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Quantification of the HIV reservoir in the gut-associated lymphoid tissue

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OBJECTIVES/GOALS: The major obstacle to an effective cure or remission for HIV infection is the integration of HIV into the genome of long-lived resting cells which constitute the so-called viral reservoir. With this study we want to elucidate the changes of the gut-associated HIV reservoir at different stages of viral suppression.

METHODS/STUDY POPULATION: Recent studies have shown that after long-term (>7 years) clinical suppression of peripheral HIV RNA, the circulating viral reservoir does not seem to decline further and, in fact may expand. The gastrointestinal associated lymphoid tissue (GALT) harbors by far the largest fraction of the latently infected cells, however not much is known about its changes over time. We thus quantified the HIV viral reservoir in the GALT by identifying HIV viral transcripts via 10X single-cell RNA sequencing at two GALT-sites in five PWH and compared the amount of HIV RNA found in the group of PWH with early (< 7years) vs late (> 7years) peripheral virological suppression (plasma HIV RNA <20copies/mL).

RESULTS/ANTICIPATED RESULTS: Study participants had been diagnosed with HIV infection for a median (IQR) of 31 (32-34) years and had consistently undetectable peripheral blood HIV RNA for the previous 8 (4-15) years. In PWH with consistent viral suppression < 7yrs, 4 (2-6) HIV transcripts were identified in the ileum and 25 (13 – 38) in the colon. In PWH with consistent viral suppression > 7yrs, 0 (0-4) HIV transcripts were identified in the ileum and 7 (14-11) in the colon. Based on these preliminary results we plan to expand our cohort and confirm these results using Proviral DNA quantification. We anticipate that the viral decay in the GALT will follow a slower dynamic than what has been reported for the peripheral blood achieving a steady state after more than 7 years of peripheral viral suppression.

DISCUSSION/SIGNIFICANCE: Despite the remarkable progress the survival and quality of life of PWH, after forty years from its first discovery, HIV infection remains incurable. Considering its critical role, efforts are needed to better understand the dynamics of the GALT-associated HIV reservoir.

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Maternal PTSD and Child Brain Function During Implicit Emotion Regulation

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OBJECTIVES/GOALS: Maternal mental health, such as post-traumatic stress disorder (PTSD), is closely linked to child mental health. PTSD in mothers is associated with their children's emotional responses. We examined associations between maternal PTSD and child brain function during emotion regulation.

METHODS/STUDY POPULATION: Eight children ages 10-12 years, whose mothers had trauma histories, performed the Emotional N-Back task during functional MRI scanning. Mothers and children each reported on their trauma exposure and PTSD symptom severity.

BOLD response to fearful faces during the Emotional N-Back was extracted from two specific brain regions of interest, amygdala and anterior cingulate cortex. These regions are involved in emotional response and attentional control, which are processes intrinsic to emotion regulation. An independent samples t-test was conducted on children's BOLD response to fearful faces, with maternal PTSD symptom severity (high, low) as the independent variable. A parallel analysis was conducted with child PTSD symptom severity (high, low) as the independent variable.

RESULTS/ANTICIPATED RESULTS: We found a main effect of maternal PTSD within brain regions of relevance to implicit emotion regulation. Compared to children whose mothers reported low PTSD symptom severity (n=4), children whose mothers reported high PTSD symptom severity (n=4) showed greater responsiveness to fearful faces in anterior cingulate cortex (t=2.04, p=.09, d=1.44) and amygdala (t=2.44, p=.05, d=1.72) at trending significance. A parallel analysis with child PTSD symptom severity showed no differences in brain function by this factor (ps=.55-.61).

DISCUSSION/SIGNIFICANCE: Our pilot study is the first, to our knowledge, to examine associations between maternal PTSD and brain function during emotion regulation in their children. This study lays a foundation for future work; our goal is to explore dysfunction in emotion regulation neurocircuitry as one mechanism linking maternal PTSD to their children's mental health.

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Investigating the Role of FOXA2 During the Transition to Neuroendocrine Prostate Cancer

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OBJECTIVES/GOALS: The goal of this project is to characterize the efficacy of FOXA2 as a potential biomarker for patients with metastatic castrate-resistant prostate adenocarcinoma (CRPC) before transitioning to neuroendocrine prostate cancer (NEPC). NEPC currently has no therapeutic options and poor mechanistic understanding of its origins.

METHODS/STUDY POPULATION: In our study, we have utilized a multi-omics approach to characterize the potential efficacy of FOXA2 as a prognostic biomarker in numerous patient-derived castrate-resistant prostate cancer (CRPC) models. We have performed ATAC-, ChIP-, RNA-seq and proteomics to fully characterize where FOXA2 is binding genome-wide, how FOXA2 alters chromatin accessibility dynamics, identify regulatory gene targets of FOXA2, and identify FOXA2 protein-protein interactors. We have supported these findings using publicly available data from independent CRPC and NEPC patient cohorts and prostate cancer cell models.

RESULTS/ANTICIPATED RESULTS: Our findings show that FOXA2 overexpression suppressed androgen signaling and promoted progression to a NEPC phenotype under short- and long-term androgen deprivation conditions, respectively. Further, FOXA2 redirected the chromatin accessibility landscape to be consistent with an NEPC gene expression program, including increased chromatin accessibility for key NEPC transcription factors. FOXA2 ChIP-seq showed FOXA2 to be bound at known NEPC driver genes and epigenetic modifiers across multiple stages of prostate cancer progression. Lastly, we discovered that FOXA2 physically interacts with key NEPC TFs and epigenetic regulators, suggesting that these FOXA2 physical interactions are required for NEPC