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Apoptosis as the Primary Elimination Mechanism for Cancer Cells: Mechanisms, Evidence, and Therapeutic Implications

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Abstract. Apoptosis constitutes the principal mechanism controlling the elimination of cancer cells. Apoptosis arises as a fundamental capability of multicellular organisms regulating cell number and maintaining homeostasis. It is the best-studied form of programmed cell death and broadly participates in multiple physiological processes embryogenesis, tissue remodeling, and immune cell maturation, among others. According to accumulated evidence, apoptosis acts as a potent tumor-suppressor mechanism curtailing cancer cell expansion. Cancer cells are subjected to multiple biological insults continuously exerted by their micro- and macro-environment and, when left unresolved, such detrimental events drive cells toward a neoplastic transformation. Cancer cells often acquire opposing alterations that foster adaptation to these events, evade replication barriers, and expand into tumors. Recent studies have argued that when cancer clones develop resistance, pro-apoptotic signals become a prominent component of antagonistic programs, reinforcing the notion that a majority of cancer clones are still susceptible to apoptotic removal during tumor establishment.
At least three forms of terminal cancer-cell elimination have been identified: apoptosis, senescence, and necrosis. Apoptosis distinctively leads to the generation of an immunogenic signal that facilitates the elimination of cancer-cell clones even from resistant tumors. Available genetic, molecular, and pharmacological evidence supports the notion that apoptosis operates as a major mode for the elimination of cancer cells during malignant transformation. Importantly, a wide variety of therapeutic modalities induce death predominantly through apoptosis. Because apoptosis appears to still remain a critical backup option during cancer prevention, continued further investigation into the mechanisms of apoptosis and the establishment of new therapeutics for its induction holds considerable promise for improving cancer treatment.
A multitude of stresses imparted by tumor microenvironments destabilizes normal tissues and triggers apoptosis. Treatments that cause further stresses, including DNA lesions, directly promote massive apoptosis, underscoring the still-latent vulnerability of cancer cells. Collectively, compounds that elicit extensive, unmanageable apoptosis in cancer cells, either through direct activation or relay of biochemical signals, can become new agents or be combined with existing ones for more effective therapy

1. Introduction

Apoptosis is widely recognized as a central elimination mechanism for cancer cells. Most anti-cancer treatments induce cancer cell death, primarily because damage inflicted on malignant cells activates apoptotic pathways, which are often dysregulated in tumors. Thus, fading of these damage signals or the acquisition of pro-survival mutations allows tumor cells to escape the primary elimination mechanism that therapies are designed to engage. This pivotal role of apoptosis in tumor eradication arguably positions it among the most important hallmarks of cancer, especially when discussing therapeutic options. This work compiles the existing evidence that links apoptotic execution to the clearance of tumor cells and considers the implications for the development of therapeutics that target these pathways toward the elimination of cancer (Morana *et al*., 2022). There are some types of cancer that result from chromosomal aberration, and apoptosis plays a major role in their treatment (Al-Samarraie, 2026).

Methods have been developed to induce apoptosis in cancer cells, aiming to restore pathway engagement and tumor-cell elimination. These methods are classified as pro-apoptotic agents and BH3 mimetics. Pro-apoptotic agents activate the apoptotic machinery by targeting specific players at various stages of the core pathway. The rapidly evolving landscape of BH3 mimetics directly targets pro-survival proteins of the BCL-2 family, freeing pro-apoptotic proteins from tight control and unleashing apoptosis upon cells still possessing functional executioners. Both classes have potential for improved cancer therapy, yet ensuring selective action on tumor cells remains critical to safe application (Franzese *et al*., 2024).

Apoptosis is a well-defined form of programmed cell death involving a highly regulated series of biochemical events leading to the characteristic morphological and molecular features of cellular disassembly. Apoptosis is triggered by a variety of stimuli, including developmental signals or pathogen-derived signals, and plays a crucial role in normal biological processes such as embryogenesis, tissue homeostasis, the immune response, and the response to injury (Morana *et al*., 2022). Apoptosis also acts as a key tumor-suppressive mechanism, faithfully executing developmental and homeostatic cell-death programs. Cellular transformation typically involves alterations in apoptosis control—such as the emergence of oncogenic signalling or the disruption of p53 activity—that promote cell cycle entry, progenitor-like cell states, and resistance to stress (Lim et al., 2019).

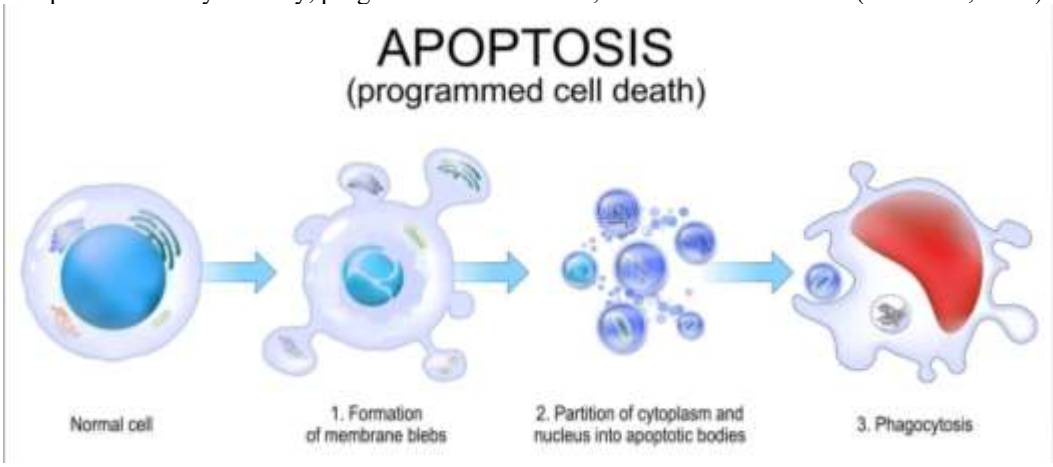

Figure (1) *Stages of Apoptosis*

2. Historical Perspective on Apoptosis in Cancer

Cell death has been an object of biological curiosity since the 1850s, when histologists began documenting the microanatomical pathways leading to the demise of individual cells in cultured tissues (Jacobson *et al*., 1997). Initial concepts of cell death were simplistic on both mechanistic and teleological levels, but advances in light microscopy and biochemistry in the 1960s prompted speculation that physiological apoptosis had evolved to facilitate selective removal of cells during development and tissue homeostasis (Boehm & Bock, 2019). Following these developments, British zoologist Sir Victor Charles Tcharles Huxley undertook pioneering, sophisticated, and painstaking studies on avian red blood cell development in the 1920s—able to distinguish and name "decidual corpuscles" of abortive red blood cells (Huxley, 1922). The discovery that excessive Huxley pathology also accompanied oncogenesis came only later (Huxley, 1949).

Apoptosis (programmed cell death) acts as a primary mechanism responsible for initiating cancer cells; it occurs in physiologically discrete stages, in both intrinsically (mitochondrially) and extrinsically (death receptor-initiated) activated forms. Current evidence substantiates the crucial function of apoptotic clearance in cancer cell initiation, instructing robust therapeutic approaches aimed at reinstating apoptosis to address the pervasive resistance to this death program within tumors. Cancer is a leading global cause of morbidity and mortality, necessitating urgent efforts to prevent and treat rampant tumor proliferation. Although exciting new therapies are emerging to tackle this reflex, observing cancer cell alterations in response to such approaches remains a fundamental challenge. Insights derived from these considerations may inform the ongoing development of more robust and transformative therapies, enabling tumors to be thwarted and precociously eradicated (Hajdu, 2011).

3. Core Mechanisms of Apoptosis

Apoptosis is a tightly regulated, conserved process that removes unwanted or damaged cells without provoking an inflammatory response. The fundamental importance of apoptosis is evident in multicellular organisms: such sensitivity to apoptotic cues renders cells highly vulnerable to therapies. A wealth of studies has illuminated apoptosis' central role in cancers arising in response to DNA damage and oncogenic signaling. In particular, both intrinsic and extrinsic apoptotic pathways can be activated during treatment, yet acquired resistance to these pathways has evolved as a major challenge in the search for effective cancer therapies (Morana *et al*., 2022).

Elimination of unwanted cells occurs via two antagonistic cell-death mechanisms: necrosis and apoptosis. Necrosis leads to cellular swelling or lysis and initiates inflammation, while apoptosis is characterized by cellular shrinking and the preservation of membrane integrity without inflammatory damage. These distinct characteristics secure the existence of the apoptotic mechanism in multicellular organisms, and substantial evidence supports its role in removing unwanted cancer cells. Whereas these three sections outline the general mechanisms for apoptosis, extensive mechanisms concerning necrosis remain to be elucidated (Sazonova *et al*., 2021).

Mammalian apoptosis is divided into three functional stages: initiation, execution, and removal. The initial stage distinguishes between two distinct pathways, termed intrinsic (mitochondrial) and extrinsic (death receptor), which are defined by non-overlapping upstream signals. The second phase generally employs cysteinyl proteases (caspases) as the primary hydrolyzing enzymes. The critical differences in the upstream signalling mechanisms determine how agonistic and antagonistic signals regulate apoptosis. The final stage facilitates the clearance of apoptotic cells by neighbouring or professional phagocytes (Morana *et al*., 2022).

3.1. Intrinsic (mitochondrial) pathway

The mitochondrial or intrinsic pathway of apoptosis is initiated by signals generated within stressed or damaged cells that lead to mitochondrial outer membrane permeabilization (MOMP). First, pro-apoptotic BH3-only proteins such as BIM, BID, and PUMA concentrate at the mitochondria, where they activate the pore-forming BCL-2 proteins BAX and BAK, leading to MOMP. Subsequently, apoptogenic factors from the intermembrane space, including cytochrome c, SMAC, and Omi, are released into the cytosol. Cytochrome c promotes apoptosis by binding to apoptotic protease-activating factor 1 (APAF-1) to form the apoptosome, which recruits pro-caspase-9 and activates the caspase cascade (Lopez & Tait, 2015). Other pro-apoptotic proteins, such as apoptosis-inducing factor (AIF), macroautophagy-related protein 2 (MAP-LC3), and arginase-1 (ARG-1) orchestrate the clearance of the dying cell. At both the cell and organismal level, apoptosis is resolved through coordinated removal of the dying cells (Wani *et al*., 2023).

3.2. Extrinsic (death receptor) pathway

The extrinsic or death receptor pathway of apoptosis occurs through ligation of death receptors on the cell's surface, which are members of the TNF superfamily, such as TNF-α/TNFR1 and FasL/FasR. Upon ligand binding, FADD forms a complex with caspase-8, creating the death-inducing signaling complex (DISC). Caspase-8 acts as the initiator caspase, cleaving effector caspases-3 and -7, which cause apoptosis typically through activation of the endonuclease CAD. Caspase-8 also functions as a molecular switch regulating apoptosis, necroptosis, and pyroptosis. Effector caspases induce chromatin condensation and cell death by cleaving various substrates, with ICAD being integral to chromatin condensation (Devoe, 2020).

The extrinsic pathway of apoptosis involves two models: the TNF-induced model and the Fas-Fas ligand-mediated model. TNF-α, produced by macrophages, is a key extrinsic apoptotic mediator. Human cells have TNFR-1 and TNFR-2; binding of TNF-α to TNFR-1 initiates a pathway leading to caspase activation. The TNFR1-associated death domain protein (TRADD) and FAS-associated death domain protein (FADD) can bind to TRAF-2, inhibiting caspase-8 activation, which may activate inflammatory and survival pathways. The first apoptosis signal, Fas (CD95 or APO-1), binds to Fas ligand, forming the DISC complex with caspase-8, caspase-10, and FADD. In type I cells, caspase-8 directly activates other caspases to execute apoptosis. In type II cells, Fas-DISC triggers mitochondrial release of pro-apoptotic factors, amplifying caspase activation (Wani *et al*., 2023).

3.3 Execution phase and caspases

The central caspases 3, 6, and 7 act as downstream executioners that mediate the final destruction of a wide variety of cellular structures and processes common to virtually all apoptotic stimuli and pathways. Evidence indicates that activation of these effector caspases marks the point of no return for cells communicating an apoptotic signal. Once active, these effectors invariably lead cells to the distinctive morphologic and biochemical endpoints of apoptosis, with a considerable degree of conservation across different species (Boland *et al*., 2013; Eskandari & J. Eaves, 2022).

4. Regulation of Apoptosis in Cancer

Cancer cells acquire several traits during their evolution, facilitating unrestricted proliferation, metabolic changes, and immune evasion. They also engage in mechanisms to evade the intrinsic and extrinsic signals that drive apoptosis, promoting tumor initiation and malignant transformation. Tumor cells often modify oncogene and tumor suppressor signaling; for example, the inactivation of p53, a critical regulator of apoptotic cell death, commonly occurs during the emergence of tumorigenesis (Morana *et al*., 2022). Even if p53 escapes inactivation and remains functional, the upregulation of anti-apoptotic mechanisms can still confer resistance to apoptotic signals. Cancer cells also reprogram the mitochondrial response of the intrinsic pathway, manipulating BCL-2 family proteins that govern mitochondrial priming and the progression of apoptosis (Wani *et al*., 2023).

Apoptosis is the target of multiple alterations favouring tumor progression. The BCL-2 family emerges as one of the main regulators of apoptosis. BCL-2, which restrains apoptosis, is overexpressed in many human cancers. The p53 gene, mutated in the majority of human tumors, regulates pro-apoptotic and anti-apoptotic factors, whereas the FAS-associated death domain protein (FADD), a central mediator of the extrinsic death receptor pathway, is downregulated in several cancer types. Survivin is ubiquitously expressed in human cancers and inhibits apoptosis by interfering with caspase activation and regulating cell division. In cancer, the signalling networks controlling pro-apoptotic and anti-apoptotic factors become rewired, shifting the balance towards pro-survival. This enables tumor cells to resist drugs that induce apoptosis and thus cooperates with other strategies to evade therapy (Jan & Chaudhry, 2019; Morana *et al*., 2022; Franzese *et al*., 2024).

4.1. Oncogenic shifts and p53 status

Only a single oncogenic shift has been shown to induce tumors. The p53 transcription factor plays a crucial role in guarding against cancer by regulating the expression of pro-apoptotic genes, and its loss of function or null mutation is often characteristic of aggressive and difficult-to-treat tumors. Active repression of the p53 transcript or of the signaling pathway by oncogenes has been reported (Mirzayans *et al*., 2012).

4.2. BCL-2 family proteins and mitochondrial priming

In the BCL-2 protein family, anti-apoptotic members inhibit the pro-apoptotic effect of multi-domain and BH3-only proteins. Even in the presence of pro-apoptotic signals, these proteins maintain mitochondrial integrity and inhibit permeabilization of the outer mitochondrial membrane (OMM). Cells reside at varying degrees of mitochondrial priming, defined by the relative expression of pro- and anti-apoptotic BCL-2 family members and the environment determined by upstream signaling to pro-apoptotic effectors. Compounds targeting the anti-apoptotic BCL-2 family have demonstrated selectivity for cancerous tissues, therapeutic enhancement when combined with classical chemotherapeutics, and the ability to overcome acquired resistance—opening a promising avenue for the development of anti-cancer treatments. Potent and selective inhibitors of individual BCL-2 family members have also been developed and shown to target various tumor types. These properties suggest that the compounds could have major implications for a wide array of malignancies, including hematological malignancies and solid tumor types, in both the preclinical and clinical stages (Campbell & Tait, 2018).

Among various therapeutic strategies, agents mobilizing the Intrinsic apoptosis pathway have been extensively studied, including the use of pro-apoptotic N19 and N4 peptides, which disrupt BCL-2:BAX and BCL-2:BAK complexes respectively. BH3 mimetics such as ABT-737, ABT-263 (Navitoclax), and Wehi-539, which selectively inhibit BCL-2 and BCL-XL, have also been explored as single agents in preclinical and clinical studies targeting a variety of hematological malignancies and solid tumors. Although initial results have been promising,

many tumors ultimately develop resistance, and preclinical models have revealed a range of intrinsic and acquired resistance mechanisms (Jan & Chaudhry, 2019).

4.3. Death receptors and extrinsic signal modulation

According to a widely accepted conceptual framework, a cancer cell is considered eliminated when its death, independent of neighboring cells, leads to a significant reduction in tumor burden. Consequently, cancer cells remain capable of proliferating, especially in the initial phases of tumor formation (Papenfuss *et al*., 2008).
Many studies have indicated that the execution stage of the apoptotic process, evidenced by features such as chromatin condensation, cell shrinkage, plasma membrane blebbing, and the exposure of phosphatidylserine residues, leads to the extinction of at least 60% of treated tumor cells. This decisive loss of cellularity contrasts with necroptosis or autophagy, two other mechanisms known to promote tumor suppression. Removal can occur in either lymphoid or nonlymphoid tissues, and substantial tumor regressions have been observed across numerous genetically diverse models, including solid malignancies like lymphomas, leukemias, gliomas, tumors driven by Ras mutations, and Ewing sarcomas characterized by an aberrant EWS–FLI fusion (Jan & Chaudhry, 2019).

Apoptosis may be directly engaged following treatment with cisplatin, etoposide, or various conventional anticancer agents. Such foundational insights into the stringent connection between an apoptotic fate and robust tumor clearance support the notion of apoptosis as the preeminent mechanism for cancer cell elimination (Mirzayans & Murray, 2024).

5. Evidence Linking Apoptosis to Cancer Cell Elimination

The anticancer activity of many therapeutics depends on their capacity to trigger cancer cell apoptosis. Numerous drugs and targeted therapies routinely used to treat various cancers are known to induce apoptotic cell death in tumor cells. For example, γ-irradiation causing DNA double-strand breaks and chemotherapeutic agents such as cisplatin, which form bulky DNA adducts and induce DNA crosslinking, readily activate apoptosis-inducing pathways in tumors (Sazonova *et al*., 2021). Further, when examined in living organisms, treatment regimens that induce the greatest levels of apoptosis often lead to the most bountiful and prolonged tumor regressions. Finally, detailed analyses of the importance of p53, a key tumor suppressor commonly lost during tumor development, have shown that p53-dependent apoptotic signaling plays a prominent role—often the predominant role—in the clearance of tumors in response to a wide range of different therapeutic agents (Morana *et al*., 2022).

Collectively, these observations suggest that, when the capacity to trigger apoptosis is added into the equation, the connection between tumor elimination and cancer cell apoptosis becomes considerably more interconnected than was previously assumed. Thus, a clearer and more compelling case can be made that cancer cell eradication emerges as one of the principal functions fulfilled during p53-dependent tumor suppression, indicating that restoring active p53 signaling in late-stage malignancies still leaves considerable preserved functionality towards cellular clearance (Chen *et al*., 2026).

5.1. In vivo models demonstrating apoptotic clearance of tumors

The association of apoptosis with cancer cell elimination is supported by multiple in vivo model systems demonstrating tumor clearance following apoptotic induction. Various experimental manipulations, including transgenic overexpression of pro-apoptotic regulators, treatment with pro-apoptotic agents, and genetic deletion of anti-apoptotic factors, have been employed to precipitate apoptosis in solid tumors of different origin. Collectively, the data show that apoptosis can mediate substantial tumor reduction across several cancer types and suggest patterns of viral, genotoxic, or metabolic stress that drive apoptotic signaling from a previously ideal state (Schirrmacher, 2019).

Tumor clearance and simultaneous reduction in proliferative marker expression or specific tumor burden measurement are frequently reported endpoints across different animal studies employing distinct transgenic models, xenografts, and drug administration strategies. Tumor volumes are typically determined by caliper measurement of external tumor diameter, with the final volume derived from $(4/3)\pi$ (D1/2) (D2/2) for ellipsoid tumor shape approximation. The time elapsed between induction of committed apoptosis and ablation of the terminally injured tumor cell population varies across settings but generally ranges from days to weeks. In terms of translational relevance, either the MCF7 or 4T1 triple-negative mammary tumor cell types or other models

could be adopted for extensive murine screening of the broad class of BH3 mimetic or other apoptosis-inducing agents (Franzese *et al*., 2024).

5.2. Clinical observations correlating apoptotic markers with outcomes

Studies of various preclinical models show that clearance of the majority of tumors in vivo correlates with apoptotic indicator expression in cancer cells. In p53-deficient models of B-cell lymphoma, tumor eradication is triggered by p53 restoration or c-Myc deletion; clearance occurs through rapid induction of apoptosis in most cancer cells, while a few resist and survive (Morana *et al*., 2022). When MDM2 is inhibited, MYC-activated B-cell tumors regress and most cells undergo apoptosis solely via p53; the majority of tumors are again eliminated from the host. In MYC-driven adult T-cell leukemia, malignant cells undergo massive apoptosis with rapid clearance and tumor-free survival when MDM2 is deleted, confirming that extensive apoptosis coupled with clearance universally marks this model. For several lymphomas and epithelial tumors, apoptosis induction through different signaling modes consistently leads to wide-scale clearance without any other manipulation (O'Donovan *et al*. 2004).

5.3. Resistance mechanisms and therapeutic escape

In most cases, cancer therapies are designed to induce apoptosis in cancer cells. However, many cancer cells, particularly cancer stem cells (CSCs), develop resistance mechanisms that block this process and increase the formation of aggressive metastatic tumors. Cancer cells can evade apoptosis through diverse genetic and epigenetic mechanisms, including increased expression of anti-apoptotic proteins and mutations in pro-apoptotic factors. For instance, upregulation of survivin, a member of the inhibitor of apoptosis (IAP) protein family, occurs in many malignancies and facilitates resistance to apoptosis triggered by diverse chemotherapeutic agents and radiotherapy (Safa, 2022). CSCs arise during tumor development and treatment and are associated with poor prognosis. They frequently acquire resistance to apoptosis and anticancer agents, further promoting tumor relapse and progression. Blocking the expression of the pro-apoptotic gene, Bax, prevents cancer cells from undergoing apoptosis. Mutations that impair the function of the tumor-suppressor genes, p53 and PTEN, are also involved in CSC biology. Downregulation of FAS and FAS-L signaling pathways occurs in multiple malignancies and promotes therapeutic escape from FAS-mediated apoptosis (Franzese *et al*., 2024). Suppression of FADD expression also assists cancer cells in avoiding apoptosis, whereas delivery of the FADD protein restores the apoptotic signal. Inhibition of other principal apoptotic genes hinders the execution of the signaling cascade. Overactivity of the onco-protein, MYC, leads to the downregulation of the miR-15/16 family, which targets BCL-2, IAP-2, and Cyclin D. Diminished levels of these targets further enhance resistance to apoptosis. Anti-apoptotic proteins such as BCL-2, MCL-1, and BCL-xL are often overexpressed in CSCs. Moreover, the phosphatidylinositol-3-kinase (PI3K) pathway, which is frequently hyperactivated in CSCs, induces resistance towards apoptosis through the down-regulation of pro-apoptotic members of the BCL2 family or upregulation of the anti-apoptotic member, BCL-XL. Depending on cell context and context, the extrinsic death receptor pathway can also be executed or inhibited. Activation of this pathway by extracellular signals can contribute to tumor initiation, maintenance, and relapse (Fulda, 2010).

Upregulation of hypoxia-inducible factors (HIF-1/2) and the levels of cytosolic IK-1– and ER–associated IRE-1α critically involved in the hypoxia, oncogenic RAS, or endoplasmic reticulum (ER) stress-responses, are also major orchestrators of both stemness maintenance and survival upon therapy. Pharmacological inhibitors of either HIF or IRE-1α render resistant cells sensitive to therapies and devoid of stemness features. Numerous other genes affect the formation and activity of CSCs (Zheng & Wang, 2025).

6. Therapeutic Strategies Targeting Apoptosis

Promoting apoptosis in cancer cells is a viable approach for boosting anticancer therapeutic strategies. Resistance to apoptosis is a hallmark of cancer and often occurs due to oncogenic activation of key components in the apoptotic suppression machinery. For example, oncogenic mutations in RAS, RAF, MYC, and the cell cycle regulator, RB, as well as loss-of-function mutations in TP53, are frequently observed. These mutations impose a greater reliance on pro-survival BCL-2 family proteins, leading to the emergence of distinct apoptotic signatures in different tumor types (Lim *et al*., 2019). More than 70% of tumors exhibit aberrant oncogenic signaling that independently regulates the BH3-only proteins BIM and PUMA, thereby facilitating the development of therapies that selectively target tumor cells by targeting the expression of these essential mediators of apoptosis. Synthetic

lethality strategies aimed at re-engaging suppressed apoptosis after targeted inhibition of early growth control oncogenes are also of considerable interest (Montero & Haq, 2022). Hope exists that combination therapies targeting tumor-specific apoptotic vulnerabilities discovered at the pre-clinical stage will soon allow further clinical testing in humans (Franzese *et al*., 2024).

Apoptotic cell death is tightly regulated by signaling systems that integrate pro-apoptotic and anti-apoptotic cues during normal physiology. In healthy cells, factors promoting survival are favored over those inducing apoptosis due to stressful conditions. In cancer cells, growth factors or similar cues are preferentially integrated to maintain malignant behaviour and oppose apoptotic cues. Thus, cancer cells often develop mutations that promote the pro-survival programme, leading to treatment resistance and facilitating adaptation to other hostile cues, such as the hypoxia encountered in detached tumors (Lim *et al*., 2019).

6.1. Pro-apoptotic agents and BH3 mimetics

Pharmacological agents that promote the intrinsic apoptotic pathway are currently being pursued as anticancer strategies. Several classes of such agents have been identified, including small-molecule agonists of the pro-apoptotic BCL-2 family of proteins (often referred to as "BH3 mimetics"). These agonists bind selectively to the hydrophobic cleft of BCL-2, BCL-XL, BFL-1, or MCL-1 proteins, thereby preventing them from sequestering their cognate BAx and bAk activator functions. This mechanism of action has been exploited in the preclinical and clinical development of a number of potent and selective BCL-2 family antagonists (Koss *et al*., 2016). Preclinical studies have demonstrated that these compounds can elicit a robust apoptotic response in a variety of cancer models and have greater efficacy in cancer cell lines than in normal cells. However, the excessive activity of these agents may lead to profound peripheral toxicities in the clinic (Lee & Fairlie, 2021) a limitation that can often be circumvented by combining them with other agents that activate "indirect" upstream signals that converge on activation of BAX and BAK. In these combined treatments, the BH3 mimetic is still required for optimal efficacy in broad-spectrum mixtures of encoding proteins. These results also demonstrate that, despite this convergence, signalling pathways normally regulated by BCL-2 family members are nevertheless disrupted (Koss *et al*., 2016).

6.2. Reinstatement of p53 signaling

Targeting p53, a potent tumor suppressor gene, presents a compelling strategy for restoring apoptosis. Loss-of-function mutations in the p53 gene occur in the majority of human cancers, illustrating the oncogenic potential of this tumor suppressor alongside RB and PTEN. Re-establishing the p53 signaling network at any point within the signal-processing hierarchy has been shown to elicit an apoptotic response in cell models devoid of functional p53 (Mirzayans *et al*., 2012). Other studies have highlighted the role of p53 in enabling and executing apoptosis during the formation of genotoxic stress, such as events associated with DNA-damage. Furthermore, a one-two hit regimen has identified apoptosis as a key mechanism in p53-driven clearance of Mas, MDM2, RAS, and E2F. Together, these findings suggest that reinstating p53 signaling in malignant cancer cells invokes a p53-centric switch and promotes cell death through the intrinsic apoptotic pathway (Feldser & Evan, 2008).

6.3. Enhancement of death receptor pathways

Apoptosis offers a means to safely eliminate unwanted cells in multicellular organisms. In mammals, cells subjected to developmental signals or damage, such as DNA breaks, misfolded proteins or oncogene activation, are eliminated through apoptosis. Two pathways have been identified for executing apoptosis: both converge on a caspase cascade, but different upstream signalling networks operate those pathways: the intrinsic pathway mediated mainly by BCL-2 proteins and the extrinsic pathway mediated by death receptors (Papenfuss *et al*., 2008).

Death receptors are members of the tumor necrosis factor (TNF) receptor superfamily. Those that have been extensively studied in the context of cancer therapy are TNF-related apoptosis-inducing ligand (TRAIL) receptor 1 (TRAIL-R1), TRAIL-R2, CD95 (Fas), and TNF receptor 1 (TNF-R1). Various human tumors exhibit resistance to apoptosis, precluding the use of currently available anticancer therapeutic agents. In many instances, the resistance is attributable to mutations of tumor suppressor genes, the most prominent of which is p53. However, the emergence of death receptors has highlighted new approaches to trigger directly apoptotic signaling in cancer cells (Jan & Chaudhry, 2019).

6.4. Combination therapies and biomarker-guided approaches

In view of a considerable body of evidence supporting the central role of apoptosis in the initiation of malignant cells, agents and drug combinations aimed at restoring apoptosis are intensively investigated as cancer treatments. To date, success has accompanied the development of monotherapies, and several major challenges that impede broad application remain unresolved. Preclinical data nonetheless point to a notable capacity for inducing significant and sustained tumor clearance when various pro-apoptotic agents are used in pairwise combinations. The lack of widely applicable tests, however, hampers rational combination design by impeding the identification of the specific pro-apoptotic signaling pathways, cellular targets, and corresponding drug combinations on which diverse tumor types depend (Ventura *et al*., 2007).

The situation has been further complicated by the discovery that even malignant cells under extreme selective pressure may engage apoptosis pathways widely considered incompatible with their survival. Cells treated with either BCL-2 or BCL-XL inhibitors, for instance, often escape death despite the loss of both anti-apoptotic molecules, by switching to the p53 network or to additional BCL-2 family members. Clarification of these aspects would enhance the efficacy of proposed combination therapies and support their translation into the clinic (Junttila *et al*., 2010). Formation of a broad international consortium could expedite progress by making all recovery data freely accessible, thus permitting comprehensive analysis of tumor dependency on different apoptosis pathways across diverse experimental models. This understanding would in turn facilitate identification of rationally selected pro-apoptotic agents and candidate combinations for each tumor type. Finally, growing insight into strategies employed by cancers to counter specific pro-apoptotic signals would inform the design of co-inhibitors aimed at overcoming such resistance mechanisms (Lim *et al*., 2019; Montero & Haq, 2022).

7. Challenges and Future Directions

The first significant challenge facing therapeutic approaches targeting apoptosis in cancer is the marked heterogeneity within tumors that arise from different patient tissues. This heterogeneity extends to the mechanisms that underpin apoptosis resistance in malignant cells, including variability in the expression and activity of pro- and anti-apoptotic proteins belonging to the BCL-2 family (Lim et al., 2019).

Apoptosis serves as the principal mechanism initiating cancer cells; mechanisms, evidence, and therapeutic implications are synthesized from rigorous, evidence-based analysis. Despite progress, critical knowledge gaps remain. Elucidation of the roles of apoptosis in oncogenesis and metastasis is necessary. Further dissection of factors, aside from pro-apoptotic signals, that prime cancer cells to elicit apoptotic responses will enhance understanding of drug responses and aid development of more effective therapeutic strategies. Insights into the positions of pro-apoptotic, anti-apoptotic, and apoptosis-independent signals along the oncogenic and metastatic continuum will also facilitate identification of exploitable targets to sensitize tumors to therapeutic agents (Morana *et al*., 2022).

Drivers of metastasis or other pro-oncogenic alterations can enable tumors to evade death. The biologically relevant contexts in which apoptosis is pro- vs. anti-tumorigenic remain to be fully delineated. Exploration of the interplay between apoptosis and other cell fate decisions—such as proliferation, quiescence, senescence, and differentiation—may illuminate non-canonical routes cancers adopt to evade cell initiation. Enhancing knowledge of these and other facets of apoptosis will further substantiate its status as the most important mechanism through which anti-cancer therapies exert their impact today (Lim *et al*., 2019).

Cascades leading to apoptosis feature prominently in the reactions activated when mutational and other carcinogenic events occur. Apoptotic signalling is initiated early in the evolution of most cancers. Yet, even the most advanced tumors often successfully avoid this fate and, therefore, remain in the population, prolonging their capacity to accumulate additional alterations. Consequently, the elucidation of even earlier events in the life of a cancer and the identification of additional cellular states on the path to full malignancy represent high-priority objectives (D'Arcy, 2015). The aggregated knowledge regarding the mechanisms of cancer initiation and the evidence linking these processes to apoptotic signalling therefore vastly outweighs that available for other routes. Apoptosis is thus regarded as the primary mechanism by which anti-cancer agents exert their effect (Boccia *et al*., 2021).

8. Conclusion

Apoptosis is a major mechanism through which cancer cells are eliminated. This synthesis of the latest evidence, reflecting a substantial body of work, demonstrates that successful cancer therapies act predominantly by inducing the apoptotic death of cancer cells, and discusses the implications this has for drug development, patient stratification, and combination therapies. Extensive datasets and multiple experimental approaches, including systems biology, live cell imaging, and mathematical modeling, indicate that apoptotic clearance of cancer cells is the main mechanism by which tumor cells are eliminated, for many different types of cancer and anticancer treatment. Analysis of the literature on clearance measurements confirms that these measurements are particularly valuable for understanding and predicting the mechanisms of action of anticancer compounds. Researchers who wish to identify compounds that act by apoptosis inducers can concentrate on those that produce a rapid drop in tumor bioluminescence or fluorescence provided that the reporter is adequately validated. A series of patent applications describing innovative strategies to enhance tumor clearance by exploiting the apoptotic mechanism following drug administration is in preparation.

Four small molecules targeting the well-established pro-apoptotic pathway have received considerable attention: the BH3-mimetics ABT-737 and navitoclax, which bind to pro-survival members of the BCL-2 family; the p53-reactivating agent APR-246; and the SMAC-mimetic LCL-161, which promotes the degradation of IAP proteins. Abiding by the principles outlined, combination regimens incorporating such agents along with conventional chemotherapy or targeted therapies are being explored for trans-national implementation. Sufficient preclinical evidence has accumulated to suggest that pro-apoptotic agents function as bona fide sensitizers across various tumor types and therapies, on the condition that cancer cells remain equipped for limited apoptotic execution. However, the shift in apoptotic sensitivity from sufficient to insufficient remains an inevitable fate for evolutionarily successful high-grade tumors that no longer require protection against unwanted apoptotic death.

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