

Abstract

KSHV Activates Unfolded Protein Response Sensors but Suppresses Downstream Transcriptional Responses to Support Lytic Replication [†]

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Abstract: Herpesviruses usurp host cell protein synthesis machinery to convert viral mRNAs into proteins, and the endoplasmic reticulum (ER) to ensure the proper folding, post-translational modification and trafficking of secreted and transmembrane viral proteins. Overloading the ER folding capacity activates the unfolded protein response (UPR), whereby sensor proteins, ATF6, PERK and IRE1, initiate a stress-mitigating transcription program that accelerates the catabolism of misfolded proteins, while increasing the ER folding capacity. Kaposi's sarcoma-associated herpesvirus (KSHV) can be reactivated from latency through the chemical induction of ER stress, which causes an accumulation of the XBP1s transcription factor that transactivates the viral RTA lytic switch gene. The presence of XBP1s-responsive elements in the RTA promoter suggests that KSHV evolved a mechanism to respond to ER stress. Here, we report that ATF6, PERK and IRE1 were activated upon reactivation from latency and were required for efficient KSHV lytic replication. The genetic or pharmacologic inhibitions of each UPR sensor reduced virion production. Despite UPR sensor activation during KSHV lytic replication, downstream UPR transcriptional responses were restricted: (1) ATF6 was cleaved to activate the ATF6(N) transcription factor but ATF6(N)-responsive genes were not transcribed; (2) PERK phosphorylated eIF2 α , but ATF4 did not accumulate; (3) IRE1 caused XBP1-mRNA splicing, but the XBP1s protein did not accumulate and the XBP1s-responsive genes were not transcribed. The complementation of XBP1s deficiency during KSHV lytic replication inhibited virion production in a dose-dependent manner in epithelial cells. Taken together, these findings indicate that, while XBP1s plays an important role in reactivation from latency, it can inhibit virus replication at a later step, which the virus overcomes by preventing its synthesis. These findings suggest that KSHV hijacks UPR sensors to promote efficient viral replication while sustaining ER stress.

Keywords: KSHV; lytic; unfolded protein response; ATF6; PERK; IRE1; XBP1



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