular underpinnings of overall capsid stability, architecture, and flexibility that govern HIV-1 capsid–host interactions. The vast majority of these interactions are mediated through recognition of higher order interfaces only present in the assembled capsid lattice. Patterns formed at these interfaces serve as signposts for capsid-binders. Here we provide a graphical summary of the intricate interactions between host factors and the HIV-1 capsid while highlighting recent research. Insights into how host proteins interact with the capsid is crucial for understanding the HIV-1 replication cycle and developing antiviral therapeutics to prevent viral genome integration.

1. Introduction

HIV-1 is a member of *Retroviridae*, a family of enveloped viruses with RNA genomes that must be reverse transcribed into DNA before integration into the host genome. Upon fusion with the host cell, the virus is tasked with ensuring the protection and delivery of its genome to the nucleus where integration occurs. HIV-1 uses a proteinaceous shell, called the capsid, which guards the transcribing viral genome from a hostile cellular environment and facilitates transport to the nucleus where it ultimately disassembles in a process known as uncoating (Fig. 1).

2. HIV-1 capsid organization

Each capsid shell is composed of repeating units of the capsid protein (CA) that assemble into hexamers or pentamers (capsomeres) (Fig. 2a). A combination of ~250 CA hexamers assembles with 7 pentamers at the broad end and 5 at the narrow end to help induce curvature and form the conical capsid according to fullerene geometry (Pornillos & et al., 2009; Zhao & et al., 2013). Recent electron microscopy (EM) as well as nuclear magnetic resonance (NMR) data of hexamer assemblies show flexibility and inherent curvature within CA hexamers, instead of the planar, symmetric capsomeres previously observed in crystal structures (Ni & et al., 2020; Lu & et al., 2020). Taken together, the assembled HIV-1 capsid can adopt variable curvature and form heterogenous structures with pentamers at points of high curvature through construction with these pseudo-symmetric building blocks (Ni & et al., 2020; Lu & et al., 2020; Welker & et al., 2000).

2.1. CA capsomere flexibility endows capsid curvature

The CA monomer contains ordered N- and C-terminal domains (NTD and CTD) that are connected through a flexible hinge that allows for capsid curvature (Fig. 2b) (Ni & et al., 2020; Lu & et al., 2020). Each NTD makes extensive polar and hydrophobic contacts with neighboring monomers within a capsomere and forms a central pore gated by the N-terminal β-hairpin. The CTDs however form two types of interfaces between neighboring capsomeres. A two-fold di-capsomere interface is mediated through hydrophobic residues on helix 9 of adjacent monomers and can be conformationally variable, allowing relaxation of curvature strain throughout the lattice of mature capsids (Fig. 2c and d) (Zhao & et al., 2013; Lu & et al., 2020). A three-fold tri-capsomere CTD interface forms a

* Corresponding author.
E-mail address: yong.xiong@yale.edu (Y. Xiong).
[1] These authors contributed equally.

https://doi.org/10.1016/j.crstbi.2020.10.002
Received 23 June 2020; Received in revised form 5 October 2020; Accepted 7 October 2020

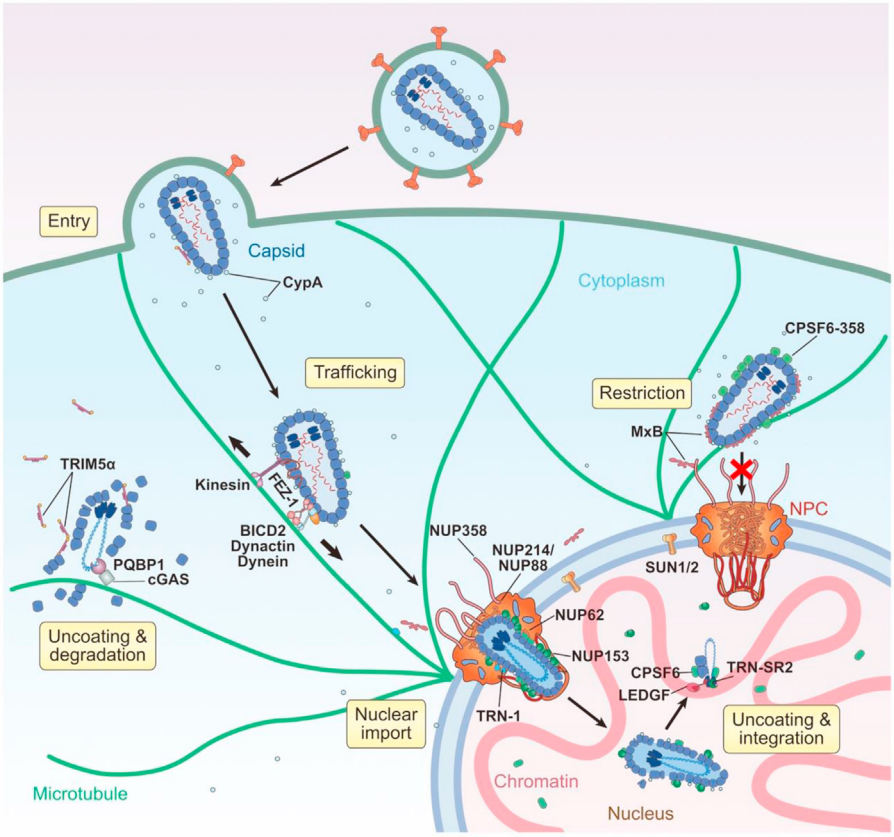

Fig. 1. Schematic of HIV-1 capsid-host interactions. The capsid, housing the viral genome, is deposited into the target cell following docking and membrane fusion. The viral genome must be reverse transcribed, trafficked, and imported into the nucleus to allow for integration with the host genome. Emerging evidence suggests the protective capsid may arrive at the nucleus mostly or completely intact (shown here) as opposed to a model of cytoplasmic uncoating and import. Some host factors serve to defend against various steps of this process that can result in restriction or aberrant uncoating and degradation. Other host factors are co-opted by HIV to ensure productive infection, for example during trafficking and nuclear import. Specific host proteins, labeled in black, depict relevant points of capsid–host interaction discussed below in this graphical review.

compact hydrophobic patch via helix 10 that is important for accommodating curvature (Fig. 2c). Pentamers induce high surface curvature and exhibit tighter packing of helix 10 at tri-capsomere interfaces, thus implicating this interface in pentamer incorporation into the lattice (Zhao & et al., 2013; Mattei & et al., 2016). Overall, inherent plasticity of CA monomers bestows the capacity for capsomeres to accommodate the curvature necessary to form the capsid.

2.2. Small molecule binding at the capsomere central pore

CA structures crystallized at various pH levels show the hexamer central pore is flexible and can exist in open and closed conformations (Fig. 2d and e) (Jacques & et al., 2016). This molecular iris resides over an electropositive channel that coordinates phosphate groups of polyanions including ATP and IP6. Emerging work shows IP6 is critical for regulating the structural integrity of both the immature Gag lattice and mature capsid, and thus is a vital cofactor for infection (Jacques & et al., 2016; Mallery & et al., 2018). Computational studies suggest IP6 binding may also govern dNTP import to fuel reverse transcription (Xu & et al., 2020). Overall, a combination of repulsive forces at the central pore of capsomeres are counteracted via small molecule binding and stabilizing hydrophobic CTD interactions (Zhao & et al., 2013), which together define a lattice geometry that offers an array of binding interfaces for host factors to engage.

3. Capsid-host interactions

The HIV-1 capsid is a primary target of diverse host proteins that work to either inhibit or promote HIV-1 infection during cellular transport, nuclear import, and genome integration (Fig. 1) (Yamashita & Engelman, 2017). An understanding of how these host proteins interact with the capsid is crucial for understanding the HIV-1 replication cycle and developing antiviral therapeutics. These interactions have been extensively investigated by cell-based infectivity studies, biochemical studies with purified virus cores, and *in vitro* experiments using CA assemblies that mimic the capsid architecture; these assemblies include capsid-like CA cones and cylindrical CA tubes (Fig. 2a) (Dick & et al., 2018), as well as soluble capsomere assemblies such as di- and tri-hexamers (Fig. 2c). These assemblies recapitulate the interfaces between capsomere building blocks that capsid interactors require for binding (Summers & et al., 2019).

3.1. Cytoplasmic restriction and protection

CypA, TRIM5α/TRIMCyp, and MxB

The viral capsid exploits and is targeted by host factors while protecting and trafficking the genome to the nucleus (Fig. 1). In humans, cyclophilin A (CypA) is necessary for and is intricately involved in many parts of the viral life cycle, from reverse transcription to genome integration (Yamashita & Engelman, 2017). CypA is a peptidyl prolyl isomerase that interacts with the flexible CypA-binding loop that protrudes from the capsid surface (Figs. 2d and 3a). The CypA-binding loop of CA tucks into a hydrophobic pocket located on CypA (Fig. 3a). Mutations at G89 and P90 in this loop abrogate the interaction and can thereby block HIV-1 infectivity, though this effect is cell type-dependent (Yamashita & Engelman, 2017; Li et al., 2009). CypA decoration of CA tubes also demonstrates two weaker, curvature-sensitive, non-canonical binding sites over di- and tri-hexamer interfaces in which each CypA molecule contacts three separate CA monomers (Ni & et al., 2020; Liu & et al., 2016; Peng & et al., 2019). The CypA-capsid interactions likely modulate the capsid stability and its capacity to bind other cellular factors. For example, human tripartite motif protein 5α (TRIM5α) is able to restrict HIV-1 infection (Ganser-Pornillos & Pornillos, 2019) but CypA may affect TRIM5α restriction by blocking the TRIM5α–capsid interaction (Jimenez-Guardeno & et al., 2019; Selyutina & et al., 2020). However, TRIM5α from other primates retains restriction against HIV-1 in the presence of CypA.

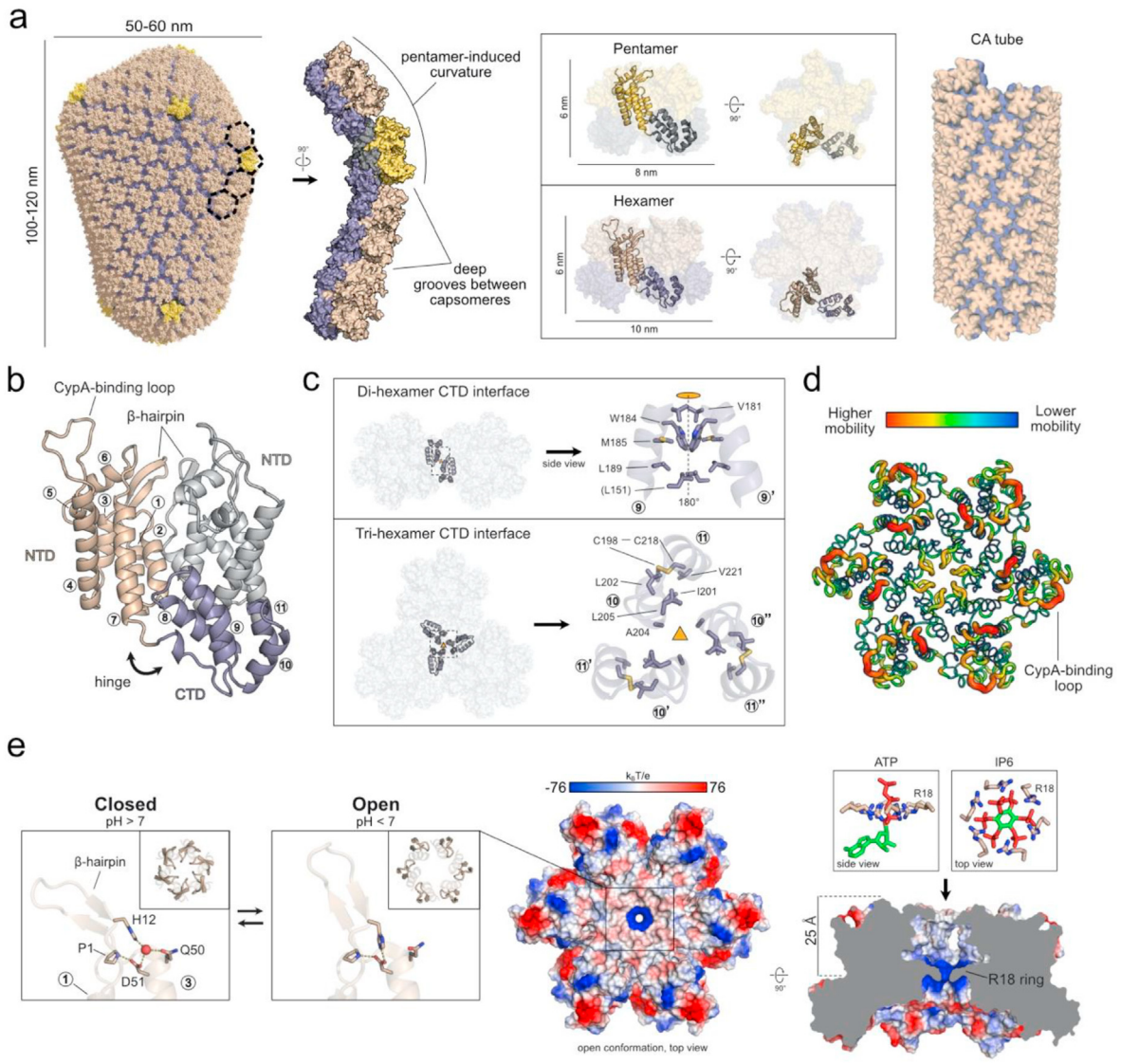

Fig. 2. Molecular details of HIV-1 capsid structure and dynamics. a. The HIV-1 capsid is comprised of CA hexamers and pentamers. Planar, symmetric crystal structures are shown. CA hexamers can polymerize into helical tubes that recapitulate a portion of the capsid architecture. b. CA NTD (beige) is connected via a flexible hinge to the CTD (slate), which interacts with a neighboring NTD (gray) in the hexamer. The NTD-CTD (gray/slate) interface forms the FG-binding pocket. c. Two types of inter-capsomere interfaces exist throughout the capsid, mediated through CTDs. Examples of these are shown between di-hexamers (top, two-fold interface) and tri-hexamers (bottom, three-fold interface). d. Mobile regions of the CA hexamer include the CypA-binding loop and β-hairpin over the central pore. e. The N-terminal β-hairpin is a gatekeeper at the top of the hexamer pore and acts as a pH-sensitive iris (water, red sphere). A top view electrostatic surface potential map of an open hexamer illustrates the highly basic pore (blue, positive charge; red, negative charge). A cross-section reveals the R18 ring which stably binds molecules such as IP6, which may be involved in ATP/dNTP import (shown above cross-section in green with phosphate moieties in red).

TRIM5 proteins, including TRIM5α and TRIMCyp, provide a barrier for cross-species transmission of lentiviruses such as HIV-1 and simian immunodeficiency virus (SIV-1). The tripartite motif consists, from N- to C-terminus, of a RING, a B-box, and a coiled-coil domain (Fig. 3b) (Ganser-Pornillos & Pornillos, 2019). The coiled-coil domain allows for dimerization, whereas the B-box domain allows for higher-order oligomerization into a cage-like structure that surrounds the HIV-1 capsid to restrict the virus. The RING domain generates ubiquitin chains to stimulate immune signaling for an additional mode of viral suppression (Zhang & et al., 2018). TRIM5 proteins have an additional CTD that can vary across primate species and is the domain responsible for HIV-1 capsid recognition. The TRIM5α CTD has a SPRY domain, which is replaced in TRIMCyp with a CypA domain. TRIM5α SPRY domains engage the capsid in various binding modes: at the center of a single hexamer, between two adjacent hexamers, and between three hexamers (Fig. 3b). The CypA domain of TRIMCyp also exhibits flexibility and multiple binding possibilities for binding capsid (Fig. 3b). A balance between TRIM5α–TRIM5α and TRIM5α–capsid interactions has been shown to be necessary for proper formation of the TRIM5α cage (Yu & et al., 2020). New advances also show that this cage adopts a para-crystalline architecture where patches of hexagonal lattice are glued together by pentameric and heptameric grain boundaries to allow for necessary curvature (Yu & et al., 2020; Skorupka & et al., 2019).

The nuclear import of HIV-1 presents an additional barrier to viral infection. Myxovirus resistance protein B (MxB) effectively restricts HIV-1 in addition to other viruses (Fricke & et al., 2014; Kane & et al., 2013; Goujon & et al., 2013). MxB, located near the NPC, inhibits HIV-1 infection by blocking the pre-integration complex (PIC) from nuclear import and subsequent integration of the viral genome into the host genome (Fig. 1). MxB is comprised of three domains: a GTPase domain, a stalk domain, and the bundling signaling element (BSE) (Fig. 3c). An N-terminal 25 residue-long region is necessary for HIV-1 restriction

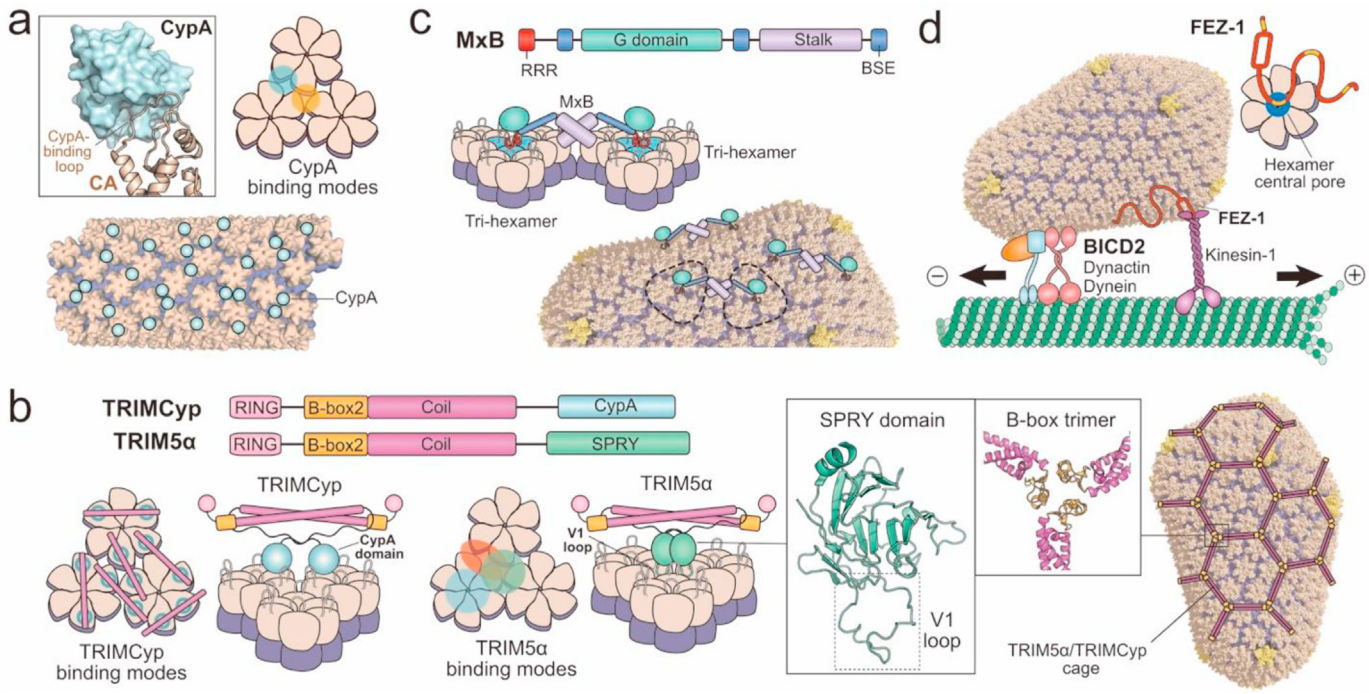

Fig. 3. HIV-1 viral-host interactions. a. Canonical interaction between CypA and the CypA-binding loop on CA (top left). General CypA binding modes are indicated above the di- and tri-hexamer interfaces (marked blue and orange), contacting 3 CA monomers each (top right). A possible pattern of CypA decoration on a CA tube is shown (bottom). b. Top, a domain schematic of TRIM proteins is shown. Left, TRIMCyp binds to a pair of inter- or intra-hexamer CypA-binding loops in a flexible and variable manner. Middle, the SPRY domain V1 loop of TRIM5α binds diverse capsid sites (marked red, green, and blue). Right, the B-box domain mediates TRIMCyp/TRIM5α formation around capsid. c. Domain schematic of MxB is shown. The N-terminal region of MxB binds the tri-hexamer interface on capsid. d. FEZ-1 binds to the central pore of the CA hexamer. The specific interaction of BICD2 with capsid is currently unknown. These adaptors facilitate transport along microtubules.

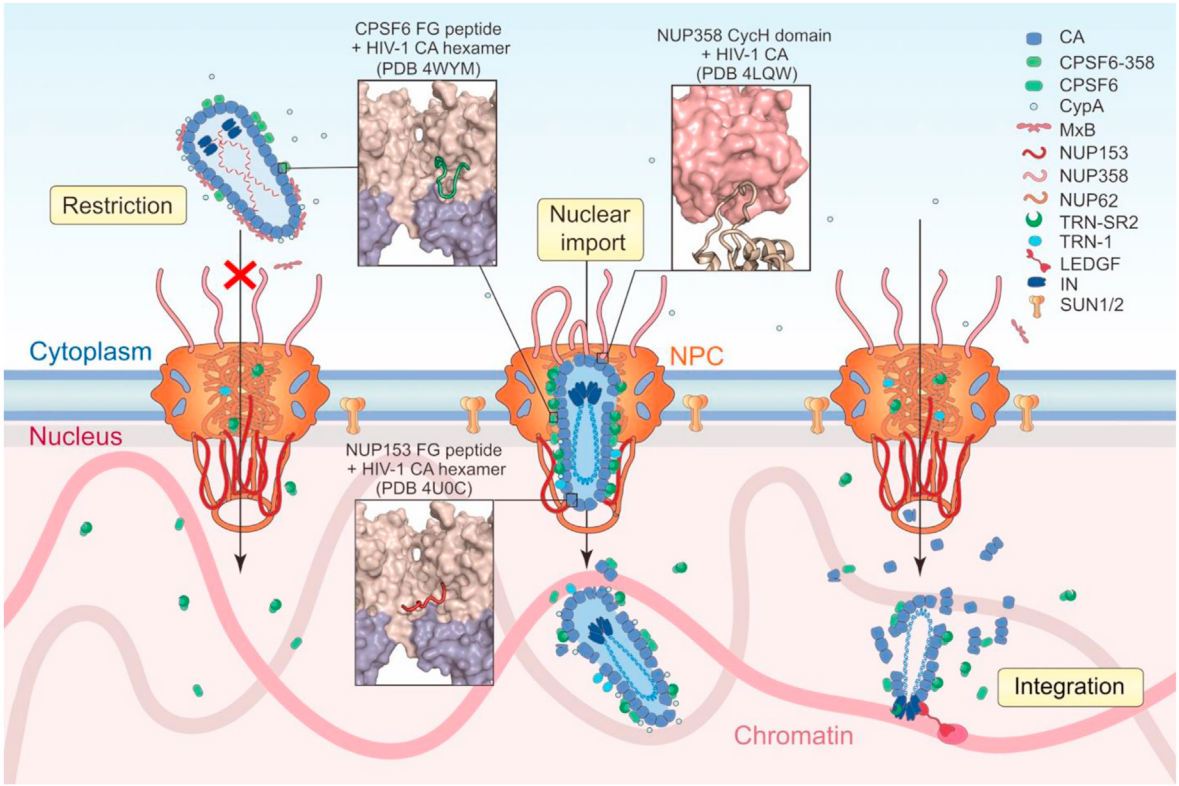

Fig. 4. HIV-1 capsid-host interactions at the nuclear pore complex. Left, MxB prevents nuclear import. CPSF6 can interact with the capsid in the cytoplasm. Center, NUP358, NUP62, and NUP153 facilitate nuclear import while CPSF6, TRN-SR2, and TRN-1 assist in translocation through the NPC. Right, CPSF6, LEDGF, and IN enable genome integration. The boxed insets show crystal structures of some of these interactions. NUP153 and CPSF6 peptides occupy the FG pocket formed at the NTD-CTD interface between adjacent CA monomers. NUP358 CycH binds to the CypA-binding loop.

(Schulte & et al., 2015), within which a triple arginine (RRR) motif is necessary for capsid binding. MxB is unable to bind to a CA monomer or individual hexamers and pentamers (Fribourgh & et al., 2014). Instead, the N-terminal RRR motif of MxB binds at the three-fold inter-hexamer interface in a pocket that contains a cluster of negatively charged residues (Summers & et al., 2019; Smaga & et al., 2019).

It has been reported that polyglutamine binding protein (PQBP1) together with cyclic GAMP synthase (cGAS) presents another layer of restriction to HIV-1 in specific cell types (Fig. 1) (Yoh & et al., 2015). However, details of PQBP1 interactions remain to be determined.

3.2. Cellular transport via the microtubule network

FEZ-1 and BICD2

The HIV-1 capsid mobilizes through the host cytoplasm towards the nucleus by hijacking microtubule motor proteins kinesin and dynein (Fig. 3d). Bicaudal 2 (BICD2) is a dynein motor adaptor protein comprised of two domains: an NTD that engages the dynein-dynactin complex and a CTD that binds to the transporting cargo. The C-terminus of BICD2 is important for capsid binding and trafficking to the nucleus (Dharan & et al., 2017). Uncharacteristically, the N-terminal domain also binds to the capsid albeit with less affinity (Carnes et al., 2018). These interactions allow BICD2 to directly link the capsid to a microtubule motor complex. HIV-1 engagement with the BICD2-dynein-dynactin complex is important for cellular transport of the capsid to the nucleus. However, how BICD2 binds capsid remains to be determined.

Fasciculation and Elongation protein Zeta 1 (FEZ-1) is a kinesin-1 adaptor protein that generally transports cargo towards the periphery of the cytoplasm and is important for HIV-1 infectivity (Malikov & et al., 2015). Counterintuitively, FEZ-1 and kinesin help navigate the capsid toward the nucleus (Fig. 3d). FEZ-1 binds to capsid assemblies, with the highest affinity known to date, in the absence of the kinesin motor which suggests that it links the capsid to kinesin for transport (Huang & et al., 2019). Binding is mediated through polyglutamate motifs of FEZ-1 that interact with the positively-charged central pore of CA hexamers, which is a common binding site for small molecule cofactors such as dNTPs and IP6 (Fig. 2e) (Mallery & et al., 2018). Multiple polyglutamate sequences throughout FEZ-1 bind at multiple hexamer pores to enhance the avidity of the interaction.

3.3. Nuclear import

NUP358, NUP62, NUP153, CPSF6, TRN-SR2, TRN-1, LEDGF, SUN1/SUN2

Following cytoplasmic trafficking, the capsid localizes to the nuclear pore complex (NPC), initiating the nuclear entry of the HIV-1 capsid and the viral genome (Fig. 1). The NPC provides the only channel for capsid translocation into the nucleus during cell interphase. The NPC contains nucleoporins (NUPs) that are critical for nuclear import of the capsid. Many NUPs interact with the capsid including NUP358, NUP214, NUP88, NUP62, and NUP153 (Kane & et al., 2018). Extensive research of NUP358 and NUP153 have led to a better understanding of the NPC in HIV-1 infectivity. NUP358 is located on the cytoplasmic side of the NPC while NUP153 is located on the nucleoplasmic side (Figs. 1 and 4). Both NUPs share binding interfaces with other host factors. NUP358 contains a CypA homology domain (CycH) that binds to the CypA-binding loop of CA (Figs. 4 and 5). NUP153 binds at the NTD-CTD interface between two CA subunits of the hexamer (Figs. 4 and 5). Multiple crystal structures

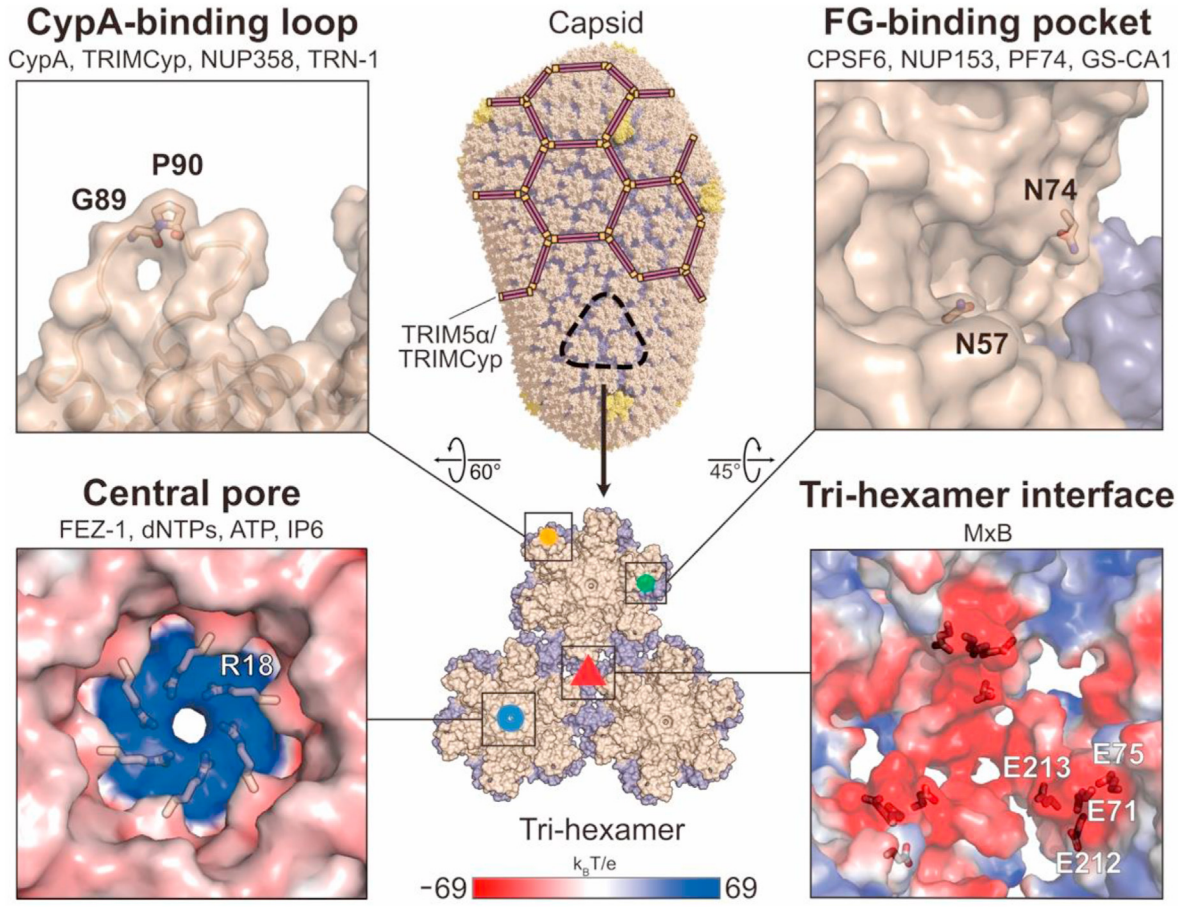

Fig. 5. Summary of binding interfaces of HIV-1 capsid with host factors and inhibitors. Selected key residues are shown for major binding sites within the capsid architecture. Key demonstrated interactors are listed. Bottom panels illustrate electrostatic surface potential at these sites.

show the FG motif-containing peptide from NUP153 bound with CA hexamer (Price & et al., 2014). NUP62 located on the interior of the NPC binds to the capsid and possibly alters MxB restriction of HIV-1 (Kane & et al., 2018). These interactions suggest that the capsid is engaged in the entire nuclear import process, from the cytoplasm to the nucleus, but the exact mechanisms remain largely unknown.

Remarkably, recent evidence shows that the HIV-1 capsid passes through the nuclear pore intact or almost intact, although this remains a controversial hypothesis and should be considered along with models of cytoplasmic and NPC-mediated uncoating. Recent evidence suggests uncoating happens after the capsid has entered the nucleus, completed reverse transcription of its genome, and moved close to integration sites (Burdick & et al., 2020). Evidence suggests that capsid interaction with the host protein cleavage and polyadenylation specificity factor 6 (CPSF6) supports entry through nuclear pores (Achuthan & et al., 2018; Bejarano & et al., 2019). CPSF6 is part of the cleavage factor Im (CFIm) complex that is important for pre-mRNA processing in cells. CPSF6 contains an N-terminal RNA binding domain, a proline-rich domain (PRD), and a serine/arginine-rich (SR) domain. Residues 314 to 322 of CPSF6 contain a FG motif that binds directly to capsid at the NTD-CTD interface between two neighboring CA monomers in a hexamer, similar to NUP153 (Figs. 2b, 4 and 5) (Bhattacharya & et al., 2014). This NTD-CTD interface is a viable drug target as it binds the HIV-1 inhibitors PF74 and the recent and more potent inhibitor GS-CA1 (Fig. 5) (Bhattacharya & et al., 2014; Carnes et al., 2018). CPSF6 with an SR domain deletion (CPSF6-358) localizes to the cytoplasm and restricts HIV-1 infection (Lee & et al., 2010). CPSF6-358 is able to disrupt CA tubes (Ning & et al., 2018); thus, CPSF6 enrichment during capsid docking in the NPC may cause capsid deformation to aid in translocation through the NPC (Fig. 4). The CPSF6-capsid interaction is also important for targeting the Lens epithelium-derived growth factor (LEDGF)/integrase (IN) complex to gene-rich positions for viral genome integration (Figs. 1 and 4) (Achuthan & et al., 2018). Several transportins facilitate the nuclear import of HIV-1 capsid. Transportin-3 (TRN-SR2) transports CPSF6 into the nucleus (Maertens & et al., 2014), while Transportin-1 (TRN-1) directly binds with capsid assemblies (Fernandez & et al., 2019), potentially through a hydrophobic pocket on TRN-1 that engages with the CypA-binding loop of CA (Fig. 5). In addition, inner nuclear membrane proteins SUN1 and SUN2 bind capsid and may modulate HIV-1 viral infectivity (Schaller & et al., 2017). Several considerations for trafficking of intact capsid to the interior of the nucleus should be considered: the heterogeneity of capsid size, the participation of other factors, and the flexibility of the NPC central channel. Further research is needed to elucidate these mechanistic details.

4. Conclusion

Here, we provide a graphical snapshot of the importance of capsid–host interactions crucial for HIV-1 infectivity. The capsid represents a hotbed of interactions by recruiting diverse host factors to its surface, often in a lattice-dependent manner (Fig. 5). These interactions and the abundance of capsid-interacting proteins in the cell depict a fine-tuned evolutionary process for the requirements of viral infection and evading restriction by host immune factors. Modulations of these interactions therefore may open up new avenues for therapeutic treatment of HIV-1 infection.

CRediT authorship contribution statement

Joshua Temple: Conceptualization, Visualization, Writing - original draft, Writing - review & editing. **Therese N. Tripler:** Conceptualization, Visualization, Writing - original draft, Writing - review & editing. **Qi Shen:** Visualization, Writing - original draft. **Yong Xiong:** Conceptualization, Project administration, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank members of the Xiong lab for continuous discussions. This work was supported by NIH grant 50GM082251/AI150481. Our funding source did not contribute to preparation of this manuscript.

References

Achuthan, V., et al., 2018. Capsid-CPSF6 interaction licenses nuclear HIV-1 trafficking to sites of viral DNA integration. Cell Host Microbe 24 (3), 392–404. https://doi.org/10.1016/j.chom.2018.08.002 e8.

Bejarano, D.A., et al., 2019. HIV-1 nuclear import in macrophages is regulated by CPSF6-capsid interactions at the nuclear pore complex. Elife 8. https://doi.org/10.7554/eLife.41800.

Bhattacharya, A., et al., 2014. Structural basis of HIV-1 capsid recognition by PF74 and CPSF6. Proc Natl Acad Sci U S A 111 (52), 18625–18630. https://doi.org/10.1073/pnas.1419945112.

Burdick, R.C., et al., 2020. HIV-1 uncoats in the nucleus near sites of integration. Proc Natl Acad Sci U S A 117 (10), 5486–5493. https://doi.org/10.1073/pnas.1920631117.

Carnes, S.K., Zhou, J., Aiken, C., 2018. HIV-1 engages a dynein-dynactin-BICD2 complex for infection and transport to the nucleus. J Virol (20), 92. https://doi.org/10.1128/JVI.00358-18.

Carnes, S.K., Sheehan, J.H., Aiken, C., 2018. Inhibitors of the HIV-1 capsid, a target of opportunity. Curr Opin HIV AIDS 13 (4), 359–365. https://doi.org/10.1097/COH.0000000000000472.

Dharan, A., et al., 2017. Bicaudal D2 facilitates the cytoplasmic trafficking and nuclear import of HIV-1 genomes during infection. Proc Natl Acad Sci U S A 114 (50), E10707–E10716. https://doi.org/10.1073/pnas.1712033114.

Dick, R.A., et al., 2018. Inositol phosphates are assembly co-factors for HIV-1. Nature 560 (7719), 509–512. https://doi.org/10.1038/s41586-018-0396-4.

Fernandez, J., et al., 2019. Transportin-1 binds to the HIV-1 capsid via a nuclear localization signal and triggers uncoating. Nat Microbiol 4 (11), 1840–1850. https://doi.org/10.1038/s41564-019-0575-6.

Fribourgh, J.L., et al., 2014. Structural insight into HIV-1 restriction by MxB. Cell Host Microbe 16 (5), 627–638. https://doi.org/10.1016/j.chom.2014.09.021.

Fricke, T., et al., 2014. MxB binds to the HIV-1 core and prevents the uncoating process of HIV-1. Retrovirology 11, 68. https://doi.org/10.1186/s12977-014-0068-x.

Ganser-Pornillos, B.K., Pornillos, O., 2019. Restriction of HIV-1 and other retroviruses by TRIM5. Nat Rev Microbiol 17 (9), 546–556. https://doi.org/10.1038/s41579-019-0225-2.

Goujon, C., et al., 2013. Human MX2 is an interferon-induced post-entry inhibitor of HIV-1 infection. Nature 502 (7472), 559–562. https://doi.org/10.1038/nature12542.

Huang, P.T., et al., 2019. FEZ1 is recruited to a conserved cofactor site on capsid to promote HIV-1 trafficking. Cell Rep 28 (9), 2373–2385. https://doi.org/10.1016/j.celrep.2019.07.079 e7.

Jacques, D.A., et al., 2016. HIV-1 uses dynamic capsid pores to import nucleotides and fuel encapsidated DNA synthesis. Nature 536 (7616), 349–353. https://doi.org/10.1038/nature19098.

Jimenez-Guardeno, J.M., et al., 2019. Immunoproteasome activation enables human TRIM5alpha restriction of HIV-1. Nat Microbiol 4 (6), 933–940. https://doi.org/10.1038/s41564-019-0402-0.

Kane, M., et al., 2013. MX2 is an interferon-induced inhibitor of HIV-1 infection. Nature 502 (7472), 563–566. https://doi.org/10.1038/nature12653.

Kane, M., et al., 2018. Nuclear pore heterogeneity influences HIV-1 infection and the antiviral activity of MX2. Elife 7. https://doi.org/10.7554/eLife.35738.

Lee, K., et al., 2010. Flexible use of nuclear import pathways by HIV-1. Cell Host Microbe 7 (3), 221–233. https://doi.org/10.1016/j.chom.2010.02.007.

Li, Y., Kar, A.K., Sodroski, J., 2009. Target cell type-dependent modulation of human immunodeficiency virus type 1 capsid disassembly by cyclophilin A. J Virol 83 (21), 10951–10962. https://doi.org/10.1128/JVI.00682-09.

Liu, C., et al., 2016. Cyclophilin A stabilizes the HIV-1 capsid through a novel non-canonical binding site. Nat Commun 7, 10714. https://doi.org/10.1038/ncomms10714.

Lu, M., et al., 2020. Atomic-resolution structure of HIV-1 capsid tubes by magic-angle spinning NMR. Nat Struct Mol Biol 27 (9), 863–869. https://doi.org/10.1038/s41594-020-0489-2.

Maertens, G.N., et al., 2014. Structural basis for nuclear import of splicing factors by human Transportin 3. Proc Natl Acad Sci U S A 111 (7), 2728–2733. https://doi.org/10.1073/pnas.1320755111.

Malikov, V., et al., 2015. HIV-1 capsids bind and exploit the kinesin-1 adaptor FEZ1 for inward movement to the nucleus. Nat Commun 6, 6660. https://doi.org/10.1038/ncomms7660.

Mallery, D.L., et al., 2018. IP6 is an HIV pocket factor that prevents capsid collapse and promotes DNA synthesis. Elife 7. https://doi.org/10.7554/eLife.35335.

Mattei, S., et al., 2016. The structure and flexibility of conical HIV-1 capsids determined within intact virions. Science 354 (6318), 1434–1437. https://doi.org/10.1126/science.aah4972.

Ni, T., et al., 2020. Intrinsic curvature of the HIV-1 CA hexamer underlies capsid topology and interaction with cyclophilin A. Nat Struct Mol Biol. https://doi.org/10.1038/s41594-020-0467-8.

Ning, J., et al., 2018. Truncated CPSF6 forms higher-order complexes that bind and disrupt HIV-1 capsid. J Virol 92 (13). https://doi.org/10.1128/JVI.00368-18.

Peng, W., et al., 2019. Functional analysis of the secondary HIV-1 capsid binding site in the host protein cyclophilin A. Retrovirology 16 (1), 10. https://doi.org/10.1186/s12977-019-0471-4.

Pornillos, O., et al., 2009. X-ray structures of the hexameric building block of the HIV capsid. Cell 137 (7), 1282–1292. https://doi.org/10.1016/j.cell.2009.04.063.

Price, A.J., et al., 2014. Host cofactors and pharmacologic ligands share an essential interface in HIV-1 capsid that is lost upon disassembly. PLoS Pathog 10 (10), e1004459. https://doi.org/10.1371/journal.ppat.1004459.

Schaller, T., et al., 2017. Effects of inner nuclear membrane proteins SUN1/UNC-84A and SUN2/UNC-84B on the early steps of HIV-1 infection. J Virol 91 (19). https://doi.org/10.1128/JVI.00463-17.

Schulte, B., et al., 2015. Restriction of HIV-1 requires the N-terminal region of MxB as a capsid-binding motif but not as a nuclear localization signal. J Virol 89 (16), 8599–8610. https://doi.org/10.1128/JVI.00753-15.

Selyutina, A., et al., 2020. Cyclophilin A prevents HIV-1 restriction in lymphocytes by blocking human TRIM5alpha binding to the viral core. Cell Rep 30 (11), 3766–3777. https://doi.org/10.1016/j.celrep.2020.02.100 e6.

Skorupka, K.A., et al., 2019. Hierarchical assembly governs TRIM5alpha recognition of HIV-1 and retroviral capsids. Sci Adv 5 (11), eaaw3631. https://doi.org/10.1126/sciadv.aaw3631.

Smaga, S.S., et al., 2019. MxB restricts HIV-1 by targeting the tri-hexamer interface of the viral capsid. Structure 27 (8), 1234–1245. https://doi.org/10.1016/j.str.2019.04.015 e5.

Summers, B.J., et al., 2019. Modular HIV-1 capsid assemblies reveal diverse host-capsid recognition mechanisms. Cell Host Microbe 26 (2), 203–216. https://doi.org/10.1016/j.chom.2019.07.007 e6.

Welker, R., et al., 2000. Biochemical and structural analysis of isolated mature cores of human immunodeficiency virus type 1. J Virol 74 (3), 1168–1177. https://doi.org/10.1128/jvi.74.3.1168-1177.2000.

Xu, C., et al., 2020. Permeability of the HIV-1 capsid to metabolites modulates viral DNA synthesis. bioRxiv 2020. https://doi.org/10.1101/2020.04.30.071217, 04.30.071217.

Yamashita, M., Engelman, A.N., 2017. Capsid-dependent host factors in HIV-1 infection. Trends Microbiol 25 (9), 741–755. https://doi.org/10.1016/j.tim.2017.04.004.

Yoh, S.M., et al., 2015. PQBP1 is a proximal sensor of the cGAS-dependent innate response to HIV-1. Cell 161 (6), 1293–1305. https://doi.org/10.1016/j.cell.2015.04.050.

Yu, A., et al., 2020. TRIM5alpha self-assembly and compartmentalization of the HIV-1 viral capsid. Nat Commun 11 (1), 1307. https://doi.org/10.1038/s41467-020-15106-1.

Zhang, Y., et al., 2018. RING-domain E3 ligase-mediated host-virus interactions: orchestrating immune responses by the host and antagonizing immune defense by viruses. Front Immunol 9, 1083. https://doi.org/10.3389/fimmu.2018.01083.

Zhao, G., et al., 2013. Mature HIV-1 capsid structure by cryo-electron microscopy and all-atom molecular dynamics. Nature 497 (7451), 643–646. https://doi.org/10.1038/nature12162.