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Epstein, Barr Virus Alters ATM-Dependent DNA Damage Responses in Germinal Centre B-Cells during Early Infection

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Abstract : Epstein-Barr virus (EBV) has been implicated in the pathogenesis of human tumours of B-cell origin. The demonstration that a proportion of Hodgkin lymphomas and all Burkitt's lymphomas harbour EBV suggests that the virus contributes to the development of these malignancies. However, the mechanisms of lymphomagenesis remain largely unknown. To determine whether EBV causes DNA damage and alters DNA damage response in cells of EBV-driven lymphoma origin, Germinal Centre (GC) B cells were infected with EBV and DNA damage responses to gamma ionising radiation (IR) assessed at early time points (12hr – 72hr) after infection and prior to establishment of lymphoblastoid (LCL) cell lines. In the presence of EBV, we observed induction of spontaneous DNA DSBs and downregulation of ATM-dependent phosphorylation in response to IR. This downregulation coincided with reduced ability of infected cells to repair IR-induced DNA double-strand breaks, as measured by the kinetics of gamma H2AX, a marker of double-strand breaks, and by the tail moment of the comet assay. Furthermore, we found that alteration of DNA damage responses coincided with the expression of LMP-1 protein. The presence of the EBV virus did not affect the localization of the ATM-dependent DNA repair proteins to sites of damage but instead lead to an increased expression of PP5, a phosphatase that regulates ATM function. The impact of the virus on DNA repair was most prominent 24h after infection, suggesting that this time point is crucial for the viral establishment in B cells. Our results suggest that during an early infection EBV virus dampens crucial cellular responses to DNA double-strand breaks which facilitate successful viral infection, but at the same time might provide the mechanism for tumor development.

Keywords : EBV, ATM, DNA damage, germinal center cells
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