FACULTY OF MEDICINE AND HEALTH SCIENCES

Development of a novel assay to characterize the HIV-1 reservoir using long-read sequencing

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Key thesis publications

Cole,B.*, **Lambrechts,L.***, Boyer,Z., Noppe,Y., De Scheerder,M.-A., Eden,J.-S., Vrancken,B., Schlub,T.E., McLaughlin,S., Frenkel,L.M., et al. (2022) Extensive characterization of HIV-1 reservoirs reveals links to plasma viremia before and during analytical treatment interruption. Cell Reports, 39, 110739. *co-first authored

Lambrechts,L., Bonine,N., Verstraeten,R., Pardons,M., Noppe,Y., Rutsaert,S., Nieuwerburgh,F.V., Criekinge,W.V., Cole,B. and Vandekerckhove,L. (2023) HIV-PULSE: A long-read sequencing assay for high-throughput near full-length HIV-1 proviral genome characterization. Nucleic Acids Research, 51, 20, e102.

Other work

Lambrechts et al. (2020). Viruses, 12, 149.
Artesi et al. (2021) Genome Biology, 22, 97.
Cole,B. et al. (2021) Nat Commun, 12, 3727.
Van Cleemput et al. (2021) Nat Commun, 12, 6612.
Cuypers et al. (2022) Viruses, 14, 2301.
Pardons et al. (2023) Nat Commun, 14, 8397.

Summary

Background

HIV-1, the virus responsible for AIDS, has been a global health crisis, claiming over 40 million lives since its identification in the 1980s. Despite advancements in antiretroviral therapy (ART) making HIV-1 a manageable chronic condition, the virus's persistence in reservoirs of infected CD4 T cells prevents a cure, necessitating lifelong treatment.

Research aims

During this PhD, I aimed to delve deeper into the nature of the HIV-1 reservoir by employing next-generation sequencing. Specifically, we sought to investigate the contribution of clonal infected cells to reservoir persistence and viral rebound (Paper 1). Furthermore, I introduced the HIV-PULSE assay, a new tool for comprehensive proviral genome analysis, aiming to enhance our understanding of the HIV-1 reservoir (Paper 2).

Results

In **Paper 1**, we performed a study on the proviral landscape, revealing a potential role of certain infected clones to contribute to viremia. In **Paper 2**, we developed the HIV-PULSE assay, utilizing long-read sequencing, which allowed for a detailed analysis of the HIV-1 reservoir at a higher throughput and lower cost than previous methods. This assay proved effective in analyzing NFL proviral genomes from individuals on ART, offering a new avenue for in-depth reservoir studies.

Conclusion

The thesis emphasizes the complexity of the HIV-1 reservoir and the importance of clonal proliferation of infected cells in its persistence and in rebound viremia. The development and application of the HIV-PULSE assay marks a significant advancement in reservoir research, providing a more efficient and comprehensive method for studying the proviral landscape. This work contributes to the ongoing effort to understand HIV-1 reservoir dynamics and to develop targeted cure strategies.

Samenvatting

Achtergrond

HIV-1, het virus dat verantwoordelijk is voor AIDS, is een wereldwijde gezondheidscrisis die sinds de jaren '80 meer dan 40 miljoen levens heeft geëist. Ondanks huidige antiretrovirale therapie (ART) die HIV-1 een beheersbare chronische aandoening maakt, verhinderen virale reservoirs genezing waardoor levenslange behandeling noodzakelijk is.

Onderzoeksdoelen

Tijdens deze PhD wilde ik meer te weten komen over de aard van het HIV-1 reservoir door gebruik te maken van next-generation sequencing. Specifiek probeerden we de bijdrage van klonaal geïnfecteerde cellen aan reservoir persistentie en virale rebound te onderzoeken (Paper 1). Verder heb ik de HIV-PULSE assay geïntroduceerd, een nieuwe tool voor uitgebreide analyse van het proviraal genoom, met als doel ons begrip van het HIV-1 reservoir te verbeteren (Paper 2).

Resultaten

In **Paper 1** hebben we een studie uitgevoerd naar het provirale landschap, waaruit bleek dat bepaalde geïnfecteerde klonen mogelijk bijdragen aan viremie. In **Paper 2** ontwikkelden we de HIV-PULSE assay, gebruikmakend van long-read sequencing, die een gedetailleerde analyse van het HIV-1 reservoir mogelijk maakte met een hogere output en lagere kosten dan eerdere methoden. Deze assay bleek effectief in het analyseren van NFL provirale genomen van individuen die ART gebruiken en biedt een nieuwe weg voor diepgaande reservoirstudies.

Conclusie

Dit onderzoek benadrukt de complexiteit van het HIV-1 reservoir en het belang van klonale proliferatie van geïnfecteerde cellen in de persistentie en in rebound viremie. De HIV-PULSE assay is een belangrijke vooruitgang in de studie naar het reservoir, wat essentieel is voor de ontwikkeling van gerichte cure strategieën.

An electronic version of the PhD thesis is available upon request by email.

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