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Tcf1 and Lef1 provide constant supervision to mature CD8⁺ T cell identity and function by organizing genomic architecture

Qiang Shan^{1,5}, Xiang Li ^{2,5}, Xia Chen³, Zhouhao Zeng², Shaoqi Zhu², Kexin Gai¹, Weiqun Peng ²✉ & Hai-Hui Xue ^{1,4}✉

T cell identity is established during thymic development, but how it is maintained in the periphery remains unknown. Here we show that ablating Tcf1 and Lef1 transcription factors in mature CD8⁺ T cells aberrantly induces genes from non-T cell lineages. Using high-throughput chromosome-conformation-capture sequencing, we demonstrate that Tcf1/Lef1 are important for maintaining three-dimensional genome organization at multiple scales in CD8⁺ T cells. Comprehensive network analyses coupled with genome-wide profiling of chromatin accessibility and Tcf1 occupancy show the direct impact of Tcf1/Lef1 on the T cell genome is to promote formation of extensively interconnected hubs through enforcing chromatin interaction and accessibility. The integrative mechanisms utilized by Tcf1/Lef1 underlie activation of T cell identity genes and repression of non-T lineage genes, conferring fine control of various T cell functionalities. These findings suggest that Tcf1/Lef1 control global genome organization and help form intricate chromatin-interacting hubs to facilitate promoter-enhancer/silencer contact, hence providing constant supervision of CD8⁺ T cell identity and function.

¹Center for Discovery and Innovation, Hackensack University Medical Center, Nutley, NJ 07110, USA. ²Department of Physics, The George Washington University, Washington, DC 20052, USA. ³Department of Critical Care Medicine, Fuxing Hospital, Capital Medical University, Beijing 100038, China. ⁴New Jersey Veterans Affairs Health Care System, East Orange, NJ 07018, USA. ⁵These authors contributed equally: Qiang Shan and Xiang Li. ✉email: wpeng@gwu.edu; haihui.xue@hnh-cdi.org