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Chemical Modulation of Tumor Cell Death Pathways and Research Progress

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Abstract. Regulated cell death (RCD) pathways function as interlinked networks, not isolated modules, presenting new chances for cancer treatment. This review focused on chemical modulation strategies for five major RCD pathways, namely apoptosis, autophagy - associated cell death, ferroptosis, pyroptosis, and cuproptosis. Druggable nodes and translational barriers are specifically emphasized. Intervention methods for each pathway are reviewed, and multi - pathway synergy is critically appraised. Compensatory crosstalk can be employed to improve the efficiency but also leads to toxicity risks. Primary translational challenges are the inadequacy of predictive biomarkers, the narrowness of therapeutic windows for emerging modalities, and the insufficiency of validation in immune - competent models. Apoptosis targeting has had clinical success in hematologic malignancies, but its effectiveness is limited in solid tumors because of compensatory buffering. Ferroptosis provides strategies to get past apoptosis resistance, and the translation to clinical use depends on biomarker - guided patient selection. Pyroptosis gives immunostimulatory vulnerabilities, while cuproptosis provides metabolic - selective ones. But both are dealing with systemic toxicity challenges that call for controllable induction ways. It is proposed that functional diagnostics, next - generation chemical tools, and network - aware trial designs be integrated to advance RCD modulation towards durable, mechanism - guided cancer therapy.

Keywords: regulated cell death, cancer therapy, chemical modulation, multi-pathway synergy

1. Introduction

One of the central dilemmas in cancer treatment is the continuing tug-of-war between externally imposed therapeutic stress and the death threshold of tumor cells. Classic thinking made cell death simpler in a binary framework of apoptosis and necrosis, and this simplified model gave a conceptual starting - point for the development of chemotherapy and radiotherapy. The research of the past decade has proven that, at the molecular scale, cell death is better comprehended as a more complicated family of "regulated cell death," with members differing basically in morphology, biochemical mechanisms, and immunological results. More significantly, these death subroutines don't act as discrete modules. They share upstream stress programs and can either offset each other or transition between states by means of feedback regulation. So, within the complex environment

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of a tumor, a "single - target killing" strategy commonly results in only momentary perturbation rather than long - term control [1] .

Considering this scenario, this review focused on five death pathways in tumor biology and therapeutics with significant "druggability discussion value": apoptosis, autophagy - associated cell death, ferroptosis, pyroptosis, and cuproptosis. "Chemical modulation" is described as a set of strategies where controllable chemical methods, like small molecules, metal complexes, nanomaterials, or natural products, directly or indirectly change the activity of key pathway nodes and network topology to make tumor cells reach death thresholds. The definition shows both the controllability of intervention and the dynamic responsiveness of pathway networks.

2. Mechanisms of tumor cell death pathways

2.1. Apoptosis

Apoptosis is a regulated program of cellular self-clearance defined by effector caspase activation and stereotyped morphological dismantling. It proceeds via two main routes: the extrinsic pathway (death receptor–DISC–caspase-8 activation) and the intrinsic pathway (mitochondrial outer membrane permeabilization [MOMP]–cytochrome c release–caspase cascade). Critical regulatory nodes determine death thresholds: the BCL-2 family (pro-apoptotic BAX/BAK; anti-apoptotic BCL-2, BCL-XL, MCL-1) gates MOMP; caspase-8 switches between apoptosis and alternative death pathways; IAPs brake caspase activity; and the p53–MDM2 axis coordinates stress competence [2]. Despite mechanistic clarity, key translational gaps persist: how to quantify apoptosis dependence under tumor heterogeneity for drug selection. BH3 profiling has been proposed as a bridge between mechanism and response, but its reproducibility in solid tumors, sensitivity to sample handling, and coupling to metabolic states remain substantial barriers. Moreover, therapy-induced apoptosis is not intrinsically immunogenic; phagocytic clearance of apoptotic fragments often leads to immune silence rather than activation. Whether apoptosis-inducing strategies must be co-designed with immune-stimulatory modules therefore remains an open question requiring causal experimentation.

2.2. Autophagy

In tumor biology, "autophagy" typically refers to macroautophagy: initiation complexes sense energy stress and trigger phagophore nucleation; ATG-family cascades drive autophagosome formation, sequestration of cytoplasmic cargo, and fusion with lysosomes for degradation and recycling. Autophagy plays a context-dependent role in cancer—tumor-suppressive during early tumorigenesis by clearing damaged organelles, but adaptive and pro-survival under therapeutic stress or nutrient deprivation.

Autophagy is regulated by several key signaling nodes. The AMPK–mTOR axis integrates cellular energy and growth signals to oppositely regulate autophagy initiation. ULK1 kinase has emerged as a central druggable node in the initiation machinery (Fig. 1). In addition to ULK1, the VPS34-associated class III PI3K complex and lysosomal processes represent important pharmacological targets [3]. In particular, lysosomal acidification and autophagosome–lysosome fusion constitute pharmacologically accessible late-stage steps, and lysosomotropic weak bases that disrupt autophagic flux have been widely explored in early clinical studies [4].

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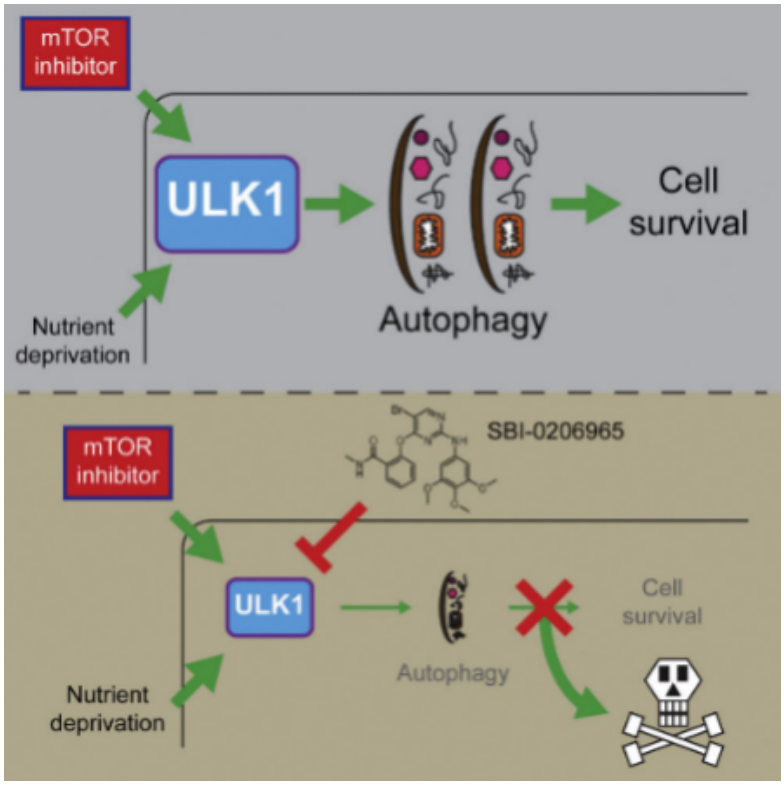

Figure 1. Role of ULK1 in autophagy regulation and the therapeutic effect of ULK1 inhibition [3]

2.3. Ferroptosis

Ferroptosis is a regulated cell death modality characterized by uncontrolled membrane lipid peroxidation following the collapse of cellular antioxidant defenses (Fig. 2). Cells import cystine via System Xc^- (SLC7A11) for glutathione synthesis; GPX4 then reduces phospholipid hydroperoxides to terminate peroxidation chains. When this defense gives way, iron - based oxidative damage to phospholipids rich in polyunsaturated fatty acids brings about death. Ferroptosis gives an alternative vulnerability in tumors that are apoptosis - resistant [5].

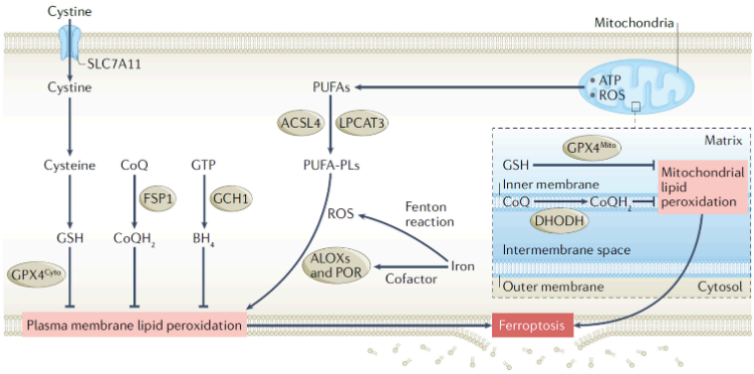

Figure 2. Core regulatory mechanisms of ferroptosis involving the SLC7A11–GSH–GPX4 defense system and iron-dependent lipid peroxidation [5]

Redundant anti - ferroptosis organization is an important feature. Besides the well - known GSH–GPX4, FSP1 suppresses lipid peroxidation via CoQ reduction independently of other factors. The

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GCH1–BH4 axis heightens membrane antioxidant capacity through radical capture. The defense mediated by mitochondrial DHODH more clearly shows a multi - organelle antioxidant network.

2.4. Pyroptosis

Pyroptosis is an inflammatory form of programmed cell death driven by gasdermin pore formation (Fig. 3). The canonical pathway involves inflammasome assembly activating inflammatory caspases (caspase-1, -4, -5 and -11), which cleave GSDMD to release its N-terminal pore-forming fragment, leading to ion flux, cell swelling and lytic rupture [6]. For tumor treatment, a non - canonical route is as important. Caspase - 3 cleaves GSDME, changing chemotherapy - induced apoptosis into pyroptotic cell death and adjusting antitumor immune responses.

The chances of chemical modulation can be found at multiple nodes. First of all, gasdermin expression varies in different tumors. GSDME is commonly epigenetically silenced or mutated in cancers, which renders caspase - 3 activation immunologically silent. Second, microenvironmental stimuli adjust the gasdermin programs. Hypoxia can promote GSDMC up - regulation by means of PD - L1 nuclear translocation, tying an immune checkpoint molecule to inflammatory death events. Thirdly, chemically speaking, pore formation is targetable. Disulfiram covalently modifies GSDMD to block the development of pores, enabling controlled pyroptosis induction and limiting tissue toxicity.

Clinical translation faces dose - and space - based challenges. Tumor - focused pyroptosis strengthens the immune response against tumors. Yet, systemic or pyroptosis in immune organs (liver, spleen) causes uncontrolled inflammatory toxicity. The optimal time to use immune checkpoint blockade is not defined. The current evidence is mainly correlational, and causal regimen - level studies to resolve T cell kinetics, myeloid reprogramming, and toxicity in immune - competent models are missing [7].

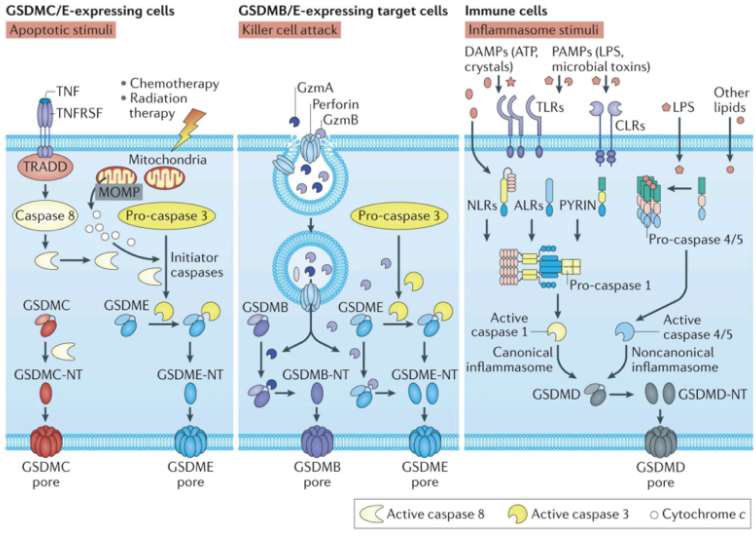

Figure 3. Mechanisms of gasdermin-mediated pyroptosis triggered by inflammasomes and apoptotic caspases [6]

2.5. Cuproptosis

Cuproptosis, a recently put - forward form of regulated death, has a link with mitochondrial metabolism. Its core feature is that copper ions, under defined conditions, directly target lipoylated

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tricarboxylic acid (TCA) cycle–related proteins, inducing protein aggregation and collapse of mitochondrial proteostasis, accompanied by dysfunction of iron–sulfur cluster proteins, ultimately generating irreversible mitochondrial toxicity. Compared to older frameworks which detail "copper-induced oxidative stress," the cuproptosis concept spotlights copper as a disrupter of coordination chemistry and protein conformation, causing selective vulnerability in cells with high respiratory needs. This change of concept remodels the way from general "metal toxicity" to an integrated "metabolism–metal interaction" perspective [8].

Multiple determinants regulate cuproptosis.On one side, ferredoxin 1 (FDX1; gene FDX1) is identified as an important upstream determinant; loss of FDX1 markedly reduces copper-induced death and alters lipoylated protein levels, implying that cuproptosis depends on mitochondrial lipoylation networks.On the flip side, tumor dependence on oxidative phosphorylation (OXPHOS) directly relates to cuproptosis sensitivity. Tumors that are biased towards glycolytic metabolism may be inherently more resistant as a result of relatively lower respiratory - chain activity. New work further shows that oncogenic signaling can hamper FDX1 expression and prompt metabolic reprogramming, including cuproptosis sensitivity in the adaptive metabolic control networks.

A key controversy lies in the boundaries between cuproptosis and other metal - related death phenotypes. In particular, when dealing with nanomaterials or copper oxide particles, cuproptosis and ferroptosis - like phenotypes can occur one by one and boost each other, making pathway assignment deviate based on the time frame and readout dimensions. One more unsolved problem is how to incorporate copper homeostasis machinery, lipoylation state, and respiratory dependence in patient samples into a predictive "cuproptosis sensitivity signature," since such signatures haven't been validated in prospective clinical cohorts.

3. Chemical modulation of tumor cell death pathways

3.1. Chemical modulation of apoptosis

Chemical modulation of apoptosis comprises three main strategies: lowering anti-apoptotic thresholds via BH3 mimetics to trigger MOMP; releasing IAP braking via Smac mimetics to restore caspase signaling; and enhancing death receptor clustering to overcome limitations of early TRAIL agents. BCL - 2 targeting within the scope of hematologic malignancies best shows mechanism - to - efficacy translation. There is clear clinical activity of Venetoclax in CLL, which enables fixed - duration combinations. Resistance commonly features an elevation of MCL - 1 or BCL - XL, driving the progress of MCL - 1 inhibitor development. But early trials show risks of myocardial toxicity that limit the therapeutic scope. Targeting the extrinsic pathway encounters unique challenges. Early rhTRAIL and DR4/DR5 agonists had a short half - life and insufficient receptor clustering. Eftozanermin and other multivalent designs show improved clustering ability and clinical signals. Nevertheless, development is limited by the insufficiency of biomarkers and vague indication positioning.

3.2. Chemical modulation of autophagy

Chemical alteration of autophagy poses a "bidirectionality" challenge: both suppression and activation might provide benefits depending on the tumor context. In a clinical context, late - stage flux inhibition by means of lysosomotropic agents (chloroquine, hydroxychloroquine) is most often done to disable adaptive survival under chemotherapy. A randomized preoperative trial for

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pancreatic cancer confirmed feasibility and set up pharmacodynamic endpoints. But efficacy varies in different studies, showing strong reliance on patient background.

Autophagy activation mostly comes from mTOR being inhibited or AMPK being activated. Even though mTOR inhibitors are approved for various cancers, the induced autophagy is frequently cytoprotective, alleviating drug stress. This reasoning backs the combination of mTOR inhibition and autophagy blockade.

3.3. Chemical modulation of ferroptosis

The main logic in chemically inducing ferroptosis is to break down the anti–lipid peroxidation defenses or increase the lipid peroxidation drive. At the small - molecule level, common schemes are to inhibit the uptake of cystine and the generation of glutathione, or directly inhibit GPX4 catalytic action. Mechanistic work is showing more and more that defense redundancy (e.g., FSP1 and DHODH as parallel systems) means that just inhibiting GPX4 doesn't necessarily give an acceptable in - vivo therapeutic window. Therefore, strategies of inducing ferroptosis are paying more attention to biomarker - guided selection and combination regimens. Especially, ferroptosis is used as additional killing against resistant states in immunotherapy or radiotherapy environments [5].

Nanomaterials and metal-related strategies are progressing rapidly. Their advantage is the potential to concentrate iron load and oxidative stress locally via tumor-targeted delivery, thereby lowering systemic toxicity while enhancing lipid-peroxidation "storms." Functionalized iron-based nanoparticles and iron-oxide platforms embedded in lipid carriers have been reported to induce ferroptosis in animal models and to generate combination benefits with other treatments.

3.4. Chemical modulation of pyroptosis

Chemical modulation of pyroptosis can proceed in two directions: induction and inhibition. From an antitumor perspective, induction is attractive because of potential immunogenicity, especially when GSDME is expressed; chemotherapy-induced caspase-3 activation can be redirected to pyroptotic lysis, promoting the tumor–immunity cycle. However, systemic toxicity risks make "controllable induction" the critical translational bottleneck; therefore, nanodelivery and localized expression systems are important engineering directions, such as mRNA lipid nanoparticles designed to induce local pore-forming activity and enhance immunotherapy response. In contrast, though pyroptosis inhibition is more usually mentioned in inflammatory diseases, it can also be useful in cancer treatment to limit chemotherapy - related tissue harm or control treatment - triggered inflammatory toxicity. It has been proven that disulfiram can covalently modify GSDMD and block the initiation of pore formation, acting as a chemically defined "point brake" on pyroptosis [7].

3.5. Chemical modulation of cuproptosis

The key chemical reasoning for inducing cuproptosis is to raise the mitochondrial - accessible copper load in tumor cells, which then brings about lipoylated protein aggregation and proteotoxic stress. Elesclomol has been re - thought of as a copper ionophore - like agent that transfers extracellular Cu(II) into mitochondria (Figure 4). Early clinical trials did not significantly improve outcomes in unstratified populations, but subsequent analyses have suggested that metabolic state and markers such as lactate dehydrogenase may correlate with sensitivity, which aligns with the theoretical expectation that cuproptosis susceptibility is linked to respiratory dependence [9].

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Nanomaterials and metal-complex strategies provide engineering routes to improve copper delivery and reduce systemic toxicity. Stimulus-responsive copper complex nanoparticles have been reported to increase tumor delivery and induce cuproptosis, supporting a plausible direction for improving tumor selectivity. At the same time, copper oxide nanoparticle exposure can induce cuproptosis while perturbing redox balance and causing a ferroptosis-like phenotype, implying that cuproptosis interventions may naturally engage multiple pathways. This multimodal coupling can produce synergy but also increase toxicity, and requires time-resolved pathway markers and genetic blockade experiments for disentanglement.

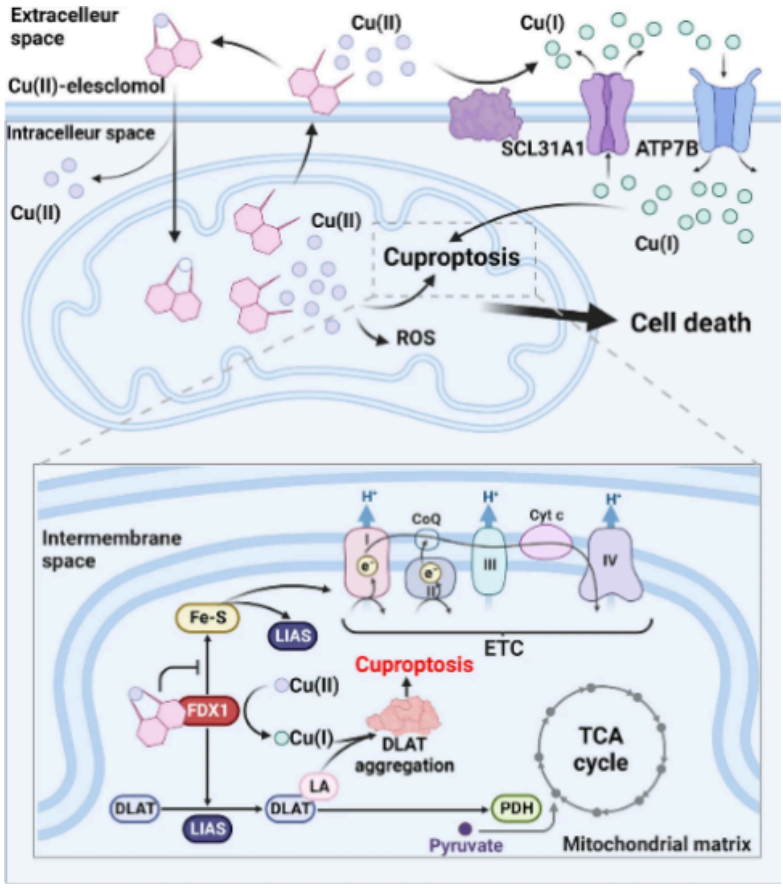

Figure 4. Schematic representation of elesclomol-induced copper accumulation in mitochondria leading to cuproptosis [9]

4. Multi-pathway synergistic modulation and roles in tumor therapy

4.1. Compensation and crosstalk

A basic fact of tumor death networks is compensation. When apoptotic thresholds are elevated, tumor cells often increase autophagic flux to maintain mitochondrial quality control and energy supply, thereby delaying death commitment. There is also structural linkage between autophagy and ferroptosis: autophagy can increase the labile iron pool through ferritinophagy, amplifying lipid peroxidation drive, which means that autophagy can be protective or ferroptosis-promoting depending on context [10]. One of the most direct apoptosis–pyroptosis crosstalk routes is caspase-3 cleavage of GSDME: when tumor cells express sufficient GSDME, apoptotic signaling can be converted into pyroptotic lysis with stronger inflammatory consequences. Crosstalk between

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cuproptosis and ferroptosis often arises from coupling between mitochondrial perturbation and cellular redox networks: copper-triggered mitochondrial proteotoxicity can disrupt redox balance and secondarily amplify lipid peroxidation, producing time-dependent transitions from cuproptosis to ferroptosis-like damage.

These interactions indicate that synergy should not be conceptualized as merely "stacking two lethal drugs." Rather, network-dynamic strategies should address three questions: whether synergy requires blocking compensatory pathways; whether execution converges on shared irreversible nodes (for example, lipid peroxidation or pore-forming lysis); and whether synergy changes immunological consequences, thereby shaping long-term control rather than short-term shrinkage.

4.2. Examples of multi-pathway synergy

Multi-pathway synergy requires mechanistic specification of compensatory blockade nodes, execution endpoints, and immunological consequences. Chemoradiation plus IAP inhibition (xevinapant) amplifies apoptotic signaling and improves survival in head and neck cancer, though immune-cell remodeling and inflammatory toxicity remain obstacles. mTOR inhibition combined with autophagy blockade (everolimus plus hydroxychloroquine) targets cytoprotective autophagy in renal cancer, but lysosomal toxicity constrains the window. Immune checkpoint blockade with cyst(e)ine depletion couples IFNγ-driven SLC7A11 downregulation to ferroptosis, creating dual immune-metabolic pressure; however, immune-cell ferroptosis may limit efficacy. Radiotherapy plus immunotherapy promotes lipid peroxidation and ferroptosis susceptibility, yet normal-tissue toxicity requires management [11].

4.3. Immunological effects of synergistic mechanisms

Among the pathways discussed, pyroptosis is most strongly linked to inflammatory mediator release through gasdermin pores and can robustly activate local immunity [12]. GSDME expression enhances macrophage phagocytosis and NK/CD8 T-cell function, while granzymes can directly cleave GSDME to amplify cytotoxicity. Ferroptosis also exhibits immune coupling: activated CD8 T cells suppress System Xc^- via IFNγ, promoting tumor ferroptosis, although excessive ferroptosis may impair immune cells [13]. Apoptosis is more context dependent and often immunologically silent unless combined with danger signals or checkpoint blockade. Major challenges for multi-pathway synergy include systemic toxicity and the need for causal validation in immune-competent models [14,15].

5. Conclusions and perspectives

Chemical modulation of tumor cell death pathways represents system-level reprogramming of tumor adaptive networks rather than simple blockade of a single pathway. Apoptosis targeting has shown clinical success in hematologic malignancies but remains limited in solid tumors due to tissue toxicity and compensatory anti-apoptotic buffering. Autophagy intervention needs flux - level evidence and disease - stage stratification so as to avoid context - dependent misinterpretation. Ferroptosis presents a way to get around the resistance to apoptosis. But for clinical translation, it is dependent on biomarker - guided patient selection and delivery engineering for safety [16]. Pyroptosis gives immunostimulatory vulnerabilities, while cuproptosis gives metabolic - selective ones. But both encounter systemic toxicity challenges that call for controllable induction strategies.

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Future studies should prioritize three directions: integrated biomarker systems combining multi-omics and functional imaging to define pathway dependence; development of next-generation chemical modalities such as degraders and antibody–drug conjugates to enhance selectivity; and trial designs that explicitly test pathway compensation and crosstalk through genetic validation, immune-competent models, and biomarker-stratified clinical studies [13].

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