Impact of BACH2 on the Formation of HIV Latent Reservoirs in Humanized Mouse model

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BACKGROUND

- Limited understanding of the mechanisms governing the formation of latent reservoirs.
- Unusually frequent integrations into the BACH2 gene.
- Inserted proviruses are nearly exclusively located upstream of the BACH2 start codon and share the same transcriptional orientation as the host gene, which leads to an increase in BACH2 transcription.
- 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

- Humanized mice engrafted with BACH2 knockout (BACH2-KO) or control CD34+ cells were generated.
- Engrafted mice were infected with CCR5-tropic HIV-1 followed by the administration of ART (FTC+TFV+RAL) for six weeks.
- The frequency of HIV total DNA in tissue was assessed.
- HIV DNA frequency in tissue CD4⁺ central memory, effector memory, and CD14⁺ cells was assessed.
- Splenic cells were transferred to immunodeficient mice for viral rebound analysis.

RESULTS

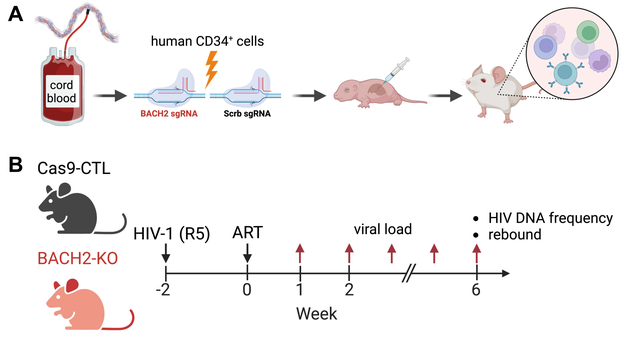


Fig.1 CCR5-tropic HIV infection and ART treatment in BACH2 -knockout humanized mice. (A) BACH2-knockout humanized mice were generated. (B) HIV infection and ART treatment scheme.

The **absence** of **BACH2** caused **decreased** HIV DNA frequency and **delayed** viral rebound, suggesting that BACH2 is **required** for the **formation** and **maintenance** of the HIV latent reservoir.

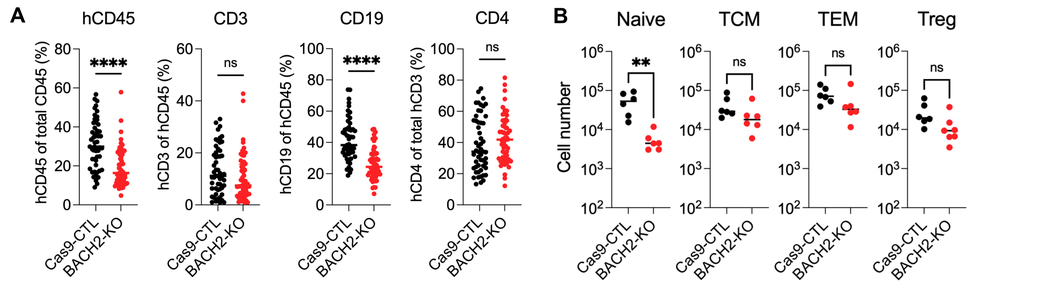


Fig.2 The absence of BACH2 caused the loss of B and CD4 naïve T cells in uninfected humanized mice. (A) PBMCs. (B) CD4⁺T cells in spleen.

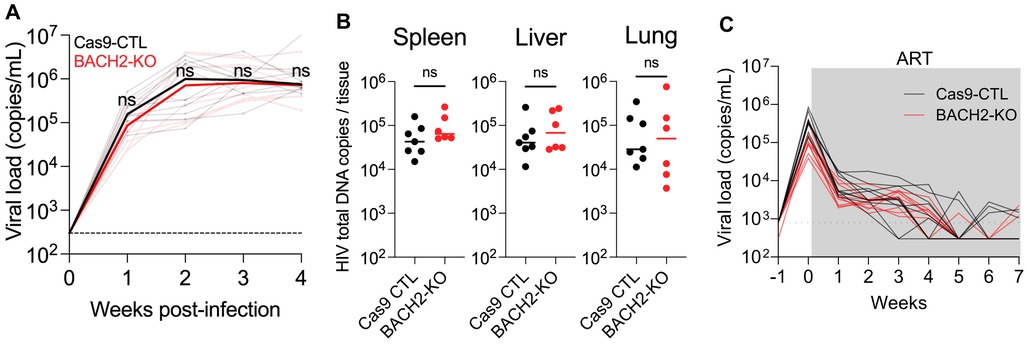


Fig.3 No difference in viral replication between BACH2-KO and Cas9-CTL groups during acute infection. (A) Viral load long-term follow-up. (B) HIV total DNA frequency in tissue. (C) Viral load during ART.

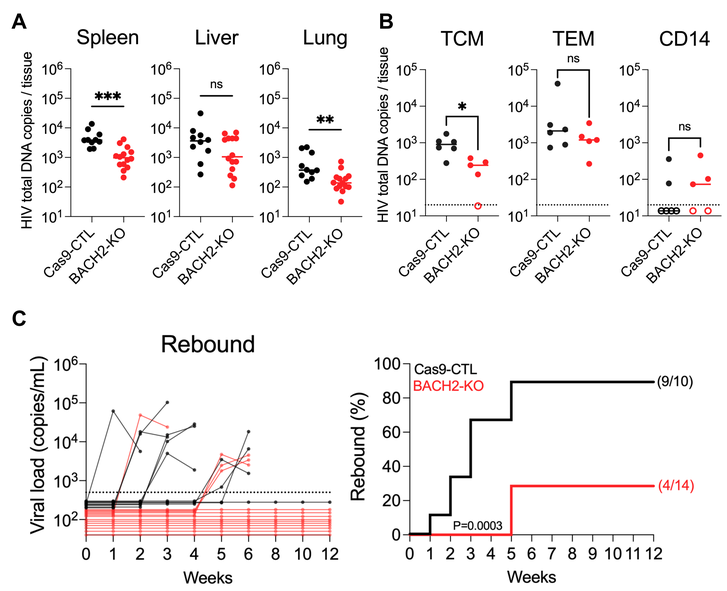


Fig.4 Reduced HIV DNA frequency and delayed viral rebound were observed in BACH2-KO mice. (A) HIV total DNA frequency in each tissue between BACK2-KO and Cas9-CTL group. (B) HIV DNA frequency in sort CD4⁺ central memory (TCM), effector memory (TEM) , and CD14⁺ cells. (C) Splenic cells of mice from each group were transferred to uninfected mice and viral rebound was measured weekly.

CONCLUSIONS

Our study shows that BACH2 is required for the formation and maintenance of HIV reservoirs in long-lived memory cells was abrogated in the absence of BACH2. Our study shows the potential role of BACH2 in the establishment and stability of HIV latent reservoirs and identifies avenues for targeted interventions.

Reference:

1. Science. 2014 Aug 1;345(6196):570-3.
2. J Immunol. 2022 Apr 1;208(7):1700-1710.
3. J Clin Invest. 2021 Feb 1;131(3):e145254.
4. Nat Med. 1999 May;5(5):512-7.
5. Nat Med. 2003 Jun;9(6):727-8.

Acknowledgements :

Our collaborators, funding organizations, and study participants.