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An ATM/Chk2-mediated DNA damage responsive signaling pathway suppresses Epstein-Barr virus transformation of primary human B cells

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Epstein-Barr virus (EBV) infection of primary B cells leads to the outgrowth of indefinitely proliferating lymphoblastoid cell lines (LCLs). However, the efficiency of immortalization is less than 10% of infected cells. We hypothesize that a robust innate tumor suppressor response prevents long-term outgrowth of the majority of infected cells. In this study we identify the DNA damage response (DDR) as a major component of this response. EBV infection of primary B cells activated hallmarks of the DDR including phosphorylated ATM, Chk2, g-H2AX, and 53BP1 foci. DDR activation was not due to lytic viral DNA replication nor did its marks co-localize with latent viral episomes. Rather, EBV induced a period of hyper-proliferation early after infection responsible for DDR activation. Microarray data supported the transient activation and subsequent attenuation of proliferation and DDR-associated mRNAs during LCL outgrowth. Importantly, activation of this pathway suppressed transformation as small molecule antagonism of the DNA damage responsive kinases ATM and Chk2 increased EBV transformation efficiency. Thus, we propose a model whereby EBV infection initially drives aberrant cellular DNA replication activating an anti-proliferative DNA damage response. Long-term outgrowth depends on attenuation of this hyper-proliferative signal through full latency III gene expression.

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