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Bim nuclear translocation and inactivation by HHV-8 interferon regulatory factor 1

Young Choi, John Nicholas*

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Viral replication efficiency is in large part governed by the ability of viruses to counteract pro-apoptotic signals induced by infection of host cells. In HHV-8, one group of proteins acting to suppress the host's innate defenses is the set of four viral interferon regulatory factors (vIRFs 1-4), which act to block cellular IRF activities in addition to targeting and inhibiting p53 and other inducers of apoptosis. We observed that in a large proportion of endothelial cells supporting lytic reactivation, the normally cytoplasmic pro-apoptotic BH3-only protein Bim, a negative regulator of HHV-8 productive replication, was localized in the nucleus. Nuclear localization of Bim could be induced in cells cotransfected with vIRF-1, and confocal microscopy identified co-localization of vIRF-1 and Bim in the nuclei of lytically reactivated cells. Physical association of vIRF-1 and Bim was identified in co-precipitation experiments using both transfected cell lysates and purified recombinant vIRF-1 and Bim. In vitro binding studies using a series of truncation and point variants of vIRF-1 enabled precise mapping of the Bim-interacting residues (Bim-binding domain, BBD) of vIRF-1. Wild-type, but not mutated, BBD fused to a nuclear localization signal was sufficient to induce Bim nuclear translocation in transfected cells; BBD-mutated vIRF-1 proteins were unable to do so or to protect cells from Bim-induced apoptosis. Depletion of endogenous vIRF-1 led to reductions in virus production and increased apoptosis in lytically reactivated endothelial cultures, while transduced expression of wild-type vIRF-1 promoted virus production and inhibited apoptosis. Experimental utilization of Bim-refractory vIRF-1 variants revealed the importance of vIRF-1:Bim interaction, specifically, for pro-replication and anti-apoptotic activity of vIRF-1. Furthermore, blocking of the interaction with cell-permeable peptide corresponding to the Bim-binding region of vIRF-1 confirmed the relevance of vIRF-1:Bim association to vIRF-1 pro-replication activity. To our knowledge, this is the first report of an IRF protein that interacts with a Bcl-2 family member and of nuclear sequestration of Bim or any other member of the family as a means of inactivation. Our data reveal a novel mechanism utilized by a virus to control replication-induced apoptosis and suggest that inhibitory targeting of vIRF-1:Bim interaction may provide an effective antiviral strategy.

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*Correspondence: nichojo@jhmi.edu
Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
Full list of author information is available at the end of the article