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Apoptosis in Cancer: From Threat to Therapy

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ABSTRACT

Apoptosis is a tightly regulated form of programmed cell death essential for tissue homeostasis and genomic integrity. Its dysregulation contributes to diverse pathological conditions, particularly cancer, where evasion of apoptosis enables malignant transformation, tumour progression, immune escape, and therapeutic resistance. Contemporary understanding recognises apoptosis as an integrated network involving mitochondrial, death receptor, and caspase-dependent signalling pathways rather than isolated linear cascades. This review synthesises current insights into the molecular mechanisms governing apoptotic regulation and examines how disruptions in BCL-2 family proteins, p53 signalling, caspase activation, and inhibitor of apoptosis proteins promote carcinogenesis. Particular emphasis is placed on translational advances in apoptosis-targeted therapy, including the clinical success of BH3 mimetics, emerging p53-modulating strategies, and combinational approaches designed to overcome apoptotic resistance. By integrating mechanistic biology with therapeutic development, this review highlights apoptosis not only as a hallmark of cancer but also as a therapeutically exploitable vulnerability in selected cancer contexts, particularly in haematological malignancies, although its translation in solid tumours remains variable and often limited. Understanding tumour-specific apoptotic dependencies may enable more precise and less toxic anticancer strategies in the evolving era of precision oncology.

KEYWORDS: Apoptosis, BCL-2 family, Caspases, p53, BH3 mimetics, Cancer therapy

INTRODUCTION

Apoptosis is a regulated, energy-dependent process essential for maintaining tissue homeostasis and genomic stability. It plays critical roles in development, immune regulation, and elimination of damaged or potentially malignant cells. Dysregulation of apoptosis contributes to multiple pathological conditions, most notably cancer, where evasion of programmed cell death enables tumour survival, progression, and resistance to therapy[1-3].

While apoptosis has historically been described as a linear cascade, contemporary evidence supports a network-based model involving interconnected mitochondrial, death receptor, and caspase-mediated pathways[4, 5]. These pathways are tightly regulated and function as a critical barrier against oncogenesis.

In cancer, disruption of apoptotic signalling occurs through alterations in BCL-2 family proteins, p53 dysfunction, impaired caspase activation, and overexpression of inhibitor of apoptosis proteins (IAPs). These changes collectively enable tumour cells to evade

cell death despite genomic instability and therapeutic stress[6-8].

Therapeutic targeting of apoptosis has gained considerable attention, particularly with the development of BH3 mimetics such as venetoclax, which have shown clinical success in haematological malignancies. However, translation into solid tumours remains challenging due to tumour heterogeneity, adaptive resistance, and redundancy in survival pathways[9-11].

This review provides a concise, critically synthesised overview of apoptotic mechanisms, their role in carcinogenesis, and current therapeutic strategies, with particular emphasis on clinical limitations and future directions.

MORPHOLOGICAL AND BIOCHEMICAL FEATURES OF APOPTOSIS

Apoptosis is defined not only by its molecular regulation but also by its distinct structural and biochemical characteristics, which differentiate it from necrosis and other forms of regulated cell death. These features are critical for diagnostic recognition and for understanding how apoptotic signalling translates into controlled cellular dismantling.

Unlike necrosis, apoptosis is characterised by preservation of membrane integrity, absence of inflammation, and orderly cellular fragmentation into apoptotic bodies[1-5].

These morphological changes are closely coordinated with underlying biochemical processes that ensure orderly cellular dismantling and non-inflammatory clearance. An early and functionally critical biochemical event in apoptosis is the externalisation of phosphatidylserine from the inner to the outer leaflet of the plasma membrane. This process, mediated by coordinated regulation of membrane phospholipid transporters, serves as an “eat-me” signal that facilitates recognition and rapid clearance of apoptotic cells by macrophages[4]. This mechanism ensures non-inflammatory removal of dying cells and preservation of tissue homeostasis[6].

Markers such as caspase activation or DNA fragmentation are useful but not definitive: apoptosis can occur with limited DNA laddering and, in some contexts, with reduced caspase dependence. Classification should integrate morphology with molecular context rather than rely on a single assay[2, 7].

Collectively, these morphological and biochemical changes reflect a highly regulated cellular self-destruction program designed to eliminate unwanted cells while preserving tissue integrity. In the context of cancer biology, disruption of these tightly controlled processes enables tumour cell survival and underpins resistance to therapy.

MECHANISMS OF APOPTOSIS

Apoptosis is best understood as an interconnected signalling network rather than a strictly linear pathway, with multiple upstream inputs converging on a common execution phase[7].

Caspases are central mediators of apoptosis and function as a hierarchical proteolytic cascade. Initiator caspases (such as caspase-8 and -9) respond to upstream activation signals and subsequently activate executioner caspases (caspase-3 and -7), which mediate cleavage of key structural and regulatory proteins, leading to the morphological and biochemical features of apoptosis[8].

The Extrinsic (Death Receptor) Pathway

The extrinsic apoptotic pathway is initiated at the cell surface following engagement of specific death receptors belonging to the tumour necrosis factor (TNF) receptor superfamily. Key receptors include TNFR1, Fas (CD95), and TRAIL receptors DR4 and DR5. Ligand binding induces receptor trimerization and recruitment of adaptor proteins such as Fas-associated death domain (FADD), resulting in assembly of the death-inducing signalling complex (DISC) [9] [Fig. 1].

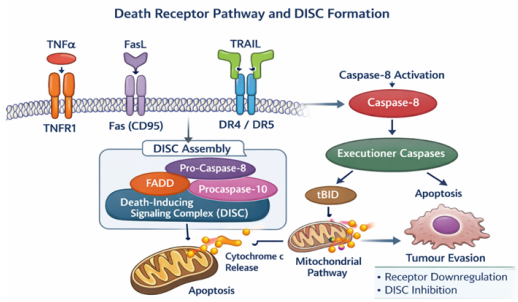
DISC assembly activates caspase-8, which triggers executioner caspases (caspase-3/-7) and, via BID cleavage to tBID, can amplify death signals through mitochondria. Tumours evade this axis through reduced receptor expression, altered DISC components, or downstream inhibition, limiting immune-mediated killing and TRAIL responses[9].

In cancer biology, defects in the extrinsic pathway-such as reduced death receptor expression, increased decoy receptors, or impaired DISC formation-contribute to resistance against immune-mediated cytotoxicity and TRAIL-based therapies. Thus, dysregulation at the receptor level has direct therapeutic implications.

The Intrinsic (Mitochondrial) Pathway

The intrinsic pathway is activated by intracellular stress signals, including DNA damage, oncogene activation, hypoxia, metabolic perturbation, and oxidative stress. The pivotal event in this pathway is mitochondrial outer membrane permeabilization (MOMP), which represents a point of no return in apoptotic commitment[10].

MOMP releases cytochrome c, enabling apoptosome formation (cytochrome c–Apaf-1–procaspase-9) and activation of caspase-9 followed by executioner caspases[10].

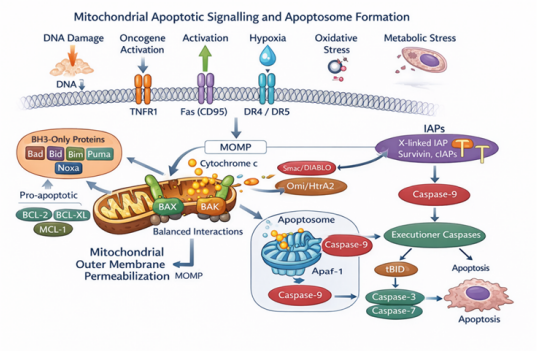


Death receptor–mediated extrinsic apoptotic pathway and DISC-dependent caspase-8 activation
Binding of death ligands (TNFα, FasL, TRAIL) to their receptors induces formation of the death-inducing signalling complex (DISC), leading to activation of caspase-8. This initiates downstream executioner caspases and amplifies apoptosis via mitochondrial cross-talk.

Fig. 1: Death Receptor–Mediated Extrinsic Apoptotic Signalling and DISC Formation

MOMP is controlled by the BCL-2 family: anti-apoptotic BCL-2/BCL-XL/MCL-1 restrain, while BAX/BAK execute, and BH3-only proteins sense stress and neutralise anti-apoptotic buffering. Cell fate depends on the balance of these interactions, explaining both tumour survival and therapeutic priming [10] [Fig. 2].

Mitochondria also release Smac/DIABLO and Omi/HtrA2 to antagonise IAP-mediated caspase suppression, amplifying execution once MOMP occurs [11].



Intrinsic mitochondrial apoptotic pathway and apoptosome formation.
Cellular stress induces mitochondrial outer membrane permeabilization, leading to release of cytochrome c and formation of the apoptosome (cytochrome c–Apaf-1–caspase-9). This activates executioner caspases, while Smac/DIABLO antagonises IAP-mediated inhibition.

Fig. 2: Intrinsic Mitochondrial Apoptotic Pathway and Apoptosome Formation

The Convergent Execution Phase

Despite distinct initiation routes, both intrinsic and extrinsic pathways converge on activation of executioner caspases, primarily caspase-3 and caspase-7. These proteases mediate the cleavage of key structural and regulatory proteins, resulting in chromatin condensation, cytoskeletal reorganisation, and formation of apoptotic bodies, which together define the morphological and biochemical features of apoptosis[8].

Caspase-3–mediated cleavage of ICAD releases caspase-activated DNase, facilitating controlled nuclear fragmentation. These coordinated processes enable efficient and non-inflammatory clearance of dying cells. Importantly, apoptosis cannot be defined solely by caspase activation or DNA fragmentation, as caspase-independent forms of programmed cell death may exhibit overlapping features[7].

Endoplasmic Reticulum Stress–Associated Apoptosis

Earlier models described a caspase-12–dependent and mitochondria-independent endoplasmic reticulum (ER) apoptotic pathway. Contemporary evidence, however, indicates that ER stress–induced apoptosis is largely integrated with mitochondrial signalling rather than functioning independently[12].

When ER stress is prolonged, the unfolded protein response shifts from adaptation to apoptosis (e.g., CHOP induction), often by modulating BCL-2 family proteins and promoting mitochondrial permeabilization rather than acting as a fully independent pathway[12, 13].

This integrated model better reflects the dynamic crosstalk between organelles and signalling networks, particularly in tumour cells where metabolic stress is common.

APOPTOSIS AND CARCINOGENESIS

Evasion of apoptosis is now recognised as a fundamental hallmark of cancer and a prerequisite for malignant transformation[1]. Tumour development is driven not only by uncontrolled proliferation but also by the failure of genetically damaged cells to undergo programmed cell death. Apoptosis functions as a critical tumour-suppressive mechanism, eliminating cells harbouring oncogenic mutations, DNA damage, or metabolic stress. When this safeguard is compromised, aberrant cells survive, accumulate additional mutations, and acquire malignant potential.

Rather than being a single defect, apoptotic resistance in cancer arises from disruption at multiple regulatory nodes. Broadly, three interconnected mechanisms contribute to apoptosis evasion: dysregulation of the BCL-2 family, impairment of tumour suppressor pathways such as p53, and overexpression of inhibitor of apoptosis proteins (IAPs).

Dysregulation of the BCL-2 Family

The intrinsic mitochondrial pathway is tightly controlled by the BCL-2 family of proteins, which determine whether mitochondrial outer membrane permeabilization (MOMP)

occurs. Anti-apoptotic members such as BCL-2, BCL-XL, and MCL-1 counteract pro-apoptotic effectors BAX and BAK, while BH3-only proteins act as stress sensors[10]. It is the relative balance between these opposing groups that defines cellular susceptibility to apoptosis.

In many malignancies, anti-apoptotic BCL-2 proteins are overexpressed, tipping the balance toward survival. This phenomenon is particularly evident in haematological malignancies such as chronic lymphocytic leukaemia and certain lymphomas, where BCL-2 upregulation contributes to chemoresistance and disease persistence[14]. Similarly, increased expression of MCL-1 and BCL-XL has been observed across solid tumours, conferring resistance to cytotoxic stress and targeted therapies[15].

Importantly, this dysregulation is not merely correlative but functionally causal. Genetic or pharmacologic modulation of BCL-2 family members alters tumour sensitivity to chemotherapy and radiation. The translational relevance of this mechanism is underscored by the clinical success of BH3 mimetics, which restore apoptotic competence by selectively inhibiting anti-apoptotic BCL-2 proteins[16].

p53 Dysfunction and Loss of Apoptotic Surveillance

The tumour suppressor protein p53 serves as a central integrator of cellular stress responses. Upon DNA damage or oncogenic activation, p53 induces transcription of genes involved in cell cycle arrest, DNA repair, senescence, and apoptosis[17]. Through activation of pro-apoptotic genes such as BAX, PUMA, and NOXA, p53 promotes mitochondrial permeabilization and elimination of genetically unstable cells.

Mutations in TP53 occur in approximately half of human cancers and represent one of the most common genetic alterations in oncology[17]. Loss of wild type p53 function disables a key apoptotic checkpoint, allowing damaged cells to survive. Moreover, certain mutant p53 proteins acquire gain-of-function properties that actively promote tumour progression, genomic instability, and therapy resistance[18].

Beyond direct mutation, p53 signalling can be functionally suppressed through MDM2 overexpression, epigenetic alterations, or disruption of upstream stress signalling. Thus, impaired p53-mediated apoptosis represents a major route by which tumours evade programmed cell death[19, 20].

Inhibitor of Apoptosis Proteins (IAPs)

IAPs constitute another critical regulatory layer within apoptotic signalling. Members of this family-including XIAP, cIAP1, cIAP2, Survivin, and Apollon-modulate caspase activity and influence cell survival pathways[21]. XIAP directly binds and inhibits caspase-3, -7, and -9, while cIAP proteins participate in ubiquitination and degradation of pro-apoptotic factors.

Overexpression of IAPs has been documented across a range of malignancies, including lung, pancreatic, colorectal, and melanoma cancers. Elevated Survivin expression, in particular, correlates with poor prognosis, enhanced proliferation, and resistance to chemotherapy and radiotherapy. Rather than acting in isolation, IAP overexpression often cooperates with BCL-2 family dysregulation and p53 loss to reinforce apoptosis resistance[22].

Importantly, mitochondrial proteins such as Smac/DIABLO physiologically counteract IAP function. Loss of this antagonistic balance further entrenches survival signalling in tumour cells[11].

Integrated View of Apoptotic Evasion

Although dysregulation of BCL-2 proteins, p53 mutation, and IAP overexpression are often described separately, in reality these alterations form an interconnected network. For example, p53 regulates transcription of BCL-2 family members, while mitochondrial release of Smac modulates IAP activity. Tumour cells frequently exhibit combined alterations at multiple nodes, creating redundancy that strengthens apoptotic resistance.

This integrated model explains why single-agent therapies targeting only one apoptotic regulator may be insufficient. It also highlights why combination strategies-such as BH3 mimetics with chemotherapy or IAP antagonists with death receptor agonists-have emerged as rational therapeutic approaches.

In summary, carcinogenesis is facilitated not merely by enhanced proliferation but by the coordinated dismantling of apoptotic safeguards. Understanding these layered regulatory mechanisms provides the conceptual foundation for modern apoptosis-targeted therapies.

CASPASE IMPAIRMENT

Caspases are indispensable mediators of apoptotic execution, and impairment at this level represents a pivotal mechanism by which tumour cells evade programmed cell death. Although upstream apoptotic signals may be initiated, insufficient activation of initiator or executioner caspases can prevent effective dismantling of the cell, thereby promoting malignant survival.

Reduced caspase-8 expression has been reported in several malignancies and is associated with impaired responsiveness to death receptor signalling and immune-mediated cytotoxicity. Similarly, compromised caspase-9 activation can blunt mitochondrial pathway execution,

particularly in tumours with defective apoptosome assembly. Impairment of executioner caspase-3 has also been described in subsets of breast and ovarian cancers, contributing to resistance to chemotherapeutic agents that rely on apoptosis induction. Importantly, these defects are rarely isolated events; they frequently coexist with BCL-2 overexpression, IAP upregulation, or p53 dysfunction, thereby reinforcing apoptotic resistance through redundant mechanisms[23].

From a therapeutic perspective, reduced caspase activity has direct implications. Agents such as Smac mimetics are designed to relieve IAP-mediated inhibition of caspases, thereby restoring apoptotic competence[11]. Similarly, strategies that enhance DISC formation or apoptosome assembly aim to overcome upstream defects in caspase activation. Thus, caspase impairment should not be viewed merely as a downstream consequence of oncogenic transformation but as a therapeutically exploitable vulnerability.

DEATH RECEPTOR RESISTANCE

The extrinsic apoptotic pathway plays a crucial role not only in developmental cell death but also in immune surveillance against malignancy. Death receptors such as Fas (CD95) and TRAIL receptors (DR4 and DR5) initiate apoptotic signalling upon ligand engagement, leading to DISC formation and caspase-8 activation[9]. In the context of cancer, impairment of this pathway represents a major mechanism of immune escape and therapeutic resistance.

Tumour cells can evade death receptor–mediated apoptosis through several mechanisms. Downregulation or mutation of death receptors reduces ligand responsiveness. Alternatively, increased expression of decoy receptors, which lack functional death domains, can sequester death ligands without initiating apoptotic signalling. Impaired recruitment of adaptor proteins or defective DISC assembly further attenuates caspase-8 activation. In addition, tumours may reduce expression of death ligands or create an immunosuppressive microenvironment that limits cytotoxic T cell–mediated apoptosis.

Beyond receptor-level alterations, post-receptor signalling defects are also common. Reduced caspase-8 expression or enhanced inhibition by cellular FLICE-inhibitory protein (c-FLIP) can prevent effective transmission of death signals. Importantly, crosstalk between extrinsic and intrinsic pathways means that even partial mitochondrial resistance can blunt death receptor–induced apoptosis[10].

Clinically, impaired death receptor signalling contributes to resistance against TRAIL-based therapeutics and may limit the efficacy of immune-mediated tumour clearance. However, this vulnerability has also inspired combinational strategies aimed at restoring extrinsic pathway sensitivity. Approaches under investigation include TRAIL receptor agonists combined with Smac mimetics or chemotherapy to overcome intrinsic resistance mechanisms[9, 11, 24].

In summary, disruption of death receptor signalling represents a critical node in apoptotic evasion. Its interaction with mitochondrial dysregulation and caspase impairment highlights the redundancy of tumour survival mechanisms and underscores the need for multi-target therapeutic strategies.

TARGETING APOPTOSIS IN CANCER THERAPY

Targeting the BCL-2 Family

Among apoptosis-targeted therapies, inhibition of anti-apoptotic BCL-2 family proteins has achieved the most significant clinical success. Tumours overexpressing BCL-2 or related proteins are often “primed” for apoptosis but are restrained by anti-apoptotic buffering. BH3 mimetics are small molecules designed to mimic endogenous BH3-only proteins and selectively bind to anti-apoptotic BCL-2 proteins, thereby restoring mitochondrial outer membrane permeabilization[25, 26].

Venetoclax, a selective BCL-2 inhibitor, has demonstrated remarkable efficacy in chronic lymphocytic leukaemia and acute myeloid leukaemia, particularly when combined with hypomethylating agents or chemotherapy[27, 28]. Its clinical success validates mitochondrial priming as a therapeutic concept. However, resistance frequently develops through upregulation of MCL-1 or BCL-XL, underscoring the adaptive plasticity of tumour survival networks[29, 31].

Despite these advances, the clinical utility of BH3 mimetics is constrained by several important limitations. Resistance frequently develops through adaptive upregulation of alternative anti-apoptotic proteins, particularly MCL-1 and BCL-XL, thereby restoring mitochondrial survival signalling. In addition, dose-limiting toxicities, including neutropenia and thrombocytopenia, restrict broader clinical applicability. Notably, the success of these agents has been largely confined to haematological malignancies, while efficacy in solid tumours remains inconsistent. This disparity reflects tumour heterogeneity, microenvironmental influences, and reduced mitochondrial priming in many solid cancers[32-34].

Targeting p53 Pathway Dysfunction

Given that TP53 is mutated in approximately half of human cancers, restoration of p53 function remains an attractive therapeutic goal. Contemporary strategies focus

less on gene replacement and more on pharmacologic modulation of p53 signalling[35].

MDM2 inhibitors aim to stabilise wild type p53 by disrupting its interaction with the negative regulator MDM2. Several agents are undergoing clinical evaluation, particularly in acute myeloid leukaemia and solid tumours[36]. Additionally, small molecules designed to restore mutant p53 conformation or function are in development, although clinical translation remains challenging[19].

Unlike early gene therapy approaches, modern p53-targeted strategies emphasise combination regimens. Reactivation of p53 can enhance sensitivity to chemotherapy, radiation, and targeted agents, suggesting that p53 modulation is most effective as part of integrated treatment strategies rather than standalone therapy[37, 38].

However, clinical translation of p53-targeted strategies remains challenging. Many tumours harbour structurally complex TP53 mutations that are not amenable to pharmacological reactivation. In addition, toxicity related to on-target effects in normal tissues and the emergence of resistance mechanisms limit sustained responses. Furthermore, variability in tumour dependency on p53 signalling reduces the predictability of therapeutic benefit, necessitating careful patient selection.

Targeting Inhibitor of Apoptosis Proteins (IAPs)

IAPs function as endogenous suppressors of caspase activity and are frequently overexpressed in cancer. Smac mimetics are small molecules designed to antagonise IAPs by mimicking the endogenous mitochondrial protein Smac/DIABLO[39-41].

A key challenge is identifying tumours with true IAP dependence and pairing Smac mimetics with partners that provide a death signal (e.g., chemotherapy, TRAIL agonism, or immunotherapy)[42].

Despite strong preclinical rationale, the clinical performance of Smac mimetics has been modest. Single-agent activity has been limited, and therapeutic efficacy often depends on combination with chemotherapy or immune-modulating agents. Resistance arises from compensatory activation of alternative survival pathways, including NF-κB signalling. In addition, variability in IAP dependency across tumour types further limits their broad applicability.

Targeting the Extrinsic Pathway

Current strategies focus on overcoming this resistance through combination therapy. Integration of TRAIL agonists with BH3 mimetics or Smac mimetics enhances apoptotic signalling by simultaneously relieving mitochondrial and caspase inhibition checkpoints [9]. These combination approaches reflect a deeper understanding of pathway crosstalk and redundancy[43, 44].

Early clinical enthusiasm for TRAIL receptor agonists was not sustained in later-phase trials, primarily due to intrinsic and acquired resistance. Tumour cells frequently exhibit reduced death receptor expression, increased decoy receptors, or impaired downstream signalling, including caspase-8 deficiency and c-FLIP overexpression. These mechanisms significantly limit the effectiveness of TRAIL-based therapies as monotherapy.

However, clinical trials of Smac mimetics have shown limited single-agent efficacy, largely due to compensatory survival signalling and tumour heterogeneity.

Direct Caspase Activation: A Limited but Emerging Strategy

Direct caspase activation remains difficult due to specificity and toxicity concerns; most approaches instead remove inhibitory constraints (e.g., IAP antagonism) or enhance upstream activation to permit endogenous execution in a tumour-selective manner.

Future therapeutic directions may involve targeted delivery systems, tumour-selective activation platforms, or integration with immunotherapeutic approaches to harness apoptosis in a controlled and tumour-specific manner.

Despite strong mechanistic rationale and promising preclinical results, the clinical translation of apoptosis-targeted therapies has been limited in several contexts. One of the principal challenges is tumour heterogeneity, wherein different tumour subclones exhibit variable dependence on apoptotic pathways, thereby reducing uniform therapeutic response. In addition, redundancy within cellular survival signalling allows tumour cells to bypass targeted inhibition through compensatory upregulation of alternative anti-apoptotic proteins such as MCL-1 or BCL-XL.

The tumour microenvironment further contributes to therapeutic resistance by providing external survival signals that attenuate apoptotic priming. Moreover, many solid tumours exhibit lower mitochondrial dependency compared to haematological malignancies, limiting the effectiveness of mitochondrial-targeted therapies such as BH3 mimetics. Pharmacological limitations, including dose-limiting toxicities and narrow therapeutic windows, also restrict clinical applicability.

Collectively, these factors highlight that successful clinical translation requires not only targeting apoptotic pathways

but also addressing tumour-specific dependencies through combination strategies and biomarker-guided patient selection.

CRITICAL SYNTHESIS

Apoptosis-targeted therapy reflects a shift from empirical cytotoxicity to exploiting tumour-specific survival dependencies. Because apoptotic networks are redundant, durable benefit is most likely with rational combinations and biomarkers that identify apoptotic priming or dependency[26, 45].

Importantly, the clinical success of apoptosis-targeted therapies has been uneven across tumour types. While BH3 mimetics have demonstrated significant efficacy in haematological malignancies, similar outcomes have not been consistently reproduced in solid tumours. This disparity is largely attributable to tumour heterogeneity, microenvironmental influences, and redundancy in survival signalling pathways that allow tumour cells to bypass apoptotic triggers. These limitations highlight the necessity for biomarker-driven patient selection and rational combination strategies to achieve meaningful clinical benefit.

Thus, the therapeutic exploitation of apoptosis is no longer conceptual but clinically validated in specific malignancies. The remaining challenge lies in identifying biomarkers that define apoptotic dependency and guide patient selection.

Collectively, these observations highlight a central challenge in apoptosis-targeted therapy: redundancy within tumour survival networks. Targeting a single apoptotic regulator is often insufficient, as tumour cells rapidly adapt through compensatory pathways. Consequently, the future of apoptosis-based therapy lies in rational combination strategies guided by tumour-specific dependency profiling, rather than single-agent approaches.

CONCLUSION

This review highlights that successful cancer therapy requires not only suppression of tumour proliferation but also restoration of the intrinsic capacity of malignant cells to undergo programmed cell death. Although significant progress has been achieved in targeting apoptotic pathways, particularly in haematological malignancies, translating these advances into broader clinical benefit will require a deeper understanding of tumour-specific apoptotic dependencies, mechanisms of therapeutic resistance, and interactions with the tumour microenvironment. Future research should focus on biomarker-driven patient selection and rational combination strategies that integrate apoptosis-targeted agents with other anticancer therapies. Such approaches have the potential to improve treatment efficacy while minimising toxicity, thereby advancing more personalised and durable cancer treatment.

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