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Abstract

Interferon Antagonism of Epstein–Barr Virus Tegument Proteins †

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Abstract: The Epstein–Barr virus (EBV) successfully infects 95% of all adults but causes Burkitt's lymphoma, Hodgkin's lymphoma, gastric carcinoma, nasopharyngeal carcinoma or other malignancies in only a small subset of infected individuals. The virus must have developed effective viral countermeasures to evade host innate immunity. In this study, we performed functional screens to identify EBV-encoded interferon (IFN) antagonists. Several tegument proteins were found to be potent suppressors of IFN production and/or signaling. The large tegument protein and deubiquitinase BPLF1 antagonized type I IFN production induced by DNA sensors cGAS and STING or RNA sensors RIG-I and MAVS. BPLF1's ability to suppress innate immune signaling required its deubiquitinase activity. BPLF1 functioned as a catalytically active deubiquitinase for both K63- and K48-linked ubiquitin chains on STING and TBK1, with no ubiquitin linkage specificity. Induced expression of BPLF1 in EBV-infected cells through CRISPRa led to effective suppression of innate DNA and RNA sensing. Another EBV tegument protein, BGLF2, was found to suppress JAK-STAT signaling. This suppression was ascribed to more pronounced K48-linked polyubiquitination and proteasomal degradation of BGLF2-associated STAT2. In addition, BGLF2 also recruited tyrosine phosphatase SHP1 to inhibit tyrosine phosphorylation of JAK1 and STAT1. A BGLF2-deficient EBV activated type I IFN signaling more robustly. Taken together, we characterized the IFN antagonism of EBV tegument proteins BPLF1 and BGLF2, which modulate ubiquitination of key transducer proteins to counteract type I IFN production and signaling in host cells. Supported by HMRF 17160822, HMRF 18170942, and RGC C7027-16G.

Keywords: Epstein-Barr virus; type I interferon; JAK-STAT