Chapter 6

Signaling Pathways Targeted by Protozoan Parasites to Inhibit Apoptosis

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Abstract

Apoptosis is a biological process carried out during maturation, remodeling, growth, and developmental processes in tissues, and also represents an important defense mechanism of cells against intracellular microorganisms. In counterpart, diverse intracellular pathogens have developed a wide array of strategies to evade apoptosis and persist inside cells. Apoptotic cell death can be triggered through different intracellular signaling pathways that lead to morphological changes and eventually cell death. Among these pathways, MAPK and PI3K play a central role. The precise control of the signaling pathways that lead to apoptosis is crucial for the maintenance of tissue homeostasis. Paradoxically, these same pathways are utilized during infection by distinct intracellular microorganisms in order to evade recognition by the immune system, inhibit apoptosis, and therefore survive, reproduce, and develop inside cells.

Keywords: apoptosis, inhibition, protozoan parasites, signaling pathways

1. Introduction

The word apoptosis has its etymological origin in the Greek *apó,* which means "from" and *ptōsis* which means "falling off." The merging of these two words is an allusion to the natural events of shedding cells and tissues, as well as the falling of old leaves during autumn. Apoptosis describes the process in which unwanted, damaged, or old cells are eliminated in multicellular organisms [1], which is necessary in all body tissues and happens naturally during

embryogenesis, metamorphosis, and constant cellular changes, being of upmost importance for the maintenance of homeostasis in all tissues [2]. The term apoptosis was coined since 1972 by Kerr, to define a type of programmed cell death with morphological and molecular characteristics different from other types of cell death. These characteristics include retraction of pseudopods with the consequent reduction of cellular volume and rounding of the cell, nuclear volume reduction (pyknosis) and fragmentation (karyorrhexis), structural modification of organelles followed by the formation of vesicles due to blebbing of the plasma membrane [3, 4]. Apart from being a fundamental process of cells for the maintenance of homesostasis, apoptotic cell death represents an important defense mechanism against intracellular pathogens. Against it, a wide spectrum of microorganisms has developed diverse strategies to inhibit apoptosis of their host cells. These strategies involve different signaling pathways that are hijacked by pathogens to achieve their goal of inhibiting apoptosis and persist inside cells. The purpose of this chapter is to better understand the signaling pathways that are targeted by protozoan parasites in order to evade the defense mechanism of apoptosis.

2. Generalities of apoptosis

2.1. Initiation of apoptosis

The activation of apoptosis requires the assembly of an intricate web of intracellular signaling pathways that occurs in three phases: initiation or activation, execution, and cellular demolition that are triggered in three different ways: the extrinsic pathway, the intrinsic pathway (subdivided in mitochondrial-induced apoptosis and endoplasmic reticulum stress-induced apoptosis) and the caspase-independent pathway [5–9].

2.1.1. The extrinsic pathway

This pathway is activated through extracellular stress signals that are detected and amplified by transmembrane receptors called death receptors [10–12]. Some of these receptors include the Tumor Necrosis Factor receptor (TNFR), Fas receptor (CD95), DR3/WSL, and Apo-2L (TRAIL-R1/DR4, TRAIL-R2/DR) [13, 14], which are characterized for the presence of intracellular domains called death domains (DD), which include the TNFR or TRADD and Fas or FADD death domains [15]. Once receptors become engaged with their respective ligands, activating proteins such as RIPK1, FADD, c-FLIP, c-IPAs, and ubiquitin ligase E3 are recruited [16–21], and in consequence, a supramolecular complex is formed by the activating protein-receptor domain that is recognized as a Death-Inducing Signaling Complex (DISC), which activates procaspase 8, the precursor of caspase 8 [16, 18–22]. In some cases, the extrinsic pathway can be triggered without a ligand as is the case of DCC and UNC5B receptors where, in the absence of a ligand, DCC interacts with cytoplasmic adapting protein DRAL to assemble an activation platform for caspase 9 [23]. In a similar manner, the UNC5B receptor, in the absence of netrins, recruits a molecular complex composed of PP2A and Death Associated Protein Kinase 1 (DAPK1) [24]. In both cases, caspase 8 is activated to initiate cell death via apoptosis.

2.1.2. The intrinsic pathway

The mitochondrial intrinsic pathway can be initiated by different intracellular stimuli such as irreversible genotoxic damage, increase in the cytoplasmic calcium (Ca^{+}) concentration, oxidative stress, among others [15]. In this pathway, a family of proteins called Bcl-2, characterized for having from 1 to 4 conserved domains that share homology with Bcl-2 or BH [6], has a leading role. This family is composed of proapoptotic proteins that, according to the BH domains that possess, are divided into Bax and "BH3 only" subfamilies. The members of the Bax subfamily are Bak, Bax, Bok, and Mtd and possess three BH domains (BH1-BH3), while the "BH3 only" subfamily, as denoted by its name, possesses a single BH3 domain and is composed of Bid, Bad, Bim, Bik, Blk, Hrk, NOXA or PUMA. On the other hand, the antiapoptotic proteins family present four BH domains (BH1-BH4) and is composed of Bcl-2, Bcl-XL, Bcl-W, Bfl-1, and Mcl-1 [6]. The BH1 and BH2 domains are structurally similar to the diphtheric toxin [25, 26]. The antiapoptotic proteins Bcl-2 and Bcl-xL are located in the outer mitochondrial membrane and prevent the release of cytochrome c, while the proapoptotic proteins Bad, Bid, Bax, and Bim are located in the cytosol and under certain stimuli are translocated to the mitochondria, where they induce the release of cytochrome c [25, 26]. Additionally, caspase 8 may take part in the intrinsic pathway through Bid proteolysis, turning it into tBid, which also translocates to the mitochondria and activates Bcl-2, Bax, and Bak [27]. Once Bax and Bak have been translocated to the mitochondrial membrane, a molecular complex referred to as PTPC is activated and induces the Mitochondrial Transition Permeability (MTP) phenomenon [28, 29]. These events culminate in the permeabilization of the outer mitochondrial membrane or MOMP, which is the rate-limiting step in apoptosis that conducts to an energetic and metabolic damage and the cell faces irreversible apoptotic cell death. The release of cytochrome c from the mitochondrion permits its association with the Apoptosis Activation Factor (Apaf-1) thus forming a structure to which procaspase 9 is incorporated, originating a molecular complex referred to as the apoptosome. As procaspase 9 is activated, it recruits executor caspases 3 and 7, which causes a proteolytic effect inducing cell death [27]. As mentioned earlier, the intrinsic pathway can also be activated via endoplasmic reticulum stress whose main stimulus is the misfolding of proteins and their subsequent accumulation in the endoplasmic reticulum (ER). Once misfolded proteins reach a critical concentration, they activate ER membrane sensors [30].

The induction of apoptosis conducts hopelessly to the activation of caspases; nevertheless, the damage to the mitochondria can, in some cases, provoke the release of some molecules with proapoptotic capacities such as HTRA2, AIF and ENDOG that have the ability to induce apoptosis without the intervention of caspases. HTRA2 has the ability to attack proteolytically the cytoskeleton, while AIF and ENDOG can enzymatically attack DNA [31].

2.2. Caspases

Caspases (**C**ysteine-dependent, **ASP**artate-specific peptid**ASE**) owe their name to the fact that their proteolytic functions lie specifically in an aspartate residue and require the presence of cysteine to perform their catalytic activity [6]. There are many types of caspases and are classified according to their function in initiation caspases: 2, 8, 9, and 10; executor caspases: 3, 6,

and 7; and inflammatory caspases: 1, 4, and 5. In addition, there are other caspases that perform diverse functions such as caspase 11, which regulates cytokines during septic shock, caspase 12 that is associated with endoplasmic reticulum stress apoptosis, and caspase 14, which has only been isolated in embryonic tissue, specifically in keratinocytes. Caspases are found in cells in an inactive state called zymogens or procaspases that possess three distinct regions: a prodomain located in the N-terminal end, a minor subunit close to the C-terminal end and, in between, the major subunit. Procaspases are activated through autoactivation or activation by another caspase or molecule that cause the excision in two sites of the aspartate residues, the first one between the prodomain region and the major subunit, and the second between the major and minor subunits [32]. The activation of caspases starts with an initiator caspase that requires the formation of a multimeric adaptor protein complex called apoptosome whose formation is mediated by Apaf-1, an inactive monomer in nonapoptotic cells [31]. MOMP-mediated release of cytochrome c triggers the formation of the apoptosome through the binding of cytochrome c to Apaf-1 on the WDR domain, following by the conversion of ADP into dATP/ATP in the NOD domain [33–35]. Finally, procaspase 9 binds to Apaf-1 through a homotypical interaction with the CARD domains [36]. The apoptosome catalyzes the autoproteolytic action of procaspase 9, and its active form, caspase 9, remains active and bound to Apaf-1 as a holoenzyme [36].

2.3. Cellular demolition

Once apoptosis is triggered through one of the different pathways just explained, the activation of caspase 9 unchains a cascade of executioner caspases [6, 15], whose proteolytic action is directed to multiple substrates that finally culminate in the demolition of the cell. One central substrate targeted by caspases is ROCK1, an actin cytoskeleton activity regulator that upon activation loses its C-terminal end, subsequent phosphorylation, and thus activation of the myosin for is subsequently phosphorylated, and thus activates the myosin light chain, which generates actin contraction that in turn triggers several phenomena such as phosphatidylserine translocation, cellular rounding and retraction, as well as vesicle formation or blebbing and loss of intercellular unions due to the proteolytical attack of desmosomes or other forms of cell to cell junctions. It also affects nuclear membrane integrity and provokes further fragmentation of DNA and degradation of proteins associated with transcription and translation [6, 37–49]. Other targets attacked by caspases are, for example, the caspase-activated DNase (CAD), whose activation culminates in DNA degradation at internucleosomal sites [49] or Golgi reassembly and stacking proteins (GRASP)that participate in Golgi apparatus conformation, cistern formation and connections leading to Golgi fragmentation and disintegration [6, 50]. Continuing with the demolition events, the mitochondrial proteins Bax and Bak are activated due to BH3 action, which in turn generate pores in the mitochondrial membranes and release of their contents. Also, the p75 subunit of the electron transport chain complex 1 is proteolytically degraded [6, 50]. One of the final acts of apoptosis is the release of chemotactic cytokines and other molecules, as well as the formation of union sites for phagocytic cells indispensable for the elimination of cellular remains by phagocytes for these cells [6, 51].

3. Signal transduction pathways in apoptosis

3.1. MAPK family

For apoptosis to be carried out an orchestrated array of signal transduction pathways needs to be put into action among which mitogen-activated protein kinases (MAPK) play a leading role.

These mitogen-activated protein kinases, as denoted by their name, are activated not only by mitogens but also by other physical and chemical stimuli, such as growth factors, UV radiation, genotoxic agents, oxidative stress, inflammatory signals, and cytokines. Once activated, MAPK go through three secuencial phosphorylation steps [52], carried out by three groups of enzymes: (1) MAPK kinase kinase (MAPKKK or MAP3K), for example ASK1; MAPK kinase (MAPKK), for example MEK 1 through 7; MAPK such as ERK 1/2, JNK, and p38. MAPKs belong to the serine-/threonine-type kinases [53, 54] and possess tyrosine (Tyr) and threonine (Thr) conserved double phosphorylation domains [52]. They are further divided in three subfamilies according to the amino acid present in both phosphorylation sites (Thr-XXX-Tyr) [53–55]:

1. The p38-MAPK subfamily features glycine between the two phosphorylation sites (Thr-Gly-Tyr) and is activated through stress signals, growth, and differentiation factors. This subfamily is composed of the p38-MAPKα, p38-MAPKβ, p38-MAPKγ, and p38-MAPKδ isoforms that share a 12-amino acid activation loop and differ in affinity for the activating protein, tissue expression, and downstream effect. The p38α isoform, commonly referred to as p38, as well as the p38β isoform are ubiquitous being present in almost every tissue, while p38γ and p38δ isoforms have a more restricted localization. When p38 is activated, it initiates the three rounds of phosphorylation that culminate in the phosphorylation of p38 specifically at Thr180 and Tyr182 sites. This phosphorylation process produces conformational changes that lead to the enzyme binding with ATP and the acceptor substrate of the phosphate [56]. This subfamily participates in the regulation of certain growth factors, kinases and phosphatases, as well as in the regulation of ATF-2, MEF2, MAPKAPK, CDC25 or MSK1/2 and their activation triggers cellular proliferation, differentiation, apoptosis, among others [57, 58].

2. The JNK subfamily features proline between the two phosphorylation sites (Thr-Pro-Tyr) and is composed by the JNK1, JNK2, and JNK3 isoforms. These proteins are also known as stress-associated MAPKs or SAPKS (stress-activated protein kinases) and participate in cellular growth, differentiation, and apoptosis [59, 60] as a response to diverse stress signals, such as UV or gamma radiation, protein synthesis inhibitors (anisomycin), hyperosmolarity, toxins, ischemic damage, thermal shock, antineoplastic drugs, peroxides, and inflammatory cytokines, among others [59]. Stress signals initiate the three cycles of phosphorylation with the activation of MAP3K, ASK1 and ASK2, among others, which in turn activate MEK4 and MEK7 through phosphorylation of two specific serine and threonine residues. Finally, MEK4 and MEK7, also known as MKK4 (SEK1/JNKK1) or MKK7 (SEK2/JNKK2) phosphorylate JNK in threonine-proline-tyrosine (Thr-Pro-Tyr) specific residues [59, 61, 62]. Interestingly, the biological roles of JNK isoforms are similar [63], although they are physically different and also differ in tissue localization. JNK1 and JNK2 are expressed in all tissues, while JNK3 isoform is found predominantly in nervous tissue, and to a lesser extent in the heart and sperm [64–66]. Although JNK1, JNK2, and JNK3 can all induce apoptosis, there is evidence suggesting that each protein induces apoptosis through a different pathway. It has been demonstrated that all of them associate with p53, a nuclear transcription factor that activates proapoptotic gene expression, such as BAX or PUMA, but interestingly their expression varies with respect to p53. In the case of JNK1, its expression is inversely proportional to p53, contrary to JNK2 expression, which is directly proportional to p53. Both JNK2 and JNK3 can phosphorylate p53, while JNK1 can only modify it post-transcriptionally [67, 68].

3. The ERK subfamily features glutamic acid between the two phosphorylation sites (Thr-Glu-Tyr) and is composed of ERK1, also known as MAPK3, and ERK2, also known as MAPK1 or p42MAPK [62, 69]. These kinases are activated by growth factors, hormones,

and neurotransmitters through binding to different G-protein coupled receptors, tyrosine-kinase receptors, and ion channels. Then, signal transduction continues with an adaptor protein that transmits the signal to a MAP3K of which several have been described for ERK such as Raf-1B-Raf, A-Raf, and TPL2 [62]. Following the described phosphorylation pattern (MAPKKK → MAPKK → MAPK), the stimulus activates MAPKKK (i.e., Raf-1), which in turn phosphorylates MEK1 and MEK2 (both MAPKK) and these finally phosphorylate and activate ERK1 and ERK2 [62].

3.2. MAPK participation in apoptosis

One of the upmost actions of MAPK is the activation of transcription factors, which regulate the expression of genes that lead to crucial molecular events in the cell regarding growth, proliferation, inflammatory cytokine production, and apoptotic cell death [56]. In relation to apoptosis, a key participant is JNK that plays its role through two different mechanisms. The first one is related to nuclear events in which JNK is translocated to the nucleus and activates c-Jun and other transcription factors that promote proapoptotic gene expression, through p53/73 or c-Jun/AP1-dependent mechanisms [70, 71]. The second mechanism relates to JNK activation and translocation to the mitochondria, where it promotes the phosphorylation of protein 14–3-3, a protein that normally inhibits Bax by being bound to it. As protein 14–3-3 is phosphorylated, Bax is released and translocates to the interior of the mitochondria where it oligomerizes and forms pores in the mitochondrial membrane with the subsequent release of cytochrome c and apoptosis induction through the intrinsic pathway. Apart from these two mechanisms, JNK can also phosphorylate "BH3-only" family members, whose antiapoptotic effect inhibits Bcl-2 and Bcl-xL and is also involved in the posttranslational modifications of Bid and Bim, both of which induce Bad and Bax activity [70, 71]. Another MAPK deeply involved in apoptosis is p38, which in many times is simultaneously activated with JNK [72]. p38 exerts its central role in apoptosis through the activation of proapoptotic proteins, mainly BimEL, BAD, and Bax [73–77] and simultaneously induces the inhibition of ERK and Akt antiapoptotic pathways [76, 77]. Also, p38 and JNK participate in TLR signaling pathways. These key participants of the innate immune response function as regulatory sensors of both apoptosis signaling through the induction of MAPK p38 and JNK [78, 79] and survival signals through PI3K and some Bcl-2 family members [80–82].

4. PI3K/Akt signaling pathway and its participation in apoptosis inhibition

As previously mentioned, MAPK p38 and JNK play an important role in apoptosis induction. On the other hand, PI3K activation promotes cellular survival. PI3K is a heterodimer formed by a p85 regulatory subunit and a p110 catalytic subunit responsible for phosphate transfer. The signaling pathway initiated by this kinase is activated by different stimuli, with growth factors standing out among them. Once a ligand binds to the tyrosine specific tyrosine-kinase receptor, an IRS adaptor protein is activated, which in turn activates the regulatory PI3K subunit and generates a conformational change that allows the binding of the catalytic subunit and thus the assembly of the active molecule that catalyzes the conversion of PIP_2 into PIP_3

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[83, 84]. PIP_3 interacts with the pleckstrine homology (PH) domain, located in the N-terminal region of the serine/threonine kinase Akt or PKB, with the final result of the kinase being recruited to the plasma membrane [85–87]. Furthermore, PDK1 phosphorylates Akt/PKB producing a conformational change that facilitates a second phosphorylation by the rictor-mTOR1 complex [88]. Finally, the PI3K/Akt pathway leads to diverse effects associated with cellular proliferation and survival [89, 90]. Specifically, it produces the inactivation of many proapoptotic signals, such as BAD, procaspase-9, and FKHR (Forkhead) transcription factors [21, 91]. It also promotes the activation of CREB, NF-κB, and HIF-1α transcription factors, which in turn activate the expression of antiapoptotic genes [92–94].

5. Apoptosis inhibition and infection

Apoptosis constitutes a very important defense mechanism against intracellular microorganisms [95], whom in order to survive inside cells need to inhibit the induction of apoptosis. It has been demonstrated that diverse intracellular pathogens including virus [96], bacteria [97], and protozoan parasites [98] have developed mechanisms to persist within host cells without inducing apoptosis.

5.1. Inhibition of apoptosis by *Leishmania*

Leishmania is an obligate intracellular parasite that infects a variety of cells such as neutrophils, macrophages (Mφ) and dendritic cells (DC). *Leishmania* has developed diverse mechanisms to manipulate host cells in order to evade the immune response and survive inside cells. Some of these strategies are the evasion of the phagosome-lysosome fusion and the inhibition of apoptosis. Studies have demonstrated that monocytes, macrophages, and dendritic cells grown in apoptogenic conditions and infected with different species of *Leishmania* present an inhibition of normal apoptosis. Also, *Leishmania* infection prevents natural apoptosis of neutrophils. The first demonstration of the inhibition of apoptosis by *Leishmania* was performed by Moore and Matlashewski in 1994 who demonstrated that the infection of bone marrow derived-macrophages (BMM) with *Leishmania donovani* promastigotes or the stimulus with LPG inhibited apoptosis induced by the deprivation of M-CSF. Interestingly, the culture supernatant of infected BMM was able to inhibit apoptosis suggesting that the effect could be due to soluble mediators [99]. A later study showed that cellular activation increased the production of TNF-α, TGF-β, IL-6, and GM-CSF, while the secretion of M-CSF and IL-1β diminished [100]. Studies performed later with another species, *Leishmania major*, showed that the infection of macrophages grown in the absence of M-CSF or in the presence of staurosporine inhibited the release of mitochondrial cytochrome c, thus delaying apoptosis. It was observed that the infection of BMM with *L. major* promastigotes inhibited caspase-3 activation owed to a decrease in MOMP and subsequent release of cytochrome c, which was not associated to NF-κB activation since the use of specific inhibitors did not affect the capacity of L. major to inhibit macrophage apoptosis. It was also demonstrated that the infection of BMM obtained from BALB/c o C57BL/6 mice with *L. major* promastigotes preserved the phenomenom of apoptosis inhibition despite the genetic background of the host or type of immune response (Th2 or Th1, respectively) [101]. Also, studies performed with cell lines reported

similar results as in the case of the monocyte cell line U937 infected with *Leishmania infantum* where inhibition of actinomycin D-induced apoptosis was observed [102] or in macrophages from the cell line RAW 264.7 infected with *Leishmania major* where apoptosis diminished even in the presence of cycloheximide [103]. In neutrophils, it has been observed that spontaneous apoptosis is inhibited by *Leishmania major* due to a decrease in caspase-3 activity [104]. It has also been demonstrated that amastigotes and promastigotes of *Leishmania mexicana* inhibit camptothecin-induced apoptosis in monocyte-derived dendritic cells [105, 106]. Moreover, *Leishmania* parasites are characterized for presenting differences among different species and also intraspecific. In particular, it has been shown that different strains of *L. major* cause diverse clinical manifestations in susceptible BALB/c mice [107]. While the infection with the strains V1 and IR137 could be resolved, the infection with the LV39 strain presents a severe course of infection, which cannot be resolved. The infection of RAW 264.7 macrophages with the less virulent strains (V1 e IR37) of *L. major* showed a lower degree of inhibition of apoptosis as compared to the infection with the more virulent (LV39) [103].

6. Signaling pathways involved in the inhibition of apoptosis by *Leishmania*

As it has been just mentioned, *Leishmania* has the capacity to inhibit apoptosis of different cells; however, the mechanisms involved in this inhibition have not been fully deciphered. MAPK and PI3K have been implicated due to their participation in apoptosis and the intervention of *Leishmania* with these kinases. Regarding the role of *Leishmania* infection in the modulation of proapoptotic pathways such as MAPK, it has been shown that *L. mexicana* amastigotes and promastigotes significantly reduced MAPK JNK and p38 phosphorylation in monocyte-derived dendritic cells [108, 109]. Other authors working with the same species showed that the inhibitoy effect in the activation of MAPK in dendritic cells was only observable in immature dendritic cells since maturation driven by the stimulation with LPS did not suppress MAPK phosphorylation, in particular JNK [110]. In bone marrow macrophages (BMM), previously stimulated with IFN-γ, it was also shown that *L. donovani* promastigotes exerted a similar effect of inhibiting the activation of p38, JNK, and ERK that was directly associated with TNF-α production, which ensured the survival of the parasite [111]. Other authors also demonstrated that inhibition of p38 was associated with an increase in the number of infected macrophages and parasite survival [112]. Interestingly, not only the parasite but also some surface components such as gp63 have been shown to inhibit the apoptotic signaling of MAPK p38 [113]. Other studies have shown that *Leishmania* infection can also activate MAPK as demonstrated with the infection of neutrophils with *L. major* that caused the transient activation of ERK1/2, which delayed apoptosis and the pharmacological inhibition of ERK1/2 phosphorylation reversed the effect. Moreover, the infection of neutrophils with *L. major* led to the enhanced and sustainable expression of the antiapoptotic proteins Bcl-2 and Bfl-1. As downstream events, the release of cytochrome c from mitochondria and processing of caspase-6 were inhibited, as well as a reduced expression of FAS on the surface of neutrophils [114]. In BMM the infection with infected with *L. amazonensis* it has been observed that ERK 1/2 activation generates an epigenetic modification in the IL-10 locus, which results in a great induction of this cytokine in the infected macrophages [115]. Also, macrophages grown in the presence

of LPG show an altered production of IL-12 associated with ERK activation and signaling [116]. Other authors demonstrated that ERK 1/2 activation induced by *L. amazonensis* yielded a lesser expression of CD40 and IL-12 production in bone marrow derived dendritic cells, with the subsequent inhibition of dendritic cell maturation. Specific ERK 1/2 inhibition induced the production of NO which caused an increase in parasite death [117]. Interestingly, *Leishmania* infection not only intervenes with signaling pathways that induce apoptosis but also with pathways that promote survival as it has been shown with the infection of BMM with *L. major* and *L. pifanoi* promastigotes that promotes resistance to apoptosis through activation of PI3K/Akt. It was also demonstrated that Akt phosphorylates Bad, which in turn interacts with the 14–3-3 protein, inhibiting it and boosting the antiapoptotic action of Bcl-2 [118]. It has also been demonstrated that infection of monocyte-derived dendritic cells with *L. mexicana* amastigotes activated antiapoptotic signals, such as PI3K/Akt phosphorylation [108]. Recently, the participation of Akt in the inhibition of apoptosis by *Leishmania* has been more widely analyzed. The infection of BMM or RAW 264.7 with *L. donovani* promastigotes and treated both with a specific Akt inhibitor or a dominant negative construct diminished the antiapoptotic effect, increased the production of IL-12, and decreased the production of IL-10, which resulted in loss of parasite survival. It was shown that in infected cells FOXO-1, a transcriptional regulator of pro-apoptotic proteins, is found mainly in the cytoplasm. The transfection of cells with FOXO-1, constitutively active that cannot be phosphorylated Akt and thus remained sequestered in the nucleus, led to a reduction of the antiapoptotic effect in infected period. Also, it was observed that the activation of Akt, induced by the infection of macrophages with L. *donovani* promastigotes, causes the inactivation of GSK-3β (Glycogen synthase kinase 3 beta), which permits the release of β-catenin in order to initiate the transcription of antiapoptotic proteins. It was shown that in infected cells and transfected with the constituvely active construct for GSK-3β by silencing β-catenin there was a loss in mitochondrial membrane potential along with the activation of caspase-3 and production of IL-12 [119]. This was the first observation showing that the reversion of the antiapoptotic effect diminishes parasite survival, which suggests that the Akt pathway is a pivotal step in the modulation of the cellular machinery since *Leishmania* through the modulation of Akt is capable of activating antiapoptotic proteins, inhibiting pro-apoptotic and also inhibiting the production of IL-12 [119].

Continuing with the role of *Leishmania* in modulating antiapoptotic pathways it has been shown that in murine macrophages infected with *L. donovani* promastigotes and treated with the apoptosis inductor, actinomycin D, there was an increase in the mRNA levels and protein level of MCL-1. Interestingly, the silencing of MCL-1 in infected cells dampened the antiapoptotic effect in a similar way as the silencing of the transcription factor CREB, which diminished the expression of MCL-1 and increased the apoptosis of cells [120]. In a different study, several populations of macrophages (derived from peripheral blood, THP-1 and murine) were infected with *L. donovani* and the expression of Bcl-2 increased twice with respect to uninfected cells. Also, the use of specific inhibitors for Bcl-2 increased the level of NO, which diminished the parasite load of the cells. Interestingly, it was shown that in patients with visceral leishmaniasis, there was an increase in the expression of Bcl-2 and the levels of NO in serum were very low [121].

Recently, the receptor of programmed death 1 (PD-1) has been associated with the effect of inhibition of apoptosis in cells infected with *Leishmania.* The induction of apoptosis with H_2O_2

in BMM and RAW 264.7 cells increased the expression of PD-1, while the infection with *L. donovani* diminished it along with the induction of apoptosis. The activation of PD-1 pathway was found to negatively regulate the phosphorylation of pro-survival AKT, which was reversed during infection [122].

During the induction of apoptosis, reactive oxygen species (ROS) are produced; on the other hand, an overproduction of (ROS) induces apoptosis. The analysis of the effect of *Leishmania* in the modulation of ROS was analyzed in RAW 264.7 macrophages treated with H_2O_2 and infected with *L. donovani* promastigotes and was observed that the parasite did not affect the level of ROS and apoptosis was inhibited along with a decrease in caspase 3 and 7, which could be due to Suppressor Of Cytokine Signaling (SOCS) along with the activity of thioredoxin and tyrosine phosphatases. The silencing of SOCS genes diminished thioredoxin levels and increased apoptosis of cells [123]. Recently, De Souza-Vieira et al. demonstrated the activation of two PI3K isoforms, PI3K γ (ROS dependent) and PI3K δ (ROS independent) in neutrophils infected with *L. amazonensis*. The activation of these isoforms, in turn, activates the ERK pathway downstream, which is associated with the process of netosis with the subsequent activation of ROS and the release of neutrophil extracellular traps (NETs) [124].

7. Inhibition of apoptosis by *Trypanosoma cruzi*

7.1. Immune response to *T. cruzi*

Chagas' disease affects nearly 8 million people in Latin America [125] and is caused by the intracellular parasite *Trypanosoma cruzi*. The infection with *T. cruzi* is characterized by an acute phase that can be controlled by the immune system of the host. Afterwards, patients can remain asymptomatic or develop a chronic phase that affects mainly the heart and peripheral nervous system [126, 127]. In some cases, patients seem asymptomatic although they present several damages. *T. cruzi* has the capacity to infect virtually any cell where infective tripomastigotes reach the cytoplasm, replicate, lyse the cell and infect other cells. One of the cells inside the mammalian host where *T. cruzi* replicates is the macrophage. These cells are crucial for the immune response against the parasite because, depending on the stimulus, can be classically or alternatively activated. Classically activated macrophages (M1) produce nitric oxide (NO) that has the capacity of killing *T. cruzi*, whereas alternatively activated macrophages, belonging to the M2 spectrum, synthesize polyamines that actually promote infection [128, 129]. Thus, one of the most important mechanisms of protective immunity against *T. cruzi* is the classical activation of macrophages for the elimination of the intracellular parasites. *T. cruzi* must control the activation of macrophages and inhibit apoptosis in order to perpetuate inside the cells. To achieve this, parasites must reduce the production of toxic molecules, including NO and its derivatives [130, 131] and must escape from the parasitophorous vacuole [132].

The development of a specific immune response against *T. cruzi* overcomes the evasion strategies displayed by the parasite. Antibodies as well as T cells are required for the control of infection [133–135], where both CD4 and CD8 T cells produce IFN-γ that activates macrophages to restrain infection [136, 137], while CD8 T cells eliminate cells harboring parasites in the cytoplasm and also promote immunopathology in the heart [138, 139]. Some of these

mechanisms are regulated by cytokines, such as IL-10 and TGF-β, which diminish inflammation and thus pathology, but might contribute to the persistence of parasites [140, 141]. Also, it has been demonstrated that apoptosis of lymphocytes in the course of *T. cruzi* infection down regulates T-cell expansion [142, 143], B-cell response [144], parasite killing by M1 [143, 145], and CD8 T-cell-mediated immunity [146, 147]. Furthermore, infection is also promoted by the phagocytosis by macrophages of apoptotic T lymphocytes in a matter dependent of prostaglandins, TGF-*β*, and polyamine biosynthesis [148], which are characteristic of M2 activation [128]. In contrast, the blockade of prostaglandin production or the inhibition of T lymphocyte apoptosis by caspase inhibitors reduces parasite growth *in vitro* and parasitemia in an experimental model of Chagas disease [148, 149].

7.2. Apoptosis modulation in *T. cruzi* infection

7.2.1. Apoptosis induction

As just mentioned, it has been demonstrated that there is intense apoptosis of T lymphocytes during the course of *T. cruzi* infection [142]. The induction of apoptosis occurs through the extrinsic pathway as the infection with *T. cruzi* provokes the expression of both Fas (CD95) and Fas ligand (FasL) [143, 145], caspase-8 activity, and activation of effector caspase-3 [143, 144] in T lymphocytes from *T. cruzi*-infected mice. CD8 T lymphocytes help in the control of infection by *T. cruzi*, and the induction of apoptosis of these cells disrupts the immune response and interestingly affects macrophage activation. Apoptosis of CD8 T lymphocytes promotes macrophage differentiation toward an M2-like phenotype, which favors *T. cruzi* infection [150].

7.2.2. Apoptosis inhibition

T. cruzi resides in the cytoplasm of diverse cells, and thus CD8 lymphocytes are important for their elimination. It has been shown that CD8 T cells are preferential targets, as compared to CD4 lymphocytes, for early effects of apoptosis inhibition in acute infection [146, 151]. In addition to macrophages, *T. cruzi* infects cardiomyocytes and it is common to find an intense myocarditis during the acute phase of infection. Despite cardiac damage, infected individuals may remain asymptomatic for decades. Thus, *T. cruzi* may directly prevent cardiomyocyte death in order to prevent heart destruction and favor its survival. It has been shown that *T. cruzi*, as well as cruzipain, an important *T. cruzi* antigen, promotes survival of cardiomyocytes cultured under serum deprivation through the expression of the antiapoptotic protein Bcl-2, but not of Bcl-xL. Also, *T. cruzi* displays other antiapoptotic strategies such as the phosphorylation of Akt and ERK 1/2, which differentially modulate Bcl-2 family members [152]. In addition, cruzipain enhances arginase activity that favors parasite growth within the cell. Interestingly, the inhibition of arginase activity by NG-hydroxy-L-arginine (NOHA) abrogated the antiapoptotic action of cruzipain suggesting that arginase activity is required for the survival effect of cruzipain [153].

Apart from invading the heart, *T. cruzi* colonizes the peripheral nervous system and it has been shown that the infection of Schwann cells by *T. cruzi* suppresses host cell apoptosis caused by growth factor deprivation. The antiapoptotic effect of the parasite has been related to the interaction of Akt with *T. cruzi* PDNF, glycosylphosphatidylinositol (GPI)-anchored parasite-derived neurotrophic factor, known mostly for its neuraminidase and sialyltransferase activities [154].

8. Apoptosis inhibition in *Toxoplasma gondii* infection

Toxoplasma gondii is an obligate intracellular parasite capable to infect almost all types of nucleated cells and has developed multiple mechanisms to avoid immune elimination. It has been reported that this parasite can modulate multiple signaling pathways in their host cells in order to inhibit apoptosis, ensuring in this way its survival and persistence during infection. As a clear example of this process, different evidences have shown a failure in the activation of caspase 8, caspase 9, and caspase 3 after apoptosis induction in *T. gondii* infected cells [155–158].

The activation of the NF-κB transcription factor has been pointed as a pivotal mechanism used by *T. gondii* to inhibit apoptosis in several host cell types [157, 159, 160]. Following infection, it has been described that *T. gondii* induces NF-κB translocation into the nucleus, where this factor induces the transcriptional upregulation of genes that codify for antiapoptotic proteins that belong to the Bcl-2 and IAP families [157, 159, 160]. The translocation of NF-κB to the nucleus and subsequent gene transcription is clearly dependent of the host cell IκB kinase (IKK), which phosphorylates the IκB inhibitor molecules that maintain NF-κB inactive, allowing after this phosphorylation the activation and nuclear translocation of this transcription factor. However, in *T. gondii*-infected cells, the existence of a novel parasite-derived IκB kinase (TgKK) has been identified at the parasitophorous membrane together with phosphorylated IκB molecules [161]. In this sense, both host IKK and TgIKK cooperate for a continuous NF-κB activation during infection, in a process in which the host IKK could be inducing the initial phosphorylation of IκB molecules, followed by a sustained participation of the TgIKK, which presence increases as the parasite replicates [162].

Besides the NF-κB-dependent inhibition of apoptosis during infection with *T. gondii*, an inhibition of caspase 9 and caspase 3 activation through a direct blockage, exerted by the parasite, of apoptosome formation and cytochrome c release has been proposed [156, 162]. In this regard, the *T. gondii*-dependent inhibition of cytochrome c release from the mitochondria is associated with a parasite direct degradation of the proapoptotic proteins Bad and Bax, without affecting the mRNA levels for these proteins in the host cell, a fact that suggests that the parasite is able to block directly antiapoptotic proteins of the Bcl-2 family in a host cell transcription machinery-independent process [163, 164]. Additionally, among other signaling pathways hijacked by *T. gondii* to tilt the balance of the Bcl-2 family proteins toward an antiapoptotic state of the host cell during infection, the modulation of the PI3-K/PKB/Akt pathway has been involved [155, 165]. In *T. gondii*-infected macrophages, it has been documented that this parasite activates PI3-Kinase (PI3-K), which in turns phosphorylates protein kinase B (PKB/Akt), which acts as an apoptosis inhibitor of the host cells [165].

In addition to the inhibition of apoptosis by *T. gondii* via the mitochondrial pathway, this parasite has also been reported to mediate the inhibition of apoptosis through the extrinsic pathway [166]. In this regard, it has been demonstrated that during infection, *T. gondii* can inhibit Fas/CD95-triggered apoptosis in host cells by inducing an aberrant processing and degradation of the initiator caspase 8, a process that results in a decrease in the recruitment of this protease to the death-inducing signaling complex and the inability to activate effector caspases, for example, caspase 3 and caspase 7 [166].

Due to the fact that host defense in chronic infections due to *T. gondii* is critically dependent on the cytotoxic activity of CD8 T cells, which induce apoptosis of the infected cells via

the secretion of granzyme proteases, it is not surprising the blockage of this pathway by the parasite. Hence, *T. gondii* has been demonstrated to protect their host cells from Granzyme B-induced apoptosis, involving a mechanism by which the parasite abrogates the activity of Granzime B in the infected cells [167].

9. Apoptosis inhibition in *Plasmodium* spp. infection

In the mammalian host, *Plasmodium* parasites infect primarily hepatocytes and erythrocytes, and modulation of apoptosis by this parasite in both host cell types has been found to be crucial during infection. After transmission by the *Anopheles* mosquito, *Plasmodium* sporozoites are rapidly transported to the liver, where they invade and develop within hepatocytes before reaching erythrocytes [168]. In the liver, sporozoites transmigrate through the cytosol of multiple hepatocytes, causing wounding in the traversed cells with the release of the hepatocyte growth factor (HGF), which helps the parasite to reach a final hepatocyte in which it will reside and multiply [158, 169, 170]. It has been proposed that HGF binds to the c-mesenchymal-epithelial transition factor (c-Met) located on the surface of hepatocytes, a process that leads to PI3-K activation and a further protection of these cells from apoptosis [171, 172]. Albeit PI3-K activation trough HGF/c-Met signaling has been proposed to protect hepatocytes from apoptosis during early liver stages of infection with *Plasmodium*, other data suggest that PI3-K activation is not required to maintain this antiapoptotic state [173].

During the blood stage of infection with *Plasmodium*, in which merozoites invade erythrocytes, multiple changes are induced in the host cell by the parasite in order to satisfy its nutritional requirements [164]. One of these changes is the activation of Ca^{2+} permeable channels in the plasmatic membrane of erythrocytes and the posterior entry of Ca^{2+} into these cells. An increase in the intracellular concentration of Ca^{2+} in erythrocytes has been demonstrated to induce a type of programmed cell death called eryptosis, which is characterized by cell shrinkage, cell membrane blebbing, and exposure of phosphatidyl serine, resembling apoptosis [174]. Due that infection with *Plasmodium* leads to the entry of Ca^{2+} into the erythrocytes and that the increment of the concentration of this ion stimulates eryptosis, it has been shown that *Plasmodium* can delay the execution of this programmed cell death mechanism by sequestering free Ca^{2+} ions present in the cytosol of erythrocytes [175].

10. Conclusion

Both apoptosis and its inhibition are fundamental biological processes for the homeostasis of an organism. Both processes are present throughout life and are essential for growth, development, and reproduction. Studies on the molecular mechanisms that inhibit apoptosis have been carried out in order to elucidate the specific signaling pathways that take place during apoptosis inhibition. Up to date, various routes implicated in apoptosis activation or inhibition have been rooted out; however, there is still much to be found. Ironically, the same pathways that are involved in homeostasis and health participate in cell death processes that occur during infections and function as a defense mechanism

against intracellular pathogens. In counterpart, microorganisms have developed a wide array of strategies to evade apoptosis of their host cell. Some of these strategies involve the hijacking of signaling pathways that participate in apoptosis. The better understanding and gaining of knowledge on these intracellular circuits and the physiopathology behind them will permit the development of new strategies and drugs to effectively treat the pertaining diseases mentioned in this work.

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