ANALYSIS OF CHROMATIN STRUCTURAL ABERRATIONS IN EPSTEIN-BARR VIRUS (+) BURKITT LYMPHOMA

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Cancer arises through accumulation of genetic or epigenetic aberrations and these aberrations lead to chromatin structural alterations which contribute to tumorigenesis. Epstein-Barr virus (EBV) is an oncovirus and associated with various types of cancer such as gastric cancer (GC), nasopharyngeal carcinoma and Burkitt lymphoma (BL). We previously presented that direct interaction between EBV and host genome leads to host-heterochromatin rewiring by activating as enhancer regions in gastric adenocarcinoma [1]. However, we still do not fully understand whether this phenomenon also induces oncogenic aberrations in other tissue.

Here, to examine the chromatin structural alterations and disruption of the transcription regulatory network, we performed chromosome conformation capture combined with high-throughput sequencing (Hi-C). We extracted the EBV-host interacting reads from Hi-C data and identified EBV-host interacting regions. When we compared the EBV-host chromatin interacting regions in EBV(+) BL and in GC, about 80% of the regions are not overlapped. To elucidate genomic and epigenomic properties of EBV-host interacting regions in BL, we performed ChIP-seq against histone modifications (H3K4me3, H3K4me1 and H3K27ac as active marks; H3K27me3 and H3K9me3 as repressive marks). EBV-host interacting regions showed AT-rich, gene-poor genomic properties and H3K9me3(+)/H3K27ac(+) bivalent modification pattern as we reported in EBV(+) GC. This result indicates that EBV targeted to host-heterochromatin regions and the difference of its interacting regions might be caused by tissue-type specific heterochromatin. When we analyzed profiles obtained from of 3 EBV(+) BL cell lines and a human lymphoblastoid cell line, we found specific B-to-A compartment shifts and the higher levels of H3K4me1/H3K27ac at EBV-host interacting regions, indicating that EBV-interacting regions are activated as enhancers and can activate neighboring genes. To further analyze regulatory network between active enhancers and promoters, we performed H3K27ac HiChIP in EBV(+) BL cell lines. The activated enhancers at EBV-interacting regions were found to form a loop with upregulate nearby genes, including cancer-related genes. These data suggest that EBV-host genomic interaction might contribute to tumorigenesis in EBV(+) BL.

1. Okabe A, Huang KK, Matsusaka K, Fukuyo M, Xing M, Ong X, Hoshii T, Usui G, Seki M, Mano Y, Rahmutulla B, Kanda T, Suzuki T, Rha SY, Ushiku T, Fukayama M, Tan P, Kaneda A, 2020, Nat Genet、52(9), 919-930