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PARTHANATOS AND APOPTOSIS: UNRAVELING THEIR ROLES IN CANCER CELL DEATH AND THERAPY RESISTANCE

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ABSTRACT

Cell death is a fundamental process that needs to be maintained to balance cellular functions and prevent disease. There are several cell death pathways; however, apoptosis and parthanatos are the most prominent and have important roles in cancer biology. As an extremely well-regulated process, apoptosis removes damaged or abnormal cells via caspase activation and mitochondrial involvement. Unlike in the healthy cells, the loss of ability to induce

apoptosis in cancer permits tumor cells to survive and multiply out of control and contribute to tumor progression and therapy resistance. On the contrary, parthanatos is a caspase-independent metabolic collapse driven by poly (ADP-ribose) polymerase 1 (PARP1) overactivation, translocation of apoptosis-inducing factor (AIF), and complete DNA damage. Several cancer models are involved with parthanatos. Deoxydophyllotoxin (DPT) induces parthanatos in glioma cells by excessive ROS generation, PARP1 upregulation, and AIF nuclear translocation. Like in acute myeloid leukemia (AML), the cannabinoid derivative WIN-55 triggers parthanatos, and the effects can be reversed by PARP inhibitors such as olaparib. Developing cancer treatment strategies involving advanced cancer treatment strategies relies on the interplay between apoptosis and parthanatos. However, such apoptosis-based cancer therapies tend to develop resistance, so there is an urgent need to look into alternative pathways like parthanatos, which may not always trigger apoptosis. In overcoming apoptosis resistance, there is evidence that combining apoptosis-inducing agents, such as BH3 mimetics, with PARP inhibitors synergistically enhances cell death. Oxidative stress modulators have been found to promote the execution of parthanatic and apoptotic pathways and allow treatment. In this review, apoptosis and parthanatos are thoroughly compared at the molecular level, and their roles in cancer pathogenesis as related to cancer therapeutic potential are discussed. We incorporate recent findings to demonstrate that not only can parthanatos be used to manage therapy resistance and enhance cancer treatment via the combination of parthanatos and apoptosis but also that immunity and bone deposition can feasibly be employed against long-circulating cancer stem cells to treat diverse forms of metastatic cancers.

Keywords: Parthanatos, apoptosis, cancer, cell death mechanisms, PARP1, caspases, therapy resistance

INTRODUCTION

Cellular homeostasis is maintained, damaged or aberrant cells are eliminated, and proper development is assured through the important biological process of programmed cell death (Qian et al., 2024). Apoptosis was widely investigated in various forms of programmed cell death due to its important role in eliminating damaged cells irreparably and ensuring that tissue and organismal health are protected (Shkarina and Broz, 2024). However, cell death dysregulation is a hallmark of cancer, a hall that allows the advancement of tumors, exposure to chemotherapies, and tumors' avoidance of immune attacks (Tufail et al., 2024). Typically, the intrinsic balance between pro-survival and pro-death signals is often perturbed in cancer, allowing it to evade immune surveillance and respond to therapies that involve pro-apoptotic activation (Plati et al., 2011). However, the unity in diversity in the controls of apoptosis and alternative cell death pathways, namely parthanatos, is extremely important to understand in order to develop effective and targeted cancer treatments (Zhou et al., 2021). Apoptosis is defined by certain morphological indicators, including DNA breakage, chromatin condensation, and the production of apoptotic bodies; it is thought to be mediated exclusively by a

caspase-dependent process (Kroemer et al., 2009). The apoptotic process is tightly controlled by both extrinsic (death receptor) and intrinsic (mitochondrial) signaling cascades, which are carried out by caspases, cytochrome c, and Bcl 2 family members (Xu and Shi, 2007). Then, parthanatos, a relatively newly identified form of programmed necrosis, is a caspase-independent process activated by the overactivation of PARP1 (Fatokun et al., 2014). When severe DNA damage triggers PARP-1 hyperactivity, the intrinsic mechanisms cause PAR polymer buildup, mitochondrial malfunction, PARP-1 nuclear translocation, large-scale DNA fragmentation, and cell death (Wang et al., 2009a). However, parthanatos is different because it is not immunologically silent, as in apoptosis, and can contribute to inflammatory signaling that, in turn, modifies the tumor microenvironment and therapeutic consequences (Gielecińska et al., 2023).

The therapeutic relevance of the distinction between apoptosis and parthanatos is based on the fact that they have complementary functions in cancer treatment (Su et al., 2016). Many tumors avoid apoptosis due to mutations in tumor suppressor genes like TP53 and overexpression of anti-apoptotic proteins like Bcl2 and IAPs (Crowe and Sinha, 2006). The resistance conferred by

these alterations is due to conventional therapies that depend upon caspase activation (Boice and Bouchier-Hayes, 2020). BH3 mimetics, for example, venetoclax, designed to restore apoptotic sensitivity by inhibiting Bcl-2, may be efficacious only in apoptosis-resistant cancers (Montero and Haq, 2022). Therefore, targeting parthanatos is a promising alternative in such cases (Zhang et al., 2024a). Deoxypodophyllotoxin (DPT) and WIN-55 can also effectively trigger parthanatos in gliomas and AML, even in tumors unresponsive to apoptotic-based treatment (Ma et al., 2016). Parthanatos is particularly relevant in both situations in which parasites are known to have roles, such as cancers being treated with DNA-damaging agents like platinum-based drugs and radiation (Huang et al., 2022). A shortage of ATP and NAD⁺, mitochondrial malfunction, and, eventually, cell death are caused by PARP-1 hyperactivation in response to severe DNA damage (Murata et al., 2019). To inhibit BRCA-mutated cancers, PARP inhibitors were first afforded as synthetic lethality inducers (Lord and Ashworth, 2017). These inhibitors have been found to selectively induce parthanatos in tumor cells with faulty DNA repair mechanisms (Xu et al., 2023). This has created new combinatorial opportunities for killing resistant cells in cancer by combining apoptosis and parthanatos (Zhou et al., 2021).

In contrast, blending PARP inhibitors with BH3 mimetics or immune checkpoint inhibitors has synergistic effects by activating multiple cell death pathways, improving treatment efficacy, and reducing resistance (Wu et al., 2021). In addition to their therapeutic potential, they have diagnostic and prognostic importance concerning such distinction between apoptosis and parthanatos (Maru et al., 2023). Because apoptotic and parthanatic pathways share distinct biochemical and morphological markers, these can be used as biomarkers of treatment response (Mustafa et al., 2024). Furthermore, the relationship between metabolic stress, mitochondrial malfunction, oxidative stress, and the reciprocal activities of parthanatos and apoptosis may

result in new treatment approaches that take advantage of this interaction in a tumor-specific manner (Chen et al., 2011). There are two distinct, though therapeutically complementary, ways of programmed cell death: apoptosis and parthanatos (Andrabi et al., 2008). Even though cancer therapy has long focused on apoptosis, a topic of increasing awareness is that parthanatos has brought new avenues for circumventing resistance to therapy, genomic instability, and metabolic adaptations of tumors (Tong et al., 2022). Cancer can be targeted through these pathways to develop more effective, personalized, and durable therapeutic strategies by distinguishing them and probing how they interact. This review synthesizes molecular mechanisms, pathological roles, and therapeutic significance of apoptosis and parthanatos, two prominent pathways regulating cellular death. It describes their impact on understanding and treating cancer biology and treatment.

APOPTOSIS: A CLASSICAL PROGRAMMED CELL DEATH

Mechanistic insights into apoptosis

Apoptosis is a basic process that preserves cellular homeostasis by getting rid of damaged or unnecessary cells, which can also be potentially risky for the organism (Ameisen, 2002). Unlike necrosis, a non-regulated and inflammatory means of cell destruction, cell death by apoptosis is a tightly controlled and non-inflammatory process whereby cell debris contained within apoptotic bodies is removed by phagocytes (Xu et al., 2019). Without this tightly controlled mechanism, normal development, immune regulation, and cancer suppression would not have occurred (Vinay et al., 2015). The intrinsic and extrinsic routes are the two main ways that apoptosis is carried out, and they both lead to a caspase cascade of proteolytic enzymes (Jan and Chaudhry, 2019).

The primary triggering signals of the intracellular route are intercellular stress signals, including oxidative stress, DNA damage, and nutritional scarcity (Su et al., 2024). They trigger the oligomerization and leakage

of the outer membrane of the mitochondria by proapoptotic members of the Bcl-2 protein family, such as Bak and Bax (Kale et al., 2018). Cytochrome c is released into the cytosol due to this MOMP, where it binds Apaf-1 and procaspase-9 to create the apoptosome (Garrido et al., 2006). The apoptosome's ability to activate caspase-9 opens the door for more caspase cleavage and the stimulation of executioner caspases, such as caspase-3 and caspase-7 (Brentnall et al., 2013). DNA breakage, chromatin condensation, cytoskeletal breakdown, and the creation of apoptotic bodies are the outcomes of apoptotic caspases' execution of a crucial cellular component degradation (Povea-Cabello et al., 2017). Specifically, anti-apoptotic proteins like Bcl-2 and Bcl-xL inhibit apoptosis in healthy cells by opposing Bax and Bak, preserving the integrity of mitochondria (Luna-Vargas and Chipuk, 2016). Both anti-apoptotic proteins are over-expressed in cancer to drive tumor cells to avoid apoptosis.

On the other hand, the extrinsic pathway is triggered by the extracellular death signal via activation of the death receptor, for instance, Fas (CD95) or tumor necrosis factor receptor (TNFR) upon ligand binding (Guicciardi and Gores, 2009). The DISC is formed due to the binding of adaptor proteins such as procaspase-8 and the death domain-containing protein FADD (Siegmond et al., 2001). After activation, caspase 8 either cleaves and activates executioner caspases directly or cleaves a proapoptotic Bcl2 family member, such as Bid, which releases Mito cytochrome c, activating the intrinsic pathway (Zhong et al., 2020). Effective cell death guarantees that the apoptotic signal is amplified by further cross-talk between the intrinsic and extrinsic pathways (Roy and Nicholson, 2000). In addition, some cancer cells can use mutations in death receptor signaling or downregulation of Fas and TNFR expression to evade apoptosis, thereby evading the immune system and becoming resistant to therapy (Leonard and Johnson, 2018). Though caspase-dependent

apoptosis is typically considered, caspase independence mechanisms exist, especially when caspase activation is impaired (McIlwain et al., 2013). Instead, induction of massive DNA fragmentation and chromatin condensation occurs independently of caspases through mitochondrial factors such as apoptosis triggering factor and endonuclease G, which go into the nucleus (Bajt et al., 2006). Under stress conditions, such non-canonical apoptotic pathways ensure that cells die in an active, programmed fashion even if primary apoptotic mechanisms are blocked to maintain cellular integrity (Mustafa et al., 2024) (Figure 1).

Dysregulation of apoptosis in cancer

Apoptosis is a fundamental aspect that helps keep the tissue balanced and prevents the cells with oncogenic potential from surviving (Wong, 2011). However, cancer is a disease of dysregulated apoptosis, a hallmark of cancer allowing tumor cells to avoid programmed cell death, grow in an uncontrolled manner, and limit their susceptibility to therapy (Pistritto et al., 2016). Cancer cells can escape apoptosis in many different ways. However, genetic changes in tumor suppressor genes, including TP53, hamper this, which stops the intrinsic pathway from activating and proapoptotic proteins like Bax and Bak from activating (Dandoti, 2021). Bcl-2, Bcl-xL and Mcl-1 are anti-apoptotic proteins overexpressed in many tumors and interfere with the apoptotic signal while maintaining mitochondrial integrity (Carrington et al., 2017). IAPs also contribute to cancer cell survival by inhibiting caspase activation, and some tumor cells downregulate death receptors or deviant the shape of DISC, impairing the extrinsic apoptotic pathway (Derakhshan et al., 2017).

In addition, these alterations enhance both tumorigenesis and therapy resistance (Dzobo et al., 2023). Tumors that have become resistant to apoptotic signaling often exhibit poor responses to treatment because many

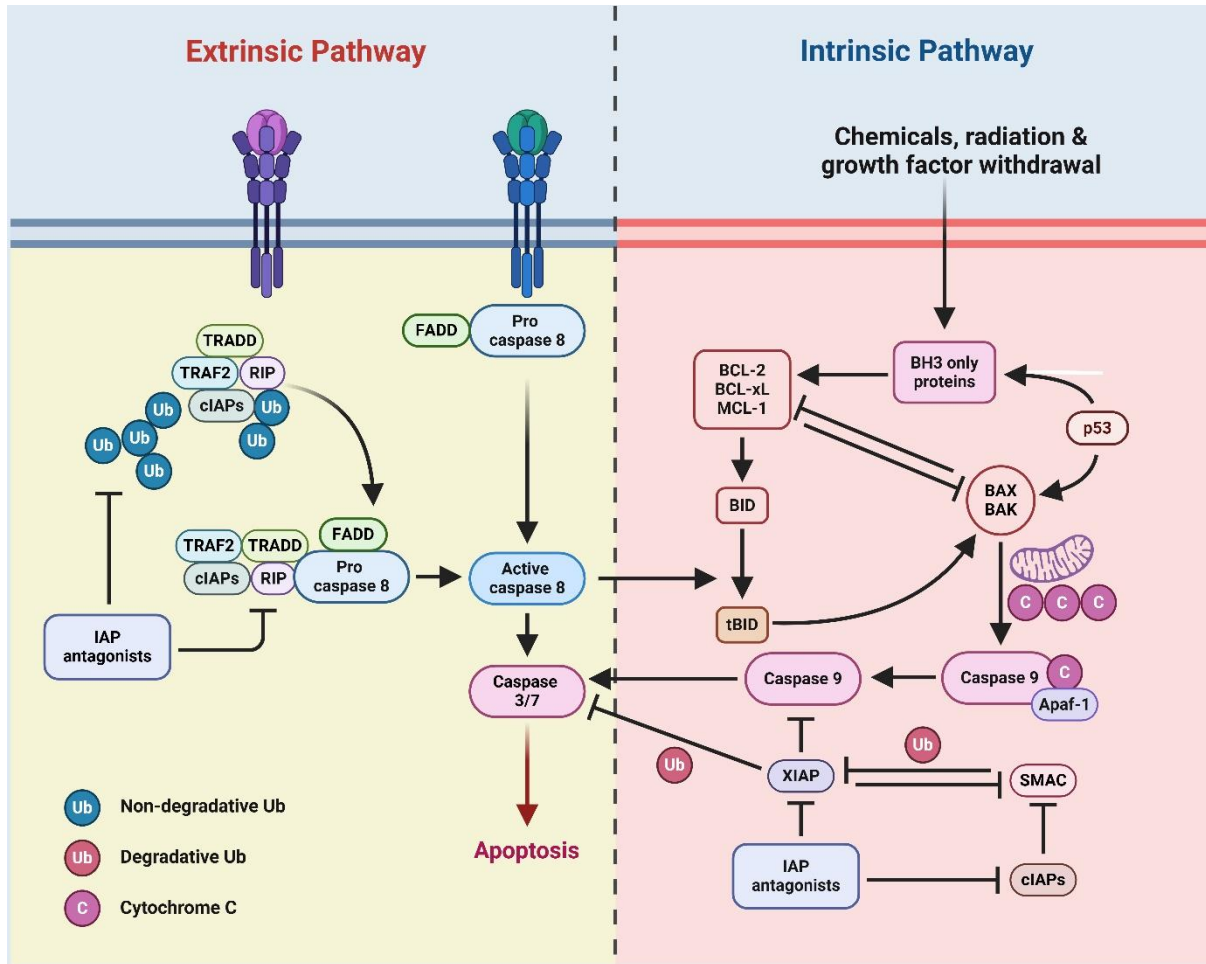


Figure 1: This figure illustrates the extrinsic and intrinsic pathways of apoptosis. The extrinsic pathway is triggered by death receptor activation, leading to the recruitment of adaptor proteins (TRADD, TRAF2, RIP) and activation of caspase-8, which subsequently activates caspases-3/7 to induce apoptosis. The intrinsic pathway is initiated by cellular stress factors such as chemicals, radiation, and growth factor withdrawal, leading to mitochondrial outer membrane permeabilization via BAX/BAK activation. This releases cytochrome C, which activates caspase-9 through Apaf-1, further activating caspases-3/7. Both pathways are regulated by inhibitors of apoptosis proteins (IAPs) and antagonists like SMAC.

chemotherapeutic agents and treatments based on radiation therapy are acting by inducing apoptosis (Wu et al., 2023b). For example, most TP53 mutated cancers resist DNA-damaging agents due to p53's lack of function to initiate the intrinsic apoptotic cascade (Wang et al., 2024a). Like those tumors, tumors that overexpress Bcl-2 or IAPs escape chemotherapy-induced apoptosis by perturbing the activation of caspases and reducing the era of chemotherapy (Buchholz et al., 2003).

To counteract these mechanisms, efforts toward developing new cancer therapies are underway to restore apoptotic signaling (Tian

et al., 2024). One method that has been proven to be effective is using small molecule inhibitors known as BH3 mimetics to treat anti-apoptotic proteins. These inhibitors neutralize Bcl 2 family members, allowing pro-apoptotic factors to initiate cell death (Delbridge and Strasser, 2015). Since then, it has shown great efficacy in treating hematological malignancies like, for example, CLL and AML (Lasica and Anderson, 2021). In addition, the intrinsic apoptotic pathway is activated through death receptor agonists (including TRAIL receptor agonists) and death receptor agonists that selectively induce tumor

cell death (Yuan et al., 2018). Another emerging strategy is using SMAC mimetics, which antagonize IAPs to enhance caspase activation further and increase apoptotic sensitivity in resistant tumors (Wu et al., 2007).

The combination therapies utilizing these agents alone or combined with conventional treatments like chemotherapy, immune checkpoint inhibitors, or targeted therapies are promising approaches to overcome resistance and improve treatment efficacy (Patel and Minn, 2018). It is well known that BH3 mimetics and PARP inhibitors alone effectively kill apoptosis-resistant tumors via both apoptotic and parthanatic pathways (Townsend et al., 2021). Oxidative stress modulators have been found to sensitize tumors to apoptosis-inducing agents, like those that increase mitochondrial dysfunction (Kuo et al., 2022). The development of effective treatments depends on understanding apoptotic mechanisms, and these multi-target approaches highlight the reality that many of the efforts to eliminate cancer cells are focused on targeting the apoptosis-related cell death cascade (Neophytou et al., 2021).

PARTHANATOS: A POLY(ADP-RIBOSE)-DEPENDENT CELL DEATH

Molecular signature of parthanatos

The paradigm of overactivation of the PARP-1 is a distinct kind of cell death termed parthanatos (David et al., 2009). Parthanatos is not caspase-dependent and is due to excess DNA damage and accumulation of poly(ADP) ribose (PAR) polymers, unlike apoptosis (Maru et al., 2023). It accumulates the cell's NAD⁺ and ATP reserves, depleting them till an energy crisis and the cell's peculiar collapse (Covarrubias et al., 2021). One of parthanatos main characteristics is the movement of AIF from the mitochondria to the nucleus, where it causes cell death (Huang et al., 2022). This process is driven to a large extent by mitochondrial dysfunction, whereby excessive PAR polymer formation causes mitochondrial membrane potential loss, oxidative stress generation of ROS, and amplifi-

cation of DNA impairment in a positive feedback loop to enhance PARP 1 activation (Ježek et al., 2018). Parthanatos differs from necrosis in that it does not promote inflammatory cell swelling or apoptotic body formation, as occurs in apoptosis (Liu et al., 2022). PARP-1 hyper activation, AIF translocation, and metabolic collapse make parthanatos a unique molecular signature unique to PARP-1 hyper activation and AIF translocation, and metabolic collapse is a very important cancer progression and therapy resistance process, as well as DNA damage in neurodegenerative disorders (Liu et al., 2022e). Multiple cancer models have been shown to respond to parthanatos induction, including in the context of oxidative stress and chemotherapeutic agents (An et al., 2024).

Furthermore, in glioma cells, Ma et al. demonstrated that deoxypodophyllotoxin (DPT) caused parthanatos by the production of excessive ROS, the overexpression of PARP-1, the accumulation of PAR polymers, and the translocation of AIF into the nucleus. DPT-induced effects were reversed by knock-down of PARP-1, treatment with antioxidants (NAC), and PARP-1 inhibitors (3AB) rescuing cells (Ma et al., 2016). Similarly, Zhang et al. identified a p53-SIRT6-PARP1 axis in colon cancer, where AKT inhibition promoted PARP-1 activation and parthanatos, whereas p53 deletion prevented its induction. However, AKT inhibition also led to protective autophagy, as shown in Figure 2, suggesting that targeting both parthanatos and autophagy could improve therapeutic outcomes (Zhang et al., 2022).

Several studies have further linked the activation of parthanatos to small-molecule compounds with anticancer properties. The glycosylated flavonoid Brachyidin A (BrA) was shown by Ribeiro et al. to cause parthanatos in metastatic prostate cancer spheroids by the disruption of mitochondrial membrane potential, activation of PARP-1, and nuclear translocation of AIF. The alteration of inflammatory indicators and anti/pro-apoptotic proteins was linked to BrA-mediated cell death (Ribeiro et al., 2022). Similarly, Medrano et

al. found that the cannabinoid derivative WIN-55 induced parthanatos in acute myeloid leukemia (AML) cells, evidenced by DNA damage, NAD⁺ depletion, and metabolic disruption. PARP inhibition with Olaparib prevented this effect, confirming that WIN-55-induced AML cell death depends on parthanatos (Medrano et al., 2024).

In addition to pharmacological triggers, environmental toxins and heavy metals have also been implicated in inducing parthanatos through oxidative stress and mitochondrial damage (Li et al., 2023). Paul et al. demonstrated that fumonisin B1 (FB1), a mycotoxin, triggers parthanatos in neuroblastoma cells by causing excessive DNA damage, leading to PARP-1 overactivation, PAR accumulation, and AIF nuclear translocation. This process was further exacerbated by increased ROS generation, intracellular calcium accumulation, and endoplasmic reticulum stress, linking environmental toxins to parthanatos-mediated neurotoxicity (Paul et al., 2021). In rat proximal tubular cells, Luo et al. investigated cadmium-induced parthanatos in more detail, showing that mitochondrial damage and oxidative stress cause PARP-1 activation and MAPK pathway participation, with JNK1/2 and p38 playing critical roles in apoptosis-parthanatos crosstalk (Luo et al., 2017).

The molecular regulation of parthanatos has also been investigated in the context of AIF translocation and alternative cell death pathways (Tang et al., 2019). Wang et al. explored the role of calpain in AIF release during parthanatos, demonstrating that AIF nuclear translocation occurs independently of calpain activation but can be prevented by PARP-1 inhibitors, suggesting that alternative mechanisms contribute to AIF release (Wang et al., 2009b). The clinical significance of parthanatos has been further validated in cancer specimens (Qiao et al., 2024). Donizy et al. analyzed breast cancer tissues and found that high PARP-1 expression correlated with the absence of apoptotic bodies and necrosis, key cytomorphological features of parthanatos.

Apoptotic bodies were connected to the redistribution PARP-1 from the nucleus to the cytoplasm, while necrosis was linked to decreased nuclear PARP-1 expression (Donizy et al., 2013). These studies present strong evidence that parthanatos is a central mechanism of genome damage-induced cell death, oxidative stress, or metabolic disruption. Despite significant challenges related to apoptosis resistance, parthanatos treatment is possible through PARP inhibitors, ROS modulators, and oncogenic pathway regulators as a novel strategy to overcome this challenge. However, because parthanatos is both a tumor suppressor and tumor promoter, this mechanism remains a target for developing more effective and less mycotoxic therapeutic approaches (Figure 2).

Role of parthanatos in cancer

In cancer, parthanatos acts as two mutually exclusive tumor-promoting and tumor-suppressing processes. The context of the cell determines whether parthanatos induces cancer or protects from it (Zhang et al., 2024b). Parthanatos is often brought about by extensive DNA damage through reactive oxygen species or chemotherapeutic agents that result in the overactivation of PARP-1, a hallmark of parthanatos (Chaitanya et al., 2010). Parthanatos induction has emerged as a promising strategy in cancer therapy to eliminate tumor cells, particularly apoptosis-resistant ones, as in cancer treatment (Lou et al., 2020). Excessive PARP-1 activation is commonly required for parthanatos downstream to such DNA-damaging agents as platinum compounds and radiation therapy. It is causative of cell death through mitochondrial dysfunction, AIF translocation, and apoptosis-inducing factor-dependent cell death (Ke et al., 2019). Also, synthetic lethality for tumors with defective DNA repair involves PARP inhibitors that leverage synthetic lethality to induce parthanatos selectively in DNA repair deficient tumors (Helleday, 2011). Although parthanatos also aids in tumor progression

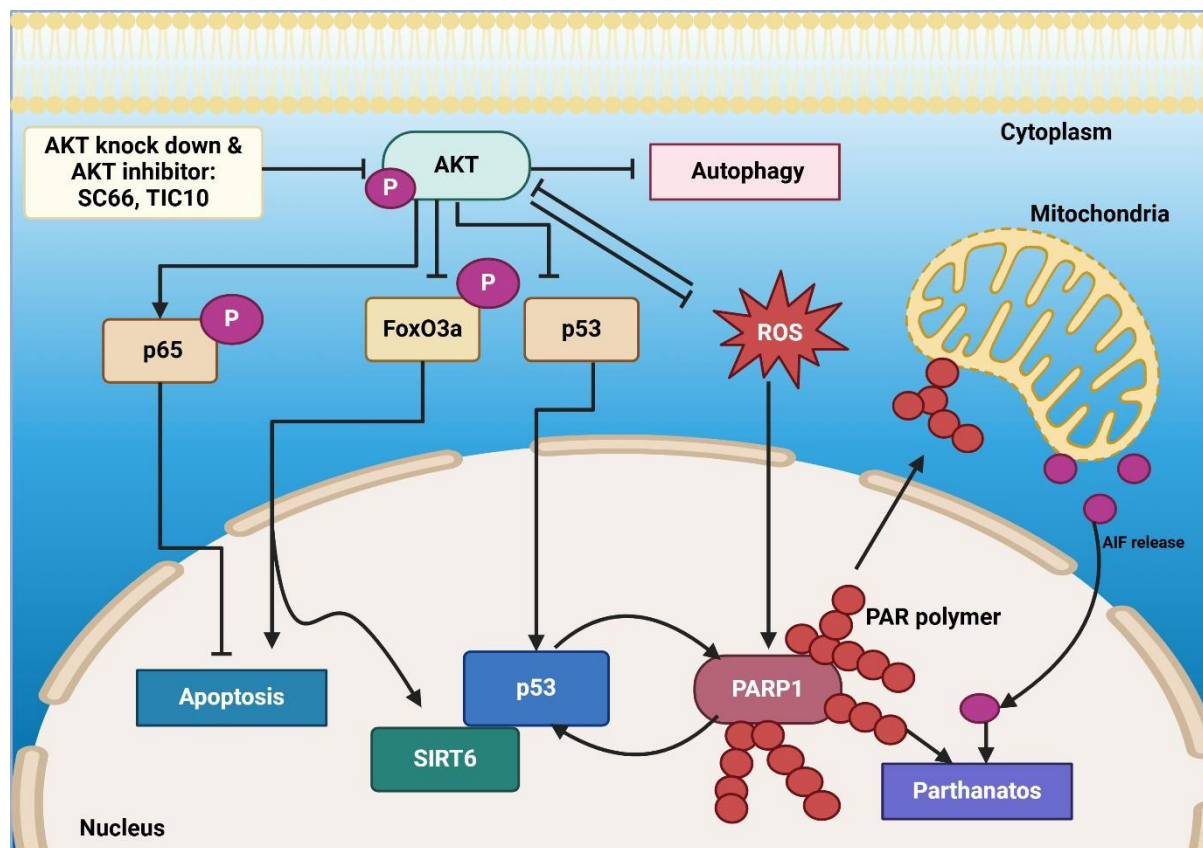


Figure 2 illustrates the regulation of apoptosis and parthanatos through AKT signaling, oxidative stress, and PARP1 activation. AKT promotes cell survival by inhibiting FoxO3a, p53, and autophagy while activating p65, which drives apoptosis. AKT knockdown or inhibition (SC66, TIC10) disrupts these pathways, enhancing p53 and FoxO3a activity. ROS accumulation induces PARP1 activation, leading to PAR polymer formation and mitochondrial AIF release, triggering parthanatos. SIRT6 modulates p53, linking apoptotic and parthanatos pathways, highlighting a complex interplay between survival and programmed cell death mechanisms.

and therapy resistance, it also plays a role in autophagy (Yang et al., 2024). Hyperactivation of PARP-1 in the tumor microenvironment may be chronic, leading to genomic instability and inflammatory signaling for tumorigenesis and metastasis (Chen et al., 2022). In addition, cancer cells develop adaptive mechanisms to resist parthanatos, allowing themselves to survive in oxidative stress or conditions of DNA damage (An et al., 2024). Zhao et al. studied the impact of survivin suppressant sepantronium bromide (YM155) on ESCC. They found that YM155 effectively inhibited tumor development by lowering survivin levels and preventing cell death by genetically knocking down AIF or PARP-1 (Zhao et al., 2015). Similarly, Boulos

et al. demonstrated that cyanopicrotin, a sesquiterpene lactone, induces parthanatos in hematopoietic tumors, including multiple myeloma and leukemia. In a zebrafish xenograft model of T-cell acute lymphoblastic leukemia, cyanopicrotin-mediated PARP-1 hyperactivation resulted in PAR polymer buildup and AIF nuclear translocation, successfully inhibiting tumor development (Boulos et al., 2023). Zheng et al. examined the parthanatos in glioma cells due to oxidative stress. They found that exposure to H_2O_2 led to ROS accumulation, PARP-1 activation, AIF nuclear translocation, and mitochondrial depolarization. Inhibiting JNK suppressed ROS production, suggesting potential therapeutic agents (Zheng et al., 2017). Similarly, in OSCC, Li et al. found that the chemotherapeutic drug

oxaliplatin causes parthanatos by causing nuclear translocation of AIF, depolarization of the mitochondrial membrane, and overactivation of PARP-1. Oxaliplatin-induced parthanatos was prevented by treatment with PARP-1 inhibitors or antioxidants, demonstrating the role of oxidative stress in inducing this kind of cell death (Li et al., 2021).

While parthanatos serves as an important cell death mechanism, chronic PARP-1 hyperactivation may paradoxically promote therapy resistance and tumor progression (Lee et al., 2018). Liu et al. identified a novel mechanism by which cyclophosphamide induces parthanatos in leukemia cells through glutathione peroxidase 4 (GPX4) degradation. This process led to AIF nuclear translocation but not ferroptosis, demonstrating an alternative pathway by which leukemia cells may evade apoptosis. Knockdown of AIFM1 or overexpression of GPX4 reversed cyclophosphamide-induced cell death, suggesting that parthanatos modulation could impact therapy resistance (Liu et al., 2022c). Zhou et al. further explored the role of parthanatos in leukemia therapy using palladium (II) complexes (J4 and J6). These compounds selectively induced PARP-1 hyperactivation and AIF nuclear translocation, overcoming apoptosis resistance in leukemia cells while sparing normal cells. Interestingly, J4 and J6 did not significantly induce apoptosis or necrosis, reinforcing the specificity of parthanatos induction as a cytotoxic strategy (Zhou et al., 2023b).

Parthanatos has also been implicated in inflammatory diseases, reinforcing its relevance beyond oncology (Vitale et al., 2023). Xu et al. demonstrated that necrotizing enterocolitis (NEC)--affected intestinal tissues exhibit elevated parthanatos markers, including AIF nuclear translocation, PAR polymer accumulation, and PARP-1 activation. Inhibition of PARP-1, either pharmacologically (3-AB) or genetically (Parp1 knockout), significantly reduced intestinal injury and inflammation, suggesting that targeting parthanatos may mitigate NEC-related epithelial damage

(Xu et al., 2024). Similarly, Xue et al. identified a novel role for parthanatos in macrophage cell death during sepsis. The study linked TLR4 upregulation to ROS-induced PARP-1 activation, leading to AIF nuclear translocation. Pharmacological inhibition of TLR4 signaling prevented parthanatos in macrophages, revealing a potential target for reducing endotoxemia-related inflammatory damage (Xue et al., 2021). These studies also show that parthanatos, while aborted, is a highly context-dependent form of cell death with both therapeutic and pyknic advantages. Inducing parthanatos in apoptosis-resistant tumors is a promising strategy, but chronic PARP-1 hyperactivation can drive genomic instability and proinflammatory signaling, resulting in tumor progression and therapy resistance (Table 1).

APOPTOSIS VS. PARTHANATOS IN CANCER

Distinct molecular and morphological features

Apoptosis and parthanatos are two definable programmed cell deaths with allowable substrate and morphology specificity (Cao et al., 2024). Apoptosis, usually called type I, is a caspase-dependent process involving chromatin condensation, DNA fragmentation into nucleosome-sized fragments, membrane blebbing, and the release of apoptotic bodies (Kari et al., 2022). If engulfed by neighboring or immune cells, these bodies are resolved non-inflammatory (Szondy et al., 2017). Intrinsic and extrinsic pathways tightly control the process, and their key players are caspases, cytochrome c, and Bcl-2 family proteins (Singh et al., 2019). It is a highly controlled mechanism that does not cause excessive tissue damage and inflammatory responses (Chen et al., 2018). Severe damage to DNA and oxidative stress can cause parthanatos, a caspase-independent cell death triggered by PARP 1 (Gao et al., 2023). In terms of appearance, parthanatos differs from necrosis and pyknosis in that it exhibits chromatin condensation, large-scale DNA fragmentation, and the absence of apoptotic structures or cellular

Table 1: Mechanistic insights of parthanatos, molecular events, and therapeutic strategies

Key Feature	Mechanism	Biological Impact	Molecular Events	Therapeutic Potential	Reference
PARP-1 Overactivation	DNA damage leads to excessive PARP-1 activation	Depletes NAD ⁺ and ATP, leading to energy crisis	PAR polymer accumulation, NAD ⁺ depletion, energy failure	PARP inhibitors (e.g., olaparib) to suppress activation	Ma et al., 2016
PARP-1 Overactivation	AKT inhibition triggers the p53-SIRT6-PARP1 axis	Induces parthanatos but also initiates protective autophagy	p53 deletion prevents parthanatos induction	Dual inhibition of PARP-1 and autophagy enhances efficacy	Mo et al., 2022
AIF Translocation	PARP-1 activation induces AIF release from mitochondria	AIF migrates to the nucleus, causing DNA fragmentation	Mitochondrial membrane permeabilization, nuclear translocation of AIF	Targeting AIF translocation for selective cell death	Ribeiro et al., 2022
AIF Translocation	Cannabinoid derivative WIN-55 induces parthanatos	DNA damage, NAD ⁺ depletion, and metabolic disruption	PARP inhibition with olaparib prevents cell death	Using PARP inhibitors to refine cannabinoid-based therapies	Medrano et al., 2024
Oxidative Stress	ROS production exacerbates DNA damage and PARP-1 activation	Enhances mitochondrial dysfunction and cell death	Increased ROS levels, mitochondrial depolarization, DNA strand breaks	ROS modulators amplify parthanatos selectively	Paul et al., 2021
Oxidative Stress	Cadmium toxicity triggers oxidative stress and mitochondrial damage	Induces apoptosis-parthanatos crosstalk	JNK1/2 and p38 MAPK pathways are activated	Targeting JNK1/2 to block oxidative stress-mediated parthanatos	Luo et al., 2017
Metabolic Collapse	Depletion of NAD ⁺ and ATP reserves	This leads to mitochondrial dysfunction and cell death	ATP depletion, mitochondrial membrane potential loss, glycolytic stress	Metabolic interventions to sensitize cancer cells	Ma et al., 2016
Metabolic Collapse	Glycosylated flavonoid BrA disrupts mitochondrial membrane potential	Triggers AIF translocation and PARP-1 activation	Modulates anti/pro-apoptotic proteins and inflammatory markers	Potential application in metastatic prostate cancer	Ribeiro et al., 2022
Small Molecule Triggers	DPT induces parthanatos via ROS generation	PARP-1 up-regulation and AIF translocation	Knockdown of PARP-1 or antioxidants rescue cells	Developing ROS-based parthanatos-targeting therapies	Ma et al., 2016
Small Molecule Triggers	YM155 suppresses survivin and activates PARP-1	PAR polymer accumulation and AIF translocation	Genetic knockdown of PARP-1 or AIF abrogates cell death	Using survivin suppression as a parthanatos-based strategy	Zhao et al., 2015
Environmental Toxins	Fumonisin B1 (FB1) induces parthanatos	Excessive DNA damage and mitochondrial dysfunction	Increased ROS, intracellular calcium accumulation, and ER stress	Developing neuroprotective strategies against mycotoxins	Paul et al., 2021

Environmental Toxins	Heavy metals (cadmium) induce parthanatos via oxidative stress	Mitochondrial dysfunction and DNA fragmentation	Increased JNK1/2 and p38 signaling pathways	Targeting oxidative stress and MAPK signaling in toxicity prevention	Luo et al., 2017
Therapy Resistance	Cyclophosphamide induces parthanatos via GPX4 degradation	AIF nuclear translocation but not ferroptosis	GPX4 overexpression prevents cell death	Targeting GPX4 for modulating parthanatos in leukemia	Liu et al., 2022d
Therapy Resistance	Palladium (II) complexes J4 and J6 induce selective parthanatos	Overcomes apoptosis resistance in leukemia	PARP-1 hyperactivation and AIF nuclear translocation without apoptosis	Developing metal-based chemotherapeutics for leukemia	Zhou et al., 2023b
Inflammatory Signaling	PARP-1 hyperactivation drives inflammation in NEC	Elevated PAR polymer levels and AIF translocation	Parp1 knockout reduces intestinal injury and inflammation	Targeting PARP-1 to mitigate NEC-related epithelial damage	Xu et al., 2024
Inflammatory Signaling	TLR4 upregulation in macrophages triggers ROS-induced PARP-1 activation	Induces macrophage parthanatos in sepsis	Pharmacological inhibition of TLR4 prevents parthanatos	Potential target for reducing endotoxemia-related inflammatory damage	Xue et al., 2021

swelling, which are hallmarks of necrosis (Tang et al., 2019). Parthanatos is characterized by the translocation of AIF from mitochondria to the nucleus, resulting in extensive DNA breakage (Mashimo et al., 2013).

In contrast to apoptosis, a cellular collapse that results from parthanatos is due to the hyperactivation of PARP-1, resulting in the depletion of cellular energy stores (NAD⁺ and ATP). Biologically, there is a distinction between the underlying means of cell death for these two mechanisms, as some cancer cells suppress apoptosis but remain a target of parthanatos (Martínez-Morcillo et al., 2021). Cheong et al. examined the role of CASK in microglial parthanatos triggered by H₂O₂ exposure in CHME3 cells. Silencing of CASK protected cells from oxidative stress-induced parthanatos by reducing PARP-1 activation, mitochondrial dysfunction, and reactive oxygen species (ROS) production, preventing mitochondrial fission and enhancing oxidative phosphorylation. Interestingly, no AIF translocation indicated a non-canonical AIF-independent form of parthanatos. CASK silencing

also altered AKT and AMPK signaling, suggesting its potential as a therapeutic target for central nervous system disorders involving oxidative stress and parthanatos (Cheong et al., 2024). Kuzhandaivel et al. investigated kainate-induced excitotoxicity in neonatal rat spinal cord neurons, revealing that parthanatos was the primary neuronal death mechanism. Strong PARP-1 activation, poly(ADP-ribose) production, and AIF nuclear translocation were observed, while caspase-3 inhibition failed to prevent neuronal damage, distinguishing parthanatos from apoptosis. Notably, pharmacological inhibition of PARP-1 reduced neuronal death, highlighting PARP-1 as a key therapeutic target in acute spinal cord injury (Kuzhandaivel et al., 2010).

Studies examining harsh environmental circumstances provide more evidence of parthanatos' involvement in stress-induced cell death (Wang and Ge, 2020). Schiefer et al. analyzed heat-induced cell death in human fibroblasts, revealing that hyperthermia primarily triggers parthanatos rather than apoptosis. Heat exposure significantly increased PARP-1 protein expression, DNA double-strand

breaks, ATP depletion, and AIF nuclear translocation, with no evidence of caspase activation or apoptotic bodies. The temporal sequence of parthanatos induction, with a peak at five hours post-heat exposure, underscores its delayed onset compared to apoptosis. These findings provide valuable insights into burn injury pathophysiology and the role of parthanatos in thermal stress responses (Schiefer et al., 2024).

The ability of cancer cells to evade apoptosis while maintaining susceptibility to parthanatos has been explored in multiple models (Wang et al., 2022). Nuclear Ca^{2+} -dependent endonucleases and CPP32/Yama protease activity, two essential apoptosis executioners, are markedly reduced in highly metastatic cells, according to research by Glinsky et al. on apoptosis resistance in metastatic cancer cell lines. According to these results, metastatic cells create defenses against apoptosis, allowing them to continue growing and surviving (Glinsky et al., 1997). Similarly, Baile et al. reported that in glioblastoma, cell death followed a caspase-dependent apoptotic pathway, whereas in pancreatic and colorectal cancer cells, it involved programmed necrosis. The latter was characterized by mitochondrial membrane depolarization, AIF nuclear translocation, and PARP-1 activation, hallmarks of parthanatos. Resistant cell lines exhibited enhanced detoxification mechanisms, emphasizing the variability in cell death pathways across different cancer types (Fuentes-Baile et al., 2020).

Additional research has highlighted the dose-dependent nature of programmed cell death mechanisms (Kopeina and Zhivotovskiy, 2022). Lennon et al. found that lower doses of toxic agents-initiated apoptosis, characterized by an internally programmed death process, while higher doses led to necrosis due to irreversible membrane failure. Furthermore, extracellular calcium was essential for apoptosis initiation, underscoring the role of calcium homeostasis in determining cell fate (Lennon et al., 1991). Fujikawa et al. reported that neuronal damage was char-

acterized by nuclear pyknosis, chromatin condensation, cytoplasmic vacuolation, and mitochondrial swelling. Although some neurons exhibited DNA fragmentation, this was associated with necrosis rather than classical apoptosis, further supporting the idea that programmed cell death mechanisms can be context-dependent (Fujikawa et al., 2000). These studies emphasize molecular and morphological differences between apoptosis and parthanatos. Whereas apoptosis proceeds through a caspase-dependent, energy-sufficient pathway characterized by the fragmentation of the cell into apoptotic bodies, parthanatos is executed by PARP-1 hyperactivation, AIF translocation to the nucleus, and subsequent massive degradation of DNA. Parthanatos differs from apoptosis and necrosis because it does not initiate apoptotic body formation and depletes cellular energy. The mechanistic differences between these cell death pathways are critical to understanding since these results have broad consequences for intervening therapeutically in cancer, neurodegeneration, and inflammatory diseases.

Overlapping pathways and interplay

The programmed cell death processes of apoptosis and parthanatos share several regulatory pathways despite being different mechanisms in terms of their cellular destruction operations (Kist and Vucic, 2021). Mutually exclusive patterns of cell death initiate due to extreme cellular pressure, such as DNA damage alongside oxidative stress or genotoxic elements, while depending on pathological mitochondrial problems as their foundation (Shimura, 2023). The apoptotic cascade triggers cytochrome c release from mitochondria to activate caspases, but parthanatos makes mitochondria release AIF that moves to the nucleus for extensive DNA fragmentation (Nguyen et al., 2023). These two distinct cellular death pathways listen to ROS and DNA damage signals, yet the degree of cellular stress and its duration guide which form of cell death will occur (Redza-Dutordoir and Averill-Bates, 2016). The cellular pathways display communication through Bid, which

enhances parthanatos by increasing membrane permeability in mitochondria (Chipuk et al., 2021).

On the other hand, if caspases are inhibited or impaired, cells may revert to parthanatos as a second line of death (Yan et al., 2020). Jiang et al. studied oxidative stress-induced cell death in stria marginal cells using a glucose oxidase/glucose model. They found that GO/G triggers parthanatos, which can be rescued by knocking down PARP-1, and autophagy plays a pro-survival role (Jiang et al., 2018). Similarly, Chiu et al. studied MNNG-induced parthanatos in MEFs, revealing it triggers rapid ROS production, JNK activation, PARP-1 activation, and intracellular calcium elevation, sustaining DNA damage and PARP-1 activation (Chiu et al., 2011).

The function of parthanatos in cancer cell death regulation has been further explored regarding p53 status and autophagy (Zhang et al., 2022). So et al. found that sodium arsenite treatment induced parthanatos in p53-deficient H1299 cells, with inhibition of autophagy enhancing parthanatos and p53 overexpression reducing it, suggesting targeting PARP-1 could be a potential strategy (So and Oh, 2023). Zhu et al. found that Stanniocalcin-1 (STC1) is upregulated in colitis models and Crohn's disease patients, causing increased parthanatos and inflammation. Knockout of STC1 reduced inflammation and disease severity. STC1 interacts with PARP-1 and activates the JNK pathway, suggesting the STC1-PARP1-JNK axis as a potential therapeutic target (Zhu et al., 2024).

The interaction between apoptosis and parthanatos is also evident in tumor repopulation mechanisms (Shoshan-Barmatz et al., 2023). Huang et al. demonstrated that caspase-3 activation in apoptotic tumor cells paradoxically promotes tumor regrowth during radiotherapy by stimulating prostaglandin E2 (PGE2) production. Caspase-3-deficient tumors exhibited enhanced sensitivity to radiotherapy, while human cancer tissues with higher caspase-3 activation levels correlated with increased recurrence and mortality rates. These findings highlight a paradoxical role of

apoptosis in therapy resistance and tumor survival, suggesting that blocking caspase-3 activation could improve radiotherapy outcomes (Huang et al., 2011). Melcher et al. further explored the immunogenic potential of different cell death modalities, revealing that apoptotic colorectal cancer cells exhibited lower immunogenicity due to reduced HSP expression, whereas non-apoptotic forms of cell death induced stronger immune responses. Overexpression of Bcl-2 inhibited apoptosis and increased HSP levels, and transfection with hsp70 further enhanced the immunogenicity of tumor cells, suggesting that promoting non-apoptotic cell death pathways may improve cancer immunotherapy (Melcher et al., 1998).

Additional studies have identified novel molecular mechanisms linking apoptosis and immunogenic cell death (ICD) (Chang et al., 2023). Panaretakis et al. found that pre-apoptotic exposure of calreticulin and ERp57, crucial markers of ICD, requires ER stress-induced activation of the PERK pathway, partial caspase-8 activation, and BAP31 cleavage. Depletion of SNAREs, caspase-8, or PERK abolished CRT/ERp57 exposure without affecting cell death, suggesting that these factors are critical for the pre-apoptotic exposure to calreticulin but do not directly influence the execution of cell death (Panaretakis et al., 2009). Furthermore, Xia et al. created a predictive model for ovarian cancer prognosis using 12 PCD patterns and identified a 20-gene set. They found high-risk patients' sensitivity to dasatinib and correlations with immune checkpoint genes and tumor microenvironment components, aiding in targeted therapy (Xiao et al., 2023). Collectively, these findings emphasize the complex interrelationship between apoptosis and parthanatos, their shared regulatory networks, and their therapeutic implications. Though apoptosis as a tumor suppressive mechanism is well established, the activation of apoptosis sometimes proves harmful to the tumor by facilitating immune evasion and repopulation. On the contrary, parthanatos represents an alternative

cell death mechanism and can be used to overcome apoptosis resistance in therapy-resistant cancer cells (Table 2).

THERAPEUTIC TARGETING OF CELL DEATH PATHWAYS

Strategies targeting apoptosis

Cancer therapy development has focused on apoptosis since researchers seek to recover cancer cells' ability to undergo programmed death (Mirzayans, 2024). Cancer cells avoid programmed cell death by producing Mcl-1, Bcl-xL, and Bcl-2, and genetic mutations cause alterations in pro-apoptotic control, such as TP53 (Akl et al., 2014). Developers have established several approaches to restore apoptotic signaling pathways against the mechanisms that prevent it (Indran et al., 2011). Venetoclax is a BH3 mimetic drug that stops anti-apoptotic Bcl-2 proteins from functioning so that pro-apoptotic Bax and Bak activation can begin the apoptosis sequence (Roberts and Huang, 2017). The clinical benefits of death receptor agonists working through TRAIL receptors to activate extrinsic apoptosis fail to produce desirable results (Kundu et al., 2022). Small molecules, called SMAC mimetics, remove the inhibitory function of apoptosis proteins (IAPs), so tumors become more apoptotically sensitive (Bai et al., 2014). Studies in recent years have evaluated different chemical approaches and molecular methods for cancer apoptosis regulation (Hassan et al., 2014). Gali-Muhtasib et al. examined thymoquinone (TQ), which originates from *Nigella sativa* as an active substance to study its cancer-fighting properties and cell apoptotic effects on HCT-116 colon cancer cells. The dosage and time duration determined how TQ caused arrest in G1 phase along with apoptosis in HCT-116 cells. The increase of p53 and p21WAF1 expression together with Bcl-2 level decrease corresponded to apoptosis development yet p53 inhibition through pifithrin- α blocked these effects. TQ demonstrated resistance to p53-null cells indicating that apoptosis derived from TQ treatment relies on p53 (Gali-Muhtasib et

al., 2004). Lucena et al. evaluated the cytotoxic and anti-inflammatory effects of 5-fluorouracil (5-FU) incorporated into Cu-BTC metal-organic frameworks (MOFs). Structural characterization confirmed stable drug loading, with a sustained release profile reaching 82 % in 48 hours. Cytotoxicity assays revealed significant apoptosis induction in MCF-7 breast cancer and HL60 leukemia cells. Additionally, the formulation reduced leukocyte counts and inflammatory cytokines in rodent models, highlighting its potential as a sustained-release chemotherapeutic agent with anti-inflammatory benefits (Lucena et al., 2013).

The role of IAP proteins as therapeutic targets has also been extensively investigated (Vucic and Fairbrother, 2007). Fulda demonstrated that IAP proteins regulate survival and cell death by controlling caspase activation and NF- κ B signaling. Since many human cancers exhibit aberrant IAP overexpression, small-molecule IAP antagonists have been developed to mimic SMAC and induce tumor cell death or sensitize tumors to cytotoxic therapies. Several IAP antagonists, including GDC-0917, LCL161, and AT-406, are undergoing clinical trials, underscoring their potential in combination therapies (Fulda, 2014). Chen et al. explored a dual-targeting strategy for inducing mitochondria-dependent apoptosis using a functionalized pro-apoptotic peptide conjugated with folic acid (FA) for receptor-mediated endocytosis and triphenylphosphonium (TPP) cation for mitochondrial localization. This system efficiently targeted cancer cells, causing severe mitochondrial damage, dysfunction, and subsequent apoptosis, demonstrating its potential as a precise cancer therapeutic (Chen et al., 2013).

Apoptosis-inducing strategies have also been linked to oxidative stress modulation (Chandra et al., 2000). Liu et al. studied Adpa-Mn, a novel manganese compound, for its anticancer activity. They found it selectively inhibited cancer cell growth through the TfR system, induced apoptosis and autophagy, and reduced its cytotoxic effects with anti-

Table 2: This table compares apoptosis and parthanatos studies, highlighting mechanisms, regulators, and therapeutic implications.

Feature	Mechanism	Morphological Characteristics	Molecular Regulators	Reference
CASK in microglial parthanatos	CASK silencing reduces oxidative stress-induced parthanatos	No AIF translocation, altered AKT and AMPK signaling	PARP-1, ROS, AKT, AMPK	Cheong et al., 2024
Parthanatos in spinal cord neurons	Kainate-induced excitotoxicity triggers PARP-1 activation	Neuronal pyknosis, absence of necrosis	PARP-1, poly(ADP-ribose), AIF	Kuzhandaivel et al., 2010
Heat-induced parthanatos	Hyperthermia activates PARP-1 and AIF translocation	Mitochondrial damage, DNA double-strand breaks, no caspase activity	PARP-1, ATP depletion	Schiefer et al., 2024
Apoptosis resistance in metastatic cancer	Highly metastatic cells exhibit apoptosis resistance	Low nuclear Ca ²⁺ -dependent endonuclease and CPP32/Yama protease activity	CPP32, Ca ²⁺ , apoptosis regulators	Glinsky et al., 1997
CLytA-DAAO-induced parthanatos	Parthanatos in pancreatic and colorectal cells	Mitochondrial membrane depolarization, PARP-1 activation, AIF translocation	PARP-1, AIF, mitochondrial dysfunction	Fuentes-Baile et al., 2020
Dose-dependent apoptosis-necrosis switch	Low doses trigger apoptosis, high doses cause necrosis	Extracellular calcium essential for apoptosis	Calcium homeostasis, caspases	Lennon et al., 1991
Neuronal death in status epilepticus	Kainic acid-induced neuronal necrosis, not apoptosis	Nuclear pyknosis, chromatin condensation, swollen mitochondria	PARP-1, neuronal damage markers	Fujikawa et al., 2000
Parthanatos-autophagy interaction	Oxidative stress-induced parthanatos modulated by autophagy	PAR polymer accumulation, mitochondrial membrane loss, AIF translocation	PARP-1, LC3, autophagy markers	Jiang et al., 2018
ROS and calcium in parthanatos	MNNG-induced parthanatos via JNK-ROS-calcium signaling	Sustained DNA damage, calcium influx, RIP1 involvement	PARP-1, JNK, ROS, RIP1	Chiu et al., 2011
Parthanatos in p53-deficient cancer cells	Sodium arsenite triggers parthanatos in p53-deficient cells	PAR polymer accumulation, AIF translocation, autophagy modulation	PARP-1, AIF, p53, autophagy regulators	So and Oh, 2023
Parthanatos in Crohn's disease	STC1 activation promotes parthanatos and inflammation	Increased PARP-1 activity, JNK pathway activation	PARP-1, JNK, STC1	Zhu et al., 2024
Apoptosis paradox in tumor regrowth	Caspase-3 activation enhances tumor regrowth post-radiotherapy	Elevated PGE2 levels, increased recurrence, and mortality	Caspase-3, prostaglandin E2 (PGE2)	Huang et al., 2011
Immunogenicity of apoptotic vs. non-apoptotic cell death	Apoptotic colorectal tumor cells have lower immunogenicity	Reduced HSP expression	Hsp70, Bcl-2, apoptosis markers	Melcher et al., 1998

Calreticulin exposure in immunogenic apoptosis	ER stress triggers CRT/ERp57 exposure in dying tumor cells	Requires PERK, caspase-8, BAP31 cleavage	PERK, caspase-8, CRT	Panaretakis et al., 2009
Cell death predictive model for ovarian cancer	The PCD-based model distinguishes cancer subtypes and prognosis	ROS-JNK interactions, immune checkpoint expression	p53, ROS, JNK, immune markers	Wang et al., 2024

oxidant treatment (Liu et al., 2015). Becattini et al. identified Bid as a promising therapeutic target for modulating apoptosis in neurodegeneration and ischemia. Using the SAR by ILOEs approach, researchers developed small-molecule inhibitors that bind Bid and prevent its activation, inhibiting SMAC release and caspase-3 activation. This represents the first known strategy targeting a proapoptotic Bcl-2 protein for therapeutic intervention (Becattini et al., 2004).

Emerging approaches also explore combination therapies integrating PDT, PTT, and immunotherapy (Kong and Chen, 2022). Li et al. (2019) developed a double endoplasmic reticulum-targeting nanosystem that combines PDT, PTT, and immunotherapy for enhanced tumor eradication. The system uses ER-targeting peptides conjugated with indocyanine green-coated hollow gold nanospheres and oxygen-delivering liposomes to induce ROS-mediated ER stress, triggering immunogenic cell death (ICD) and immune stimulation (Li et al., 2019).

The therapeutic potential of apoptosis-targeting drugs has also been demonstrated in HNSCC (Axelrod et al., 2015). Zhang et al. investigated the effects of sepantronium bromide (YM155) in HNSCC, showing that YM155 suppresses survivin expression, induces apoptosis via mitochondrial and death receptor pathways, and enhances autophagy through Beclin1 upregulation. YM155 also inhibits the mTOR signaling pathway, enhancing tumor cell death. In HNSCC xenograft models, YM155 significantly delayed tumor onset, suppressed tumor growth and exhibited synergy with docetaxel without notable toxicity. These findings support the clinical potential of YM155 as a targeted therapy

for HNSCC (Zhang et al., 2015). This research presents various methods for restoring cancer cell apoptosis through small-molecule protein inhibitors, optimal drug delivery methods, and combined treatment approaches. Proper cancer treatment necessitates apoptosis induction, but new methodologies that combine oxidative stress regulation with immunogenic cell death and site-specific drug delivery will likely create advanced solutions. Future investigations must expand their effort toward developing optimized combination therapies that make cancer cells more sensitive to apoptosis while decreasing resistance factors to achieve better clinical results in refractory and aggressive cancer cases.

Innovations in parthanatos modulation

Pioneering drug treatments targeted at parthanatos represent promising therapeutic options mainly used to address cancers resistant to conventional apoptosis-based treatments (D'Amico and De Amicis, 2024). Efforts to control PARP-1 have become important because it functions as the main driver of parthanatos (Wang et al., 2011). PARP inhibitors, including olaparib and rucaparib, are therapeutic agents that use synthetic lethality within DNA repair-deficient tumors with BRCA mutations (Kim and Nam, 2022). Scientists are investigating new approaches to enhance the parthanatos pathway activity (Wu et al., 2023a). Combining reactive oxygen species (ROS) enhancement agents or direct mitochondrial dysfunction inducers with PARP activators creates more potent than additive effects for parthanatos development (Yu et al., 2022). Researchers use AIF nuclear translocation inhibitors to explore ways of op-

timizing treatment effects and reducing adverse side effects (Doti et al., 2014). Research conducted recently has expanded knowledge about how to modify parthanatic death in cancer therapy and various pathological settings (Liu et al., 2022a). Zhou et al. identified ZINC253504760, a synthetic cardenolide, as a novel anticancer agent capable of inducing parthanatos in multidrug-resistant (MDR) leukemia cells. The compound effectively induced G2/M phase arrest and triggered a distinct form of cell death marked by PARP overactivation, AIF nuclear translocation, DNA damage, and mitochondrial membrane collapse. Interestingly, parthanatos induction by ZINC253504760 was ROS-independent, suggesting a unique mechanism of action. Additionally, the compound acted as an ATP-competitive MEK inhibitor, positioning it as a dual-function agent for overcoming MDR in leukemia (Zhou et al., 2023a). Han et al. explored the role of parthanatos in subarachnoid hemorrhage (SAH) and demonstrated that the PARP-1 inhibitor AG14361 significantly reduced oxidative stress, inflammation, and neuronal apoptosis in SAH models. Treatment with AG14361 improved neurological function and blood-brain barrier integrity by suppressing parthanatos, highlighting the potential of PARP-1 inhibitors beyond oncology in neuroprotective therapies (Han et al., 2024).

The bioenergetic regulation of parthanatos has also been investigated in the context of metabolic stress (Huang et al., 2014). Huang et al. examined how mitochondrial dysfunction contributes to parthanatos in Atg5-deficient cells. The study found that the parthanatic inducer MNNG triggered ATP depletion in wild-type (WT) mouse embryonic fibroblasts (MEFs), but Atg5-deficient MEFs exhibited impaired energy restoration due to reduced SIRT1 activity and mitochondrial dysfunction. Interestingly, treatment with PD98059 enhanced mitochondrial activity and ATP restoration during parthanatos without interfering with DNA damage responses, as shown in Figure 3. These findings suggest energy-based therapeutic strategies

for mitigating parthanatos-related disorders (Huang et al., 2014). Wang et al. further investigated the molecular regulation of AIF nuclear translocation in parthanatos and identified AIF as a high-affinity poly(ADP-ribose) (PAR)-binding protein. PAR binding facilitated AIF release from mitochondria and its nuclear translocation, which was essential for PARP-1-mediated cell death. Mutation of AIF's PAR-binding site prevented its release and nuclear translocation while preserving its NADH oxidase function. These findings highlight the PAR-AIF interaction as a potential target for modulating parthanatos (Wang et al., 2011).

Emerging evidence suggests that parthanatos may contribute to reproductive aging and ovarian dysfunction (Chiang et al., 2020). Batnasan et al. demonstrated that cumulus granulosa cells (GCs) from patients with diminished ovarian reserve (DOR) exhibited increased PARP-1 activation and AIF nuclear translocation, indicative of parthanatos-mediated cell death. Using an *in vitro* model of H₂O₂-induced parthanatos in ovarian cells, the study showed that melatonin inhibited PARP-1 activation, reduced AIF translocation, and mitigated oxidative stress-induced parthanatos. These findings suggest that melatonin may protect against ovarian aging and oxidative damage (Batnasan et al., 2020).

The role of parthanatos in chemotherapeutic responses has also been explored in leukemia models (Messikommer et al., 2021). Maru et al. demonstrated that cytarabine and idarubicin induced parthanatos in acute myeloid leukemia (AML) cells, particularly in M4/M5 subtypes. Parthanatos induction was observed in 30 % of AML cell lines and 46 % of AML patient samples, with patients exhibiting parthanatos showing significantly improved survival rates. Furthermore, optimal PARP-1 expression levels correlated with drug sensitivity, whereas overexpression or suppression reduced chemotherapy efficacy. These findings highlight parthanatos as a crucial determinant of treatment response in AML (Maru et al., 2023).

Mitochondrial dysfunction and oxidative stress are key drivers of parthanatos in gliomas (Liu et al., 2022d). Wang et al. investigated the role of Tax1 binding protein 1 (TAX1BP1) in deoxy podophyllotoxin (DPT)-induced parthanatos in glioma cells. The study found that DPT treatment led to excessive ROS production, PARP-1 overactivation, and mitochondrial TAX1BP1 redistribution, facilitating AIF nuclear translocation. TAX1BP1 enhanced respiratory chain complex I activity by upregulating ND1, ND2, NDUFS2, and NDUFS4, leading to superoxide generation, mitochondrial depolarization, and DNA damage. DPT treatment in U87 xenografts suppressed tumor growth via NAD⁺ depletion and parthanatos induction, identifying TAX1BP1 as a key mediator of parthanatos in gliomas (Wang et al., 2023).

In addition to targeting parthanatos, novel platinum-based drugs have been developed to bypass apoptosis resistance (Al-Khayal et al., 2020). Guo et al. introduced Mono-Pt, a monofunctional platinum(II) complex that induces autophagic cell death in apoptosis-resistant ovarian cancer cells. Unlike cisplatin, which primarily induces apoptosis, Mono-Pt triggered cytoplasmic vacuolation, LC3-II accumulation, and autophagic vacuole formation, dependent on BECN1 and ATG7 expression. The study further demonstrated that Mono-Pt's effects were mediated through the AKT1-MTOR and MAPK1/3 pathways, offering a potential alternative for overcoming chemotherapy resistance in ovarian cancer (Guo et al., 2013). The research confirms that parthanatos modulation strategies show promise for treating cancer and other medical conditions. PARP inhibitors continue as central parthanatos-targeted treatments, but future therapeutic developments include enhancements of reactive oxygen species production, mitochondrial control adaptations, and AIF translocation regulations. The clinical importance of parthanatos expands into neuroprotection, reproductive aging, immune modulation, and its relevance in oncology research (Figure 3).

Dual-pathway targeting

The research confirms that parthanatos modulation strategies show promise for treating cancer and other medical conditions (Damiescu et al., 2024). The discovery of PARP inhibitors is essential in parthanatos-targeting methods, but investigators have identified three new therapeutic strategies involving ROS enhancement and mitochondrial control alongside AIF regulation mechanisms (Koehler et al., 2021). The clinical importance of parthanatos expands into neuroprotection, reproductive aging, immune modulation, and its relevance in oncology research (Chen et al., 2024). Dual-pathway targeting gives effective results during the treatment of tumors that exhibit resistance to apoptosis through p53 or caspase dysfunction (Hassin and Oren, 2023). The combination therapy shows promise for handling aggressive tumors and therapy-resistant cancer types (Bahreyni et al., 2024).

Numerous research evaluations confirm that targeting two protective pathways yields successful results when treating cancer (Kelley et al., 2014). Wen et al. investigated arnicolide D, a compound derived from *Centipede minima*, and its anti-tumor effects in breast cancer cells. Arnicolide D induced oxidative stress, increasing ROS levels, mitochondrial dysfunction, and LDH release while significantly reducing cell viability. Notably, it activated multiple cell death pathways, including apoptosis, parthanatos (via PARP-1 activation and AIF nuclear translocation), and ferroptosis (via GPX4 suppression and Fe²⁺/MDA accumulation). Additionally, arnicolide D inhibited cell invasion by downregulating MMP-2 and MMP-9, highlighting its potential as a multi-target therapeutic agent (Wen et al., 2024). Li et al. further explored ROS-inducing agents in cervical cancer and found that massive DNA strand breaks caused by excessive 8-oxoG excision by OGG1 led to parthanatos induction. Inhibition of MTH1

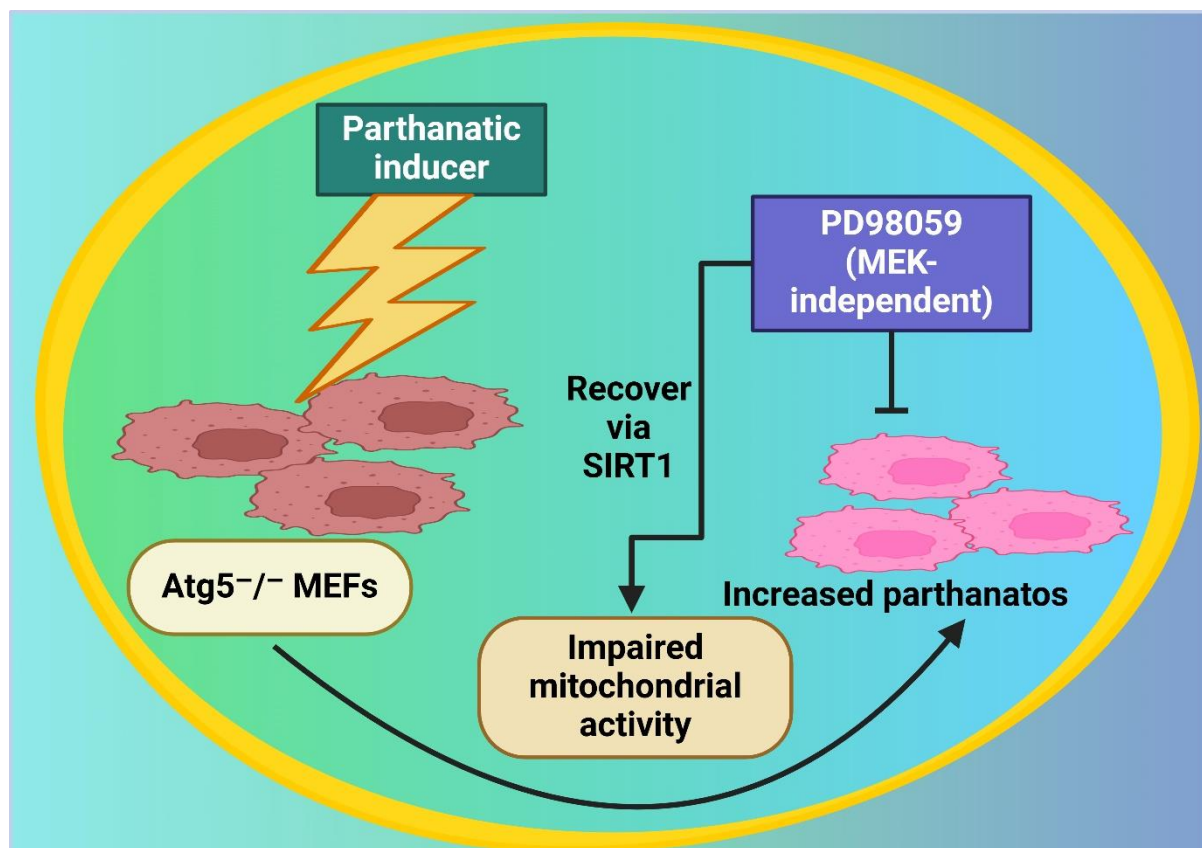


Figure 3 illustrates the regulation of parthanatos and mitochondrial activity in $Atg5^{-/-}$ mouse embryonic fibroblasts (MEFs). A parthanatic inducer triggers cell death, leading to impaired mitochondrial activity. SIRT1 facilitates recovery from mitochondrial dysfunction. However, treatment with PD98059, a MEK-independent inhibitor, enhances parthanatos, suggesting its role in promoting cell death. The interplay between autophagy deficiency, mitochondrial impairment, and SIRT1-mediated recovery highlights the complex regulatory mechanisms of parthanatos in cellular stress responses.

enhanced this effect by increasing 8-oxoG incorporation into DNA, creating a synergistic effect with ROS-inducing agents. *In vivo*, this combination significantly suppressed tumor xenograft growth, particularly in OGG1-proficient models, demonstrating a selective and safer chemotherapeutic strategy (Li et al., 2024).

Dual-pathway targeting has also been explored in apoptosis-resistant tumors (Fitzgerald et al., 2022). Xavier et al. demonstrated that ursolic acid (UA) effectively induced caspase-independent apoptosis in p53-mutant HCT15 CRC cells while enhancing the effects of 5-FU via JNK pathway activation. UA also modulated autophagy, as indicated by increased LC3 and p62 expression, contributing to JNK-dependent cell death. *In vivo*, UA significantly reduced tumor growth in HCT15

xenograft models, underscoring its potential to overcome chemotherapy resistance (Xavier et al., 2013). Similarly, Mujumdar et al. showed that triptolide induces caspase-dependent apoptosis in some pancreatic cancer cells and CICD in metastatic lines. Blocking autophagy shifted cell death to apoptosis while inhibiting both pathways rescued cells, highlighting triptolide's dual mechanism as a therapeutic strategy (Mujumdar et al., 2010).

The interplay between apoptosis and autophagy has also been investigated in prostate and breast cancers (Bhutia et al., 2010). In MCF-7 breast cancer cells, resveratrol causes both caspase-dependent and independent cell death, according to research by Scarlatti et al. It causes Beclin 1-independent autophagy in cells lacking caspase-3, while it causes both autophagy and apoptosis in cells expressing

caspase-3. This supports the therapeutic potential of resveratrol by indicating that its induction of autophagy compensates for a lack of apoptosis (Scarlati et al., 2008). Kim et al. discovered that geraniol suppresses mTOR by blocking AKT and activating AMPK, which causes PC-3 prostate cancer cells to undergo apoptosis and autophagy. Cell mortality was increased by co-treatment with an AMPK activator and an AKT inhibitor, indicating a dual-pathway approach to prostate cancer treatment (Kim et al., 2012).

Oxidative stress modulation has become crucial in dual-pathway targeting (Liu et al., 2022c). According to Wu et al., ginsenoside Rh4 inhibits the development of colorectal cancer by triggering autophagy, caspase-dependent apoptosis, and G0/G1 arrest. ROS buildup triggers apoptosis by activating the JNK-p53 pathway. Cell mortality was decreased by blocking ROS, JNK, or p53, demonstrating Rh4's potential as an anti-cancer drug that targets oxidative stress (Wu et al., 2018). Wang et al. demonstrated that co-treatment of curcumin and berberine suppresses the development of breast cancer cells by causing autophagic cell death via the JNK/Bcl-2/Beclin1 pathway and caspase-dependent apoptosis via ERK. JNK inhibition decreased cytotoxicity and autophagy indicators, demonstrating the combination's therapeutic potential (Wang et al., 2016). Combining targeted strategies toward two cell death pathways enhances cancer treatment quality by unifying parthanatos with apoptosis and combining apoptosis with autophagy and oxidative stress regulation. Occurring concurrently with multiple cell death pathways provides dual-pathway targeting an effective solution for resisting therapeutic resistance, most notably in difficult-to-treat aggressive cancers. Further research needs to find optimal medications that produce synergistic cancer cell death effects with low toxic side effects for advancing advanced multi-target cancer treatments.

CONCLUSION AND FUTURE PERSPECTIVE

Both apoptosis and parthanatos establish different yet vital death programs that control cancer development and therapeutic response. Apoptosis functions as a robust caspase-dependent mechanism, but cancer treatments base their approach on this method because numerous tumors manage to avoid apoptosis through elevated anti-apoptotic protein levels or mutated p53 regulatory elements. The cell death mechanism known as parthanatos functions as a caspase-independent pathway through PARP-1 overactivation combined with AIF nuclear movement, representing a new method for destroying resistant cancer cells. Multiple studies indicate that parthanatos functions as a vital mechanism in the development of gliomas, leukemia, and ovarian cancer, and exposure to deoxypodophyllotoxin (DPT) and WIN-55 facilitates parthanatos development in drug-resistant tumors. Several compounds modulating oxidative stress have demonstrated enhanced effects on apoptotic and parthanatic pathways in parallel to the development of the new small molecule ZINC253504760, which shows potential as a treatment for multidrug-resistant (MDR) leukemia cells by inducing parthanatos.

Dual-pathway targeting strategies become new opportunities for cancer treatment because apoptosis interacts with parthanatos. Both tumor cell death and tumor killing reach a higher level when BH3 mimetics are combined with PARP inhibitors because these strategies simultaneously activate apoptosis and parthanatos pathways. Scientists observe that MTH1 inhibitors, when administered together with ROS-inducing agents in cervical cancer, lead to elevated DNA damage with activated parthanatos. The therapeutic value is expanded through natural compounds, including arnicolide D and ursolic acid, because these regulate apoptosis and parthanatos and ferroptosis mechanisms. Thresholds requiring further improvement exist for parthanatos-targeting therapies to deliver targeted therapy without adverse effects in healthy cells. Clin-

ical application of parthanatos remains restricted because no biomarkers are available to determine tumor sensitivity to this mechanism.

Research must focus on discovering the exact molecular factors controlling the apoptosis-parthanatos regulatory switch for better therapeutic intervention. New therapeutic mixtures need evaluation because they should activate parthanatos in treatment-resistant cancer types, and scientists should explore approaches to mitigate mitochondrial impairment and metabolic disturbances to achieve treatment aims. Studies must expand their focus regarding parthanatos applications to explore their effect on neurodegenerative disorders and inflammatory diseases. The use of clinical progress with mechanistic knowledge about apoptosis and parthanatos modulation shows crucial potential to surpass therapy resistance and improve cancer therapy results.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GG, MA, EM and AG: Conceptualization, methodology, software. WHA, KG, MR: Writing – original draft preparation. HA, AR, IK: Data curation, writing – review & editing. SIA: Data curation and methodology. SKS: Methodology, software. All authors read and approved the final manuscript.

REFERENCES

Akl H, Vervloessem T, Kiviluoto S, Bittremieux M, Parys JB, De Smedt H, et al. A dual role for the anti-apoptotic Bcl-2 protein in cancer: Mitochondria versus endoplasmic reticulum. *Biochim Biophys Acta*. 2014; 1843:2240-52. doi: 10.1016/j.bbamcr.2014.04.017.

Al-Khayal K, Vaali-Mohammed M-A, Elwatidy M, Bin Traiki T, Al-Obeed O, Azam M, et al. A novel coordination complex of platinum (PT) induces cell death in colorectal cancer by altering redox balance and modulating MAPK pathway. *BMC Cancer*. 2020; 20(1): 685. doi: 10.1186/s12885-020-07165-w.

Ameisen JC. On the origin, evolution, and nature of programmed cell death: a timeline of four billion years. *Cell Death Differ*. 2002;9:367-93. doi: 10.1038/sj.cdd.4400950.

An X, Yu W, Liu J, Tang D, Yang L, Chen X. Oxidative cell death in cancer: mechanisms and therapeutic opportunities. *Cell Death Dis*. 2024;15(8):556. doi: 10.1038/s41419-024-06939-5.

Andrabi SA, Dawson TM, Dawson VL. Mitochondrial and nuclear cross talk in cell death: parthanatos. *Ann N Y Acad Sci*. 2008;1147:233-41. doi: 10.1196/annals.1427.014.

Axelrod MJ, Mendez RE, Khalil A, Leimgruber SS, Sharlow ER, Capaldo B, et al. Synergistic apoptosis in head and neck squamous cell carcinoma cells by co-inhibition of insulin-like growth factor-1 receptor signaling and compensatory signaling pathways. *Head Neck*. 2015;37:1722-32. doi: 10.1002/hed.23822.

Bahreyni A, Mohamud Y, Luo H. Oncolytic virus-based combination therapy in breast cancer. *Cancer Letters*. 2024;585:216634. doi: 10.1016/j.canlet.2024.216634.

Bai L, Smith DC, Wang S. Small-molecule SMAC mimetics as new cancer therapeutics. *Pharmacol Ther*. 2014;144(1):82-95. doi: 10.1016/j.pharmthera.2014.05.007.

Bajt ML, Cover C, Lemasters JJ, Jaeschke H. Nuclear translocation of endonuclease G and apoptosis-inducing factor during acetaminophen-induced liver cell injury. *Toxicol Sci*. 2006;94:217-25. doi: 10.1093/toxsci/kfl077.

Batnasan E, Xie S, Zhang Q, Li Y. Observation of parthanatos involvement in diminished ovarian reserve patients and melatonin's protective function through inhibiting ADP-ribose (PAR) expression and preventing AIF translocation into the nucleus. *Reprod Sci*. 2020; 27(1):75-86. doi: 10.1007/s43032-019-00005-8.

Becattini B, Sareth S, Zhai D, Crowell KJ, Leone M, Reed JC, et al. Targeting apoptosis via chemical design: inhibition of bid-induced cell death by small organic molecules. *Chem Biol*. 2004;11:1107-17. doi: 10.1016/j.chembiol.2004.05.022.

- Bhutia SK, Dash R, Das SK, Azab B, Su ZZ, Lee SG, et al. Mechanism of autophagy to apoptosis switch triggered in prostate cancer cells by antitumor cytokine melanoma differentiation-associated gene 7/interleukin-24. *Cancer Res.* 2010;70:3667-76. doi: 10.1158/0008-5472.can-09-3647.
- Boice A, Bouchier-Hayes L. Targeting apoptotic caspases in cancer. *Biochim Biophys Acta.* 2020;1867(6):118688. doi: 10.1016/j.bbamcr.2020.118688.
- Boulos JC, Omer EA, Rigano D, Formisano C, Chatterjee M, Leich E, et al. Cynaropicrin disrupts tubulin and c-Myc-related signaling and induces parthanatos-type cell death in multiple myeloma. *Acta Pharmacol Sin.* 2023;44:2265-81. doi: 10.1038/s41401-023-01117-3.
- Brentnall M, Rodriguez-Menocal L, De Guevara RL, Cepero E, Boise LH. Caspase-9, caspase-3 and caspase-7 have distinct roles during intrinsic apoptosis. *BMC Cell Biology.* 2013;14(1):32. doi: 10.1186/1471-2121-14-32.
- Buchholz TA, Davis DW, McConkey DJ, Symmans WF, Valero V, Jhingran A, et al. Chemotherapy-induced apoptosis and Bcl-2 levels correlate with breast cancer response to chemotherapy. *Cancer J.* 2003;9(1):33-41. doi: 10.1097/00130404-200301000-00007.
- Cao K, Zhu J, Lu M, Zhang J, Yang Y, Ling X, et al. Analysis of multiple programmed cell death-related prognostic genes and functional validations of necroptosis-associated genes in oesophageal squamous cell carcinoma. *eBioMedicine.* 2024;99:104920. doi: 10.1016/j.ebiom.2023.104920.
- Carrington EM, Zhan Y, Brady JL, Zhang JG, Sutherland RM, Anstee NS, et al. Anti-apoptotic proteins BCL-2, MCL-1 and A1 summate collectively to maintain survival of immune cell populations both in vitro and in vivo. *Cell Death Differ.* 2017;24:878-88. doi: 10.1038/cdd.2017.30.
- Chaitanya GV, Alexander JS, Babu PP. PARP-1 cleavage fragments: signatures of cell-death proteases in neurodegeneration. *Cell Commun Signal.* 2010;8(1):31. doi: 10.1186/1478-811X-8-31.
- Chandra J, Samali A, Orrenius S. Triggering and modulation of apoptosis by oxidative stress. *Free Radic Biol Med.* 2000;29:323-33. doi: 10.1016/s0891-5849(00)00302-6.
- Chang X, Bian M, Liu L, Yang J, Yang Z, Wang Z, et al. Induction of immunogenic cell death by novel platinum-based anticancer agents. *Pharmacol Res.* 2023;187:106556. doi: 10.1016/j.phrs.2022.106556.
- Chen F, Kang R, Tang D, Liu J. Ferroptosis: principles and significance in health and disease. *J Hematol Oncol.* 2024;17(1):41. doi: 10.1186/s13045-024-01564-3.
- Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget.* 2018;9:7204-18. doi: 10.18632/oncotarget.23208.
- Chen M, Linstra R, van Vugt MATM. Genomic instability, inflammatory signaling and response to cancer immunotherapy. *Biochim Biophys Acta.* 2022;1877(1):188661. doi: 10.1016/j.bbcan.2021.188661.
- Chen S-D, Yang D-I, Lin T-K, Shaw F-Z, Liou C-W, Chuang Y-C. Roles of oxidative stress, apoptosis, PGC-1 α and mitochondrial biogenesis in cerebral ischemia. *Int J Mol Sci.* 2011;12:7199-215.
- Chen WH, Xu XD, Luo GF, Jia HZ, Lei Q, Cheng SX, et al. Dual-targeting pro-apoptotic peptide for programmed cancer cell death via specific mitochondria damage. *Sci Rep.* 2013;3:3468. doi: 10.1038/srep03468.
- Cheong KJH, Huang D-Y, Sekar P, Chen RJ, Cheng IH-J, Chan C-M, et al. CASK mediates oxidative stress-induced microglial apoptosis-inducing factor-independent parthanatos cell death via promoting PARP-1 hyperactivation and mitochondrial dysfunction. *Antioxidants.* 2024;13(3):343.
- Chiang JL, Shukla P, Pagidas K, Ahmed NS, Karri S, Gunn DD, et al. Mitochondria in ovarian aging and reproductive longevity. *Ageing Res Rev.* 2020;63:101168. doi: 10.1016/j.arr.2020.101168.
- Chipuk JE, Mohammed JN, Gelles JD, Chen Y. Mechanistic connections between mitochondrial biology and regulated cell death. *Dev Cell.* 2021;56:1221-33. doi: 10.1016/j.devcel.2021.03.033.
- Chiu LY, Ho FM, Shiah SG, Chang Y, Lin WW. Oxidative stress initiates DNA damager MNNG-induced poly(ADP-ribose)polymerase-1-dependent parthanatos cell death. *Biochem Pharmacol.* 2011;81:459-70. doi: 10.1016/j.bcp.2010.10.016.
- Covarrubias AJ, Perrone R, Grozio A, Verdin E. NAD(+) metabolism and its roles in cellular processes during ageing. *Nat Rev Mol Cell Biol.* 2021;22:119-41. doi: 10.1038/s41580-020-00313-x.
- Crowe DL, Sinha UK. p53 apoptotic response to DNA damage dependent on bcl2 but not bax in head and neck squamous cell carcinoma lines. *Head Neck.* 2006;28(1):15-23. doi: 10.1002/hed.20319.
- D'Amico M, De Amicis F. Challenges of regulated cell death: implications for therapy resistance in cancer. *Cells.* 2024;13(13):1083.

- Damiescu R, Efferth T, Dawood M. Dysregulation of different modes of programmed cell death by epigenetic modifications and their role in cancer. *Cancer Lett.* 2024;584:216623. doi: 10.1016/j.canlet.2024.216623.
- Dandoti S. Mechanisms adopted by cancer cells to escape apoptosis—A review. *Biocell.* 2021;45:863-84. doi: 10.32604/biocell.2021.013993.
- David KK, Andrabi SA, Dawson TM, Dawson VL. Parthanatos, a messenger of death. *Front Biosci (Landmark Ed).* 2009;14:1116-28. doi: 10.2741/3297.
- Delbridge AR, Strasser A. The BCL-2 protein family, BH3-mimetics and cancer therapy. *Cell Death Differ.* 2015;22:1071-80. doi: 10.1038/cdd.2015.50.
- Derakhshan A, Chen Z, Van Waes C. Therapeutic small molecules target inhibitor of apoptosis proteins in cancers with deregulation of extrinsic and intrinsic cell death pathways. *Clin Cancer Res.* 2017;23:1379-87. doi: 10.1158/1078-0432.ccr-16-2172.
- Donizy P, Halon A, Surowiak P, Pietrzyk G, Kozyra C, Matkowski R. Correlation between PARP-1 immunoreactivity and cytomorphological features of parthanatos, a specific cellular death in breast cancer cells. *Eur J Histochem.* 2013;57(4):e35. doi: 10.4081/ejh.2013.e35.
- Doti N, Reuther C, Scognamiglio PL, Dolga AM, Plesnila N, Ruvo M, et al. Inhibition of the AIF/CypA complex protects against intrinsic death pathways induced by oxidative stress. *Cell Death Dis.* 2014;5(1):e993. doi: 10.1038/cddis.2013.518.
- Dzobo K, Senthebane DA, Dandara C. The tumor microenvironment in tumorigenesis and therapy resistance revisited. *Cancers (Basel).* 2023;15(2):376. doi: 10.3390/cancers15020376.
- Fatokun AA, Dawson VL, Dawson TM. Parthanatos: mitochondrial-linked mechanisms and therapeutic opportunities. *Br J Pharmacol.* 2014;171:2000-16. doi: 10.1111/bph.12416.
- Fitzgerald M-C, O'Halloran PJ, Connolly NMC, Murphy BM. Targeting the apoptosis pathway to treat tumours of the paediatric nervous system. *Cell Death Dis.* 2022;13(5):460. doi: 10.1038/s41419-022-04900-y.
- Fuentes-Baile M, García-Morales P, Pérez-Valenciano E, Ventero MP, Sanz JM, de Juan Romero C, et al. Cell death mechanisms induced by CLytA-DAAO chimeric enzyme in human tumor cell lines. *Int J Mol Sci.* 2020;21(22):8522. doi: 10.3390/ijms21228522.
- Fujikawa DG, Shinmei SS, Cai B. Kainic acid-induced seizures produce necrotic, not apoptotic, neurons with internucleosomal DNA cleavage: implications for programmed cell death mechanisms. *Neuroscience.* 2000;98(1):41-53. doi: 10.1016/S0306-4522(00)00085-3.
- Fulda S. Molecular pathways: targeting inhibitor of apoptosis proteins in cancer—from molecular mechanism to therapeutic application. *Clin Cancer Res.* 2014;20:289-95. doi: 10.1158/1078-0432.ccr-13-0227.
- Gali-Muhtasib H, Diab-Assaf M, Boltze C, Al-Hmaira J, Hartig R, Roessner A, et al. Thymoquinone extracted from black seed triggers apoptotic cell death in human colorectal cancer cells via a p53-dependent mechanism. *Int J Oncol.* 2004;25:857-66. doi: 10.3892/ijo.25.4.857.
- Gao X, Wang L, Lu X, Yan Y, Guo Y, Wang J, et al. The expression of parthanatos markers and miR-7 mimic protects photoreceptors from parthanatos by repressing α -synuclein in retinal detachment. *Am J Pathol.* 2023;193:1833-44. doi: 10.1016/j.ajpath.2023.06.011.
- Garrido C, Galluzzi L, Brunet M, Puig PE, Didelot C, Kroemer G. Mechanisms of cytochrome c release from mitochondria. *Cell Death Differ.* 2006;13:1423-33. doi: 10.1038/sj.cdd.4401950.
- Gielecińska A, Kciuk M, Yahya EB, Ainane T, Mujwar S, Kontek R. Apoptosis, necroptosis, and pyroptosis as alternative cell death pathways induced by chemotherapeutic agents? *Biochim Biophys Acta.* 2023;1878(6):189024. doi: 10.1016/j.bbcan.2023.189024.
- Glinsky GV, Glinsky VV, Ivanova AB, Hueser CJ. Apoptosis and metastasis: increased apoptosis resistance of metastatic cancer cells is associated with the profound deficiency of apoptosis execution mechanisms. *Cancer Lett.* 1997;115:185-93. doi: 10.1016/s0304-3835(97)04738-1.
- Guicciardi ME, Gores GJ. Life and death by death receptors. *Faseb J.* 2009;23:1625-37. doi: 10.1096/fj.08-111005.
- Guo WJ, Zhang YM, Zhang L, Huang B, Tao FF, Chen W, et al. Novel monofunctional platinum (II) complex Mono-Pt induces apoptosis-independent autophagic cell death in human ovarian carcinoma cells, distinct from cisplatin. *Autophagy.* 2013;9:996-1008. doi: 10.4161/auto.24407.

- Han Y, Wang C, Li X, Liang G. PARP-1 dependent cell death pathway (Parthanatos) mediates early brain injury after subarachnoid hemorrhage. *Eur J Pharmacol.* 2024;978:176765. doi: 10.1016/j.ejphar.2024.176765.
- Hassan M, Watari H, AbuAlmaaty A, Ohba Y, Sakuragi N. Apoptosis and molecular targeting therapy in cancer. *Biomed Res Int.* 2014;2014:150845. doi: 10.1155/2014/150845.
- Hassin O, Oren M. Drugging p53 in cancer: one protein, many targets. *Nat Rev Drug Discov.* 2023;22:127-44. doi: 10.1038/s41573-022-00571-8.
- Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Mol Oncol.* 2011;5:387-93. doi: 10.1016/j.molonc.2011.07.001.
- Huang C-T, Huang D-Y, Hu C-J, Wu D, Lin W-W. Energy adaptive response during parthanatos is enhanced by PD98059 and involves mitochondrial function but not autophagy induction. *Biochim Biophys Acta.* 2014;1843:531-43. doi: 10.1016/j.bbamcr.2013.12.001.
- Huang P, Chen G, Jin W, Mao K, Wan H, He Y. Molecular mechanisms of parthanatos and its role in diverse diseases. *Int J Mol Sci.* 2022;23(13):7292. doi: 10.3390/ijms23137292.
- Huang Q, Li F, Liu X, Li W, Shi W, Liu FF, et al. Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. *Nat Med.* 2011;17:860-6. doi: 10.1038/nm.2385.
- Indran IR, Tufo G, Pervaiz S, Brenner C. Recent advances in apoptosis, mitochondria and drug resistance in cancer cells. *Biochim Biophys Acta.* 2011;1807:735-45. doi: 10.1016/j.bbabi.2011.03.010.
- Jan R, Chaudhry GE. Understanding apoptosis and apoptotic pathways targeted cancer therapeutics. *Adv Pharm Bull.* 2019;9:205-18. doi: 10.15171/apb.2019.024.
- Ježek J, Cooper KF, Strich R. Reactive oxygen species and mitochondrial dynamics: the yin and yang of mitochondrial dysfunction and cancer progression. *Antioxidants.* 2018;7(1):13.
- Jiang HY, Yang Y, Zhang YY, Xie Z, Zhao XY, Sun Y, et al. The dual role of poly(ADP-ribose) polymerase-1 in modulating parthanatos and autophagy under oxidative stress in rat cochlear marginal cells of the stria vascularis. *Redox Biol.* 2018;14:361-70. doi: 10.1016/j.redox.2017.10.002.
- Kale J, Osterlund EJ, Andrews DW. BCL-2 family proteins: changing partners in the dance towards death. *Cell Death Differ.* 2018;25(1):65-80. doi: 10.1038/cdd.2017.186.
- Kari S, Subramanian K, Altomonte IA, Murugesan A, Yli-Harja O, Kandhavelu M. Programmed cell death detection methods: a systematic review and a categorical comparison. *Apoptosis.* 2022;27:482-508. doi: 10.1007/s10495-022-01735-y.
- Ke Y, Wang C, Zhang J, Zhong X, Wang R, Zeng X, et al. The role of PARPs in inflammation—and metabolic—related diseases: molecular mechanisms and beyond. *Cells.* 2019;8(9):1047.
- Kelley MR, Logsdon D, Fishel ML. Targeting DNA repair pathways for cancer treatment: what's new? *Future Oncol.* 2014;10:1215-37. doi: 10.2217/fon.14.60.
- Kim D, Nam HJ. PARP inhibitors: clinical limitations and recent attempts to overcome them. *Int J Mol Sci.* 2022;23(15):8412. doi: 10.3390/ijms23158412.
- Kim SH, Park EJ, Lee CR, Chun JN, Cho NH, Kim IG, et al. Geraniol induces cooperative interaction of apoptosis and autophagy to elicit cell death in PC-3 prostate cancer cells. *Int J Oncol.* 2012;40:1683-90. doi: 10.3892/ijo.2011.1318.
- Kist M, Vucic D. Cell death pathways: intricate connections and disease implications. *Embo J.* 2021;40(5):e106700. doi: 10.15252/emboj.2020106700.
- Koehler RC, Dawson VL, Dawson TM. Targeting parthanatos in ischemic stroke. *Front Neurol.* 2021;12:662034. doi: 10.3389/fneur.2021.662034.
- Kong C, Chen X. Combined photodynamic and photothermal therapy and immunotherapy for cancer treatment: a review. *Int J Nanomedicine.* 2022;17: 6427-46. doi: 10.2147/ijn.s388996.
- Kopeina GS, Zhivotovsky B. Programmed cell death: Past, present and future. *Biochem Biophys Res Commun.* 2022;633:55-8. doi: 10.1016/j.bbrc.2022.09.022.
- Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, et al. Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. *Cell Death Differ.* 2009;16(1):3-11. doi: 10.1038/cdd.2008.150.
- Kundu M, Greer YE, Dine JL, Lipkowitz S. Targeting TRAIL death receptors in triple-negative breast cancers: challenges and strategies for cancer therapy. *Cells.* 2022;11(23):3717. doi: 10.3390/cells11233717.

- Kuo CL, Ponneri Babuharisankar A, Lin YC, Lien HW, Lo YK, Chou HY, et al. Mitochondrial oxidative stress in the tumor microenvironment and cancer immunoescape: foe or friend? *J Biomed Sci.* 2022;29(1):74. doi: 10.1186/s12929-022-00859-2.
- Kuzhandaivel A, Nistri A, Mladinic M. Kainate-mediated excitotoxicity induces neuronal death in the rat spinal cord in vitro via a PARP-1 dependent cell death pathway (parthanatos). *Cell Mol Neurobiol.* 2010;30:1001-12. doi: 10.1007/s10571-010-9531-y.
- Lasica M, Anderson MA. Review of venetoclax in CLL, AML and multiple myeloma. *J Pers Med.* 2021;11(6):463. doi: 10.3390/jpm11060463.
- Lee SY, Ju MK, Jeon HM, Jeong EK, Lee YJ, Kim CH, et al. Regulation of tumor progression by programmed necrosis. *Oxid Med Cell Longev.* 2018;2018(1):3537471. doi: 10.1155/2018/3537471.
- Lennon SV, Martin SJ, Cotter TG. Dose-dependent induction of apoptosis in human tumour cell lines by widely diverging stimuli. *Cell Prolif.* 1991;24(1):203-14. doi: 10.1111/j.1365-2184.1991.tb01150.x.
- Leonard BC, Johnson DE. Signaling by cell surface death receptors: Alterations in head and neck cancer. *Adv Biol Regul.* 2018;67:170-8. doi: 10.1016/j.jbior.2017.10.006.
- Li C, Xue Y, Wu J, Zhang L, Yang T, Ai M, et al. MTH1 inhibition synergizes with ROS-inducing agents to trigger cervical cancer cells undergoing parthanatos. *Biochim Biophys Acta Mol Basis Dis.* 2024;1870(5):167190. doi: 10.1016/j.bbadis.2024.167190.
- Li D, Kou Y, Gao Y, Liu S, Yang P, Hasegawa T, et al. Oxaliplatin induces the PARP1-mediated parthanatos in oral squamous cell carcinoma by increasing production of ROS. *Aging (Albany NY).* 2021;13:4242-57. doi: 10.18632/aging.202386.
- Li K, Geng Y, Lin B, Xi Z. Molecular mechanisms underlying mitochondrial damage, endoplasmic reticulum stress, and oxidative stress induced by environmental pollutants. *Toxicol Res.* 2023;12:1014-23. doi: 10.1093/toxres/tfad094.
- Li W, Yang J, Luo L, Jiang M, Qin B, Yin H, et al. Targeting photodynamic and photothermal therapy to the endoplasmic reticulum enhances immunogenic cancer cell death. *Nat Commun.* 2019;10(1):3349. doi: 10.1038/s41467-019-11269-8.
- Liu J, Guo W, Li J, Li X, Geng J, Chen Q, et al. Tumor-targeting novel manganese complex induces ROS-mediated apoptotic and autophagic cancer cell death. *Int J Mol Med.* 2015;35:607-16. doi: 10.3892/ijmm.2015.2073.
- Liu L, Li J, Ke Y, Zeng X, Gao J, Ba X, et al. The key players of parthanatos: opportunities for targeting multiple levels in the therapy of parthanatos-based pathogenesis. *Cell Mol Life Sci.* 2022a;79(1):60. doi: 10.1007/s00018-021-04109-w.
- Liu L, Liu B, Guan G, Kang R, Dai Y, Tang D. Cyclophosphamide-induced GPX4 degradation triggers parthanatos by activating AIFM1. *Biochem Biophys Res Commun.* 2022b;606:68-74. doi: 10.1016/j.bbrc.2022.03.098.
- Liu R, Bian Y, Liu L, Liu L, Liu X, Ma S. Molecular pathways associated with oxidative stress and their potential applications in radiotherapy (Review). *Int J Mol Med.* 2022c;49(5):65. doi: 10.3892/ijmm.2022.5121.
- Liu S, Dong L, Shi W, Zheng Z, Liu Z, Meng L, et al. Potential targets and treatments affect oxidative stress in gliomas: An overview of molecular mechanisms. *Front Pharmacol.* 2022d;13:921070. doi: 10.3389/fphar.2022.921070.
- Liu S, Luo W, Wang Y. Emerging role of PARP-1 and PARthanatos in ischemic stroke. *J Neurochem.* 2022e;160(1):74-87. doi: 10.1111/jnc.15464.
- Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. *Science.* 2017;355(6330):1152-8. doi: 10.1126/science.aam7344.
- Lou J, Zhou Y, Feng Z, Ma M, Yao Y, Wang Y, et al. Caspase-independent regulated necrosis pathways as potential targets in cancer management. *Front Oncol.* 2020;10:616952. doi: 10.3389/fonc.2020.616952.
- Lucena FR, de Araújo LC, Rodrigues Mdo D, da Silva TG, Pereira VR, Militão GC, et al. Induction of cancer cell death by apoptosis and slow release of 5-fluoracil from metal-organic frameworks Cu-BTC. *Biomed Pharmacother.* 2013;67:707-13. doi: 10.1016/j.biopha.2013.06.003.
- Luna-Vargas MPA, Chipuk JE. Physiological and pharmacological control of BAK, BAX, and beyond. *Trends Cell Biol.* 2016;26:906-17. doi: 10.1016/j.tcb.2016.07.002.
- Luo T, Yuan Y, Yu Q, Liu G, Long M, Zhang K, et al. PARP-1 overexpression contributes to Cadmium-induced death in rat proximal tubular cells via parthanatos and the MAPK signalling pathway. *Sci Rep.* 2017;7(1):4331. doi: 10.1038/s41598-017-04555-2.
- Ma D, Lu B, Feng C, Wang C, Wang Y, Luo T, et al. Deoxypodophyllotoxin triggers parthanatos in glioma cells via induction of excessive ROS. *Cancer Lett.* 2016;371:194-204. doi: 10.1016/j.canlet.2015.11.044.

- Martínez-Morcillo FJ, Cantón-Sandoval J, Martínez-Navarro FJ, Cabas I, Martínez-Vicente I, Armistead J, et al. NAMPT-derived NAD⁺ fuels PARP1 to promote skin inflammation through parthanatos cell death. *PLoS Biol.* 2021;19(11):e3001455. doi: 10.1371/journal.pbio.3001455.
- Maru B, Messikommer A, Huang L, Seipel K, Kovacs O, Valk PJM, et al. PARP-1 improves leukemia outcomes by inducing parthanatos during chemotherapy. *Cell Rep Med.* 2023;4(9):101191. doi: 10.1016/j.xcrm.2023.101191.
- Mashimo M, Kato J, Moss J. ADP-ribosyl-acceptor hydrolase 3 regulates poly (ADP-ribose) degradation and cell death during oxidative stress. *Proc Natl Acad Sci U S A.* 2013;110:18964-9. doi: 10.1073/pnas.1312783110.
- McIlwain DR, Berger T, Mak TW. Caspase functions in cell death and disease. *Cold Spring Harb Perspect Biol.* 2013;5(4):a008656. doi: 10.1101/cshperspect.a008656.
- Medrano M, Contreras M, Caballero-Velázquez T, Martínez L, Bejarano-García JA, Calderón-Ruiz R, et al. Cannabinoids induce cell death in leukaemic cells through Parthanatos and PARP-related metabolic disruptions. *Brit J Cancer.* 2024;130:1529-41. doi: 10.1038/s41416-024-02618-6.
- Melcher A, Todryk S, Hardwick N, Ford M, Jacobson M, Vile RG. Tumor immunogenicity is determined by the mechanism of cell death via induction of heat shock protein expression. *Nat Med.* 1998;4:581-7. doi: 10.1038/nm0598-581.
- Messikommer A, Maru B, Seipel K, Valk PJM, Theodorides APA, Pabst T, et al. Cancer prognosis according to parthanatos features. *bioRxiv.* 2021:2021.05.24.445484. doi: 10.1101/2021.05.24.445484.
- Mirzayans R. When therapy-induced cancer cell apoptosis fuels tumor relapse. *Onco.* 2024;4(1):37-45. doi: 10.3390/onco4010003.
- Mo Y, Wang Y, Wang Y, Deng X, Yan Q, Fan C, et al. Circular RNA circPVT1 promotes nasopharyngeal carcinoma metastasis via the β -TrCP/c-Myc/SRSF1 positive feedback loop. *Mol Cancer.* 2022;21(1):192. doi: 10.1186/s12943-022-01659-w.
- Montero J, Haq R. Adapted to survive: targeting cancer cells with BH3 mimetics. *Cancer Discov.* 2022;12:1217-32. doi: 10.1158/2159-8290.cd-21-1334.
- Mujumdar N, Mackenzie TN, Dudeja V, Chugh R, Antonoff MB, Borja-Cacho D, et al. Triptolide induces cell death in pancreatic cancer cells by apoptotic and autophagic pathways. *Gastroenterology.* 2010;139:598-608. doi: 10.1053/j.gastro.2010.04.046.
- Murata MM, Kong X, Moncada E, Chen Y, Imamura H, Wang P, et al. NAD⁺ consumption by PARP1 in response to DNA damage triggers metabolic shift critical for damaged cell survival. *Mol Biol Cell.* 2019;30:2584-97. doi: 10.1091/mbc.E18-10-0650.
- Mustafa M, Ahmad R, Tantry IQ, Ahmad W, Siddiqui S, Alam M, et al. Apoptosis: a comprehensive overview of signaling pathways, morphological changes, and physiological significance and therapeutic implications. *Cells.* 2024;13(22):1838.
- Neophytou CM, Trougakos IP, Erin N, Papageorgis P. Apoptosis deregulation and the development of cancer multi-drug resistance. *Cancers (Basel).* 2021;13(17):4363. doi: 10.3390/cancers13174363.
- Nguyen TT, Wei S, Nguyen TH, Jo Y, Zhang Y, Park W, et al. Mitochondria-associated programmed cell death as a therapeutic target for age-related disease. *Exp Mol Med.* 2023;55:1595-619. doi: 10.1038/s12276-023-01046-5.
- Panaretakis T, Kepp O, Brockmeier U, Tesniere A, Bjorklund AC, Chapman DC, et al. Mechanisms of pre-apoptotic calreticulin exposure in immunogenic cell death. *Embo J.* 2009;28:578-90. doi: 10.1038/emboj.2009.1.
- Patel SA, Minn AJ. Combination cancer therapy with immune checkpoint blockade: mechanisms and strategies. *Immunity.* 2018;48:417-33. doi: 10.1016/j.immuni.2018.03.007.
- Paul S, Jakhar R, Bhardwaj M, Chauhan AK, Kang SC. Fumonisin B1 induces poly (ADP-ribose) (PAR) polymer-mediated cell death (parthanatos) in neuroblastoma. *Food Chem Toxicol.* 2021;154:112326. doi: 10.1016/j.fct.2021.112326.
- Pistrutto G, Trisciuglio D, Ceci C, Garufi A, D'Orazi G. Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. *Aging (Albany NY).* 2016;8:603-19. doi: 10.18632/aging.100934.
- Plati J, Bucur O, Khosravi-Far R. Apoptotic cell signaling in cancer progression and therapy. *Integr Biol (Camb).* 2011;3:279-96. doi: 10.1039/c0ib00144a.

- Povea-Cabello S, Oropesa-Ávila M, De la Cruz-Ojeda P, Villanueva-Paz M, De la Mata M, Suárez-Rivero JM, et al. Dynamic reorganization of the cytoskeleton during apoptosis: the two coffins hypothesis. *Int J Mol Sci.* 2017;18(11):2393.
- Qian S, Long Y, Tan G, Li X, Xiang B, Tao Y, et al. Programmed cell death: molecular mechanisms, biological functions, diseases, and therapeutic targets. *MedComm* (2020). 2024;5(12):e70024. doi: 10.1002/mco2.70024.
- Qiao X, Sun J, Ren P, Guo H, Xu H, Bao C, et al. Integrated single-cell sequencing, spatial transcriptome sequencing and bulk RNA sequencing highlights the molecular characteristics of parthanatos in gastric cancer. *Aging (Albany NY).* 2024;16:5471-500. doi: 10.18632/aging.205658.
- Redza-Dutordoir M, Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. *Biochim Biophys Acta.* 2016;1863:2977-92. doi: 10.1016/j.bbamcr.2016.09.012.
- Ribeiro DL, Tuttis K, Oliveira LCBd, Serpeloni JM, Gomes INF, Lengert AvH, et al. The antitumoral/anti-metastatic action of the flavonoid brachyidin in metastatic prostate tumor spheroids in vitro is mediated by (parthanatos) PARP-related cell death. *Pharmaceutics.* 2022;14(5):963.
- Roberts AW, Huang D. Targeting BCL2 with BH3 mimetics: basic science and clinical application of venetoclax in chronic lymphocytic leukemia and related B cell malignancies. *Clin Pharmacol Ther.* 2017;101:89-98. doi: 10.1002/cpt.553.
- Roy S, Nicholson DW. Cross-talk in cell death signaling. *J Exp Med.* 2000;192(8):F21-5.
- Scarlatti F, Maffei R, Beau I, Codogno P, Ghidoni R. Role of non-canonical Beclin 1-independent autophagy in cell death induced by resveratrol in human breast cancer cells. *Cell Death Differ.* 2008;15:1318-29. doi: 10.1038/cdd.2008.51.
- Schiefer JL, Wergen NM, Grieb G, Bagheri M, Seyhan H, Badra M, et al. Experimental evidence for Parthanatos-like mode of cell death of heat-damaged human skin fibroblasts in a cell culture-based in vitro burn model. *Burns.* 2024;50:1562-77. doi: 10.1016/j.burns.2024.03.014.
- Shimura T. Mitochondrial signaling pathways associated with DNA damage responses. *Int J Mol Sci.* 2023;24(7):6128. doi: 10.3390/ijms24076128.
- Shkarina K, Broz P. Selective induction of programmed cell death using synthetic biology tools. *Semin Cell Dev Biol.* 2024;156:74-92. doi: 10.1016/j.semcdb.2023.07.012.
- Shoshan-Barmatz V, Arif T, Shteinifer-Kuzmine A. Apoptotic proteins with non-apoptotic activity: expression and function in cancer. *Apoptosis.* 2023;28:730-53. doi: 10.1007/s10495-023-01835-3.
- Siegmund D, Mauri D, Peters N, Juo P, Thome M, Reichwein M, et al. Fas-associated death domain protein (FADD) and caspase-8 mediate up-regulation of c-Fos by Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) via a FLICE inhibitory protein (FLIP)-regulated pathway. *J Biol Chem.* 2001;276:32585-90. doi: 10.1074/jbc.M100444200.
- Singh R, Letai A, Sarosiek K. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. *Nat Rev Mol Cell Biol.* 2019;20:175-93. doi: 10.1038/s41580-018-0089-8.
- So KY, Oh SH. Arsenite-induced cytotoxicity is regulated by poly-ADP ribose polymerase 1 activation and parthanatos in p53-deficient H1299 cells: The roles of autophagy and p53. *Biochem Biophys Res Commun.* 2023;656:78-85. doi: 10.1016/j.bbrc.2023.03.018.
- Su J, Song Y, Zhu Z, Huang X, Fan J, Qiao J, et al. Cell-cell communication: new insights and clinical implications. *Signal Transduct Target Ther.* 2024;9(1):196. doi: 10.1038/s41392-024-01888-z.
- Su Z, Yang Z, Xie L, DeWitt JP, Chen Y. Cancer therapy in the necroptosis era. *Cell Death Differ.* 2016;23:748-56. doi: 10.1038/cdd.2016.8.
- Szondy Z, Sarang Z, Kiss B, Garabuczi É, Köröskényi K. Anti-inflammatory mechanisms triggered by apoptotic cells during their clearance. *Front Immunol.* 2017;8:909. doi: 10.3389/fimmu.2017.00909.
- Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. *Cell Res.* 2019;29:347-64. doi: 10.1038/s41422-019-0164-5.
- Tian X, Srinivasan PR, Tajiknia V, Sanchez Sevilla Uruchurtu AF, Seyhan AA, Carneiro BA, et al. Targeting apoptotic pathways for cancer therapy. *J Clin Invest.* 2024;134(14):e179570. doi: 10.1172/jci179570.
- Tong X, Tang R, Xiao M, Xu J, Wang W, Zhang B, et al. Targeting cell death pathways for cancer therapy: recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. *J Hematol Oncol.* 2022;15(1):174. doi: 10.1186/s13045-022-01392-3.

- Townsend PA, Kozhevnikova MV, Cexus ONF, Zamyatnin AA Jr, Soond SM. BH3-mimetics: recent developments in cancer therapy. *J Exp Clin Cancer Res.* 2021;40(1):355. doi: 10.1186/s13046-021-02157-5.
- Tufail M, Hu J-J, Liang J, He C-Y, Wan W-D, Huang Y-Q, et al. Hallmarks of cancer resistance. *iScience.* 2024;27(6):109979. doi: 10.1016/j.isci.2024.109979.
- Vinay DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol.* 2015;35:S185-98. doi: 10.1016/j.semcancer.2015.03.004.
- Vitale I, Pietrocola F, Guilbaud E, Aaronson SA, Abrams JM, Adam D, et al. Apoptotic cell death in disease—Current understanding of the NCCD 2023. *Cell Death Differ.* 2023;30:1097-154. doi: 10.1038/s41418-023-01153-w.
- Vucic D, Fairbrother WJ. The inhibitor of apoptosis proteins as therapeutic targets in cancer. *Clin Cancer Res.* 2007;13:5995-6000. doi: 10.1158/1078-0432.ccr-07-0729.
- Wang C, Tan JYM, Chitkara N, Bhatt S. TP53 mutation-mediated immune evasion in cancer: mechanisms and therapeutic implications. *Cancers (Basel).* 2024a;16(17):3069. doi: 10.3390/cancers16173069.
- Wang H, Liu M, Zeng X, Zheng Y, Wang Y, Zhou Y. Cell death affecting the progression of gastric cancer. *Cell Death Discov.* 2022;8(1):377. doi: 10.1038/s41420-022-01161-8.
- Wang K, Zhang C, Bao J, Jia X, Liang Y, Wang X, et al. Synergistic chemopreventive effects of curcumin and berberine on human breast cancer cells through induction of apoptosis and autophagic cell death. *Sci Rep.* 2016;6:26064. doi: 10.1038/srep26064.
- Wang S, Li B, Cai Z, Hugo C, Li J, Sun Y, et al. Cellular senescence induced by cholesterol accumulation is mediated by lysosomal ABCA1 in APOE4 and AD. *Res Sq [Preprint].* 2024b May 14:rs.3.rs-4373201. doi: 10.21203/rs.3.rs-4373201/v1. Update in: *Mol Neurodegener.* 2025;20(1):15. doi: 10.1186/s13024-025-00802-7.
- Wang X, Ge P. Parthanatos in the pathogenesis of nervous system diseases. *Neuroscience.* 2020;449:241-50. doi: 10.1016/j.neuroscience.2020.09.049.
- Wang XZ, Liang SP, Chen X, Wang ZC, Li C, Feng CS, et al. TAX1BP1 contributes to deoxypodophyllotoxin-induced glioma cell parthanatos via inducing nuclear translocation of AIF by activation of mitochondrial respiratory chain complex I. *Acta Pharmacol Sin.* 2023;44:1906-19. doi: 10.1038/s41401-023-01091-w.
- Wang Y, Dawson VL, Dawson TM. Poly(ADP-ribose) signals to mitochondrial AIF: a key event in parthanatos. *Exp Neurol.* 2009a;218:193-202. doi: 10.1016/j.expneurol.2009.03.020.
- Wang Y, Kim NS, Li X, Greer PA, Koehler RC, Dawson VL, et al. Calpain activation is not required for AIF translocation in PARP-1-dependent cell death (parthanatos). *J Neurochem.* 2009b;110:687-96. doi: 10.1111/j.1471-4159.2009.06167.x.
- Wang Y, Kim NS, Haince JF, Kang HC, David KK, Andrabi SA, et al. Poly(ADP-ribose) (PAR) binding to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos). *Sci Signal.* 2011;4(167):ra20. doi: 10.1126/scisignal.2000902.
- Wen W, Jin K, Che Y, Du LY, Wang LN. Arnicolide D inhibits oxidative stress-induced breast cancer cell growth and invasion through apoptosis, ferroptosis, and parthanatos. *Anticancer Agents Med Chem.* 2024;24:836-44. doi: 10.2174/1871520623666221208102021.
- Wong RS. Apoptosis in cancer: from pathogenesis to treatment. *J Exp Clin Cancer Res.* 2011;30(1):87. doi: 10.1186/1756-9966-30-87.
- Wu H, Tschopp J, Lin SC. Smac mimetics and TNF α : a dangerous liaison? *Cell.* 2007;131:655-8. doi: 10.1016/j.cell.2007.10.042.
- Wu H, Li Y, Zhang Q, Wang H, Xiu W, Xu P, et al. Crocetin antagonizes parthanatos in ischemic stroke via inhibiting NOX2 and preserving mitochondrial hexokinase-I. *Cell Death Dis.* 2023a;14(1):50. doi: 10.1038/s41419-023-05581-x.
- Wu Q, Deng J, Fan D, Duan Z, Zhu C, Fu R, et al. Ginsenoside Rh4 induces apoptosis and autophagic cell death through activation of the ROS/JNK/p53 pathway in colorectal cancer cells. *Biochem Pharmacol.* 2018;148:64-74. doi: 10.1016/j.bcp.2017.12.004.
- Wu Y, Song Y, Wang R, Wang T. Molecular mechanisms of tumor resistance to radiotherapy. *Molecular Cancer.* 2023b;22(1):96. doi: 10.1186/s12943-023-01801-2.

- Wu Z, Cui P, Tao H, Zhang S, Ma J, Liu Z, et al. The synergistic effect of PARP inhibitors and immune checkpoint inhibitors. *Clin Med Insights Oncol.* 2021; 15:1179554921996288. doi: 10.1177/1179554921996288.
- Xavier CP, Lima CF, Pedro DF, Wilson JM, Kristiansen K, Pereira-Wilson C. Ursolic acid induces cell death and modulates autophagy through JNK pathway in apoptosis-resistant colorectal cancer cells. *J Nutr Biochem.* 2013;24:706-12. doi: 10.1016/j.jnutbio.2012.04.004.
- Xiao Y, Ji L, Xu Z, Sun Y. Predicting prognosis and drug sensitivity of ovarian cancer patients using different programmed cell death patterns. *Research Square*, 06 Mar 2023, preprint. doi: 10.21203/rs.3.rs-2586903/v1
- Xu G, Shi Y. Apoptosis signaling pathways and lymphocyte homeostasis. *Cell Res.* 2007;17:759-71. doi: 10.1038/cr.2007.52.
- Xu L, Ma S, Qu M, Li N, Sun X, Wang T, et al. Parthanatos initiated by ROS-induced DNA damage is involved in intestinal epithelial injury during necrotizing enterocolitis. *Cell Death Discov.* 2024;10 (1):345. doi: 10.1038/s41420-024-02114-z.
- Xu X, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Biosci Rep.* 2019;39(1):BSR20180992. doi: 10.1042/bsr20180992.
- Xu X, Sun B, Zhao C. Poly (ADP-Ribose) polymerase 1 and parthanatos in neurological diseases: From pathogenesis to therapeutic opportunities. *Neurobiol Dis.* 2023;187:106314. doi: 10.1016/j.nbd.2023.106314.
- Xue Q, Liu X, Chen C, Zhang X, Xie P, Liu Y, et al. Erlotinib protects against LPS-induced parthanatos through inhibiting macrophage surface TLR4 expression. *Cell Death Discov.* 2021;7(1):181. doi: 10.1038/s41420-021-00571-4.
- Yan G, Elbadawi M, Efferth T. Multiple cell death modalities and their key features (Review). *World Acad Sci J.* 2020;2(2):39-48. doi: 10.3892/wasj.2020.40.
- Yang L, Guttman L, Dawson VL, Dawson TM. Parthanatos: Mechanisms, modulation, and therapeutic prospects in neurodegenerative disease and stroke. *Biochem Pharmacol.* 2024;228:116174. doi: 10.1016/j.bcp.2024.116174.
- Yu W, Tu Y, Long Z, Liu J, Kong D, Peng J, et al. Reactive oxygen species bridge the gap between chronic inflammation and tumor development. *Oxid Med Cell Longev.* 2022;2022(1):2606928. doi: 10.1155/2022/2606928.
- Yuan X, Gajan A, Chu Q, Xiong H, Wu K, Wu GS. Developing TRAIL/TRAIL death receptor-based cancer therapies. *Cancer Metastasis Rev.* 2018;37:733-48. doi: 10.1007/s10555-018-9728-y.
- Zhang J, Hu X, Geng Y, Xiang L, Wu Y, Li Y, et al. Exploring the role of parthanatos in CNS injury: Molecular insights and therapeutic approaches. *J Adv Res.* 2024a; epub ahead of print. doi: 10.1016/j.jare.2024.04.031.
- Zhang L, Zhang W, Wang YF, Liu B, Zhang WF, Zhao YF, et al. Dual induction of apoptotic and autophagic cell death by targeting survivin in head neck squamous cell carcinoma. *Cell Death Dis.* 2015;6(5):e1771. doi: 10.1038/cddis.2015.139.
- Zhang W, Sun H, Zhao W, Li J, Meng H. Suppression of JNK pathway protects neurons from oxidative injury via attenuating parthanatos in glutamate-treated HT22 neurons. *Sci Rep.* 2024b;14(1):25793. doi: 10.1038/s41598-024-76640-2.
- Zhang Y, Zhang C, Li J, Jiang M, Guo S, Yang G, et al. Inhibition of AKT induces p53/SIRT6/PARP1-dependent parthanatos to suppress tumor growth. *Cell Commun Signal.* 2022;20(1):93. doi: 10.1186/s12964-022-00897-1.
- Zhao N, Mao Y, Han G, Ju Q, Zhou L, Liu F, et al. YM155, a survivin suppressant, triggers PARP-dependent cell death (parthanatos) and inhibits esophageal squamous-cell carcinoma xenografts in mice. *Oncotarget.* 2015;6:18445-59. doi: 10.18632/oncotarget.4315.
- Zheng L, Wang C, Luo T, Lu B, Ma H, Zhou Z, et al. JNK activation contributes to oxidative stress-induced parthanatos in glioma cells via increase of intracellular ROS production. *Mol Neurobiol.* 2017;54:3492-505. doi: 10.1007/s12035-016-9926-y.
- Zhong B, Liu M, Bai C, Ruan Y, Wang Y, Qiu L, et al. Caspase-8 induces lysosome-associated cell death in cancer cells. *Mol Ther.* 2020;28:1078-91. doi: 10.1016/j.ymthe.2020.01.022.
- Zhou M, Boulos JC, Klauck SM, Efferth T. The cardiac glycoside ZINC253504760 induces parthanatos-type cell death and G2/M arrest via downregulation of MEK1/2 phosphorylation in leukemia cells. *Cell Biol Toxicol.* 2023a;39:2971-97. doi: 10.1007/s10565-023-09813-w.

Zhou M, Boulos JC, Omer EA, Rudbari HA, Schirmeister T, Micale N, et al. Two palladium (II) complexes derived from halogen-substituted Schiff bases and 2-picolyamine induce parthanatos-type cell death in sensitive and multi-drug resistant CCRF-CEM leukemia cells. *Eur J Pharmacol.* 2023b;956:175980. doi: 10.1016/j.ejphar.2023.175980.

Zhou Y, Liu L, Tao S, Yao Y, Wang Y, Wei Q, et al. Parthanatos and its associated components: Promising therapeutic targets for cancer. *Pharmacol Res.* 2021; 163:105299. doi: 10.1016/j.phrs.2020.105299.

Zhu L, Xie Z, Yang G, Zhou G, Li L, Zhang S. Stanniocalcin-1 promotes PARP1-dependent cell death via JNK activation in colitis. *Adv Sci (Weinh).* 2024;11 (5):e2304123. doi: 10.1002/advs.202304123.