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Infection Drives Dnmt3a-loss of function Clonal Hematopoiesis via IFNg Signaling

Katherine Y. King MD PhD is Associate Professor of Pediatric Infectious Diseases at Baylor College of Medicine, where she is part of the faculty for the Stem Cells and Regenerative Medicine Center and serves as a co-director of the BCM MSTP. A native Houstonian, Dr. King received her BA in Biochemical Sciences from Harvard University and her MD and PhD degrees from Washington University in St. Louis. Her research focuses on the molecular mechanisms by which inflammation affects blood and immune cell production by hematopoietic stem cells in the bone marrow. Dr. King has been the recipient of a NIH K08 mentored physician scientist training award, the March of Dimes Basil O'Connor Starter Scholar Award, and in 2019 she received the Presidential Early Career Award for Scientists and Engineers (PECASE). When not seeing patients at Texas Children's Hospital or conducting research in the lab, Dr. King enjoys running, yoga, spending time with her husband and 7-year-old daughter, and volunteering for health care advocacy.

Abstract: 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 used a murine model to investigate the prediction that infection provides selective pressure favoring expansion of Dnmt3a-mutant hematopoietic stem cells (HSCs). We created Dnmt3a mosaic mice by transplanting a mixed population of Dnmt3a-/- and WT HSCs into WT mice and observed substantial expansion of Dnmt3a-/- HSCs during chronic mycobacterial infection. Transcriptional profiling and functional studies indicate reduced differentiation and reduced secondary stress-induced apoptosis account for Dnmt3a-/- clonal expansion during infection. Both injection of recombinant IFNγ alone and infecting mice transplanted with HSCs lacking the differentiation factor Batf2 partially phenocopied CH by Dnmt3a-mutant HSCs upon infection. This is the first study demonstrating that IFNγ signaling induced during chronic infection can drive DNMT3A-loss of function CH.