Transcriptional Analysis of Intestinal Immune Cells in People With HIV Receiving bNAbs

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Connie A Zhao[1], Divya Jha [1], Katrina Millard[2], Darwin D'souza[1], Vladimir Roudko[1], Francesca Cossarini[1], Marina Caskey[2], Saurabh Mehandru[1]
[1]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [2]The Rockefeller University, New York, NY, United States

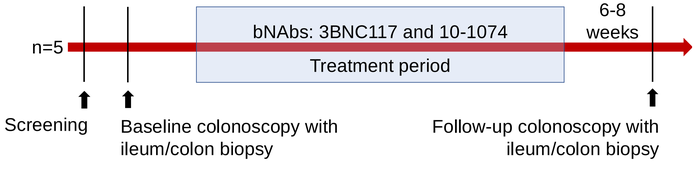
BACKGROUND

- Antiretroviral therapy (ART) does not address the **latent reservoir** in people with HIV (PWH) so virologic rebound inevitably occurs after treatment interruption.
- The **gut-associated lymphoid tissue (GALT)** is a major site of early infection and immune cell depletion, chronic viral replication and immune activation, and the latent reservoir.
- Combination **broadly neutralizing antibody (bNAb)** therapy has been shown to reduce the intact proviral reservoir in peripheral blood and delay viral rebound after treatment interruption, but little is known about their effect in key tissues such as the GALT.

OBJECTIVE: To identify transcriptional changes in GALT immune cells in PWH who received bNAbs.

METHODS

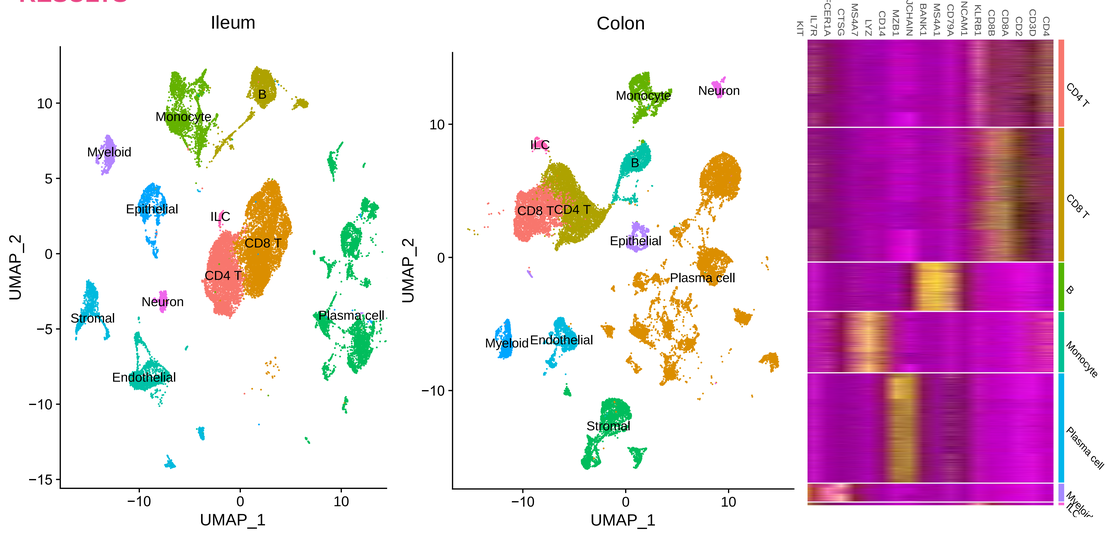
- Prospective enrolment of study participants with suppressed HIV infection on ART and receiving a single infusion of two long-acting bNAbs, 3BNC117-LS and 10-1074-LS.
- Single-cell RNA sequencing (scRNA-seq) analysis of freshly processed tissue biopsies, using Seurat and Enrichr platforms for data analysis.
- Baseline tissue from 5 study participants + post-infusion tissue from 2 participants = aggregated dataset of 85,899 cells with 28,504 unique molecular identifiers (UMIs).
- Human Primary Cell Atlas reference cell annotations and canonical genes used to annotate cell clusters.



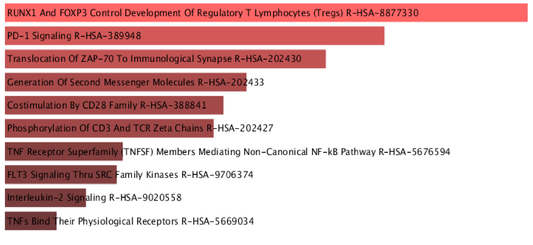
Study Participants	HIV014	HIV018	HIV022	HIV026	HIV032
Demographics	58 yo M Hispanic Dx 2004 Nadir CD4 298	55 yo F African American Dx 2000 Nadir CD4 193	30 yo F African American Dx 1989 Nadir CD4 129	30 yo M African American Dx 2014 Nadir CD4 200	63 yo F African American Dx 2003 Nadir CD4 400
Baseline	CD4 440 TAF/FTC/c/EVG	CD4 793 TDF/FTC/c/EVG	CD4 1092 TAF/FTC/RPV	CD4 569 TAF/FTC/BIC	CD4 1113 TAF/FTC/RPV
Follow-up	Completed		Completed		

bNAb exposure may modulate TNF/NF-kB and interferon signaling in CD4+ and CD8+ T cells in the _GALT_ of individuals with well-controlled _HIV_ on ART.

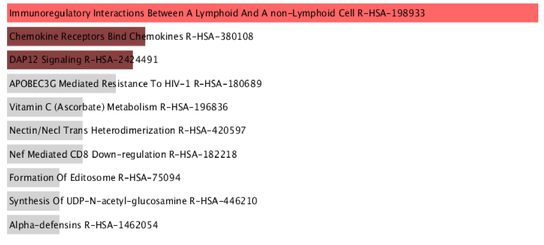
RESULTS



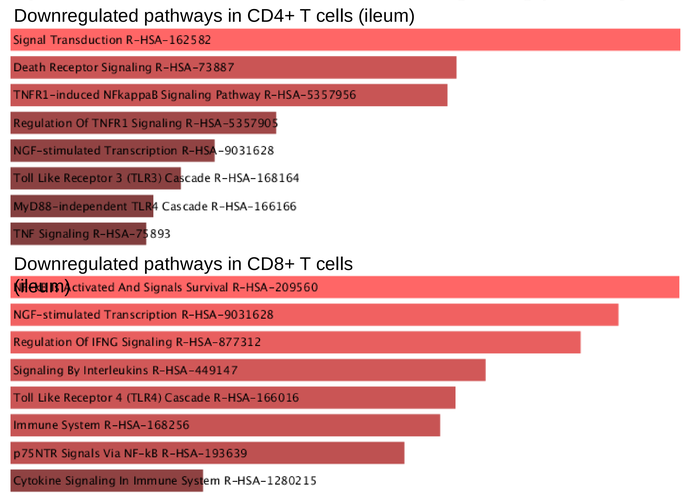
Baseline CD4+ T cells (4,213 in ileum, 4,615 in colon) are characterized by regulatory T lymphocyte development *(IL2, IL2RA, CTLA4, FOXP3)* and TNF/NF-kB signaling *(LTA, LTB, TNFSF).*

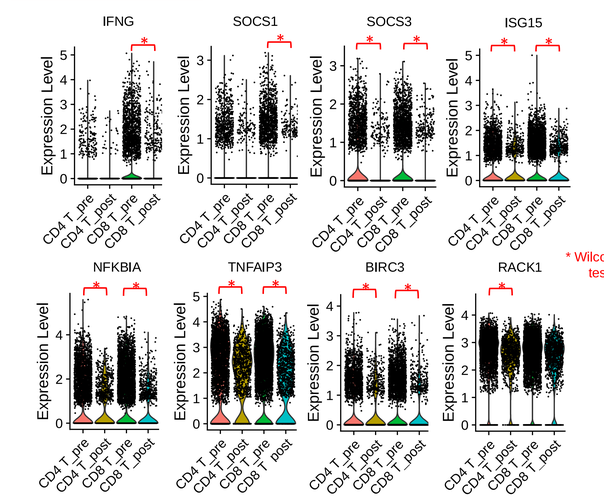


Baseline CD8+ T cells (6,459 in ileum, 3,537 in colon) are characterized by by chemokine receptor signaling (*CCL4, CCR9)* and lymphoid and non-lymphoid cell immunoregulatory interactions (*CD247, ZAP70).*



Post-infusion CD4+ and CD8+ T cells showed significantly lower expression of TNF/NF-kB and interferon signaling pathways.





* Wilcoxin rank-sum test, adjusted p-value < 0.05

CONCLUSIONS

- Transcriptional changes in the GALT of individuals with well-controlled HIV infection on ART suggest that bNAb exposure may modulate tumor necrosis factor (TNF)/nuclear factor kappa B (NF-kB) and interferon signaling in CD4+ and CD8+ T cells.
- Limitations: lack of post-infusion samples for all study participants, short duration between infusion and follow-up, and transcriptome-only evaluation.
- Use of scRNA-seq on tissue biopsy from colonoscopy is a promising experimental method for studying the GALT that may be incorporated into future study of HIV cure strategies.

Connie Zhao, MD | Connie.zhao@mountsinai.org | 212-241-6741