# The Mitochondria as an Essential Regulator of Apoptosis

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The process of apoptosis refers to programmed cell death, an essential mechanism for eliminating damaged cells. It is initiated through the intrinsic mitochondrial or the extrinsic death receptor pathways. This paper aims to unveil the pivotal role of mitochondria in regulating the apoptotic process. This paper is a systematic review based on thoroughly examining nineteen articles that align with my search criteria and cross-examining them to find principal concepts to clarify the answer to the research question. Through rigorous analysis, it became apparent that the mitochondria house the intrinsic apoptotic pathway and facilitate communication with the extrinsic apoptotic pathway through crosstalk, which cements the mitochondria's integral role in controlled cell death.

**Keywords:** Apoptosis, Programmed cell death, Intrinsic apoptosis, Mitochondrial apoptosis

## Introduction

Apoptosis refers to the fundamental and highly regulated process of controlled cell death. This process can occur through the two main apoptotic pathways: the intrinsic and extrinsic, each with a unique apoptotic process. The intrinsic pathway occurs at the outer mitochondrial membrane and is activated by signals inside the mitochondria. Those signals amplify the intrinsic pathway through cytochrome c[1]. Factors outside the cell activate the extrinsic pathway[1]. Generally, these main apoptotic pathways are initiated by cellular damaging factors such as excessive reactive oxygen species (ROS), Deoxyribonucleic Acid (DNA) damage, and mitochondrial dysfunction[1]. The primary enzymes involved in both apoptotic processes are caspases. Caspases are proteases critical in orchestrating cell death by degrading cellular components.

Numerous key enzymes regulate the intrinsic mitochondrial pathway including cytochrome c, caspase 9, caspase 3, OMA1 zinc metalloendopeptidase (OMA1), and B-cell lymphoma 2 (Bcl-2) family proteins[2]. In contrast, many death receptors in the Tumor necrosis factor receptor (TNFR) family, which are pro-apoptotic cell membrane proteins, regulate the extrinsic apoptotic pathway[3]. These receptors include: Fas, TNFR1, TNFR2, death receptor 4 (DR4), and DR5 ect[3]. BH3 Interacting Domain Death Agonist (BID) is the pro-apoptotic protein that connects the intrinsic and the extrinsic pathways[4]. BID binds to and activates the proteins Bcl-2-associated X (BAX) and Bcl-2 antagonist killer 1 (BAK) in the intrinsic mitochondrial pathway[4]. These Bcl-2 family proteins oligomerize and create pores in the mitochondrial membrane, forming mitochondrial outer membrane permeability (MOMP)[4]. MOMP triggers the release of cytochrome c, which facilitates the activation of caspases and ultimately initiates apoptosis[4].

Moreover, in the extrinsic pathway, death receptor TNFR proteins bind to their corresponding death ligands and trigger the formation of Fas-associated death domain protein (FADD) and caspase 8, creating the death-inducing signaling complex (DISC)[4]. Activation of caspase 8 or caspase 10 at the signaling complex leads to the cleavage of BID and presents communication with the mitochondria[5]. The mutual crosstalk between apoptosis and autophagy regulates cell death or survival[5]. This interaction is also imperative for regulating mitochondrial DNA (mtDNA) release, which is released when there is an increase in cell death stressors[5].

The intrinsic mitochondrial pathway is characterized by pro-apoptotic and anti-apoptotic Bcl-2 family members, which modulate the release of cytochrome c from the mitochondria[2]. Anti-apoptotic Bcl-2 members halt the release of apoptotic factors into the cytosol, unlike pro-apoptotic members, which initiate the release and activity of apoptotic factors[2]. Interactions between Bcl-2 family members control the beginning steps of the intrinsic apoptotic process[2]. For instance, pro-apoptotic members such as BAX and BAK will bind to anti-apoptotic members, which negatively regulates their activity, allowing for the progression of apoptosis[1]. During the mitochondrial outer membrane permeabilization process, Bcl-2 family members BAX and BAK form pores in the outer mitochondrial membrane[4]. This permeabilization activates OMA1, which initiates cytochrome c release from the intermembrane space[4]. Cytochrome c binds to Apoptotic protease activating factor-1 (APAF-1) to form the apoptosome (a complex of proteins that moderate the initiation of caspases)[4,6]. Procaspase 9, an active enzyme that initiates cell death, binds to this apoptotic complex[4]. Caspase 9 then gets activated by dimerization and activates caspase 3, which

executes programmed cell death[4,5].

Conversely, the extrinsic pathway consists of death receptors crucial in initiating apoptosis[3]. When bound to ligands such as Fas Cell Surface Death Receptor Ligand (FAS-L), Tumor necrosis factor (TNF), or TNF-related apoptosis-inducing ligand (TRAIL), the formation of DISC occurs[3]. This complex activates caspase 8, which triggers the apoptotic signal, killing the cell[4].

In addition to housing the intrinsic apoptotic pathway, the mitochondria play additional roles in the overall maintenance of cellular health. For example, the generation of Adenosine Triphosphate (ATP) through the electron transport chain (ETC) occurs in the inner mitochondrial membrane[7]. The ETC contains five protein complexes that work together to facilitate oxidative phosphorylation[7]. Oxidative phosphorylation is a metabolic process that generates energy for a cell[7]. The process is characterized by the transfer of electrons among the first four protein complexes[7]. This electron transfer powers the simultaneous pumping of protons to generate a potential difference, which is then used to power the synthesis of ATP by the fifth and final protein complex[7]. Electrons that pass through this chain ultimately convert oxygen to water[7]. During this conversion process, an increased output of ROS occurs[7]. ROS produced without sufficient antioxidant counteraction may lead to oxidative stress and mitochondrial dysfunction[7]. ROS reacts with proteins and nucleic acids, causing damage to oxidative phosphorylation proteins and mitochondrial DNA[7]. This disturbance to mitochondrial homeostasis results in dysfunctional mitochondria, which can trigger apoptosis through the intrinsic pathway[7].

Generally, dysfunctional mitochondria will overproduce ROS and release pro-apoptotic cytochrome c, which initiates intrinsic apoptosis[1]. Usually, cells will attempt to remove these dysfunctional mitochondria through mitophagy, a process imperative in mitochondrial quality control[8]. A lack of mitophagy due to the deletion of the minimal essential region (MER) domain can result in damaged mitochondria accumulating, creating cellular stress and disease in the worst cases[8]. Over time, this increase in cellular stress results in mitochondrial disease or other types of disease like certain cancers in the host[8]. This paper will primarily focus on the crucial role of mitochondria in regulating apoptosis and the implications that dysfunctional mitochondria can have on this vital process. Hypothetically, mitochondrial dysfunction may trigger the initiation of the intrinsic pathway, and this review seeks to elucidate this possibility.

## Purpose of Apoptosis and Consequences of Dysregulation

As mentioned previously, apoptosis occurs via the intrinsic mitochondrial pathway and the extrinsic death receptor pathway. Each pathway contains several enzymes that jointly regulate and activate the apoptotic process[4]. The intrinsic mitochondrial pathway includes cytochrome c, caspase 9, caspase 3, OMA1, and Bcl-2 family proteins[4]. Contrastingly, the extrinsic death receptor pathway is regulated by the receptors Fas, TNFR1, TNFR2, DR4, and DR5, etc[4]. These receptors are considered pro-apoptotic death receptors belonging to the TNFR family[4]. Though apoptosis can be highly beneficial to the functionality of an organism when left unchecked, apoptosis can have crippling repercussions for the health of the organism. Dysregulated apoptosis can result in the damage of tissues due to the uncontrolled loss of healthy cells[9].

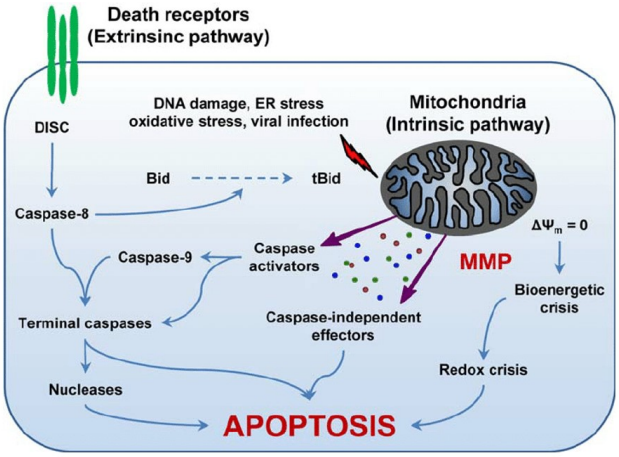


**Fig. 1** The illustration of the intrinsic mitochondria and extrinsic death receptor apoptotic pathways (Galluzzi L. et. al., 2008)[10].

### Apoptotic Pathways

Apoptosis can occur via either the intrinsic mitochondrial pathway or extrinsic death receptor pathway[1]. Both pathways are activated by damaging cellular factors such as the excessive production of ROS, mutations in the mtDNA, and overall cellular stress[1]. The intrinsic pathway is triggered by signals within the cell and is located in the mitochondria[1]. The activation of pro-apoptotic proteins and caspases takes place in the cytosol[1]. Stress signals are produced when there are inappropriate amounts of ROS and mtDNA mutations[11]. This signal, which indicates dysfunction, initiates the intrinsic mitochondrial pathway[11].

The apoptotic process begins on the surface of the mitochondria, where the BAX and BAK proteins are located[11]. These pro apoptotic proteins are activated by an apoptotic signal from oxidative stress or mtDNA damage which marks the start of the intrinsic cell death process[5]. BAX and BAK can activate OMA1, which cleaves optic atrophy 1 (OPA1)[11]. This cleaved OPA1 then prompts mitochondrial cristae remodeling, which

are the inner folds of the mitochondria[11]. During this process, the cristae junctions narrow to prevent cytochrome c release[1]. In the outer mitochondrial membrane, BAX and BAK, triggered by mitochondrion permeabilizing peptide truncated BID (tBID), oligomerize and form pores, creating macropores[9]. These pores lead to MOMP[9]. The formation of MOMP initiates the release of intermembrane space (IMS) proteins, including cytochrome c, into the cytosol, which forms the apoptosome[9]. The apoptosome is a complex of proteins that mediate the initiation of caspases[9]. Caspases belong to a family of cysteine proteases that cleave many other proteins during the apoptotic process[9]. The apoptosome is formed when cytochrome c binds to APAF1[12]. The release of cytochrome c is positively regulated by pro-apoptotic Bcl-2 family members BAX, BAK, BID, and a p53 modulator of apoptosis (PUMA)[4]. Conversely, cytochrome c release is negatively regulated by anti-apoptotic Bcl-2 family members BCL-XL, Bcl-w, A1, and MCL 1[4]. The apoptosome initiates the activation of caspases and is bound to the death-inducing enzyme Procaspase 9[12]. The apoptosome activates caspase 9, which activates caspase 3, leading to the execution of cell death[12].

Moreover, the extrinsic death receptor pathway is also regulated by various ligands, proteins, and receptors[3]. External stimuli such as DNA damage signals activate the following receptors[6]. The process begins with the initiation of death receptors (also known as cellular membrane proteins) such as TNFR1, TNFR2, DR4, and DR5[3]. DR4 and DR5 directly bind to FADD, whereas TNFR1 has to bind to the adapter protein TRADD, which then recruits FADD[3]. The binding of a death receptor such as FAS-R, TNF-R1, TNF-R2, TRAIL-R1, and TRAIL-R2 to FADD and caspase 8 results in a trimerization and the creation of DISC[3]. The activation of caspase 8 or caspase 10 by the DISC results in the cleavage of BID[4]. tBID eventually relocates to the mitochondria[3]. It prompts cytochrome c release and caspase 9 activation, which triggers caspase 3[4]. The activation of caspase 3 ultimately induces the apoptotic signal, which incites cell death[4].

## Mitochondrial Apoptosis

Because the intrinsic mitochondrial apoptotic pathway is activated by signals from the mitochondria and is located in the outer mitochondrial membrane, the mitochondria arguably play a critical role in supporting apoptosis[4]. Mitochondria are the source of the pro-apoptotic factor cytochrome c, which primarily activates caspase 9 and caspase 3 during the apoptotic process[4]. The mitochondria release cytochrome c under damaging conditions, such as excessive ROS and mtDNA damage/mutations, which negatively interfere with mitochondrial function[8]. These stressors may be alleviated by mitochondrial fusion, which is a process that entails the generation of a singular mitochondrion by combining dysfunctional mitochondria, which is necessary because mitochondria are imperative to the apoptotic process[9]. In the presence of stressors such as excessive amounts of ROS, mitochondrial fusion is upregulated[13].

Decreased or increased apoptosis occurring in both apoptotic pathways can cause numerous types of cancers and neurodegenerative diseases[8]. Apoptosis occurs in an adult human body in large amounts, and around ten billion cells are made daily to make up for the amount lost due to cell death[14]. This increase in apoptosis in adults could be due to age-related cellular decline, which elicits the need for increases in apoptosis[14]. There is a baseline level of activity in both apoptotic pathways to maintain cellular homeostasis and to ensure that the amount of dysfunctional cells does not increase through cellular proliferation4. The amount of apoptosis also depends on the activation of caspases, whose activity positively upregulates mitochondrial apoptosis[1]. Cell-death-inducing signals and stimuli generally activate caspases[15].

The level of apoptotic activity of the intrinsic mitochondrial pathway depends on signals from the Bcl-2 family members in the mitochondria, which are activated due to death stimuli such as DNA damage[1]. In healthy mitochondria, the apoptotic process is not necessarily activated since cellularly stressful and damaging factors trigger apoptosis[1,5]. However, excessive ROS significantly impacts cell division and proliferation, which can trigger apoptosis[8]. Dysfunctional mitochondria can also induce cell death because they increase the production of ROS, which creates an excess amount of oxidative stress, damaging the cell and causing mutations to mtDNA[8]. This impairment can activate the apoptotic signal, which kills the cell[8].

## Relationship Between Mitochondrial Apoptosis and Other Apoptotic Pathways

Although the intrinsic mitochondrial pathway is triggered mainly by signals inside the mitochondria and the extrinsic death receptor pathway is activated by external stimuli, both pathways may be activated due to damaging factors[9]. The intrinsic pathway is triggered by ROS and mtDNA mutations, which are stressors that negatively interfere with the function of mitochondria[9]. Conversely, extracellular ligands such as TNF and FAS-L can trigger the extrinsic pathway[4]. The intrinsic and extrinsic pathways ultimately activate the same caspase 3, which, when cleaved by an initiator caspase, triggers the execution pathway of apoptosis[14]. This pathway is where the formation of apoptotic bodies and the irreversible death of the cell occur[14].

The intrinsic mitochondrial pathway is triggered by stress signals inside the cell, such as oxidative stress and mtDNA mutations, while external factors trigger the extrinsic death receptor pathway[6]. The apoptosome is the protein complex formed in the intrinsic pathway, while the DISC is the protein complex formed in the extrinsic pathway[6]. Both the apoptosome and DISC result in the initiation or activation of specific caspases that are the

gateway to the final executioner pathway of apoptosis, ultimately resulting in cell death[6]. The apoptosome activates caspase 9, which triggers caspase 3, causing cell death via the executioner pathway[6]. On the contrary, the DISC is where caspase 8 is activated and separates from the signaling complex to initiate the execution of the apoptotic pathway[6].

While the extrinsic pathway is regulated by death ligands such as TNF, FAS-L, and TRAIL, the intrinsic pathway activates apoptotic proteins from the Bcl-2 family to function[6]. The intrinsic and extrinsic pathways of apoptosis each consist of numerous different caspases, which assist in the function of each pathway respectively[4]. In the intrinsic pathway, the cleavage of caspase 9 at the apoptosome activates caspase 3, which initiates the execution of cell death[4]. Similarly, in the extrinsic pathway, caspases 8 and 10 are activated at DISC, which triggers the cleavage of BID and initiates the apoptotic signal, killing the cell[4].

The intrinsic mitochondrial and the extrinsic death receptor pathways merge and induce the final apoptotic execution pathway[6]. This phase of the apoptotic process occurs due to executioner caspases, such as caspase 3 and caspase 7[6]. When activated, these caspases carry out apoptosis to kill the cell[6]. The pro-apoptotic protein BID and the final executioner apoptotic pathway link the intrinsic and extrinsic apoptotic pathways[4,6]. In the intrinsic pathway, pro-apoptotic factors BID, BAX, and BAK positively regulate the release of cytochrome c, which binds to APAF-1 and forms the apoptosome[12]. Procaspase 9, found only in the intrinsic pathway, binds to this complex, cleaves, and activates caspase 3, which is activated in both the intrinsic and extrinsic pathway[4]. Caspase 3 then activates the executioner pathway, which completes cell death[4]. In the extrinsic pathway, death receptors bind to FAS-L, TNF, and TRAlL ligands, forming the DISC complex and causing the death receptors to trimerize, activating caspases 8 and 10 and cleavage of BID[7]. The extrinsic death receptor pathway communicates with the intrinsic mitochondrial pathway through the cleavage of BID by caspase 8, resulting in tBID[4]. tBID translocates to the mitochondria, which stimulates the release of cytochrome c[1,4]. This escalates the cytochrome c death signal, leading to apoptosis[4]. Furthermore, extrinsic apoptosis can occur without the mitochondria's involvement. This is the case when caspase 3 is activated by caspase 8, leading to the executioner pathway[4]. This process still leads to apoptotic cell death without involving the mitochondria[4].

## How is Apoptosis Handled When Mitochondria Are Dysfunctional?

Dysfunctional mitochondria, due to mitochondrial ROS, mtDNA damage, and calcium signaling can indirectly lead to cell death[9]. An additional mechanism for counteracting mitochondrial dysfunction is mitochondrial fission. This process will occur in a cell to separate the damaged mitochondrial parts of a mitochondrion, which are then removed through mitophagy[9]. The process of mitochondrial fission is characterized by the detachment of damaged parts of the mitochondria by DRP1[9]. These damaged parts are then removed through mitophagy to assure mitochondrial quality[9]. Ensuring mitochondrial function and quality is necessary for apoptosis since the mitochondria are responsible for housing the intrinsic apoptotic pathway[9].

Following fission, the process of mitophagy occurs to remove unwanted dysfunctional mitochondria to maintain mitochondrial homeostasis and function, as well as the cell's overall health[8]. A cell will undergo mitophagy to remove only the defective mitochondria in a cell, whereas apoptosis is the death of the entire cell[8]. Mitophagy can be categorized as either ubiquitin-mediated mitophagy or receptor-mediated mitophagy[8]. The PTEN-induced kinase 1 (PINK)/Parkin pathway is considered ubiquitin-mediated mitophagy, while Bcl-2 and adenovirus E1B19 kDa-interacting protein 3 (BNIP3) mitophagy and FUN14 domain-containing protein 1 (FUNDC-1) mitophagy are considered receptor-mediated mitophagy[8]. PINK1/Parkin mitophagy begins when PINK1 is collected at the outer mitochondrial membrane in response to mitochondrial damage and dysfunction[8]. This collection prompts the recruitment of Parkin, which modifies elements of the outer membrane[8]. Then, phosphorylated Poly-ubiquitination chains located on mitochondrial proteins modify other proteins such as TBK1, which phosphorylates optineurin (OPTN) and then signals the process of autophagy[8]. Additionally, receptor-mediated mitophagy includes BNIP3 and FUNDC1, which are mitophagy receptors[8]. BNIP3 and FUNDC-1 interact with OPA1 and dynamin-related protein 1 (DRP1) in order to trigger mitophagy[8]. Moreover, the apoptotic protein BNIP3 has the ability to attach itself to proteins called Ras homolog enriched in brain (RHEB) to prevent the activation of mTOR to initiate mitophagy[8]. Mitophagy with FUNDC-1 depends on hypoxia-induced dephosphorylation[8]. Excessive accumulation of unhealthy cells can lead to disease. When a cell holds an excessive amount of mitochondrial dysfunction, processes such as mitophagy cannot fix the damage[9]. This leads to an accumulation of dysfunctional mitochondria, increasing oxidative stress and triggering apoptosis[9].

In mitochondrial dysfunction, the intrinsic pathway is initiated to eliminate damaging factors such as mtDNA damage and dysregulated ROS production through cell death[4]. It is unlikely that the extrinsic pathway compensates for the loss of apoptosis directed by the intrinsic pathway during mitochondrial dysfunction since the intrinsic pathway is triggered by mitochondrial dysfunction. In contrast, factors outside the mitochondria trigger the extrinsic pathway.

## Discussion

The strictly regulated process of programmed cell death is known as apoptosis. This paper strived to clarify the critical role of the mitochondria in the apoptotic process and the potential implications that mitochondrial dysfunction can have on this fundamental procedure. The two primary pathways in which the apoptotic process occurs are the intrinsic mitochondrial and the extrinsic death receptor pathways. Both pathways are activated in response to cellular stressors and are connected by the pro-apoptotic protein BID. BID connects the extrinsic and intrinsic apoptotic pathways when it is cleaved by caspase-8. In the extrinsic pathway, the DISC complex, which functions as the site where cell death is initiated, triggers the cleavage of BID by caspase 8 to create tBID, which translocates to the mitochondria, prompting the release of cytochrome c. tBID binds to APAF-1 to form the apoptosome, which activates Procaspase-9. As a result, caspase 3 and the apoptotic death signal are activated, resulting in cell death.

The extrinsic apoptotic pathway begins with the initiation of cellular membrane death receptors, which bind to ligands to form a DISC where caspase 8 or caspase 10 are activated. Caspase 8 can trigger the apoptotic death signal in mitochondria-independent apoptosis. Additionally, activated caspase 8 has the ability to cleave BID, which causes the mitochondria to release cytochrome c. This cytochrome c attaches to APAF-1 to create the apoptosome, leading to the activation of Procaspase-9. Consequently, the activation of caspase 3 occurs, and the apoptotic death signal is initiated, resulting in cell death. The articles reviewed don't explicitly state precisely where the extrinsic apoptotic pathway is located. I hypothesize that the extrinsic death receptor pathway may be located near the mitochondria's outer membrane, where the intrinsic pathway is located. This may be due to BID's communication between the two apoptotic pathways. tBID in the extrinsic pathway can translocate to the mitochondrial intrinsic pathway to release cytochrome c. For tBID to move to the intrinsic pathway (facilitating crosstalk between the two apoptotic pathways), the extrinsic pathway may have to be located close to the mitochondria.

Both apoptotic pathways are necessary for maintaining cellular health since different factors trigger them. The intrinsic mitochondrial pathway is triggered by stressors inside the mitochondria, such as mtDNA mutations, excessive ROS levels, and mitochondrial dysfunction. On the other hand, the extrinsic pathway is triggered by signals outside of the mitochondria, such as DNA damage. Cells can be characterized as "damaged" due to the accumulation of dysfunctional mitochondria or overall cellular damage. This is why both apoptotic pathways are necessary so that each pathway can account for signals coming from inside the mitochondria or from anywhere else in the cell to maintain the host's health.

Suppose apoptosis is halted due to either of the two pathways being impaired. In that case, it can contribute to the development of various types of cancers and neurodegenerative diseases due to the overaccumulation of damaged cells. These can include Alzheimer's disease, Parkinson's disease, and Huntington's disease [16]. The functionality of the intrinsic pathway can be compromised due to deformities in BAX and BAK, such as the eradication of BAX [16]. Since Bcl-2 proteins are essential to the apoptotic process, the deletion of BAX may hinder the completion of the cell death process. The functionality of apoptosis may also be hindered in the apoptosome with the deactivation of APAF-1 [16]. Cancer cells evade cell death because they upregulate anti-apoptotic proteins, which prevent apoptosis. Suppose we could manipulate the expression of pro-apoptotic Bcl-2 family proteins, which would elicit the release of cytochrome c. In that case, this may allow the apoptotic process to commence by creating the apoptosome, eradicating cancerous cells.

Additionally, understanding the mechanisms that cause upregulation of pro-apoptotic factors in the intrinsic pathway can be used to comprehend why cancerous cells prevent apoptosis through the upregulation of anti-apoptotic Bcl-2 proteins. The levels at which Bcl-2 family members are expressed depend on their transcriptional regulation [17]. For instance, the pro-apoptotic protein BAX is made from mRNA, which p53 regulates to induce apoptosis. DNA damage activates p53, which causes it to facilitate transcription of the genes of BAX and trigger apoptosis [17]. P53, activated by stress signals, initiates the expression of PUMA. This creates the PUMA-BclXL complex, which releases p53 to activate BAX [18]. If cancer cells can be stopped downregulating pro-apoptotic proteins by providing them with a pro-apoptotic protein such as p53, it may eventually allow for MOMP to occur, making apoptosis inevitable. This idea could help cancer treatment by stopping cancerous cells from overriding cell death.

The mitochondria house the intrinsic apoptotic pathway, making it unquestionably essential to intrinsic apoptosis. The mitochondria also can send signals through ROS to indicate a disturbance. This signal triggers the apoptotic process. Since mitochondria are critical in maintaining overall cellular health, damaged mitochondria are removed to prevent disturbances in maintaining homeostasis. The presence of mitochondrial dysfunction due to mtDNA damage and excessive levels of ROS can ultimately lead to cell death to stop dysfunctional mitochondria from multiplying. Various cancers may result from uncontrolled cell proliferation of unhealthy cells, and unhealthy cells might directly result from mitochondrial dysfunction. Cells utilize the process of mitophagy to remove dysfunctional mitochondria and maintain cellular homeostasis. Mitophagy is imperative in mitochondrial quality control. This process eliminates mitochondrial damage by removing all of the impaired mitochondria. Similarly, mitochondrial fusion and fission are integral to ensuring the health of mitochondria so they can facilitate the apoptotic process. Mitochondrial fusion allows damaged mitochondria to

combine to create a singular mitochondrion[9]. Combining may improve mitochondrial function by allowing the mitochondria to compensate for each other's damage. Alternatively, fission allows the eradication of dysfunctional parts of mitochondria by separating the exact damaged part and then removing it through mitophagy[9]. This process indicates that mitochondria are on the verge of elimination due to their damage and are activated by oxidative stress[19].

## Conclusion

The term "apoptosis" refers to the closely monitored process of programmed cell death. The two pathways that enable the occurrence of the apoptotic process are the intrinsic mitochondrial and the extrinsic death receptor pathways. These pathways are activated by cellular damage and malfunction, such as mitochondrial dysfunction and other external stressors. This paper aimed to explore the critical role of mitochondria in regulating apoptosis. The mitochondria house the intrinsic apoptotic pathway and utilize Bcl-2 family proteins and numerous caspases to execute cell death. In the presence of mitochondrial dysfunction, the mitochondria signal to the intrinsic apoptotic pathway that there is a disturbance within the organelle, initiating the process. Additional investigation and research may be necessary to determine the precise location of the cell's extrinsic death receptor apoptotic pathway.

| Abbreviation | Full Name |
|---|---|
| ROS | Reactive oxygen species |
| DNA | Deoxyribonucleic Acid |
| OMA-1 | OMA1 zinc metalloendopeptidase |
| Bcl-2 | B-cell lymphoma 2 |
| TNFR | Tumor necrosis factor receptor |
| DR4 | Death receptor 4 |
| BID | BH3 Interacting Domain Death Agonist |
| BAX | Bcl-2-associated X |
| BAK | Bcl-2 antagonist killer 1 |
| MOMP | Mitochondrial outer membrane permeability |
| FADD | Fas-associated death domain protein |
| DISC | Death-inducing signaling complex |
| mtDNA | Mitochondrial DNA |
| APAF-1 | Apoptotic protease activating factor-1 |
| FAS-L | Fas Cell Surface Death Receptor Ligand |
| TNF | Tumor necrosis factor |
| TRAIL | TNF-related apoptosis-inducing ligand |
| ATP | Adenosine Triphosphate |
| ETC | Electron transport chain |
| MER | Minimal essential region |
| OPA1 | Optic atrophy 1 |
| tBID | truncated BID |
| IMS | Intermembrane space |
| PUMA | p53 modulator of apoptosis |
| PINK | PTEN-induced kinase 1 |
| BNIP3 | Bcl-2 and adenovirus E1B19 kDa-interacting protein 3 |
| FUNDC-1 | FUN14 domain-containing protein 1 |
| OPTN | Optineurin |
| DRP1 | Dynamin-related protein 1 |
| RHEB | Ras homolog enriched in brain |

**Table 1** Abbreviation Table

## Methodology

To determine the role of the mitochondria in regulating apoptosis, a systematic review was conducted. The following search engines were utilized to gather over twenty relevant research articles: Google Scholar and PubMed. A rigorous quality assessment of all data presented was conducted. Papers referenced were found only through the reputable databases previously mentioned to ensure the merit of the research and to prevent the use of illegitimate evidence. Papers used also had to include the following keywords and follow the search criteria. Keywords used include apoptosis, mitochondrial dysfunction, intrinsic pathway, and extrinsic pathway. Search criteria were predicated on the following items: articles must have been published within the last decade, have been cited at least three times, must include at least two of the keywords described above, and should be either a primary research article or a literature review. A rigorous literature review of the chosen articles was completed by thoroughly examining the papers aligned with the search criteria and creating concise summaries containing the overall findings of each report. Summaries were then analyzed to find key recurring themes and differences across the studied papers. These themes or differences were used to generate answers to the research question presented in this paper. Discrepancies identified were considered potential knowledge gaps and were further investigated and resolved through educated inferences. Ideas for future investigations and questions that require further exploration were proposed at the end of the analysis.

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## References

1 C. Wang and R. Youle, *Annual Review of Genetics*, **43**, 95–118.

2 J. Estaquier, F. Vallette, J.-L. Vayssiere and B. Mignotte, *Advances in Experimental Medicine and Biology*, **942**, 157–183.

3 S.-M. Park, R. Schickel and M. Peter, *Current Opinion in Cell Biology*, **17**, 610–616.

4 B. Carneiro and W. El-Deiry, *Nature Reviews Clinical Oncology*, **17**, 395–417.

5 A. Picca, R. Calvani, H. J.Coelho-Junior and E. Marzetti, *Cells*, **10**, 537.

6 R. Jan and G.-S. Chaudhry, *Advanced Pharmaceutical Bulletin*, **9**, 205–218.

7 J. Winter, T. Yadav and J. Rutter, *Molecular Cell*, **82**, 3321–3332.

8 A. Li, M. Gao, B. Liu, Y. Qin, L. Chen, H. Liu, H. Wu and G. Gong, *Cell Death Disease*, **13**, 444.

9 Q. Chu, X. Gu, Q. Zheng, J. Wang and H. Zhu, *Analytical Cellular Pathology*, **8900122**, year.

10 L. Galluzzi, C. Brenner, E. Morselli, T. Zahia and G. Kroemer, *PLoS pathogens*, **4**, 1000018.

11 X. Jiang, H. Jiang, Z. Shen and X. Wang, *Proceedings of the National Academy of Sciences*, **111**, 14782–14787.

12 Q. Hu, D. Wu, W. Chen, Z. Yan, C. Yan, T. He, Q. Liang and Y. Shi, Proceedings of the National Academy of Sciences of the United States of America, p. 16254–16261.

13 R. Youle and A. Bliek, *Science*, **337**, 1062–1065.

14 S. Elmore, *Toxicologic Pathology*, **35**, 495–516.

15 Y. Shi, *Protein Science*, **13**, 1979–1987.

16 B. Favaloro, N. Allocati, V. Graziano, C. Ilio and V. Laurenzi, *Aging*, **4**, 330–349.

17 R. Singh, A. Letai and K. Sarosiek, *Nature Reviews Molecular Cell Biology*, **20**, 175–193.

18 J. Chen, *Cold Spring Harbor Perspectives in Medicine*, **6, a026104**, year.

19 M. Frank, S. Duvezin-Caubet, S. Koob, A. Occhipinti, R. Jagasia, A. Petcherski, M. Ruonala, M. Priault, B. Salin and A. Reichert, *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, **1823**, 2297–2310.