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ENGINEERING CELL DEATH PATHWAYS FOR CANCER THERAPY: EMERGING CONCEPTS IN APOPTOSIS AND AUTOPHAGY

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ABSTRACT

Cancer is characterised by resistance to programmed cell death, and of the various known cell death mechanisms, apoptosis and autophagy continue to be the most well characterised and treatable. The molecular architecture of the intrinsic and extrinsic apoptotic pathways, the fundamental autophagy mechanism, and the complex communication network focused on mTOR signalling, BCL-2/Beclin-1 and p53 interactions that determine whether a stressed cell survives or dies are summarised in this review. We look at different methodologies for "engineering" pathways such as BH3 mimetics, epigenetic modulators, CRISPR/Cas9 and RNA interference-based gene editing and delivery systems which enabled by nanotechnology which is enabled the accurate, tumor-selective death induction. We also discuss the integration with synthetic lethality, immunotherapy, and artificial intelligence-driven drug discovery to tackle the specific characteristics of autophagy.

Therapeutic agents such as venetoclax, temsirolimus, hydroxychloroquine, and everolimus are examples of potential therapeutic approaches but also have some drawbacks like resistance, delivery, and heterogeneity. Perhaps, we concluded that combination therapeutic approaches, which are biomarker-guided, multi-target, and locally targeted as compared to single pathway modalities, are the future of programmed cell death engineering.

KEYWORDS: Apoptosis, Autophagy, Cancer Therapeutics, Nanomedicine, Synthetic Lethality, BCL2 family, BH3 mimetics.

INTRODUCTION

One of the most daunting challenges for modern medicine is cancer. The most recent GLOBOCAN estimates compiled by the American Cancer Society and International Agency for Research on Cancer (IARC) show that 20.6 million people were diagnosed with cancer and 9.6 million died from cancer in 2024 alone.[1] Approximately one in five people will have a chance to develop cancer at some point in their lives.

Indeed, lung cancer is most commonly diagnosed and the leading cause of cancer death worldwide, followed by stomach, colorectal, prostate, and breast cancer. As per IARC, the number of new cases of cancer is expected to increase to 34.4 million per year worldwide by 2050, an increase of 67% from the current trend as of 2024 due to aging and growth of the population and the ongoing shift of developing nations toward “Westernized” risk factor profiles. Therapeutic approaches that go beyond the traditional cytotoxic models to more precisely targeted and mechanistically specific interventions, like the intentional manipulation of the cellular models that determine life and death, are necessary to address this rapidly growing burden.

Hanahan and Weinberg identified resistance to cell death as one of the initial hallmarks of cancer in their foundational and continuously updated framework, and it remains a central feature of 14 hallmarks in their most recent update, while 6 hallmarks were initially published in 2000.[2] Genetically damaged or mutation-prone cells that can proliferate, avoid programmed cell death, and eventually exhibit the full malignant phenotype. The Nomenclature Committee on Cell Death has identified different forms of cell death in addition to apoptosis, such as Pyroptosis, parthanatos, ferroptosis, Necroptosis, cuproptosis, and autophagy-dependent cell death. Single-pathway therapeutic approaches are becoming less effective because tumour cells often take advantage of multiple layers of this model at

once, overexpressing anti-apoptotic proteins, inhibiting death receptor signalling, and repurposing autophagy as a survival mechanism under metabolic stress.

The apoptosis and autophagy pathways are particularly selected for review because they are the most molecularly characterized and druggable of these pathways, and they are interconnected: the anti-apoptotic protein BCL-2 directly interacts with the protein Beclin-1, which initiates autophagosome formation, and this single molecular interaction controls both survival programs.[3,4] The term "engineering" refers to targeted rewiring of the molecular switches that control cell fate through the application of targeted nanocarriers, gene editing, epigenetic reprogramming, and small-molecule mimetics.

The objectives of this review are

1) Summarize the foundation of autophagy and apoptosis and their integration.
2) investigate tools for engineering pathways.
3) Assess the translation into combination regimens and precision oncology.
4) Study approved agents and active clinical investigations.

Overview of programmed cell death in cancer

Apoptosis and necrosis are no longer the only two variants of Regulated Cell Death (RCD). There are eight therapeutically significant modalities in cancer research, which are recognized in the following classification.

Apoptosis: Cell shrinkage, chromatin condensation, and membrane blistering without intracellular contents leakage are characteristics of a caspase-dependent, immunologically "quiet" type of death.

Autophagy (dependent cell death): A lysosome-mediated self-digestion mechanism which is either pro-death or pro-survival depending on the situation.

Ferroptosis: An iron-dependent type of death that causes unchecked lipid peroxidation, which is usually associated with inhibiting glutathione peroxidase 4 (GPX4).

Pyroptosis: A pro-inflammatory lytic death that is linked to inflammasome activation and is mediated by gasdermin.

Parthanatos: An energetic catastrophe and excessive DNA damage that induced PARP-1 dependent death pathway.

Necroptosis: A type of programmed necrosis driven by RIPK1/RIPK3/MLKL core signalling pathways, which are caspase-independent and release the damage-associated molecular patterns (DAMPs).

Cuproptosis: A newly introduced copper-dependent death mechanism pathway that involves the lipoylated tricarboxylic acid (TCA) cycle.

Immunogenic cell death (ICD): ICD is a functional descriptor for modes of programmed cell death such as Pyroptosis, Ferroptosis, and particular types of apoptosis which are releases the DAMPs that can further regulate antitumor immunity instead of a distinct morphological category.

Table 1: Programmed cell death types and their key molecular regulators.

Type of cell death	Key molecular regulators	Potential features	Relevance to cancer therapy	References
Apoptosis	BCL-2/BCL-XL/MCL-1, BAX/BAK, Apaf-1, Caspase-9/ caspase-3/caspase-7, TRAIL-R1/TRAIL-R2, FAS/FASL	Chromatin condensation and caspase-dependent shrinkage.	Target for BH3 mimetic drugs	[5]
Autophagy	Beclin-1, ATG5/ATG7/ATG12, p62, ULK1 complex, VPS34, and LC3-II	Lysosome-mediated self-digestion	Dual tumor formation promoter or inhibitor	[3]
Ferroptosis	Iron, GPX4, and SLC3A2/SLC7A11	Iron-dependent cell death which causes lipid peroxidation	Elevate T-cell tumor clearance	[6,7]
Pyroptosis	Caspase-1/Caspase-4/Caspase-5/Caspase-11, Gasdermin-D/ Gasdermin-E	Oligomerization of Gasdermin-N-terminal membrane, which ruptures the cell membrane (pore formation)	Releases pro-inflammatory cytokines and DAMPs as ICD inducers	[8]
Parthanatos	MIF, PARP1, and AIF	ATP/NAD^+ depletion	Binding with PARP inhibitors	[9]
Necroptosis	MLKL, RIPK1, and RIPK3	Activation by TNFR1 or viral sensors, DAMPs release	Complex, acting as both tumor promoter and inhibitor	[9]
Cuproptosis	Copper, Lipoylated Tricarboxylic acid (TCA) proteins, FDX1	Severe mitochondrial Proteotoxic stress	Copper ionophores and nanoparticle-induced targets	[9]
Immunological cell death (ICD)	ATP, Calreticulin (CRT): HMGB1, ANXA1, and IFN-1	DAMP release	Bridges to immunotherapy	[3]

Cell death dysregulation in tumorigenesis and cancer progression

Dysregulation of cell death is a functional, systematic driver of tumorigenesis instead of a secondary effect in cancer. Mutations that cause loss of function in anti-apoptotic genes and amplification (BCL-2 and MCL-1) and pro-apoptotic genes (TP53 and BAX): epigenetic repression of cell death receptor mechanisms, and upregulation of apoptotic genes in cancer contribute to cell survival. BECN1 is located next to tumor inhibitor BRCA1 on chromosome 17q21, and it encodes the crucial autophagy regulator Beclin-1; both genes are frequently co-deleted in breast and ovarian cancers. Whereas new research indicates that defective autophagy instead of loss of BRCA1 alone.[10]

In addition to initiation, dysregulation of cell death influences tumor progression, metastasis, and therapy resistance. In advanced tumors, autophagy can enhance metabolic adaptation in hypoxic and nutrient-poor conditions, which aid in immune evasion by inhibiting the antigen-presenting mechanism and promotes dormancy of disseminated tumor cells. Similarly, it has been discovered that the anti-apoptotic BCL-2 class, which includes solely death inhibitors, actively promotes cell migration, invasion, and metastatic colonization apart from their canonical apoptotic role.[10,11] Cell death pathways should be viewed as integrated signalling hubs that must be "engineered" with relevance to precision, rather than as on/off switches, as demonstrated by a dual mechanism that serves as both a survival pathway and an active promoter of aggressive phenotypes.

Molecular basis of Apoptosis

Intrinsic (Mitochondrial) pathway

Mitochondrial outer membrane permeabilization (MOMP) is regulated by the BCL-2 family, which includes the apoptotic inhibitor guardian proteins (BCL-XL, BCL-2, and MCL-1): BH3-only sensors (BID, PUMA, NOXA, and BIM): and apoptotic-promoting executioners (BAK, BAX). The guardians are neutralized by stress-induced BH3-only proteins, which permit cytochrome c release and caspase-9 activation, followed by execution caspases-3 and caspases-7, BAX/BAK oligomerization, and apoptosome formation with Apaf-1. The BCl-2 family is one of the most actively targeted therapeutic targets, as tumors often overexpress anti-apoptotic proteins.[5,12]

Extrinsic (death receptor) pathway

Adaptor proteins and procaspase-8 are induced into a death-inducing signalling complex (DISC) by activation of TNFR1, Fas, or TRAIL receptors. In "type-II" cells, caspase-8

breaks down BID to enhance the signal via the mitochondrial pathway, which brings together both apoptotic arms, while in "type-I" cells, caspase-8 activates the specific caspase-3.[4]

Resistance Mechanisms

Overexpression of BCL-2/BCL-XL/MCL-1, cancer-causing TP53 mutations, upregulation of IAPs, inhibition of death receptors or their cellular signalling receptors, and acquired immunity alterations occurring at the drug binding interface itself are some of the numerous, frequently recurrent cellular processes by which tumor cells develop resistance to apoptosis. Tumor cells can maintain pro-survival activity while avoiding pharmacological suppression; for example, the BCL-2 F104L and F104C mutations decrease binding affinity to BH-3 mimetic venetoclax without affecting BCL-2 affinity for BAX and BIM.

Regulatory Nodes

A complex regulatory network incorporates apoptosis. In response to the effects of malignant stress, DNA damage, and the tumor suppressor protein p53, which activates apoptosis-promoting genes (BAX, PUMA, and NOXA): acting as a master mediator of the choice to recover, suppress, or kill. Usually persistently active in malignancies, NF-kB signalling provides a pro-survival balance by upregulating apoptotic inhibitory genes and inhibitors of apoptosis proteins (IAPs). In addition to phosphorylating and deactivating apoptotic-promoting BAD and forkhead-associated transcription factors, the AKT/PI3K pathway effectively stabilizes MDM2-mediated p53 degradation. In many situations, the ERK/MAPK pathway is comparable to and stimulates survival signalling; however, depending on the length and intensity of activation, it may also trigger apoptosis in other cases. Caspases-3, Caspases-7 and caspases-9 are directly bound and inhibited by members of the IAP family proteins/genes, such as XIAP and surviving which directly impact the final checkpoint against irrational death.

Molecular basis of Autophagy

Types

In mammalian cells, there are three main types of autophagy. The most researched and therapeutically significant type is "macroautophagy", which involves the spontaneous growth of the double-layered autophagosome that engulfs cytoplasmic material before integrating with the lysosome for cellular destruction. In "Microautophagy", cytoplasmic material is directly engulfed by the lysosomal membrane without the need for an additional vesicle. Proteins with a KFERQ-like domain are specifically targeted by chaperone-mediated

autophagy (CMA). These proteins are identified by the chaperone HSC70 and transferred across the lysosomal membrane via receptor LAMP-2A.[9]

Core molecular mechanism of Autophagy

Autophagy is activated by the ULK1 complex (ATG13, ATG101, ULK1, and FIP200): which is triggered in nutrient-deficient or stressful contexts. This combination phosphorylates and activates the VPS34 and beclin-1-containing class III PI3K complex at the forming phagophore membrane, generating phosphatidylinositol-3-phosphate (PI3P): a lipid messenger that stimulates ATG proteins downstream. Membrane elongation is consequently induced by two ubiquitin-like conjugation systems, such as the ATG12-ATG5-ATG16L1 complex and the conversion of LC3-I into lipidated LC3-II, which is integrated into the forming autophagosomal membrane and serves as the most widely used biochemical indicator of autophagic activity. By physically connecting substrates to the autophagosome for destruction, the selective autophagy receptor P62/SQSTM1 binds both LC3-II and ubiquitinated materials. In both therapeutic and experimental contexts, p62 deposition is employed as a measure of preventing autophagy or blockage, as this has been compromised in over-efficient autophagic flux.[13]

Upstream Regulation

In nutrient-rich contexts, mTORC1, the master negative-regulating protein, negatively regulates ULK1; in energetic stress, AMPK stimulates ULK1 and inhibits mTORC1; in cancer, PI3K/AKT signalling activates mTORC1 and prevents autophagy; and in hypoxic environments, HIF-1α promotes autophagy genes to enhance tumor proliferation.

Dual Role

By removing damaged mitochondria and reducing genotoxic stress, autophagy suppresses cancer in the early stages of tumor growth. Once tumors have developed, it promotes metabolic modifications, chemoresistance, malignant stem cell survival, and immune suppression by dividing into granzyme B and antigen-presenting mechanisms.

Table 2: Key genes, signalling pathways involved in apoptosis and autophagy.

Gene/protein	Signalling pathway	Function of gene/protein
BCL-2/BCL-XL/MCL-1	Intrinsic (mitochondrial) pathway	Anti-apoptotic proteins which prevent cytochrome c release and ensure integrity of the mitochondrial membrane
BAX/BAK	Intrinsic (mitochondrial) pathway	Proteins that promote the trigger permeabilization and apoptosis by polymerization in the outer layer of the mitochondrial membrane.
Caspase-9/ caspase-3/caspase-7	Intrinsic (mitochondrial) pathway / Extrinsic (Death receptor) pathway	Caspase-3, along with caspase-7, activates caspases that break down the cell in apoptosis; caspase-9 is an activating caspase in the apoptosome.
Apaf-1	Intrinsic (mitochondrial) pathway	Cytochrome c-binding adaptor protein that requires caspase-9 to synthesize the apoptosome.
TRAIL-R1/TRAIL-R2, and FAS/FASL	Extrinsic (Death receptor) pathway	Death receptor pathway which is triggered by ligand binding, activates initiator caspases to cause extrinsic apoptosis.
TP53	Both apoptosis/autophagy	Tumor suppressor that, in reaction to stimuli or DNA damage, induces autophagy, apoptosis, and cell-cycle inhibition.
NOXA, BIM, BID, and PUMA	Intrinsic (mitochondrial) pathway	BH-3 proteins that promote the neutralization of apoptotic inhibitor BCL-2 family to activate mitochondrial apoptosis.
Beclin-1	Autophagy induction pathway	Essential autophagy regulator which helps in the development of the autophagosome.
ATG5/ATG7/ATG12, LC3-II	Membrane expansion/ autophagy elongation	Proteins in the autophagy mechanism are necessary for the elongation and expansion of the autophagosome membrane.
p62 (SQSTM1)	Autophagy target/ substrate	Ubiquitinated cargo is bound by a selective autophagy receptor and transported to autophagosomes for destruction.
ULK1 complex	Autophagy induction pathway	Detects the state of nutrients and triggers the early production of autophagosomes to start autophagy.
VPS34	Autophagy regulation pathway	Class III PI3K promotes the start of autophagy by releasing phosphatidylinositol 3-phosphate.
AMPK	Energy depletion sensor pathway	Autophagy is triggered by an energy sensor when mitochondrial energy is low.
mTORC1/ PI3K/AKT	Autophagy inhibition or promoter pathway	Mechanism that monitors growth and inhibits autophagy as growth signals and nutrients are adequate.
BIRC5 (survivin)	Apoptosis inhibition pathway	Apoptosis inhibiting proteins which promotes cell survival by reducing caspase activation.
HIF1A	Hypoxia-inducing autophagy	Hypoxia-sensitive gene transcription factor which can stimulate autophagy and assist cells in reacting to low oxygen concentrations.

Interaction between Apoptosis and Autophagy

These two approaches are not just parallel; they are practically similar. Beclin-1's BH3 domain enables BCL-2/ BCL-XL to sequester it, which directly connects apoptotic guardians to the start of autophagy; when this relationship is disrupted by stress or medications that mimic BH-3 and beclin-1 is released, BAX/BAK-mediated apoptosis is signalled. Nuclear p53 stimulates autophagy proteins, but cytoplasmic p53 inhibits autophagy without transcription. These two effects of p53 are localization-dependent. Beclin-1 and ATG5 can be fragmented by caspases, transforming autophagic factors into apoptosis-promoting effectors (fragmented ATG5 increases cytochrome c release).[14] Although the effects are dependent on the situation, mTOR inhibition promotes autophagy and may generate cell more sensitive to apoptotic stimuli because mTORC1 is downstream of the identical PI3K/AKT pathway controlling apoptosis resistance. While prolonged or extreme stress generally promotes autophagy-dependent death or apoptosis-a threshold-driven switch which makes proper cellular pathway programming and moderate stress typically support cytoprotective autophagy and survival.

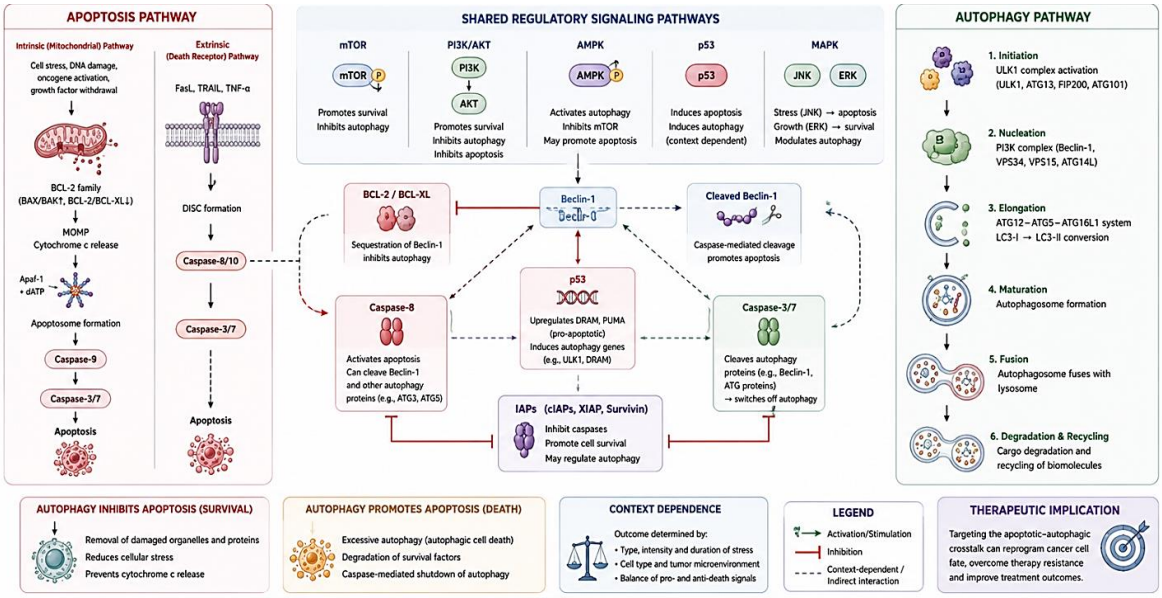

Fig. 1: Crosswalk between apoptosis and autophagy.

Tools and technologies for programming cell death pathways

Small-molecule modulators

BH3 mimetics are the most developed class of therapeutic agents used for cell apoptosis regulation. These small compounds replace sequestered Beclin-1, BAX, and BAK by effectively binding to the hydrophobic gap of apoptotic inhibitor BCL-2 family members,

structurally replicating the BH3 domain characteristic of apoptotic-promoting sensor proteins.[12,15] The first BH3 mimetic to receive approval from regulatory authorities was venetoclax (ABT-199): a highly selective BCL-2 inhibitor that has altered the treatment of acute myeloid cell leukaemia and chronic lymphocytic leukaemia. Though on-target thrombocytopenia (caused by BCL-XL activity in platelet proliferation) has prevented the clinical progress of BCL-XL inhibitors, equivalent drugs are currently being developed against BCL-XL and MCL-1.[16,17]

The goal of **caspase activators** is to directly initiate the executioner process of apoptosis, avoiding upstream resistance mechanisms. However, considering that caspases are broadly recognized and expressed, it is difficult to ensure tumor selectivity, which has inhibited tumor progression.

The only therapeutic medication in this class with regulatory clearance (for non-cancer indications) is **autophagy inhibitors**, including chloroquine and its derivative hydroxychloroquine (HCQ): which prevent autophagosome-lysosome fusion. However, these drugs are currently under consideration for comprehensive clinical evaluation for malignancy. The relatively limited performance of hydroxychloroquine identified in clinical trials can potentially be addressed by novel, more effective, and selective ULK1- and VPS34-inhibiting agents that are in the initial phases of scientific investigation.[18]

Autophagy activators, such as rapamycin derivatives (rapalogs): induce cellular autophagy by blocking mTORC1. They have been used to exploit the tumor-suppressive properties of autophagy and, more frequently in oncology, to make cancer-resistant tumor cells more susceptible to subsequent apoptotic triggers.

Table 3: Small molecule modulators for apoptosis and autophagy.

Agents/class	Target	Mechanism	Stage
Venetoclax	BCL-2	BH-3 mimetics, restores apoptosis	FDA-approved
MCL-1 inhibitors	MCL-1	BH-3 mimetics	Early-phase trials
TRAIL agonists	DR4/DR5	DISC activation	Clinical trials
Navitoclax	BCL-2 / BCL-XL	Dual BH-3 mimetics	Clinical trials
Hydroxychloroquine	Lysosome	Blocks autophagic flux	Approved
Oblimersen	BCL-2 mRNA	Antisense silencing	Clinical trial
Rapalogs	mTORC1	Induces autophagy	FDA approved
ULK1/VPS34	ULK1, VPS34	Blocks autophagy	Pre-clinical

inhibitors		initiation	
Pevenodistat	Neddylation pathway	Autophagy/proteostasis modulator	Clinical trials

Gene Editing Techniques

Cell-death defects have been discovered and specifically programmed with the integration of CRISPR/Cas9 technology. Several synthetic toxic mechanisms associated with cellular apoptosis engineering have been determined by genetically engineered CRISPR amplification characterizations. Specifically, a computational CRISPR screening showed a LIG1 loss as a precursor to PARP inhibitory activity, which triggered standard replication stress, double-strand breaks in DNA, and eventually triggered apoptosis across a variety of tumors such as colorectal carcinoma, lung carcinoma, prostate carcinoma, and breast carcinoma.[4] Similarly, by suppressing BCL-XL along with phosphorylated AKT/BAD while promoting pro-apoptotic BAX activation, CRISPR-mediated amplification of CD133 in malignant stem cells stimulated cells with resistance to trametinib-mediated cell apoptosis. Although delivery and undesirable outcomes continue to be significant translational challenges, CRISPR-based suppression or desirable mediated techniques are under consideration as direct therapeutic approaches to silence apoptotic inhibitor genes or recover functional malignant inhibiting agents. Without the reactivity or non-targeting potential of genomic editing, antisense oligonucleotides and RNA interference (siRNA/shRNA): respectively, provide complementary, frequently more clinically developed methods for suppressing particular death-pathway components (example: BCL-2 mRNA and Survivin). Several antisense BCL-2 inhibitors such as oblimersen have been tested in clinical investigations, though with modest efficacy compared to a monotherapy treatment.[17,19]

Epigenetic Regulation

Apoptotic promoters and death receptor-mediated transcriptional inhibition induced by chromatin and methylation can be overcome by HDAC and DNMT inhibitors. A further regulating mechanism is developed by microRNAs, IncRNAs, and CircRNAs, which concentrate on BECN1, BCL-2, as well as ATG gene expression in tumor-dependent pathways, which exhibits therapeutic and diagnostic potential.

Nanotechnology-Based Delivery

Optimizing tumor-targeted medication delivery along with maintaining normal cellular structure serves as a persistent challenge for cellular death engineering therapeutics,

particularly for conventional medications with narrow clinical efficacy intervals (e.g., autophagy modulators and BCL_XL inhibitors).[20] By incorporating autophagy-modulating agents, BH3 mimetics, nucleic acid-based therapies, and lipid nanoparticles composed of polymers can improve pharmacokinetics and promote passive tumor formation through elevated permeability and cellular retention. Exosome-based delivery methods transport therapeutic materials with lower immunogenic properties through the advantage of natural intracellular exchange channels.[21] Cell-death inducers are being paired with stimuli-responsive nanocarriers, which have been developed to discharge their target molecule exclusively in response to tumor-associated triggering conditions such as acidic pH, enhanced glutathione, or specific enzyme activity to promote localized and temporally regulated cellular activation.[22,23] However, in comparison to systemic pharmacological delivery, nanocarriers have been successfully utilized to co-deliver chemotherapeutic drugs with autophagy-modulating agents such as hydroxychloroquine or chloroquine directly to tumor cells, enhancing precision. In addition to both apoptosis and autophagy, nanoparticles and metal-organic framework (MOF) substrates have been engineered to co-induce multiple immunogenic cell death pathways at similar intervals. For example, nano-MOFs designed to cause both ferroptosis and Pyroptosis in melanoma indicate the way nanotechnology is enabling multi-pathway death engineering compared to single-target intervention.

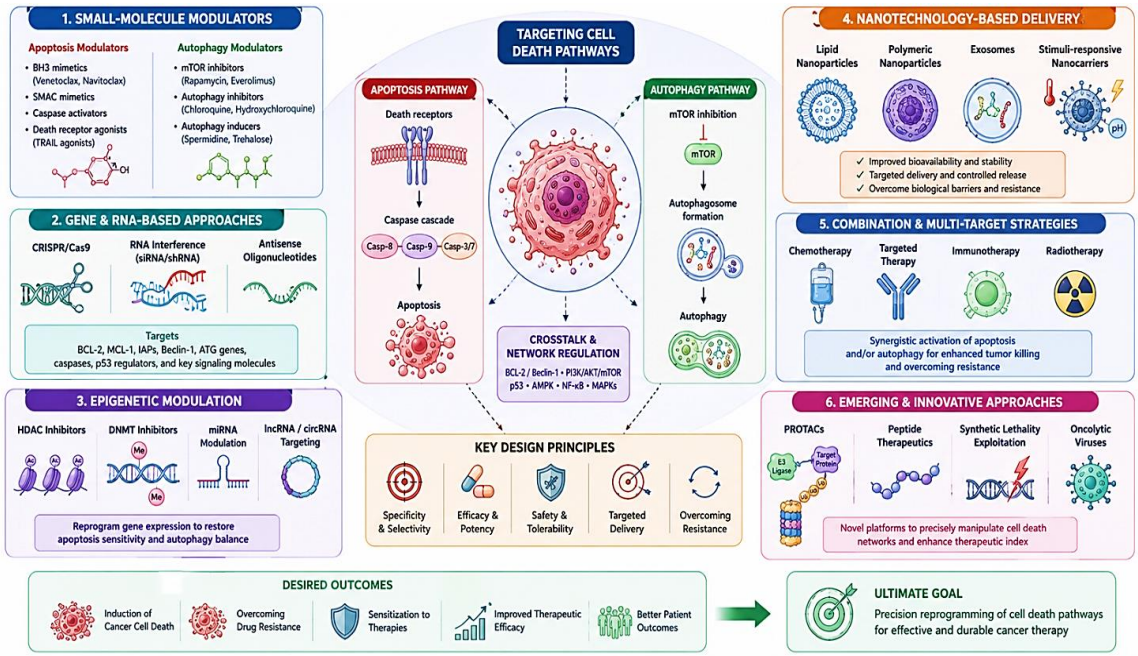

Fig. 2: Engineering strategies targeting cell death pathways.

Emerging Therapeutic strategies for Programming cell death pathways

Combination therapy

Combination approaches that interact cell-death-engineering drugs with conventional cancer treatments, tumor-targeting drugs, or immunotherapy have become the traditional cancer therapy models, as cancers rarely rely on a single death evasion mechanism. Using the synergy between BCL-2 inhibition and epigenetic reprogramming, utilizing venetoclax in conjugation with hypomethylating drugs (decitabine or azacitidine) has become the accepted form of therapy for elderly or unfit individuals with acute myeloid leukemia. In renal cell carcinoma, autophagy inhibitors like hydroxychloroquine have been combined with mTOR inhibitors like temsirolimus; in this particular situation, hydroxychloroquine (HCQ) has been combined with mTOR inhibitors like temsirolimus, where HCQ elevated cytotoxicity and triggered apoptosis by a different pathway in comparison to other autophagy inhibitors like bafilomycin. By releasing DAMPs, many cellular death mechanisms like Pyroptosis, ferroptosis, and immunogenic apoptosis alter immune-mediated “cold” tumors into “hot” tumors, which promotes the use of checkpoint-blocking agents.[24]

Precision Oncology

Multi-omics strategies are generating pathway-specific dependency signals that go more than gene-specific biomarker detection, and molecular mapping of BCL-2 family expression parameters, TP53 status, and autophagy flux markers progressively directs patient preference.

Synthetic Lethality

One of the most effective methods for creating selective tumor cell death is synthetic lethality, which is the concept that simultaneous disruption of two normally non-essential genes or pathways results in cell death while interference with single genes or pathways is tolerated and normal. The traditional example remains a PARP blockage in homologous-deficient recombination (BRCA1/2-mutant) tumors, where the absence of the two homologous recombination and PARP-dependent strand-specific break repair mechanisms exceed the cells' ability to repair DNA, triggering apoptosis and replication disasters. This expanding collection of synthetic lethal pathways constitutes a reliable, genetically matched approach to identifying combination therapies that promote apoptosis for individual patients.[25,26]

Artificial Intelligence

Cell-death engineering agents are being discovered and optimized more quickly with the use of a combination of AI and machine learning techniques. Preclinical research finding intervals can potentially be reduced by using conventional deep learning models developed on structural and chemical evidence to anticipate emerging BH-3 mimetic substrates, identify potential synthetic lethal pairs of genes via comprehensive screening databases, and predict patient-specific drug susceptibility from multi-omics profiles.[27,28] Similarly, stimulation-responsive nanocarrier-based structures modified for cancer environment-specific carrier diffusion are being generated via AI-assisted simulated screening. Thus, computational drug development is being explored alongside the nanomedicine delivery methodologies traditionally explored.[29]

Clinical translation for programmed cell death

FDA-approved and clinically established therapeutic agents

Several substances that immediately trigger autophagy or apoptosis are being recognised by regulatory authorities or proven to be effective in clinical conditions. Venetoclax is a selective BCL-2 inhibitor that induces the intrinsic (mitochondrial) apoptosis pathway by leading to sequestered BAX/BAK. It has been approved for use in combination medications for acute myeloid leukemia and chronic lymphocytic leukemia; however, a majority of patients treated using venetoclax subsequently recover, emphasizing the importance of targeting other cellular death mechanisms in combination therapy. Both temsirolimus and everolimus are rapalogs that inhibit mTORC1, promote autophagy, and produce inhibitory effects in neuroendocrine tumors, renal cell carcinoma, and some types of breast cancer; however, in typical cases, their therapeutic effect is primarily cytostatic rather than cytotoxic. The primary cellular autophagy suppressor that is available commercially. Hydroxychloroquine (HCQ) is being extensively investigated in combination trials and has proven its activity in promoting chemosensitivity. However, its relatively low and unstable efficacy at tolerable doses remains a significant disadvantage.[24]

Table 4: FDA-Approved Drugs and Mechanism of Action.

Drug	Pathway	Mechanism of action	Approved indications
Venetoclax	BCL-2 (Intrinsic Mitochondrial apoptosis)	BH-3 mimetic, displaces BAK/BAX, triggers MOMP, cytochrome c release, and caspase activation	CLL/SLL; AML (with azacitidine/decitabine or low-dose cytarabine)
Temsirolimus	mTORC1 (Proliferation/autophagy)	Prodrug of sirolimus; inhibits mTORC1, inducing autophagy and cytostasis	Advanced renal cell carcinoma
Hydroxychloroquine	Autophagosome – lysosome fusion	Raises lysosomal pH, blocking terminal autophagic degradation	Approved for malaria/autoimmune disease; investigational in oncology trials
Everolimus	mTORC1 (autophagy/proliferation)	Inhibits mTORC1, inducing autophagy and blocking cell-cycle progression	Renal cell carcinoma, neuroendocrine tumors, breast cancer (with exemestane): SEGA

Ongoing clinical trials

Combination regimens based on cell-death programming are presently being evaluated in several major phase I-III trials. For treating a variety of solid tumor types, hydroxychloroquine and chloroquine are still being investigated concurrently with tamoxifen, mTOR inhibitors, and cytotoxic chemotherapy. These drugs typically exhibit acceptable tolerability but insufficient therapeutic effectiveness signals, which probably reflect inadequate autophagy-inhibiting agents at clinically acceptable doses. In hematologic tumors, novel autophagy pathway-mediated medicines are being tested, such as pevenodistat, a neddylation pathway inhibitor with an autophagy-regulating effect. An initial phase of a neoadjuvant trial of hydroxychloroquine (HCQ) suggested that apoptosis initiation in patient cancer tumors was linked with plasma levels of tumor suppressor Par-4 instead of triggering the conventional autophagy inhibitory marker p62. These results indicate the relevance of pathway-dependent pharmacodynamic biomarkers in initial-phase clinical trial design, along with the kinetic complexity of expressing autophagy-regulating effects.

Table 5: Ongoing Clinical Trials for targeting cell death pathways.

Trial Identifier	Phase / Status	Agents	Target Pathway	Tumor type
NCT06611839	Phase I/II	Venetoclax + Ivosidenib + Azacitidine	BCL-2 inhibition + epigenetic reprogramming	IDH1-mutated AML
NCT04386057	Phase II	LY3214996 (ERK inhibitor) + HCQ	ERK inhibition + autophagy inhibition	Metastatic Pancreatic cancer
NCT37113580	Phase I / Active	Venetoclax + BEAM conditioning	BCL-2 Inhibition (pre-transplant)	Relapsed / refractory non-Hodgkin lymphoma
NCT01506973	Phase II completed	Gemcitabine/nab paclitaxel + HCQ	Chemotherapy + autophagy inhibition	Metastatic pancreatic cancer
NCT05518110	Phase II	Trametinib + HCQ	MEK inhibition + autophagy inhibition	Metastatic refractory pancreatic cancer
Neoadjuvant HCQ phase I trial	Phase I completed	Hydroxychloroquine monotherapy	Autophagy inhibition	Diverse solid tumors
Preoperative HCQ trial	Phase II Randomized, completed	Gemcitabine/nab paclitaxel + high dose	Chemotherapy + autophagy inhibition	Pancreatic adenocarcinoma

Biomarker selection for patient selection

Biomarkers that can identify pathway which depends for successful translation into clinical practice of cell death-engineered therapeutics. BCL-2 family expression parameters (MCL-1: NOXA and BCL-2: BIM) as predictors of BH3 mimetic sensitivity, BRCA1 and BRCA-2 and broader homologous recombination protein deficiency characteristics for the identification of synthetic lethal PARP inhibitors, autophagy flux markers (LC3-II conversion, p62 turnover) for autophagy modulating medications and circulating DAMP levels (ATP, HMGB1) as pharmacodynamic indicators of the induction of immunologic cell death.[30,31] The predictive strength of HER2 genotype in breast cancer, for example, is still not reached by any of the above biomarkers, indicating an essential issue for further biomarker discovery.

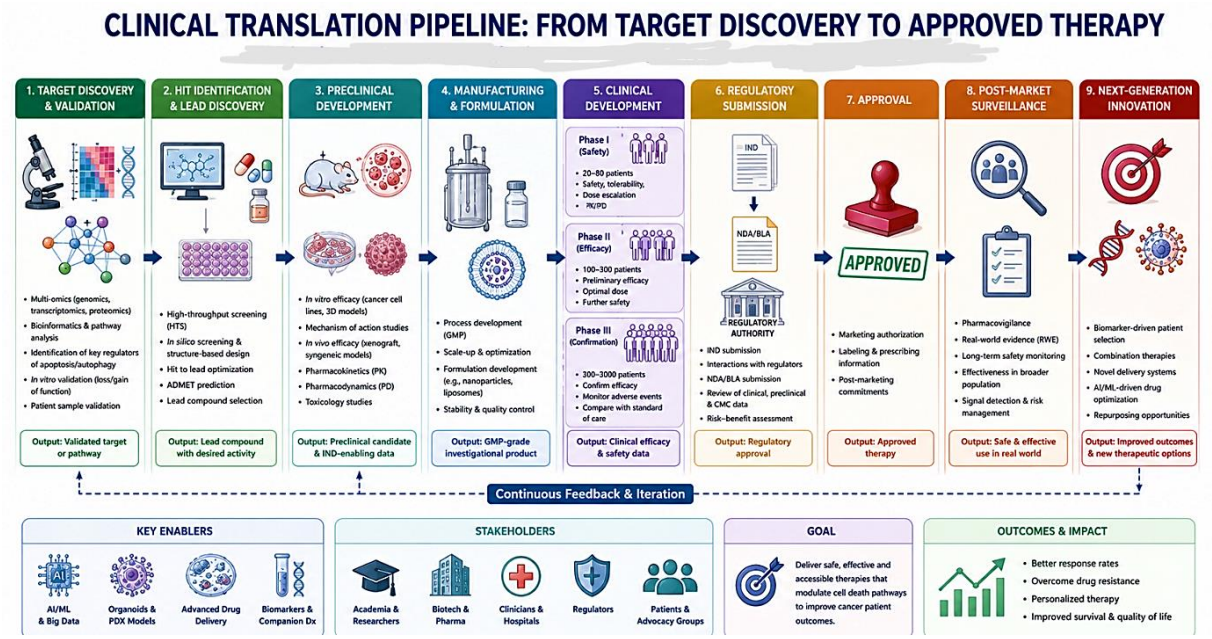

Fig. 3.: Clinical translation pipeline from target discovery to approved therapy.

Challenges and limitations

The therapeutic significance of cell death programming techniques is limited by several enduring issues, despite significant advancements in mechanisms and pharmacology.

Drug resistance: Cancer cells develop resistance to drugs via binding site alterations (e.g., BCL-2 F104c/F104L leading to venetoclax resistance): mediated by enhanced expression of substitute anti-apoptotic receptor proteins (e.g., MCL-1 upregulation in response to BCL-2 inhibition) and reactivation of survival signalling pathways (e.g., ERK/RAF/MEK pathway stimulation driving PARP inhibitor resistance).

Tumor variation: both intramural and intertumoral, enabling resistant tumor subpopulations to evolve under treatment choice stress, while a specific death-pathway susceptibility may only occur in a subcellular ratio of malignant cells.

Toxicity: BCL-XL is crucial for platelet survival, while BCL-XL inhibitors induce dose-specific thrombocytopenia; in other aspects, chronic autophagy suppression exhibits the potential to damage autophagy-dependent homeostasis processes in healthy tissues like liver, immune cells, and muscles.

Biomarker limitations: As already mentioned, biomarker limitations lead to imprecise patient selection for several programmed cell death medicines, which leads to heterogeneous

trial conclusions and makes it complex to differentiate between typical responders and non-responders who receive inadequate therapeutic doses.[30]

Delivery challenges: The release of CRISPR systems or RNA interference complexes in vivo remains significantly more challenging than the administration of small-molecule therapeutics. It is accurate for gene editing and nucleic acid-based approaches.

Future Perspectives

The subsequent decade of cell-death programming in oncology is anticipated to be shaped by several converging innovations. The inefficiency which constraints single-pathway based therapeutics is potentially overcome through **broad-spectrum therapeutics** such as BH3 – mimetic/autophagy modulator combination therapies or bispecific medications that can sequentially stimulate apoptotic and immunogenic cell death pathways. Selectivity and synergistic efficacy should be improved by **next-generation nanomedicine**, specifically stimuli-responsive nanomedicine, along with multi-cargo nanocarriers that can combine immune-modulatory targets and cell death stimuli. Target characterization, synthetic lethal pair estimation, and de novo molecule synthesis are all domains in which **AI-assisted drug design** should significantly reduce discovery intervals and enable precise comparison of therapeutics to malignant genetic parameters. The previously mentioned biomarker gap is potentially addressed by utilizing **patient-based cellular organoids** along with other advanced cellular ex vivo models to efficiently assess cell-death pathway dependence in a specific manner ahead of therapy initiation. Molecular deficiencies and relatively specific microenvironmental variables (like hypoxic core-triggered autophagy dependency) that are suppressed by bulk sequencing approaches have been identified by **single-cell genomics and spatial transcriptomics techniques**, which are increasingly being utilized to characterize death-pathway variability within individual malignancies at previously unidentified conclusions. While utilized as such, these techniques promote a broader approach toward **cancer precision modalities**, in which death-pathway modelling corresponds specifically to the type of cancer as well as to the specific molecular and cellular characteristics of an individual's medical condition. This is performed via **next-generation combination therapies** that combine standard immunotherapy and synthetic cytotoxic combinations with specially selected cancer pathway modulatory agents.

CONCLUSION

A stressed cancer cell's ability to survive, evolve, or kill itself depends on the balance of the two complexly linked regulatory programs, such as apoptosis and autophagy. This review has identified their structural framework. Epigenetic modulators, BH3 mimetics, nanotechnology delivery systems, and CRISPR-based modifications are some of the methods that can be used to modify proteins. Hydroxychloroquine, everolimus, venetoclax, and temsirolimus are examples of approved therapeutic agents with significant clinical applications, especially in hematologic malignancies. Still, they also present challenges with resistance, toxicity, heterogeneity, and inaccurate patient selection. Autophagy has a dual function as a promoter in advanced disease and an inhibitor in early disease, serving as an example of why death pathways must be regulated with consideration for genetics, microenvironment, and stage rather than being controlled as binary switches. Combining single-cell profiling, synthetic lethality, AI-driven characterization, and multi-target combination therapies provides a feasible approach to advance cell-death programming from a conceptual construct into an integral part of precise cancer therapy. Continuous contributions to predictive biomarkers, more intelligent delivery systems, and clinical trial study designs that can match the appropriate death -pathway interventions to relevant patients at a suitable stage of illness will be essential to realize this opportunity.

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