Epigenomic identification of novel cancer genes and tumor biomarkers

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Cancer is a genetic disease, caused by accumulated alterations of multiple cancer genes including oncogenes and tumor suppressor genes (TSG). Thus, huge effort has been put into the identification of somatic gene mutations in cancers through large-scale genome sequencing, with the discovery of a few limited, mutated cancer genes in various tumors. Epstein-Barr virus (EBV) is a herpesvirus associated with a variety of epithelial and lymphoid malignancies, especially the lymphoepithelioma-like carcinomas of nasopharyngeal (NPC), gastric and lung tissues, all prevalent in Hong Kong. A common genomic feature of EBV-associated carcinomas (EBV+Ca) is that very few somatic mutations could be detected, compared to other tumors or their EBV-negative counterparts. This unique cancer genomic feature strongly suggests special pathogenic mechanism of EBV+Ca: epigenetic alterations, rather than genetic mutations, play a critical role in the carcinogenesis. We thus established the epigenomes (CpG methylome) of EBV+Ca and identified a series of novel and known TSGs (*RASAL1, ZNF382, DLEC1, ZBTB28, ZDHHC1, TUSC6/KIAA0495, etc*), predominantly inactivated by promoter CpG methylation. We further characterized their biologic functions and related molecular mechanisms in carcinogenesis. The epigenetic silencing of these TSGs leads to the disrupting of normal cell signaling and deregulation of cell cycle, apoptosis and stemness. As these TSGs are frequently methylated in tumors in a tumor-specific manner, their epigenetic abnormalities are also useful cancer diagnostic biomarkers and therapeutic targets.