EBNA3C reprograms host 3D genome organization to control the growth of lymphoblastoid cell line (LCL).

Chong Wang[1], Weiyue Ding[1], Hongbo Wang[1], Yohei Narita[1], Merrin Leong[1], Mingxiang Teng[2], Bo Zhao[1]

1. Dept. of Medicine, Brigham and Women's Hospital, Harvard Medical School
2. Moffitt Cancer Center

EBNA3C is essential for EBV to transform primary resting B lymphocytes into LCLs. EBNA3C repression of $p16^{ink4a}$ is required for transformation and continuous LCL growth. EBNA3C can recruit transcription repressor Sin3A to the CDKN2A loci that encodes $p16^{ink4A}$ and $p14^{ARF}$ to repress gene expression. EBNA3C ChIP-seq identifies thousands of EBNA3C binding sites in LCLs, many are remote enhancers. To determine the effect of EBNA3C on enhancer looping, EBNA3C conditional LCL H3K27ac HiChIP was used. Cells were grown under permissive or non-permissive condition for EBNA3C expression for 14 days. Cells were first crosslinked and DNA was cut by MboI. The DNA ends were filled in by biotinylated nucleotides and then ligated. H3K27ac ChIP was used to enrich the ligation products. Avidin beads captured ligated DNA and DNA was paired-end sequenced. EBNA3C inactivation greatly changed enhancer-enhancer, enhancer-promoter looping. EBNA3C inactivation increased enhancer looping at the CDKN2A loci. Accompanied with the looping changes, H3K27ac cut & run signals were greatly increased at these loci upon EBNA3C inactivation. Looping factor CTCF binding also greatly changed at the loci. EBNA3C inactivation also reduced enhancer looping at many genes essential for LCL growth. This study provides new insight into EBNA3C's role in controlling host transcription.