Capsid adaptation defines pandemic HIV

Pandemic viruses cause major global disease burden and economic disruption. We investigated pandemic HIV-1(M) to understand its unique characteristics by comparing it with HIV strains that did not achieve pandemic human-to-human spread. We observed structural adaptations in the HIV-1(M) capsid that reduce detection by innate immune sensors.

This is a summary of:
Zuliani-Alvarez, L. et al. Evasion of cGAS and TRIM5 defines pandemic HIV. *Nat. Microbiol.* https://doi.org/10.1038/s41564-022-01247-0 (2022).

Published online:
Published online: 26 October 2022

The question

Viruses are defined as pandemic by the World Health Organization when they have spread globally, infecting many thousands of people. Typically, pandemic viruses have jumped from an animal host to humans, a process called zoonosis.

Pandemic viruses are rare because most zoonoses do not lead to much human-to-human spread. Humans are usually successful at suppressing animal virus infections, individually and at the population level, owing to millions of years of immune system evolution. However, some zoonoses transmit well in humans and become pandemic. A series of zoonoses from chimpanzees, gorillas and sooty mangabey monkeys resulted in 13 human immunodeficiency viruses (HIVs)[1], but only one, HIV-1(M), transmits among humans well enough to cause the HIV–AIDS pandemic and has infected around 80 million people (https://www.who.int/data/gho/data/themes/hiv-aids). Here, we investigated what features of HIV-1(M) confer its pandemic potential.

The discovery

In this study, we compared replication and infectivity of pandemic and non-pandemic HIV strains in human macrophages. As immunity to infection derives in part from individual cells suppressing incoming viruses, using a system called intracellular innate immunity, we assessed the activation of innate immunity by measuring the induction of genes involved in cellular defence. We also used phylogenetic analyses to study the evolution of HIV, comparing the lineage that led to the HIV pandemic with those that led to less successful human viruses. Lastly, we used X-ray crystallography to study the structures of the HIV capsid (the protein that makes up the inner core of the virus, which contains the genome and enzymes) particularly at the electrostatic pore, a channel in the capsid that we previously found to import nucleotides to fuel encapsidated DNA synthesis[2].

We found that pandemic HIV-1(M) is much less visible to human innate immunity than its non-pandemic counterparts, and induced limited expression of defensive genes, which enabled it to replicate better (that is, infecting more macrophages). Indeed, we found that HIV-1(M) could escape detection by both DNA sensor cyclic GMP-AMP synthase (cGAS) and capsid sensor TRIM5 (tripartite motif-containing protein 5). We linked this evasion to the viral capsid protein. The HIV capsid contains and regulates the processes of viral DNA synthesis, and controls nuclear transport and genome release before viral genome integration into host chromatin. Phylogenetic studies highlighted specific amino acid adaptations in the capsid protein that were unique to the pandemic lineage. Capsid X-ray structures demonstrated how these adaptations increased the capsid flexibility by enabling the opening and closing of its electrostatic pore. By contrast, non-pandemic capsids seem to be fixed open. Once we had identified these differences, we were able to make pandemic HIV-1(M) behave like non-pandemic HIV (specifically activating interferon (IFN) expression, which suppresses macrophage replication), by making two mutations in the pandemic capsid protein (Fig. 1). Thus, pandemic HIV-1(M) has uniquely evolved to evade human innate immunity, suggesting that this evasion has contributed to it becoming pandemic.

Future directions

Our observation that pandemic HIV effectively evades innate immune sensing might be generalizable to other pandemic viruses. We wonder whether we can determine which viruses are most likely to become pandemic by assessing their capacity to evade human sensing. For example, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Alpha variant, which became dominant in late 2020, has adapted to enhance its innate immune evasion[3].

A roadblock in our understanding of the HIV capsid is that the mechanism by which capsid adaptation alters visibility to cGAS and TRIM5 remains poorly understood. We hypothesize that evasion of cytoplasmic DNA sensor cGAS depends on keeping the viral DNA safe inside the capsid until release in the nucleus. But how capsid adaptation regulates uncoating and how TRIM5 sensitivity is altered remain unclear. Recruitment of the host factor cyclophilin A by the capsid has a role in regulation of uncoating and TRIM5 recruitment[4], but whether cyclophilin A is changing capsid dynamics or conformation, or simply obstructing TRIM5 binding, remains unclear.

Improved understanding of how the capsid functions and adapts to its new host on zoonosis will depend on studying larger complexes of capsid proteins, ideally whole cone-shaped cores and their interactions with recombinant cofactors. Cryo-electron microscopy studies are likely to provide the biggest breakthroughs in our understanding of HIV capsid function in the near future, and we look forward to contributing to those studies.

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EXPERT OPINION

"The manuscript builds on prior evidence that HIV-1(M) is poorly sensed by cGAS and largely evades TRIM5 restriction in myeloid cells. The authors now show that HIV-2 and HIV-1 (O-type), which did not cause similar pandemic spread, require blockage of the IFN receptor for spreading infection and induce various cytokines upon infection of myeloid cells. This finding is very well analysed in a highly systematic manner." **Hans-Georg Kräusslich, Heidelberg University, Heidelberg, Germany.**

FIGURE

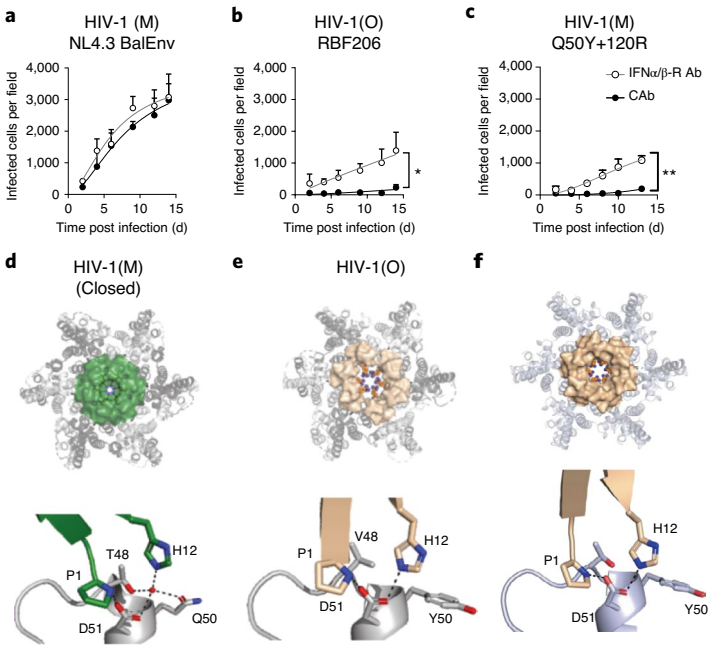

Fig. 1 | Capsid conformation links to interferon triggering and suppression of replication in macrophages. a–**c**, Replication of pandemic HIV-1(M) (**a**), non-pandemic HIV-1(O) (**b**) and mutant HIV-1(M) capsid Q50Y+120R (**c**) in human monocyte-derived macrophages in the presence of anti-IFN α/β receptor antibody (IFNα/β-R Ab, white circles) or control antibody (CAb, black circles). NL4.3 BalEnv, strain of pandemic HIV-1(M); RBF206, strain of non-pandemic HIV-1(O). **d**–**f**, Corresponding HIV-1 capsid hexamer structures highlighting β-hairpin (BHP) position in closed (green) or open (wheat) conformation (top panels). Bottom panels detail residues in the hinge region that closes BHP by increasing the distance between His12 and Asp51.

BEHIND THE PAPER

We started working on this project directly after our 2013 study[5]. We wondered whether, similar to the pandemic HIV mutants, non-pandemic viruses might trigger innate immunity more than the pandemic strain does. They did, but understanding why took years. Lorena Zuliani-Alvarez discovered that innate immune activation was downstream of cGAS and TRIM5 sensing. David A. Jacques and Leo C. James solved non-pandemic capsid X-ray structures — it was a big surprise finding that they were fixed in open conformations. Chris Monit's phylogenetic work helped to explain why, pinpointing the specific adaptations in HIV-1(M) that make the capsid flexible. The clincher was reversing the adaptations in pandemic HIV-1(M) and finding that the resulting mutant behaved like non-pandemic HIV, activating expression of innate immune genes and displaying an open capsid. This work was predominantly funded by a Wellcome collaborative award that specifically encourages the cross-disciplinary collaboration essential for this study. **G.J.T.**

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FROM THE EDITOR

"What is fascinating here is that the authors characterize specific, amino acid-level structural differences between the capsids of pandemic and non-pandemic HIV isolates, then reverse those differences and validate their role in innate immune evasion, thereby shedding light on the potential evolution of the pandemic HIV-1(M) strain". **Susan Jones, Chief Editor, Nature Microbiology.**