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The BART miRNA Cluster Modulates Multiple Functions in Primary B Cells

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The Epstein-Barr virus (EBV) is a B lymphotropic virus that infects the majority of the human population. All EBV strains transform B-lymphocytes, but some strains, such as M81, also induce spontaneous virus replication. EBV encodes 22 microRNAs (miRNAs) that form a cluster within the BART region of the virus and have been previously been found to stimulate tumor cell growth. Here we describe their functions in B cells infected by M81. We found that the BART miRNAs are downregulated in replicating cells and that exposure of B cells in vitro or in vivo to a BART miRNA knockout virus resulted in an increased proportion of spontaneously replicating cells, relative to wild type virus. The BART miRNAs subcluster 1, and to a lesser extent subcluster 2, prevented expression of BZLF1, the key protein for initiation of lytic replication. The BART miRNAs also downregulated pro- and anti-apoptotic mediators such as caspase 3 and LMP1, and their deletion did not sensitize B-cells to apoptosis. To the contrary, the majority of humanized mice infected with the BART miRNA knockout mutant developed tumors more rapidly, probably due to enhanced LMP1 expression, although deletion of the BART miRNAs did not modify the virus transforming abilities in vitro. This ability to slow cell growth could be confirmed in non-humanized immunocompromized mice. Injection of resting B cells exposed to a virus that lacks the BART miRNAs resulted in accelerated tumor growth, relative to wild type controls. Importantly, a virus that lacks both the BART miRNAs and BZLF1 retains the increased transforming abilities of the single miRNA knockout that are therefore independent of lytic replication. M81 BART miRNAs inhibit the spontaneous lytic replication in the infected B cells. By using animal models we found that the M81 BART miRNAs do not enhance B-cell tumorigenesis but rather repress it.