BCL6 Enhances Tfh Cells Susceptible to HIV Infection by Dampening Intrinsic Antiviral Machineries

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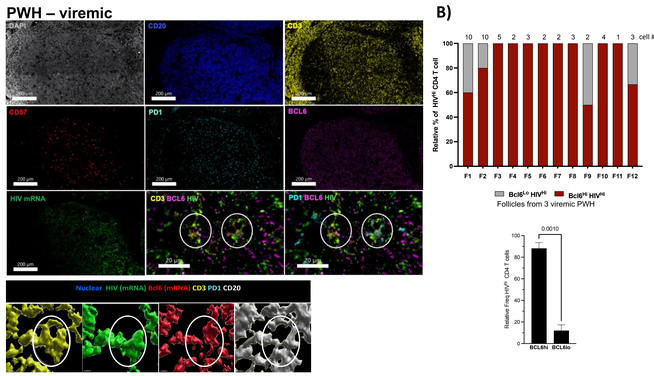
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BACKGROUND

Lymph nodes (LNs) constitute a key anatomical sanctuary for HIV. Follicular helper T (Tfh) cells expand early upon infection and represent a principal cellular target for initial viral seeding. However, the intrinsic and tissue-driven mechanisms that make Tfh cells highly permissive to HIV infection remain unclear. Here we identified the transcription factor BCL6, a Tfh-lineage defining marker, as central in favoring the infection of Tfh cells in LNs during the untreated phase of infection. *In situ* and *ex vivo* analyses of LN from people with HIV (PWH) in absence of antiretroviral therapy (ART) revealed preferential enrichment of viral RNA within BCL6hi Tfh cells, which also presented significantly lower expression of proteins with antiviral functions (IRF7, MX1, APOBEC3G, pSTAT1). In vitro genetic (genome wide CRISPR knockouts) and pharmacologic perturbations confirmed that BCL6 enhances the cellular permissiveness of Tfh cells to HIV infection. IL-10 and TGF-β were enriched in LNs from people without HIV (PWoH), and cooperatively induced bona fide BCL6hi Tfh differentiation *in vitro*, with repressed antiviral pathways. IL-10 and TGF-β blockade limited Tfh differentiation, confirming their contribution to Tfh and LN biology.

RESULTS

Fig. 1 BCL6^{hi} Tfh cells are highly susceptible to HIV infection



We identify an IL-10/TGF-β/BCL6 axis that drives a Tfh state with suppressed antiviral programs, making these cells highly permissive to HIV and seeding lymphoid reservoirs.
Disrupting this pathway restores antiviral machinery, reduces Tfh infection, and shrinks tissue reservoir size, highlighting a targetable circuit for reservoir destabilization.

Fig. 2 BCL6 suppresses interferon-driven antiviral programs in germinal center Tfh cells

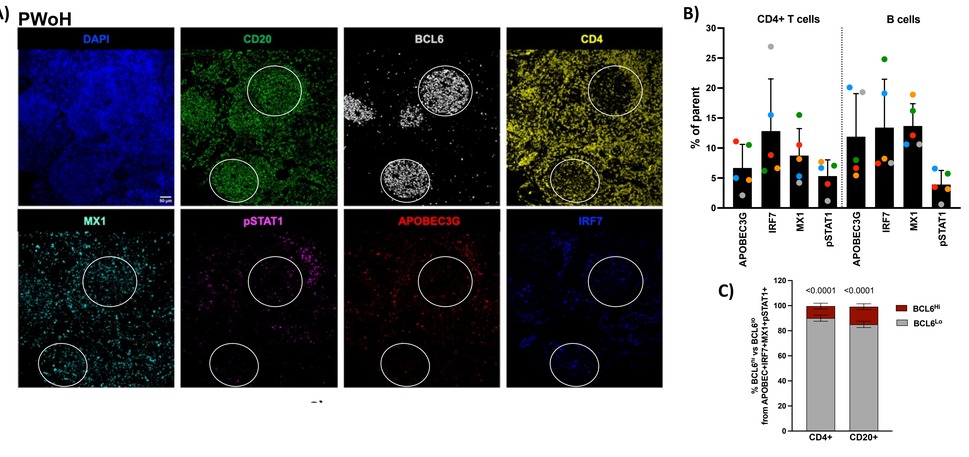
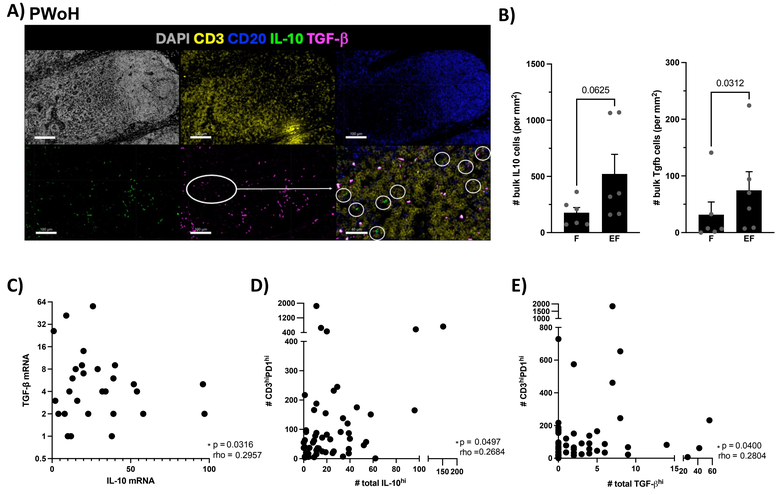


Fig. 3 IL-10 and TGF-β are enriched in lymph nodes and associated with Tfh cell numbers



CONCLUSIONS

Here we identify an IL-10/TGF-β/BCL6 axis that concomitantly induce Tfh differentiation and suppresses antiviral programs thus increasing Tfh susceptibility to HIV. Targeting this pathway reprograms Tfh cells, limits infection, and reduces tissue reservoir size, supporting a new therapeutic avenue for cure strategies.

Fig.4 IL-10 and TGF-β cooperatively drive Tfh differentiation and suppress antiviral programs

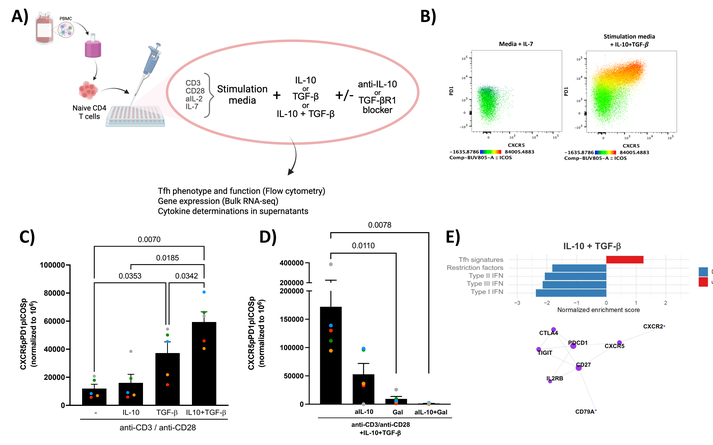


Fig. 5 Human genetic variation in IL-10 and TGF-β associates with HIV control phenotype

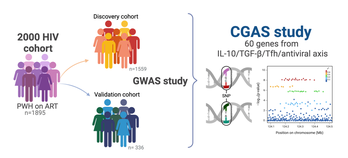
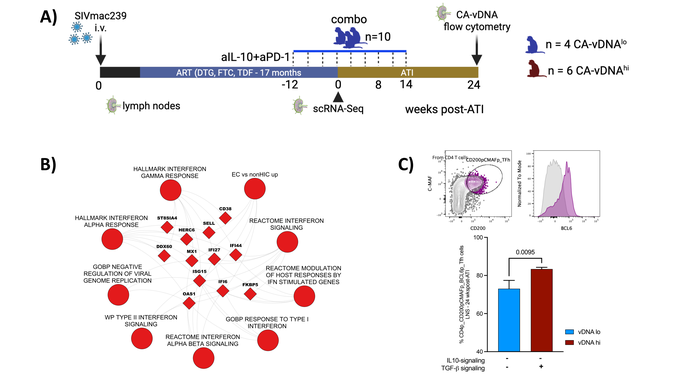


Fig. 6 Therapeutic down-modulation of IL-10 and TGF-β signaling pathways decreases LN BCL6^{+} Tfh cells, boosts antiviral programs and reduces LN reservoir



PLAIN LANGUAGE SUMMARY

We found immune signals (IL-10 and TGF-β acting through BCL6) that make a specific type of immune cell in the lymph nodes lower its virus-fighting defenses, allowing HIV to infect those cells more easily and hide there. Blocking this pathway helps these cells fight back, reduces infection, and shrinks the hidden virus in the body.

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