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Whole-genome and Epigenome Sequencing Identified Novel Epstein–Barr Virus-Associated Functional Mutations and Epigenetic Gene Silencing in Gastric Cancer

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Abstract

The molecular mechanisms of Epstein-Barr virus (EBV)-associated gastric cancer remains largely unclear. We applied integrative genomic approaches to uncover EBV-associated genomic and epigenomic variations in gastric cancer. Whole genome, transcriptome and epigenome sequencing was performed in EBV-infected AGS cells (AGS-EBV) and its parental EBV-negative AGS cells. The identified novel mutations and epigenetic alterations by genome sequencing were verified and characterized in 134 primary gastric cancers with (n=34) or without (n=100) EBV infection. Transcriptome analysis of AGS-EBV revealed expression of 9 well-known and 71 un-reported EBV genes in gastric cancer, top 10 of which were recapitulated in primary EBV(+) gastric cancers. Whole genome sequencing identified 45 novel EBV-associated non-synonymous mutations. Novel mutated genes were validated to be significantly associated with EBV (+) gastric cancers, including AKT2 ($P<0.0001$), CCNA1 ($P=0.004$), MAP3K4 ($P<0.05$) and TGFBR1 ($P<0.05$). Notably, AKT2 mutation was associated with poorer survival in EBV (+) gastric cancer patients ($P=0.006$). Integration of epigenome and transcriptome analyses identified 216 genes transcriptionally downregulated by EBV-associated promoter methylation. Novel downregulated genes including ACSS1, FAM3B, IHH and TRABD were confirmed to be significantly methylated in primary EBV (+) gastric cancers. Moreover, KEGG pathway enrichment analysis revealed five inter-correlated pathways (Axon Guidance, Focal Adhesion, Cytokine-cytokine Receptor Interaction, MAPK Signaling and Regulation of Actin Cytoskeleton) being commonly affected by EBV-associated genomic and epigenomic alterations. These data provide an extensive and high-quality genomic landmark for EBV-associated gastric cancer and demonstrate the novel genomic and epigenomic abnormalities and signaling networks that may govern EBV-associated gastric carcinogenesis.

Biography

Dr. Liang has completed her PhD at 27 from Zhejiang University and is now a postdoctoral fellow in The Chinese University of Hong Kong.She has identified and designated three novel cancer-related genes and established one prenatal diagnosis method with granted patent.Her broad research interests include cancer genomics, metagenomics, human endogenous retrovirusesand functional studies on cancer-related genes. Dr. Liang has 11peer-reviewed research articles (9 first authorships) and one first authorship book chapter published. She is now principal investigator for three projects supported by national foundation of China, as well as being co-investigator to 6 other projects.