Gene expression regulation for persons with HIV who inject drugs

Mingkuan Lin¹,², Amy C. Justice²,³, Vincent Marconi⁴, So-Armah K⁵ Bradley E. Aouizerat⁶,⁷, and Ke Xu¹,²*

¹Department of Psychiatry, Yale School of Medicine; ²VA Connecticut Healthcare System; ³Department of Internal Medicine, Yale University School of Medicine; 4. Division of Infectious Diseases, Emory University School of Medicine, Atlanta; 5. Boston University School of Medicine, Massachusetts; 6. Bluestone Center for Clinical Research, College of Dentistry, New York University; 7. Department of Oral and Maxillofacial Surgery, College of Dentistry, New York University

Injection drug use (IDU) significantly impacts the course of HIV progression. However, little is known about the mechanisms of the adverse effects of IDU on HIV infection. We hypothesize that IDU dysregulates gene expression in the host transcriptome and the differentially expressed genes are associated with worse HIV outcomes. To test the hypothesis, we performed a transcriptome-wide association study in 176 individuals with HIV (IDU=83, non-IDU=93) from the Veteran Aging Cohort Study. Total RNA was extracted from peripheral blood mononuclear cells and sequenced. We used the Salmon package for transcriptome mapping and Deseq2 package to identify differentially expressed genes. Compared to non-IDU, IDU displayed increased expression of 38 genes and decreased expression of 7 genes (False Discovery Rate, FDR < 0.05). Significant genes included HIF1A, a gene associated with increased HIV-1 replication and latency, and NFKB1B, an important gene for inflammatory signaling. In an enrichment analysis using the top 687 genes with FDR<0.2, we identified multiple statistically significant perturbation of Gene Ontology (GO) pathways associated with IDU. The identified GO pathways included immune system activation, cytokine and intracellular signal transduction, cell development/differentiation/migration, cell stress/apoptotic process, transcription regulation, and double strand break repair (FDR<0.05). When Enriched in the Reactome database, the significant pathways for IDU included immune/TLR/Interleukin response, GPCR signaling, and cell growth signaling. The DNA repair system pathway showed a net down regulation among IDU compared to non-IDU. Overall, the results indicated that IDU impacts the immune and inflammation signaling systems, which may contribute to accelerated HIV disease progression.