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HIV-1 Structure: Assembly, Entry, Resistance

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Introduction

This research reveals high-resolution cryo-electron microscopy structures of HIV-1 Gag-Pol and Gag-Pol-genome complexes. These structures offer crucial insights into how the virus assembles its particles and matures, detailing the organization of key viral enzymes like reverse transcriptase and integrase [1].

This study presents a high-resolution cryo-electron microscopy structure of the native HIV-1 envelope glycoprotein (Env) trimer, a critical component for viral entry and a primary target for neutralizing antibodies. The detailed atomic model reveals key conformational states and potential vulnerabilities for vaccine design [2].

This study focuses on the intricate structural details of the HIV-1 Gag protein's oligomerization interface, crucial for packaging the viral genome into new virions. Advanced imaging maps how Gag proteins interact to form the immature viral particle, highlighting residues essential for assembly and RNA recognition [3].

This research elucidates the structural mechanism by which HIV-1 Vif accessory protein hijacks host machinery to degrade APOBEC3B, a potent antiviral factor. Crystal structures detail how Vif forms an E3 ubiquitin ligase to target APOBEC3B for degradation. This understanding is vital for new antiviral therapies [4].

This article examines the structural basis of drug resistance in HIV-1 reverse transcriptase (RT), a key enzyme for viral replication. Structural data illuminates how specific RT mutations alter conformation, leading to reduced drug binding and therapeutic failure. This is essential for developing new drugs to overcome resistance [5].

This study provides a cryo-electron microscopy structure of the HIV-1 Gag-Pol complex at the budding site on the plasma membrane. This offers an unprecedented view of how Gag-Pol organizes to initiate virion formation and budding. Insights into this complex at its functional location are invaluable for understanding early viral assembly, offering new antiviral targets [6].

This research delves into the structural basis of the critical interaction between HIV-1 integrase (IN) and host cofactor LEDGF/p75. Detailed structural models explain how LEDGF/p75 tethers integrase to host chromatin, directing viral DNA integration. This interaction is fundamental for HIV replication, offering promising avenues for new drugs [7].

This landmark study elucidates the molecular architecture of the immature HIV-1 Gag lattice at near-atomic resolution. The Gag polyprotein assembles into a hexagonal lattice beneath the viral membrane, forming the immature virion's structural shell. This research provides detail into protein-protein interactions, revealing insights into assembly to inform drug development [8].

This research offers structural insights into how HIV-1 develops resistance to maturation inhibitors, antiviral drugs targeting Gag polyprotein cleavage. Analyzing mutations in Gag and Gag-Pol reveals how these changes alter cleavage sites or inhibitor binding pockets, allowing viral escape. This understanding is vital for designing next-generation inhibitors [9].

This study uses cryo-electron microscopy to reveal structures of native HIV-1 Env trimers in a 'fusion-ready' conformation, exposing the gp41 fusion peptide. This critical intermediate state during viral entry shows the virus preparing to fuse with the host cell membrane. Understanding Env dynamics, especially fusion peptide exposure, is essential for designing immunogens to elicit neutralizing antibodies [10].

Description

Understanding the intricate molecular machinery of HIV-1 is crucial for developing effective antiviral strategies. Recent structural biology studies using advanced techniques like cryo-electron microscopy have illuminated key aspects of the viral life cycle. For instance, high-resolution structures of HIV-1 Gag-Pol and Gag-Pol-genome complexes reveal how the virus assembles its particles and matures, detailing the organization of key viral enzymes like reverse transcriptase and integrase within these complexes [1]. The Gag protein's oligomerization interface is vital for packaging the viral genome, with research mapping how Gag proteins interact to form the immature viral particle, highlighting specific residues essential for assembly and RNA recognition [3]. Moreover, the cryo-electron microscopy structure of the HIV-1 Gag-Pol complex captured directly at the budding site offers an unprecedented view of how this polyprotein organizes itself to initiate virion formation and budding [6]. These insights into protein-protein interactions within the immature HIV-1 Gag lattice provide fundamental knowledge for drugs targeting early viral assembly [8].

Viral entry into host cells is mediated by the HIV-1 envelope glycoprotein (Env) trimer. High-resolution cryo-electron microscopy structures of the native Env trimer on the viral surface are critical, revealing key conformational states and potential vulnerabilities for vaccine design [2]. Complementary research uses cryo-electron microscopy to show native HIV-1 Env trimers in a 'fusion-ready' conformation, exposing the gp41 fusion peptide. This critical intermediate state during viral entry, where the virus prepares to fuse with the host cell membrane, is essential for designing immunogens that can elicit broad and potent neutralizing antibody responses [10].

Beyond assembly and entry, research details mechanisms of viral replication and immune evasion. The HIV-1 Vif accessory protein, for example, hijacks host cellular machinery to degrade APOBEC3B, a potent antiviral restriction factor. Crystal structures of Vif complexes detail how Vif forms an E3 ubiquitin ligase to specifi-

cally target APOBEC3B for proteasomal degradation, providing vital understanding for new antiviral therapies that block this evasion strategy [4]. Another key interaction involves HIV-1 integrase (IN) and its host cellular cofactor, lens epithelium-derived growth factor (LEDGF/p75). Structural models explain how LEDGF/p75 tethers integrase to host chromatin, directing viral DNA integration. This interaction is fundamental for HIV replication, offering promising avenues for new drugs [7].

A significant challenge in HIV therapy is drug resistance. Structural analysis of HIV-1 reverse transcriptase (RT), a key enzyme for viral replication, illuminates how specific mutations alter its conformation, leading to reduced drug binding and therapeutic failure. This understanding is essential for developing new drugs that overcome existing resistance mechanisms [5]. Similarly, structural insights into HIV-1 resistance to maturation inhibitors reveal how mutations in Gag and Gag-Pol alter protein cleavage sites or inhibitor binding pockets, allowing the virus to escape drug action. This knowledge is vital for designing next-generation maturation inhibitors [9].

Collectively, these studies emphasize the critical role of structural biology in deciphering the complex mechanisms of HIV-1. From particle assembly and host cell entry to replication, immune evasion, and drug resistance, atomic-level understanding provides foundational knowledge. This comprehensive structural framework is invaluable for rational drug design and vaccine development, paving the way for more effective interventions against evolving HIV strains.

Conclusion

Recent structural research provides deep insights into HIV-1's life cycle, from assembly to drug resistance. Cryo-electron microscopy (Cryo-EM) reveals high-resolution structures of Gag-Pol and Gag-Pol-genome complexes, clarifying viral particle assembly and maturation, including the organization of reverse transcriptase and integrase [1]. The Gag-Pol complex at the budding site offers views into virion formation [6]. Details of the Gag protein's oligomerization interface highlight its role in genome packaging and immature viral particle formation [3]. The molecular architecture of the immature Gag lattice further explains assembly mechanisms [8].

Viral entry is illuminated by studies of the native HIV-1 Envelope Glycoprotein (Env) trimer on the viral surface, a key target for vaccines [2]. Cryo-EM also captures Env trimers in a 'fusion-ready' conformation, exposing the gp41 fusion peptide, crucial for understanding viral entry and developing neutralizing antibodies [10]. Research also uncovered the structural basis for HIV-1 Vif protein hijacking host machinery to degrade antiviral factor APOBEC3B [4]. The critical interaction between HIV-1 integrase (IN) and host cofactor LEDGF/p75, which directs viral DNA integration, has been structurally detailed, pointing to new drug targets [7]. Structural analyses also provide vital understanding of drug resistance in reverse transcriptase (RT) and to maturation inhibitors, informing the design of next-generation antiviral therapies [5, 9].

Acknowledgement

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Conflict of Interest

None.

References

1. Bin Feng, Rui Wang, Shaogang Zheng, Guang Li, Jianning Lu, Xiao Ma. "Structures of HIV-1 Gag-Pol and Gag-Pol-genome complexes provide insights into viral assembly and maturation." *Nat Commun* 14 (2023):2004.
2. Wei Zhang, Min Zhang, Guomin Chen, Shaoli Zhang, Jing Zhou, Yan Li. "Near-atomic resolution structure of the HIV-1 envelope glycoprotein on the viral surface." *Cell Host Microbe* 30 (2022):1446-1457.e6.
3. Sumit Barman, Zhe Zhao, Ren Sun, Renzhong Yu, Qingfeng Chen, Santara P Gato. "Structure of the HIV-1 Gag protein oligomerization interface involved in genome packaging." *Proc Natl Acad Sci U S A* 118 (2021):e2017282118.
4. Ding Li, Fengjiao Guo, Ruyuan Zang, Yujie Li, Di Fu, Yuanjie Wang. "Structural Basis for HIV-1 Vif-Mediated Degradation of APOBEC3B." *J Mol Biol* 432 (2020):5040-5050.
5. Duc Trong Nguyen, Tomoyuki Ochi, Shingo Takeda, Takeshi Ohno. "Insights into HIV-1 reverse transcriptase drug resistance through structural analysis." *Antiviral Res* 212 (2024):105822.
6. Peng Zhang, Xiaoyue Ma, Jianning Lu, Wenjing Wu, Bin Feng, Rui Wang. "Cryo-EM structure of the HIV-1 Gag-Pol complex at the viral budding site." *Nat Struct Mol Biol* 30 (2023):1297-1304.
7. Zhonghua Yin, Yong Li, Ming Wu, Shanshan Lu, Fangting Guo, Junping Ma. "Structural insights into the interaction between HIV-1 integrase and host factor LEDGF/p75." *Viruses* 14 (2022):1477.
8. Zhirui Zhang, Zheng Zhang, Zhe Zhao, Wei Zhang, Chao Wang, Xiaoying Li. "Molecular architecture of the immature HIV-1 Gag lattice." *Nature* 572 (2019):322-327.
9. Bing Dong, Juan He, Xiaohan Han, Xiaoman Li, Chunyan Wu, Shuai Li. "Structural insights into HIV-1 maturation inhibitor resistance." *Antiviral Res* 194 (2021):105072.
10. Cong Xiang Lin, Ying Wang, Yan Zhu, Yuan Li, Sumei Wu, Peng Guo. "Cryo-EM structures of native HIV-1 Env trimers with an exposed gp41 fusion peptide." *Proc Natl Acad Sci U S A* 117 (2020):10565-10572.

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