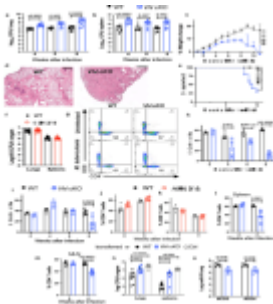


Inhibiting Mycobacterium tuberculosis infection



The hypoxia-inducible factors ([HIFs](#)) regulate the main transcriptional pathway of response to hypoxia in T cells and are negatively regulated by von Hippel-Lindau factor (VHL). The role of [HIFs](#) in the regulation of CD4 T cell responses during infection with *M. tuberculosis* isn't well understood.

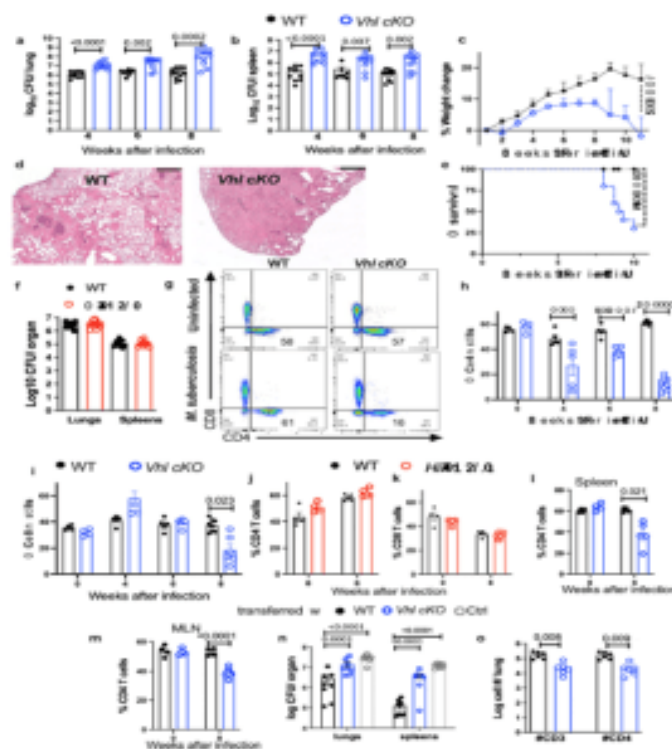


Figure 1: VHL expression in T cells is critical for the control of *M. tuberculosis* infection in mice a,b, Vhl cKO and WT mice were infected via aerosol with 250 *M. tuberculosis* and sacrificed at

indicated time points after infection. The log₁₀ CFU in the lung (a) and spleen (b) of individual mice (n WT = 10, 9, 12; n Vhl cKO = 9, 9, 10 mice at 4-, 6- and 8-weeks post infection (w.p.i.) respectively) are represented. cThe weight change with respect to the uninfected group mean (day 0) during infection with *M. tuberculosis* of Vhl cKO and WT mice (n = 11 per group) is depicted. D Representative micrographs from hematoxylin-eosin-stained paraffin lung sections from Vhl cKO and WT mice 8 w.p.i. with *M. tuberculosis* (bar: 400 μm). E The cumulative mortality of Vhl cKO and WT mice (n = 9 per group) after *M. tuberculosis* infection is depicted. F The log₁₀ CFU in the lungs and spleens of Hif1a cKO (n = 11) and WT (n = 9) mice 8 w.p.i. with *M. tuberculosis* are shown. g–I The representative dot plots of CD4 and CD8 (gated on T cells) in the lungs of Vhl cKO and WT mice before and 8 w.p.i. with *M. tuberculosis* (g), and the frequency of CD4 (h) and CD8 (i) T cells in the lungs (WT n = 4, 4, 6, 8 and Vhl cKO n = 4, 5, 6 and 8 mice at 0, 4, 6 and 8 w.p.i. respectively). j, k The frequency of CD4 and CD8 T cells in the lungs of Hif1a cKO and WT mice before (n = 4 per group) and 8 w.p.i. (n = 5 per group) are

depicted. l, m The frequency of CD4 in spleens (l) and mediastinal lymph nodes (m) before and 8 w.p.i. with *M. tuberculosis* are shown (Vhl cK0 n = 4, 7 and WT n = 4, 4 mice at 0 and 8 w.p.i., respectively). Rag2^{-/-}-mice were administered i.v. with either 2.10⁶ Vhl cK0 or WT CD4 T cells (n = 6) or left untreated 3 days after *M. tuberculosis* infection. The log₁₀ CFU in the lungs and spleens (n) (n = 8 animals per group) and number of CD4 T cells (o) in lungs (n = 6 mice per group) 4 w.p.i. Each symbol represents one mouse, and the data are presented as the mean ± s.e.m. The p-values were calculated using either a two-tailed unpaired t test with Welch's correction for no homoscedasticity and FDR approach for multiple comparison (a,b,f,h-m,o), a one-way ANOVA with Welch's correction (n), a 2-way ANOVA with Sidak's multiple comparison test (c), or a χ^2 test (e). Source data are provided as a Source Data file.

The authors show that mice lacking VHL in T cells (Vhl cK0) are highly susceptible to infection with *M. tuberculosis*, which is associated with a low accumulation of mycobacteria-specific T cells in the lungs that display reduced proliferation, altered differentiation and enhanced expression of inhibitory receptors. In contrast, the absence of HIF-1 in T cells is redundant in *M. tuberculosis* control. Vhl cK0 mice also exhibit diminished immunisation responses. Moreover, upon

TCR activation, VHL promotes appropriate MYC-activation, cell-growth responses, DNA synthesis, proliferation, and survival of CD4 T⁺ cells. The VHL-deficient T cell responses are rescued by the lack of HIF-1, demonstrating that the enhanced susceptibility to *M. tuberculosis* is mediated by HIF-1. HIF-1 is required for tuberculosis infection and the poor responses of Vhl-deficient T cells.

Journal article: Liu, R., et al., 2022. [*HIF-1 stabilization in T cells hampers the control of Mycobacterium tuberculosis infection*](#). Nature communications.

Summary by Brian Munansangu