EPSTEIN-BARR VIRUS INFECTION REWIRES HOST CHROMATIN STRUCTURE AND EPIGENETICALLY CONTRIBUTES TO TUMORIGENESIS IN TISSUE WIDE MANNER

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Epstein-Barr virus (EBV) is an oncovirus associated with various types of cancer such as gastric cancer (GC), nasopharyngeal carcinoma (NPC), and hematopoietic malignancies. We previously presented that EBV plays an epi-mutagenic role in the infected host cells [1]. The epigenetic aberrations include DNA hypermethylation, and EBV(+) GC exhibits the most extreme DNA hypermethylation phenotype among whole human malignancies [2]. Within 4 weeks after EBV infection, gastric epithelial cells acquired DNA hypermethylation at promoter CpG islands of >3,000 genes including genes associated with growth suppression or cell adhesion, accompanied with upregulation of DNMT1 and downregulation of TET2 [3]. Not only such epigenetic inactivation of tumor suppressor genes by DNA hypermethylation, but epigenetic activation of oncogenes via aberrant interaction between enhancer regions and proto-oncogenes also contributes to tumorigenesis of EBV(+) GC significantly [4,5]. We comprehensively analyzed 3D chromatin structures and epigenomes of GC and normal samples by Hi-C and ChIP-seq, revealing compartment changes specific to EBV(+) GC, from inactive to active state. EBV infection *in vitro* demonstrated preferential binding of episomal EBV DNA to heterochromatin of the host genome, and H3K9me3(+) heterochromain was converted to H3K4me1(+)/H3K27ac(+) euchromatin in such EBV-host interacting regions (EBVIRs). The latent enhancer regions in heterochromatin were thus activated by EBV (named “enhancer infestation”), leading to aberrant chromatin interaction with and activation of neighboring proto-oncogenes e.g. *MZT1* [6]. We further analyzed other EBV-associated malignancies e.g. NPC and Burkitt lymphoma, and identified EBVIRs in each cancer type. EBVIRs were partly overlapped among all types, but mostly observed in tissue-specific manner. Interestingly, EBVIRs were AT-rich, gene-poor, and H3K9me3(+) heterochromatin, regardless cancer types. Inactive-to-active compartment changes, and aberrant activation of neighboring proto-oncogenes were also commonly observed. Thus epigenetic aberrations significantly contribute to EBV-associated tumorigenesis, where EBV commonly rewires host chromatin structure by “enhancer infestation” or similar activation mechanisms.

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