THE EPSTEIN-BARR VIRUS DEUBIQUITINATING ENZYME BPLF1 REGULATES ER HOMEOSTASIS BY PREVENTING UFMYLATION

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The N-terminal domains of the herpesvirus large tegument proteins encode a conserved cysteine protease with ubiquitin- and NEDD8-specific deconjugase activity. To gain insights on the substrates and signaling pathways targeted by the viral enzymes, we have used co-immunoprecipitation and mass spectrometry analysis to identify cellular proteins that interact with the Epstein-Barr virus encoded homologue. The only known UFM1 ligase, UFL1, and several putative UFMylation substrates were identified as BPLF1 interactors together with ER-associated proteins and components of protein translation machinery. UFMylation is a ubiquitin-like modification that regulates a variety of cellular functions including ER stress responses. UFMylation of the ribosomal subunit RPL26 and components of the ER-translocation machinery maintain ER homeostasis by promoting the lysosomal degradation of stalled polypeptides in a process known as ER-Phagy. We found that catalytically active BPLF1 inhibits the UFMylation of RPL26 during ribosome stalling induced by treatment with Anisomycin and prevents ER-phagy. This was accompanied by the activation of ER stress responses, including phosphorylation of eIF2α, with consequent inhibition of cap-dependent translation and robust activation of the ATF4 transcription factor. Induction of the productive virus cycle was accompanied by decreased RPL26 UFMylation and enhanced eIF2α phosphorylation in lymphoid cell lines (LCLs) carrying recombinant EBV encoding the active BPLF1 compared LCLs expressing the inactive enzyme. Thus, by regulating protein UFMylation BPLF1 is likely to play an important role in the remodeling of the protein translation machinery that favors the production of viral proteins during productive infection.

Oral presentation, appropriate topic: EBV infection and viral replication