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The histone methyltransferase EZH2 primes the differentiation of follicular helper T cells during acute viral infection

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Epigenetic modifications to histones dictate the differentiation of naïve CD4+ T cells into different subsets of effector T helper (T_H) cells. The role of histone methyltransferase enhancer of zeste homolog 2 (EZH2) has been implicated in the differentiation of T_H1, T_H2 and regulatory T (Treg) cells. However, whether and how EZH2 regulates follicular helper T (T_{FH}) cell differentiation remains unknown. Using a mouse model of acute lymphocytic choriomeningitis virus (LCMV) infection, we found that ablation of EZH2 in LCMV-specific $CD4^+$ T cells led to impairment of early T_{FH} cell fate commitment. Mechanistically, our data showed that EZH2 catalyzes the trimethylation of lysine 27 of histone 3 (H3K27me3) to mark Klf4, which led to the silencing of TF KLF4 expression. KLF4 directly bound to the Tcf7 and Bcl6 loci to repress the expression of TCF-1 and Bcl-6, which are TFs initiating T_{FH} cell fate commitment. Thus, we identified the chromatin-modifying enzyme EZH2 as a novel regulator of early T_{FH} differentiation priming that acts by silencing the transcription repressor KLF4 to facilitate TCF-1/Bcl6 axis during acute viral infection.