Title: Immunological consequences of spontaneous HIV reservoir activity during suppressive ART

Abstract

Current antiretroviral therapy (ART) is highly effective in suppressing viral replication in people with HIV (PWH). However, ART does not eradicate HIV, which persists in long-lived reservoirs from which the virus rebounds upon therapy interruption. A major knowledge gap for many years has been the question whether these reservoirs, aside from being a barrier to cure, can affect the immune system. Recent evidence suggests that HIV persistence spans a spectrum, ranging from deep latency to residual transcription and translation originating from integrated proviruses. Studying these active viral reservoirs (aVR) has been challenging due to a lack of suitable experimental approaches.

To study HIV reservoirs at the single-cell level, our lab has developed novel methods combining fluorescent in situ RNA hybridization for viral genes with detection of HIV proteins, cell phenotyping, and single-cell vDNA sequencing. We can analyze aVR in clinical samples without the need for in vitro reactivation, a requirement in most studies. Our findings reveal active HIV transcription in most PWH on ART. It positively correlates with HIV-specific T cell responses. Most of these aVR consist of defective proviruses. These findings raise key questions about the interaction between aVR and the immune system. We investigate different unresolved, related knowledge gaps for interested students. They include:

Aim 1: Define the relationships between active HIV reservoirs and HIV-specific CD4 and CD8 T cell responses in elite controllers.

Aim 2: Examine the relationships between spontaneous viral reservoir activity and alterations of molecular programs and functions of HIV-specific T cells

Aim 3: Pinpoint the links between spontaneous viral reservoir activity and systemic inflammation.

Relevance. This study employs state-of-the-art technologies to delve deeper into the effects of spontaneous viral reservoir activity in PWH on suppressive ART. Key points include: i) The interplay between reservoir activity and HIV-specific T cell immunity, as the efficacy of CD4 and CD8 T cell responses can dictate the potential for immunosurveillance in cure strategies; ii) The contribution of active reservoirs to sustained immune activation and suboptimal immune restoration. The knowledge gained may also help identify subpopulations of PWH that could benefit from adjuvant therapies.

MD-PhD student projects: A specific thesis subject will be tailored to each PhD candidate based on their background and interests. These studies are envisioned within a 'bench to bedside' translational continuum: we aim to link advanced immunovirological investigations with clinical outcomes in humans. This type of research program provides an ideal training environment for young candidates considering a career as physician-scientists."

Key related publications from the Kaufmann lab:

Baxter, A. E., Niessl, J., Fromentin, R., Richard, J., Porichis, F., Charlebois, R., . . . Kaufmann, D. E. (2016). Single-Cell Characterization of Viral Translation-Competent Reservoirs in HIV-Infected Individuals. ***Cell Host & Microbe**, 20*(3), 368-380. doi:10.1016/j.chom.2016.07.015

Dube, M., Tastet, O., Dufour, C., Sannier, G., Brassard, N., Delgado, G. G., . . . Kaufmann, D. E. (2023). Spontaneous HIV expression during suppressive ART is associated with the magnitude and function of HIV-specific CD4(+) and CD8(+) T cells. ***Cell Host & Microbe**, 31*(9), 1507-1522 e1505. doi:10.1016/j.chom.2023.08.006

Porichis, F., Hart, M. G., Griesbeck, M., Everett, H. L., Hassan, M., Baxter, A. E., . . . Kaufmann, D. E. (2014). High-throughput detection of miRNAs and gene-specific mRNA at the single-cell level by flow cytometry. ***Nature Communications**, 5*, 5641. doi:10.1038/ncomms6641

Sannier, G., Dube, M., Dufour, C., Richard, C., Brassard, N., Delgado, G. G., . . . Kaufmann, D. E. (2021). Combined single-cell transcriptional, translational, and genomic profiling reveals HIV-1 reservoir diversity. ***Cell Reports**, 36*(9), 109643. doi:10.1016/j.celrep.2021.109643