

Viruses and the TNF-related cytokines, an evolving battle

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Abstract

Tumor necrosis factor (TNF)-related cytokines are critical effector molecules in the immune response to viral pathogens. Engagement of the TNF receptors by their cognate ligands activates apoptotic and non-apoptotic signaling pathways, both of which can mediate antiviral activity. In response, viruses have evolved mechanisms to inhibit signaling by some cytokines of the TNF superfamily. These strategies are largely unique to each class of virus, but are similar in that they all target key regulatory checkpoints of the TNF pathway. In recent years, studies directed towards dissecting the mechanisms of TNF signaling and the viral retort have led to several significant discoveries, and form the basis for this review.

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1. Introduction

Signaling by the tumor necrosis factor (TNF)-related cytokines contributes to the immune response against foreign pathogens through various mechanisms including the formation of secondary and tertiary lymphoid tissues, promoting NK and lymphocyte differentiation and acting as direct effector molecules in host defense [1]. Consequently, TNF-family ligands impose significant pressure

upon viruses to evolve counterstrategies in order to complete their replication cycle, or in the case of persistent viruses such as the herpesviruses, to establish a lifelong infection. The advances in our understanding made in recent years dissecting the molecular mechanisms of TNF receptor (TNFR) signaling has in turn led to the identification of a multitude of viral proteins that regulate this pathway. Viruses target virtually every step of TNF signaling from expression, to inhibition of ligand–receptor binding, to the modulation of downstream signaling pathways [2], and several examples of convergent evolution directed towards key regulatory checkpoints of the cellular apoptotic machinery exist.

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2. The TNF superfamily

The role of TNF-family ligands in modulating various developmental processes and immune responses can largely be attributed to the ability of these cytokines to regulate cell death and survival. TNF-related cytokines are type II transmembrane glycoproteins that signal via their cognate receptors, which are single transmembrane domain glycoproteins. The trimeric structure of the ligand clusters receptors, initiating signal transduction. Signal-

ing by the TNFRs can be generally subdivided into two pathways, induction of apoptosis by those receptors that encode a cytoplasmic death domain (DD), and promotion of inflammation and/or cell survival through TNF receptor-associated factor (TRAF) adaptors that propagate signals leading to the activation of transcription factors and gene induction. Importantly, these signaling pathways are not mutually exclusive, and several of the DD encoding receptors activate both proapoptotic and cell survival pathways.

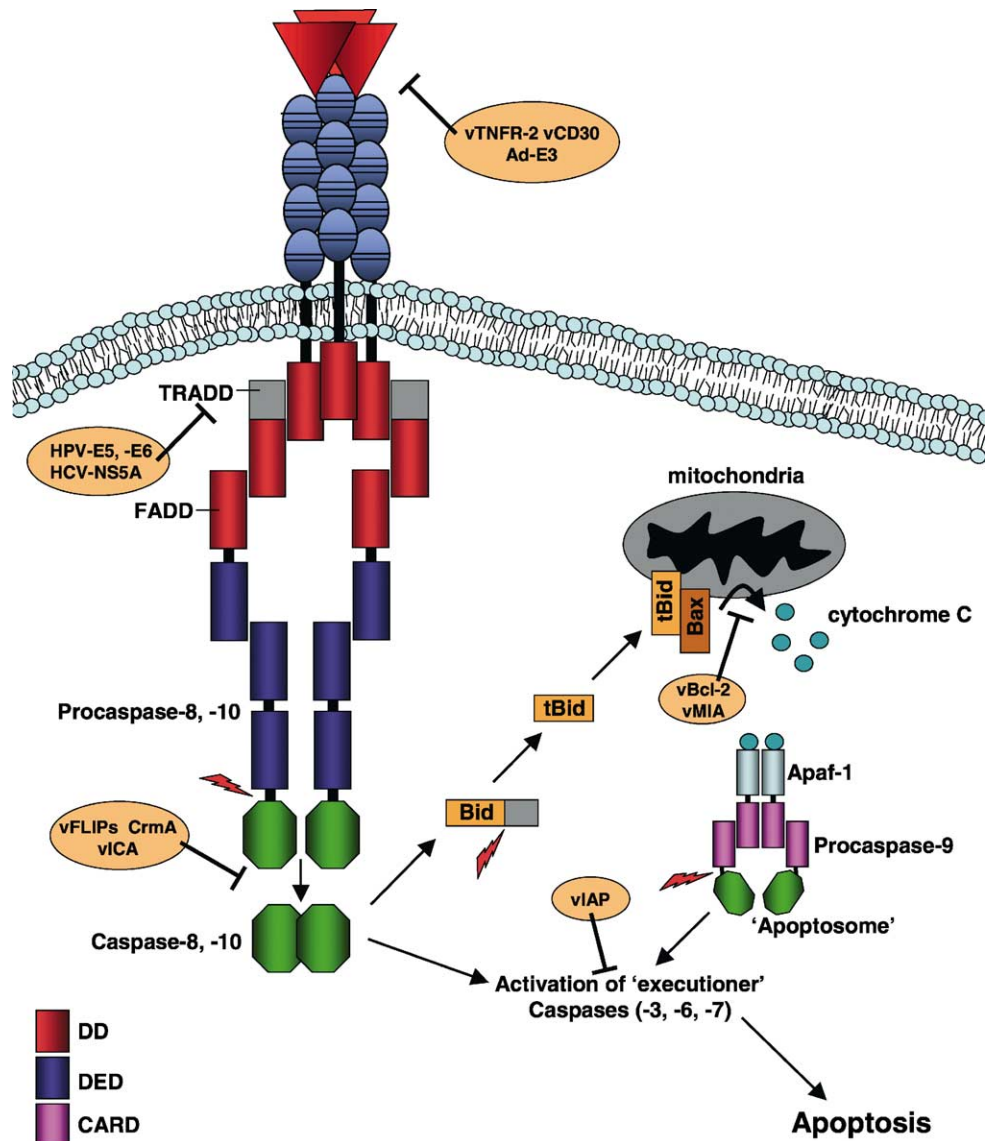


Fig. 1. Viral inhibition of death receptor signaling. Viruses have evolved strategies to target virtually every level of death receptor signaling. Secreted orthologues of TNFR-2 and CD30 are encoded by poxviruses, and can bind their respective ligands in the extracellular space. Adenoviral E3 region proteins can mediate Fas, TRAIL-R1 and TRAIL-R2 downregulation from the cell surface, desensitizing cells to apoptosis. HPV proteins E5 and E6 and HCV NS5A alter TNFR DISC formation by competing for or directly binding to TRADD. The viral FLIPs (vFLIPs) encoded by several γ -herpesviruses and MCV can interact directly with FADD and caspase-8. Cowpox CrmA inhibits activation of caspase-8 and caspase-1, and vICA of HCMV blocks activation of caspase-8. The death receptor pathway can cross-talk with the mitochondrion death pathway through cleavage of Bid to tBid by caspase-8. Viral Bcl-2 orthologues (vBcl-2) can inhibit mitochondrion-dependent apoptosis, and vMIA of HCMV may function by a similar mechanism. A viral IAP (viAP) orthologue exists in African swine fever virus.

2.1. Apoptotic signaling by TNFRs

The DD-containing receptors (including Fas, TNF-related apoptosis inducing ligand (TRAIL)-receptor 1 (TRAIL-R1) and TRAIL-R2, and TNFR-1) initiate apoptosis following ligand binding through the recruitment of adaptor proteins and procaspases (cysteine-based aspartate-directed proteases) to the plasma membrane to form the death inducing signaling complex (DISC) (see Fig. 1). This recruitment occurs through protein–protein interactions mediated by homologous, modular domains that include DD, death effector domains (DEDs) and caspase recruitment domains (CARDs) [3]. Upon formation of the DISC, the proximal positioning of procaspase-8 and/or procaspase-10 (the ‘initiator’ caspases) in the DISC is thought to lead to autocatalysis and conversion to an active enzyme. Activated caspase-8 or caspase-10 can then directly convert procaspase-3 (an ‘executioner’ caspase) to its active form, completing the initiation phase of the pathway [4]. Death receptor-initiated apoptosis is commonly referred to as the ‘extrinsic’ pathway, and contrasts with the ‘intrinsic’ cell death pathway, which senses the general metabolic status of the cell and is dependent upon signals propagated through the mitochondria. However, it is likely that there is cross-talk between the extrinsic and intrinsic cell death pathways through death receptor-induced cleavage of the proapoptotic Bcl-2 family member Bid [5,6].

2.2. Non-apoptotic TNFR signals

The second, non-apoptotic, TNFR signaling pathway involves the recruitment of TRAFs and/or kinases (e.g. receptor interacting protein (RIP)) to the receptor following ligand binding, resulting in the downstream activation of transcription factors (e.g. NF κ B and AP-1) and subsequent expression of proinflammatory and cell survival genes [7]. For the TNFR superfamily, activation of NF κ B and AP-1 has been most well studied in the case of TNF binding to TNFR-1 and TNFR-2. AP-1 activation is dependent upon the mitogen activated protein kinases (MAPKs), with the p38 MAPKs and the c-Jun amino-terminal kinases (JNKs) being the most relevant to TNFR signaling [8]. Activation of NF κ B (p50 and p65/RelA) occurs through phosphorylation and ubiquitin-mediated degradation of cytoplasmic inhibitor proteins, the I κ Bs, by the I κ B kinase (IKK) complex, and subsequent translocation of NF κ B to the nucleus. Other NF κ B family members (p100/NF κ B2) are phosphorylated directly by the IKK complex, resulting in proteolytic processing of p100 to form p52 and transport of a transcriptionally active p52/RelB heterodimer to the nucleus [9]. Signaling by TNFR-1 results in activation of the ‘classical’ p50/p65 NF κ B pathway through an I κ B-dependent mechanism requiring IKK γ [10]. Recent results indicate that the LT β receptor (LT β R) can activate both the classical NF κ B pathway and an ‘alternative’ pathway that is independent of IKK γ but dependent upon IKK α and NF κ B inducing kinase

(NIK) and requires the processing of p100 [11]. The TNFR superfamily members CD40 [12] and B cell activating factor (BAFF) receptor [13] also induce processing of p100, indicating that the alternative NF κ B pathway plays a significant role in signaling by several, but not all, TNF-family ligands.

3. Viral targeting of the death receptors

3.1. Modulating ligand expression

The death receptors Fas, TRAIL-R1 and TRAIL-R2 are expressed constitutively on most cell types, but expression of their cognate ligands is tightly regulated. Several viruses target this critical control point through their induction of Fas ligand (FasL) and/or TRAIL in infected cells. Induction of these death receptor ligands has been reported in cells infected with human cytomegalovirus (CMV) [14–17], herpes simplex virus (HSV) [18], adenovirus [19,20], reovirus [21] and human immunodeficiency virus (HIV) [22]. Although the mechanism for induction of FasL and TRAIL has not been delineated, viral replication is not required in the case of CMV and adenovirus [16,19,20]. It is known that both interferon (IFN) γ and type I IFN (IFN α/β) can up-regulate TRAIL expression in various cell types [14,23,24]. Thus, a possible mechanism for viral induction of TRAIL observed in cell culture systems could be via an autocrine loop through the production of IFN α/β by the infected cells themselves (see Fig. 2).

One possible consequence of FasL and TRAIL induction following virus infection may be to arm the infected cell, allowing it to kill infiltrating immune effector cells, thereby functioning as an immune evasion tactic. HSV infection of T cells promotes apoptosis of HSV-specific T cell clones in culture [18], and FasL/TRAIL-dependent death of activated T cells is also observed upon co-incubation with human CMV-infected dendritic cells [17]. Additionally, induction of FasL on the surface of HIV-infected T cells [22] may contribute to the death of uninfected, ‘bystander’ T cells observed in lymph nodes [25]. Although inducible expression of death receptor ligands by NK and T cells serves as an important antiviral host response, it appears that expression of these ligands in the infected cells themselves may turn the host against itself in an example of virus-mediated fratricide (Fig. 2).

3.2. Inhibiting ligand–receptor interactions

The bioavailability of the TNF-related ligands in the extracellular space can be regulated by soluble ‘decoy’ receptors generated by proteolysis uncoupling the ecto domain of the receptor from its signaling domain (e.g. TNFR-1 and TNFR-2), or specific binding proteins (e.g. OPG and DcR3). These strategies for neutralization of TNF-related ligand activity have been usurped by several members of the poxvirus family which contain orthologues of TNFR-2

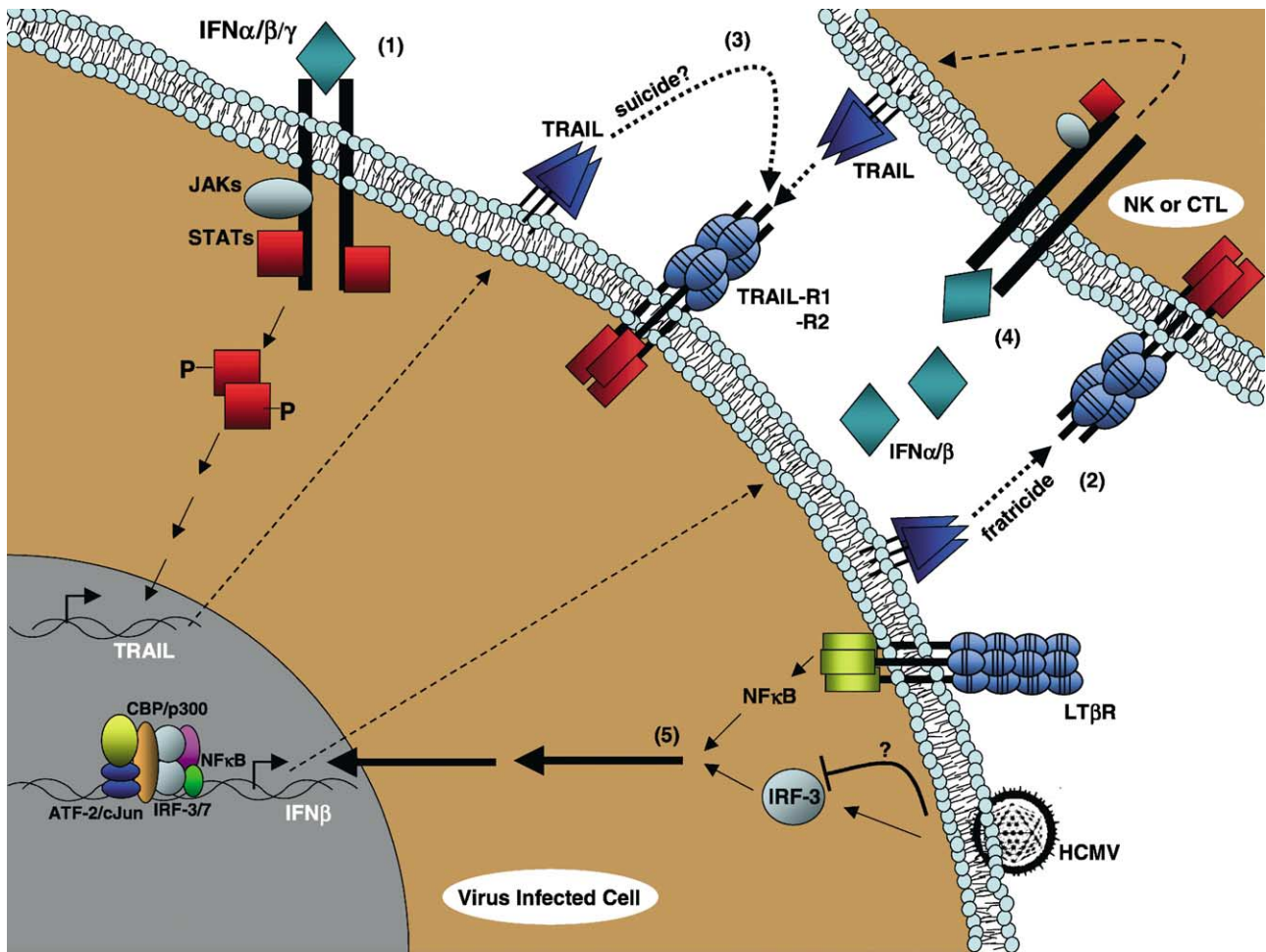


Fig. 2. Cross-talk between the interferon and death receptor pathways. IFN α/β and IFN γ produced by host immune effector cells (e.g. NK/CTL/dendritic cells) can activate the janus kinase (JAK) and signal transducers and activators of transcription (STATs), ultimately leading to transcription of TRAIL (1). Viral infection upregulates TRAIL, and this may occur through production of IFN α/β by the infected cell itself or by a distinct mechanism. TRAIL expressed on the surface of a virally infected cell may function as an immune evasion tactic, mediating apoptosis of infiltrating immune effector cells (fratricide) (2). In the infected cell itself, TRAIL could potentially signal apoptosis in an autocrine fashion (suicide) if the virus cannot inhibit death receptor signaling, for instance, in the case of replication defective virus (3). Release of IFN α/β by the virally infected cell can induce TRAIL expression on the surface of immune effector cells (NK or CTL) (4). HCMV can suppress induction of IFN α/β , and this may involve the modulation of interferon response factor-3 (IRF-3). Signaling by the LT β R in HCMV-infected cells can induce high levels of IFN α/β , circumventing this block (5).

secreted by virus infected cells [26] (Fig. 1). Interestingly, cowpox contains four separate TNFR-2 orthologues that bind TNF and/or LT α (CrmB, CrmC, CrmD and CrmE), strongly supporting an important role for these cytokines in controlling viral infection [27–30]. The secreted TNFR-2 orthologue (*M-T2*) in myxoma virus (rabbitpox) is one of a very few viral immunomodulatory genes that has been shown to contribute to viral pathogenesis in vivo [31], albeit these experiments were performed in European rabbits, which are not the native host for myxoma and die rapidly from viral induced myxomatosis.

In addition to poxviral orthologues of TNFR-2, an orthologue of CD30 (vCD30) has recently been identified in cowpox and mousepox [32,33]. CD30 is expressed at low levels on resting lymphocytes, macrophages and NK cells, and enhanced levels are seen on activated or virally transformed lymphocytes [34]. CD30 can be shed from the cell surface

in a form that can bind CD30 ligand (CD30L/CD153) [35], and the level of soluble CD30 in the serum is used as a prognostic indicator for patients with Hodgkin's lymphoma [36]. CD30L is expressed by activated hematopoietic cells, and functions in host defense as a costimulation signal supporting B and T cell survival and proliferation [39], among other roles [37,38]. vCD30 binds to CD30L with high affinity [32,33], effectively antagonizing the ability of CD30L to signal via cell surface CD30, and can inhibit type I cytokine responses in a murine model of antigen-induced granuloma [33]. A role for vCD30 in poxviral pathogenesis has not yet been established, but the conservation of this orthologue in the poxviral genome suggests a previously unappreciated role for CD30 in mounting antiviral immune responses.

A separate strategy for inhibiting the interaction between death receptors and their ligands is employed by adenovirus

which specifically downregulates the proapoptotic receptors for FasL [40,41] and TRAIL [42,43] from the surface of infected cells. Two transmembrane proteins present in the E3 region of the adenoviral genome, E3-10.4K/RID α and E3-14.5K/RID β , function together in a heteromeric complex to downregulate Fas and target it for degradation in lysosomes [40,41]. Highlighting the complexity involved in receptor modulation by adenovirus, a third E3 protein, E3-6.7K, is required for downregulation of TRAIL-R2 and contributes to downregulation of TRAIL-R1 [42]. Interestingly, adenoviral gene therapy vectors that lack the E3 locus induce significant levels of apoptosis in transduced hepatocytes, and this death is neutralized by treating with soluble TRAIL-R2 protein [20]. These data suggest that downregulation of TRAIL receptors by adenovirus, perhaps in combination with additional immunomodulatory functions of other E3 proteins [44], may be critical for the virus to complete its replication cycle in some cell types. E3 proteins function to downregulate receptors in several cell types, including bronchial epithelium [42] and lymphocytes [45], and may also aid in the establishment of a persistent/latent infection in lymphoid tissue [46].

Notably, the function of E3-10.4K/14.5K is not restricted to death receptors as evidenced by their ability to downmodulate the epidermal growth factor receptor (EGF-R) from the cell surface [47,48]. However, various other death receptors and protein tyrosine kinase receptors are unaffected [42,49], indicating a significant degree of specificity. Because Fas and TRAIL receptors do not show any primary sequence homology with EGF-R, one plausible hypothesis is that the E3 proteins may pirate the endosomal compartments where these receptors traffic. This hypothesis is supported by recent evidence indicating that mutation of a tyrosine-based protein-sorting motif in the cytoplasmic tail of E3-14.5K abolishes downregulation of Fas [50].

3.3. Applying DISC breaks

In addition to the ‘first line of defense’ strategies directed towards inhibiting ligand–receptor interactions, viruses have evolved several mechanisms to block death receptor signaling downstream of ligand binding. One of the most well-characterized examples of this is the viral FLIP proteins (FLICE/caspase-8 inhibitory proteins), which inhibit activation of the initiator caspases in the DISC and represent a successful example of molecular burglary by the large DNA viruses (Fig. 1). The vFLIPs were first identified in the sequence database as DED-containing proteins, and are encoded in the genomes of various γ -herpesviruses including equine herpesvirus-2 (EHV-2), herpesvirus saimiri (HVS), KSHV and bovine herpesvirus-4 (BHV-4), as well as the human poxvirus, molluscum contagiosum virus (MCV) [51–54]. The cellular orthologue of vFLIP was subsequently cloned [55], and has been shown to exist in both a short (\sim 26 kDa, cFLIP_S) and long (\sim 55 kDa, cFLIP_L) form generated by alternative splicing.

cFLIP_S is essentially the cellular orthologue of vFLIP, encoding two DED, while cFLIP_L encodes an additional carboxy terminal domain with high homology to caspase-8 and caspase-10. Although both isoforms of cFLIP are recruited to the DISC and inhibit caspase activation, their mechanism of action is distinct. Complete inhibition of caspase-8 processing is seen by cFLIP_S (similar to vFLIP), while cFLIP_L allows partial caspase processing [56]. In turn, the precise requirements for the function of vFLIP from MCV encompass more than just binding to FADD and caspase-8 [57,58]. Finally, in addition to inhibiting death receptor apoptosis, the vFLIPs have also been shown to interact in over expression systems with various adaptor proteins known to regulate expression of NF κ B, including TRAF2, RIP, NIK and IKK β [59], suggesting that these proteins may function to regulate multiple aspects of death receptor signaling.

Human papillomavirus type 16 (HPV-16) encodes two separate proteins that have been reported to inhibit apoptosis at the level of the DISC (Fig. 1). The HPV-16 E5 protein inhibits apoptosis and decreases DISC formation in a human keratinocyte cell line treated with TRAIL [60], and the E6 protein binds directly to the cytoplasmic tail of TNFR1, competing for the binding of TRADD (TNFR1-associated DD-containing protein) and inhibiting TNF killing of murine fibroblasts [61]. The NS5A protein of hepatitis C virus has also been reported to interact with TRADD, and inhibit TNF killing of hepatocytes in vivo when expressed as a transgene in mice [62]. Taken together, it seems clear that modulating death receptor signaling by altering the recruitment of cytoplasmic adaptor proteins must be an effective strategy as evidenced by its general utilization by viruses.

3.4. Capturing the caspases

Several other viral strategies for the inhibition of caspase activation by the death receptors also exist (Fig. 1). The human CMV *UL36* gene product (vICA) can inhibit Fas induced apoptosis by directly interacting with caspase-8 [63], but shows no primary sequence homology to any known cellular proteins. African swine fever virus (ASFV) encodes an orthologue of the cellular inhibitor of apoptosis proteins (IAPs) that is capable of inhibiting TNF-mediated killing and activation of caspase-3 when overexpressed in Vero cells [64]. IAPs were originally identified in baculovirus [65], and require their zinc-binding baculoviral IAP repeat (BIR) domains to inhibit caspase activity [66–68]. However, deletion of the vIAP in ASFV does not alter viral pathogenesis [69]. Many poxviruses encode serpins (serine protease inhibitors) that can bind and inhibit the activation of cellular caspases [70], and the cowpox serpin CrmA can block or delay apoptosis of mammalian cells in response to TNF, FasL and TRAIL through its interaction with caspase-8 [71–74]. Finally, p35, the pan caspase inhibitor from baculovirus, which functions as a suicide substrate, inhibits death receptor-mediated apoptosis when overexpressed in mammalian cells [75]. Although p35 and the poxviral serpins

can suppress death receptor signaling in cell culture models, these proteins have evolved to block a broad spectrum of protease-dependent processes, and are likely to have multiple functions in promoting viral replication in vivo.

3.5. Targeting the mitochondria

Upon receiving a variety of apoptotic signals that activate the intrinsic pathway of cell death, the proapoptotic Bcl-2 family proteins (e.g. Bad, Bid, Bak, Bim, Bax) can translocate from the cytoplasm to the mitochondrial membrane, promoting the release of cytochrome *c* into the cytoplasm. Cytochrome *c* then associates with Apaf-1 and procaspase-9 (forming the apoptosome), resulting in the activation of caspase-9 and subsequent downstream activation of the executioner caspases (e.g. caspase-3) [76]. This pathway can be countered by the anti-apoptotic members of the family (e.g. Bcl-2 and Bcl-X_L), most likely through their ability to heterodimerize with the proapoptotic members. As mentioned above, the extrinsic (death receptor) pathway can cross-talk to the intrinsic pathway through the cleavage of Bid. Cleaved Bid (tBid) can then either heterooligomerize with Bak or Bax [77,78] or homooligomerize [79] in association with the mitochondrial membrane.

Not unexpectedly, several examples exist for viral inhibition of the mitochondrion-dependent cell death pathway (Fig. 1). Several of the oncogenic γ -herpesviruses encode identifiable viral orthologues of the Bcl-2 family (vBcl-2). Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) and herpesvirus saimiri all encode a vBcl-2 that can inhibit apoptosis when overexpressed in tissue culture [80–82]. The vBcl-2 of murine γ -herpesvirus 68 (MHV-68) inhibits killing of HeLa cells by Fas and TNF [83] and is critical for efficient reactivation of latent virus in vivo [84], and stands as the first evidence for a vBcl-2 protein contributing to virulence. The adenovirus vBcl-2 (E1B-19K) inhibits TNF-mediated apoptosis by directly interacting with Bax, presumably disrupting the function of tBid and ultimately resulting in blockade of procaspase-9 activation [85]. In contrast, the human CMV *UL37* gene product (vMIA) shows no primary sequence homology to Bcl-2, but appears to be functionally similar as it associates with the adenine nucleotide translocator in the mitochondrial membrane and inhibits Fas-mediated apoptosis when overexpressed [86]. Finally, the LMP-1 multimembrane spanning protein of EBV functions essentially as a constitutively active form of the TNFR family member CD40 [87], and can upregulate cellular Bcl-2, potentially desensitizing cells to death receptor mediated apoptosis [88].

4. It's a good day to die, or is it?

Although apoptosis can be an effective strategy for clearing virally infected cells, it does not come without potential cost to the host. In this regard, activation of non-apoptotic,

proinflammatory signaling by the TNF-related cytokines can contribute to host defense in several models. During the acute phase of hepatitis B virus (HBV) infection a large percentage of hepatocytes are actively replicating virus. In this case, unmitigated induction of apoptosis would result in liver destruction with serious consequences to the host, requiring that the immune system adopt a non-cytolytic strategy for controlling virus spread [89]. Consequently, the clearance of HBV genomic DNA from the liver in murine and primate models has been shown to be non-apoptotic and dependent upon both TNF and IFN γ production by virus-specific T cells [90,91]. More recently, the antiviral mechanism of TNF in HBV-transgenic mice has been shown to be through its synergy with IFN γ [92], and IFN α/β also exhibits potent, non-cytolytic anti-HBV activity in this model [92,93]. The synergy between TNF and IFNs to suppress virus replication has been recognized for some time [94,95], but the underlying mechanism for this synergy is still unclear and is likely to be virus and cell-type specific.

Another non-cytolytic, IFN-dependent antiviral pathway has recently been described for LT α and LIGHT, members of the 'core' TNF family. In human CMV-infected fibroblasts, signaling by these cytokines through either TNFR-1 or the LT β R induces high level expression of IFN β that reversibly inhibits viral replication in an autocrine fashion [96] (Fig. 2). FasL or TRAIL are unable to activate this pathway or provide an antiviral activity. Importantly, IFN β is not induced by receptor signaling in the absence of CMV infection, highlighting the need for viral and host factors to establish a state of détente. Human CMV actively suppresses induction of IFN β [15,16], and signaling by LT/LIGHT may function to circumvent this block. Additionally, since TNF has previously been reported to induce IFN β in serum starved fibroblasts [97], it suggests that non-apoptotic signaling by both DD and non-DD-containing TNFRs may cross-talk to the interferon response pathway in cells receiving a 'second signal' (such as viral infection, growth factor deprivation, etc.). Physiologic significance is added to these in vitro observations by the fact that mice deficient in LT α or that express a soluble decoy inhibitor of LT β R signaling (LT β R-Fc) [98] are highly susceptible to infection by mouse CMV [96].

5. Costimulation

Several TNF-related ligands and their receptors are classified as costimulatory molecules for T or B cell activation (CD40L, CD30L, OX40L, 4-1BBL, LIGHT and CD27L), and impairment of some of these signaling pathways can alter the development of specific antiviral immune responses. CD40L-deficient mice show decreased humoral responses and CD4⁺ T cell responses after infection with lymphocytic choriomeningitis virus (LCMV), vesicular stomatitis virus (VSV), Pichinde virus and HSV [99–101], and inhibition of CD40/CD40L signaling can negate the ability to

control a persistent LCMV infection [102]. Additionally, an agonistic anti-CD40 antibody can substitute for the absence of CD4+ T cells to control reactivation of latent MHV-68 [103]. In contrast, 4-1BBL-deficient mice show decreased CD8+ T cell responses to LCMV [104]. Finally, as mentioned previously, CD30/CD30L signaling is likely to play a role in controlling poxvirus pathogenesis based on the presence of a soluble CD30 orthologue in the mousepox and cowpox genome [32,33].

6. Summary

In summary, it is clear that in order for a virus to successfully propagate it must exert some control over the host immune response. Signaling by the TNFR superfamily can mediate antiviral activity via both apoptotic and non-apoptotic mechanisms, requiring that viruses evolve strategies to deal with both. The discussion in this review is limited to the TNF family, however, it is important to remember that the non-cytolytic, antiviral activity of TNF-family ligands may be closely linked to the induction of, or synergy with, the interferons, and IFN-regulated genes. The majority of TNF signaling modulators to date have been described for the large DNA viruses. However, this may merely be a product of the fact that their larger genome size allows for the retention of usurped genes, with readily identifiable primary sequence homology to their cellular counterparts. The smaller RNA and DNA viruses are likely to practice similar modulation of the TNF-related cytokines. These viral proteins may have evolved to perform multiple functions, losing their primary sequence homology to cellular orthologues. Further characterization of the mechanisms utilized by viruses to thwart immune surveillance should yield attractive targets for therapeutic intervention.

References

- [1] Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell* 2001;104(4):487–501.
- [2] Benedict CA, Norris PS, Ware CF. To kill or be killed: viral evasion of apoptosis. *Nat Immunol* 2002;3(11):1013–8.
- [3] Hofmann K. The modular nature of apoptotic signaling proteins. *Cell Mol Life Sci* 1999;55(8–9):1113–28.
- [4] Zimmermann KC, Bonzon C, Green DR. The machinery of programmed cell death. *Pharmacol Ther* 2001;92(1):57–70.
- [5] Luo X, Budihardjo I, Zou H, Slaughter C, Wang X. Bid, a Bcl2 interacting protein, mediates cytochrome *c* release from mitochondria in response to activation of cell surface death receptors. *Cell* 1998;94(4):481–90.
- [6] Li H, Zhu H, Xu CJ, Yuan J. Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. *Cell* 1998;94(4):491–501.
- [7] Baud V, Karin M. Signal transduction by tumor necrosis factor and its relatives. *Trends Cell Biol* 2001;9:372–7.
- [8] Aggarwal BB. Tumour necrosis factors receptor associated signalling molecules and their role in activation of apoptosis, JNK and NF-kappaB. *Ann Rheum Dis* 2000;59(Suppl 1):i6–i16.
- [9] Solan NJ, Miyoshi H, Carmona EM, Bren GD, Paya CV. RelB cellular regulation and transcriptional activity are regulated by p100. *J Biol Chem* 2002;277(2):1405–18.
- [10] Yamaoka S, Courtois G, Bessia C, Whiteside ST, Weil R, Agou F, et al. Complementation cloning of NEMO, a component of the IkkappaB kinase complex essential for NF-kappaB activation. *Cell* 1998;93(7):1231–40.
- [11] Dejardin E, Droin NM, Delhase M, Haas E, Cao Y, Makris C, et al. The lymphotoxin-beta receptor induces different patterns of gene expression via two NF-kappaB pathways. *Immunity* 2002;17(4):525.
- [12] Coope HJ, Atkinson PG, Huhse B, Janzen J, Holman MJ, et al. CD40 regulates the processing of NF-kappaB2 p100 to p52. *EMBO J* 2002;21(20):5375–85.
- [13] Claudio E, Brown K, Park S, Wang H, Siebenlist U. BAFF-induced NEMO-independent processing of NF-kappaB2 in maturing B cells. *Nat Immunol* 2002;3(10):958–65.
- [14] Sedger LM, Shows DM, Blanton RA, Peschon JJ, Goodwin RG, Cosman D, et al. IFN-gamma mediates a novel antiviral activity through dynamic modulation of TRAIL and TRAIL receptor expression. *J Immunol* 1999;163:920–6.
- [15] Simmen KA, Singh J, Luukkonen BG, Lopper M, Bittner A, Miller NE, et al. Global modulation of cellular transcription by human cytomegalovirus is initiated by viral glycoprotein B. *Proc Natl Acad Sci USA* 2001;98(13):7140–5.
- [16] Browne EP, Wing B, Coleman D, Shenk T. Altered cellular mRNA levels in human cytomegalovirus-infected fibroblasts: viral block to the accumulation of antiviral mRNAs. *J Virol* 2001;75:12319–30.
- [17] Raftery MJ, Schwab M, Eibert SM, Samstag Y, Walczak H, Schonrich G. Targeting the function of mature dendritic cells by human cytomegalovirus: a multilayered viral defense strategy. *Immunity* 2001;15:997–1009.
- [18] Raftery MJ, Behrens CK, Muller A, Krammer PH, Walczak H, Schonrich G. Herpes simplex virus type 1 infection of activated cytotoxic T cells: induction of fratricide as a mechanism of viral immune evasion. *J Exp Med* 1999;190(8):1103–4.
- [19] Hall SJ, Canfield SE, Yan Y, Hassen W, Selleck WA, Chen SH. A novel bystander effect involving tumor cell-derived Fas and FasL interactions following Ad.HSV-tk and Ad.mIL-12 gene therapies in experimental prostate cancer. *Gene Ther* 2002;9(8):511–7.
- [20] Zhang HG, Xie J, Xu L, Yang P, Xu X, Sun S, et al. Hepatic DR5 induces apoptosis and limits adenovirus gene therapy product expression in the liver. *J Virol* 2002;76:5692–700.
- [21] Vidalain PO, Azocar O, Lamouille B, Astier A, Rabourdin-Combe C, Servet-Delprat C. Measles virus induces functional TRAIL production by human dendritic cells. *J Virol* 2000;74:556–9.
- [22] Xu XN, Laffert B, Screaton GR, Kraft M, Wolf D, Kolanus W, et al. Induction of Fas ligand expression by HIV involves the interaction of Nef with the T cell receptor zeta chain. *J Exp Med* 1999;189(9):1489–96.
- [23] Kayagaki N, Yamaguchi N, Nakayama M, Eto H, Okumura K, Yagita H. Type I interferons (IFNs) regulate tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expression on human T cells: a novel mechanism for the antitumor effects of type I IFNs. *J Exp Med* 1999;189(9):1451–60.
- [24] Fanger NA, Maliszewski CR, Schooley K, Griffith TS. Human dendritic cells mediate cellular apoptosis via tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). *J Exp Med* 1999;190(8):1155–64.
- [25] Finkel TH, Tudor-Williams G, Banda NK, Cotton MF, Curiel T, Monks C, et al. Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes. *Nat Med* 1995;1(2):129–34.
- [26] Everett H, McFadden G. Poxviruses and apoptosis: a time to die. *Curr Opin Microbiol* 2002;5(4):395.
- [27] Hu F-Q, Smith CA, Pickup DJ. Cowpox virus contains two copies of an early gene encoding a soluble secreted form of the type II TNF receptor. *Virology* 1994;204:343–56.

- [28] Smith CA, Hu F-Q, Smith TD, Richards CL, Smolak P, Goodwin RG, et al. Cowpox virus genome encodes a second soluble homologue of cellular TNF receptors, distinct from CrmB, that binds TNF but not LT α . *Virology* 1996;223:132–47.
- [29] Loparev VN, Parsons JM, Knight JC, Panus JF, Ray CA, Buller RL, et al. A third distinct tumor necrosis factor receptor of orthopoxviruses. *Proc Natl Acad Sci USA* 1998;95:3786–91.
- [30] Saraiva M, Alami A. CrmE, a novel soluble tumor necrosis factor receptor encoded by poxviruses. *J Virol* 2001;75(1):226–33.
- [31] Upton C, Macen J, Schreiber M, McFadden G. Myxoma virus expresses a secreted protein with homology to the tumor necrosis factor receptor gene family that contributes to viral virulence. *Virology* 1991;184:370–82.
- [32] Panus JF, Smith CA, Ray CA, Smith TD, Patel DD, Pickup DJ. Cowpox virus encodes a fifth member of the tumor necrosis factor receptor family: a soluble, secreted CD30 homologue. *Proc Natl Acad Sci USA* 2002;99(12):8348–53.
- [33] Saraiva M, Smith P, Fallon PG, Alami A. Inhibition of type I cytokine-mediated inflammation by a soluble CD30 homologue encoded by ectromelia (mousepox) virus. *J Exp Med* 2002;196(6):829–39.
- [34] Chiarle R, Podda A, Prolla G, Gong J, Thorbecke GJ, Inghirami G. CD30 in normal and neoplastic cells. *Clin Immunol* 1999;90(2):157–64.
- [35] Hargreaves PG, Al-Shamkhani A. Soluble CD30 binds to CD153 with high affinity and blocks transmembrane signaling by CD30. *Eur J Immunol* 2002;32(1):163–73.
- [36] Gause A, Pohl C, Tschiersch A, Da Costa L, Jung W, Diehl V, et al. Clinical significance of soluble CD30 antigen in the sera of patients with untreated Hodgkin's disease. *Blood* 1991;77(9):1983–8.
- [37] Kurts C, Carbone FR, Krummel MF, Koch KM, Miller JF, Heath WR. Signalling through CD30 protects against autoimmune diabetes mediated by CD8 T cells. *Nature* 1999;398(6725):341–4.
- [38] Amakawa R, Hakem A, Kundig TM, Matsuyama T, Simard JJ, Timms E, et al. Impaired negative selection of T cells in Hodgkin's disease antigen CD30-deficient mice. *Cell* 1996;84:551–62.
- [39] Shanebeck KD, Maliszewski CR, Kennedy MK, Picha KS, Smith CA, Goodwin RG. Regulation of murine B cell growth and differentiation by CD30 ligand. *Eur J Immunol* 1995;25(8):2147–53.
- [40] Shisler J, Yang C, Walter B, Ware C, Gooding L. The adenovirus E3-10.4K/14.5K complex mediates loss of cell surface Fas (CD95) and resistance to Fas-induced apoptosis. *J Virol* 1997;71(11):8299–306.
- [41] Tollefson AE, Hermiston TW, Lichtenstein DL, Colle CF, Tripp RA, Dimitrov T, et al. Forced degradation of Fas inhibits apoptosis in adenovirus-infected cells. *Nature* 1998;392(6677):726–30.
- [42] Benedict CA, Norris PS, Prigozy TI, Bodmer JL, Mahn JA, Garnett CT, et al. Three adenovirus E3 proteins cooperate to evade apoptosis by tumor necrosis factor-related apoptosis-inducing ligand receptor-1 and -2. *J Biol Chem* 2001;276:3270–8.
- [43] Tollefson AE, Toth K, Doronin K, Kuppaswamy M, Doronina OA, Lichtenstein DL, et al. Inhibition of TRAIL-induced apoptosis and forced internalization of TRAIL receptor 1 by adenovirus proteins. *J Virol* 2001;75(19):8875–87.
- [44] Burgert HG, Ruzsics Z, Obermeier S, Hilgendorf A, Windheim M, Elsing A. Subversion of host defense mechanisms by adenoviruses. *Curr Top Microbiol Immunol* 2002;269:273–318.
- [45] McNees AL, Garnett CT, Gooding LR. The adenovirus E3 RID complex protects some cultured human T and B lymphocytes from Fas-induced apoptosis. *J Virol* 2002;76(19):9716–23.
- [46] Garnett CT, Erdman D, Xu W, Gooding LR. Prevalence and quantitation of species C adenovirus DNA in human mucosal lymphocytes. *J Virol* 2002;76(21):10608–16.
- [47] Carlin CR, Tollefson AE, Brady HA, Hoffman BL, Wold WS. Epidermal growth factor receptor is down-regulated by a 10,400 MW protein encoded by the E3 region of adenovirus. *Cell* 1989;57(1):135–44.
- [48] Tollefson AE, Stewart AR, Yei SP, Saha SK, Wold WS. The 10,400- and 14,500-dalton proteins encoded by region E3 of adenovirus form a complex and function together to down-regulate the epidermal growth factor receptor. *J Virol* 1991;65(6):3095–105.
- [49] Kuivinen E, Hoffman BL, Hoffman PA, Carlin CR. Structurally related class I and class II receptor protein tyrosine kinases are down-regulated by the same E3 protein coded for by human group C adenoviruses. *J Cell Biol* 1993;120:1271–9.
- [50] Lichtenstein DL, Krajcsi P, Esteban DJ, Tollefson AE, Wold WS. Adenovirus RIDbeta subunit contains a tyrosine residue that is critical for RID-mediated receptor internalization and inhibition of Fas- and TRAIL-induced apoptosis. *J Virol* 2002;76(22):11329–42.
- [51] Thome M, Schneider P, Hofmann K, Fickenscher H, Meinl E, Neipel F, et al. Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors. *Nature* 1997;386:517–21.
- [52] Bertin J, Armstrong RC, Otilie S, Martin DA, Wang Y, Banks S, et al. Death effector domain-containing herpesvirus and poxvirus proteins inhibit both Fas- and TNFR1-induced apoptosis. *Proc Natl Acad Sci USA* 1997;94:1172–6.
- [53] Hu S, Vincenz C, Buller M, Dixit VM. A novel family of viral death effector domain-containing molecules that inhibit both CD-95- and tumor necrosis factor receptor-1-induced apoptosis. *J Biol Chem* 1997;272:9621–4.
- [54] Wang GH, Bertin J, Wang Y, Martin DA, Wang J, Tomaselli KJ, et al. Bovine herpesvirus 4 BORFE2 protein inhibits Fas- and tumor necrosis factor receptor 1-induced apoptosis and contains death effector domains shared with other gamma-2 herpesviruses. *J Virol* 1997;71:8928–32.
- [55] Thome M, Tschopp J. Regulation of lymphocyte proliferation and death by FLIP. *Nat Rev Immunol* 2001;1:50–8.
- [56] Krueger A, Schmitz I, Baumann S, Krammer PH, Kirchhoff S. Cellular FLICE-inhibitory protein splice variants inhibit different steps of caspase-8 activation at the CD95 death-inducing signaling complex. *J Biol Chem* 2001;276:20633–40.
- [57] Garvey TL, Bertin J, Siegel RM, Wang GH, Lenardo MJ, Cohen JL. Binding of FADD and caspase-8 to molluscum contagiosum virus MC159 v-FLIP is not sufficient for its antiapoptotic function. *J Virol* 2002;76(2):697–706.
- [58] Garvey T, Bertin J, Siegel R, Lenardo M, Cohen J. The death effector domains (DEDs) of the molluscum contagiosum virus MC159 v-FLIP protein are not functionally interchangeable with each other or with the DEDs of caspase-8. *Virology* 2002;300(2):217–25.
- [59] Chaudhary PM, Jasmin A, Eby MT, Hood L. Modulation of the NF- κ B pathway by virally encoded death effector domains-containing proteins. *Oncogene* 1999;18:5738–46.
- [60] Kabsch K, Alonso A. The human papillomavirus type 16 E5 protein impairs TRAIL- and FasL-mediated apoptosis in HaCaT cells by different mechanisms. *J Virol* 2002;76(23):12162–72.
- [61] Filippova M, Song H, Connolly JL, Dermody TS, Duerksen-Hughes PJ. The human papillomavirus 16 E6 protein binds to tumor necrosis factor (TNF) R1 and protects cells from TNF-induced apoptosis. *J Biol Chem* 2002;277(24):21730–9.
- [62] Majumder M, Ghosh AK, Steele R, Zhou XY, Phillips NJ, Ray R, et al. Hepatitis C virus NS5A protein impairs TNF-mediated hepatic apoptosis, but not by an anti-FAS antibody, in transgenic mice. *Virology* 2002;294(1):94–105.
- [63] Skaletskaya A, Bartle LM, Chittenden T, McCormick L, Mocarski ES, Goldmacher VS. A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation. *Proc Natl Acad Sci USA* 2001;98(14):7829–34.
- [64] Nogal ML, Gonzalez de Buitrago G, Rodriguez C, Cubelos B, Carrascosa AL, Salas ML, et al. African swine fever virus IAP homologue inhibits caspase activation and promotes cell survival in mammalian cells. *J Virol* 2001;75(6):2535–43.
- [65] Clem RJ. Baculoviruses and apoptosis: the good, the bad, and the ugly. *Cell Death Differ* 2001;8(2):137–43.

- [66] Deveraux QL, Reed JC. IAP family proteins—suppressors of apoptosis. *Genes Dev* 1999;13(3):239–52.
- [67] Hay BA. Understanding IAP function and regulation: a view from *Drosophila*. *Cell Death Differ* 2000;7(11):1045–56.
- [68] Shi Y. Mechanisms of caspase activation and inhibition during apoptosis. *Mol Cell* 2002;9(3):459–70.
- [69] Neilan JG, Lu Z, Kutish GF, Zsak L, Burrage TG, Borca MV, et al. A BIR motif containing gene of African swine fever virus, 4CL, is nonessential for growth in vitro and viral virulence. *Virology* 1997;230(2):252–64.
- [70] Ekert PG, Silke J, Vaux DL. Caspase inhibitors. *Cell Death Differ* 1999;6(11):1081–6.
- [71] Marsters SA, Pitti RM, Donahue CJ, Ruppert S, Bauer KD, Ashkenazi A. Activation of apoptosis by Apo-2 ligand is independent of FADD but blocked by CrmA. *Curr Biol* 1996;6(6):750–2.
- [72] Miura M, Friedlander RM, Yuan J. Tumor necrosis factor-induced apoptosis is mediated by a CrmA-sensitive cell death pathway. *Proc Natl Acad Sci USA* 1995;92(18):8318–22.
- [73] Talley AK, Dewhurst S, Perry SW, Dollard SC, Gummuluru S, Fine SM, et al. Tumor necrosis factor alpha-induced apoptosis in human neuronal cells: protection by the antioxidant *N*-acetylcysteine and the genes *bcl-2* and *crmA*. *Mol Cell Biol* 1995;15(5):2359–66.
- [74] Tewari M, Dixit VM. Fas- and tumor necrosis factor-induced apoptosis is inhibited by the poxvirus *crmA* gene product. *J Biol Chem* 1995;270(7):3255–60.
- [75] Beidler DR, Tewari M, Friesen PD, Poirier G, Dixit VM. The baculovirus p35 protein inhibits Fas- and tumor necrosis factor-induced apoptosis. *J Biol Chem* 1995;270(28):16526–8.
- [76] Wolf BB, Green DR. Suicidal tendencies: apoptotic cell death by caspase family proteinases. *J Biol Chem* 1999;274(29):20049–52.
- [77] Eskes R, Desagher S, Antonsson B, Martinou JC. Bid induces the oligomerization and insertion of Bax into the outer mitochondrial membrane. *Mol Cell Biol* 2000;20(3):929–35.
- [78] Korsmeyer SJ, Wei MC, Saito M, Weiler S, Oh KJ, Schlesinger PH. Pro-apoptotic cascade activates BID, which oligomerizes BAK or BAX into pores that result in the release of cytochrome *c*. *Cell Death Differ* 2000;7(12):1166–73.
- [79] Grinberg M, Sarig R, Zaltsman Y, Frumkin D, Grammatikakis N, Reuveny E, et al. tBID homo-oligomerizes in the mitochondrial membrane to induce apoptosis. *J Biol Chem* 2002;277(14):12237–45.
- [80] Henderson S, Huen D, Rowe M, Dawson C, Johnson G, Rickinson A. Epstein-Barr virus-coded BHRF1 protein, a viral homologue of Bcl-2, protects human B cells from programmed cell death. *Proc Natl Acad Sci USA* 1993;90(18):8479–83.
- [81] Sarid R, Sato T, Bohenzky RA, Russo JJ, Chang Y. Kaposi's sarcoma-associated herpesvirus encodes a functional bcl-2 homologue. *Nat Med* 1997;3(3):293–8.
- [82] Nava VE, Cheng EH, Veluona M, Zou S, Clem RJ, Mayer ML, et al. Herpesvirus saimiri encodes a functional homolog of the human *bcl-2* oncogene. *J Virol* 1997;71(5):4118–22.
- [83] Wang GH, Garvey TL, Cohen JL. The murine gammaherpesvirus-68 M11 protein inhibits Fas- and TNF-induced apoptosis. *J Gen Virol* 1999;80(Pt 10):2737–40.
- [84] Gangappa S, van Dyk LF, Jewett TJ, Speck SH, Virgin HWT. Identification of the in vivo role of a viral bcl-2. *J Exp Med* 2002;195(7):931–40.
- [85] Perez D, White E. TNF-alpha signals apoptosis through a bid-dependent conformational change in Bax that is inhibited by E1B-19K. *Mol Cell* 2000;6(1):53–63.
- [86] Goldmacher VS, Bartle LM, Skaletskaya A, Dionne CA, Kedersha NL, Vater CA, et al. A cytomegalovirus-encoded mitochondria-localized inhibitor of apoptosis structurally unrelated to Bcl-2. *Proc Natl Acad Sci USA* 1999;96(22):12536–41.
- [87] Klein E, Teramoto N, Gogolak P, Nagy N, Bjorkholm M. LMP-1, the Epstein-Barr virus-encoded oncogene with a B cell activating mechanism similar to CD40. *Immunol Lett* 1999;68(1):147–54.
- [88] Henderson S, Rowe M, Gregory C, Croom-Carter D, Wang F, Longnecker R, et al. Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. *Cell* 1991;65(7):1107–15.
- [89] Guidotti LG, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. *Annu Rev Immunol* 2001;19:65–91.
- [90] Guidotti LG, Ishikawa T, Hobbs MV, Matzke B, Schreiber R, Chisari FV. Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes. *Immunity* 1996;4(1):25–36.
- [91] Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral clearance without destruction of infected cells during acute HBV infection. *Science* 1999;284(5415):825–9.
- [92] Pasquetto V, Wieland SF, Uprichard SL, Tripodi M, Chisari FV. Cytokine-sensitive replication of hepatitis B virus in immortalized hepatocyte cultures. *J Virol* 2002;76(11):5646–53.
- [93] McClary H, Koch R, Chisari FV, Guidotti LG. Relative sensitivity of hepatitis B virus and other hepatotropic viruses to the antiviral effects of cytokines. *J Virol* 2000;74(5):2255–64.
- [94] Wong GH, Goeddel DV. Tumor necrosis factors alpha and beta inhibit virus replication and synergize with interferons. *Nature* 1986;323:819–22.
- [95] Reis LFL, Lee TH, Vilcek J. Tumor necrosis factor acts synergistically with autocrine interferon β and increases interferon β mRNA levels in human fibroblasts. *J Biol Chem* 1989;264(28):16351–4.
- [96] Benedict CA, Banks TA, Senderowicz L, Ko M, Britt WJ, Angulo A, et al. Lymphotoxins and cytomegalovirus cooperatively induce interferon- β , establishing host-virus détente. *Immunity* 2001;15:617–26.
- [97] Reis LF, Lee HT, Vilcek J. Tumor necrosis factor acts synergistically with autocrine interferon-beta and increases interferon-beta mRNA levels in human fibroblasts. *J Biol Chem* 1989;264:16351–4.
- [98] Ettinger R, Browning JL, Michie SA, van Ewijk W, McDevitt HO. Disrupted splenic architecture, but normal lymph node development in mice expressing a soluble lymphotoxin- β receptor-IgG1 fusion protein. *Proc Natl Acad Sci USA* 1996;93:13102–7.
- [99] Borrow P, Tishon A, Lee S, Xu J, Grewal IS, Oldstone MB, et al. CD40L-deficient mice show deficits in antiviral immunity and have an impaired memory CD8+ CTL response. *J Exp Med* 1996;183:2129–42.
- [100] Whitmire JK, Flavell RA, Grewal IS, Larsen CP, Pearson TC, Ahmed R. CD40-CD40 ligand costimulation is required for generating antiviral CD4 T cell responses but is dispensable for CD8 T cell responses. *J Immunol* 1999;163(6):3194–201.
- [101] Edelmann KH, Wilson CB. Role of CD28/CD80–86 and CD40/CD154 costimulatory interactions in host defense to primary herpes simplex virus infection. *J Virol* 2001;75(2):612–21.
- [102] Williams MA, Onami TM, Adams AB, Durham MM, Pearson TC, Ahmed R, et al. Cutting edge: persistent viral infection prevents tolerance induction and escapes immune control following CD28/CD40 blockade-based regimen. *J Immunol* 2002;169(10):5387–91.
- [103] Sarawar SR, Lee BJ, Reiter SK, Schoenberger SP. Stimulation via CD40 can substitute for CD4 T cell function in preventing reactivation of a latent herpesvirus. *Proc Natl Acad Sci USA* 2001;98(11):6325–9.
- [104] Tan JT, Whitmire JK, Ahmed R, Pearson TC, Larsen CP. 4-1BB ligand, a member of the TNF family, is important for the generation of antiviral CD8 T cell responses. *J Immunol* 1999;163(9):4859–68.