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Review Article

MITOCHONDRIAL STRESSORS AND THEIR ROLE IN PROGRAMMED CELL DEATH

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ABSTRACT

The mitochondrion is a double membrane organelle that is involved in various biosynthetic and metabolic pathways including regulation of cell death through apoptosis. Apoptosis is a highly complex process which involved an energy-dependent cascades of molecular event. Intrinsic pathway is the apoptotic pathway which is initiated from the mitochondria. On the other hand, the pathway that involved the cell surface receptor is identified as the extrinsic pathway. The role of mitochondrion in apoptosis in the mammalian cell was emphasized when several mitochondrial proteins were identified. These proteins were discovered to be able to stimulate cellular apoptotic programmed cell death directly. The intermembrane space proteins, such as cytochrome c, Smac/DIABLO, and Omi/Htra2, involve activation of various caspases to undergo apoptosis. However, there is some that act in a caspase-independent manner, such as AIF and endonuclease G. Cytochrome *c* release into the cytosol is directed by the Bcl-2 family of protein following the permeabilization of the outer mitochondrial membrane, mediated by pro-apoptotic Bcl-2 family proteins. Due to the involvement of various proteins that act as mitochondrial stressors in theinduction of apoptosis, this review will emphasize the role of different stressor proteins towards this important organelle that regulate apoptosis.

INTRODUCTION

Mitochondrion is a crucial organelle responsible for the fate of a cell as determinant whether a cell lives or dies (Ernster and Schatz, 1981). Mitochondria are complex organelles that play a central role in energy metabolism, control of stress responses and are a hub for biosynthesis processes. Mitochondria are critical mediators of signals to produce various cellular outcomes (Vakifahmetoglu-Norberg *et al,* 2017). Mitochondria consist of an outer and an inner membrane with folded cristae that divides into two aqueous compartments which are the intermembrane space that contains mitochondrial proteins and the matrix that comprises of its DNA (Ding, *et al,* 2012). These double-membrane organelles continuously change shape and position and contain complete metabolic machinery for the oxidative conversion of pyruvate, fatty acids, and amino acids into ATP.

Mitochondria are eukaryotic organelles involved in numerous and various essential biosynthetic and metabolic pathways including energy transduction, iron or sulphur synthesis, copper homeostasis and lipid metabolism (Koopman *et al,* 2010). Moreover, they are a continuous source of reactive oxygen species (ROS) produced by the leakiness of the electron transport chain (Wang *et al,* 2008). Mitochondria need an efficient system to repair damaged DNA because they generate a dangerous superoxide anion radical as a by-product of respiration (Barja, 2002). The superoxide anion radical can be converted to other types of reactive oxygen species (ROS) (Adam-Vizi and Chinopoulos, 2006). Other than that, mitochondria are significant organelles in the regulation of apoptotic cell death induced by intrinsic stimuli (Scorrano, 2009).

Mitochondria contain a self-destructive arsenal of apoptogenic factor and undergo active process involving different mitochondrial protein in the regulation of the pathway that lead to cell death (van Loo *et al,* 2002; Vakifahmetoglu-Norberg *et al,* 2017). There are some intermembrane space proteins that can induce caspase activation for the cell to undergo apoptosis, such as cytochrome c, Smac/DIABLO, and Omi/Htra2. On the

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other hand, other proteins such as AIF and endonuclease G, may act in a caspase-independent manner (Kuwana and Newmeyer, 2003). Cytochrome *c* release into the cytosol is directed by the Bcl-2 family of protein via the permeabilization of the outer mitochondrial membrane mediated by pro-apoptotic Bcl-2 family proteins (Orrenius, 2004). In this review, various mitochondrial stressors and proteins will be discussed in particular on their role in the event of programmed cell death.

Mitochondria Structure

In healthy cells, cytochrome *c* (Cyt *c*) is located in the mitochondrial intermembrane spaces, where it functions as an electron shuttle in the respiratory chain and interacts with cardiolipin (CL). The mitochondrial intermembrane space is where cytochrome c that acts as an electron shuttle in the respiratory chain and interacts with cardiolipin (Garrido *et al,* 2006). A number of proapoptotic stimuli induce the permeabilization of the outer membrane, facilitate the interaction between intermembrane and intercristae spaces and promote the mobilization and release of cytochrome c (Garrido *et al,* 2006).

The matrix of mitochondria is finely granular with crystalline or fibrous inclusions (Munn, 2014). The matrix is the site where DNA replication, transcription, protein biosynthesis and various enzymatic reactions occur (Kukat *et al,* 2011; Kühlbrandt, 2015).The topology of a membrane is a complex function of intrinsic and extrinsic factors that comprises binding to other cellular constituents (such as cytoskeletal filaments and membrane-binding proteins), spontaneous curvature (protein and lipid composition) and dynamics (ability to undergo fusion and fission) (Manella, 2006). There is likely a major change on the shape of the inner membrane when it has physical interactions with the outer membrane (Manella, 2006).

Mitochondria contain their own genetic material and machineries to produce RNAs and proteins. The small circular mitochondrial genome encodes only approximately 13 polypeptides in human (Stojanovki *et al,* 2012). Because of the way the mitochondrion is divided into four sub compartments – two membranes (outer membranes and inner membranes and two aqueous chambers (intermembrane space and matrix), there are several pathways for protein translocation into the mitochondria. Most of the ~1,000 mitochondrial proteins are encoded by the nuclear genome, synthesized in the cytosol on free ribosomes as precursor proteins and then transported into or across mitochondrial membranes with the help of distinct complexes (Truscott *et al,* 2003).

Fig 1 Structure of mitochondrion under electron microscopy. The membranes of mitochondrion appeared to be distinctive only when they are perpendicular to the plane of the section (Munn, 2014).

Mitochondria stressors

The role of mitochondria in the regulation of apoptosis is influenced by a number of stressors like loss of growth signals, hypoxia, oxidative stress and DNA damage (Kubli and Gustafsson, 2012). In addition to that, mitochondrial mutation, heat, ethidium bromide treatment, electron transport chain (ETC) protein mutation and physiological stimuli-induced accumulation of reactive oxygen species (ROS) can induce stress towards mitochondria either by disrupting membrane potential or increase the load of misfolded proteins (Hu and Liu, 2011).

Mitochondria in apoptosis

The role of mitochondria in mammalian cell apoptosis was emphasized when several mitochondrial proteins were identified. These proteins were discovered to be able to stimulate cellular apoptotic cell death programs directly (Wang, 2001). Apoptosis or known as programmed cell death is a vital physiological process that plays an important role in the development and tissue homeostasis where it is involved in healthy tissues and responsible for the elimination of cells (Kerr *et al,* 1972). Apoptosis is defined by characteristic changes such as altered nuclear morphology including chromatin condensation and fragmentation, changes in cytoplasmic organelles, cell shrinkage, blebbing of plasma membrane, and apoptotic body formation (Hillario *et al,* 2010). During apoptotic death, cells are carved up by caspases and packed into apoptotic bodies as a mechanism to avoid immune activation (Edinger and Thompson, 2004).

On the other hand, necrotic cells display loss of membrane integrity which eventually results in release of intracellular materials into the extracellular environmentleading to inflammatory responses by immune cells (Ouyang *et al,* 2012). Those characteristics indicated that apoptosis is an orderly genetic programme, which could potentially be controlled at various points, while necrosis is a form of cell death that lacks these control points (Doonan and Cotter, 2008).

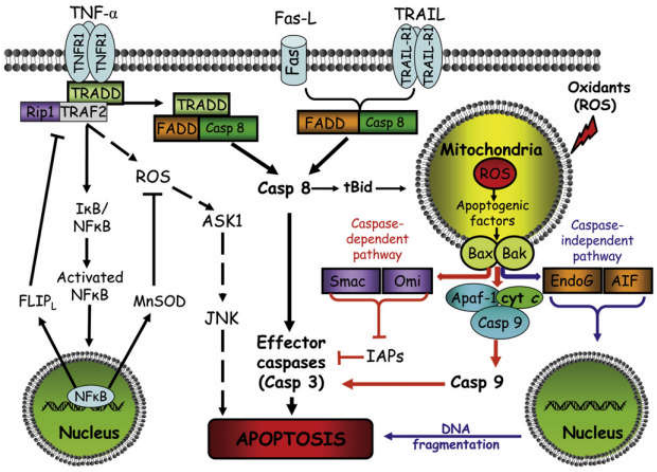

Fig 2 Extrinsic and Intrinsic Pathway of Apoptosis. The extrinsic pathway or death receptor-mediated pathway includes TNFR1/TNFα, Fas/FasL and TRAIL-R1/TRAIL. The intrinsic pathway can be mediated by several stimuli (e.g., ROS) which eventually cause permeabilization of the mitochondrial outer membrane at first place. This leads to the release of cytochrome-c from the mitochondria and activation of the death signal through cascade activity of caspase (Circu and Aw, 2010)

The mechanisms of apoptosis are highly complex and involving an energy-dependent cascade of molecular events. Apoptosis expresses in two main execution programs downstream of the death signal which are the caspase pathway and the organelle dysfunction, of which mitochondrial dysfunction is best regarded as (Zimmerman *et al,* 2001). There are two major apoptotic pathways known to date, initiated by either the mitochondria via the intrinsic pathwayor the cell surface receptor via the extrinsic pathway (Youle and Strasser, 2008).

Receptor-mediated apoptosis (Extrinsic Pathway)

The extrinsic signalling pathways are initiated by transmembrane receptor-mediated interactions through the binding of extracellular ligands to the respective death receptors(Elmore 2007). Fas (also called Apo-1 or CD95) and tumour-necrosis factor receptors (TNF-R)are the typical death receptors which activate receptor-mediated apoptosis.

In the extrinsic pathway, ligands such as tumour-necrosis factor (TNF), FAS ligand/CD95L, or TNF-related apoptosis-inducing ligand (TRAIL/APO2 ligand (APO2L)) or TNF ligand super family member 10) interact with their respective death receptors (TNF receptor 1 (TNFR1), FAS/CD95 and death receptor 4 (DR4, also known as TRAIL receptor 1 (TRAILR1) or DR5/TRAILR2, respectively). These interactions ultimately lead to the recruitment of the FAS-associated death domain (FADD) and the activation of the protease caspase 8. Caspase 8 cleaves and activates caspase 3 (the executioner caspase) and other downstream caspases, which results in a proteolytic cascade that gives rise to the cell death (Fesik 2005; Ribas *et al,* 2016). Caspase-8 can also cleave the BH3-only protein Bid thus allow the resulting truncated Bid (tBid) to move to the mitochondria and triggers cytochrome c release that leads to activation of caspase-9 and caspase-3 (Lawen, 2003).

Mitochondria-mediated apoptosis (Intrinsic pathway)

The intrinsic pathway known as mitochondria-mediated apoptosis occurs in response to a wide range of death stimuli, including activation of tumor suppressor proteins (such as p53) and oncogenes (c-Myc as an example), DNA damage, chemotherapeutic agents and ultraviolet radiation. The intrinsic pathway involves the destabilization of the mitochondria outer membrane and the release of mitochondrial proteins that active effector caspases (Ribas *et al,* 2016).Generally, it is known that this pathway must be inactivated in all cancer cells (Shi, 2001). The intrinsic pathway leads to apoptosis under the regulation of mitochondrial pro-enzymes (Ouyang *et al,* 2012). In this pathway, the release of cytochrome c and apoptosis inducing factors along with the induction of a mitochondrial permeability transition pore initiates apoptosis (Kroemer *et al,* 2007). The large, nonspecific channel protein of mitochondrial permeability transition pore spans the outer mitochondria membrane and inner mitochondria membrane thus, mediates the permeability changes of the mitochondrial membranes leading to mitochondria-mediated death (Muravchick and Levy, 2006).

The mitochondrial pathway is initiated by the release of apoptogenic factors such as cytochrome c, apoptosis-inducing factor (AIF), Smac (second mitochondria-derived activator of caspase)/DIABLO (direct inhibitor of apoptosis protein (IAP)-binding protein with low PI), Omi/HtrA2 or Endonuclease G from the mitochondrial intermembrane space (Fulda and Debatin, 2006). Mitochondrial outer membrane integrity is highly controlled, primarily through interactions between pro-apoptotic and anti-apoptotic members of the B cell lymphoma 2 (Bcl-2) protein family (Li and Dewson, 2015). Following mitochondrial outer membrane permeabilization by pro-apoptotic Bcl-2-associated X protein (BAX) or Bcl-2 antagonist (BAK), additional regulatory mechanisms govern the mitochondrial release of intermembrane space proteins and caspase activity (Tait and Green, 2010).

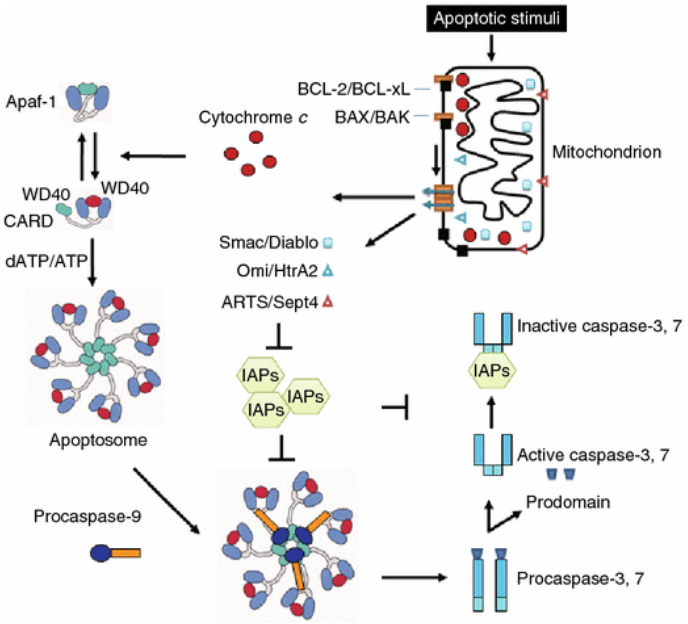

Fig 3 Overview of mitochondria-mediated pathway (Intrinsic pathway) (Xiong *et al,* 2014)

Cytochrome c

Normally, cytochrome c is bound to the inner mitochondrial membrane by an association with the anionic phospholipid cardiolipin (Ott *et al,* 2007). In mammalian cells, a major caspase activation pathway is the cytochrome c-initiated pathway. In this pathway, a variety of apoptotic stimuli cause the release of cytochrome c from mitochondria, which triggers a series of biochemical reactions thus lead to caspase activation and cell death (Jiang and Wang, 2004). When a cell was initiated by either extracellular stimuli or intracellular signals, outer mitochondrial membranes become permeable to internal cytochrome *c*, which is then released into the cytosol. A large internal pool of cytochrome c was mobilized in conjunction with a severe change in the topology of the inner membrane. The crista junctions were wider and slot-like, and the curvature of the membrane was reversed in many regions, forming tubes that enclosed matrix (Manella 2008).

Cytochrome *c binds to* Apaf–1, a cytosolic protein with an N-terminal caspase-recruitment domain (CARD) thus facilitates the association of dATP with Apaf-1 and exposes its N-terminal CARD, which could oligomerize and become a platform for which the initiator caspase-9 is recruited and then activate pro-caspase-9 to compose the apoptosome (Ghobrial *et al,* 2005). Activation of procaspase-9 is mediated by Apaf-1 through cleavage by zymogens, thereby cleaving and in turn activating caspase-3, an effector caspase (Chipuk and Green,

2005). Caspase-3 then cleaves key substrates in the cell to produce many of the cellular and biochemical events of cell death by apoptosis (Fulda and Debatin, 2006).The release of cytochrome c from mitochondria is controlled by proteins of the Bcl-2 family: those that inhibit cell death, for example, Bcl-2 and Bcl-xL prevent the release of cytochrome c whereas those that promote cell death such as Bax and Bak induce this release (Martinou *et al,* 2000).Cytochrome c release can also occur in death receptor-dependent, extrinsic apoptotic pathways by cleavage and activation of the proapoptotic Bcl-2 family member Bid through caspase 8, the apical caspase activated by cell surface death receptors such as Fas and TNF (Luo *et al,* 1998).

SMAC/Diablo

Endogenous antagonists of IAPs help to keep these apoptosis suppressors in check, promoting apoptosis. The naturally occurring IAP-antagonists, SMAC (second mitochondria-derived activator of caspase)/DIABLO (direct inhibitor of apoptosis protein (IAP)-binding protein with low PI) are isolated inside mitochondria and released into the cytosol during apoptosis in response to various apoptotic stimuli (Reed 2002). Smac/DIABLO is synthesized as a 239 amino acid precursor protein and targets to mitochondria via its N-terminal domain. This mitochondria localization sequence is removed via proteolytic after it is imported into the intermembrane space (Ravagnan *et al,* 2002).

Smac/DIABLO promotes caspase activation in the cytochrome c/Apaf-1/caspase-9 pathway by binding to inhibitor of apoptosis proteins, IAPs, and removing their inhibitory activity. Mitochondrial import and cleavage of its signal peptide are required for Smac/DIABLO to gain its apoptotic activity (Du *et al,* 2000). Smac/DIABLO may promote apoptosis by binding to IAPs and preventing them from inhibiting caspases (Verhagen *et al,* 2000). For example, when Smac/DIABLO binds to XIAP, it prevents caspase-9 to be processed and therefore promotes cell death following UV irradiation (Ekert *et al,* 2001). Overexpression of Smac increases cells' sensitivity to apoptotic stimuli. Smac is the second mitochondrial protein, along with cytochrome c, that promotes apoptosis by activating caspases (Du *et al,* 2000).

Omi/HtrA2

Structurally, the mature HtrA2 protein consists of 7 α-helices and 19 β-strands, forming two well-defined domains. The serine protease domain adopts the same fold as trypsin (Li *et al,* 2002). The full-length of HtrA2 protein holds 458 amino acids, of which the N-terminal 133 residues are cleaned out to be activated after released from mitochondria, therefore generating a 36-kDa active form (Bhuiyan *et al,* 2008). The mature serine protease Omi, also known as HtrA2 (high-temperature requirement protein A2) was identified as a mitochondrial direct BIR3-binding protein and a caspase activator (Hedge *et al,* 2002). HtrA2 is upregulated in mammalian cells in response to stress induced by both heat shock and tunicamycin treatment (Gray *et al,* 2000). Omi and its related family members could control protein stability and turnover under thermal, osmotic, pH, and other stress conditions (Hedge *et al,* 2002).

Omi/ HtrA2 is released in the cytosol, where it contributes to apoptosis through both caspase-independent and caspase-dependent pathways (Walle *et al,* 2008). One mechanism is through binding to the IAPs and disrupts the association of active caspases with IAPs while another depends on its protease activity to cleave bound IAPs and aims them for further degradation by the proteosomal pathway (Srinivasula *et al,* 2003). Omi/HtrA2 cleavage of bound IAP is catalytic and irreversible. Omi/HtrA2 cleaves and/or degrades IAPs and an unidentified substrate(s), causing inactivation of IAPs and permeabilization of the outer mitochondrial membrane continued by cytochrome *c*-dependent caspase activation, respectively (Yang *et al,* 2003; Suzuki *et al,* 2004).

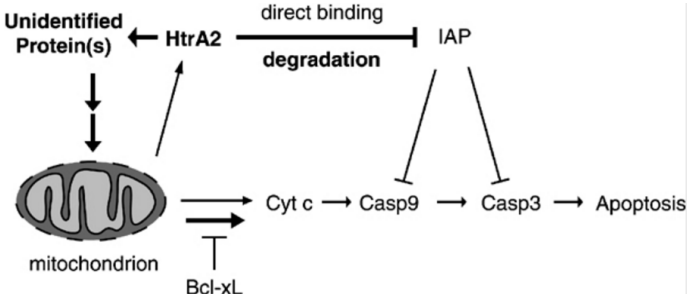

Fig 4 Protease activity of Omi/HtrA2 develops caspase activation and apoptosis by at least two different mechanisms: 1) Direct cleavage and/or degradation of IAPs leading to inactivation of IAPs and, 2) Cleavage of an unidentified substrate(s) leading to permeabilization of the mitochondrial outer membrane and release of Cytochrome c which triggers a caspase 9/3 signalling cascade in apoptosis (Suzuki *et al,* 2004).

AIF (Apoptosis Inducing Factor)

The pro-apoptotic factor, Apoptosis Inducing Factor (AIF) is a 57-kDa mitochondrial flavoprotein, located in the mitochondrial intermembrane space of a healthy cell (Donovan and Cotter 2004). AIF has three domains which are an N-terminal region that bears a mitochondrial localization sequence, a central spacer sequence and a C-terminal area (Ravagnan *et al,* 2002). AIF normally stabilizes mitochondrial membrane permeability and supports oxidative phosphorylation (Vahsen *et al,* 2004). However, if released through the outer membrane into the cytosol, AIF can produce terminal damage to nDNA (Muravchick and Levy, 2006). Upon lethal signalling, AIF undergo translocation via the cytosol, to the nucleus where it binds to DNA and provokes caspase-independent chromatin condensation (Candé *et al,* 2002). AIF induces caspase-independent cell death primarily with some features of apoptosis, such as phosphatidylserine exposure, partial chromatin condensation and cellular shrinkage (Loeffler *et al,* 2001).AIF induces nuclear condensation and large-scale DNA fragmentation (Susin *et al,* 2000).

Endo G

Endonuclease G is a mitochondrial nuclease that has been suggested to play a role in mitochondrial DNA replication (Cote and Ruiz-Camilo, 1993). EndoG undergoes a caspase-independent apoptotic pathway initiated from the mitochondria. When treated with the active form of the pro-apoptotic protein Bid, Endo G can be recovered from mitochondria. Once released into the cytosol, Endo G translocates towards the nucleus where it generated oligonucleosomal DNA fragmentation even in the absence of caspases (Li *et al,* 2001). Endo G catalyzes both high molecular weight DNA cleavage and oligonucleosomal DNA breakdown in a sequential fashion

(Ravagnan *et al,* 2002). The apoptotic release of mitochondrial endonuclease G was completely blocked in conditions where Bcl-2 was overexpressed (Van Loo *et al,* 2001).

Bcl-family

Although the caspases symbolize a central point in apoptosis, their activation is regulated by a diversity of other factors. Among these, Bcl-2 family plays an essential part in caspase activation by determining the fate of a cell whether it lives or dies (Burlacu, 2003; Li and Dewson, 2015).Bcl-2 is an integral membrane protein located in the outer mitochondrial membrane, the endoplasmic reticulum, and the nuclear membrane (Kluck *et al,* 1997). Its NH_2-terminal is facing the cytosol and the rest of the other members of its family, Bcl-2 possess a hydrophobic domain at COOH-terminal that allows the protein to enter into the cytosolic surface of the intracellular membrane (Puthalakath and Strasser, 2002).

Traditionally, the member of the Bcl-2 family have been classified into 3 groups: the first group is the members of the Bcl-2 that inhibits apoptosis that comprises of Bcl-2, Bcl-xL, and Mcl-1. Cells undergoing apoptosis were found to have an elevation of cytochrome c in the cytosol and a reduction in the mitochondria. Overexpression of Bcl-2 prevented the efflux of cytochrome c from the mitochondria and the initiation of apoptosis. Thus, one role of Bcl-2 in inhibition of apoptosis is to block a release of cytochrome c from mitochondria (Yang *et al,* 1997). The second group of the Bcl-2 family stimulates apoptosis that consists of Bax, Bok, Bak which includes BH1, BH2 and BH3 domains (Li and Dewson, 2015). Pro-apoptotic member of this family, trigger the release of caspases from death antagonists via heterodimerization and also by triggering the release of mitochondrial apoptogenic factor into the cytoplasm through acting on mitochondrial permeability transition pore, thereby activates caspases (Tsujimoto, 1998). Last of all, the third group is the members of BH3-only proteins, such as Bad, Bid, Bik, Bim, Noxa and PUMA (Li and Dewson, 2015). They have a conserved BH3 domain that develops apoptosis by regulation of antiapoptotic Bcl-2 proteins (Donovan and Cotter, 2004).

Apoptotic signals can activate the BH3-only proteins, thereby inactivating the antiapoptotic Bcl-2 protein. This relieves inhibition of the proapoptotic Bcl-2 protein and promotes apoptosis (Nishida *et al,* 2008). Generally, BH3-only protein aids as sensor of intrinsic stimuli because in response to DNA damage or ER stress, specific member become activated by transcriptional induction proteins such as Puma and Noxa, posttranslational modification protein (Bad), or limited proteolysis for example, Bid (Bender and Martinuo, 2013).

Caspases

The apoptotic caspases are initiators or effectors, reliant on their point of access to the apoptotic pathway. Caspases are a family of aspartate-specific cysteine proteases responsible for the biochemical and morphological changes during apoptosis (Inoue *et al,* 2009). Caspases can be divided into three subclasses. Functionally, we can distinguish three classes of caspases; i) the initiator caspases that are characterized by long prodomains (>90 amino acids) containing either DED domains (caspase-8 and caspase-10) or a caspase recruitment domain (CARD) (caspase-2 and caspase-9; CED-3); ii) the executioner or effector caspase containing short prodomain (caspase-3, caspase-6 and caspase-7) and iii) the remaining caspases that involve in cytokine maturation (Grütter, 2000; Shalini *et al,* 2015). Both intrinsic and extrinsic apoptotic signalling pathways converge at the level of the specific protease which is the caspases (Kumar, 2006).

Caspases are widely expressed in an inactive proenzyme form in most cells and once activated can often activate other pro-caspases, allowing initiation of a protease cascade. Some pro-caspases can also aggregate and auto-activate. This proteolytic cascade, in which one caspase can activate other caspases, amplifies the apoptotic signalling pathway and thus leads to rapid cell death. Caspases have proteolytic activity and are able to cleave proteins at aspartic acid residues, although different caspases have different specificities involving recognition of neighbouring amino acids. Once caspases are initially activated, there seems to be an irreversible commitment towards cell death (Elmore, 2007).

In human, there are two independent initiation pathways which are the extrinsic pathway, defined by the activation of caspase-8 through transmembrane receptors of the tumour necrosis factor type-I (TNF-1) receptor family and the intrinsic pathway which reacts to stress, genotoxic damage by the activation of caspase-9.Caspase-9 is a key component of the mitochondrial death pathway (the intrinsic pathway) that is regulated primarily by the Bcl-2 family and the BH-3 (Bcl-2 homology domain-3)-only proteins (Fuentes-Prior and Salvesen, 2004). Activated caspases might target the permeabilized mitochondria, increasing apoptosis through a positive feedback loop (Rasola and Bernardi, 2007). Caspase-2 activates the effector caspases after death receptor ligation or other apoptotic stimuli through cleavage of Bid because translocation of Bid to the mitochondria is triggered by its cleavage and subsequent myristoylation at glycine (Zha *et al,* 2000). Remarkably, caspase-2 can directly trigger the release of cytochrome c, AIF (apoptosis-inducing factor), and Smac (second mitochondria-derived activator of caspases protein) from isolated mitochondria, independent of Bid or other cytosolic factors (Guo *et al,* 2002). The executioner caspase of apoptosis cleaves a variety of cellular target, causing in morphological changes, degradation of genomic DNA, and, ultimately, phagocytic removal of the apoptotic cell (Taylor *et al,* 2008). Caspase-1 and caspase-11 play a role in inflammation and mediating inflammatory cell death by pyroptosis (Shalini *et al,* 2015). Caspase-3 is the main downstream effector caspase that cleaves the majority of the cellular substrates in apoptotic cells (Porter and Janicke, 1999). Caspase-3 controls DNA fragmentation and morphologic changes of apoptosis, whereas caspase-7 is less involved in these processes. Caspase-7 seems to be more significant to the loss of cellular viability, although the combined role of both caspases is crucial (Lakhani *et al,* 2006).

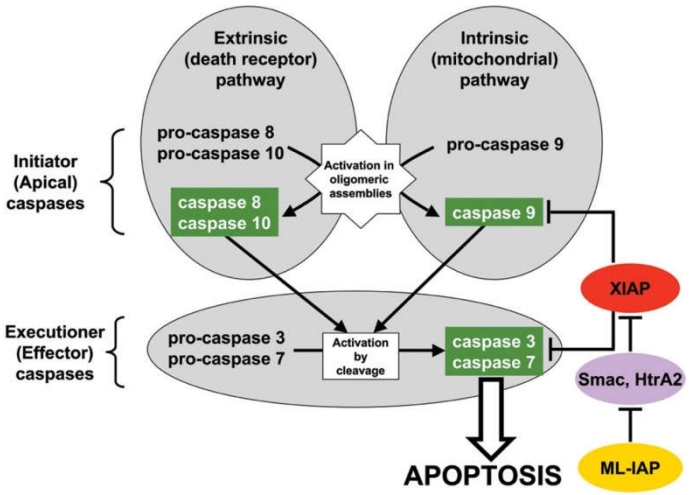

Fig. 5 The framework of apoptosis involving caspases. Cell death is signalled by binding of ligand-receptors at the cell surface, which leads to the activation of initiator caspase-8 and caspase-10. These caspases then directly cleave and activate the effector caspase-3 and caspase-7. Genotoxic damage triggers the release of cytochrome c from mitochondria, thus engages the same effector caspases. The common execution phase is regulated through direct caspase inhibition by XIAP, which can also regulate the active form of caspase-9. XIAP is under the influence of antagonist proteins such as Smac/DIABLO and HtrA2 that compete with caspase for IAPs (Fuentes-Prior and Salvesen, 2004).

p53

The p53 tumor suppressor gene plays a role in cell cycle regulation, DNA repair, and programmed cell death (Schuler *et al,* 2000). As a result, cells in which p53 is stabilized are sensitized for activation of the mitochondrial cell death pathway. In addition, p53 may directly affect mitochondrial integrity without the need for gene activation. Indeed, it has been reported that p53 can bind to Bcl-2 and Bcl-XL at the mitochondria, thereby promoting mitochondrial destabilization (Mihara *et al,* 2003). The role that p53 plays is evident by the tumor that bears a mutation in this gene (Zhang *et al,* 2016). Loss of p53 in cancer leads to genomic instability, impaired cell cycle regulation and inhibition of apoptosis. After DNA damage, p53 holds the cell at a checkpoint until the damage is repaired. If the damage is irreversible, apoptosis is triggered (Yu *et al,* 2003).

CONCLUSION

Mitochondria play a prominent role in the regulation of cell death through the intrinsic pathway of apoptosis. When a cell was initiated by either extracellular stimuli or intracellular signals, changes in the inner mitochondrial membrane occur that results in an opening of the mitochondrial permeability transition pre, loss of mitochondrial transmembrane potential and release of pro-apoptotic proteins from the intermembrane space into the cytosol. There are proteins that activate the caspase-dependent mitochondrial pathway which consists of cytochrome c, Smac/DIABLO, HtrA2/Omi whereas other proteins such as AIF and endo G activates apoptosis through caspase independent pathway. When there is an apoptotic stimulus, the outer mitochondrial membranes become permeable to internal cytochrome *c*, which is then released into the cytosol. Cytochrome *c binds to* Apaf–1 and recruitinitiator caspase-9 and then activates pro-caspase-9 to compose the apoptosome.

Pro-caspase-9 cleaves and activates caspase-3 thus produce many of the cellular and biochemical events of cell death by apoptosis. Smac/DIABLO promotes caspase activation in the cytochrome c/Apaf-1/caspase-9 pathway by binding to inhibitor of apoptosis proteins, IAP and removing their inhibitory activity. Omi/ HtrA2 is released into the cytosol, where it contributes to apoptosis through both caspase-independent and caspase-dependent pathways. One mechanism is through binding to the IAPs and disrupts the association of active caspase with IAP while another cleaves bound IAPs and undergo further degradation by the proteosomal pathways. AIF undergo translocation via the cytosol, to the nucleus where it binds to DNA and provokes caspase-independent chromatin condensation. Endo G translocases to the nucleus and cleaves nuclear chromatin to produce DNA fragments. Bcl-2 family plays an essential part in caspase activation by determining the fate of a cell. One role of Bcl-2 is in inhibition of apoptosis is to block the release of cytochrome c from mitochondria initiated by the members of the Bcl-2 that inhibits apoptosis that comprises of Bcl-2, Bcl-xL and Mcl-1. Another role of Bcl-2 family is to stimulate apoptosis that include Bax and Bak.

The members of BH3-only proteins, such as Bad, Bid, Bik, Bim, Noxa and PUMA have a conserved BH3 domain that develops apoptosis by regulation of antiapoptotic Bcl-2 protein. In addition, p53 may directly affect mitochondrial integrity without the need for gene activation. Indeed, it has been reported that p53 can bind to Bcl-2 and Bcl-XL at the mitochondria, thereby promoting mitochondrial destabilization. This review concludes the proteins and stressors of mitochondria and its role in apoptosis.

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References

1. Ernster, L., Schatz G. “Mitochondria: a historical review”. In: *The Journal of Cell Biology* 91(3). 1981: p. 227s-255s.
2. Vakifahmetoglu-Norberg, H, Ouchida A. T., Norberg E. “The role of mitochondria in metabolism and cell death”. In: *Biochemical and Biophysical Research Communication*. 482(3). 2017: p. 426-431.
3. Ding, W.X, Li M, Biazik J.M, Morgan D.G, Guo F, Ni H.M, Goheen M, Eskelinen E.L., Yin X.M. “Electron microscopic analysis of a spherical mitochondrial structure”. In: *Journal of Biological Chemistry*. 287(50).2012: p.42373-42378.
4. Koopman, W.J, Nijtmans L.G, Dieteren C.E, Roestenberg P, Valsecchi F, Smeitink J.A., Willems P.H. “Mammalian mitochondrial complex I: biogenesis, regulation, and reactive oxygen species generation”. In:*Antioxidants and Redox Signalling.*12(12). 2010: p. 1431-1470.
5. Wang, W, Fang H, Groom L, Cheng A, Zhang W, Liu J, Wang X, Li K, Han P, Zheng M, Yin J, Wang W, Mattson M.P, Kao J.P, Lakatta E.G, Sheu S.S, Ouyang K, Chen J, Dirksen R.T., Cheng H. “Superoxide flashes in single mitochondria”. In:*Cell.*134. 2008: p. 279-290.
6. Barja, G. “Rate of generation of oxidative stress-related damage and animal longevity”. In:*Free Radical Biology and Medicine.*33(9).2002: p. 1167–1172

7. Adam-Vizi, V., Chinopoulos C. "Bioenergetics and the formation of mitochondrial reactive oxygen species". In:*Trends in Pharmacological Sciences.*27(12).2006: p. 639-645.
8. Scorrano, L. "Opening the doors to cytochrome c: changes in mitochondrial shape and apoptosis". In:*The International Journal of Biochemistry and Cell Biology.*41(10). 2009: p. 1875-1883.
9. Van Loo, G, Saelens X, Van Gurp M, MacFarlane M, Martin S.J., Vandenabeele P. "The role of mitochondrial factors in apoptosis: a Russian roulette with more than one bullet". In:*Cell Death and Differentiation.*9(10). 2002: p. 1031-1042.
10. Kuwana, T., Newmeyer D.D. "Bcl-2-family proteins and the role of mitochondria in apoptosis". In: *Current Opinion in Cell Biology.*15(6).2003: p. 691-699.
11. Orrenius, S. "Mitochondrial regulation of apoptotic cell death". In: *Toxicology Letters.*149(1). 2004: p. 19-23.
12. Garrido, C, Galluzzi L, Brunet M, Puig PE, Didelot C., Kroemer G. "Mechanisms of cytochrome C release from Mitochondria". In: *Cell Death Differentiation.*3(9).2006: p. 1423-1433.
13. Munn, E.A. "The structure of mitochondria". In:*Academic Press*.2014.
14. Kukat, C, Wurm C.A, Spahr H, Falkenberg M, Larsson N.G., Jakobs S. "Super-resolution microscopy reveals that mammalian mitochondrial nucleoids have a uniform size and frequently contain a single copy of mtDNA". In: *Proceedings of the National Academy of Sciences of the United States of America.*108 (33). 2011: p. 13534–13539.
15. Kühlbrandt, W. "Structure and function of mitochondrial membrane protein complexes". In: *BMC Biology.*13 (1). 2015: p. 1-11.
16. Mannella, C.A. "Structure and dynamics of the mitochondrial inner membrane cristae". In: *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research.* 1763(5). 2006: p. 542-548.
17. Stojanovski, D, Bohnert M, Pfanner N., Van der lan, M. "Mechanism of protein sorting in mitochondria". In: *Cold Spring Harbor Perspectives in Biology.*4(10). 2012: p. a011320
18. Truscott, K.N, Brandner K., Pfanner N. "Mechanisms of protein import into mitochondria". In:*Current Biology.*13(8). 2003: p. R326-R337.
19. Kubli, D.A., Gustafsson A.B. "Mitochondria and mitophagy". In: *Circulation Research.*111 (9). 2012: p. 1208-1221.
20. Hu, F., Liu F. "Mitochondrial stress: A bridge between mitochondrial dysfunction and metabolic disesas?" In:*Cellular Signalling.*23(2011). 2011: p. 1528-1533.
21. Wang, X. "The expanding role of mitochondria in apoptosis". In: *Genes and development.15* (22): 2001: p. 2922-2933.
22. Kerr, J.F.R, Wyllie A.H. and Currie, A.R. "Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics". In: *British Journal of Cancer*. 26(4).1972:p. 239–257.
23. Hillario, E, Canavate M.L, Lacelle J, Alonso-Alconada D, Lara-Celador I, Alvarez-Granda L., Alvarez A. "Cell death. A comprehensive approximation. Delayed cell death*".* In: *Microscopy: Science, Technology, Application and Education.*2010: p.1025-1032.
24. Edinger, A.L., Thompson C.B. "Death by design: apoptosis, necrosis and autophagy". In: *Current Opinion Cell Biology.*16(6). 2004: p. 663– 669.
25. Ouyang, L, Shi Z, Zhao S, Wang F.-T, Zhou T.-T, Liu B., Bao J.-K. "Programmed cell death pathways in cancer: a review of apoptosis, autophagy and programmed necrosis". In:*Cell Proliferation*. 45(6).2012: p. 487–498.
26. Doonan, F., Cotter T.G. "Morphological assessment of apoptosis". In:*Methods.*44(3). 2008: p. 200-204.
27. Zimmermann, K. C, Bonzon C., Green, D. R. "The machinery of programmed cell death". In:*Pharmacology and Therapeutics.*92(1). 2001: p. 57-70.
28. Youle, R.J., Strasser A. "The Bcl-2 protein family: opposing activities that mediate cell death". In: *Nature Reviews Molecular Cell Biology.*9(1). 2008: p. 47-59.
29. Circu, M.L., Aw T.Y. "Reactive oxygen species, cellular redox systems and apoptosis".In: *Free Radical Biology and Medicine.48*(6).2010: p. 749-762.
30. Elmore, S. "Apoptosis: a review of programmed cell death". In: *Toxicologic Pathology.*35(4). 2007: p. 495-516.
31. Fesik, S.W. "Promoting apoptosis as a strategy for cancer drug discovery". In: *Nature Reviews Cancer. 5*(11). 2005: p. 876-885.
32. Ribas, V, García-Ruiz C., Fernández-Checa, J.C. "Mitochondria, cholesterol and cancer cell metabolism". In:*Clinical and Translational Medicine.*5(1). 2016: p. 22-46
33. Lawen, A. "Apoptosis-an introduction". In: *Bio Essays.*25(9).2003: p. 888-896.
34. Shi, Y. "A structural view of mitochondria-mediated apoptosis". In:*Nature Structural & Molecular Biology.*8(5).2001: p. 394-401.
35. Kroemer, G, Galluzzi L., Brenner, C. "Mitochondrial membrane permeabilization in cell death". In:*Physiological Reviews.*87(1).2007: p. 99-163.
36. Muravchick, S., Levy R.J. "Clinical implications of mitochondrial dysfunction. In:*Anesthesiology".*105(4). 2006: p. 819–837.
37. Fulda, S., Debatin K.M. "Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy". In:*Oncogene.* 25(34). 2006:p. 4798-4811.
38. Li, M.X., Dewson G. "Mitochondria and apoptosis: emerging concepts". In:*F1000Prime Rep.* 7. 2015: p. 7-42
39. Tait, S.W., Green D.R. "Mitochondria and cell death: outer membrane permeabilization and beyond". In:*Nature Reviews Molecular Cell Biology.*11(9). 2010:p. 621-632.
40. Xiong, S, Mu T, Wang G, Jiang X. "Mitochondria-mediated apoptosis in mammals". In:*Protein and Cell.* 5(10). 2014: p. 737-749.
41. Ott, M, Gogvadze V., Orrenius S., Zhivotovsky B. "Mitochondria, oxidative stress and cell death". In:*Apoptosis.*12 (5). 2007: p. 913-922.
42. Jiang, X., Wang X. "Cytochrome C-mediated apoptosis". In: *Annual Review of Biochemistry.*73 (1). 2004: p. 87-106.

43. Mannella, C.A. "Structural diversity of mitochondria". In: *Annals of the New York Academy of Sciences.*1147(1). 2008: p. 171-179.
44. Ghobrial, I.M, Witzig T.E., Adjei A.A. "Targeting apoptosis pathways in cancer therapy". In: *CA: A Cancer Journal for Clinicians.*55 (3). 2005: p. 178–194.
45. Chipuk, J.E., Green D.R. "Do inducer of apoptosis trigger caspase-independent cell death?" In:*Nature Reviews Molecular Cell Biology.* 6(3). 2005: p. 268–275.
46. Martinou, J.C, Desagher S., Antonsson B. "Cytochrome c release from mitochondria: all or nothing". In: *Nature Cell Biology.*2(3). 2000: p. E41-E43.
47. Luo, X, Budihardjo I, Zou H, Slaughter C., Wang X. "Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors". In: *Cell*. 94(4). 1998: p. 481-490.
48. Reed, J.C. "Apoptosis-based therapies". In:*Nature Reviews Drug Discovery.*1(2). 2002: p. 111-121.
49. Ravagnan, L, Roumier T., Kroemer G. "Mitochondria, the killer organelles and their weapons". In:*Journal of Cellular Physiology.*192(2). 2002: p. 131-137.
50. Du, C, Fang M, Li Y, Li L., Wang X. "Smac, a mitochondrial protein that promotes cytochrome c–dependent caspase activation by eliminating IAP inhibition".In:*Cell.*102(1). 2000: p. 33-42.
51. Verhagen, A.M, Ekert P.G, Pakusch M, Silke J, Connolly L.M, Reid G.E, Moritz R.L, Simpson R.J., Vaux D.L. "Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to and antagonizing IAP proteins". In:*Cell.* 102(1).2000: p. 43-53.
52. Ekert, P.G, Silke J, Hawkins C.J, Verhagen A.M., Vaux D.L. "DIABLO promotes apoptosis by removing MIHA/XIAP from processed caspase 9". In:*The Journal of Cell Biology.*152(3). 2001: p. 483-490.
53. Li, W, Srinivasula S.M, Chai J, Li P, WuJ.W, Zhang Z, Alnemri E.S., Shi Y. "Structural insights into the pro-apoptotic function of mitochondrial serine protease HtrA2/Omi". In: *Nature Structural and Molecular Biology.*9(6). 2002:p. 436-441.
54. Bhuiyan, M., Fukunaga K. "Activation of HtrA2, a mitochondrial serine protease mediates apoptosis: current knowledge on HtrA2 mediated myocardial ischemia/reperfusion injury". In: *Cardiovascular Therapeutics.*26(3). 2008: p. 224-232.
55. Hegde, R, Srinivasula S.M, Zhang Z, Wassell R, Mukattash R, Cilenti L, DuBois G, Lazebnik Y, Zervos A.S, Fernandes-Alnemri T., Alnemri E.S. "Identification of Omi/HtrA2 as a mitochondrial apoptotic serine protease that disrupts inhibitor of apoptosis protein-caspase interaction". In: *Journal of Biological Chemistry.* 277(1).2002: p. 432-438.
56. Gray, C.W, Ward R.V, Karran E, Turconi S, Rowles A, Viglienghi D, Southan C, Barton A, Fantom K.G, West A., Savopoulos J. "Characterization of human HtrA2, a novel serine protease involved in the mammalian cellular stress response". In: *European Journal of Biochemistry.*267(18). 2000: p. 5699-5710.
57. Walle, L.V, Lamkanfi M., Vandenabeele P. "The mitochondrial serine protease HtrA2/Omi: an overview". In:*Cell Death and Differentiation.*15(3).2008: p. 453-460.
58. Srinivasula, S.M, Gupta S, Datta P, Zhang Z, Hegde R, Cheong N, Fernandes-Alnemri T., Alnemri E.S. "Inhibitor of apoptosis proteins are substrates for the mitochondrial serine protease Omi/HtrA2". In:*Journal of Biological Chemistry.*278(34).2003: p. 31469-31472.
59. Yang, Q.H, Church-Hajduk R, Ren J, Newton M.L., Du C. "Omi/HtrA2 catalytic cleavage of inhibitor of apoptosis (IAP) irreversibly inactivates IAPs and facilitates caspase activity in apoptosis". In:*Genes and development.*17(12). 2003: p. 1487-1496.
60. Suzuki, Y, Takahashi-Niki K, Akagi T, Hashikawa T., Takahashi R. "Mitochondrial protease Omi/HtrA2 enhances caspase activation through multiple pathways". In:*Cell Death and Differentiation.*11(2). 2004: p. 208-216.
61. Donovan, M., Cotter T.G. "Control of mitochondrial integrity by Bcl-2 family members and caspase-independent cell death". In: *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research.*1644(2). 2004: p. 133-147.
62. Vahsen, N, Cande C, Briere J.J, Benit P, Joza N, Larochette N, Mastroberardino P.G, Pequignot M.O, Casares N, Lazar V, Feraud O, Debili N, Wissing S, Engelhardt S, Madeo F, Piacentini M, PenningerJ.M, Schagger H, Rustin P., Kroemer G. "AIF deficiency compromises oxidative phosphorylation". In:*European Molecular Biology Organization Journal.* 23.2004: p. 4679–89.
63. Candé, C, Cecconi F, Dessen P., Kroemer G. "Apoptosis-inducing factor (AIF): key to the conserved caspase-independent pathways of cell death?" In:*Journal of Cell Science.*115(24). 2002: p. 4727-4734.
64. Loeffler, M, Daugas E, Susin S. A, Zamzami N, Métivier D, Nieminen A.-L, Brothers G, Penninger J. M., Kroemer G. "Dominant cell death induction by extramitochondrially targeted apoptosis inducing factor". In: *Federation of American Societies for Experimental Biology Journal.*15(3). 2001: p. 758 -767.
65. Susin, S.A, Daugas E, Ravagnan L, Samejima K, Zamzami N, Loeffler M, Costantini P, Ferri K.F, Irinopoulou T, Prévost M.C., Brothers G. "Two distinct pathways leading to nuclear apoptosis". In: *The Journal of Experimental Medicine.*192(4).2000: p. 571-580.
66. Cote, J., Ruiz-Carrillo A. "Primers for mitochondrial DNA replication generated by endonuclease G". In: *Science.*261(5122). 1993: p. 765 – 769.
67. Li, L.Y, Luo X., Wang X. "Endonuclease G is an apoptotic DNase when released from mitochondria". In:*Nature.*412(6842). 2001: p. 95-99.
68. Van Loo, G, Schotte P, Van Gurp M, Demol H, Hoorelbeke B, Gevaert K, Rodriguez I, Ruiz-Carrillo A, Vandekerckhove J, Declercq W., Beyaert R. "Endonuclease G: a mitochondrial protein released in apoptosis and involved in caspase-independent DNA degradation". In: *Cell Death and Differentiation.*8 (12).2001: p. 1136-1142.
69. Burlacu, A. "Regulation of apoptosis by Bcl-2 family proteins". In: *Journal of Cellular and Molecular Medicine.* 7 (3). 2003: p.249-257.

70. Kluck, R.M, Bossy-Wetzel E, Green D.R., Newmeyer D.D. "The release of cytochrome c from mitochondria: a primary site for Bcl-2 regulation of apoptosis". In: *Science.* 275 (5303). 1997: p. 1132-1136.
71. Puthalakath, H., Strasser A. "Keeping killers on a tight leash: transcriptional and post-translational control of the pro-apoptotic activity of BH3-only proteins". In: *Cell Death and Differentiation.*9 (5).2002: p. 505-512.
72. Yang, J, Liu X, Bhalla K, Kim C.N, Ibrado A.M, Cai J, Peng T.I, Jones D.P., Wang X. "Prevention of apoptosis by Bcl-2: release of cytochrome c from mitochondria blocked". In: *Science.* 275(5303).1997: p. 1129-1132.
73. Tsujimoto, Y. "Role of Bcl-2 family proteins in apoptosis: apoptosomes or mitochondria?" In:*Genes to Cells.*3(11).1998: p. 697–707.
74. Nishida, K, Yamaguchi O., Otsu K. "Crosstalk between autophagy and apoptosis in heart disease". In:*Circulation Research.*103(4). 2008: p. 343-351.
75. Bender, T., Martinou J.C. "Where killers meet-permeabilization of the outer mitochondrial membrane during apoptosis". In: *Cold Spring Harbour Perspectives in Biology.*5(1).2013: p. 11106.
76. Inoue, S, Browne G, Melino G., Cohen G.M. "Ordering of caspases in cells undergoing apoptosis by the intrinsic pathway". In: *Cell Death and Differentiation.*16 (7). 2009: p. 1053-1061.
77. Grütter, M.G. "Caspases: key players in programmed cell death". In:*Current Opinion in Structural Biology.*10(6). 2000: p. 649-655.
78. Shalini, S, Dorstyn L, Dawar S., Kumar S. "Old, new and emerging functions of caspases". In: *Cell Death Differ.* 22(4).2015: p. 526-539
79. Kumar, S. "Caspase function in programmed cell death". In:*Cell Death and Differentiation*. 14(1).2006: p. 32-43
80. Fuentes-Prior, P., Salvesen G.S. "The protein structures that shape caspase activity, specificity, activation and inhibition". In: *Biochemical Journal.*384 (2).2004: p. 201-232.
81. Rasola, A., Bernardi P. "The mitochondrial permeability transition pore and its involvement in cell death and in disease pathogenesis". In: *Apoptosis.*12 (5). 2007: p. 815-833.
82. Zha, J, Weiler S, Oh K.J, Wei M.C., Korsmeyer S.J. "Posttranslational N-myristoylation of BID as a molecular switch for targeting mitochondria and apoptosis". In:*Science.* 290(5497).2000: p.1761-1765.
83. Guo, Y, Srinivasula S. M, Druilhe A, Fernandes-Alnemri T., Alnemri E.S. "Caspases-2 Induces Apoptosis by Releasing Proapoptotic Proteins from Mitochondria". In: *The Journal of Biological Chemistry.*277(16). 2002: p. 13430-13437.
84. Taylor, R.C, Cullen S.P., Martin S.J. "Apoptosis: Controlled demolition at the cellular level". In: *Nature Reviews Molecular Cell Biology.*9(3). 2008: p. 231–241.
85. Porter, A.G., Janicke R.U. "Emerging roles of caspase-3 in apoptosis". In:*Cell Death and Differentiation.*6(2).1999: p. 99–104.
86. Lakhani, S.A, Masud A, Kuida K, Porter G.A, Booth C.J, Mehal W.Z, Inayat I., Flavell R.A." Caspases 3 and 7: key mediators of mitochondrial events of apoptosis". In: *Science.* 311(5762). 2006: p. 847-851.
87. Schuler, M, Bossy-Wetzel E, Goldstein J.C, Fitzgerald P., Green D.R. "p53 induces apoptosis by caspase activation through mitochondrial cytochrome c release". In: *Journal of Biological Chemistry.*275(10). 2000: p. 7337-7342.
88. Zhang, X, Li C.F, Zhang L, Wu C.Y, Han L, Jin G, Rezaeian A.H, Han F, Liu C, Xu C,Xu X, Huang C.Y, Tsai F.J, Tsai C.H, Watabe K., Lin H.K."TRAF6 restricts p53 mitochondrial translocation, apoptosis, and tumor suppression". In: *Molecular Cell.* 64(4).2016: p. 803-817.
89. Mihara, M, Erster S, Zaika A, Petrenko O, Chittenden T, Pancoska P., Moll U.M. "p53 has a direct apoptogenic role at the mitochondria". In: *Molecular Cell.*11(3).2003: p. 577-590.
90. Yu, J, Wang Z., Kinzler K.W. "PUMA mediates the apoptotic response to p53 in colorectal cancer cells". In: *Proceedings of the National Academy of Sciences of the United States of America.* 100(4).2003: p. 1931–1936.

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