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An EBV microRNA targets DICE1 tumor suppressor gene

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MicroRNAs (miRNAs) play a critical role in post-transcriptional regulation of gene expression. Several herpesviruses have been shown to express viral miRNAs. Identification of the targets of these miRNAs might derive mechanistic insight into viral pathogenesis. We have previously demonstrated that Epstein-Barr virus (EBV)-encoded miR-BART5 targets p53-upregulated modulator of apoptosis (PUMA) in nasopharyngeal carcinoma (NPC) and this regulation is important for the EBV persistence and survival of EBV-infected cell survivals. In addition to the anti-apoptotic role of miR-BART5, other oncogenic activities of EBV miRNAs may also contribute to the development of lymphocytic or epithelial malignancies. In this study, we screened for potential targets of EBV miRNAs and found that EBV miR-BART3-5p potently suppressed the expression of DICE1 tumor suppressor in cultured cells. DICE1 is known to be inactivated genetically or epigenetically in different types of tumor. We identified the target site of miR-BART3-5p in the 3' untranslated region of DICE1. Mutation of its seed sequence abolished the suppressive effect. Overexpression of miR-BART3-5p or its precursor mitigated the expression of endogenous DICE1. On the other hand, knockdown of miR-BART3-5p expression by LNA-miRNA inhibitor triggered re-expression of DICE1 in C666-1 NPC cells constitutively carrying EBV. Underexpression of DICE1 protein was frequently detected in human NPC tumor samples. Forced expression of DICE1 in cultured cells inhibited cellular proliferation and this inhibition was reversed by the expression of miR-BART3-5p. Taken together, our findings suggest that EBV encodes miR-BART3-5p to promote epithelial cell growth and transformation by targeting DICE1 tumor suppressor. This work was supported by Hong Kong Research Grants Council (HKU 7668/09M and AoE/M-06/08), Hong Kong Research Fund for the Control of Infectious Diseases (11100602) and SK Yee Medical Research Fund (2011).

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Expression of microRNAs in nasal natural killer/T-cell lymphoma

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Nasal NK/T-celllymphoma has distinct clinical and histological features and is characterized by a poor prognosis and progressive necrotic lesion with tumor and inflammatory cell infiltrations in the nasal cavity, nasopharynx, and plate. Recent reports suggest that this lymphoma may be derived from NK or γδT-cell lineages, both of which express the NK cell marker, CD56. MicroRNAs are noncoding, single-stranded RNAs recently implicated in the regulation of several biological processes. In late years, carcinogenesis due to the aberrant expression of microRNA has been reported for various cancers. In this study, we examined the microRNAs expressed specifically by SNK-6, SNK-1 and SNT-8 cells which were established from nasal NK/T-cell lymphomas. To determine which microRNAs are expressed specifically in nasal NK/T-cell lymphoma, we performed microarray analysis of microRNA. We found that miR-15a is down-regulated in nasal NK/T-cell lymphoma cell lines. Gain-of-function analysis revealed that miR-15a transfectants are induced apoptosis. These results suggested that down-regulation of miR-15a might be associated with lymphomagenesis and progression in nasal NK/T-cell lymphoma.