ROLE OF EPSTEIN-BARR VIRUS *LNC-BARTS*/BRD4 AXIS IN PROMOTING NASOPHARYNGEAL CARCINOMA

Jiayan LIU[1], Songtao HE[1], Honglin CHEN[1]

[a] *Department of Microbiology and State Key Laboratory for Emerging Infectious Diseases, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*

liujy621@hku.hk

Among the Epstein-Barr virus (EBV) associated tumors, EBV genome is found in 100% of nasopharyngeal carcinoma (NPC) tumor cells. EBV establishes a latent infection in NPC cells, expressing few viral proteins, but elevated levels of non-coding RNAs transcribed from the *BamHI*-A rightward transcripts (BARTs) region of the EBV genome. The family of BART RNAs contain BART-microRNAs (miRNAs) and long non-coding RNAs (*lnc-BARTs*). While versatile functions of BART miRNAs continue to be revealed, little is known about EBV *lnc-BARTs*. In this study, we provided evidence to show that BARTs which derived from multiple BART exons function as regulatory long non-coding RNA, namely *lnc-BARTs*, in modulating the core network for maintaining EBV latency and NPC development through epigenetic mechanisms. Our study first identified that *lnc-BARTs* were abundantly expressed in NPC biopsies by RNAscope. In CARPID assay, lnc-BARTs were found to physically interact with a complex consists of transcription factors, including BRD4. Notably, *lnc-BARTs* co-localized with BRD4 and P-TEFb complex in the nuclear speckle in RNA FISH and such complexes can be disrupted by treatment of JQ1, a BRD4 competitive inhibitor. RNA immunoprecipitation and RNA pulldown assay showed that *lnc-BARTs* directly binding to BRD4. In addition, transcriptome analysis revealed that knockdown of BART in EBV-positive NPC cell line, C666-1, resulted in downregulation of oncogenes MYC and BCL2. The cell proliferation and apoptosis rate of C666-1 cell line with the BART knockdown was significantly decreased. BRD4-ChIP and ATAC sequencing analysis further demonstrated that knockdown of *lnc-BARTs* reduced both BRD4-mediated epigenetic modulation of host gene expression and chromatin accessibility. We suggest that EBV *lnc-BARTs* are involved in epigenetic modulation of host gene expression through functional interaction with BRD4 regulatory machinery to drive tumorigenesis in NPC, and simultaneously maintain EBV latency.