CCNT1 is a Nonessential Gene in Jurkat T Cells Required for HIV Release from Latency

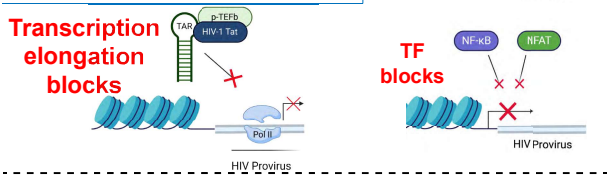
440

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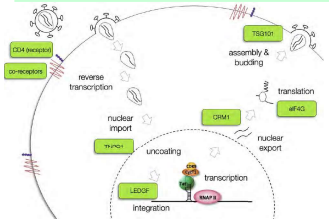
A major barrier to HIV cure is the persistent latent provirus which reactivates if antiretroviral therapy is stopped.

HIV latency involves several mechanisms that contribute to transcriptional silencing of HIV provirus.



What host factors enable HIV to come out of latency?

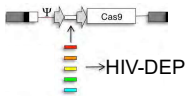
We hypothesized that genes required for infection of host cells – known as HIV dependency factors – may be also required for latency reversal.



- Goal: find novel host genes to target and prevent reactivation from the latent reservoir.
- Previous work used a CRISPR screen to identify novel genes required for HIV replication across several HIV strains.[1]

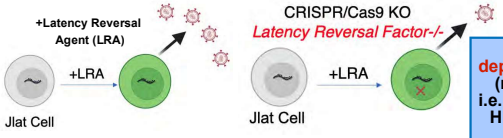
Dependency Factor gRNA Library
525 genes

8 sgRNAs/ gene
+
210 NTCs



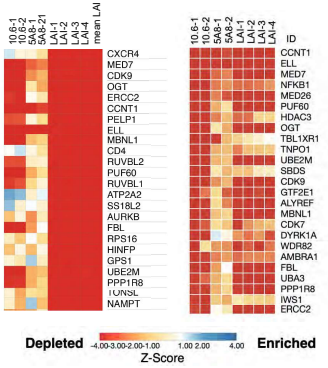
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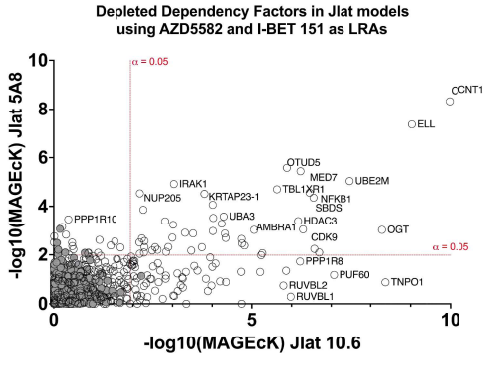
Latency HIV-CRISPR Screen using Jlat Models[2]

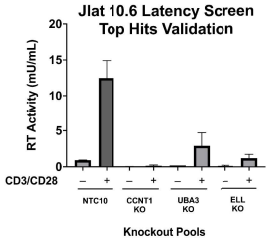


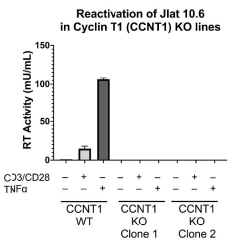
What guides are depleted in supernatant (relative to control)? i.e. without these genes HIV does not emerge from latency

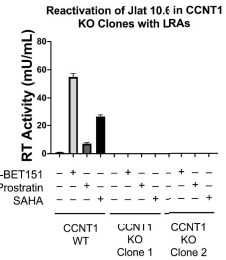
Our CRISPR screen shows HIV dependency factors are required both for establishing infection and for latency reversal.

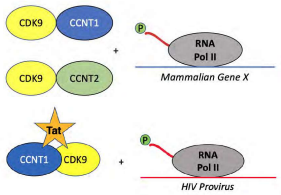


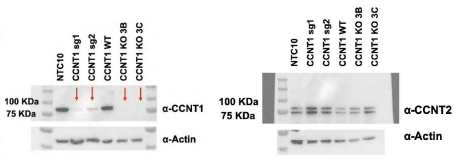




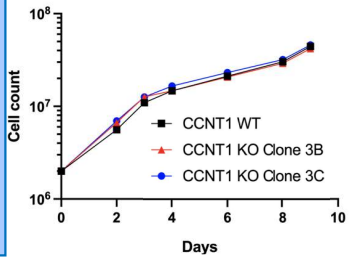








Targeting CCNT1 is a promising target to prevent latency reactivation.



- Cell growth is not affected in Cyclin T1 clonal knockout lines
- Cyclin T1 knockouts prevent latency reactivation from a wide range of stimuli
- Preliminary data suggests CCNT1 KO are viable in Browne Lab model of latency.

Main Findings

- A significant subset of HIV dependency factors also play a role in reactivation from latency and are a potential source of novel host genes required for proviral transcription in latent cell populations.
- The top hit, CCNT1, is nonessential in a Jurkat cell model. We predict this is due to CCNT1 paralog CCNT2 which can form p-TEFb in addition to CCNT1 in host cell, but cannot participate in HIV-1 proviral transcription.

Future Directions

- RNA sequencing of Jlat 10.6 CCNT1 KO clones
- Understanding the effect of CCNT1 KO on T-cell activation
- Characterization of CCNT1 knockouts in CD4+ T cells isolated from healthy donors - Browne lab latency model

Selected References

1. Montoya, V. and Emerman, M. et al. *mBio*. 6 Feb 2023.
2. Hsieh, E. and Emerman, M. et al. *PLOS Pathogens*. 27 Jan 2023.

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