Chapter 12

Apoptosis and Infections

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Additional information is available at the end of the chapter

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Abstract

Apoptosis is a process that plays a critical role in the elimination of infected cells. Infectious diseases modulate apoptosis, and this contributes to disease pathogenesis. Apoptosis is initiated by various kinds of stimuli, including infections, radiation, etc. Increased apoptosis may assist the dissemination of intracellular pathogens or induce immunosuppression. However, apoptosis may also help eradicate pathogens from the host in many cases. Consequently, several viruses, bacteria, and parasites have evolved mechanisms to inhibit host cell by apoptosis as a strategy that may support intracellular survival and persistence of the pathogen. Bacteria are recognized by cellular receptors and elicit a multitude of signal transduction events that alter the cell's response toward apoptotic stimuli. The result of pathogenic bacteria entering into mammalian cells evokes variety of responses, including internalization or phagocytosis of the bacteria, release of cytokines, secretion of defensins, production of oxygen radicals and the triggering of apoptosis. Bacteria can trigger apoptosis through a large variety of mechanisms that include the secretion of protein synthesis inhibitors and pore forming proteins. They can also activate apoptotic proteins such as caspases, inactivate antiapoptotic proteins, or lead to upregulation of the endogenous receptor/ligand system. However, new research has shown that many bacterial pathogens can in fact prevent apoptosis during infection. As in bacteria, many viral genomes encode proteins that repress apoptosis to escape from immune attack by the host or viruses promote apoptotic death of the host cells. Virus-host interactions may determine viral persistence, extent and severity of inflammation, and pathology associated with infectious disease. The elucidation of the signaling pathways, the cellular receptors, and/or the microbial factors involved in the induction or reduction of apoptosis could reveal new therapeutic targets for blocking microbial-induced apoptosis. This chapter will summarize the most recent research on microorganisms' apoptotic and antiapoptotic strategies and the mechanisms relating to disease.

Keywords: apoptosis, infection, bacteria, viruses, parasitis

1. Introduction

1.1. Apoptosis regulators

Programmed cell death or apoptosis is an intrinsic death program that occurs in various physiological and pathological situations. Apoptosis is also a physiological process that is critical for tissue homeostasis. It is essential for the regulation of immune responses. The main regulators of apoptosis are caspases, Bcl-2 family, p53, tumor necrosis factor (TNF) family, and/or inhibitors of apoptosis proteins (IAPs).

2. Caspases

Caspases are a family of proteins that are one of the main effectors of apoptosis. Their activation is a hallmark of apoptosis. Caspases are synthesized as inactive zymogens, the so-called procaspases. Upon maturation, the procaspases are proteolytically processed between the large and small subunit resulting in a small and a large subunit.

Based on their function, the caspases can be classified into three groups: (1) inflammatory caspases—this group includes caspases 1, 4, 5, 11, 12, 13, and 14, which are involved in inflammation instead of apoptosis; (2) apoptotic initiator caspases that possess long prodomains containing either a death effector domain (DED) (caspases 8 and 10) or a caspase activation and recruitment domain (CARD) (caspases 2 and 9), which mediate the interaction with upstream adaptor molecules; and (3) apoptotic effector caspases. This executioner class (caspases 3, 6, 7) is characterized by the presence of a short prodomain [1]. Apoptotic signals trigger the oligomerization of death adaptor proteins, while death adaptor oligomers in turn induce the aggregation of procaspases. It was previously believed that the initiator caspases are autoproteolytically activated when brought into close proximity of each other. This is called the "induced proximity" model. Effector procaspases are normally cleaved and activated by active initiator caspases. They then cleave various death substrates to induce cell death [2].

3. IAPs

The IAPs represent a family of evolutionarily conserved apoptosis suppressors. Although IAP family proteins may possess other functions, several of them have been shown to bind and potently inhibit activated caspases. Among the caspases inhibited by human IAP family members, XIAP, cIAP1, and cIAP2 are the effector caspases 3 and 7 as well as the initiator caspase 9 [3]. IAP expression can be upregulated in response to survival signals such as those coming from growth factor receptors, e.g., by the activation of the transcription factor. Nuclear factor-kappa B (NF-κB), however, provides a means to suppress apoptosis signaling. IAP inhibitor SMAC/Diablo was recently described as those that bind multiple IAP family members and those that allow caspases to induce apoptosis [4].

4. Bcl-2 family

The Bcl-2 family consists of both antiapoptotic and proapoptotic proteins that share sequence homology within conserved regions known as Bcl-2 homology (BH) domains. All antiapoptotic members such as Bcl-2 and Bcl-$_{XL}$ and a subset of proapoptotic family members such as Bax and Bak are multidomain proteins sharing sequence homology within three to four BH domains [5].

5. p53

One of the most important p53 functions is its ability to activate apoptosis. The disruption of this process can promote tumor progression and chemoresistance. p53 tumor suppressor protein blocks cell cycle progression allowing time to repair the damage or induces apoptosis largely through the upregulation of the Bcl-2 family BH3-only protein Puma (p53 upregulated modulator of apoptosis). Many apoptosis-related genes that are transcriptionally regulated by p53 have been identified. p53-dependent apoptosis is frequently the one induced following DNA damage caused by irradiation, UV or viral infections. p53-independent pathways are usually those resulting from growth factor deprivation. The activation of p53 by DNA damage induces either cell cycle arrest or apoptosis. p53 mediates apoptosis through a linear pathway that involves Bax transactivation, Bax translocation from the cytosol to membranes, cytochrome *c* release from mitochondria, and caspase 9 activation followed by the activation of caspases 3, 6, and 7 [6,7].

5.1. Apoptosis signaling pathways

Apoptosis can be induced in response to various signals from inside and outside the cell. Apoptosis process involves two pathways: (1) by the release of cytochrome *c* from mitochondria—intrinsic pathway and/or (2) by the activation of cell-surface death receptor—extrinsic pathway [8].

5.2. Intrinsic pathway

Mitochondria is a central regulator of intrinsic apoptotic pathways. Intrinsic apoptotic pathways are initiated inside cells. Numerous cytotoxic stimuli and proapoptotic signal-transducing molecules converge on mitochondria to induce outer mitochondrial membrane permeabilization. Mitochondria are known as an important intracellular organelle for producing energy. Mitochondria also play a key role in the modulation of Ca^{2+} homeostasis and oxidative stress. The dysfunction of mitochondria induced by DNA damage or other genotoxic factors leads to an irreversible event, apoptotic cell death. The intrinsic apoptotic pathway is also called "mitochondrial pathway." A pivotal event in the mitochondrial pathway is mitochondrial outer membrane permeabilization (MOMP). MOMP is mainly mediated and controlled by Bcl-2 family members [9]. Many proteins of the Bcl-2 family either with antiapoptotic (e.g., Bcl-2, Bcl$_{XL}$, or Mac1) or proapoptotic (Bax, Bak, or Bik) functions reside in the

outer membrane of the mitochondria. In healthy cells, a small proportion of Bak molecules are bound to voltage-dependent anionic channel (VDAC; part of the [permeability transition] [PT]). The antiapoptotic molecules Bcl-2 and Bcl_{XL} prevent the translocation of cytochrome *c* from the mitochondria, while the induced expression or enforced dimerization of Bax results in dysfunction leading to cytochrome *c* release [10].

Specific stimuli such as oxidants, calcium overload, or ceramide cause a decrease in mitochondrial inner transmembrane potential ($\Delta\Psi_m$) and result in the release of cytochrome *c* from the mitrochondrion. Active Bax/Bak causes the release of cytochrome *c*, which then binds to APAF-1 and causes its oligomerization. The release of cytochrome *c* from the mitochondrial intermembrane space to the cytosol contributes to the formation of the apoptosome that consists of cytochrome *c*, APAF-1, and dATP. Caspase 9 is recruited into the complex and activated in this process. The apoptosome activates caspase 9, which is another initiator caspase. Active caspase 9 cleaves and thereby activates effector caspases (most notably caspase 3), and active effector caspases cause the morphological signs of apoptosis by cleavage of other effector proteins [11]. During apoptosis, cells undergo several morphological and biochemical changes. Due to endonuclease activation, the chromatin is cleaved into oligonucleosomal fragments. Recently, it was shown that structural changes in the plasma membrane of the apoptotic cell are functional in signaling the process of cell death to the environment [12]. Active proteases, including caspases, calpains, cathepsins, and/or serine proteases, can promote the activation of DNases in different ways. Effector caspases cleave and inactivate DNA repair enzyme poly-ADP-ribose polymerase (PARP). Regulators of the cell cycle such as retinoblastoma protein and structural proteins of the nucleus and cytoskeleton such as lamins, growth arrest-specific protein 2, gelsolin, fodrin, and survival proteins such as protein kinase C-δ (PKC-δ) cause cell death [13].

Caspase 3 is responsible for degradation of the nuclear protein PARP, which is involved in DNA repair. Apoptosis inducing factor (AIF) is a proapoptotic factor in mitochondria. It triggers chromatin condensation and DNA degradation in a cell in order to induce apoptosis [14].

5.3. Extrinsic pathway

The extrinsic pathway is activated by ligand-bound death receptors, mainly including (a) TNF-TNFR1, (b) FasL-Fas, and (c) TNF-related apoptosis-inducing ligand (TRAIL) DR4 or DR5. Death receptors belong to the tumor necrosis factor receptor gene (TNFR) superfamily and can generally have several functions that include initiating apoptosis. The TNFR superfamily is characterized by the presence of cysteine-rich domains that mediate binding between ligands and these type I transmembrane domain receptors. Among them, the death receptors, including TNF-R1, Fas (or CD95), and the TRAIL receptors DR4 and DR5, are best characterized for induction of apoptosis [15].

5.3.1. TNF pathway

TNF is a multifunctional proinflammatory cytokine mainly produced by macrophages. There are two major TNF receptors, TNF-R1 and TNF-R2. TNF-R1 is ubiquitously expressed in most

tissues and is the major mediator of TNF signaling, whereas TNF-R2 is mainly found in the immune system and only can be fully activated by membrane bound TNF [16].

TNF-induced activation of NF-κB, JNK, and apoptosis has been intensively studied. NF-κB is a transcription factor that can be induced by a variety of signals. Inhibitor of KB (I-KB) binds to NF-κB and inactivates it by localizing NF-κB to the cytosol, where it is unable to regulate transcription. The phosphorylation of I-KB targets it for ubiquitination and degradation. In the absence of I-KB, NF-κB's nuclear localization signal is exposed, and NF-κB localizes to the nucleus where it is able to induce transcription. The role of NF-κB was originally described as a factor associated with apoptosis. This process is triggered by the phosphorylation of I-KB by the I-KB kinase (IKK) complex. Different activation pathways of NF-κB may cause the expression of proteins that promote apoptosis (e.g., Fas, c-myc, p53, TNF, DR, and caspase 11) or inhibit apoptosis (e.g., IAP proteins, Bcl-2-like proteins) [17]. It was subsequently shown that the inhibition of NF-κB activation potentiates apoptosis [18]. In addition, the inhibition of I-KB expression by oligonucleotides led to cell transformation. Consistent with this role, NF-κB has been shown to induce transcription of antiapoptotic proteins. Akt is reported to phosphorylate and activate IKK. The activation of IKK causes phosphorylation and degradation of I-KB, which leads to the localization of NF-κB to the nucleus where it can induce transcription of antiapoptotic genes. Thus, Akt can inhibit apoptosis by activating NF-κB [19].

TNF also induces the activation of the stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK) pathway. Upon activation, JNK kinases translocate into the nucleus and enhance the transcriptional activity of transcription factors, for example, c-Jun and activating transcription factor-2 by the phosphorylation of their amino-terminal activation domains. c-Jun belongs to a group of basic region-leucine zipper proteins that dimerize to form transcription factors commonly designated as activator protein 1 (AP-1). The AP-1 proteins have an important role in a variety of cellular processes, including proliferation, differentiation, and induction as well as prevention of apoptosis [20].

5.3.2. FAS pathway

Fas is involved in the cytotoxic T lymphocyte (CTL)-mediated killing of cells (e.g., CTL-mediated killing of virus-infected cells), destruction of inflammatory and immune cells in immune-privileged sites, and deletion of self-reacting B cells and activated T cells at the end of an immune response [21]. Fas binding to Fas ligand results in intracellular clustering of death domains (DD) followed by its internalization into an endosomal pathway. This allows an adaptor protein called Fas-associated death domain (FADD) to associate with the receptor through an interaction between homologous death domains on both molecules. FADD also contains a DED that allows binding of procaspase 8 to the CD95-FADD complex. Procaspase 8 (also known as FLICE) associates with FADD through its own death effector domain. Caspase 8, the main initiator caspase in CD95 signaling, is expressed as two isoforms, caspases 8/a and 8/b, which are both recruited to the activated CD95 receptor. FasL-induced clustering of Fas, FADD, and caspase 8 within the death-inducing signaling complex leads to autoproteolytic processing of caspase 8 by induced proximity and dimerization followed by the release of the processed active proteases [22]. Cells can be divided into two types according to their require-

ment for mitochondrial pathway in FAS-induced apoptosis. In type I cells, processed caspase 8 is sufficient to directly activate other members of the caspase family. In type II cells, the efficient activation of effector caspases by Fas depends on an amplification loop that relies on caspase-8-mediated cleavage of Bid and subsequent release of mitochondrial proapoptotic factors such as SMAC/Diablo or cytochrome *c* to drive the formation of the caspase-9-activating apoptosome. Active caspase 9 activates the executioner caspase 3, which in turn activates caspase 8 [23].

5.3.3. TRAIL pathway

Like Fas, TRAIL may also be involved in the immune response and in tumor surveillance. Five distinct TRAIL receptors have been identified: death receptor 4 (TRAIL-R1), 125 KILLER/DR5 (TRAIL-R2, TRICK2), DcR1 (TRID, TRAIL-R3), DcR2 (TRUNDD OR TRAIL-R4), and osteoprotegerin. The apoptotic signaling induced by TRAIL is similar to that induced by FAS. Binding of TRAIL to its receptors DR4 or DR5 triggers the formation of a death-inducing signaling complex by recruiting FADD and/or caspases 8 and/or 10. TRAIL-induced apoptosis also involves the mitochondrial pathway, like Fas-induced apoptosis, in type II cells [24,25].

6. Apoptosis and bacterial infections

During a microbial infection, organism faces the challenge of recognizing and combating the invading organism. The entrance of bacterial pathogens into human organism initiates the innate immune response characterized by the recruitment of leukocytes to sites of infection [26]. After phagocytosis by human macrophages, microorganisms are destroyed by reactive oxygen species (ROS) microbicidal products contained within granules [27]. Otherwise, bacterial pathogens that cause apoptosis target immune cells such as macrophages and neutrophils [28]. Bacteria can trigger apoptosis by different mechanisms, including the secretion of protein synthesis inhibitors, pore forming proteins, molecules activating the endogenous death machinery in the infected cell, or lipopolysaccharides and other superantigens [29]. These molecules might be either proapoptotic and activated by the bacteria or antiapoptotic and inhibited upon infection to trigger apoptotic death of the infected cell [30] (Table 1).

Bacteria	Apoptosis	Proposed or demonstrated mechanism	Cell type
Pseudomonas aeruginosa	Induction	Fas/Fas ligand system	Endothelial cells
		Cytochrome *c* release	Epithelial cells
Neisseria gonorrhoeae	Induction	Increases mitochondrial permeability	Epithelial cells
	Inhibition	Increases antiapoptotic genes	PMLs
			Epithelial cells
Neisseria meningitidis	Inhibition	Prevents cytochrome *c* release	HeLa cells

Shigella flexneri	Induction	Caspase 1 activation	Macrophages
	Inhibition	Prevents cytochrome *c* release	Epithelial cells
Shiga toxins	Induction	Extrinsic and intrinsic pathways	Epithelial, endothelial, neurons
			myeloid and lymphoid cells
Salmonella typhimurium	Induction	Caspase 1 activation	Macrophages
	Inhibition	PI3K-Akt/PKB-pathway	Epithelial cells
Listeria monocytogenes	Induction	Cytochrome c release	Hepatocytes, lymphocytes
			dendritic cells
Chlamydia trachomatis	Inhibition	Prevents cytochrome *c* release	Epithelial cells, macrophages
Chlamydia pneumoniae	Inhibition	Bcl-2	HeLa cells
		Raf/MEK/ERK survival pathway	
Yersinia pseudotuberculosis	Induction	Inhibits ERK and the NFKB	Macrophages, dendritic cells
Yersinia enterocolitica		TLR4	
Yersinia pseudotuberculosis	Inhibition	Inhibits ROS production	PMLs
Yersinia enterocolitica			
Yersinia pestis	Induction	Caspase 1 activation	Macrophages
		Inhibits ERK and the NFKB	
Legionella pneumophila	Induction	Caspase 3	Macrophages, epithelial cells
	Inhibition	Up regulating of anti-apoptotic genes	Monocyte, U937,A549 cells
		NF-κB pathway	
Escherichia coli K1	Induction	Extrinsic and intrinsic pathways	Epithelial cells
	Inhibition	Expression Bcl_{XL}	Macrophages
Rickettsia rickettsii	Inhibition	Activation of cell survival pathways	Endothelial cells
	Induction	DNA fragmentation	Neurons
Mycobacterium tuberculosis	Induction	TNF pathway	Macrophages
		Intrinsic pathway	
	Inhibition	Activation of the NF-κB	Epithelial cells
		Expression of Bcl-2	
Viruses	**Apoptosis**	**Proposed or demonstrated mechanism**	**Cell type**
Hepatitis C virus	Induction	Extrinsic pathway	Cytotoxic T lymphocytes, macrophages

	Inhibition	Inhibits both Fas pathway and intrinsic pathway	Hepatocytes
HIV-1 gp120 protein	Induction	Fas pathway	CD4+ T cells
HIV-1 proteins Env	Induction	p53-dependent genes Puma and Bax	
HIV Nef	Induction	Extrinsic pathway	
Rabies virus	Induction	Expression of Bax and caspase 1	Neuroblastoma cell
	Induction	Caspase gene Nedd-2	Neurons
		Activation of caspase 8	
		Upregulation of AIF	
Epstein-Barr virus	Inhibition	Bcl-2 proteins, BHRF1, and BALF1	B cells
		NF-κB pathway	lymphoblastoid cell lines
		Upregulation of antiapoptotic genes	
Baculovirus	Inhibition	Antiapoptotic genes (p35 and IAP)	Insect cells
HPV E2 protein	Induction	p53 pathway	HeLa cells
HPV E6 protein	Induction	Degradation p53 pathway	Epithelial cells
	Induction	Extrinsic pathway	Cervical carcinoma cells
	Inhibition	Caspase inactivation	fibroblasts, osteosarcoma cells
HPV E7 protein	Induction	Retinoblastoma gene	Lens
Adenoviral proteins			
E1A	Induction	p53 pathway	REF52 cells
E4orf4	Induction	p53 pathway, caspase activation	H1299, 293 cells
E4orf6	Induction	PARP-induced cell death	U251 cells
E1B-19K	Inhibition	Inhibits extrinsic pathway	HeLa cells ,A549 lung carcinoma cells
E1B-55K	Inhibition	Inactivates p53	293 cells
E3-6.7	Inhibition	Blocks TRAIL-induced apoptosis	Cytotoxic T cells
E3 RID	Inhibition	Inhibits E1A or TNF-induced apoptosis	HT29.14S cells
		Decreased presentation of Fas on the cell surface	Jurkat, CEM, and HuT78 cell lines
E3-14.7K	Inhibition	Inhibits TNF and TRAIL-induced apoptosis	Fibroblast C3HA cell lines
	Inhibition	inhibits MHC class I transport to the cell surface	T lymphoma cell line
E4 orf 6	Inhibition	Blocks p53	H1299 cells
Human cytomegalovirus			

UL36 protein	Inhibition	Inhibits Fas and caspase-mediated apoptosis	MRC-5 fibroblasts, HeLa cells
	Inhibition	Inhibits TNF-induced apoptosis	HeLa cells
Parasites	**Apoptosis**	**Proposed or demonstrated mechanism**	**Cell type**
Toxoplasma gondii	Inhibition	Increased antiapoptotic Bcl-2 family	Fibroblasts
		Inhibition of the cytochrome *c* release	
		Upregulation of IAPs	
		Activation of NF-κB	
		Degradation of PARP	
	Induction	IFN-γ	T cell
Plasmodium falciparum		Increased Ca level	Erythrocytes
		Caspase 8 and caspase 9 activation	Endothelial cells
Trypanosoma brucei	Induction	Intrinsic pathway	Neuronal cell
Trypanosoma cruzi	Inhibition	PI3-K/PKB pathway	Schwann cells
Leishmania donovani	Induction	Intrinsic pathway	Neutrophils

Table 1. Microorganisms that induce and/or inhibit host cell apoptosis

Apoptosis is induced by both intrinsic and extrinsic pathways. Due to their key role in cell survival, mitochondria represent attractive targets for pathogens. Several pathogens, including both viruses and bacteria, have been shown to target mitochondria in order to interfere with the host cell apoptotic machinery. For example, bacterial pore-forming toxins such as the neisserial porin PorB, which causes rapid Ca^{+2} influx into target cells and induces apoptosis, exhibit striking structural and functional homology with the mitochondrial anion channels that mediate mitochondrial permeability transition and apoptosis [31]. Apoptosis, which is executed by caspase activity, can be induced either by the ligation of death receptors or by the release of another proapoptotic factor cytochrome *c* from mitochondria. Apoptotic stimuli (either death ligands, binding to death receptors, or any of the multitude of agents that induce apoptosis) are received by some cellular receptor. In the case of death receptors, this directly causes caspase activity [32].

New studies have shown that many bacterial pathogens can prevent apoptosis during infection. Bacteria inhibits apoptosis by the use of multiple mechanisms: the protection of the mitochondria and prevention of cytochrome *c* release (i.e., *Chylamidia* sp. and/or *Neisseria* sp.), the activation of cell survival pathways (i.e., *Salmonella* sp. and/or *Rickettsia* sp.), the inhibition of caspases, and the activation of phosphoinositide 3-kinase (PI3K)-Akt/protein kinase B (PKB) pathway and interaction with cellular caspases (i.e., *Shigella* sp. and/or *Legionella* sp.) [33]. The PI3K/Akt pathway is also a strong activator of cyclin D1, a critical player in cell cycle progression. Cyclin D1 protein levels are also regulated by glycogen synthase kinase 3 (GSK-3). GSK-3 is the primary kinase that phosphorylates cyclin D1 at this residue. Rapid cyclin D1 degrada-

tion induced by GSK-3 is inhibited by the activation of PI3K/Akt pathway because Akt directly phosphorylates and inactivates GSK-3 [34]. c-Fos is a transcriptional regulator that can elevate the expression of many proliferatory genes. PI3K/Akt pathway executes some of its antiapoptotic effects through transcription factors such as Elk-1 and c-Fos. The activation of the Raf/MEK/ERK pathway is associated with the increased expression of antiapoptotic proteins. The Raf/MEK/ERK cascade can also activate the PI3K/Akt pathway. Raf has been shown to directly phosphorylate Bad and Bcl-2 to exert antiapoptotic effects. Depending on cell type as well as apoptotic stimulus, Raf can inhibit or promote apoptosis [35]. Toll-like receptors (TLR) have been described to have both apoptosis-inducing and inhibiting capacity. Early reports have linked the activation of TLR2 to the induction of apoptosis through the adapter MyD88 [36]. At the same time, TLR-signaling has clearly an antiapoptotic activity via NF-κB and the PI3Kpathways. NF-κB induces antiapoptotic gene expression [37].

6.1. *Pseudomonas*

Pseudomonas aeruginosa can cause disease in animals, including humans. The symptoms of such infections are generalized inflammation and sepsis. If such colonizations occur in critical body organs such as the lungs, the urinary tract and kidneys, the results can be fatal [38]. *P. aeruginosa* kills mammalian cells by an activation of the endogenous CD95 (Fas)/CD95 ligand (Fas-ligand) system. An upregulation of cell surface CD95 and CD95 ligand resulting in the activation of this death receptor has been recently shown to be pivotal for the induction of apoptosis by several *P. aeruginosa* strains. The upregulation of CD95 and the CD95 ligand on cells infected with *P. aeruginosa* depends on the function of the type III secretion system (T3SS). The ligation of the receptor stimulates caspases, mitochondrial changes, and finally execution of apoptosis *in vitro* and *in vivo* [30]. The binding of CD95 by the CD95 ligand upon upregulation induces the activation of caspases and JNK. In addition, reactive oxygen intermediates in the induction of *P. aeruginosa* triggered death [39].

6.2. *Neisseria*

Neisseria gonorrhoeae is the etiological agent of the sexually transmitted disease gonorrhea. It penetrates the mucosa, enters phagocytes and epithelial cells, and causes a massive inflammatory response in the subepithelial tissue [40]. Several factors play a role in infection, for example, the pili, which mediates primary adherence; the Opa proteins, which mediate adhesion and invasion; and the PorB porin [41,42]. There is conflicting information regarding the effects of neisserial porins on apoptosis. These discrepancies may be due to the specific responses of different cell types, culture conditions, and bacterial strains. *N. gonorrhoeae* porin PorB1B interacts with HeLa cell mitochondria and induces calcium eflux and apoptosis [43]. Massari *et al*. [44] showed that Neisserial PorB is translocated to the mitochondria of HeLa cells infected with *Neisseria meningitidis* and prevent apoptosis by the inhibition of cytochrome *c* release. Massari *et al.* [44] speculated that differences in cell types or porin purification explain the discrepancies between the results. *N. gonorrhoeae* also increases the transcription of host antiapoptotic genes. These genes include bfl-1, cox-2 and c-IAP-2, each coding for a product that acts to inhibit apoptosis.

Bfl-1 is a member of the Bcl-2 family of apoptotic regulators and has been characterized to have a protective effect on host cells when overexpressed. Anti-apoptotic Bcl-2/Bcl-$_{XL}$ interact with the mitochondrial porin VDAC, thus blocking the opening of the PT and/or mitochondrial membrane depolarization and inhibiting cytochrome *c* release [45]. *N. gonorrhoeae* can inhibit apoptosis induced by the intrinsic and extrinsic apoptosis inducers staurosporine (STS) and TRAIL in HL-60 cells and primary polymorphonuclear leukocytes (PMLs) [46]. In addition Follows *et al.* [47] showed that *N. gonorrhoeae* infection in human endocervical epithelial cells induced NF-κB activation and resulted in the increased gene expression of the NF-κB-regulated antiapoptotic genes Bfl-1 and/or cIAP-2.

6.3. *Shigellas*

The genus *Shigella* consists of four pathogenic "species": *S. dysenteriae*, *S. flexneri*, *S. sonnei*, and *S. boydii. S. flexneri* causes dysentery (shigellosis) by invading the human colonic mucosa. It directly activates proapoptotic signaling pathways to initiate apoptosis in macrophages. It crosses epithelium and goes to lamina propria of intestinal villi. The three proposed effectors of *S. flexneri* internalization are invasion plasmid antigens (Ipa) IpaB, IpaC, and IpaD, all of which are encoded on the pathogen's 230-kb virulence plasmid. These effectors cause caspase 1 activation. Activated caspase 1 then cleaves and activates prointerleukin (proIL)-1β and proIL-18, which are proinflammatory cytokines involved in host inflammatory [48,49]. The secretion of Ipa proteins is dependent on T3SS, which is encoded by 20 genes in the mxi-spa locus of the virulence plasmid. Additional T3SS effector proteins are secreted through the T3 needle when the bacteria are inside the cytoplasm of the host cell [50]. *S. flexneri* kills more of macrophages and promotes the spreading of the bacteria because of the release of interleukin 1β (IL-1β). IL-1β recruits PMLs to the infection sites. The PMLs cross the intestinal epithelium altering the integrity of this epithelial barrier. This promotes massive secondary invasion of the bacteria and acute inflammation [51]. *S. flexneri* infects enterocytes from the basolateral side. The ultrastructural morphology of infected macrophages includes condensation of chromatin at the nuclear boundary blebbing at the cell surface, dilation of the endoplasmic reticulum, and cytoplasmic vacuolization. This is identical to the morphology of cells undergoing apoptosis [52]. *Shigella* does not induce apoptosis in epithelial cells because these intestinal cells are the primary sites for intracellular bacterial proliferation during shigellosis. It was shown that in the presence of STS, *S. flexneri* inhibits apoptosis by preventing the activation of caspase 3. This happens because of both cytochrome *c* release from the mitochondria and caspase 9 activation [53]. Faherty *et al.* [54] suggested that *Shigella* is protected from apoptosis in epithelial cells by various mechanisms. The bacteria prevent cytochrome *c* release from the mitochondria through the upregulation of Bcl-2 proteins. Second, the extrinsic pathway of apoptosis is inhibited from *in vivo* stimuli such as TNF and FasL. Third, infection leads to the induced expression of JNK and NF-κB, which has many prosurvival effects, including the increased expression of the IAPs (BIRC4, BIRC1, BIRC5, and BIRC7), the Bcl-2 family, and the caspase 8 inhibitors. Finally, the bacteria prevent caspase 3 activation to provide downstream protection in the presence of strong apoptosis inducers. Through the use of T3SS effector proteins, the bacteria could directly generate mitochondrial protection, extrinsic pathway inhibition, and caspase 3 inhibition [54].

Shiga toxins comprise a family of structurally and functionally related protein toxins expressed by *S. dysenteriae* serotype 1 and multiple serotypes of *Escherichia coli.* Shiga toxins cause bloody diarrheal diseases, which may progress to life-threatening extraintestinal complications. The kidneys and central nervous system are the organs most frequently involved [55]. Shiga toxins induce apoptosis in human epithelial, endothelial, myeloid, and lymphoid cells *in vitro* and appear to induce apoptosis in rabbit neurons *in vivo*. Apoptosis induction involves the activation of both extrinsic (caspases 8, 6, and 3 activation) and intrinsic (Bid generation, cytochrome *c* release, and/or caspase 9 activation) pathways. Alterations in the balanced expression of pro- and antiapoptotic Bcl-2 family members also contribute to apoptosis induction [56].

6.4. *Salmonellas*

Salmonella cause an acute localized inflammation in the intestine. *Salmonella enterica* serovar *Typhimurium*, one of the most common food-borne pathogens, causes self-limiting gastroenteritis in humans and a similar diarrheal disease in calves and pigs. *Salmonella typhimurium* can access systemic tissue (mainly spleen and liver) via the lymphatic system and the Peyer's patches. *Salmonella* uses specific virulence factors to invade other cell types such as T3SS. *S. typhimurium* directly activate apoptosis in macrophages [57]. *Salmonella* invasion protein (Sip)B activates ICE (IL-1β converting enzyme). Caspase 1 activation in *Salmonella*-infected macrophages results in the production of active IL-1β and IL-18 and rapid cell lysis with the release of proinflammatory intracellular contents [58]. Knodler *et al.* [59] showed that *S. enterica* serovar *typhimurium* effector protein SopB protects epithelial cells from apoptosis by sustained the activation of Akt. SopB has antiapoptotic activity in infected epithelial cells, which is dependent on the phosphatase activity of SopB and the presence of Akt. PI3K-Akt/PKB-pathway protect against apoptosis by the phosphorylation of the proapoptotic Bad. This pathway prevents cytochrome *c* release.

6.5. *Listeria monocytogenes*

Listeria monocytogenes, a facultative anaerobe and/or intracellular bacterium, is the causative agent of listeriosis. *L. monocytogenes*, similar to *Shigella*, lyses the phagosomal membrane and escapes into the cytosol to initiate an intracellular infection, a process that is mediated by a secreted pore-forming toxin, listeriolysin O (LlyO). *L. monocytogenes* induces LlyO-dependent apoptosis in a variety of cell types, including hepatocytes, lymphocytes, and dendritic cells. LlyO might insert into the mitochondrial membrane causing the release of cytochrome *c*. In addition, the insertion of LlyO into the mitochondrial and/or endoplasmic reticulum membrane may stimulate calcium efflux, thereby activating the calpain and/or caspases [60,61]. Stavru and Cossart [62] showed that LlyO is responsible for mitochondrial network disruption along with a decrease in mitochondrial membrane potential and intracellular ATP levels. However, *L. monocytogenes* does not induce apoptosis in macrophages but causes LlyO-mediated necrosis [63].

6.6. *Chlamydiae*

Two species of chlamydiae commonly infect humans, *Chlamydia trachomatis* and *Chlamydia pneumoniae. C. trachomatis* causes trachoma, a scarring eye infection in developing countries. *C. pneumoniae* causes pneumonia [64]. *Chlamydia* species require differentiation to produce sufficient infectious elementary bodies to spread to adjacent cells. In an infection, elementary bodies are taken up by a host cell and begin their cycle inside a membrane-bound vacuole in the host cell cytosol. During the early stages of infection, *Chlamydia* has antiapoptotic effect that helps to maintain the metabolic activities of the infected cell. It was shown that *C. trachomatis* has antiapoptotic effect in epithelial cells and macrophages by blocking the release of cytochrome *c* [65]. *C. pneumoniae* also inhibited apoptosis through an additional activity that was described as blocking caspase activation by cytochrome *c* in a cell-free system [66]. The activation of the host cell apoptotic pathways in the late stages of infection may facilitate dispersal of the bacteria and initiate a host inflammatory response. The various subfamilies of the Bcl-2-family of proteins play a decisive role in this event. The trigger of cytochrome *c*-release is the activation of one or several BH3-only proteins. Bcl-2 and its antiapoptotic homologues can bind active BH3-only proteins and probably by this interaction block apoptosis [67]. Du *et al.* [68] demonstrated another way of that inhibiting apoptosis involves the activation of Raf/MEK/ERK survival pathway.

6.7. *Yersinia*

Yersinia invades epithelial cells, fibroblasts, and M cells in mammalian cells *in vitro* and *in vivo* [69,70]. *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* are transmitted by fecal-oral route and cause gastrointestinal syndromes lymphadenitis and septicemia. *Yersinia pestis* is typically transmitted through the bite of an infected flea and causes bubonic and/or septicemic plague. Yersinia virulence plasmid encodes T3SS and 6 known effector proteins termed Yersinia outer proteins (Yops) [71]. The translocation of the effector molecule YopJ (*Y. pseudotuberculosis*), YopP (*Y. enterocolitica*), or $YopJ^{KIM}$ (*Y. pestis*) into the cells has been shown to rapidly activate apoptosis in macrophages and dendritic cells but not in human epithelial cells [72,73]. Yersinia YopJ/P represses the activation of ERK and the NFKB. More recent studies indicate that YopJ has acetyltransferase activity, acetylating Ser and Thr residues critical for the activation of IKK-B and ERK kinases in *Yersinia*-infected macrophages [74,75]. Also, the TLR4 has been shown to act as a potent inducer of apoptosis in macrophage [76]. $YopJ^{KIM}$ has two amino acid changes that give it an enhanced ability to inhibit survival signals in macrophages. The increased apoptosis may cause membrane permeability resulting in the efflux of K^+ and activation of caspase 1. It was suggested that caspase 1 activation is a normal outcome of a type of apoptosis that is triggered in naive macrophages by TLR4 signaling combination with pathogen interference with ERK and NF-κB pathways [77]. YopJ and/or YopP did not induce pronounced apoptosis in human PMLs. It was suggested that Yersinia inhibition of PML_S ROS production plays a role in evasion of the human innate immune response in part by limiting PMLs apoptosis [78].

6.8. *Legionella*

Legionella pneumophila invades and replicates within alveolar macrophages, monocytes, and possibly alveolar epithelial cells and causes Legionnaires disease. The expression and/or export of apoptosis-inducing factor(s) in *L. pneumophila* is regulated by the Dot/Icm type IV-like secretion system [79,80].

L. pneumophila utilizes several strategies to ensure intracellular replication and protect itself against the host immune system. These are the following: (1) upon entry into a human phagocyte, *L. pneumophila* becomes contained in a vacuole called *Legionella*-containing phagosome that avoids the typical fusion with the lysosome. *L. pneumophila* promotes the cleavage of Rabaptin-5 by caspase 3, thus preventing the default phagosome-lysosome fusion. (2) *L. pneumophila* promotes the cleavage of Rabaptin-5 by caspase 3, thus preventing the default phagosome-lysosome fusion. (3) *L. pneumophila* does not activate caspases 1 and 7 in human monocytes consequently aborting the phagosome-lysosome fusion. (4) *L. pneumophila* inhibits host cell apoptosis by upregulating antiapoptotic genes. (5) *L. pneumophila* controls the local balance of activating cytokines (IFN-γ and/or TNF-α) that inhibit its replication and inhibiting cytokines (IL-10) that allow its survival. (6) *L. pneumophila* activates the NF-κB pathway to maintain host cell survival and/or 7-*L. pneumophila* modulates other innate immune responses to establish a replicative niche [81].

6.9. *Escherichia coli*

E. coli K1 is a leading causative agent of neonatal meningitis. OmpA of *E. coli* can directly interact with monocytes and macrophages for entry. Some *E. coli* serotypes produce a Shiga-like toxin that can bind to human intestinal epithelium and produce Shiga-like toxins, which are associated with hemorrhagic colitis and the hemolytic-uremic syndrome [82]. One pathway involving apoptosis is mediated by death receptors such as CD95 and TNF-R. Intrinsic apoptotic pathway is involved in the Shiga-like toxin-mediated apoptosis of epithelial cells [83]. *E. coli K1* induces the expression of the antiapoptotic protein Bcl_{XL} for its own survival and that of host macrophages. In addition, the bacteria may also block the activation of caspases. Besides upregulating Bcl_{XL}, $OmpA^+$ *E. coli* interaction with macrophages may alter the signaling pathways of the host cell to use it as a protected reservoir for the time required to reach septic levels [84,85].

6.10. *Rickettsia*

Rickettsia is a genus of nonmotile, Gram-negative, non-spore-forming, and/or highly pleomorphic bacteria. *Rickettsia rickettsii* is a unicellular Gram-negative coccobacillus. *R. rickettsii is* most commonly known as the causative agent of Rocky Mountain spotted fever [86]. *R. rickettsii* prevents apoptosis by the activation of cell survival pathways. *R. rickettsii* induces NF-κB activity and the upregulation of prosurvival proteins, the downregulation of proapoptotic proteins, and a lack of cytochrome *c* release in endothelial cells. Bechelli *et al.* [87] performed a screening of pro- and antiapoptotic genes that were differentially expressed in human microvascular endothelial cells during *R. rickettsii* infection and after staurosporine challenge.

A total of 14 genes were significantly upregulated of which 8 (TRAF1, BNIP2, BCL2L1, TRAF3, BIRC2, BNIP3L, AKT1, and BIRC5) are known apoptosis suppressors while 6 are known to promote apoptosis (BOK, BCL2L13, DAPK2, TP53, ABL1, and BAK1). However, *R. rickettsii* efficiently infects neuronal cells and that the infection causes apoptotic death of neuron [88].

6.11. *Mycobacterium*

Mycobacterium tuberculosis is the causative agent of most cases of tuberculosis. *M. tuberculosis* infected macrophages die by (a) necrosis, a death modality defined by cell lysis, or (b) apoptosis, a form of death that maintains an intact plasma membrane. Necrosis is a mechanism used by bacteria to exit the macrophage, evade host defenses, and spread. *M. tuberculosis* is complex and includes both the induction of cell-death and cell-survival signals. It induces apoptosis in macrophages *in vitro* and *in vivo* [89]. Apoptosis occurs by TNF pathway. In addition, MOMP leading to the activation of the intrinsic apoptotic pathway is required. Both pathways lead to caspase 3 activation which then results in apoptosis [90]. Bacteria cell wall components connect TLR-2 molecules. *M. tuberculosis* also protects cells against apoptosis via two key pathways: first, through the induction of TLR-2-dependent activation of the NF-κB cell survival pathway, and second, by enhancing the production of soluble TNFR-2 (sTNFR2), which neutralizes the proapoptotic activity of TNF-α. *M. tuberculosis* can prevent apoptosis in alveolar epithelial cells. Danelishvili *et al.* [91] showed that *M. tuberculosis* infection of macrophages results in the downregulation of the Bcl-2 gene and the upregulation of Bax and Bad proapoptotic genes. In contrast, the increased expression of Bcl-2 and the inhibition of Bax and Bad genes were observed in alveolar epithelial cells. *M. tuberculosis* infection was associated with the repression of the Bcl-2 gene and the induction of p53 in human macrophages. In alveolar epithelial cells, the expression of p53 was unchanged during *M. tuberculosis* infection [92].

7. Viral infections

After infecting target cells, viruses replicate to produce large number of progeny virions and spread the progeny to initiate the next round of infection. Some viruses encode specific proteins to optimize their replication. Infection by viruses, however, triggers the apoptosis of the infected cell to restrict virus infection. This is done by reprogramming of the host cell apoptotic pathway to effect death of the infected host cell before the release of progeny viruses. In order to ablate host defense mechanisms, viruses have evolved proteins that are able to inhibit or delay the host protective actions by targeting strategic points in the apoptotic pathways [93]. Apoptosis can be induced by intrinsic or extrinsic signals (Table 1). Intrinsic signals may result from viral infection and include stress, cell cycle arrest, cytoplasmic calcium perturbation, and DNA damage. Extrinsic signals arise as a result of the host immune response through TNF-receptor or Fas activation or via delivery of proteases by cytotoxic lymphocytes. Once induced, apoptosis may eliminate infected cells prior to release of viral progeny [94, 95]. Many viruses have been shown to induce apoptosis, either as a mechanism for the release and dissemination of progeny virions or as a defense strategy of multicellular host organisms for the destruction

of infected cells and therefore preventing the spread of the virus [96]. Innate and the acquired immune system induce apoptosis as a host defense against viral infections. The innate immune system directly activates inflammatory cells such as macrophages (e.g., granulocytes, Kupffer cells in the liver) and natural killer (NK) cells, which may directly cause death of the infected cells. On the other hand, viral RNA or proteins can bind to intracellular molecules that modulate or directly induce cell death [97]. In this immune cell-independent, virus-induced apoptosis of the host cell protein kinase R (PKR) and the cytoplasmic RNA helicase RIG-I play important roles [98]. PKR acts via the downstream transcription factor eIF-2α [99]. At the same time, acquired immune system works to eliminate the virus and the recognition of viral antigens presented by specific cells (e.g., dendritic cells). The antigen-primed $CD8^+$-T-lymphocytes cytotoxic T lymphocytes directly kill infected cells via direct cell-cell contact and release of cytotoxic and/or antiviral cytokines (e.g., interferons IFNs and/or TNF-α), whereas IFN-γ and IFN-α are also able to eliminate the virus without killing the host cell [100].

The IFNs are considered to play a critical role in innate immunity to viral infection and aside from effectively preventing intracellular viral replication can also mediate the activation and recruitment of the adaptive immune response. The IFNs can be induced by a number of stimuli, including viruses and dsRNA through mechanisms involving the activation of interferon regulatory factor (IRF-3), NF-κB, and perhaps the dsRNA-dependent PKR and the JNK2 pathway, all of which have been reported to be mediators of cell death [101,102].

7.1. Hepatitis C virus

Hepatitis C virus (HCV) causes liver cirrhosis and hepatocellular carcinoma [103]. In hepatocytes, apoptosis induction via cytotoxic T lymphocytes and macrophages largely occurs via extrinsic pathway. Ligand binding activates caspase 8 signaling cascade [104]. Another mechanism of apoptosis involves viral protein and their interactions. HCV core protein has been shown to be proapoptotic and antiapoptotic effects [105]. Machida *et al*. [106] showed that the expression of HCV proteins may directly or indirectly inhibit Fas-mediated apoptosis and death in mice by repressing the release of cytochrome *c* from mitochondria.

7.2. HIV

Human immunodeficiency virus type 1 (HIV-1)-infected individuals often suffer from neurological complications such as memory loss, mental slowing, and gait disturbance [107]. HIV infection is associated with a progressive decrease in and/or loss of $CD4^+$ and the decline of $CD8^+$ T cells and viral replication [108]. Inappropriate signaling through the binding of the HIV-1 envelope to the CD4 may induce abnormal programmed $CD4^+$ T-cell death. Viral proteins such as HIV-1 gp120 have an important role development in HIV-associated apoptosis. HIV proteins implicated in the induction of apoptosis *in vitro* include tat, nef, vpr, and protease. Cross-linking of bound gp120 on human $CD4^+$ T cells followed by signaling through the T-cell receptor for antigen was found to increase susceptibility to Fas and result in apoptosis [109,110]. In addition, deregulation in cytokine production occurs during HIV infection, perturbing the immune response. The overproduction of IL-4 and/or IL-10 cytokines is known to increase susceptibility to activation-induced cell death. IFN-α produced by HIV-1-infected

dendritic cells contributes to CD4 T-cell apoptosis by the TRAIL/DR5 pathway [111]. HIV-1 protein Env triggers apoptosis by the transactivation of the p53-dependent genes Puma and Bax [112]. HIV Nef is able to induce apoptosis by extrinsic pathway [113,114].

7.3. Rabies virus

Rabies virus (RV) is a neurotropic virus and travels to the brain by following the peripheral nerves. RV, a member of the genus *Lyssavirus* of the family Rhabdoviridae, is known to cause fatal encephalomyelitis in many mammalian species. RV has developed two main mechanisms to escape the host defenses: (1) its ability to kill protective migrating T cells and (2) its ability to sneak into the nervous system without triggering the apoptosis of the infected neurons and preserving the integrity of neurites [115]. In one of the studies, Ubol *et al.* [116] showed the expression of Bax and caspase 1 activation in RV-infected neuroblastoma cells. In another study, the expression of caspase gene Nedd-2 was significantly upregulated in infected adult and suckling mice [117]. Thoulouze *et al.* [118] showed that apoptosis induced by rabies virus involves the activation of caspase 8 and disappearance of procaspases 9 and 3. In addition, AIF translocated from the cytoplasm to the nucleus, suggesting that caspase-independent pathway is also involved in RV-induced apoptosis. Sarmento *et al.* [119] showed that AIF, a caspase-independent apoptotic protein, was upregulated and translocated from the cytoplasm to the nucleus postinfection, suggesting that apoptosis induced by RV induces apoptosis by both the caspase-dependent and caspase-independent pathways.

7.4. Epstein-Barr virus

Infection with Epstein-Barr virus (EBV) is very common and usually occurs in childhood or early adulthood. In fact, up to 95% of people in the U.S. have been infected with EBV. EBV is the cause of infectious mononucleosis (also termed "mono"), an illness associated with fever, sore throat, swollen lymph nodes in the neck, and sometimes enlarged spleen. Less commonly, EBV can cause more serious disease. To establish a persistent latent infection, EBV must access the memory B-cell compartment and reside within long-lived peripheral B cells where few viral gene products are expressed in order to escape immune detection [120]. EBV encodes two viral Bcl-2 proteins, BHRF1 and BALF1, with apparently redundant functions. The viral BHRF1 gene expresses a Bcl-2 homologue protein that resembles Bcl-2 in its subcellular localization and capacity to enhance B-cell survival [121]. *In vitro*, EBV infects resting human B lymphocytes and transforms them into lymphoblastoid cell lines (LCLs). In LCLs, 11 so-called latent genes are consistently expressed. These are the EBV nuclear antigens EBNA1, EBNA2, EBNA-LP, EBNA3A, B, and/or C and the latent membrane proteins LMP1, LMP2A, and B and two noncoding RNAs [122]. LMP1 indirectly inhibits apoptosis by upregulating several cellular antiapoptotic genes presumably through the induction of the NF-κB pathway [123].

7.5. Baculovirus

Baculovirus antiapoptotic genes include p35, which encodes the most broadly acting caspase inhibitor protein known and IAP genes [124]. The baculovirus IAP blocks apoptosis induced by caspase activation. All viral IAPs (vIAPs) contain a carboxyl ring finger and a variable

number of highly conserved Cys/His motifs known as baculoviral IAP repeats (BIRs). The BIR domains bind directly to caspases and inhibit their proteolytic activity and molecules that contain an IAP-binding motif (second mitochondrial-derived activator of caspases and Omi) antagonize IAP function via binding to BIR motifs displacing IAP binding to caspases or by promoting their degradation. Therefore, vIAPs act downstream of mitochondria, inhibiting the activity of procaspase 9 and effector caspases 3 and 7 [125]. The antiapoptotic protein p35 from baculovirus is thought to prevent the suicidal response of infected insect cells by inhibiting caspases [126]. Zhou *et al.* [127] showed that purified recombinant p35 inhibits human caspases 1, 3, 6, 7, 8, and 10. There may be interaction of the baculovirus antiapoptotic protein p35 with caspases. Sah *et al.* [128] demonstrated the ability of the p35 gene to inhibit oxidative stress-induced apoptosis. Oxidative damage to cellular macromolecules such as nuclear and mitochondrial DNA and proteins caused by reactive oxygen species is considered to be of key importance in the aging process. The chain of oxidative reactions initiated by ROS eventually knocks down the crucial biomolecules, thereby driving the cellular machinery to undergo apoptosis via the activation of caspases, which ultimately brings about the execution of cell death. p35 is able to directly mop out free radicals and prevent cell death by also acting in an oxidant-dependent pathway at a very upstream step in the cascade of events associated with oxidative stress-induced apoptosis [129].

7.6. Human papillomavirus (HPV)

HPVs are small DNA viruses that are known to be the most common etiological agents in cervical cancer. HPVs are implicated in the mucosal and epithelial infections that may range from a benign lesion to a malignant carcinoma [130]. Recent studies have shown that 13 different types of HPV are associated with carcinogenesis. HPVs are DNA tumor viruses whose genome is organized in three regions: the early gene (E1 to E7), the late gene (L1 and L2) regions, and the upper regulatory region (URR). The late region units, L1 and L2, encode for viral capsid proteins during the late stages of virion assembly. E1 and E2 encode proteins that are vital for extrachromosomal DNA replication and the completion of the viral life cycle. The E4 protein plays an important role for the maturation and replication of the virus. The E5 in open reading frame (ORF) interacts with various transmembrane proteins like the receptors of the epidermal growth factor, platelet-derived growth factor β, and colony stimulating factor-1. E6 and E7 ORF encode for oncoproteins that allow replication of the virus and the immortalization and transformation of the cell that hosts the HPV DNA [131]. The HPV E2 regulates the transcription of E6/E7 and facilitates apoptosis via p53-dependent pathway in HeLa cells [132]. HPV E7 is involved with cell cycling and binds to the retinoblastoma tumor suppressor protein and related proteins and induces apoptosis in mouse lens [133]. The inactivation of p53 by E6 should lead to a reduction in cellular apoptosis. Numerous studies showed that E6 could in fact sensitize cells to apoptosis. HPV E6 induce the degradation of p53. E6 expression correlated with the prolonged expression of Bcl-2 reduces the elevation of Bax and loss of p53. Several studies have shown that E2 could also induce apoptosis independent of its effects on transcription of E6 and E7 [134-136]. Tan *et al.* [137] showed that HPV16 E6 RNA interference enhances cisplatin and death receptor-mediated apoptosis in human cervical carcinoma cells. Moreover, HPV-16 E6 was shown to bind TNF R1 and protect cells

from TNF-induced apoptosis in mouse fibroblasts and human histiocyte/monocyte and osteosarcoma cells. Caspase 3 and caspase 8 activation were significantly reduced in E6-expressing cells [138].

7.7. Adenovirus

Adenoviruses (Ads) were first described as the etiological agents isolated from human adenoids and respiratory secretions that cause spontaneous cytopathic effects in cultures of human cells. Adenovirus has evolved ways to commandeer host cell machinery for successful entry, viral DNA replication, and propagation of progeny virions. Adenoviral proteins interact with host-cell proteins to either exploit or inhibit cellular functions for the purpose of viral propagation. The Ad genome is a 36 kbp linear double-stranded DNA molecule that encodes five early transcription units (E1A, E1B, E2, E3, and E4), two delayed early units, and one major late unit that is processed to make five families of late mRNAs. The early genes are transcribed before viral DNA replication begins, and the late proteins are made following the onset of replication [139]. At least 51 serotypes have been distinguished based on resistance to neutralization by antibodies specific to other known serotypes. These are divided into six subgroups (A-F) based on hemagglutination patterns, oncogenicity, and genome homologies. The common subgroup C Ads, which include Ad serotypes 1, 2, 5, and 6, are endemic virtually all over the world. They cause mild upper respiratory tract infections in young children [140]. Early in infection, the expression of E1A drives the host cell into the S phase of the cell cycle in order to induce DNA synthesis that is required for viral replication. The genes in the E3 region of Ad encode several proteins that function to protect the virus-infected cell from host immune responses [141]. Table 1 describes the adenovirus immunoregulatory proteins and how they function to block or induce apoptosis of infected cells [142-150].

7.8. Human cytomegalovirus

Human cytomegalovirus (CMV), a beta herpes virus with a widespread distribution, is a major cause of morbidity and mortality in immunocompromised individuals such as organ transplant recipients and patients with AIDS. During pregnancy, CMV is a major cause of congenital disease [151]. CMV genes UL36 and UL37 encode viral inhibitor of caspase-8-induced apoptosis (vICA) and viral mitochondria inhibitor of apoptosis (vMIA), respectively. Skaletskaya *et al.* [152] identified a human cytomegalovirus cell-death suppressor denoted vICA and encoded by the viral UL36 gene. vICA inhibits Fas-mediated apoptosis by binding to the prodomain of caspase 8 and preventing its activation. vMIA blocks cytochrome *c* release and activation of downstream effector caspases in a manner analogous to Bcl-2 homologues. Like Bcl-2, vMIA localizes to mitochondria and inhibits mitochondrial permeabilization induced by apoptotic signals [153]. vMIA also counteracts serine protease HtrA2/Omi (high temperature requirement protein A2/Omi stress-regulated endonuclease)-dependent cell death and allows infected cells to survive and continuously produce a virus for several days [154]. Additional human CMV gene products, including IE1 and IE2, as well as the murine CMV UL45 homologue may influence cell susceptibility to apoptosis [155]. Transient transfection assays indicate that the IE1 and IE2 proteins regulate transcription. The IE1 and IE2 proteins

each inhibit the induction of apoptosis by TNF or by the E1B 19-kDa-protein-deficient adenovirus. IE1 and IE2 proteins inhibit apoptosis in part by modulating the activity of p53[156]. In addition, IE1 and IE2 and the viral RNA beta 2.7, which bind to the mitochondrial respiratory complex I, maintain ATP production late in infection and prevent death induced by mitochondrial poison [157].

8. Apoptosis and parasitic infections

Apoptosis plays crucial roles in the interaction between the host and the parasite. This includes innate and adaptive defense mechanisms to restrict intracellular parasite replication as well as regulatory functions to modulate the host's immune response. During their evolution, parasites have developed mechanisms to induce or avoid host cell apoptosis in order to be able to survive and complete their life cycle (Table 1). Among the factors involved in that balance in infected organisms, the time of apoptosis (early or late occurrence), the cell type, and the type of parasitism (intracellular or not) are the major modulators. For example, the early apoptosis of host cells could contribute toward their fight against infection by intracellular parasites; equally, early apoptosis could favor the penetration of the parasite. The late apoptosis of cells of the defense system could be beneficial to the host clearing excess cells, thereby avoiding the detrimental effects of excessive inflammatory response in the tissue that they would cause [158].

8.1. *Toxoplasma gondii*

Toxoplasma gondii is a species of parasitic protozoa in the genus *Toxoplasma*. Humans can become infected with *T. gondii*, either through contact with soil contaminated by cat feces or by eating infected meat. Toxoplasmosis is usually asymptomatic because our immune system keeps the parasite from causing illness. The disease is more problematic for pregnant women and people who have weakened immune systems. Some results indicate a strong correlation between schizophrenia, brain cancer, and toxoplasmosis [159]. Toxoplasma promote or inhibit apoptosis. Begum-Haque *et al.* [160] demonstrated marked difference in the death of activated T cells between early (day 3 post infection) and acute (day 6 post infection) stage of *T. gondii*. The decreased production of IL-2 and augmented synthesis of IL-10 during acute stage of *T. gondii* infection may have a role in the enhanced level of apoptosis. It has been suggested that the apoptosis of T lymphocytes in *T. gondii* infection is associated with the virulence and density of the parasite in the host. In *T. gondii* infection, IFN-γ locally produced in Peyer's patches contributes to the induction of apoptosis in Peyer's patch T cells [160]. *T. gondii* inhibits the apoptosis of host cells by indirect and direct mechanisms. Granulocyte colony-stimulating factor and granulocyte-macrophage cerebrospinal fluid secreted by *T. gondii*-infected human fibroblasts increased the expression of antiapoptotic Bcl-2 family member Mcl-1 and abolished apoptosis in neutrophils *in vitro* indirectly [161]. Many studies have shown that *T. gondii* has evolved strategies to directly inhibit cell apoptosis by various mechanisms: (a) increased expression of antiapoptotic members of the Bcl-2 protein family; (b) inhibition of the cytochrome *c* release; (c) upregulation of IAP_s; (d) activation of NF-κB by *T. gondii* in distinct cell

types or under distinct conditions thereby inducing the transcription of genes encoding antiapoptotic molecules, including Bfl-1 and IAPs; and/or (e) degradation of the PARP as described is involved in the inhibition of apoptosis. Although direct evidence is still lacking, it appears plausible that diminished PARP levels in *Toxoplasma*-infected cells may inhibit apoptosis in a caspase-independent fashion [162].

8.2. *Plasmodium falciparum*

Plasmodium falciparum is the agent of malaria. Enhanced levels of RBC apoptosis have been observed in clinical disorders in which anemia is a common feature such as iron and renal insufficiency, thalassemia, sickle-cell disease, and apoptosis has been associated to cerebral malaria, thrombocytopenia, and lymphocytopenia in malaria infection [163].

P. falciparum induces oxidative stress, which in turn activates the Ca^{+2} permeable cation channels followed by Ca^{+2} entry, and the stimulation of eryptosis has been coined to describe the suicidal erythrocyte death. The Ca^{+2} uptake, however, eventually triggers eryptosis of the parasitized erythrocyte, and thus the parasitized erythrocytes is doomed to be phagocytosed by macrophages [164].

P. falciparum firstly enter red blood cells. Second, parasitized red blood cell sticks endothelial cells, inducing the expression of iNOS in brain cells. The activation of caspases 8 and 9 results in apoptosis and blood-brain barrier disruption [165].

8.3. Trypanosomatids

Trypanosomatids are the causative agents of diseases such as the Chagas disease and the African sleeping sickness [166]. Trypanosomatids lack some of the key molecules contributing to apoptosis in metazoans like caspase genes, Bcl-2 family genes, and the TNF-related family of receptors. Apoptosis triggered in response to heat shock, prostaglandins, antibodies, and mutations in cell cycle regulates genes [167]. These stimuli result in loss of $\Delta\Psi m$, generation of ROS, lipid peroxidation, and increase in cytosolic Ca^{2+}. This also potentiates the release of cytochrome *c* and EndoG into the cytoplasm and the activation of proteases and nucleases to dismantle the parasites in an ordered fashion. Upon release from the mitochondrion, EndoG translocates to the nucleus to degrade DNA. These events finally lead to the execution of apoptosis [168]. *Trypanosoma brucei* causes neuronal demyelination and apoptosis after blood-brain barrier damage. This leads to apoptosis in cells of the cerebellum and brain stem. Welburn *et al.* [170] described cytoplasmic vacuolization and marginalization, extensive membrane blebbing, and condensation of nuclear chromatin in *Trypanosoma cruzi* and *T. brucei* respectively. Lectins such as ConA were among the first compounds shown to induce the expression of apoptotic markers in *T. brucei* [169]. *T. cruzi* is the etiological agent of Chagas disease. It also inhibits apoptosis through the action of parasite-derived neurotrophic factor, a parasite-derived protein in neuronal and glial cells. The parasite-derived neurotrophic factor is both a substrate and an activator of the serine-threonine kinase Akt and an antiapoptotic molecule binding to the neurotrophic surface receptor TrkA (neurotrophic tyrosine kinase receptor type 1) triggering the PI3-K/PKB pathway resulting in increased Bcl-2 expression.

This results in protection of Schwann cells from apoptosis induced by H_2O_2 and TNF-α/TGF-β (transforming growth factor b) [170-172].

8.4. *Leishmania*

Leishmanias are agents of ulcerative skin lesions (cutaneous leishmaniasis) and disseminated visceral infection (visceral leishmaniasis or kala-azar). Leishmania is able to inhibit the spontaneous apoptosis of short-lived neutrophils, increasing their life span and providing a safe place for the parasites during the first days of the infection [173]. With most apoptosis inducing stimuli, *Leishmania donovani* shows typical features of apoptotic death like cell shrinkage, nuclear condensation, and DNA fragmentation. Ca^{2+} appears to be a vital ion involved in Leishmania apoptosis. Extracellular or intracellular Ca^{2+} during oxidative stress results in the significant rescue of the fall of the mitochondrial membrane potential and consequently apoptosis [174].

9. Concluding remarks

- Apoptosis is a genetically programmed process of cellular destruction that is indispensable for the normal development and homeostasis of multicellular organisms.
- Microorganisms induce apoptosis by intrinsic and extrinsic pathway in the host cell.
- T3SS effectors have also been shown to tamper with the host's cell cycle, and some of them are able to induce apoptosis bacteria such as *Pseudomonas*, *Shigella*, *Salmonella*, and *Yersinia*.
- Microorganisms inhibit apoptosis by multiple mechanisms: protection of the mitochondria and prevention of cytochrome *c* release (i.e., *Chylamidia* sp. and/or *Neisseria* sp.), activation of cell survival pathways (i.e., *Salmonella* sp. and/or *Rickettsia* sp.), inhibition of caspases, activation of phosphoinositide 3-kinase (PI3K)-Akt/protein kinase B (PKB) pathway, and interaction with cellular caspases (i.e., *Shigella* sp. and/or *Legionella* sp.)
- Prevention of apoptosis enables microorganisms to replicate and survive in host.
- A clear understanding of the molecular basis of apoptosis inhibition or induction is needed.
- Elucidation of the mechanisms, the cellular receptors, and/or the microbial factors involved in modulating of apoptosis could reveal insights into the host-pathogen relationship and new therapeutic targets.

10. Abbreviations

AIF: apoptosis inducing factor

AP-1: activator protein 1

BH: Bcl-2 homology

CARD: caspase activation and recruitment domain

CMV: cytomegalovirus

CTL: cytotoxic T lymphocyte

DD: death domains

DED: death effector domain

$\Delta\Psi_m$: transmembrane potential

EBV: Epstein-Barr virus

FADD: Fas-associated death domain

GSK-3: Glycogen synthase kinase 3

JNK: c-Jun N-terminal kinase

HIV-1: human immunodeficiency virus type 1

IAPs: inhibitors of apoptosis proteins

IL-1β: interleukin 1β

ICE: IL-1β converting enzyme

I-KB: inhibitor of KB

IKK: I-KB kinase

IPA: invasion plasmid antigens

LlyO: listeriolysin O

MOMP: mitochondrial outer membrane permeabilization

NF-κB: nuclear factor-kappa B

TLR: toll-like receptors

TNF: tumor necrosis factor

TNFR: tumor necrosis factor receptor gene

TRAIL: tumor necrosis factor (TNF)-related apoptosis-inducing ligand

T3SS : type III secretion system

PI3K: phosphoinositide 3-kinase

PKB: protein Kinase B

PMLs: polymorphonuclear leukocytes

proIL: prointerleukin

PT: permeability transition

ROS: reactive oxygen species

RV: Rabies virus

SAPK: stress-activated protein kinase

STS: staurosporine

VDAC: voltage-dependent anionic channel

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