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BACH2 Controls Seeding and Establishment of Long-Lived HIV-1 Reservoir in Memory CD4⁺ T cells

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BACKGROUND

- A better understanding of the early events in HIV-1 reservoir seeding may help prevent latent reservoir formation.
- Unlike **quiescent** reservoir cells, CD4⁺CCR5⁺ T cells as the primary targets present an **activated** Th1 or Th17 effector phenotype, indicating phenotypic and functional changes in cells after HIV-1 entry.
- The recurrent HIV-1 integration at the BACH2 locus and upregulation of the host gene expression suggest that ***BACH2* plays an important role in HIV reservoir seeding and maintenance**.

METHODS

- CD4⁺CCR5⁺ T cells were profiled and in-vitro re-differentiation of activated CCR5⁺ cells were evaluated to explore how terminal effectors reprogram into quiescent memory cells.
- The role of BACH2 in memory-precursor conversion of CCR5⁺cells was validated through BACH2-knockout and overexpression assays.
- BACH2 knockout humanized mice were infected with R5-tropic virus and treated with ART (FTC+TFV+RAL) for seven weeks. The frequency of HIV total DNA and viral rebound were assessed.

RESULTS

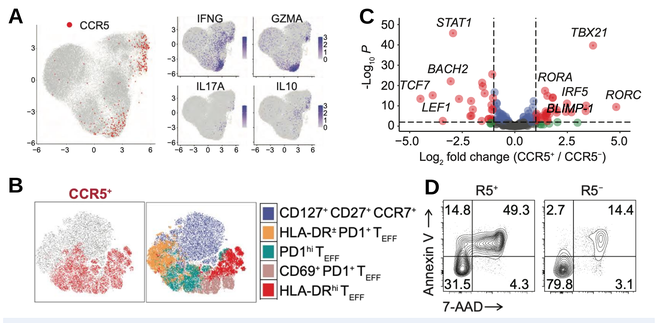


Fig.1 CCR5⁺ CD4⁺ T cells are short-lived effector cells. (A) scRNA-seq data from lymphoid tissue CD4⁺ cells. (B) Phenotypic profiling of activated CD4⁺ T cells by flow cytometry. (C) Transcriptome analyses of activated CCR5⁺ and CCR5⁻ blood CD4⁺ T cells. (D) Viability upon TCR restimulation.

BACH2 **reverses** CD4⁺ CCR5⁺ T cells, the primary HIV-1 targets, from terminal differentiated cells to memory precursors post viral entry. Loss of BACH2 **reduces** HIV DNA frequency and **delays** viral rebound, suggesting that BACH2 is essential to the seeding and establishment of long-lived HIV-1 reservoir in memory CD4⁺ T cells.

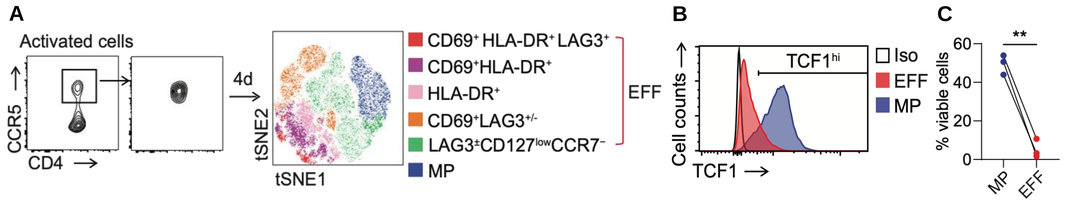


Fig.2 Bifurcated differentiation of CCR5⁺ cells. (A) Differentiation of activated CCR5⁺ cells. (B) TCF1 expression of MP and EFF cells. (C) Viability of MP and EFF cells upon TCR restimulation.

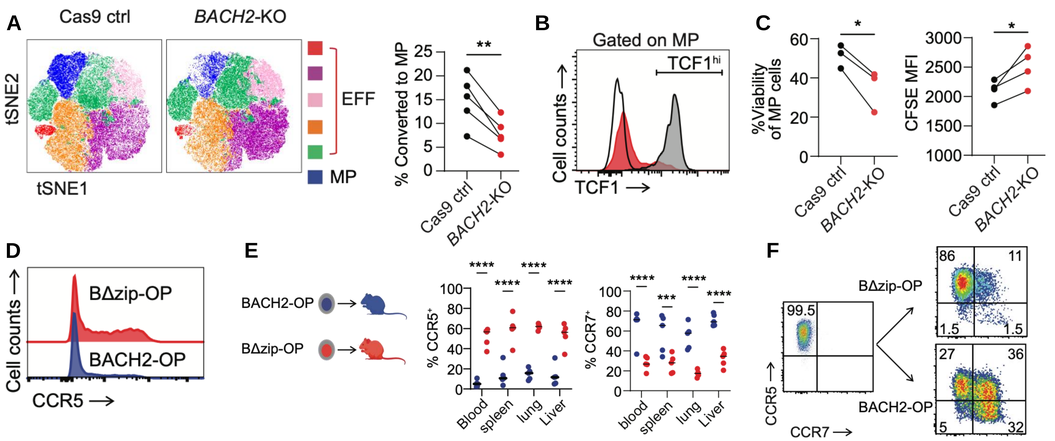


Fig.3 BACH2 regulates differentiation and functional maintenance of CCR5-derived memory precursor cells. (A) Phenotypic profiling of differentiated BACH2-KO or control CCR5⁺ cells by flow cytometry. (B) TCF1 expression in BACH2-KO or control MP cells. (C) Viability and proliferation of BACH2-KO or control MP cells upon TCR restimulation. (D) BACH2 overexpression in CD4⁺ T cells in vitro and (E) in vivo. (F) BACH2 overexpression in CD4⁺ CCR5⁺ cells.

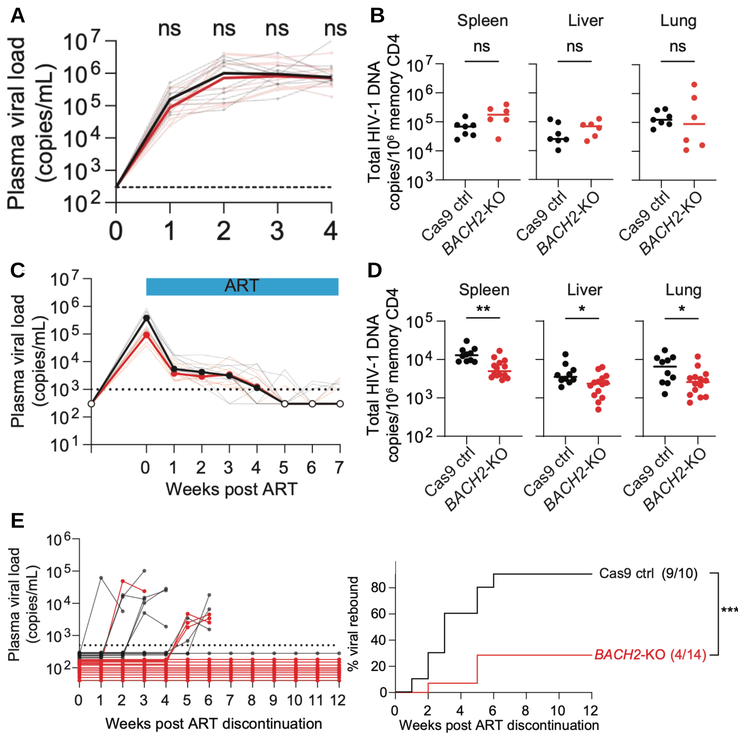


Fig.4 Reduced HIV DNA frequency and delayed viral rebound were observed in BACH2-KO mice. (A) Plasma viral loads in the control and BACH2-KO groups. (B) HIV total DNA frequency between BACK2-KO and Cas9-CTL group in viremic mice. (C) HIV-1 infection and ART in the control and BACH2-KO groups. (D) HIV total DNA frequency between groups from aviremic mice on ART. (E) Splenic cells of mice from each group were transferred to uninfected mice and viral rebound was measured weekly.

CONCLUSIONS

Our study shows that BACH2 reverses CCR5⁺ cells from terminal differentiated cells to memory precursors. The absence of BACH2 abrogates the seeding of latent reservoirs, revealing the essential role of BACH2 in the seeding and establishment of long-lived HIV-1 reservoir in memory CD4⁺ T cells. Our finding identifies a potential avenue for targeted interventions.

ACKNOWLEDGEMENTS

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