Role of exosomes as a proinflammatory 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 and diffuse large B-cell lymphoma. Here, we show that EBV acts in trans on noninfected 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 2 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 reportedly contain EBV-derived noncoding RNAs such as BamHI fragment A rightward transcript (BART) micro-RNAs (miRNAs) and EBV-encoded RNA. 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 patients with diffuse large B-cell lymphoma. These results implicate BART miRNAs as 1 of the factors regulating the severity of lymphoproliferative disease and as a diagnostic marker for EBV+ B-cell lymphoma.

Keywords

KeyWords Plus: EPSTEIN-BARR-VIRUS; B-CELL LYMPHOMA; DENDRITIC CELLS; MACROPHAGES; MICRORNAS; INFECTION; MIRNAS; CANCER; STRAINS; TRANSFORMATION

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