Global Epitranscriptomic Alterations in HIV-Infected Monocyte-Derived Macrophages

Elena Alvarez-Periel[1], Xinglong Shi[1,†], Xiaokang Wang[1,†], Shiden Solomon[1], Zuwen Zhong[1], Peiming Li[1], , Jiemin Lou[1], Yu Li[1], Kelly L. Jordan-Sciutto[1,*], Cagla Akay-Espinoza[1,*], and Yijing Su[1,2,3,*]

[1]Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, [2]Department of Cell and Developmental Biology, Perelman School of Medicine, University of Pennsylvania, [3]Penn Epigenetics Institute, Perelman School of Medicine, University of Pennsylvania

HIV-1 infection induces extensive transcriptional reprogramming in macrophages, yet its impact on the epitranscriptome, i.e., the biochemical modifications regulating gene regulation post-transcriptionally, remains poorly understood. These include chemical base modifications, such as N6-methyladenosine (m6A), 5-methylcytosine (m5C), and pseudouridine (Ψ), and poly(A) tail length. Importantly, these RNA features are key regulators of RNA stability, translation efficiency and innate immune responses.

In this study, we have used Oxford Nanopore direct RNA sequencing technology to profile global epitranscriptomic alterations in HIV-infected monocyte-derived macrophages. This approach enables single-molecule analysis of native RNA, overcoming the limitations of prior techniques relying on amplification, and allowing direct detection of RNA base modifications and measurement of poly(A) tail length.

Comparative analysis reveals global and transcript-specific changes in m6A, m5C, and Ψ modification patterns affecting genes involved in antiviral defense, interferon signaling, RNA metabolism, and macrophage activation, providing the first simultaneous profiling of three RNA modifications within host cell genes following HIV-1 infection. Concurrently, we identify widespread HIV-associated remodeling of poly(A) tail length distribution, with distinct classes of host transcripts exhibiting tail shortening or elongation following infection.

Overall, our study provides new insights into the post-transcriptional signatures that shift cellular RNA and protein expression profiles in response to HIV infection and, which maybe leveraged to reverse viral persistence in macrophages.