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How do viruses control mitochondria-mediated apoptosis?

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ABSTRACT

There is no doubt that viruses require cells to successfully reproduce and effectively infect the next host. The question is what is the fate of the infected cells? All eukaryotic cells can "sense" viral infections and exhibit defence strategies to oppose viral replication and spread. This often leads to the elimination of the infected cells by programmed cell death or apoptosis. This "sacrifice" of infected cells represents the most primordial response of multicellular organisms to viruses. Subverting host cell apoptosis, at least for some time, is therefore a crucial strategy of viruses to ensure their replication, the production of essential viral proteins, virus assembly and the spreading to new hosts. For that reason many viruses harbor apoptosis inhibitory genes, which once inside infected cells are expressed to circumvent apoptosis induction during the virus reproduction phase. On the other hand, viruses can take advantage of stimulating apoptosis to (i) facilitate shedding and hence dissemination, (ii) to prevent infected cells from presenting viral antigens to the immune system or (iii) to kill non-infected bystander and immune cells which would limit viral propagation. Hence the decision whether an infected host cell undergoes apoptosis or not depends on virus type and pathogenicity, its capacity to oppose antiviral responses of the infected cells and/or to evade any attack from immune cells. Viral genomes have therefore been adapted throughout evolution to satisfy the need of a particular virus to induce or inhibit apoptosis during its life cycle. Here we review the different strategies used by viruses to interfere with the two major apoptosis as well as with the innate immune signaling pathways in mammalian cells. We will focus on the intrinsic mitochondrial pathway and discuss new ideas about how particular viruses could activately engage mitochondria to induce apoptosis of their host.

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1. Extrinsic apoptotic pathway and its inhibition by viral proteins

Apoptosis is a highly conserved, physiological type of cell death, which is required to eliminate damaged, used-up and misplaced cells within a multicellular organism (Kerr et al., 1972; Hotchkiss et al., 2009). In contrast to necrosis or necroptosis, which often leads to pathological, chronic inflammatory immune reactions due to cell lysis, apoptotic cells do not fall apart but are discretely eaten up by macrophages and other non-professional phagocytes in a regulated and non-inflammatory manner (Vanlangenakker et al., 2012). Apoptosis is induced by two distinct, yet tightly interconnected signaling pathways: the extrinsic (Fig. 1) and the intrinsic (Fig. 2) apoptotic pathways. The extrinsic pathway is triggered by extracellular ligands such as those of the TNF superfamily (FasL, TNFα or TRAIL), which specifically bind to their respective surface receptors causing their oligomerization (Strasser et al., 2009; Guicciardi and Gores, 2009; Gonzalvez and Ashkenazi, 2010; Li et al., 2013a, 2013b). A conformational change on the cytoplasmic side of these receptors leads to the recruitment of the adapter protein FADD whose function is to attract pro-caspase-8 from the cytosol to the death receptor in order to bring two monomeric pro-caspase-8 molecules in close proximity for autoprocessing and subsequent activation (Fig. 1). This complex, referred to as death inducing signaling complex (DISC), then interacts with already dimerized effector pro-caspase-3 and/or -7, which become activated through caspase-8-mediated cleavage followed by autoprocessing. Active effector caspases then cleave numerous substrates that lead to the

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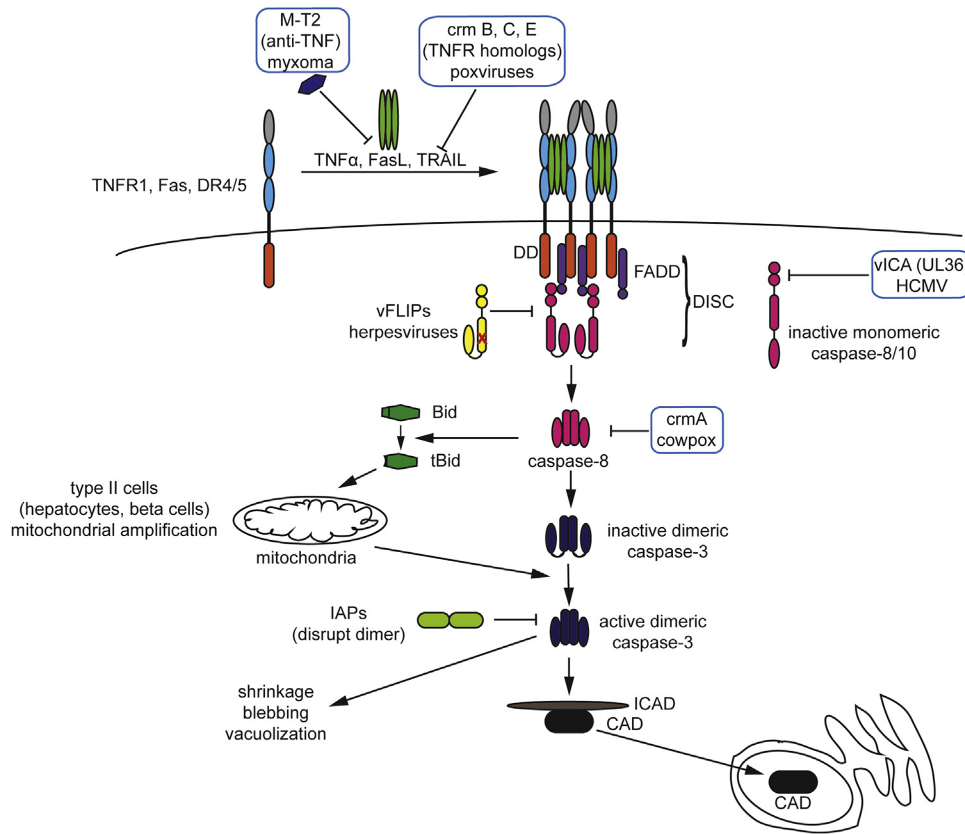

Fig. 1. Extrinsic death receptor signaling pathway and its inhibition by viral proteins. Viral proteins inhibiting apoptosis are boxed in blue. For details, see text.

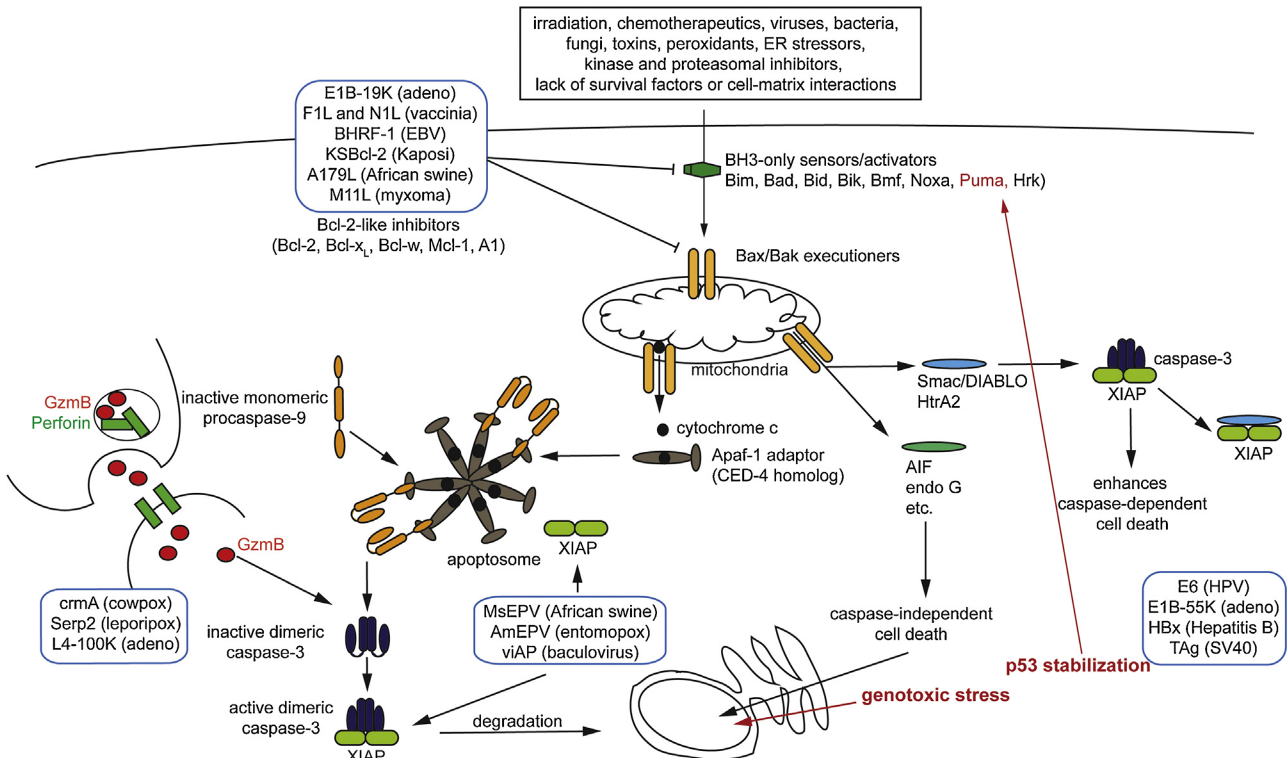

Fig. 2. Intrinsic mitochondrial signaling pathway and its inhibition by viral proteins. Viral proteins inhibiting apoptosis are boxed in blue. For details, see text.

disruption of the cytoskeleton, inhibition of DNA repair, initiation of DNA fragmentation and the exposure of so-called eat-me signals, which mediate the uptake and elimination of apoptotic cells by macrophages.

The extrinsic, death receptor pathway is indispensable for the execution and limitation of both innate and adaptive immune responses. Cells of the innate immune system such as dendritic or natural killer (NK) cells generate a rapid antiviral immune response by directly detecting viral products such as dsRNA by Toll-like receptor 3 (TLR), by upregulating death ligands such as FasL, TRAIL and TNFα and/or by killing infected cells by granule exocytosis (NK cells) (Medzhitov, 2001). Later during adaptive immunity, virally infected cells are killed by antigen-specific cytotoxic T cells (CTLs) via both the perforin/granzyme and the FasL/Fas pathways (Chavez-Galan et al., 2009). Subsequently, activated T cells are eliminated by activation-induced cell death involving FasL/Fas-mediated killing of the same or an activated neighboring cell after an acute infection (Arakaki et al., 2014). This ensures that highly proliferative, superfluous killer cells are disposed of accordingly, preventing the development of autoimmune or leukemic cells. It is therefore not surprising that viruses have evolved strategies to inhibit the death receptor signaling pathway at several steps although these cells may still be killed by granule exocytosis (Benedict et al., 2002; Hay and Kannouraki, 2002). As a consequence infected cells are at least partially protected from cytolysis by CTLs, NK cells or neighboring cells which express FasL or TRAIL upon activation (Ashkenazi and Dixit, 1999) and TNFα may not be able to induce a sufficient inflammatory response.

For example, the Shope fibroma virus (rabbit poxvirus) produces a TNF receptor ortholog (TNFR2), which neutralizes TNFα (Smith et al., 1991) (Fig. 1). Other TNFR orthologs have been identified in the genomes of lepri- and orthopoxviruses, including cowpox (CrmB) (Hu et al., 1994) and smallpox (CrmE) (Reading et al., 2002) and in the genome of CMV (UL144 orf) (Benedict et al., 1999). They can either be expressed in the plasma membrane of infected cells or be shed as soluble decoy receptors (for example myxoma virus T2 protein) (Upton et al., 1991; Reading et al., 2002). These TNF signaling inhibitors clearly contribute to the high virulence of poxviruses because they are mutated in vaccinia viruses, an attenuated form of smallpox. In addition, a TRAIL receptor ortholog (TRAILR2) was detected in the genome of avian leukocytosis virus (Brojatsch et al., 1996). On the other hand adenoviruses use several proteins encoded in the E3 gene region to promote the internalization and lysosomal degradation of Fas, TNFR, TRAILR1 and R2 (Shisler et al., 1997; Tollefson et al., 1998; Stewart et al., 1995; Benedict et al., 2001). Finally, several viruses produce proteins capable of blocking extrinsic death receptor signaling at the level of the DISC, i.e. by either inhibiting caspase-8 activation or its proteolytic activity. For example, the viral FLIP proteins (vFLIPs) are inactive caspase-8 homologs, which are recruited by FADD to form a DISC that lacks caspase activity (Thome and Tschopp, 2001; Krueger et al., 2001; Subramaniam et al., 2013). In addition, they can recruit TRAF2, RIP, NIK and IKK2, which favor the induction/activation of NFκB, a crucial anti-apoptotic transcription factor (Kataoka et al., 2000; Subramaniam et al., 2013). vFLIPs are present in the genome of γ-herpesviruses, including equine herpesvirus 2 (EHV-2), herpesvirus saimiri (HVS), KSHV (Kaposi), bovine herpesvirus (BHV-4) and moluscum contagiosum virus (MCV) (Bertin et al., 1997; Thome and Tschopp, 2001; Benedict et al., 2002). The vICA protein produced by the HCMV viral gene UL36 also associates with caspase-8 and blocks its activation but it has no sequence homology with caspases (Skaletskaya et al., 2001). Last but not least, the CrmA protein from cowpox virus is able to inhibit the proteolytic activity of caspase-8 by binding to and blocking the catalytic center (Zhou et al., 1997).

2. Intrinsic apoptotic pathway and its inhibition by viral proteins

The intrinsic apoptotic pathway is activated by the lack of soluble survival factors or hormones, cell–cell or cell–matrix interactions (deprivation-induced cell death, also called anoikis), the exposure of cells to pathogens such as fungi, bacteria or viruses or the treatment with genotoxic/DNA damaging stimuli (irradiation, chemotherapeutic drugs), toxins or pro-oxidants, agents which stress the endoplasmic reticulum, inhibit protein kinases, proteasomal degradation, transcription, translation or perturb the cytoskeleton (Fig. 2) (Youle and Strasser, 2008; Hotchkiss et al., 2009; Chipuk et al., 2010). The critical step of this pathway is the permeabilization of the mitochondrial outer membrane (MOMP), which results in the release of several apoptogenic factors from the intermembrane space of mitochondria. One such protein, cytochrome c, binds to the adapter Apaf-1 which then recruits cytosolic pro-caspase-9 into a heptameric complex, called the apoptosome (Fig. 2). In a similar way as caspase-8 aggregates on the DISC, monomeric caspase-9 dimerizes on the apoptosomal platform leading to proximity-induced autoprocessing and activation. Active caspase-9 then cleaves and activates effector caspase-3 and -7. Other proteins released from mitochondria either stimulate yet unknown caspase-independent cell death processes or they enhance caspase-9 and -3 activation (Fig. 2). For example Smac/DIABLO and Htr2A/Omi bind to XIAP, a member of the Inhibitors of Apoptosis Proteins (IAPs). XIAP is an endogenous caspase-9 and -3 inhibitor, which prevents accidental autoprocessing and activation of these caspases in healthy cells (Deveraux and Reed, 1999; Shi, 2002). Upon sequestration by Smac or Omi, XIAP no longer binds to caspase-9 or -3, therefore allowing the full activation of these caspases in response to apoptotic stimuli, activating the intrinsic mitochondrial pathway (Fig. 2).

Since MOMP results in both caspase-dependent and independent cell death signaling it is a crucial life-or-death decision checkpoint ("a point of no return") (Fig. 2). This checkpoint is controled by the Bcl-2 family of proteins (Youle and Strasser, 2008; Chipuk et al., 2010). The Bcl-2 family is subdivided on the basis of structural conservation of so-called Bcl-2 homology (BH) domains and comes in three flavors. The pro-apoptotic BH3-only proteins (Bim, Bid, Bad, Bik, Bmf, Hrk, Puma, Noxa) only share a ca. 20–30 amino acid long alpha-helical BH3 domain with the rest of the Bcl-2 family. They act as sentinels/sensors of apoptotic stimuli which activate the intrinsic mitochondrial pathway (Happo et al., 2012). Depending on the apoptotic stimulus, particular sets of BH3-only proteins get transcriptionally induced or posttranslationally modified, migrate to and insert into the MOM and then activate at this site a second pro-apoptotic subclass of Bcl-2 family proteins, the so-called "effectors" Bax and Bak (Happo et al., 2012). For example, Bim is transcriptionally induced by Foxo3B in response to growth factor deprivation or phosphorylated by JNK during thymic selection and upon exposure to UV or gliotoxin (Happo et al., 2012; Geissler et al., 2013). By contrast, Puma and Noxa are target genes of p53 after genotoxic stress. Bid is proteolytically cleaved to truncated tBid by caspase-8 in response to death receptor ligands such as FasL, TRAIL or TNFα defining a second, so called type II death receptor pathway that crosstalks with the mitochondrial pathway (Youle and Strasser, 2008; Chipuk et al., 2010; Happo et al., 2012).

Bax and Bak directly induce MOMP. They contain BH1, BH2 and BH3 domains, which form an elongated hydrophobic binding pocket interacting with other members of the Bcl-2 family (Suzuki et al., 2000; Czabotar et al., 2013; Brouwer et al., 2014; Volkmann et al., 2014; Westphal et al., 2014; Borner and Andrews, 2014). In healthy cells, Bax resides inactive in the cytoplasm (Suzuki et al., 2000; Schinzel et al., 2004) and constantly shuttles between the cytoplasm and the periphery of the MOM without stably inserting

in the membrane (retrotranslocation) (Wolter et al., 1997; Edlich et al., 2011). Bak on the other hand is stably inserted into the MOM but held in check by inhibitory proteins such as VDAC2 and Bcl-2 survival factors (Wang et al., 2001; Cheng et al., 2003; Willis et al., 2005). Three BH3-only proteins Bim, tBid and Puma are capable of directly activating Bax/Bak on the MOM (Letai et al., 2002; Cartron et al., 2004; Kuwana et al., 2005; Gavathiotis et al., 2008; Czabotar et al., 2013). Recent structural analysis of the activation process suggests that after their translocation to and insertion into the MOM, Bim and tBid bind to the hydrophobic pocket in Bax/Bak via their BH3-domain (Czabotar et al., 2013; Brouwer et al., 2014). This changes the conformation of Bax and Bak in a way that their BH3-regions become exposed for dimeric interaction with the hydrophobic pocket of another Bax or Bak molecule (Dewson et al., 2009; Czabotar et al., 2013; Brouwer et al., 2014). For that purpose the BH3-only protein has to dissociate from the hydrophobic binding pocket, which explains why direct interaction between BH3-only proteins and Bax/Bak is only transient and difficult to detect biochemically. Presumably through an additional interaction site in the rear part of the molecule, Bax/Bak dimers can then assemble into multimers (Dewson et al., 2009). It is not yet clear if these multimers form a protein pore or perturb the lipid bilayer of the MOM to rearrange into a lipid pore that may be generated by a hemifusion intermediate (Montessuit et al., 2010; Bleicken et al., 2014; Borner and Andrews, 2014). Newest findings from lipid nanodiscs and fluorescence measurements indicate that Bax/Bak may form pores of different sizes depending on whether they are monomeric, di- or multimeric (Xu et al., 2013; Volkmann et al., 2014). At one point the pores are large enough to allow the passage of cytochrome c or even bigger molecules such as Smac and Omi to the cytoplasm.

The third subgroup of the Bcl-2 family is formed by the anti-apoptotic proteins Bcl-2, Bcl-x_L, Mcl-1, Bcl-w and A1 (Youle and Strasser, 2008; Chipuk et al., 2010). They also contain BH1, BH2 and BH3 domains and some even have an additional BH4 domain at the N-terminus. The 3-dimensional structure of these survival factors looks very similar to that of Bax/Bak (Muchmore et al., 1996; Suzuki et al., 2000). However, in contrast to Bax/Bak, they are unable to undergo conformational changes to expose their BH3-domain, multimerize and form pores, except under unphysiological conditions such as low pH (Minn et al., 1997; Schendel et al., 1997). Instead their hydrophobic binding pocket interacts with BH3-only proteins in a high affinity manner. On one hand this inhibits the pro-apoptotic action of BH3-only proteins. On the other hand, pre-bound Bim, tBid and Puma can be released from the Bcl-2 survival factors by other BH3-only proteins activated by apoptotic stimuli such as Bik, Bad, Bmf, Hrk and Noxa (Borner and Andrews, 2014). Bim, tBid and Puma can then directly activate Bax/Bak as described above. This explains the effectiveness of BH3-mimetics in anti-cancer therapy. These are small molecule compounds that bind with high affinity to the hydrophobic pocket of Bcl-2 survival factors and thereby release pre-bound Bim, tBid and Puma for MOMP activation (Oltersdorf et al., 2005; Happo et al., 2012). It turns out that many cancer cells do not only upregulate Bcl-2 survival factors but also Bim, tBid and Puma, a mechanism called “addiction” (Certo et al., 2006). This may explain the high sensitivity of cancer cells to be killed by BH3-mimetics such as ABT-267, ABT-199 and others (Tse et al., 2008; Wilson et al., 2010; Vandenberg and Cory, 2013). Apart from interacting with BH3-only proteins, Bcl-2 survival factors also sequester accidently activated Bax and Bak in healthy cells. Since active Bax/Bak expose their BH3-domain, this region can interact with the hydrophobic pocket of Bcl-2 survival factors and hence Bax/Bak are inhibited (Chen et al., 2005; Willis et al., 2005, 2007; Uren et al., 2007). This may also constitute one of the mechanisms by which MOM-inserted Bak is kept in check by Bcl-2 survival factors. When large amounts of Bax/Bak are bound by Bcl-2 survival factors, BH3-only proteins can displace appreciable numbers of Bax/Bak molecules from Bcl-2 and therefore make more pore-forming proteins available for the activation of MOMP (Youle and Strasser, 2008; Borner and Andrews, 2014). Since Bcl-2 survival factors are able to sequester both the “activators” (BH3-only proteins) and the “effectors” (Bax/Bak) of MOMP and MOMP triggers both caspase-dependent and -independent cell death, overexpression of these survival factors is the most efficient way to block apoptosis, even allowing clonogenic survival (which caspase inhibitors are not able to do) (Borner, 2003).

Given the importance of the intrinsic mitochondrial pathway for apoptosis induced by numerous stimuli, viruses have acquired gene products which mimick the action of Bcl-2 survival factors to potently inhibit MOMP in their host cells. Functional homologs of Bcl-2 are collectively called vBcl-2s. They are present in various members of the Poxviridae (F1L, N1L, M11L, A179L, ORFV125), Herpesviridae (BHRF1, BALF1, vMIA, KSBcl-2, MHVBcl-2), Adenoviridae (E1B-19K) and Birnaviridae (VP5) family of viruses (Fig. 2) (Benedict et al., 2002; Galluzzi et al., 2008; Postigo and Ferrer, 2009). While some of them like E1B-19K have extensive sequence homology with cellular Bcl-2 survival factors in all regions (White, 1998), others such as FPV039 from Fowlpoxvirus only retain sequence homology with the BH1 and BH2 domains while ORFV125 of Parapoxvirus is homologous in the BH1 and BH3 regions (Galluzzi et al., 2008; Westphal et al., 2007; Banadyga et al., 2007). Other vBcl-2s such as vaccinia virus F1L and N1L, myxoma virus M11L and vMIA from cytomegalovirus do not even show any sequence homology with mammalian Bcl-2 proteins (Galluzzi et al., 2008). However, the crystal structure of some of these vBcl-2s reveals a close conservation of the Bcl-2 family structural conformation. Thus, it is not the primary amino acid sequence and/or the conserved BH-domains per se, which determine the function of a Bcl-2 survival factor but the helical bundle structure that makes up the hydrophobic pocket where BH3-only proteins and Bax/Bak are sequestered.

Other viral proteins inhibit the intrinsic, mitochondrial signaling pathway by modulating Bcl-2 family members on the transcriptional level or via post-translational modifications. The tumor suppressor p53 is known to induce the transcription of the BH3-only proteins Noxa and Puma in response to genotoxic stress (Oda et al., 2000; Nakano and Vousden, 2001) and growth factor deprivation (Jabbour et al., 2010) contributing to the elimination of stressed and damaged cells (Fig. 2). Cells lacking functional p53 survive and proliferate and accumulate gene mutations eventually leading to cancer (Harvey et al., 1993). Also, p53-deficient mice are more prone to certain viral infections, indicating that p53 is not only crucial to prevent cancer but also to induce apoptosis of some infected host cells. Therefore, viruses have evolved strategies to inactivate p53. The SV40 large T antigen binds to p53 and sequesters it in an inactive complex (Lane and Crawford, 1979; Linzer and Levine, 1979). The human papillomavirus (HPV) E6 protein and the adenovirus E1B-55K protein induce the ubiquitination and proteasomal degradation of p53 (Scheffner et al., 1990; Werness et al., 1990; Steegenga et al., 1998; Querido et al., 2001). Also, the X protein of hepatitis B virus (HBx) interacts with p53 and prevents its transcriptional activation of target genes, thereby inhibiting apoptosis (Wang, 1995) (Fig. 2). A similar strategy is used by the measles virus V protein, which blocks apoptosis by sequestering the p53 homolog p73 (Cruz et al., 2006). A p53-independent mechanism to inhibit MOMP is exploited by the human T cell leukemia virus type I (HTLV-1) which uses the Tax protein to activate the Bcl-x_L promoter and to repress the Bax promoter (Tsukahara et al., 1999). Moreover, viruses can effectively block both the intrinsic mitochondrial and the extrinsic death receptor signaling by engaging the transcription factor NFκB (Sun and Cesarman, 2011). NFκB induces transcription of the survival factor Bcl-x_L, the caspase-8 inhibitor FLIP or inhibitor of apoptosis proteins (IAPs), which often directly or indirectly act

as caspase inhibitors (DiDonato et al., 2012). For example, herpes simplex virus-1 (HSV-1), through its envelope glycoprotein D uses a TNFR family member, herpes virus entry mediator (HVEM) for host surface binding and infection. Activation of this receptor triggers a signaling cascade that leads to NFκB activation and apoptosis inhibition (Medici et al., 2003; Sciortino et al., 2008). Similarly, the major B cell-transforming protein in EBV, LMP1, mimics activated CD40 and engages TRADD and TRAFs, which are crucial adaptors used by TNFR to activate NFκB. Thereby LMP1 prevents B cells from localizing to the follicle and protects cells harboring latent virus from interactions with T cells (Uchida et al., 1999). Finally, the Nef protein of HIV (Wolf et al., 2001) and the U(S)3 protein kinase of HSV-1 (Munger and Roizman, 2001) were found to mediate phosphorylation of the BH3-only protein Bad, thereby preventing it from inducing apoptosis.

Another possibility for viruses to interfere with apoptosis signaling is to block caspases. As pointed out above cowpox viruses can effectively block initiator caspase-8 of the extrinsic death receptor pathway because this pathway is strictly caspase-dependent (Zhou et al., 1997). The major initiator and effector caspases of the intrinsic mitochondrial pathway, caspase-9 and caspase-3/-7 are held in check by cellular IAPs, in particular XIAP (Fig. 2) (Deveraux and Reed, 1999; Shi, 2002). However, MOMP also leads to caspase-independent death signaling (Fig. 2). Therefore blocking caspase-9 and/or -3 by viruses may not be sufficient to save infected host cells from apoptosis. This explains why an IAP-ortholog strategy is infrequently used in mammalian viruses (in contrast to baculoviruses infecting insect cells) (Taylor and Barry, 2006). Accordingly, although African swine fever virus and Entomopoxviruses encode viral vIAP such as MsEPV and AmEPV these proteins do not contribute to the virulence of these viruses (Neilan, 1993; Taylor and Barry, 2006) (Fig. 2).

3. Mechanisms by which the intrinsic, mitochondrial apoptosis pathway is activated after viral infection

Since viruses have developed so many ways to oppose the intrinsic mitochondrial apoptosis pathway, the question arises, why and when this pathway is activated in infected cells. Three scenarios are possible: (i) the infected cell is killed by an external apoptotic signal, (ii) the infected cell “senses” virus entry or assembly and mounts an antiviral stress response which does not only eliminate the virus but also the infected cell or (iii) the virus actively induces apoptosis of its host by using particular viral components expressed in the infected cells (viral proteases, dsRNA, dsDNA, etc.).

3.1. Killing of virally infected cells by CTLs and NK cells

In addition to the activation of the Fas signaling pathway (described above), CTLs and NK cells also kill virally infected target cells via the perforin/granzyme pathway. After successful activation, these cells release perforin and granzyme A and B from their cytotoxic granules at the immunosynapse where they contact the virally infected cell via MHC-I/peptide/TCR and costimulatory molecular interactions (Chavez-Galan et al., 2009; Ewen et al., 2012; Thiery and Lieberman, 2014) (Fig. 2). Perforin oligomerizes into variously sized high molecular structures in the target cell membrane (Metkar et al., 2015). Most likely through membrane lipid perturbation, similar to what is proposed for Bax and Bak on the MOM (Bleicken et al., 2014), perforin forms a pore, which allows the entry of the serine proteases granzyme A and B (Metkar et al., 2015) (Fig. 2). While granzyme A provokes a still not entirely identified caspase-independent death pathway and is also responsible for inflammatory responses (Pardo et al., 2009a, 2009b; Joeckel and Bird, 2014), granzyme B induces classical apoptosis in the target cell by two pathways, (i) a direct cleavage and activation of caspase-3 and (ii) the cleavage of Bid (similar to what caspase-8 does) and the triggering of Bax/Bak-mediated MOMP (Pardo et al., 2009a, 2009b; Ewen et al., 2012; Thiery and Lieberman, 2014). Viruses counteract the granzyme B killing pathway by expressing vBcl-2 survival factors. Alternatively they produce inhibitors of granzyme B, such as the L4-100K assembly protein from adenovirus (Andrade et al., 2001), CrmA from cowpox virus (which also inhibits caspase-8) (Komiyama et al., 1996) or Serp2 encoded by the leporipoxvirus myxoma virus (Turner et al., 1999) (Fig. 2). All these inhibitors clearly block granzyme B action in cell free systems. But while the L4-100K protein also potently inhibited granzyme B-mediated cell death (Andrade et al., 2001), this could not be effectively observed with cells overexpressing CrmA or Serp2 or infected with poxviruses (Müllbacher et al., 1999; Barry et al., 2000; Screpanti et al., 2001; Pardo et al., 2009a, 2009b).

3.2. Recognizing/sensing viruses in endosomal and cytosolic compartments and mounting an antiviral innate immune response

In the following section we focus on RNA viruses (Fig. 3) but similar mechanisms have either been reported or are expected to occur for DNA viruses (Goubau et al., 2013; Unterholzner, 2013). Irrespective of whether virus replication and spread are blocked and viruses are finally eliminated by non-apoptotic or apoptotic mechanism, the infected host cells first have to recognize, i.e. “sense” the respective viruses. This places the molecular mechanisms of sensing at the heart of all anti-viral effects, including the initation of cell death. Virus spread is prevented if host cell apoptosis occurs before a virus can form progeny, or if an infected cell is successfully eliminated by CTLs. If however the virus can inhibit cell death by expressing own survival factors after infection or if it kills cells after its reproduction, it can successfully propagate and evade the immune system. The best known antiviral “sensing” mechanism of hosts for RNA viruses triggers the so called type I interferon response (Takeuchi and Akira, 2009; Ivashkiv and Donlin, 2014). Type I interferons such as IFNα and IFNβ are transcriptionally induced after viral infections and play a critical role in mounting innate responses against viruses (Fig. 3). They are secreted and bind to specific interferon receptors on the same as well as on neighboring cells in order to ensure a spreading of the antiviral state to as many cells as possible. Activated interferon receptors then trigger a signaling cascade via the Janus protein kinase-signal transducer and activators of transcription pathway (JAK-STAT) that results in the induction of IFN-stimulated genes (ISGs) which can interfere with the viral life cycle at different steps, induce host cell apoptosis or both (Fig. 3) (Ivashkiv and Donlin, 2014). Two major components of this IFN-induced signaling system are the RNA-dependent protein kinase (PKR) (Garcia et al., 2007) and the 2′,5-oligoadenylate and RNase-L systems (Hovanessian, 2007). Activation of RNaseL leads to the degradation of viral RNA therefore blocking further RNA replication and transcription. On the other hand PKR activation inhibits host-cell protein translation via the phosphorylation of elongation initiation-factor 2a (eIF2α) (Garcia et al., 2007) (Fig. 3). In addition, active PKR was proposed to induce host cell apoptosis via NFκB and IRF-1 activation, which then upregulated FasL and TRAIL respectively (Tan and Katze, 1999; Jagus et al., 1999). Although TRAIL is induced by IFNs in a variety of paradigms of viral infections and may indeed contribute to apoptosis of host cells, it is unclear if this is really mediated via the PKR/NFκB axis (Allen and El-Deiry, 2012). Also, NFκB often acts as a cell death protective rather than apoptosis-inducing transcription factor (DiDonato et al., 2012). Moreover, we recently reported that PKR was not required for apoptosis induced by the RNA virus SFV although it

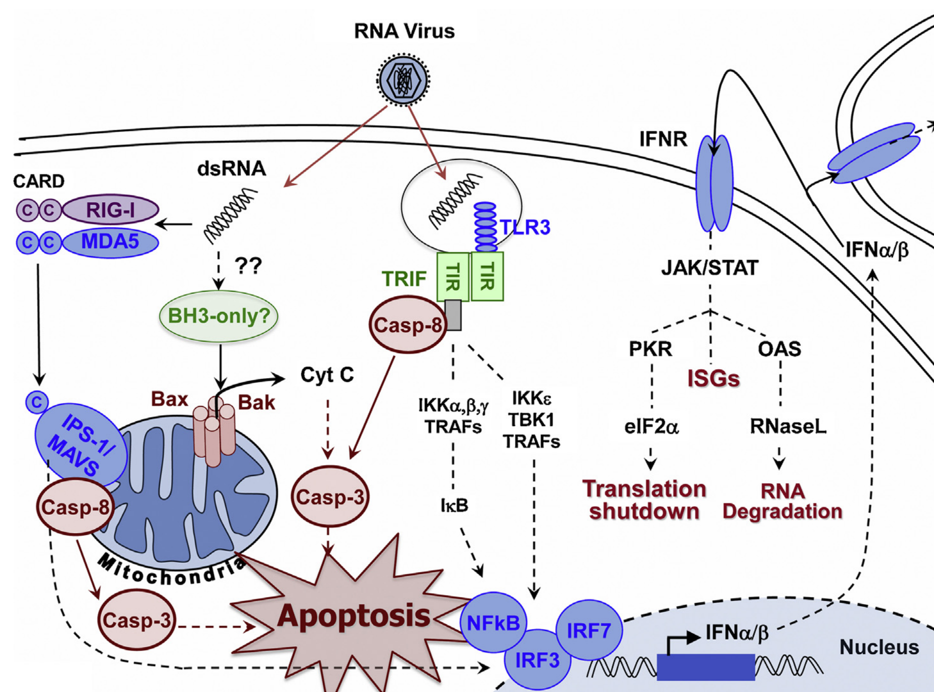

Fig. 3. Innate immune and apoptosis signaling induced by RNA viruses. For details, see text.

was clearly activated and blocked protein synthesis via eIF2α phosphorylation (El Maadidi et al., 2014).

In order for a host cell to sense a virus it has to recognize it as non-self. This occurs through two principle mechanisms. First, viruses are detected on the host cell surface by so-called pattern recognition receptors (PRR) which bind to pathogen associated molecular patterns (PAMPs) on the virus and other pathogens (Pichlmair and Reis e Sousa, 2007; Kumar et al., 2011). A major class of cell surface transmembrane PRR are the Toll-like receptors (TLRs) whose PAMP-binding domains contain leucine-rich repeats (LRR). TLR3, TLR7, TRL9 detect viral nucleic acid ligands such as long dsRNA, ssRNA or CpG DNA, respectively, mostly in the endosomal compartments (subsequent to endocytosis of the virus). After binding, they recruit adaptor proteins such as TRIF (for TLR3) or MyD88 (TLR7/TLR9), which bind specific members of the TRAF adaptor and activate the IRAK kinase families. This ultimately leads to the nuclear translocation of NFκB and IRF3 and IRF7 transcription factors through respective phosphorylation and activation of the IkB kinase (IKK) α,β,γ and IKKε/TBK1 complexes (Pichlmair and Reis e Sousa, 2007; Bowie and Unterholzer, 2008; Kawai and Akira, 2008; Kumar et al., 2011) (Fig. 3). NFκB and IRF3/7 then cooperate to induce the transcription of IFNα and IFNβ. Recently, it was reported that activation of the TLR3 pathway by the synthetic dsRNA homologs polyIC can induce apoptosis by recruiting caspase-8 to TLR3 (Weber et al., 2010; Estornes et al., 2012). In an earlier report, TRIF, an adaptor for TLR3 was shown to induce apoptosis in a FADD/caspase-8-dependent manner (Kaiser and Offermann, 2005) (Fig. 3). In all cases caspase-8 was activated by proximity-induced dimerization and then cleaved and activated caspase-3 (Fig. 3). This defines a novel, death receptor- and mitochondria-independent death signaling pathway involving caspase-8.

Viruses evolved strategies to inhibit this signaling pathway downstream of TLRs to avoid the transcription of type I interferons. For instance, the NS3-4A protease of hepatitis C virus (HCV) cleaves the adaptor TRIF (Roy and Mocarski, 2007) while the NS5A protein decreases the expression of TLR4 (Tamura et al., 2011). Vaccinia virus uses its A46 protein to inhibit all TLR-adaptors (MyD88, MAL, TRIF, TRAM), the A52 protein to block TRAF6 and the protein kinase IRAK2, the B14 protein to antagonize the IKKα,β,γ complex and the K7 protein to prevent the IKKε/TBK1 complex from activating IRF3/7 (Bowie and Unterholzer, 2008). The latter strategy is also used by HCV NS3, rabies virus phosphoprotein and hantavirus G1.

In addition to the recognition of viruses in the endosomal compartment, cells also contain viral sensors in the cytosol (Pichlmair and Reis e Sousa, 2007; Kawai and Akira, 2008; Takeuchi and Akira, 2009). These are the RIG-like helicases (RLH) RIG-I, MDA5 and LGP-2 (Yoneyama et al., 2004; Kato et al., 2006). RIG-I and MDA5 both contain two caspase recruitment domains (CARDs), an ATPase and a helicase domain (Fig. 3). The helicase domain is used to recognize different kinds of nucleic acids. While MDA5 mainly senses long viral dsRNA molecules, RIG-I is often activated by short dsRNA fragments and ssRNAs that have a 5′ triphosphate (Pichlmair and Reis e Sousa, 2007). This concept ensures that cellular RNAs whose 5′ ends are either capped or contain monophosphates, are not recognized by RLHs. Activated RIG-I and MDA5 then use their CARD domains to interact with the mitochondria-located adaptor protein MAVS (also known as IPS-1, VISA or Cardif) (Kawai et al., 2005; Meylan et al., 2005; Seth et al., 2005; Xu et al., 2005) (Fig. 3). MAVS in turn then triggers IKKα,β,γ as well as IKKε/TBK1 phosphorylation that activate NFkB and IRF3 and IRF7 transcription factors for IFNα and IFNβ induction (Takeuchi and Akira, 2009). Similar to TLR3 signaling, sensing through RIG-I/MDA5/MAVS is heavily antagonized by viruses. Influenza NS1 binds the RIG-I/MAVS complex and thereby interferes with its signaling. Moreover, paramyxovirus V and polivirus are able to inhibit the function of MDA5. Finally, HCV NS3-4 abrogates MAVS signaling by cleaving it from the mitochondrial membrane. Similarly, MAVS is degraded by mitochondria-targeted hepatitis A virus 3ABC protein (Bowie and Unterholzer, 2008). The latter examples show that MAVS functions on mitochondria and suggests that this organelle either plays a so far unrecognized role in antiviral type I interferon signaling or that MAVS also mediates apoptosis and thereby crosstalks with Bax/Bak-induced MOMP. Indeed, Besch et al. reported that both RIG-1 and MDA5 could induce apoptosis of human melanoma cells

in a type I interferon-independent manner, i.e. at a step before IFNα/β induction (Besch et al., 2009). The molecular mechanisms of this new death signaling pathway had however not been defined at that time.

Recently, we published new insights into the mechanisms of host cell apoptosis induced by a single stranded, positive-sense RNA virus which does not encode for any cell death protective proteins (El Maadidi et al., 2014). Semliki Forest virus (SFV) is a neurotropic virus that kills mice during the first 21 days of their life, probably due to the induction of apoptosis of immature neurons (Strauss and Strauss, 1994). It also causes encephalitis in various animals but is mostly apathogenic for humans (Fazakerley, 2002). We and others however found that SFV induces effective apoptosis of a variety of human and mouse cells in vitro via the intrinsic mitochondrial pathway, i.e. requiring Bax/Bak and the induction of MOMP (Ubol et al., 1994; Grandgirard et al., 1998; Murphy et al., 2001; Urban et al., 2008). After infection, SFV produces high amounts of dsRNA during the RNA replication cycle, and although it is not entirely clear whether dsRNA is the trigger for SFV-induced apoptosis and how it could activate Bax/Bak (via which BH3-only protein?, see below) (Fig. 3), we reported that SFV-induced apoptosis is clearly RNA replication dependent (Urban et al., 2008). Moreover, Bax/Bak double knock-out cells are not entirely protected from SFV-induced apoptosis but exhibit a Bax/Bak-independent cell death that still requires caspases but does not involve death-receptor signaling. We then found that this novel Bax/Bak-independent death signaling pathway requires a MDA5-mediated activation of MAVS on mitochondria (El Maadidi et al., 2014). MAVS recruits caspase-8 from the cytosol to mitochondria forming a novel death inducing signaling complex that is capable of processing and activating caspase-3 and inducing apoptosis (Fig. 3). Our results indicate that not only the TLR3/TRIF axis can induce apoptosis in addition to activating NFκB, IRF3/7 and an antiviral type I interferon response (Kaiser and Offermann, 2005; Weber et al., 2010; Estornes et al., 2012), but the same can be achieved by the MDA5/MAVS pathway (El Maadidi et al., 2014). Both Bax/Bak- and death receptor-independent death signaling pathways use the initiator caspase-8 on novel death platforms (TLR3/TRIF/caspase-8 or MAVS/caspase-8) to activate caspase-3/-7 (Fig. 3). Whether this innate immune signaling pathway also accounts for interferon responses and/or apoptosis in response to DNA viruses, which use TLR9 (Hemmi et al., 2000) and other intracellular sensors such as cGAS/STING (Sun et al., 2013) or DAI (Takaoka et al., 2007) remains to be determined. Interestingly, it was recently shown that IPS-1/MAVS may also mediate innate immune signaling in response to DNA viruses (Zhang et al., 2011; Unterholzner, 2013). Thus, this novel mitochondria-associated pathway may be used as a general defence mechanism of host cells against viruses.

3.3. Host cell apoptosis induced by ER stress caused by viral overload

Another possibility how cells can sense and react to virus infection is by mounting an ER-stress response (Li et al., 2013a, 2013b). This is particularly the case for RNA viruses such as alphaviruses where the envelope proteins are co-translationally inserted into the ER membrane and travel through the exocytotic system to the cell surface for virus budding (Li and Stollar, 2004; He, 2006; Barry et al., 2010; Jheng et al., 2014). In this case the high amount of ER-localized viral proteins induce a classical unfolded protein response (UPR). While UPR responses are often cell protective by triggering the transcriptional upregulation of chaperones such as BiP/grp78 which help in the folding of the massive amount of proteins, a persistent, prolonged UPR response, for example via the IREα/XBP1 pathway can also lead to apoptosis of the infected host cells (Lin et al., 2007; Sano and Reed, 2013; Lu et al., 2014). In this case, the transcription factor CHOP1 is activated which upregulates the BH3-only proteins Bim and Puma, leading to Bax/Bak activation and MOMP via the intrinsic mitochondrial pathway (Reimertz et al., 2003; Puthalakath et al., 2007; Ghosh et al., 2012). Viruses would then counteract host cell death by the expression of Bcl-2 orthologs (vBcl-2s).

3.4. Viral components that directly impinge on the host cell apoptotic machinery

Some viruses have developed strategies to actively kill their infected hosts, probably to avoid the presentation of viral antigens to the adaptive immune system. If this happens viruses have replicated and assembled into new virions so that host cell apoptosis does not eliminate the virus as well. Both the activation of the extrinsic as well as the intrinsic apoptosis pathways have been observed. Targeting the extrinsic pathway, the Nef protein of HIV downregulates CD4 and MHC-1 from the cell surface by crosslinking these proteins to the endocytic compartment (Piguet et al., 1999). As a consequence membrane-bound TNFα and LIGHT are constitutively expressed on the surface of T cells, potentially contributing to the cytotoxic effects of HIV on infected T cells and uninfected bystander lymphocytes (Lama and Ware, 2000). Moreover, HCMV and reoviruses were shown to actively induce the expression of TRAIL (Sedger et al., 1999; Vidalain et al., 2000) and HSV and HCMV can enhance the expression of FasL (Raftery et al., 1999, 2001). This mechanism is thought to constitute another viral immune evasion tactic to eliminate infiltrating immune cells such as CTLs and DCs by counterattack.

To activate the intrinsic mitochondrial pathway, the Vpr protein from HIV-1 induces swelling of mitochondria and MOM permeabilization in lymphoid and transformed cells (Stewart et al., 1999; Jacotot et al., 2000; Muthumani et al., 2002; Deniaud et al., 2004). Severe acute respiratory syndrome coronavirus (SARS-CoV) 7a protein can directly inhibit Bcl-xL and other survival factors (Tan et al., 2007). Although to date viruses have not been found to express BH3-only orthologs, there is increasing evidence that they somehow activate cellular BH3-only proteins to engage the Bax/Bak pore machinery on the MOM. However, the exact molecular mechanism how this is done has remained enigmatic. The Tat protein of HIV-1 was shown to release Bim from its inhibitory contraints on the cytoskeleton so that it can directly activate Bax/Bak (Puthalakath et al., 1999; Chen et al., 2002). Whether Bim indeed is held in check at the cytoskeleton is largely debated. Moreover the mechanism of release has not been investigated. IFNα/β production in response to vesicular stomatitis viral infection has been shown to induce expression of Noxa (Galluzzi et al., 2008), but the transcription factors involved were not identified. Based on the finding that viruses can activate p53 and its homologs such as p73 (Kaelin, 1999), it is possible that Noxa, and maybe also Puma are transcriptionally induced by these factors in response to certain infections (Cruz et al., 2006; Liu et al., 2014). Alternatively, virus-specific protein kinases could phosphorylate BH3-only proteins, as it was shown for the U(S)3 protein kinase of HSV-1 on Bad (Munger and Roizman, 2001).

We have recently shown that Bim phosphorylation on three sites by JNK1/2 enhances its proapoptotic activity toward Bax/Bak activation (Geissler et al., 2013). Moreover, we have obtained evidence that dsRNA produced by SFV does not only trigger a Bax/Bak-independent death signaling pathway involving the formation of a mitochondrial MAVS/caspase-8 complex (see above) (El Maadidi et al., 2014) but also uses a so far unknown BH3-only protein to activate Bax/Bak and MOMP (Papaianni et al., submitted) (Fig. 3). How dsRNA links to such a BH3-only protein is currently investigated in our lab. Finally, it is possible that virus-encoded proteases may cleave BH3-only proteins such as

Bid. These proteases are required for the viral life cycle because they process large non-structural and structural polypeptide precusors into mature viral proteins (Strauss and Strauss, 1994). Since they often show degenerate substrate specificity, they could cleave important components of apoptosis signaling and thereby activate them. For example, PLV viruses express proteases (2Apro and 3Cpro), which activate caspase-dependent apoptosis (Barco et al., 2000; Goldstaub et al., 2000; Calandria et al., 2004). In addition, HIV-encoded protease is known to process and activate caspase-8 both in vitro and in T cells, which then leads to Bid cleavage and mitochondria-mediated apoptosis (Nie et al., 2002). Indeed Bcl-2 overexpression protects cells from the pro-apoptotic effects of the HIV-protease and prevents apoptosis induced by HIV-1 infection of human lymphocytes (Strack et al., 1996).

4. Concluding remarks and outlook

There is increasing evidence that innate immune signaling via TLRs and intracellular PRRs do not only trigger an antiviral interferon response and other mechanisms to limit the replication, assembly and spread of viruses, but they also cooperate with the intrinsic Bax/Bak-mediated mitchondrial pathway to induce apoptosis of the infected host cells. As discussed above, some viruses have clearly evolved strategies to counteract both the intrinsic as well as the innate signaling branch so that they can effectively replicate and reproduce. However, other viruses, such as SFV and other alphaviruses, do not express any cell survival factors and may therefore use these pathways to kill their host cells after their successful reproduction, e.g. to evade detection by the immune system. While we clearly understand how virus-encoded decoy receptors, caspase-8 and other caspase inhibitors as well as Bcl-2 orthologs work to inhibit apoptosis of infected cells, we need to further understand how viruses manage to activate BH3-only proteins and/or directly perturb the balance between Bcl-2-like survival factors and pore-forming Bax/Bak proteins on the MOM. Further challenges will be to identify all the components of the TLR3/TRIF/caspase-8 and MAVS/caspase-8 complexes, which seem to constitute novel DISCs enhancing Bax/Bak-mediated MOMP and to investigate if other viruses such as DNA viruses also use innate signaling strategies to kill their hosts. Irrespective of whether viruses use apoptotic or anti-apoptotic mechanisms to win their competition with the host, a better understanding will continue to provide considerable insight into both viral and cellular biology, from initial virus sensing to viral clearance or persistence. It is the hope that this will ultimately lead to the generation of more effective vaccines against viruses.

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References

Allen, J.E., El-Deiry, W.S., 2012. Regulation of the human TRAIL gene. Cancer Biol. Ther. 13, 1143–1151.

Andrade, F., Bull, H.G., Thornberry, N.A., Ketner, G.W., Casciola-Rosen, L.A., Rosen, A., 2001. Adenovirus L4-100K assembly protein is a granzyme B substrate that potently inhibitis granzme B-mediated cell death. Immunity 14, 751–761.

Arakaki, R., Yamada, A., Kudo, Y., Hayashi, Y., Ishimaru, N., 2014. Mechanism of activation-induced cell death of T cells and regulation of FasL expression. Crit. Rev. Immunol. 34, 301–314.

Ashkenazi, A., Dixit, V., 1999. Apoptosis control by death and decoy receptors. Curr. Opin. Cell Biol. 11, 255–260.

Banadyga, L., Gerig, J., Stewart, T., Barry, M., 2007. Fowlpox virus encodes a Bcl-2 homologue that protects cells from apoptotic death through interaction with the proapoptotic proteins Bak. J. Virol. 81, 11032–11045.

Barco, A., Feduchi, E., Carrasco, L., 2000. Poliovirus protease 3C(pro) kills cells by apoptosis. Virology 266, 352–360.

Barry, M., Heibein, J.A., Pinkoski, M.J., Lee, S.F., Moyer, R.W., Green, D.R., Bleackley, R.C., 2000. Granzyme B short-circuits the need for caspase-8 activity during granule-mediated cytotoxic T-lymphocyte killing by directly cleaving Bid. Mol. Cell. Biol. 20, 3781–3794.

Barry, G., Fragkoudis, R., Ferguson, M.C., Lulla, A., Merits, A., Kohl, A., Fazakerley, J.K., 2010. Semliki forest virus-induced endoplasmic reticulum stress accelerates apoptotic death. J. Virol. 84, 7369–7377.

Benedict, C.A., Butrovich, K.D., Lurain, N.S., Corbell, J., Rooney, I., Schneider, P., Tschopp, J., Ware, C.F., 1999. Cutting edge: a novel viral TNF receptor superfamily member in virulent strains of human cytomegalovirus. J. Immunol. 126, 6967–6970.

Benedict, C.A., Norris, P.S., Prigozy, T.I., Bodmer, J.L., Mahr, J.A., Garnett, C.T., Martinon, F., Tschopp, J., Gooding, L.R., Ware, C.F., 2001. Three adenovirus E3 proteins cooperate to evade apoptosis by tumor necrosis factor-related apoptosis-inducing ligand receptor-1 and -2. J. Biol. Chem. 276, 3270–3278.

Benedict, C.A., Norris, P.S., Ware, C.F., 2002. To kill or be killed: viral evasion of apoptosis. Nat. Immunol. 3, 1013–1018.

Bertin, J., Armstrong, R.C., Ottilie, S., Martin, D.A., Wang, Y., Banks, S., Wang, G.H., Senkevich, T.G., Alnemri, E.S., Moss, B., Lenardo, M.J., Tomaselli, K.J., Cohen, J.I., 1997. Death effector domain-containing herpesvirus and poxvirus proteins inhibit both Fas- and TNFR1-induced apoptosis. Proc. Natl. Acad. Sci. U. S. A. 94, 1172–1176.

Besch, R., Poeck, H., Hohenauer, T., Senft, D., Häcker, G., Berking, C., Hornung, V., Endres, S., Ruzicka, T., Rothenfusser, S., Hartmann, G., 2009. Proapoptotic signaling induced by RIG-I and MDA-5 results in type I interferon-independent apoptosis in human melanoma cells. J. Clin. Invest. 119, 2399–2411.

Bleicken, S., Jeschke, G., Stegmueller, C., Salvador-Gallego, R., Garcia-Saez, A.J., Bordignon, E., 2014. Structural model of active bax at the membrane. Mol. Cell 56, 496–505.

Borner, C., 2003. Bcl-2 protein family: sensors and checkpoints for life-or-death decisions. Mol. Immunol. 39, 615–647.

Borner, C., Andrews, D.W., 2014. The apoptotic pore on mitochondria: are we breaking through or still stuck. Cell Death Differ. 21, 187–191.

Bowie, A.G., Unterholzer, L., 2008. Viral evasion and subversion of pattern-recognition receptor signalling. Nat. Rev. Immunol. 8, 911–922.

Brojatsch, J., Naughton, J., Rolls, M.M., Zingler, K., Young, J.A., 1996. CAR1, a TNFR-related protein, is a cellular receptor for cytopathic avian leukosis-sarcoma viruses and mediates apoptosis. Cell 87, 845–855.

Brouwer, J.M., Westphal, D., Dewson, G., Robin, A.Y., Uren, R.T., Bartolo, R., Thompson, G.V., Colman, P.M., Kluck, R.M., Czabotar, P.E., 2014. Bax core and latch domains separate during activation, and freed core domains form symmetric homodimers. Mol. Cell 55, 1–9.

Calandria, C., Irurzun, A., Barco, A., Carrasco, L., 2004. Individual expression of poliovirus 2Apro and 3Cpro induces activation of caspase-3 and PARP cleavage in HeLa cells. Virus Res. 104, 39–49.

Cartron, P.-F., Gallenne, T., Bougras, G., Gautier, F., Manero, F., Vusio, P., Meflah, K., Vallette, F.M., Juin, P., 2004. Mol. Cell 16, 807–818.

Certo, M., Del Gaizo Moore, V., Nishino, M., Wei, G., Korsmeyer, S., Armstrong, S.A., Letai, A., 2006. Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members. Cancer Cell 9, 351–365.

Chavez-Galan, L., Arenas-Del Angel, M.C., Zenteno, E., Chavez, R., Lascurain, R., 2009. Cell death mechanisms induced by cytotoxic lymphocytes. Cell. Mol. Immunol. 6, 15–25.

Chen, D., Wang, M., Zhou, S., Zhou, Q., 2002. HIV-1 Tat targets microtubules to induce apoptosis, a process promoted by the pro-apoptotic Bcl-2 relative Bim. EMBO J. 21, 6801–6810.

Chen, L., Willis, S.N., Wei, A., Smith, B.J., Fletcher, J.I., Hinds, M.G., Colman, P.M., Day, C.L., Adams, J.M., Huang, D.C.S., 2005. Differential targeting of pro-survival Bcl-2 proteins by their BH3-only ligands allows complementary apoptotic function. Mol. Cell 17, 393–403.

Cheng, E.H., Sheiko, T.V., Fisher, J.K., Craigen, W.J., Korsmeyer, S.J., 2003. VDAC2 inhibits BAK activation and mitochondrial apoptosis. Science 301, 513–517.

Chipuk, J.E., Moldoveanu, T., Llambi, F., Parsons, M.J., Green, D.R., 2010. The BCL-2 family reunion. Mol. Cell 37, 299–310.

Cruz, C.D., Palosaari, H., Parisien, J.-P., Devaux, P., Cattaneo, R., Ouchi, T., Horvath, C.M., 2006. Measles virus V protein inhibits p53 family member p73. J. Virol. 80, 5644–5650.

Czabotar, P.E., Westphal, D., Dewson, G., Ma, S., Hockings, C., Fairlie, W.D., Lee, E.F., Yao, S., Robin, A.Y., Smith, B.J., Huang, D.C.S., Kluck, R., Adams, J.M., Colman, P.M., 2013. Bax crystal structures reveal how BH3 domains activate Bax and nucleate its oligomerization to induce apoptosis. Cell 152, 519–531.

Deniaud, A., Brenner, C., Kroemer, G., 2004. Mitochondrial membrane permeabilization by HIV-1 Vpr. Mitochondrion 4, 223–233.

Deveraux, Q.L., Reed, J.C., 1999. IAP family proteins-suppressors of apoptosis. Genes Dev. 13, 239–252.

Dewson, G., Kratina, T., Czabotar, P., Day, C.L., Adams, J.M., Kluck, R.M., 2009. Bak activation for apoptosis involved oligomerization of dimers via their α6 helices. Mol. Cell 36, 696–703.

DiDonato, J.A., Mercurio, F., Karin, M., 2012. NF-κB and the link between inflammation and cancer. Immunol. Rev. 246, 379–400.

Edlich, F., Banerjee, S., Suzuki, M., Cleland, M.M., Arnoult, D., Wang, C., Neutzner, A., Tjandra, N., Youle, R.J., 2011. Bcl-x(L) retrotranslocates Bax from the mitochondria into the cytosol. Cell 145, 104–116.

El Maadidi, S., Faletti, L., Berg, B., Wenzl, C., Wieland, K., Chen, Z.J., Maurer, U., Borner, C., 2014. A novel mitochondrial MAVS/caspase-8 platform links RNA virus-induced innate antiviral signaling to Bax/Bak-independent apoptosis. J. Immunol. 192, 1171–1183.

Estornes, Y., Toscano, F., Virard, F., Jacquemin, G., Pierrot, A., Vanbervliet, B., Bonnin, M., Lalaoui, N., Mercier-Gouy, P., Pacheco, Y., Salaun, B., Renno, T., Micheau, O., Lebecque, S., 2012. dsRNA induces apoptosis through an atypical death complex associating TLR3 to caspase-8. Cell Death Differ. 19, 1482–1494.

Ewen, C.L., Kane, K.P., Bleackley, R.C., 2012. A quarter century of granzymes. Cell Death Differ. 19, 28–35.

Fazakerley, J.K., 2002. Pathogenesis of Semliki Forest virus encephalitis. J. Neurovirol. 8, 66–74.

Galluzzi, L., Brenner, C., Morselli, E., Touat, Z., Kroemer, G., 2008. Viral control of mitochondrial apoptosis. PLoS Pathog. 4, 1000018, http://dx.doi.org/10.1371/journal. ppat.1000018.

Garcia, M.A., Meurs, E.F., Esteban, M., 2007. The dsRNA protein kinase PKR: virus and cell control. Biochimie 89, 799–811.

Gavathiotis, E., Suzuki, M., Davis, M.L., Pitter, K., Bird, G.H., Katz, S.G., Tu, H.C., Kim, H., Cheng, E.H., Tjandra, N., Walensky, L.D., 2008. BAX activation is initiated at a novel interactions site. Nature 455, 1076–1081.

Geissler, A., Haun, F., Frank, D., Wieland, K., Simon, M., Idzko, M., Davis, R., Maurer, U., Borner, C., 2013. Apoptosis induced by the fungal pathogen gliotoxin requires a triple phosphorylation of Bim by JNK. Cell Death Differ. 20, 1317–1329.

Ghosh, A.P., Klocke, B.J., Ballestas, M.E., Roth, K.A., 2012. CHOP potentially cooperates with FOXO3a in neuronal cells to regulate PUMA and BIM expression in response to ER stress. PLoS ONE 7, e39586.

Goldstaub, D., Gradi, A., Bercovitch, Z., Grosmann, Z., Nophar, Y., Luria, S., Sonenberg, N., Kahana, C., 2000. Poliovirus 2A protease induces apoptotic cell death. Mol. Cell. Biol. 20, 1271–1277.

Gonzalvez, F., Ashkenazi, A., 2010. New insights into apoptosis signaling by Apo2L/TRAIL. Oncogene 29, 4752–4765.

Goubau, D., Deddouche, S., Reis e Sousa, C., 2013. Cytosolic sensing of viruses. Immunity 38, 855–869.

Grandgirard, D., Studer, E., Monney, L., Belser, T., Fellay, I., Borner, C., Michel, M., 1998. Alphaviruses induce apoptosis in Bcl-2-overexpressing cells: evidence for a caspase-mediated, proteolytic inactivation of Bcl-2. EMBO J. 17, 1268–1278.

Guicciardi, M.E., Gores, G.J., 2009. Life and death by death receptors. FASEB J. 23, 1625–1637.

Happo, L., Strasser, A., Cory, S., 2012. BH3-only proteins in apoptosis at a glance. J. Cell Sci. 125, 1081–1087.

Harvey, M., McArthur, M.J., Montgomery Jr., C.A., Butel, J.S., Bradley, A., Donehower, L.A., 1993. Spontaneous and carcinogen-induced tumorigenesis in p53-deficient mice. Nat. Genet. 5, 225–229.

Hay, S., Kannouraki, G., 2002. A time to kill: viral manipulation of the cell death program. J. Gen. Virol. 83, 1547–1564.

He, B., 2006. Viruses, endoplasmic reticulum stress, and interferon responses. Cell Death Differ. 13, 393–403.

Hemmi, H., Takeuchi, O., Kawai, T., Kaisho, T., Sato, S., Sanjo, H., Matsumoto, M., Hoshino, K., Wagner, H., Takeda, K., Akira, S., 2000. A Toll-like receptor recognizes bacterial DNA. Nature 408, 740–745.

Hotchkiss, R.S., Strasser, A., McDunn, J.E., Swanson, P.E., 2009. Cell death. N. Engl. J. Med. 361, 1570–1583.

Hovanessian, A.G., 2007. On the discovery of interferon-inducible, double-stranded RNA activated enzymes: the 2′–5′ oligoadenylate synthetases and the protein kinase PKR. Cytokine Growth Factor Rev. 18, 351–361.

Hu, F.Q., Smith, C.A., Pickup, D.J., 1994. Cowpox virus contains two copies of an early gene encoding a soluble secreted form of the type II TNF receptor. Virology 204, 343–356.

Ivashkiv, L.B., Donlin, L.T., 2014. Regulation of type I interferon responses. Nat. Rev. Immunol. 14, 36–49.

Jabbour, A.M., Daunt, C.P., Green, B.D., Vogel, S., Gordon, L., Lee, R., Silke, N., Pearson, R.B., Vandenberg, C.J., Kelly, P.N., Nutt, S.L., Strasser, A., Borner, C., Ekert, P.G., 2010. Myeloid progenitor cells lacking p53 exhibit delayed upregulation of Puma and prolonged survival after cytokine deprivation. Blood 115, 344–352.

Jacotot, E., Ravagnan, L., Loeffler, M., Ferri, K.F., Vieira, H.L., Zamzami, N., Costantini, P., Druillennec, S., Hoebeke, J., Briand, J.P., Irinopoulou, T., Daugas, E., Susin, S.A., Cointe, D., Xie, Z.H., Reed, J.C., Roques, B.P., Kroemer, G., 2000. The HIV-1 viral protein R induces apoptosis via a direct effect on the mitochondrial permeability transition pore. J. Exp. Med. 191, 33–46.

Jagus, R., Joshi, G., Barber, G.N., 1999. PKR, apoptosis and cancer. Int. J. Biochem. Cell Biol. 31, 123–138.

Jheng, J.R., Ho, J.Y., Horng, J.T., 2014. ER stress, autophagy, and RNA viruses. Front. Microbiol. 5, 388, http://dx.doi.org/10.3389/fmicb.2014.00388. eCollection 2014.

Joeckel, L.T., Bird, P.I., 2014. Are all granzymes cytotoxic in vivo? Biol. Chem. 395, 181–202.

Kaelin, W., 1999. The emerging p53 gene family. J. Natl. Cancer Inst. 91, 594–598.

Kaiser, W.J., Offermann, M.K., 2005. Apoptosis induced by the toll-like receptor adaptor TRIF is dependent on its receptor interacting protein homotypic interaction motif. J. Immunol. 174, 4942–4952.

Kataoka, T., Budd, R.C., Holler, N., Thome, M., Martinon, F., Irmler, M., Burns, K., Hahne, M., Kennedy, N., Kovacsovics, M., Tschopp, J., 2000. The caspase-8 inhibitor FLIP promotes activation of NF-kappaB and Erk signaling pathways. Curr. Biol. 10, 640–648.

Kato, H., Takeuchi, O., Sato, S., Yoneyama, M., Yamamoto, M., Matsui, K., Uematsu, S., Jung, A., Kawai, T., Ishli, K.J., Yamaguchi, O., Otsu, K., Tsujimura, T., Koh, C.S., Reis e Sousa, C., Matsuura, Y., Fujita, T., Akira, S., 2006. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature 441, 101–105.

Kawai, T., Takahashi, K., Sato, S., Coban, C., Kumar, H., Kato, H., Ishii, K.J., Takeuchi, O., Akira, S., 2005. MAVS, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. Nat. Immunol. 6, 981–988.

Kawai, T., Akira, S., 2008. Toll-like receptor and RIG-I-like receptor signaling. Ann. N. Y. Acad. Sci. 1143, 1–20.

Kerr, J.F., Wyllie, A.H., Currie, A.R., 1972. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br. J. Cancer 26, 239–257.

Komiyama, T., Quan, L.T., Salvesen, G.S., 1996. Inhibition of cysteine and serine proteinases by the cowpox virus serpin CRMA. Adv. Exp. Med. Biol. 389, 173–176.

Krueger, A., Schmitz, I., Baumann, S., Krammer, P.H., Kirchhoff, S., 2001. Cellular FLICE-inhibitory protein splice variants inhibit different steps of caspase-8 activation at the CD95 death-inducing signaling complex. J. Biol. Chem. 276, 20633–20640.

Kumar, H., Kawai, T., Akira, S., 2011. Pathogen recognition by the innate immune system. Int. Rev. Immunol. 30, 16–34.

Kuwana, T., Bouchier-Hayes, L., Chipuk, J.E., Bonzon, C., Sullivan, B.A., Green, D.R., Newmeyer, D.D., 2005. BH3 domains of BH3-only proteins differentially regulate Bax-mediated mitochondrial membrane permeabilization both directly and indirectly. Mol. Cell 17, 525–535.

Lama, J., Ware, C.F., 2000. Human immunodeficiency virus type 1 Nef mediates sustained membrane expression of tumor necrosis factor and the related cytokine LIGHT on activated T cells. J. Virol. 74, 9396–9402.

Lane, D.P., Crawford, L.V., 1979. T antigen is bound to a host protein in SV40-transformed cells. Nature 278, 261–263.

Letai, A., Bassik, M., Walensky, L., Sorcinelli, M., Weiler, S., Korsmeyer, S., 2002. Distinct BH3 domains either sensitize or activate mitochondrial apoptosis, serving as prototype cancer therapeutics. Cancer Cell 2, 183–192.

Li, M.L., Stollar, V., 2004. Alphaviruses and apoptosis. Int. Rev. Immunol. 23, 7–24.

Li, J., Yin, Q., Wu, H., 2013a. Structural basis of signal transduction in the TNF receptor superfamily. Adv. Immunol. 119, 135–153.

Li, S., Kong, L., Yu, X., 2013b. The expanding roles of endoplasmic reticulum stress in virus replication and pathogenesis. Crit. Rev. Microbiol. 9, 1–15.

Lin, J.H., Li, H., Yasumura, D., Cohen, H.R., Zhang, C., Panning, B., Shokat, K.M., Lavail, M.M., Walter, P., 2007. IRE1 signaling affects cell fate during the unfolded protein response. Science 318, 944–949.

Linzer, D.I., Levine, A., 1979. Characterization of a 54K dalton cellular SV40 tumor antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. Cell 17, 43–52.

Liu, B., Meng, D., Wei, T., Zhang, S., Hu, Y., Wang, M., 2014. Apoptosis and pro-inflammatory cytokine response of mast cells induced by influenza A viruses. PLOS ONE 9, e100109.

Lu, M., Lawrence, D.A., Marsters, S., Acosta-Alvear, D., Kimmig, P., Mendez, A.S., Paton, A.W., Paton, J.C., Walter, P., Ashkenazi, A., 2014. Cell death. Opposing unfolded-protein-response signals converge on death receptor 5 to control apoptosis. Science 345, 98–101.

Medici, M.A., Sciortino, M.T., Perri, D., Amici, C., Avitabile, E., Ciotti, M., Balestrieri, E., De Smaele, E., Franzoso, G., Mastino, A., 2003. Protection by herpes simplex virus glycoprotein D against Fas-mediated apoptosis – role of nuclear factor kappa B. J. Biol. Chem. 278, 36059–36067.

Medzhitov, R., 2001. Toll-like recepors and innate immunity. Nat. Rev. Immunol. 1, 135–145.

Metkar, S.S., Marchioretto, M., Antonini, V., Lunelli, L., Wang, B., Gilbert, R.J., Anderluh, G., Roth, R., Pooga, M., Pardo, J., Heuser, J.E., Serra, M.D., Froelich, C.J., 2015. Perforin oligomers form arcs in celllular membranes: a locus for intracellular delivery of granzymes. Cell Death Differ. 22, 74–85.

Meylan, E., Curran, J., Hofmann, K., Moradpour, D., Binder, M., Bartenschlager, R., Tschopp, J., 2005. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature 437, 1167–1172.

Minn, A.J., Velez, P., Schendel, S.L., Liang, H., Muchmore, S.W., Fesik, S.W., Fill, M., Thompson, C.B., 1997. Bcl-x(L) forms an ion channel in synthetic lipid membranes. Nature 385, 353–357.

Montessuit, S., Prakash Somasekharan, S.P., Terrones, O., Lucken-Ardjomande, S., Herzig, S., Schwarzenbacher, R., Manstein, D.J., Bossy-Wetzel, E., Basanez, G., Martinou, J.-C., 2010. Membrane remodeling induced by the dynamin-related protein Drp stimulates Bax oligomerization. Cell 142, 889–901.

Muchmore, S.W., Sattler, M., Liang, H., Meadows, R.P., Harlan, J.E., Yoon, H.S., Nettesheim, D., Chang, B.S., Thompson, C.B., Wong, S.L., Ng, S.L., Fesik, S.W., 1996. X-ray and NMR structure of human Bcl-xL, an inhibitor of programmed cell death. Nature 381, 335–341.

Müllbacher, A., Wallich, R., Moyer, R.W., Simon, M.M., 1999. Poxvirus-encoded serpins do not prevent cytolytic T cell-mediated recovery from primary infections. J. Immunol. 162, 7315–7321.

Munger, J., Roizman, B., 2001. The US3 protein kinase of herpes simplex virus 1 mediates the posttranslational modification of BAD and prevents BAD-induced

programmed cell death in the absence of other viral proteins. Proc. Natl. Acad. Sci. U. S. A. 98, 10410–10415.
Murphy, A.M., Sheahan, B.J., Atkins, G.J., 2001. Induction of apoptosis in BCL-2-expressing rat prostate cancer cells using the Semliki Forest virus vector. Int. J. Cancer 94, 572–578.
Muthumani, K., Hwang, D.S., Desai, B.M., Zhang, D., Dayes, N., Green, D.R., Weiner, D.B., 2002. HIV-1 Vpr induces apoptosis through caspase 9 in T cells and peripheral blood mononuclear cells. J. Biol. Chem. 277, 37820–37831.
Nakano, K., Vousden, K.H., 2001. PUMA, a novel proapoptotic gene, is induced by p53. Mol. Cell 7, 683–694.
Neilan, J.G., 1993. An African swine fever virus gene with similarity to the proto-oncogene bcl-2 and the Epstein–Barr virus gene BHRF1. J. Virol. 67, 4391–4394.
Nie, Z., Phenix, B.N., Lum, J.J., Alam, A., Lynch, D.H., Beckett, B., Krammer, P.H., Sekaly, R.P., Badley, A.D., 2002. HIV-1 protease processes procaspase 8 to cause mitochondrial release of cytochrome c, caspase cleavage and nuclear fragmentation. Cell Death Differ. 9, 1172–1184.
Oda, E., Ohki, R., Murasawa, H., Nemoto, J., Shibue, T., Yamashita, T., Tokino, T., Taniguchi, T., Takana, N., 2000. Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis. Science 288, 1053–1058.
Oltersdorf, T., Elmore, S.W., Shoemaker, A.R., Armstrong, R.C., Augeri, D.J., Belli, B.A., Bruncko, M., Deckwerth, T.L., Dinges, J., Hajduk, P.J., Joseph, M.K., Kitada, S., Korsmeyer, S.J., Kunzer, A.R., Letai, A., Li, C., Mitten, M.J., Nettesheim, D.G., Ng, S., Nimmer, P.M., O'Connor, J.M., Oleksijew, A., Petros, A.M., Reed, J.C., Shen, W., Tahir, S.K., Thompson, C.B., Tomaselli, K.J., Wang, B., Wendt, M.D., Zhang, H., Fesik, S.W., Rosenberg, S.H., 2005. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. Nature 435, 677–681.
Pardo, J., Aguilo, J.I., Anel, A., Martin, P., Joeckel, L., Borner, C., Wallich, R., Müllbacher, A., Froelich, C.J., Simon, M.M., 2009a. The biology of cytotoxic cell granule exocytosis pathway: granzymes have evolved to induce cell death and inflammation. Microbes Infect. 11, 452–459.
Pardo, J., Gálvez, E.M., Koskinen, A., Simon, M.M., Lobigs, M., Regner, M., Müllbacher, A., 2009b. Caspase-dependent inhibition of mousepox replication by gzmB. PLoS ONE 4, e7512.
Pichlmair, A., Reis e Sousa, C., 2007. Innate recognition of viruses. Immunity 27, 370–383.
Piguet, V., Schwartz, O., Le Gall, S., Trono, D., 1999. The downregulation of CD4 and MHC-I by primate lentiviruses: a paradigm for the modulation of cell surface receptors. Immunol. Rev. 168, 51–63.
Postigo, A., Ferrer, P.E., 2009. Viral inhibitors reveal overlapping themes in regulation of cell death and innate immunity. Microbes Infect. 11, 1071–1078.
Puthalakath, H., Huang, D.C., O'Reilly, L.A., King, S.M., Strasser, A., 1999. The proapoptotic activity of the Bcl-2 family member Bim is regulated by interaction with the dynein motor complex. Mol. Cell 3, 287–296.
Puthalakath, H., O'Reilly, L.A., Gunn, P., Lee, L., Kelly, P.N., Huntington, N.D., Hughes, P.D., Michalak, E.M., McKimm-Breschkin, J., Motoyama, N., Gotoh, T., Akira, S., Bouillet, P., Strasser, A., 2007. ER stress triggers apoptosis by activating BH3-only protein Bim. Cell 129, 1337–1349.
Querido, E., Blanchette, P., Yan, Q., Kamura, T., Morrison, M., Boivin, D., Kaelin, W.G., Conaway, R.C., Conaway, J.W., Branton, P.E., 2001. Degradation of p53 by adenovirus E4orf6 and E1B55K proteins occurs via a novel mechanism involving a Cullin-containing complex. Genes Dev. 15, 3104–3117.
Raftery, M.J., Behrens, C.K., Müller, A., Krammer, P.H., Walczak, H., Schönrich, G., 1999. Herpes simplex virus type 1 infection of activated cytotoxic T cells: induction of fratricide as a mechanism of viral immune evasion. J. Exp. Med. 190, 1103–1114.
Raftery, M.J., Schwab, M., Eibert, S.M., Samstag, Y., Walczak, H., Schönrich, G., 2001. Targeting the function of mature dendritic cells by human cytomegalovirus: a multilayered viral defense strategy. Immunity 15, 997–1009.
Reading, P.C., Khanna, A., Smith, G.L., 2002. Vaccinia virus CrmE encodes a soluble and cell surface tumor necrosis factor receptor that contributes to virus virulence. Virology 292, 285–298.
Reimertz, C., Kögel, D., Rami, A., Chittenden, T., Prehn, J.H., 2003. Gene expression during ER stress-induced apoptosis in neurons: induction of the BH3-only protein Bbc3/PUMA and activation of the mitochondrial apoptosis pathway. J. Cell Biol. 162, 587–597.
Roy, C.R., Mocarski, E.S., 2007. Pathogen subversion of cell-intrinsic innate immunity. Nat. Immunol. 8, 1179–1187.
Sano, R., Reed, J.C., 2013. ER stress-induced cell death mechanisms. Biochim. Biophys. Acta 1833, 3460–3470.
Scheffner, M., Werness, B.A., Huibregtse, J.M., Levine, A., Howley, P.M., 1990. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. Cell 63, 1129–1136.
Schendel, S.L., Xie, Z., Montal, M.O., Matsuyama, S., Montal, M., Reed, J.C., 1997. Channel formation by antiapoptotic protein Bcl-2. Proc. Natl. Acad. Sci. U. S. A. 94, 5113–5118.
Shi, Y., 2002. Mechanisms of caspase activation and inhibition during apoptosis. Mol. Cell 8, 459–470.
Schinzel, A., Kaufmann, T., Schuler, M., Martinalbo, J., Grubb, D., Borner, C., 2004. Conformational control of Bax localization and apoptotic activity by Pro168. J. Cell Biol. 164, 1021–1032.
Sciortino, M.T., Medici, M.A., Marino-Merlo, F., Zaccaria, D., Giuffrè-Cuculletto, M., Venuti, A., Grelli, S., Mastino, A., 2008. Involvement of HVEM receptor in activation of nuclear factor kB by HSV-1 glycoprotein D. Cell. Microbiol. 10, 2297–2311.
Screpanti, V., Wallin, R.P., Ljunggren, H.G., Grandien, A., 2001. A central role for death receptor-mediated apoptosis in the rejection of tumors by NK cells. J. Immunol. 167, 2068–2073.
Sedger, L.M., Shows, D.M., Blanton, R.A., Peschon, J.J., Goodwin, R.G., Cosman, D., Wiley, S.R., 1999. IFN-gamma mediates a novel antiviral activity through dynamic modulation of TRAIL and TRAIL receptor expression. J. Immunol. 163, 920–926.
Seth, R.B., Sun, L., Ea, C.K., Chen, Z.J., 2005. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. Cell 122, 669–682.
Shisler, J., Yang, C., Walter, B., Ware, C., Gooding, L., 1997. The adenovirus E3-10.4K/14.5K complex mediates loss of cell surface fas (CD95) and resistance to fas-induced apoptosis. J. Virol. 71, 8299–8306.
Skaletskaya, A., Bartle, L.M., Chittenden, T., McCormick, A.L., Mocarski, E.S., Goldmacher, V.S., 2001. A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation. Proc. Natl. Acad. Sci. U. S. A. 98, 7829–7834.
Smith, C.A., Davis, T., Wignall, J.M., Din, W.S., Farrah, T., Upton, C., McFadden, G., Goodwin, R.G., 1991. T2 open reading frame from the Shope fibroma virus encodes a soluble form on the TNF receptor. Biochem. Biophys. Res. Commun. 176, 335–342.
Steegenga, W.T., Riteco, N., Jochemsen, A.G., Fallaux, F.J., Bos, J.L., 1998. The large E1B protein together with E4orf6 protein target p53 for active degradation in adenovirus infeced cells. Oncogene 16, 349–357.
Stewart, A.R., Tollefson, A.E., Krajcsi, P., Yei, S.P., Wold, W.S., 1995. The adenovirus E3 10.4K and 14.5K proteins, which function to prevent cytolysis by tumor necrosis factor and to down-regulate the epidermal growth factor receptor, are localized in the plasma membrane. J. Virol. 69, 172–181.
Stewart, S.A., Poon, B., Jowett, J.B., Xie, Y., Chen, I.S., 1999. Lentiviral delivery of HIV-1 Vpr protein induces apoptosis in transformed cells. Proc. Natl. Acad. Sci. U. S. A. 96, 12039–12043.
Strack, P.R., Frey, M.W., Rizzo, C.J., Cordova, B., George, H.J., Meade, R., Ho, S.P., Corman, J., Tritch, R., Korant, B.D., 1996. Apoptosis mediated by HIV protease is preceded by cleavage of Bcl-2. Proc. Natl. Acad. Sci. U. S. A. 93, 9571–9576.
Strasser, A., Jost, P.J., Nagata, S., 2009. The many roles of FAS receptor signaling in the immune system. Immunity 30, 180–192.
Strauss, J.H., Strauss, E.G., 1994. The alphaviruses: gene expression, replication and evolution. Microbiol. Rev. 58, 491–562.
Subramaniam, K., Hirpara, J.L., Tucker-Kellogg, L., Tucker-Kellogg, G., Pervaiz, S., 2013. FLIP: a flop for execution signals. Cancer Lett. 332, 151–155.
Sun, S.C., Cesarman, E., 2011. NF-κB as a target for oncogenic viruses. Curr. Top. Microbiol. Immunol. 349, 197–244.
Sun, L., Wu, J., Du, F., Chen, X., Chen, Z.J., 2013. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science 339, 786–791.
Suzuki, M., Youle, R.J., Tjandra, N., 2000. Structure of Bax: coregulatoin of dimer formation and intracellular localization. Cell 10, 645–654.
Takaoka, A., Wang, Z., Choi, M.K., Yanai, H., Negishi, H., Ban, T., Lu, Y., Miyagishi, M., Kodama, T., Honda, K., Ohba, Y., Taniguchi, T., 2007. DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. Nature 448, 501–505.
Takeuchi, O., Akira, S., 2009. Innate immunity to virus infection. Immunol. Rev. 227, 75–86.
Tamura, R., Kanda, T., Imazeki, F., Wu, S., Nakamoto, S., Tanaka, T., Arai, M., Fujiwara, K., Saito, K., Roger, T., Wakita, T., Shirasawa, H., Yokosuka, O., 2011. Hepatitis C Virus nonstructural 5A protein inhibits lipopolysaccharide-mediated apoptosis of hepatocytes by decreasing expression of Toll-like receptor 4. J. Infect. Dis. 204, 793–801.
Tan, S.L., Katze, M.G., 1999. The emerging role of the interferon-induced PKR protein kinase as an apoptotic effector: a new face of death? J. Interferon Cytokine Res. 19, 543–554.
Tan, Y.X., Tan, T.H., Lee, M.J., Tham, P.Y., Gunalan, V., Druce, J., Birch, C., Catton, M., Fu, N.Y., Yu, V.C., Tan, Y.J., 2007. Induction of apoptosis by the severe acure respiratory syndrome coronavirus 7a protein is dependent on its interaction with the Bcl-xL protein. J. Virol. 81, 6346–6355.
Taylor, J.M., Barry, M., 2006. Near death experiences: poxvirus regulation of apoptotic death. Virology 344, 139–150.
Thiery, J., Lieberman, J., 2014. Perforin: a key pore-forming protein for immune control of viruses and cancer. Subcell. Biochem. 80, 197–220.
Thome, M., Tschopp, J., 2001. Regulation of lymphocyte proliferation and death by FLIP. Nat. Rev. Immunol. 1, 50–58.
Tollefson, A.E., Hermiston, T.W., Lichtenstein, D.L., Colle, C.F., Tripp, R.A., Dimitrov, T., Toth, K., Wells, C.E., Doherty, P.C., Wold, W.S., 1998. Forced degradation of Fas inhibits apoptosis in adenovirus-infected cells. Nature 392, 725–730.
Tse, C., Shoemaker, A.R., Adickes, J., Anderson, M.G., Chen, J., Jin, S., Johnson, E.F., Marsh, K.C., Mitten, M.J., Nimmer, P., et al., 2008. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. Cancer Res. 68, 3421–3428.
Tsukahara, T., Kannagi, M., Ohashi, T., Kato, H., Arai, M., Nunez, G., Iwanaga, Y., Yamamoto, N., Ohtani, K., Nakamura, M., Fujii, M., 1999. Induction of Bcl-x_L expression by human T-cell leukemia virus type I Tax through NFκB in apoptosis-resistant T-cell transfectants with Tax. J. Virol. 73, 7981–7987.
Turner, P.C., Sancho, M.C., Thoennes, S.R., Caputo, A., Bleackley, R.C., Moyer, R.W., 1999. Myxoma virus Serp2 is a weak inhibitor of granzyme B and interleukin-1beta-converting enzyme in vitro and unlike CrmA cannot block apoptosis in cowpox virus-infected cells. J. Virol. 73, 6394–6404.
Ubol, S., Tucker, P.S., Griffin, D.E., Hardwick, J.M., 1994. Neurovirulent strains of Alphavirus induce apoptosis in bcl-2-expressing cells: role of a single amino acid change in the E2 protein. Proc. Natl. Acad. Sci. U. S. A. 91, 5202–5206.
Uchida, J., Yasui, T., Takaoka-Shichijo, Y., Muraoka, M., Kulwichit, W., Raab-Traub, N., Kikutani, H., 1999. Mimicry of CD40 signals by Epstein-Barr virus LMP1 in B lymphocyte responses. Science 286, 300–303.

Unterholzner, L., 2013. The interferon response to intracellular DNA: why so many receptors? Immunobiology 218, 1312–1321.

Upton, C., Macen, J., Schreiber, M., McFadden, G., 1991. Myxoma virus expresses a secreted protein with homology to the tumor necrosis factor receptor gene family that contributes to viral virulence. Virology 184, 370–382.

Urban, C., Rheme, C., Maerz, S., Berg, B., Pick, R., Nitschke, R., Borner, C., 2008. Apoptosis induced by Semliki Forest virus is RNA replication dependent and mediated via Bak. Cell Death Differ. 15, 1396–1407.

Uren, R.T., Dewson, G., Chen, L., Coyne, S.C., Huang, D.C.S., Adams, J.M., Kluck, R.M., 2007. Mitochondrial permeabilization relies on BH3 ligands engaging multiple pro-survival Bcl-2 relatives, not Bak. J. Cell Biol. 177, 277–287.

Vandenberg, C.J., Cory, S., 2013. ABT-199, a new Bcl-2-specific BH3 mimetic, has in vivo efficacy against aggressive Myc-driven mouse lymphomas without provoking thrombocytopenia. Blood 121, 2285–2288.

Vanlangenakker, N., Vanden Berghe, T., Vandenabeele, P., 2012. Many stimuli pull the necrotic trigger an overview. Cell Death Differ. 19, 75–86.

Vidalain, P.O., Azocar, O., Lamouille, B., Astier, A., Rabourdin-Combe, C., Servet-Delprat, C., 2000. Measles virus induces functional TRAIL production by human dendritic cells. J. Virol. 74, 556–559.

Volkmann, N., Marassi, F.M., Newmeyer, D.D., Hanein, D., 2014. The rheostat in the membrane: BCL-2 family proteins and apoptosis. Cell Death Differ. 21, 206–215.

Wang, X.W., 1995. Abrogation of p53-induced apoptosis by the hepatitis B virus X gene. Cancer Res. 55, 6012–6016.

Wang, G.Q., Gastman, B.R., Wieckowski, E., Goldstein, L.A., Gambotto, A., Kim, T.H., Fang, B., Rabinovitz, A., Yin, X.M., Rabinowich, H., 2001. A role for mitochondrial Bak in apoptotic response to anticancer drugs. J. Biol. Chem. 2001 (276), 34307–34317.

Weber, A., Kirejczyk, Z., Besch, R., Potthoff, S., Leverkus, M., Häcker, G., 2010. Proapoptotic signalling through Toll-like receptor-3 involves TRIF-dependent activation of caspase-8 and is under the control of inhibitor of apoptosis proteins in melanoma cells. Cell Death Differ. 17, 942–951.

Werness, B.A., Levine, A.J., Howley, P.M., 1990. Association of human papillomavirus types 16 and 18 E6 proteins with p53. Science 248, 76–79.

Westphal, D., Ledgerwood, E.C., Hibma, M.H., Fleming, S.B., Whelan, E.M., Mercer, A.A., 2007. A novel Bcl-2-like inhibitor of apoptosis is encoded by the parapoxvirus ORF virus. J. Virol. 81, 7178–7188.

Westphal, D., Kluck, R.M., Dewson, G., 2014. Building blocks of the apoptotic pore: how Bax and Bak are activated and oligomerize during apoptosis. Cell Death Differ. 21, 196–205.

White, E., 1998. Regulation of apoptosis by adenovirus E1A and E1B oncogenes. Semin. Virol. 8, 505–513.

Willis, S.N., Chen, L., Dewson, G., Wei, A., Naik, E., Fletcher, J.I., Adams, J.M., Huang, D.C., 2005. Proapoptotic Bak is sequestered by Mcl-1 and Bcl-xL, but not Bcl-2, until displaced by BH3-only proteins. Genes Dev. 19, 1294–1305.

Willis, S., Fletcher, J.I., Kaufmann, T., van Delft, M.F., Chen, L., Czabotar, P.E., Ierino, H., Lee, E.F., Fairlie, W.D., Bouillet, P., et al., 2007. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. Science 315, 856–859.

Wilson, W.H., O'Connor, O.A., Czuczman, M.S., Lacasce, A.S., Gerecitano, J.F., Leonard, J.P., Tulpule, A., Dunleavy, K., Xiong, H., Chiu, Y.L., 2010. Navitoclax, a targeted high-affinity inhibitor of BCL-2, in lymphoid malignancies: a phase 1 dose-escalation study of safety, pharmacokinetics, pharmacodynamics, and antitumour activity. Lancet Oncol. 11, 1149–1159.

Wolf, D., Witte, V., Laffert, B., Blume, K., Stromer, E., Trapp, S., d'Aloja, P., Schürmann, A., Baur, A.S., 2001. HIV-1 Nef associated PAK and PI3-kinases stimulate Akt-independent Bad-phosphorylation to induce anti-apoptotic signals. Nat. Med. 7, 1217–1224.

Wolter, K.G., Hsu, Y.T., Smith, C.L., Nechushtan, A., Xi, X.G., Youle, R.J., 1997. Movement of Bax from the cytosol to mitochondria during apoptosis. J. Cell Biol. 139, 1281–1292.

Xu, L.G., Wang, Y.Y., Han, J.J., Li, L.Y., Zhai, Z., Shu, H.B., 2005. VISA is an adapter protein required for virus-triggered IFN-beta signaling. Mol. Cell 19, 727–740.

Xu, X.-P., Zhai, D., Kim, E., Swift, M., Reed, J.C., Volkmann, N., Hanein, D., 2013. Three-dimensional structure of Bax-mediated pores in lipid membrane bilayers. Cell Death Dis. 4, e683, http://dx.doi.org/10.1038/cddis.2013.210.

Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imaizumi, T., Miyagishi, M., Taira, K., Akira, S., Fujita, T., 2004. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat. Immunol. 5, 730–737.

Youle, R.J., Strasser, A., 2008. The BCL-2 protein family: opposing activities that mediate cell death. Nat. Rev. Mol. Cell Biol. 9, 47–59.

Zhang, Z., Yuan, B., Lu, N., Facchinetti, V., Liu, Y.J., 2011. DHX9 pairs with IPS-1 to sense double-stranded RNA in myeloid dendritic cells. J. Immunol. 187, 4501–4508.

Zhou, Q., Snipas, S., Orth, K., Muzio, M., Dixit, V.M., Salvesen, G.S., 1997. Target protease specificity of the viral serpin CrmA. Analysis of five caspases. J. Biol. Chem. 272, 7797–7800.