Induction of Noxa-mediated apoptosis by modified vaccinia virus Ankara depends on viral recognition by cytosolic helicases, leading to IRF-3/IFN-α-dependent induction of pro-apoptotic Noxa.

Abstract:
Viral infection is a stimulus for apoptosis, and in order to sustain viral replication many viruses are known to carry genes encoding apoptosis inhibitors. F1L, encoded by the orthopoxvirus modified vaccinia virus Ankara (MVA) has a Bcl-2-like structure. An MVA mutant lacking F1L (MVA?F1L) induces apoptosis, indicating that MVA infection activates and F1L functions to inhibit the apoptotic pathway. In this study we investigated the events leading to apoptosis upon infection by MVA?F1L. Apoptosis largely proceeded through the pro-apoptotic Bcl-2 family protein Bak with some contribution from Bax. Of the family of pro-apoptotic BH3-only proteins, only the loss of Noxa provided substantial protection, while the loss of Bim had a minor effect. In mice, MVA preferentially infected macrophages and DCs in vivo. In both cell types wt MVA induced apoptosis albeit more weakly than MVA?F1L. The loss of Noxa had a significant protective effect in macrophages, DC and primary lymphocytes, and the combined loss of Bim and Noxa provided strong protection. Noxa protein was induced during infection, and the induction of Noxa protein and apoptosis induction required transcription factor IRF3 and type I interferon signalling. We further observed that helicases RIG-I and
MDA5 and their signalling adapter MAVS contribute to Noxa induction and apoptosis in response to MVA infection. RNA isolated from MVA-infected cells induced Noxa expression and apoptosis when transfected in the absence of viral infection. We thus here describe a pathway leading from the detection of viral RNA during MVA infection by the cytosolic helicase-pathway, to the up-regulation of Noxa and apoptosis via IRF3 and type I IFN signalling.