Role of secretary small RNAs as a pro-inflammatory mediator in the development of EBV-associated lymphoma

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Abstract

Epstein-Barr virus (EBV) causes various diseases in the elderly including B-cell lymphoma such as Hodgkin's lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL). Here, we show that EBV acts *in trans* on non-infected macrophages in the tumor through exosome secretion and augments the development of lymphomas. In a humanized mouse model, the different formation of lymphoproliferative disease (LPD) between two EBV strains (Akata and B95-8) was evident. Furthermore, injection of Akata derived exosomes affected LPD severity possibly through the regulation of macrophage phenotype *in vivo*. Exosomes collected from Akata- lymphoblastoid cell lines (LCLs) reportedly contain EBV-derived non-coding RNAs such as BamHI fragment A rightward transcript (BART) miRNAs and EBV-encoded RNA (EBER). We focused on the exosome-mediated delivery of BART miRNAs. *In vitro*, BART miRNAs could induce the immune regulatory phenotype in macrophages characterized by the gene expressions of *interleukin-10*, *tumor necrosis factor-alpha*, and *arginase 1*, suggesting the immune regulatory role of BART miRNAs. The expression level of an EBV-encoded miRNA was strongly linked to the clinical outcomes in elderly diffuse large B-cell lymphoma patients. These results implicate BART miRNAs as one of the factors regulating the severity of lymphoproliferative disease and as a diagnostic marker for EBV+ B-cell lymphoma.