A Tissue Microenvironment Analogous to Specific Tumor Microenvironments May Enable HIV Persistence

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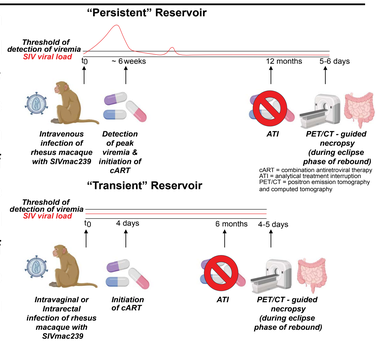
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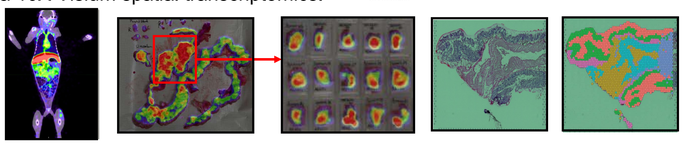
BACKGROUND

The persistence of HIV-1 reservoirs during therapy, particularly in mucosal and lymphoid tissues, constitutes the main barrier to the development of a functional cure. Previous studies in the Lorenzo-Redondo and Hope Labs in rhesus macaques comparing transient reservoirs (formed after early antiretroviral therapy [ART] initiation) vs. persistent reservoirs (established after late ART initiation) identified biomarkers associated with the tumor microenvironment (TME). The objective of this study is to compare spatial transcriptomics patterns associated with the tissue microenvironments of rebound foci of early- and late-ART initiation to transcriptional features of various TMEs. We hypothesize that viral persistence in well-established tissue reservoirs occurs through the development of a microenvironment analogous to certain TMEs.

METHODS

We have developed an immunoPET/CT-guided spatial transcriptomics pipeline for the study of tissue viral reservoirs. This approach is leveraged in conjunction with immunofluorescence detection of viral proteins on an adjacent tissue sample to generate a multimodal dataset that enables the association of foci of viral infection with gene expression patterns detected in situ via 10X Visium spatial transcriptomics.

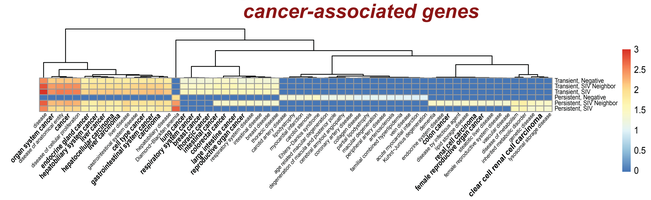


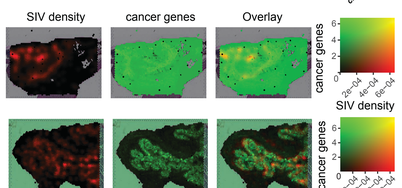


1. PET/CT scan of rhesus macaque infected with Simian Immunodeficiency Virus (SIV)
2. Scan of gut to identify hotspot regions
3. Scan of individual tissue sections to visualize localized hotspot regions
4. Mount tissue sample onto a slide with a barcoded grid
5. Spatial transcriptomics analysis of gene expression

RESULTS

Disease ontology analysis reveals spatial enrichment of cancer-associated genes

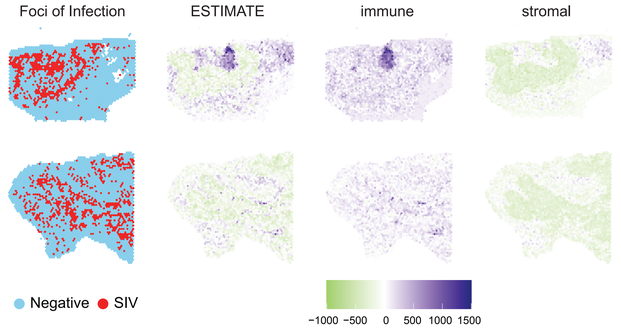


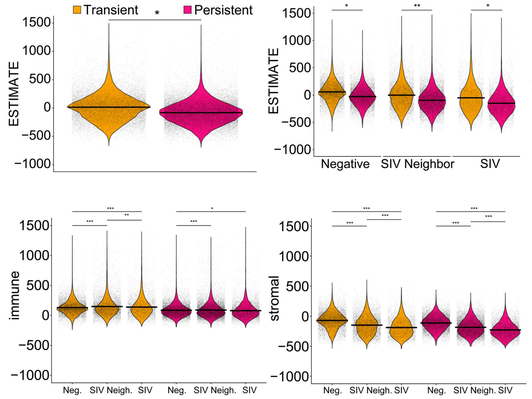


The microenvironment of transient viral reservoirs in the gut may reflect hallmark features of "hot" tumor microenvironments while persistent reservoirs have features more consistent with "cold" tumor microenvironments.

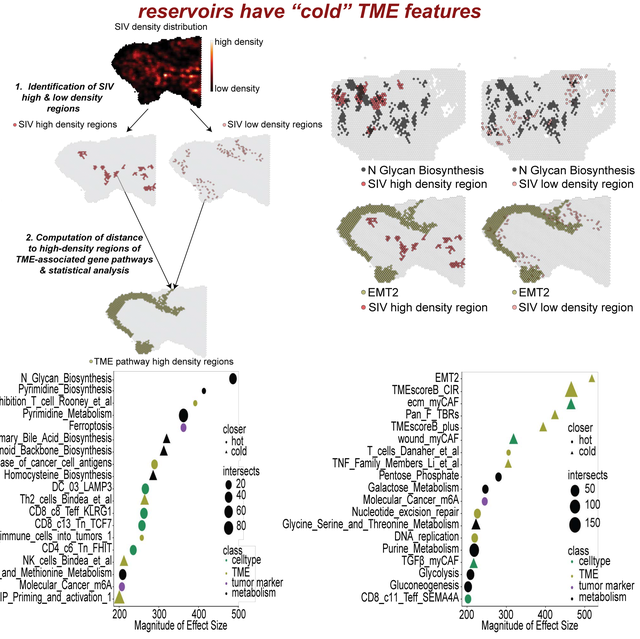
RESULTS

The Estimation of STromal and Immune Cells in MAlignant Tumor tissues using Expression data (ESTIMATE) TME scoring method revealed persistent reservoirs and SIV dense regions have varied immune and stromal signatures

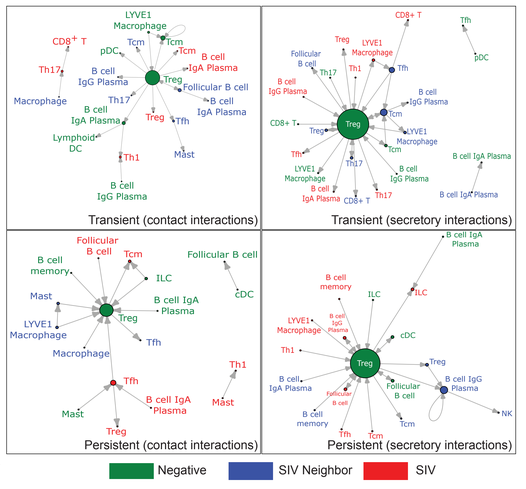




Niches within transient reservoirs have "hot" TME features whereas niches within persistent reservoirs have "cold" TME features

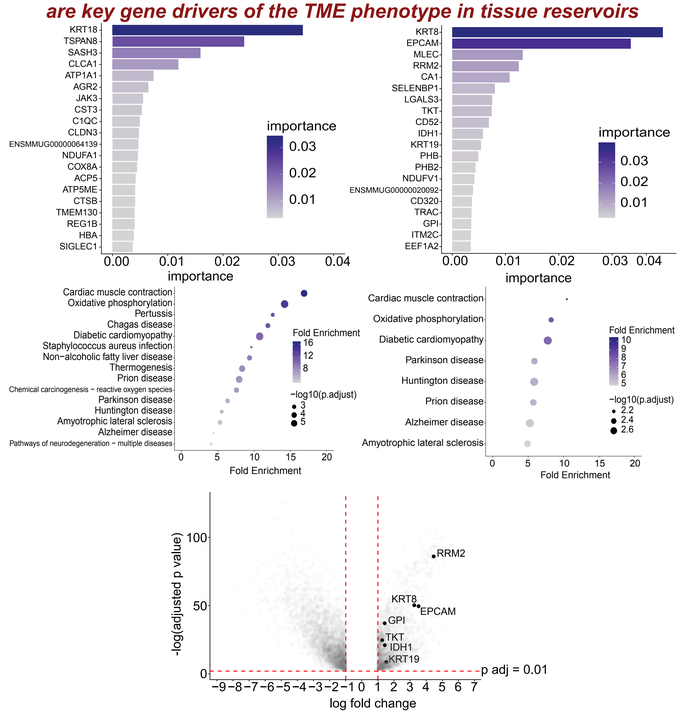


Regulatory T cells have key roles in tissue reservoirs, predominantly sending signals to adaptive immune cells in the transient reservoir, and receiving signals from innate and immunosuppressive cells in persistent reservoirs



RESULTS

Keratins, among other genes associated with carcinogenic processes, are key gene drivers of the TME phenotype in tissue reservoirs



CONCLUSIONS

Our results indicate that HIV/SIV reservoirs share transcriptional features with certain tumor microenvironments (TMEs). Transient reservoirs have a phenotype that resembles "hot" TMEs with immune infiltration and metabolic activation, while persistent reservoirs have similar features to "cold" TMEs with immune exclusion and surrounding stromal activation. Our findings suggest that HIV promotes this tissue microenvironment in order to establish persistent reservoirs during ART. Key gene drivers of the "cold" TME phenotype identified potential therapeutic targets of interest towards the eradication of persistent reservoirs.

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Thus far, we have been unable to cure HIV because it is able to survive under therapy by "hiding" in multiple places in the body. Our study indicates that the virus can do this by inducing the formation of an environment similar to specific cancers. This allows HIV to hide from the immune system, survive for a long time, and remain prepared to restart infection. Therapies that target important components of this process could lead to an effective HIV cure.