Infection as a Driver of Dnmt3a-loss of function Clonal Hematopoiesis

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Age-related clonal hematopoiesis (CH) is a risk factor for malignancy, cardiovascular disease and all-cause mortality. Somatic mutations in *DNMT3A* are drivers of CH, but decades may elapse between acquisition of a mutation and CH, suggesting that environmental factors contribute to clonal expansion. We tested whether infection provides selective pressure favoring expansion of *Dnmt3a*-mutant hematopoietic stem cells (HSCs) in mouse chimeras. We created *Dnmt3a*-mosaic mice by transplanting *Dnmt3a*$^{-/-}$ and WT HSCs into WT mice and observed substantial expansion of *Dnmt3a*$^{-/-}$ HSCs during chronic mycobacterial infection. Injection of recombinant IFNγ alone was sufficient to phenocopy CH by *Dnmt3a*$^{-/-}$ HSCs upon infection. Transcriptional and epigenetic profiling and functional studies indicate reduced differentiation associated with widespread methylation alterations and reduced secondary stress-induced apoptosis account for *Dnmt3a*$^{-/-}$ clonal expansion during infection. *DNMT3A*-mutant human HSCs similarly exhibit defective IFNγ-induced differentiation. We thus demonstrate that IFNγ signaling induced during chronic infection can drive DNMT3A-loss of function CH.

[1] Hormaechea-Agulla D, Matatall K, Le DT, Kain B, Long X, Kus P, Jaksik R, Challen GA, Kimmel M, and **King KY**. (2021) Chronic infection drives Dnmt3a-loss of function clonal hematopoiesis via IFNg signaling. Cell Stem Cell. Epub ahead of print. PMID: 33743191.