REVIEW ARTICLE

Apoptosis: Implications in Viral and Mycobacterium tuberculosis infections

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Abstract
Apoptosis is a form of programmed cell death leading to genetically controlled self-destruction of cells. It is essential in the development, maintenance, and regulation of cells during physiological as well as pathological conditions. Deregulation of apoptotic mechanisms is associated with various pathological diseases including cancer, autoimmune disorders, viral and bacterial infections. Virus and *Mycobacterium tuberculosis* elicit host cell apoptosis as a part of host immune defense or pathogen dissemination. They inhibit both extrinsic and intrinsic pathways of apoptotic mechanisms facilitating pathogen survival and escape from host immune defense.

Keywords: apoptosis, virus, *Mycobacterium tuberculosis*, immune response

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Introduction
Apoptosis is a form of programmed cell death which is the most common form of physiological cell death in eukaryotes, evolutionarily conserved from yeast to humans. It leads to the genetically controlled sequence of events that eventually give rise to spatially and temporally regulated self-destruction of cells [1,2]. Apoptotic mode of cell death is an active process, critical in the development of multicellular organisms and the maintenance and regulation of cell populations during physiological and pathological conditions [3,4]. Deregulation of apoptosis leads to various pathological conditions including cancer, autoimmune disorders, and spreading of viral infections while AIDS, Neurodegenerative disorders, and ischemic diseases are caused or enhanced by accelerated apoptosis [3,5–8]. Both viral and *Mycobacterium tuberculosis* (Mtb) infections modulate host cell apoptosis for their benefits [6,9–11]. This review briefly summarizes the mechanisms of apoptotic deaths and their regulation and significances in viral and mycobacterial infections.

Apoptosis
Various extracellular and intracellular stimuli trigger apoptosis. Ligation of cell surface receptors, DNA damage (because of defects in DNA repair mechanism, cytotoxic drugs, or irradiation), lack of survival signals, contradictory cell cycle signaling or developmental death signals are some of the signals evoking apoptosis [1]. Apoptosis depends on the activation of a proteolytic cascade of pro-caspases into active caspases. These caspases are synthesized in cells as inactive zymogens called as pro-caspases. Pro-caspases are cleaved by pre active caspases at one or two specific aspartic acids splitting them into two subunits, one small and another large. The assembly of two heterodimers of small and large subunits results in the formation of active caspases. The pro-caspases fall into two classes-initiator and executioner [12,13]. Apoptotic stimuli trigger activation of initiator caspases (caspases 2, 8, 9, 10) which in turn cleave and activate the executioner caspases (caspases 3, 6, 7) [14]. The executioner caspases cleave thousands of substrates responsible for the characteristic morphological and biochemical features of apoptotic cells [14]. The three main established routes of apoptosis in mammals are extrinsic, intrinsic and perforin/granzyme pathways [2,15]. Irrespective of the death stimuli or apoptotic paths, all the three routes lead to the activation of executioner caspases 3, 6 and 7 (**Figure 1**).

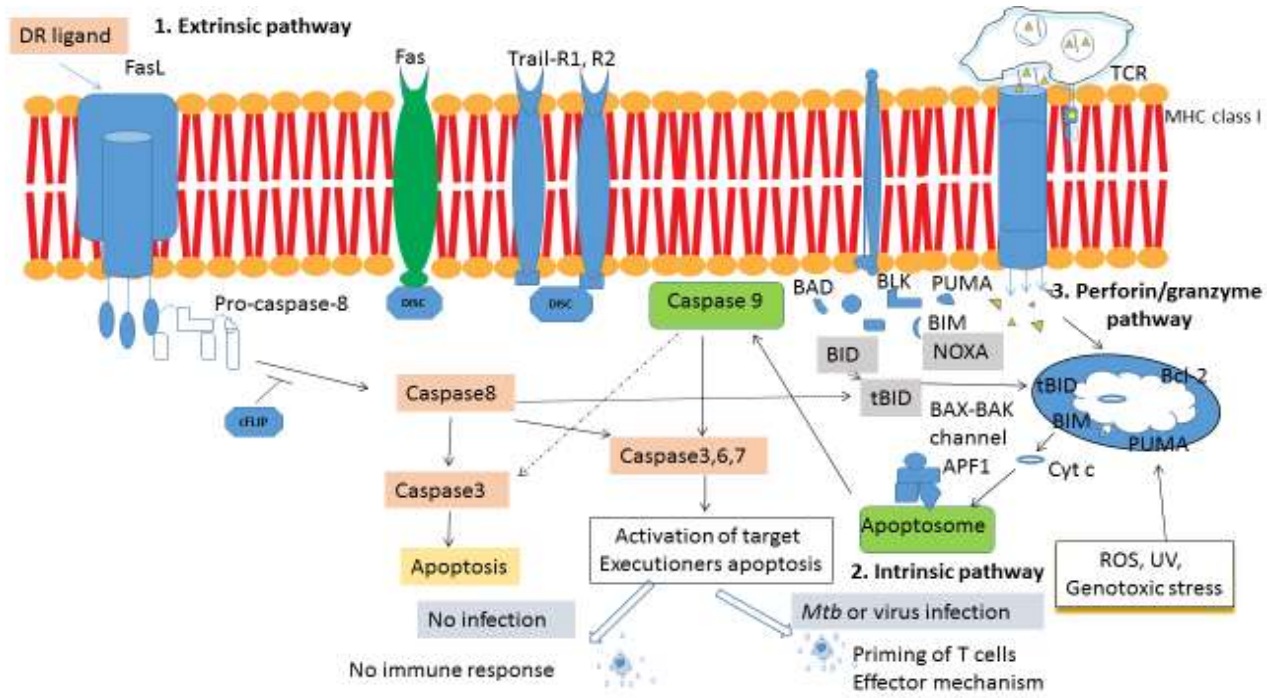

Figure 1. Diagram showing general apoptosis process through three main pathways: Extrinsic (death receptor-mediated viz. FasL, Fas, Trail-R1, and R2) pathway, intrinsic (mitochondria-dependent) pathway and perforin (granzyme)-mediated pathway. The extrinsic pathway starts with the binding of death receptor ligand (DR ligand) to the cell surface death receptors including tissue necrosis factor (TNF) receptor superfamily include CD95 and TNF-related apoptosis-inducing ligand (TRAIL)-R1/-R2, with the rapid activation of the initiator caspase 8. In the intrinsic pathway, stress (reactive oxygen species, ROS, UV, genotoxic stress, etc.) results in the perturbation of mitochondria membrane permeability, release of the proteins such as cytochrome *c* from the inner mitochondrial membrane space. The release is regulated in part by Bcl2 family members, with anti-apoptotic (Bcl2/Bcl−XL/Mcl1) and pro-apoptotic (Bax, Bak, and tBid). Once released, cytochrome *c* binds to apoptotic protease-activating factor 1 (Apaf1), which results in the formation of the Apaf1-caspase 9 apoptosome complex and activation of the initiator caspase 9. The activated initiator Caspases 8 and 9 then activate the effector caspase 3, 6 and7 with normal cell apoptosis or another T-cell effector mechanism. Cytotoxic T lymphocytes (CTL) or natural killer (NK) cells secrete the transmembrane pore-forming molecule perforin and release cytoplasmic granules (Granzyme A/B) into tumor cells or virus-infected cells. Granzyme A activates DNA degradation by DNase NM23-H1while granzyme B cleaves pro-caspase 8, pro-caspase 3 or Bid.

Extrinsic pathway of apoptosis

External apoptotic signaling mediates the activation of transmembrane death receptors that transmit apoptotic signals after binding to extracellular death ligands such as FasL or tumor necrosis factor-α (TNFα) [16]. Death receptors belong to tumor necrosis factor receptor (TNFR) superfamily including TNFR-1, Fas/CD95 and TNF receptor-related apoptosis-inducing ligand (TRAIL) receptors DR-4 and DR-5 [17]. Proteins of TNFR family result in trimerization and activation of intracellular death domain after ligand binding. Adaptor proteins like FADD or TRADD get recruited through their death domains to the death domains of activated death receptors forming death inducing silencing complex (DISC). Death effector domains of FADD or TRADD recruit pro-caspase 8 leading to their autocatalytic activation and release of active caspase 8. Activated caspase 8 then cleaves and activates downstream executioner caspases 3 and 7. In some cases, the extrinsic death signals can crosstalk with an intrinsic pathway through caspase 8-mediated proteolysis of the BH3-only protein Bid. Truncated Bid can translocate to mitochondria and induce the release of cytochrome *c* and assembly of apoptosome triggering activation of pro-caspase 9 [18–20] (Figure 1).

Intrinsic pathway of apoptosis

Intracellular death signals such as DNA damage, oxidative stress, starvation and others trigger intracellular apoptotic pathway. All of these stimuli cause changes in inner mitochondrial membrane resulting in the opening of the mitochondrial permeability transition (MPT) pore, loss of the mitochondrial transmembrane potential ($\Delta\Psi m$) and release of two groups of pro-apoptotic proteins from the intermembrane space into the cytosol [21]. The first group of released proteins constitutes cytochrome *c*, Smac/DIABLO, and the serine protease HtrA2/Omi that promotes caspase-dependent mitochondrial pathway [22–24]. Cytochrome *c* binds and activates Apaf-1 (apoptosis protease activating factor 1) which hydrolyzes bound dATP to dADP. Replacement of dADP with dATP/ATP leads to Apaf-1-cytochrome *c* complex to oligomerize into a wheel like a heptamer called apoptosome. Pro-caspase 9 gets recruited in the apoptosome through its caspase recruitment domain (CARD) [25] and gets activated and cleaved which then triggers activation of downstream executioner caspases (Figure 1) [25]. Smac/DIABLO and the serine protease HtrA2/Omi, on the other hand promote apoptosis by inhibiting IAP (inhibitors of apoptosis) proteins [23,24]. The second group of released proteins includes AIF, endonuclease G, and CAD which translocate to the nucleus and cause DNA fragmentation and condensation of peripheral nuclear chromatin [26–28]. In addition to the release of mitochondrial factors, the loss of the $\Delta\Psi m$ leads to regulation of biochemical homeostasis of the cell viz. ATP synthesis gets stopped, redox molecules like NADH, NADPH and glutathione are oxidized, and reactive oxygen species are enhanced [29–32].

Perforin/ Granzyme pathway of apoptosis

Cytotoxic T lymphocytes (CTL) or natural killer (NK) cells can exert their cytotoxic effects on tumor cells and virus-infected cells by secretion of the transmembrane pore-forming molecule perforin with the subsequent release of cytoplasmic granules through the pore into the target cell [33]. These granules constitute the serine proteases granzyme A and B. Granzyme B can cleave proteins at aspartate residues and thus activate pro-caspase 8 and Bid. Direct activation of pro-caspase 3 and cleavage of ICAD could also be the results of granzyme B. Thus granzyme B dependent routes of apoptosis may be mitochondrial or direct [26]. Granzyme A activates caspase-independent apoptosis [34] (Figure 1). Inside the cell, it enables DNA degradation by DNase NM23-H1. Granzyme A cleaves SET complex (nucleosome assembly protein that usually inhibits DNase NM23-H1 gene) thereby releasing the inhibition of DNase NM23-H1 leading to DNA degradation [34].

Regulation of apoptosis

The components of apoptotic pathways are genetically encoded and ready for action. Most cells are just waiting for the death stimuli to trigger these pathways. Thus a tight regulation of apoptosis is mandatory. B-cell lymphoma-2 (Bcl-2) family proteins play a crucial role in the regulation of apoptosis through their ability to control mitochondrial permeability [35]. Bcl-2 family comprises three subfamilies that contain between one and four Bcl-2 homology (BH) domains. Anti-apoptotic Bcl-2 subfamily includes four BH domains, and most of them are membrane-associated proteins. The pro-apoptotic Bax-like subfamily comprises membrane-associated proteins that lack BH4 domains, while the BH3-only subfamily includes a diverse group of proteins containing only BH3 domains [36]. The mammalian BH3-only protein family currently consists of eight members (Bid, Bad, Bim, Bak, Bik, NOXA, PUMA, and HRK). Among eight members, NOXA, PUMA, and Bid are transcriptionally upregulated by p53. Bid is activated by caspase 8-dependent proteolysis. Phosphorylated Bad is trapped by 14-3-3 protein and sequestered in the cytoplasm. Once Bad is unphosphorylated, it gets freed and is translocated to mitochondria. Bim and BMF are microtubules, and actin microfilaments tethered proteins and disruption of cytoskeleton liberates them [37,38]. The anti-apoptotic Bcl-2 family of proteins (Bcl-2, Bcl-XL, Bcl-W, Mcl1, Bcl2A1 and Bcl-B) blocks apoptosis by preventing BH3-only

Table 1: List of viral and Mtb proteins involved in apoptosis deregulation

Viruses/Mtb (proteins)	Modulation in apoptotic process	References
Adenovirus proteins (E3-10.4K and E3-14.5K)	Reduce Fas presentation, inhibit TNF-mediated apoptosis	[42, 43]
Epstein-Barr virus LMP-1 protein	Acts like constitutively activated TNF receptor	[44]
Myxoma virus protein M-T2	Viral mimic protein of TNF receptor	[45]
Cowpox virus CRM protein	Prevents TNF-mediated apoptosis	[46]
Vaccinia virus protein A53R	Prevents TNF-mediated apoptosis	[47]
HIV-1 Tat	Decreases susceptibility to TRAIL, TNFα, and Fas. Upregulates FasL, Bax, caspase 8 and RCAS-1 expression, upregulates Bcl2 and c-FLIP expression, downregulates caspase 10 expression	[50,68-72]
Herpesviruses: FLICE	Inhibits DISC formation	[51]
Human Cytomegalovirus: vICA	Inhibits caspase 8	[52]
SV40 virus large T antigen	Binds to and sequesters p53	[53]
Human papillomavirus E6 protein	p53 ubiquitination and degradation	[55]
Adenovirus E1B-55K protein	p53 ubiquitination and degradation	[56]
Adenovirus E1B-19K	Binds to Bak preventing Bax-Bak oligomerization	[56]
Human herpesviruses: Bcl-2 ortholog	Blocks the mitochondrial release of cytochrome *c*	[59]
Epstein-Barr virus: Bcl-2 ortholog	Blocks the mitochondrial release of cytochrome *c*	[60]
Kaposi's sarcoma-associated γ-herpes virus: Bcl-2 ortholog	Blocks the mitochondrial release of cytochrome *c*	[59]
Human CMV protein: vMIA	Inhibits Fas-mediated apoptosis	[61,62]
Poxviruses serpin CrmA	Suppresses caspase 1 and 8, inhibits TNF and Fas-mediated apoptosis	[63]
Baculovirus protein p35	Inhibits caspases 1, 3, 6, 7, 8 and 10	[64,65]
African swine flu virus: vIAP	Inhibits caspase 3	[66]
HIV-1 gp120	Syncytia formation, upregulates Fas, FasL, and TNFα expression, upregulates TRAIL receptors: DR4 and DR5, acts as a molecular mimic of Fas, reduces expression of Bcl2, phosphorylates mTOR and p53, increases expression of PUMA and activates p38	[48,67]
HIV-1 Nef	Increases the membrane expression of TNF	[49]
Hepatitis B virus pX protein	Inactivates p53	[57]
West Nile capsid protein	Binds to and sequesters p53	[54]
Arenaviruses matrix protein Z	Activation of BH3-only proteins?, an indirect interaction with p53 and PI3K/Akt with the help of PML?	[74-78]
Enterovirus 71 2B protein	Direct interaction with and activation of Bax	[80,81]
Mtb proteins (Mcl-1, A1?)	Upregulates TNF, Fas, and caspase 8 expression, stimulates ROS-dependent activation of apoptosis signal-regulating kinase, phosphorylates and degrades FLIP, MOMP-mediated apoptosis, upregulates FLIP expression, secretes more sTNFR2, increases expression of anti-apoptotic protein Bcl-w, inhibition of the pro-apoptotic protein Bad	[101,104-106, 113-115]

? Refers to mechanism not yet verified.

protein induced oligomerization of the pro-apoptotic Bcl-2 proteins Bax and Bak in the mitochondrial outer membrane. Some BH3-only proteins (Bid and Bim) interact with almost all anti-apoptotic Bcl-2 proteins whereas others (NOXA) interact only with specific Bcl-2 members [35,37,38].

In conclusion, under distinct apoptotic stress signals, BH3-only proteins interfere the fine-tuned balance of homo or hetero-oligomerization between pro-apoptotic members Bax/Bak and anti-apoptotic members Bcl-2/Bcl-XL and release the intermembrane space proteins like cytochrome *c* to trigger apoptosis.IAPs (inhibitors of apoptosis proteins) are a family of proteins having anti-apoptotic activity [32]. Including NAIP, c-IAP1, c-IAP2, XIAP, and survivin, there are eight human IAP homologs. XIAP, c-IAP1, and c-IAP2 directly inhibit caspases 3, 7, and 9. Smac/Diablo, when released from mitochondria, binds to XIAP and releases caspases from XIAP-caspase complex thereby enabling their activation [39,40]. The cellular FLICE-like inhibitory proteins (c-FLIPs) inhibit activation of caspase 8 and thus prevent apoptosis [34].

Virus-mediated modulation of apoptosis

In most cases of viral infections, immune and inflammatory responses, as well as apoptosis of the infected host cell, are triggered. Meanwhile, some viruses utilize apoptosis as a mechanism of killing cells and spreading virus by targeting a variety of crucial steps in the pathways that block or delay apoptosis. Thus viral infection elicits host cell apoptosis as a part of host immune defense or viral survival component [41].

Virus modulates the extrinsic pathway of apoptosis

Many viruses can efficiently modulate the extrinsic pathway of apoptosis. Adenovirus proteins E3-10.4K and E3-14.5K reduce the presentation of Fas molecules on the surface of the cells that results in resistance to Fas-mediated cell death [42]. These proteins also resist TNF-mediated apoptosis [43]. Epstein-Barr virus LMP-1 (latent membrane-1) protein acts like constitutively activated TNF receptor which interacts with TNF receptor-associated death domain (TRADD) protein [44]. The myxoma virus protein M-T2, a viral mimic protein of TNF receptor, Cowpox virus cytokine response modifying (CRM) proteins and vaccinia virus protein A53R inhibits TNF-mediated apoptosis [45, 46, 47]. Membrane-bound HIV-1 gp120 induces apoptosis through syncytia formation while it triggers apoptosis by various mechanisms like upregulation of Fas, FasL, and TNFα expression, upregulation of TRAIL receptors DR4 and DR5, and acting as a molecular mimic of Fas [48]. HIV-1 Nef protein downregulates the expression of CD4 and MHC I molecules but heightens the membrane expression of TNF and related cytokines [49]. HIV-1 Tat mediates apoptotic resistance in the infected cells by decreasing susceptibility to TRAIL, TNFα, and Fas, but it reconciles apoptosis in uninfected bystander cells by upregulation of FasL [50]. Various herpes viruses encode viral FLICE-like inhibitory proteins (FLIPs), which contain death effector domain but lack caspase activity, inhibit extrinsic apoptotic pathway at the point of DISC formation [51]. The human cytomegalovirus encodes vICA, which associates with caspase 8 and blocks its activation [52] (**Table 1**).

Virus modulates the intrinsic pathway of apoptosis

Many viruses alter apoptosis utilizing the tumor suppressor p53. SV40 virus large T antigen and West Nile capsid protein binds to p53 and sequesters it in an inactive complex [53,54]. Moreover, Human papillomavirus E6 protein and adenovirus E1B-55K protein promote ubiquitin mediated degradation of p53 [55,56] and Hepatitis B virus pX protein binds and inactivates p53 [57]. Virus-encoded orthologs of anti-apoptotic Bcl2 proteins are also crucial players in the modulation of apoptosis. Adenovirus E1B-19K is similar to Bcl2 which binds to Bak preventing Bax-Bak oligomerization [58]. Human herpes viruses, Epstein-Barr virus and Kaposi's sarcoma-

associated γ-herpes virus use Bcl-2 orthologs to block the mitochondrial release of cytochrome *c* [59,60]. Although human cytomegalovirus (CMV) protein vMIA shares no sequence homology to Bcl2, it is functionally similar to Bcl-2 and inhibits Fas-mediated apoptosis [61,62]. Some viruses use IAP orthologs that can inhibit caspases. For example, Poxviruses serpin CrmA suppresses caspase 1 and 8 and inhibits TNF and Fas-mediated apoptosis [63]. Likewise, African swine flu virus produces vIAP that inhibits caspase 3 and Baculovirus protein p35 is another vIAP with a potential to inhibit caspases 1, 3, 6, 7, 8 and 10 [64,65,66]. HIV-1 gp120 triggers apoptosis by reduced expression of Bcl2, phosphorylation of mTOR and p53, increased expression of pro-apoptotic protein PUMA and activation of p38 [67]. HIV-1 Tat inhibits apoptosis in infected cells by upregulation of Bcl2 and c-FLIP expression [68,69] and downregulation of caspase 10 expression [70]. The same protein triggers apoptosis in bystander cells by upregulation of Bax, caspase 8 and RCAS-1 expression [71,72], and Bim-mediated intrinsic apoptosis [73]. Matrix protein Z of some arenaviruses (New World arenavirus, Tacarible virus (TCRV), and the attenuated vaccine strain of Junín virus (JUNV) Candid #1) activates caspase 9 thereby triggering the intrinsic apoptotic pathway [74,75]. Though the exact molecular mechanism of viral protein Z-mediated apoptosis is still not clear, *in vitro* experiments suggest a direct activation of BH3-only proteins and an indirect interaction with proteins like p53 and PI3K/Akt through cellular oncoprotein promyelocyte leukemia protein (PML) [74–76]. The Old World arenaviruses, the lymphocytic choriomeningitis virus (LCMB) and Lassa virus (LASV) do not cause apoptosis of infected cells [77,78]. Caspase-mediated cleavage of nucleoproteins (NPs) of Old World areanviruses generates multiple truncated isoforms of NPs [74,79]. A decoy function of NPs has been proposed in which the cleavage of highly expressed NPs within the cell suppresses the cellular targets of caspases thereby inhibiting the apoptosis of the infected cell [74]. Enterovirus 71 2B protein directly interacts with and activates the proapoptotic protein Bax leading to the activation of mitochondrial pathway of apoptosis [80,81] (**Table 1**).

Mycobacterium-mediated modulation of apoptosis

Bacterial pathogens are known to have anti-apoptotic mechanisms. *Mycobacterium tuberculosis* (Mtb) causes persistent infection indicating that it employs effective mechanisms to inhibit host cell death [82]. Published studies highlight both pro-apoptotic as well as anti-apoptotic capabilities of virulent Mtb [83,84], however the underlining molecular mechanisms are still not well understood. Though there is a lack of published data favoring Mtb-mediated apoptosis of host cells, increased apoptosis of primary human macrophages or human macrophage-like cell lines (U937 and THP1) were reported upon infection with virulent Mtb *in vitro* [85–87]. Human alveolar macrophage-derived from bronchoalveolar lavage of tuberculosis patients also showed increased apoptotic death compared to healthy subjects [88,89]. Apoptosis of Mtb infected cells accompanied by the recruitment of uninfected macrophages through upregulation of MMP9 on epithelial cells surrounding the granuloma helps in the dissemination of the bacteria [90]. In the studies involving the zebrafish and mouse lung models, the pro-apoptotic nuoG Mtb mutant induced enhance innate response, longer survival and rapid dissemination of the bacteria [91,92]. Thus, evidence suggests that host cell apoptosis is crucial for host resistance to Mtb infection. Considerable less apoptosis of human alveolar macrophage or macrophage-like cell lines when infected with virulent Mtb compared to infection with less virulent strains was reported [93–96]. Furthermore, fact that inhibition of apoptosis of human and murine macrophages by Apoptosis-inducing species *M. kansaii* after over-expression of Mtb-nuoG/SecA2/PknE [97–99] and resistance to FasL and TNFα-mediated apoptosis of Mtb

infected cells provide the evidence that Mtb inhibits host cell apoptosis [100].

Mtb modulates the extrinsic pathway of apoptosis

Gene expression profiling study suggests that numerous apoptosis-related genes are down-regulated in active tuberculosis patients compared to latently infected subjects. Though expressions of TNF, Fas, and caspase 8 upregulate in active tuberculosis patients, simultaneous marked expression of FLIP, inhibits host cell apoptosis [101]. Mtb infected macrophages are known to secrete more soluble TNF receptor 2 (sTNFR2) which binds to TNFα thereby inhibiting its binding with the TNFR1 [100,102–104]. Upon infection with Mtb, TNF production in the mouse cell line RAW264 stimulates ROS-dependent activation of apoptosis signal-regulating kinase thereby phosphorylating FLIP [105]. Ubiquitin-proteasome-mediated degradation of phosphorylated FLIP activates caspase 8 leading to apoptosis [105] (**Table 1**).

Mtb modulates the intrinsic pathway of apoptosis

Mtb infection upregulates the expression of anti-apoptotic genes like *mcl-1* and *A1*, both of which encodes for anti-apoptotic Bcl-2-like proteins [106–110]. Alternative splicing gives rise to two isoforms of Myloid cell leukemia-1 (Mcl-1) protein. One is the anti-apoptotic full length Mcl-1L that possesses BH domains 1, 2 and 3 and a transmembrane domain. Another is the pro-apoptotic short variant Mcl-1S that lacks BH1, BH2 and the transmembrane domain. Mcl-1S dimerizes with and antagonizes the function of Mcl-1L thereby regulates the mitochondrial permeability [109,111]. Furthermore, chemical inhibition of Mcl-1 in mouse peritoneal macrophages infected with Mtb significantly triggered apoptosis [112]. It will be interesting to dissect the role of both isoforms of Mcl-1 in Mtb-mediated apoptosis evasion. Also, the expression of anti-apoptotic protein Bcl-w gets upregulated [113], while the inactivation of the pro-apoptotic Bad protein occurs upon Mtb-H37Rv infection [114]. Infection of macrophages with attenuated Mtb leads to MOMP-mediated apoptosis without MPT induction [10,115] (**Table 1**). In contrast, macrophages infected with virulent Mtb induce both MOMP and MPT causing irreversible mitochondrial swelling leading to necrosis [115].

Conclusion

Programmed cell death via apoptosis is crucial in maintaining cells in health and pathological conditions. Both viral and Mtb infections modulate the apoptotic pathways of infected as well as neighboring bystander cells. Though the majority of virally infected cells undergo apoptosis favoring viral dissemination, viral proteins help specific host cells to evade apoptosis thereby preferring viral persistence. Mtb infection prominently evades host cell apoptosis leading to the persistent survival of the pathogen. Understanding the molecular mechanisms of deregulation of apoptosis in viral and Mtb infection may provide insights into revealing new targets for curing these pathological conditions.

Conflict of Interest

Both authors declare that there is no conflict of interest.

Authors Contribution

Both authors contributed equally to this work

References

1. Elmore S. Apoptosis: **A Review of Programmed Cell Death.** *Toxicol Pathol*. 2007 **35**(4):495–516.
2. Taylor RC, Cullen SP, Martin SJ: **Apoptosis: controlled demolition at the cellular level**. *Nat Rev Mol Cell Biol*. 2008 **9**(3):231–241.
3. Labi V, Erlacher M. **How cell death shapes cancer**. *Cell Death Dis*. 2015 **6**(3):e1675.
4. Singh N: **Apoptosis in health and disease and modulation of apoptosis for therapy: An overview.** *Indian J Clin Biochem* 2007 **22**(2):6–16.
5. Mattson MP: **Apoptosis in neurodegenerative disorders.** *Nat Rev Mol Cell Biol*. 2000 **1**(2):120–130.
6. Barber GN; **Host defense, viruses and apoptosis.** *Cell Death Differ*. 2001 **8**(2):113–126.
7. Kühtreiber WM, Hayashi T, Dale EA, Faustman DL: **Central role of defective apoptosis in**

autoimmunity. *J Mol Endocrinol.* 2003 **31**(3):373–399.
8. Lopez-Neblina F, Toledo AH, Toledo-Pereyra LH: **Molecular biology of apoptosis in ischemia and reperfusion**. *J Investig Surg Off J Acad Surg Res.* 2005 **18**(6):335–350.
9. Hardwick JM: **Apoptosis in viral pathogenesis**. *Cell Death Differ.* 2001 **8**(2):109–110.
10. Behar SM, Martin CJ, Booty MG, Nishimura T, Zhao X, Gan H-X, et al: **Apoptosis is an innate defense function of macrophages against Mycobacterium tuberculosis.** *Mucosal Immunol.* 2011 **4**(3):279–287.
11. Briken V: **Mycobacterium tuberculosis genes involved in regulation of host cell death**. *Adv Exp Med Biol.* 2013 **783**:93–102.
12. McIlwain DR, Berger T, Mak TW: **Caspase Functions in Cell Death and Disease.** *Cold Spring Harb Perspect Biol.* 2013 **5**(4):a008656.
13. Shi Y: **Mechanisms of Caspase Activation and Inhibition during Apoptosis**. *Mol Cell.* 2002 **9**(3):459–470.
14. Slee EA, Adrain C, Martin SJ: **Executioner Caspase-3, -6, and -7 Perform Distinct, Non-redundant Roles during the Demolition Phase of Apoptosis**. *J Biol Chem.* 2001 **276**(10):7320–7326.
15. Arandjelovic S, Ravichandran KS: **Phagocytosis of apoptotic cells in homeostasis.** *Nat Immunol.* 2015 **16**(9):907–917.
16. Sayers TJ: **Targeting the extrinsic apoptosis signaling pathway for cancer therapy**. *Cancer Immunol Immunother.* 2011 **60**(8):1173–1180.
17. Schmitz I, Kirchhoff S, Krammer PH: **Regulation of death receptor-mediated apoptosis pathways**. *Int J Biochem Cell Biol.* 2000;**32**(11-12):1123–1136.
18. Strasser A, Jost PJ, Nagata S: **The many roles of FAS receptor signaling in the immune system**. *Immunity.* 2009 **30**(2):180–192.
19. Keller N, Grütter MG, Zerbe O: **Studies of the molecular mechanism of caspase-8 activation by solution NMR.** *Cell Death Differ.* 2010 **17**(4):710–718.
20. Kominami K, Nakabayashi J, Nagai T, Tsujimura Y, Chiba K, Kimura H, *et al*: **The molecular mechanism of apoptosis upon caspase-8 activation: Quantitative experimental validation of a mathematical model.** *Biochim Biophys Acta BBA - Mol Cell Res.* 2012 **1823**(10):1825–1840.
21. Zamzami N, Larochette N, Kroemer G: **Mitochondrial permeability transition in apoptosis and necrosis**. *Cell Death Differ.* 2005 **12**(S2):1478–1480.
22. Ott M, Robertson JD, Gogvadze V, Zhivotovsky B, Orrenius S: **Cytochrome c release from mitochondria proceeds by a two-step process**. *Proc Natl Acad Sci.* 2002 **99**(3):1259–1263.
23. Adrain C, Creagh EM, Martin SJ: **Apoptosis-associated release of Smac/DIABLO from mitochondria requires active caspases and is blocked by Bcl-2.** *EMBO J.* 2001 **20**(23):6627–6636.
24. Martins LM, Iaccarino I, Tenev T, Gschmeissner S, Totty NF, Lemoine NR, et al: **The Serine Protease Omi/HtrA2 Regulates Apoptosis by Binding XIAP through a Reaper-like Motif**. *J Biol Chem.* 2002 **277**(1):439–444.
25. Cain K, Bratton SB, Cohen GM: **The Apaf-1 apoptosome: a large caspase-activating complex.** *Biochimie.* 2002 **84**(2-3):203–214.
26. Candé C, Cohen I, Daugas E, Ravagnan L, Larochette N, Zamzami N, *et al*: **Apoptosis-inducing factor (AIF): a novel caspase-independent death effector released from mitochondria.** *Biochimie.* 2002 **84**(2-3):215–222.
27. Li LY, Luo X, Wang X: **Endonuclease G is an apoptotic DNase when released from mitochondria.** *Nature.* 2001 **412**(6842):95–99.
28. Enari M, Sakahira H, Yokoyama H, Okawa K, Iwamatsu A, Nagata S: **A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD.** *Nature.* 1998 **391**(6662):43–50.
29. Tsujimoto Y, Shimizu S: **Role of the mitochondrial membrane permeability transition in cell death.** *Apoptosis Int J Program Cell Death.* 2007 **12**(5):835–840.
30. Jo W-S, Jeong M-H, Jin Y-H, Jang J-Y, Nam B-H, Son S-H, *et al*: **Loss of mitochondrial membrane potential and caspase activation enhance apoptosis in irradiated K562 cells treated with herbimycin A**. *Int J Radiat Biol.* 2005 **81**(7):531–543.
31. Leist M, Single B, Castoldi AF, Kühnle S, Nicotera P: **Intracellular Adenosine Triphosphate (ATP) Concentration: A Switch in the Decision Between Apoptosis and Necrosis**. *J Exp Med.* 1997 **185**(8):1481–1486.
32. Chen Q, Crosby M, Almasan A: **Redox Regulation of Apoptosis before and after Cytochrome C Release.** *Korean J Biol Sci.* 2003 **7**(1):1–9.
33. Lieberman J: **Granzyme A activates another way to die**. *Immunol Rev.* 2010 **235**(1):93–104.
34. Shresta S, Graubert TA, Thomas DA, Raptis SZ, Ley TJ: **Granzyme A Initiates an Alternative Pathway for Granule-Mediated Apoptosis**. *Immunity.* 1999 **10**(5):595–605.
35. Burlacu A: **Regulation of apoptosis by Bcl-2 family proteins**. *J Cell Mol Med* 2003;**7**(3):249–257.
36. Mayer B, Oberbauer R: **Mitochondrial regulation of apoptosis.** *News Physiol Sci Int J Physiol Prod Jointly Int Union Physiol Sci Am Physiol Soc.* 2003 **18**:89–94.

37. Tsujimoto Y: **Role of Bcl-2 family proteins in apoptosis: apoptosomes or mitochondria?** *Genes Cells Devoted Mol Cell Mech.* 1998 **3**(11):697–707.
38. Shamas-Din A, Kale J, Leber B, Andrews DW: **Mechanisms of Action of Bcl-2 Family Proteins.** *Cold Spring Harb Perspect Biol.* 2013 **5**(4). doi:10.1101/cshperspect.a008714.
39. Paulsen M, Ussat S, Jakob M, Scherer G, Lepenies I, Schütze S, et al: **Interaction with XIAP prevents full caspase-3/-7 activation in proliferating human T lymphocytes**. *Eur J Immunol.* 2008 **38**(7):1979–1987.
40. Chang DW, Xing Z, Pan Y, Algeciras-Schimnich A, Barnhart BC, Yaish-Ohad S, *et al*: **c-FLIP(L) is a dual function regulator for caspase-8 activation and CD95-mediated apoptosis.** *EMBO J.* 2002 **21**(14):3704–3714.
41. Timilsina U, Gaur R: **Modulation of apoptosis and viral latency – an axis to be well understood for successful cure of human immunodeficiency virus.** *J Gen Virol.* 2016 **97**(4):813–824.
42. Elsing A, Burgert H-G: **The adenovirus E3/10.4K–14.5K proteins down-modulate the apoptosis receptor Fas/Apo-1 by inducing its internalization.** *Proc Natl Acad Sci.* 1998 **95**(17):10072–10077.
43. Krajcsi P, Dimitrov T, Hermiston TW, Tollefson AE, Ranheim TS, Vande Pol SB, *et al*: **The adenovirus E3-14.7K protein and the E3-10.4K/14.5K complex of proteins, which independently inhibit tumor necrosis factor (TNF)-induced apoptosis, also independently inhibit TNF-induced release of arachidonic acid.** *J Virol.* 1996 **70**(8):4904–4913.
44. Gires O, Zimber-Strobl U, Gonnella R, Ueffing M, Marschall G, Zeidler R, *et al*: **Latent membrane protein 1 of Epstein-Barr virus mimics a constitutively active receptor molecule**. *EMBO J.* 1997 **16**(20):6131–6140.
45. McFadden G, Schreiber M, Sedger L: **Myxoma T2 protein as a model for poxvirus TNF receptor homologs**. *J Neuroimmunol.* 1997 **72**(2):119–126.
46. Veyer DL, Maluquer de Motes C, Sumner RP, Ludwig L, Johnson BF, Smith GL: **Analysis of the anti-apoptotic activity of four vaccinia virus proteins demonstrates that B13 is the most potent inhibitor in isolation and during viral infection**. *J Gen Virol.* 2014 **95**(Pt 12):2757–2768.
47. Zhai D, Yu E, Jin C, Welsh K, Shiau C, Chen L, et al: **Vaccinia virus protein F1L is a caspase-9 inhibitor**. *J Biol Chem.* 2010 **285**(8):5569–5580.
48. Perfettini J-L, Castedo M, Roumier T, Andreau K, Nardacci R, Piacentini M, *et al*: **Mechanisms of apoptosis induction by the HIV-1 envelope**. *Cell Death Differ.* 2005 **12 Suppl 1**:916–923.
49. Lama J, Ware CF: **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.* 2000 **74**(20):9396–9402.
50. Kumar A, Abbas W, Herbein G: **TNF and TNF Receptor Superfamily Members in HIV infection: New Cellular Targets for Therapy?** *Mediators Inflamm.* 2013 **2013**:e484378.
51. Jerome KR, Fox R, Chen Z, Sears AE, Lee H, Corey L: **Herpes Simplex Virus Inhibits Apoptosis through the Action of Two Genes, Us5 and Us3**. *J Virol.* 1999 **73**(11):8950–8957.
52. Skaletskaya A, Bartle LM, Chittenden T, McCormick AL, Mocarski ES, Goldmacher VS: **A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation.** *Proc Natl Acad Sci.* 2001 **98**(14):7829–7834.
53. Carbone M, Rizzo P, Grimley PM, Procopio A, Mew DJY, Shridhar V, *et al*: **Simian virus-40 large-T antigen binds p53 in human mesotheliomas**. *Nat Med.* 1997 **3**(8):908–912.
54. Yang M-R, Lee SR, Oh W, Lee E-W, Yeh J-Y, Nah J-J, et al: **West Nile virus capsid protein induces p53-mediated apoptosis via the sequestration of HDM2 to the nucleolus**. *Cell Microbiol.* 2008 **10**(1):165–176.
55. Lechner MS, Laimins LA: **Inhibition of p53 DNA binding by human papillomavirus E6 proteins**. *J Virol.* 1994 **68**(7):4262–4273.
56. Querido E, Blanchette P, Yan Q, Kamura T, Morrison M, Boivin D, et al: **Degradation of p53 by adenovirus E4orf6 and E1B55K proteins occurs via a novel mechanism involving a Cullin-containing complex.** *Genes Dev.* 2001 **15**(23):3104–3117.
57. Chirillo P, Pagano S, Natoli G, Puri PL, Burgio VL, Balsano C, *et al*: **The hepatitis B virus X gene induces p53-mediated programmed cell death**. *Proc Natl Acad Sci.* 1997 **94**(15):8162–8167.
58. Cuconati A, Degenhardt K, Sundararajan R, Anschel A, White E: **Bak and Bax Function To Limit Adenovirus Replication through Apoptosis Induction.** *J Virol.* 2002 **76**(9):4547–4558.
59. Cheng EH-Y, Nicholas J, Bellows DS, Hayward GS, Guo H-G, Reitz MS, *et al*: **A Bcl-2 homolog encoded by Kaposi sarcoma-associated virus, human herpesvirus 8, inhibits apoptosis but does not heterodimerize with Bax or Bak**. *Proc Natl Acad Sci.* 1997 **94**(2):690–694.
60. Marshall WL, Yim C, Gustafson E, Graf T, Sage DR, Hanify K, *et al*: **Epstein-Barr Virus Encodes a Novel Homolog of the bcl-2 Oncogene That Inhibits Apoptosis and Associates with Bax and Bak**. *J Virol.* 1999 **73**(6):5181–5185.
61. Arnoult D, Bartle LM, Skaletskaya A, Poncet D, Zamzami N, Park PU, *et al:* **Cytomegalovirus cell death suppressor vMIA blocks Bax- but not Bak-mediated apoptosis by binding and**

sequestering Bax at mitochondria. *Proc Natl Acad Sci U S A*. 2004 **101**(21):7988–7993.
62. Terhune S, Torigoi E, Moorman N, Silva M, Qian Z, Shenk T, *et al*: **Human Cytomegalovirus UL38 Protein Blocks Apoptosis**. *J Virol*. 2007;**81**(7):3109–3123.
63. Turner S, Kenshole B, Ruby J: **Viral modulation of the host response via crmA/SPI-2 expression.** *Immunol Cell Biol*. 1999 **77**(3):236–241.
64. Vier J, Fürmann C, Häcker G: **Baculovirus P35 protein does not inhibit caspase-9 in a cell-free system of apoptosis**. *Biochem Biophys Res Commun*. 2000 **276**(3):855–861.
65. Qiao Zhou, Joseph F. Krebs, Scott J. Snipas, Annamarie Price, Emad S. Alnemri ⊥, Kevin J. Tomaselli, *et al*: **Interaction of the Baculovirus Anti-apoptotic Protein p35 with Caspases. Specificity, Kinetics, and Characterization of the Caspase/p35 Complex†**. 1998. http://pubs.acs.org/doi/abs/10.1021/bi980893w (accessed 5 Dec 2017).
66. Nogal ML, González de Buitrago G, Rodríguez 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):2535–2543.
67. Badley AD, Pilon AA, Landay A, Lynch DH: **Mechanisms of HIV-associated lymphocyte apoptosis**. *Blood* 2000 **96**(9):2951–2964.
68. Zhang M, Li X, Pang X, Ding L, Wood O, Clouse KA, *et al*: **Bcl-2 upregulation by HIV-1 tat during infection of primary human macrophages in culture.** *J Biomed Sci* 2002 **9**(2):133–139.
69. López-Huertas MR, Mateos E, Sánchez Del Cojo M, Gómez-Esquer F, Díaz-Gil G, Rodríguez-Mora S, *et al*: **The presence of HIV-1 Tat protein second exon delays fas protein-mediated apoptosis in CD4+ T lymphocytes: a potential mechanism for persistent viral production**. *J Biol Chem* 2013 **288**(11):7626–7644.
70. Gibellini D, Re MC, Ponti C, Vitone F, Bon I, Fabbri G, *et al*: **HIV-1 Tat protein concomitantly down-regulates apical caspase-10 and up-regulates c-FLIP in lymphoid T cells: a potential molecular mechanism to escape TRAIL cytotoxicity**. *J Cell Physiol* 2005 **203**(3):547–556.
71. Macho A, Calzado MA, Jiménez-Reina L, Ceballos E, León J, Muñoz E: **Susceptibility of HIV-1-TAT transfected cells to undergo apoptosis. Biochemical mechanisms.** *Oncogene* 1999 **18**(52):7543–7551.
72. Bartz SR, Emerman M: **Human immunodeficiency virus type 1 Tat induces apoptosis and increases sensitivity to apoptotic signals by up-regulating FLICE/caspase-8**. *J Virol* 1999 **73**(3):1956–1963.
73. Chen D, Wang M, Zhou S, Zhou Q: **HIV-1 Tat targets microtubules to induce apoptosis, a process promoted by the pro-apoptotic Bcl-2 relative Bim**. *EMBO J* 2002 **21**(24):6801–6810.
74. Meyer B, Groseth A: **Apoptosis during arenavirus infection: mechanisms and evasion strategies.** *Microbes Infect* 2017 doi:10.1016/j.micinf.2017.10.002.
75. Wolff S, Groseth A, Meyer B, Jackson D, Strecker T, Kaufmann A, *et al*: **The New World arenavirus Tacaribe virus induces caspase-dependent apoptosis in infected cells.** *J Gen Virol* 2016 **97**(4):855–866.
76. Salomoni P, Bellodi C. **New insights into the cytoplasmic function of PML**. *Histol Histopathol* 2007 **22**(8):937–946.
77. Pythoud C, Rothenberger S, Martínez-Sobrido L, de la Torre JC, Kunz S. **Lymphocytic Choriomeningitis Virus Differentially Affects the Virus-Induced Type I Interferon Response and Mitochondrial Apoptosis Mediated by RIG-I/MAVS**. *J Virol* 2015 **89**(12):6240–6250.
78. Baize S, Kaplon J, Faure C, Pannetier D, Georges-Courbot M-C, Deubel V. **Lassa virus infection of human dendritic cells and macrophages is productive but fails to activate cells**. *J Immunol Baltim Md 1950* 2004 **172**(5):2861–2869.
79. Clegg JC, Lloyd G. **Structural and cell-associated proteins of Lassa virus**. *J Gen Virol* 1983 **64**(Pt 5):1127–1136.
80. Han X, Cong H. **Enterovirus 71 induces apoptosis by directly modulating the conformational activation of pro-apoptotic protein Bax**. *J Gen Virol* 2017 **98**(3):422–434.
81. Cong H, Du N, Yang Y, Song L, Zhang W, Tien P. **Enterovirus 71 2B Induces Cell Apoptosis by Directly Inducing the Conformational Activation of the Proapoptotic Protein Bax.** *J Virol* 2016 **90**(21):9862–9877.
82. Pérez-Lago L, Navarro Y, Montilla P, Comas I, Herranz M, Rodríguez-Gallego C, *et al*. **Persistent Infection by a Mycobacterium tuberculosis Strain That Was Theorized To Have Advantageous Properties, as It Was Responsible for a Massive Outbreak**. *J Clin Microbiol* 2015;**53**(11):3423–3429.
83. Briken V, Miller JL. **Living on the edge: Inhibition of Host Cell Apoptosis by Mycobacterium tuberculosis**. *Future Microbiol* 2008 **3**:415–422.
84. Lam A, Prabhu R, Gross CM, Riesenberg LA, Singh V, Aggarwal S. **Role of apoptosis and autophagy in tuberculosis.** *Am J Physiol Lung Cell Mol Physiol* 2017 **313**(2):L218–L229.
85. Danelishvili L, McGarvey J, Li Y-J, **Bermudez LE. Mycobacterium tuberculosis infection causes different levels of apoptosis and necrosis in**

human macrophages and alveolar epithelial cells. *Cell Microbiol* 2003 **5**(9):649–660.
86. Ciaramella A, Cavone A, Santucci MB, Garg SK, Sanarico N, Bocchino M, *et al*. **Induction of apoptosis and release of interleukin-1 beta by cell wall-associated 19-kDa lipoprotein during the course of mycobacterial infection**. *J Infect Dis* 2004 **190**(6):1167–1176.
87. Arcila ML, Sánchez MD, Ortiz B, Barrera LF, García LF, Rojas M. **Activation of apoptosis, but not necrosis, during Mycobacterium tuberculosis infection correlated with decreased bacterial growth: role of TNF-alpha, IL-10, caspases and phospholipase A2**. *Cell Immunol* 2007 **249**(2):80–93.
88. Placido R, Mancino G, Amendola A, Mariani F, Vendetti S, Piacentini M, *et al*. **Apoptosis of human monocytes/macrophages in Mycobacterium tuberculosis infection**. *J Pathol* 1997 **181**(1):31–38.
89. Keane J, Balcewicz-Sablinska MK, Remold HG, Chupp GL, Meek BB, Fenton MJ, *et al*. **Infection by Mycobacterium tuberculosis promotes human alveolar macrophage apoptosis**. *Infect Immun* 1997 **65**(1):298–304.
90. Chen W-L, Sheu J-R, Chen R-J, Hsiao S-H, Hsiao C-J, Chou Y-C, *et al*. **Mycobacterium tuberculosis Upregulates TNF-α Expression via TLR2/ERK Signaling and Induces MMP-1 and MMP-9 Production in Human Pleural Mesothelial Cells**. *PLoS ONE* 2015 **10**(9). doi:10.1371/journal.pone.0137979.
91. Volkman HE, Pozos TC, Zheng J, Davis JM, Rawls JF, Ramakrishnan L. **Tuberculous granuloma induction via interaction of a bacterial secreted protein with host epithelium**. *Science* 2010 **327**(5964):466–469.
92. Srinivasan L, Ahlbrand S, Briken V. **Interaction of Mycobacterium tuberculosis with Host Cell Death Pathways.** *Cold Spring Harb Perspect Med* 2014 **4**(8). doi:10.1101/cshperspect.a022459.
93. Keane J, Remold HG, Kornfeld H. **Virulent Mycobacterium tuberculosis strains evade apoptosis of infected alveolar macrophages**. *J Immunol Baltim Md 1950* 2000;**164**(4):2016–2020.
94. Riendeau CJ, Kornfeld H. **THP-1 cell apoptosis in response to Mycobacterial infection.** *Infect Immun* 2003 **71**(1):254–259.
95. Dhiman R, Raje M, Majumdar S. **Differential expression of NF-kappaB in mycobacteria infected THP-1 affects apoptosis.** *Biochim Biophys Acta* 2007 **1770**(4):649–658.
96. Zhang J, Jiang R, Takayama H, Tanaka Y. **Survival of virulent Mycobacterium tuberculosis involves preventing apoptosis induced by Bcl-2 upregulation and release resulting from necrosis in J774 macrophages.** *Microbiol Immunol* 2005 **49**(9):845–852.
97. Velmurugan K, Chen B, Miller JL, Azogue S, Gurses S, Hsu T, *et al*. **Mycobacterium tuberculosis nuoG is a virulence gene that inhibits apoptosis of infected host cells**. *PLoS Pathog* 2007 **3**(7):e110.
98. Hinchey J, Lee S, Jeon BY, Basaraba RJ, Venkataswamy MM, Chen B, *et al*. **Enhanced priming of adaptive immunity by a proapoptotic mutant of Mycobacterium tuberculosis.** *J Clin Invest* 2007 **117**(8):2279–2288.
99. Jayakumar D, Jacobs WR, Narayanan S. **Protein kinase E of Mycobacterium tuberculosis has a role in the nitric oxide stress response and apoptosis in a human macrophage model of infection.** *Cell Microbiol* 2008 **10**(2):365–374.
100. Oddo M, Renno T, Attinger A, Bakker T, MacDonald HR, Meylan PR. **Fas ligand-induced apoptosis of infected human macrophages reduces the viability of intracellular Mycobacterium tuberculosis**. *J Immunol Baltim Md 1950* 1998 **160**(11):5448–5454.
101. Lee S-W, Wu LS-H, Huang G-M, Huang K-Y, Lee T-Y, Weng JT-Y. **Gene expression profiling identifies candidate biomarkers for active and latent tuberculosis.** *BMC Bioinformatics* 2016 **17 Suppl 1**:3.
102. Loeuillet C, Martinon F, Perez C, Munoz M, Thome M, Meylan PR. **Mycobacterium tuberculosis subverts innate immunity to evade specific effectors.** *J Immunol Baltim Md 1950* 2006 **177**(9):6245–6255.
103. Balcewicz-Sablinska MK, Keane J, Kornfeld H, Remold HG. **Pathogenic Mycobacterium tuberculosis evades apoptosis of host macrophages by release of TNF-R2, resulting in inactivation of TNF-alpha**. *J Immunol Baltim Md 1950* 1998 **161**(5):2636–2641.
104. Fratazzi C, Arbeit RD, Carini C, Balcewicz-Sablinska MK, Keane J, Kornfeld H, *et al.* **Macrophage apoptosis in mycobacterial infections**. *J Leukoc Biol* 1999 **66**(5):763–764.
105. Kundu M, Pathak SK, Kumawat K, Basu S, Chatterjee G, Pathak S, *et al*. **A TNF- and c-Cbl-dependent FLIP(S)-degradation pathway and its function in Mycobacterium tuberculosis-induced macrophage apoptosis.** *Nat Immunol* 2009 **10**(8):918–926.
106. Sly LM, Hingley-Wilson SM, Reiner NE, McMaster WR. **Survival of Mycobacterium tuberculosis in host macrophages involves resistance to apoptosis dependent upon induction of antiapoptotic Bcl-2 family member Mcl-1**. *J Immunol Baltim Md 1950* 2003 **170**(1):430–437.
107. Kremer L, Estaquier J, Brandt E, Ameisen JC, Locht C. **Mycobacterium bovis Bacillus Calmette Guérin infection prevents apoptosis**

of resting human monocytes. *Eur J Immunol* 1997 **27**(9):2450–2456.

108. Kausalya S, Somogyi R, Orlofsky A, Prystowsky MB. **Requirement of A1-a for bacillus Calmette-Guérin-mediated protection of macrophages against nitric oxide-induced apoptosis**. *J Immunol Baltim Md 1950* 2001 **166**(7):4721–4727.
109. Morciano G, Giorgi C, Balestra D, Marchi S, Perrone D, Pinotti M, *et al*. **Mcl-1 involvement in mitochondrial dynamics is associated with apoptotic cell death.** *Mol Biol Cell* 2016 **27**(1):20–34.
110. Maurer U, Charvet C, Wagman AS, Dejardin E, Green DR. **Glycogen synthase kinase-3 regulates mitochondrial outer membrane permeabilization and apoptosis by destabilization of MCL-1**. *Mol Cell* 2006 **21**(6):749–760.
111. Bae J, Leo CP, Hsu SY, Hsueh AJW. **MCL-1S, a Splicing Variant of the Antiapoptotic BCL-2 Family Member MCL-1, Encodes a Proapoptotic Protein Possessing Only the BH3 Domain.** *J Biol Chem* 2000 **275**(33):25255–25261.
112. Wang F-Y, Wang X-M, Wang C, Wang X-F, Zhang Y-Q, Wu J-D, *et al*. **Suppression of Mcl-1 induces apoptosis in mouse peritoneal macrophages infected with Mycobacterium tuberculosis.** *Microbiol Immunol* 2016 **60**(4):215–227.
113. Spira A, Carroll JD, Liu G, Aziz Z, Shah V, Kornfeld H, *et al*. **Apoptosis genes in human alveolar macrophages infected with virulent or attenuated Mycobacterium tuberculosis: a pivotal role for tumor necrosis factor**. *Am J Respir Cell Mol Biol* 2003 **29**(5):545–551.
114. Maiti D, Bhattacharyya A, Basu J. **Lipoarabinomannan from Mycobacterium tuberculosis promotes macrophage survival by phosphorylating Bad through a phosphatidylinositol 3-kinase/Akt pathway**. *J Biol Chem* 2001 **276**(1):329–333.
115. Chen M, Gan H, Remold HG. **A mechanism of virulence: virulent Mycobacterium tuberculosis strain H37Rv, but not attenuated H37Ra, causes significant mitochondrial inner membrane disruption in macrophages leading to necrosis**. *J Immunol Baltim Md. 1950* 2006 **176**(6):3707–3716.