Reprogramming of cell death in gastric cancer: From molecular mechanisms to therapeutic potential (Review)

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Abstract. Malignant progression and limited therapeutic response in gastric cancer (GC) cannot be explained solely by increased proliferation or oncogenic alterations. Instead, they reflect how tumor cells regulate their death threshold under sustained damage, metabolic stress and immune pressure. Evidence indicates that GC cells largely retain the capacity for cell death but reduce its effective execution by attenuating signal propagation, weakening key execution steps and altering microenvironmental interactions. As a result, cellular stress persists without effective clearance, promoting survival, resistance and metastasis. The present review synthesized current evidence on the mechanisms and interplay of cell death in GC, with emphasis on their relationships with the tumor microenvironment, host factors and therapeutic stress. It further evaluated their implications for resistance, patient stratification and therapeutic intervention. Reframing GC through the lens of cell death regulation provides a more coherent basis for understanding its biological heterogeneity and for improving therapeutic strategies.

Contents

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1. Introduction

Gastric cancer (GC) remains a major global health burden and one of the most lethal malignancies of the digestive system (1). Recent epidemiological data report nearly 1 million new cases and ~650,000 deaths annually, ranking GC among the leading causes of cancer incidence and mortality, with a particularly high burden in East Asia (2). Although screening and early detection have reduced incidence rates in some regions, the absolute number of cases continues to rise due to population aging and growth, and projections estimate that global incidence will increase by >60% by 2040, reaching ~1.77 million new cases, highlighting a sustained and escalating public health challenge (3). Etiologically, *Helicobacter pylori (H. pylori)* infection is the most well-established and modifiable risk factor, accounting for 85-90% of non-cardia GC cases, while dietary patterns, smoking, metabolic disturbances and genetic susceptibility further contribute to tumor initiation and progression (4,5). At the molecular level, GC represents a heterogeneous disease characterized by diverse genomic alterations, tumor microenvironmental features and evolutionary trajectories, which drive variability in responses to chemotherapy, targeted therapy and immunotherapy, as well as clinical outcomes (6). Clinically, the 5-year survival rate for advanced or metastatic GC remains <10%, emphasizing the urgent need to define its pathogenic networks and develop more precise and effective therapeutic strategies (7).

This molecular heterogeneity is further reflected by established genomic classifications of GC, including Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), chromosomal instability (CIN) and genomically stable (GS) subtypes, which exhibit distinct biological characteristics and therapeutic vulnerabilities (8-10). EBV-positive tumors are characterized by immune-rich microenvironments and frequent alterations in immune regulatory pathways, potentially influencing inflammatory cell death responses and immunotherapy sensitivity. MSI tumors harbor high mutational burdens and enhanced neoantigen generation, which may reshape interactions between regulated cell death (RCD) pathways and antitumor immunity. By contrast, CIN and GS tumors are associated with genomic instability, altered signaling networks and metabolic adaptations, which may contribute to differential dependencies on apoptotic regulation,

ferroptosis susceptibility and stress adaptation mechanisms. Therefore, understanding how molecular subtype-specific features influence cell death regulation may provide a more precise framework for interpreting therapeutic responses and identifying vulnerabilities in GC.

Dysregulated cell death is a core mechanism that drives tumor initiation, progression and variability in therapeutic responses (11,12). Apoptosis has long served as the principal effector pathway in anticancer therapy, and standard chemotherapeutic agents for GC, including fluorouracil and platinum compounds, act largely by inducing apoptotic cell death (13,14). However, growing insights into RCD show that GC cells do not depend on suppression of a single pathway for survival. Instead, they reprogram multiple death programs to adapt to sustained proliferation, metabolic stress, redox imbalance and chronic inflammation (15,16). In this context, 'cell death reprogramming' refers to the dynamic remodeling of cellular death susceptibility and execution patterns, rather than the simple activation or inhibition of an individual death pathway. This process involves alterations in death thresholds, transitions or compensation between distinct cell death modalities, and adaptive rewiring of death signaling networks in response to therapeutic pressure and changes within the tumor microenvironment (TME). Through this plasticity, cancer cells can evade lethal stress, maintain survival advantages and reshape their responses to anticancer interventions. This reprogramming alters both the activity and threshold of canonical apoptotic signaling and differentially regulates inflammatory cell death, autophagy-dependent cell death, ferroptosis and cuproptosis across distinct molecular contexts and disease stages (17). These death modalities interact through shared signaling axes and organelle stress responses, forming interconnected networks that enable functional compensation and cross-regulation. As a result, they shape tumor growth, invasive capacity, and sensitivity to chemotherapy, targeted therapy and immunotherapy (18,19). In GC, dissecting these pathways clarifies the molecular basis of resistance and recurrence and supports patient stratification, response prediction and therapeutic development (20,21). Accordingly, the present review systematically reviews the molecular mechanisms and interaction networks of cell death modalities in GC, integrating intracellular signaling, metabolic reprogramming and TME regulation to refine the framework of cell death reprogramming and guide multi-target therapeutic strategies.

2. RCD in GC

GC cell survival and death are not controlled by a single pathway but are coordinated by multiple forms of RCD with distinct molecular mechanisms. Across different genetic backgrounds and disease stages, these RCD modalities display differential activation patterns and marked heterogeneity in magnitude, signaling intensity and biological effects. Together, they form an integrated regulatory network that determines tumor cell fate.

Apoptosis-related cell death. Apoptosis is a well-characterized form of RCD that integrates extrinsic death receptor and intrinsic mitochondrial pathways to convert stress signals into caspase activation and irreversible execution (Fig. 1) (22). In cancer, tumor cells rarely lose apoptotic capacity; instead, they attenuate therapy-induced cell death by blocking signaling at multiple regulatory levels or by increasing the apoptotic threshold (23). Therefore, defining the functional status and plasticity of key apoptotic nodes is essential for understanding tumor biology and developing precise therapeutic strategies.

Mechanism of apoptosis. Apoptotic signaling integrates extrinsic death receptor and intrinsic mitochondrial pathways, with caspase cascades executing cell death and mitochondrial outer membrane permeabilization (MOMP) serving as the commitment event that determines cell fate (13). The intrinsic pathway responds to diverse stresses, including DNA damage, oxidative stress, endoplasmic reticulum stress, growth factor deprivation and metabolic imbalance. These signals induce or activate BH3-only proteins through transcriptional and post-translational mechanisms and converge on the BCL-2 family regulatory network (11). Activator BH3 proteins, such as BH3-Interacting Domain Death Agonist (BID), Bcl-2 interacting mediator of cell death (BIM), p53 upregulated modulator of apoptosis (PUMA) and NOXA, promote conformational activation and oligomerization of BAX and BAK at the mitochondrial outer membrane (24,25). Sensitizer BH3 proteins displace anti-apoptotic family members and lower the apoptotic threshold. By contrast, anti-apoptotic proteins, including BCL-2, BCL-xL and myeloid cell leukemia 1 (MCL1), sequester BH3 proteins and BAX/BAK to maintain a dynamic threshold for apoptosis (26,27). Once this control is overcome, BAX/BAK form pores that release intermembrane proteins such as cytochrome c and second mitochondria-derived activator of caspases (SMAC). Cytochrome c assembles with apoptotic protease-activating factor 1 (APAF1) and deoxyATP (ATP) into the apoptosome, which activates caspase-9 and subsequently caspase-3 and caspase-7 (28). In parallel, SMAC antagonizes inhibitor of apoptosis (IAP) family proteins such as X-linked inhibitor of apoptosis protein (XIAP) and enhances caspase activity and death signaling flux (29,30). The extrinsic pathway is initiated by death receptors, including FAS, tumor necrosis factor receptor 1 (TNFR1) and TNF-related apoptosis-inducing ligand (TRAIL) receptors. Ligand binding induces receptor trimerization and recruitment of Fas-associated via death domain (FADD) and pro-caspase-8 to form the death-inducing signaling complex, where caspase-8 undergoes activation. Activated caspase-8 directly cleaves executioner caspases or processes BID into tBID to engage the mitochondrial pathway and amplify the signal (31-34). TNFR1 signaling exhibits ubiquitin-dependent branching. Ubiquitinated receptor-interacting serine/threonine-protein kinase 1 (RIPK1) primarily promotes NF-κB- and MAPK-mediated survival signaling, whereas deubiquitinated RIPK1 associates with FADD and caspase-8 to form pro-apoptotic complexes (35). Cellular FLICE-like inhibitory protein (c-FLIP) isoforms further fine-tune caspase-8 activity through competitive regulation and thereby control the strength of apoptotic execution (36).

As a context-dependent extension of apoptosis, anoikis is triggered by loss of adhesion to the extracellular matrix or neighboring cells and retains substantial overlap with the canonical mitochondrial pathway (37). Loss of adhesion disrupts integrin-mediated survival signaling and induces intracellular stress reprogramming, thereby lowering the

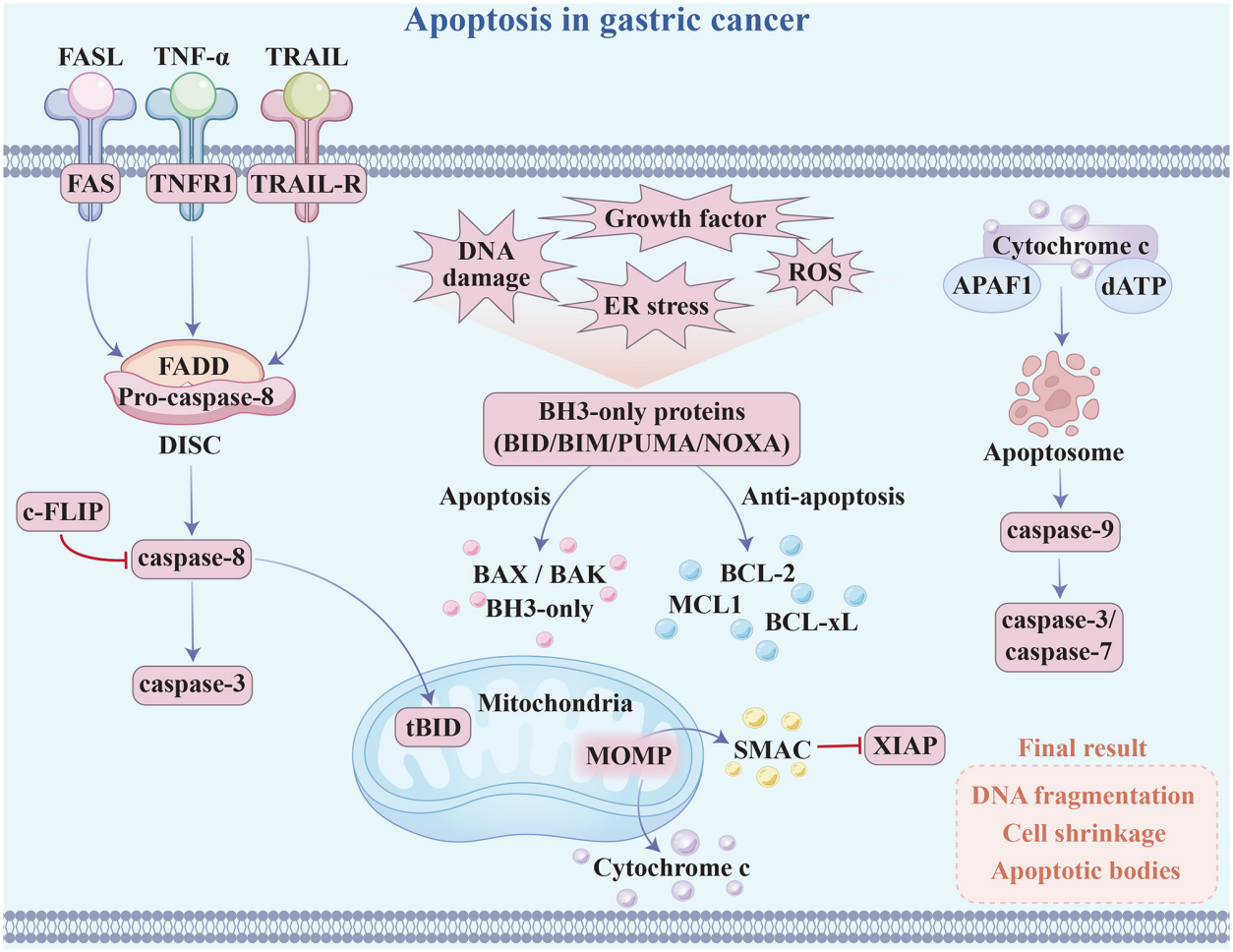

Figure 1. Molecular mechanisms and regulatory framework of apoptosis in gastric cancer. Apoptosis in gastric cancer is regulated through coordinated interactions between the extrinsic death receptor pathway and the intrinsic mitochondrial pathway. Extrinsic apoptotic signaling is initiated by FASL, TNF-α or TRAIL binding to their corresponding receptors, leading to DISC formation, caspase-8 activation, and downstream executioner caspase signaling, whereas c-FLIP negatively regulates this process. Intrinsic apoptotic signaling is triggered by intracellular stresses, including DNA damage, oxidative stress, growth factor deprivation, and endoplasmic reticulum stress, which activate BH3-only proteins such as BID, BIM, PUMA and NOXA. These signals converge on the BCL-2 family network to determine MOMP through the balance between pro-apoptotic proteins (BAX/BAK) and anti-apoptotic proteins (BCL-2, BCL-xL and MCL1). MOMP promotes the release of cytochrome c and SMAC from mitochondria. Cytochrome c associates with APAF1 and dATP to form the apoptosome and activate caspase-9 and downstream caspase-3/7 signaling, whereas SMAC antagonizes XIAP-mediated caspase suppression. Crosstalk between extrinsic and intrinsic pathways is mediated in part through caspase-8-dependent BID cleavage into tBID, which amplifies mitochondrial apoptotic signaling. MOMP, mitochondrial outer membrane permeabilization; ER, endoplasmic reticulum; FASL, Fas ligand; TRAIL, TNF-related apoptosis-inducing ligand; c-FLIP, cellular FLICE-like inhibitory protein; BID, BH3-interacting domain death agonist; BIM, Bcl-2 Interacting Mediator of cell death; PUMA, p53 upregulated modulator of apoptosis; NOXA, NADPH oxidase activator 1; SMAC, second mitochondria-derived activator of caspases; APAF1, Apoptotic Peptidase Activating Factor 1; ROS, reactive oxygen species; TNFR1, TNF receptor 1; XIAP, X-linked inhibitor of apoptosis protein.

threshold for BCL-2 family-regulated MOMP and initiating caspase activation and programmed cell clearance (38,39). Under physiological conditions, this process removes displaced cells to maintain tissue architecture and homeostasis, whereas during tumor progression it acts as a critical barrier to metastasis. Tumor cells overcome this barrier by attenuating apoptotic signaling, sustaining pro-survival pathways or reprogramming metabolism and phenotype, thereby acquiring anoikis resistance that enables anchorage-independent survival and supports distant colonization (40). Overall, apoptosis functions as an RCD program centered on mitochondrial commitment, integrates death receptor-mediated inputs, and executes cell dismantling through caspase cascades, with its activity controlled by coordinated, multilayered networks including the BCL-2 family, IAP family and epigenetic regulators; this plastic threshold-control system provides a molecular basis for tumor cell survival advantage and for the development of targeted therapeutic strategies.

Regulation of apoptosis in GC. In GC, apoptotic pathways are preserved but functionally reprogrammed through threshold remodeling. Compared with normal epithelial cells, GC cells show reduced apoptotic sensitivity and limited access to the commitment point, especially at the level of mitochondrial decision-making, resulting in decreased apoptotic priming (41). At the input level, peripheral myelin protein 22 suppresses p53 transcriptional activity and downregulates pro-apoptotic genes such as *BAX* and *PUMA*, thereby weakening mitochondrial signaling strength (42). TRIM family E3 ubiquitin ligase 17 further promotes BAX ubiquitination and degradation, which reduces the probability of MOMP and attenuates chemotherapy-induced apoptotic flux (43). Metabolic and redox buffering also elevate the

apoptotic threshold. Nicotinamide nucleotide transhydrogenase sustains NADPH production and glutathione (GSH) reduction capacity, limits reactive oxygen species (ROS) accumulation and suppresses mitochondrial stress amplification, thereby enhancing resistance to apoptosis and anoikis under nutrient deprivation or detachment conditions (44). On the contrary, loss of tumor suppressors further increases the activation threshold. Downregulation of gastrokine-2 impairs NF-κB/JNK-mediated stress signal routing and prevents efficient transmission of oxidative stress into caspase-9/3 activation (45). Promoter methylation-mediated silencing of heart- and neural crest derivatives-expressed protein 1 (HAND1) disrupts coupling of endoplasmic reticulum stress to the CHOP-BAK axis, whereas restoration of HAND1 enhances cisplatin-induced apoptosis (46). Metabolic regulation also modulates apoptosis in GC by reshaping cellular energy metabolism, redox homeostasis and mitochondrial function. UMP suppresses NR4A1 and limits its mitochondrial translocation, thereby reducing cytochrome c release, whereas relieving this constraint or combining with NR4A1 agonists enhances apoptosis in xenograft and patient-derived xenograft (PDX) models (47). Beyond mitochondrial control, extrinsic signaling is also tightly regulated. O-GlcNAc modification of DR4 is required for TRAIL-DISC assembly and caspase-8 recruitment, and its disruption leads to receptor-level signaling defects and TRAIL resistance (48). 3-hydroxybutyrate dehydrogenase type 2 (BDH2) downregulation sustains Nrf2-dependent antioxidant transcription and Akt/mTOR survival signaling, which limits ROS accumulation and attenuates caspase-3 activation (49). By contrast, stromal interaction molecule 1-mediated store-operated calcium entry increases cytosolic Ca^{2+} levels and activates endoplasmic reticulum stress pathways, thereby upregulating BAX and cleaved caspase-3 to enhance apoptotic execution (50). At the execution stage, GC cells further dampen apoptosis by reducing caspase activation amplitude and substrate cleavage efficiency, leading to suboptimal or reversible activation states. In a gp130F/F intestinal-type GC model, the ASC-IL18 axis suppresses caspase-8-dependent apoptosis within tumor epithelium, whereas loss of ASC or IL18 enhances TUNEL positivity and cleaved caspase-8 while reducing tumor burden (51). During apoptosome assembly, long non-coding RNA (lncRNA) ABL competitively binds APAF1 and blocks its interaction with cytochrome c, thereby inhibiting caspase-9/3 activation and promoting chemoresistance (52). At the post-transcriptional level, N6-methyladenosine (m6A)-modified proteasome 20S subunit α 3 antisense RNA 1 and mir22HG suppress caspase-related outputs through competing endogenous RNA (ceRNA) and protein interaction networks while maintaining stem-like phenotypes (53). Caspase-3-mediated cleavage of CAD at Asp1371 is required for chemotherapy-induced apoptosis, and disruption of this process or CAD overexpression reduces cell death and promotes resistance (54,55). In CIN and GS GCs, where genomic instability and survival pathway activation are prominent features, alterations in apoptotic thresholds may represent important mechanisms underlying therapeutic resistance (56). Overall, GC attenuates signal strength and transmission efficiency across key nodes, including upstream inputs, mitochondrial commitment and execution cascades, thereby preventing apoptotic stimuli from exceeding the clearance threshold and establishing a low-sensitivity state associated with therapeutic resistance.

Clinical implications of apoptosis in GC. Apoptosis is a central execution endpoint for tumor clearance in GC during chemotherapy and targeted therapy. The efficacy of platinum agents, including cisplatin and oxaliplatin, depends on activation of the mitochondrial apoptotic pathway, and modulation of metabolic or redox states can further amplify apoptotic flux without increasing toxicity. Metformin enhances oxaliplatin-induced tumor cell clearance by regulating the BCL-2/BAX balance and activating caspase-3 (57). In neoadjuvant chemotherapy cohorts, cellular retinoic acid-binding protein 2 mediates oxaliplatin resistance by promoting BAX ubiquitination and degradation, thereby suppressing mitochondrial apoptosis; its inhibition restores apoptosis and reverses resistance in cell line-derived xenograft and PDX models (58). Natural compounds also enhance apoptotic responses. WZ35 inhibits thioredoxin reductase 1, induces ROS accumulation and activates p38/JNK signaling to potentiate cisplatin-induced apoptosis (59). Isorhamnetin suppresses NF-κB signaling and downregulates anti-apoptotic proteins such as survivin to amplify capecitabine-induced apoptosis (60). Components of *Tripterygium wilfordii*, a traditional Chinese medicinal herb, induce mitochondrial apoptosis by inhibiting peroxiredoxin 2 (PRDX2), and high PRDX2 expression is associated with poor prognosis; related clinical studies are ongoing (61-63). Organoid-PDX models show that Ailanthone disrupts the p23/HSP90 axis, destabilizes x-ray repair cross-complementing protein 1 and impairs base excision repair, allowing DNA damage to exceed the apoptotic threshold (64). Direct targeting of anti-apoptotic pathways has entered clinical evaluation. The pan-BCL-2 inhibitor AT-101 combined with chemoradiotherapy shows favorable response rates (65). In tumors with high EGFR copy number, pyrotinib activates endoplasmic reticulum stress-related apoptosis through the EGFR-GRP78 axis and suppresses DNA repair, thereby enhancing chemosensitivity and enabling stratified therapy (66). Anti-programmed cell death protein 1 (PD-1) immunotherapy also provides survival benefit in a subset of patients, partly through T cell-mediated induction of tumor cell apoptosis via death receptor and granzyme pathways (67). Increasing tumor susceptibility to apoptosis while limiting apoptotic stress in effector T cells may therefore improve the durability of therapeutic responses (68).

Beyond therapy, apoptosis-related molecules also contribute to diagnosis and prognostic assessment. Gastrokine-1 expression decreases during gastric carcinogenesis, and its restoration enhances 5-FU-induced apoptosis (69). Apogossypolone enables real-time *in vivo* monitoring of apoptosis through bioluminescence imaging, supporting its use as a quantifiable pharmacodynamic readout (70). Dual-modal imaging combined with ultrasound-guided delivery further enhances caspase- and PARP-associated apoptosis while enabling integrated imaging and histological validation (71,72). Several apoptosis regulators are associated with patient outcomes. Caspase-3 is an independent prognostic factor (73); hypermethylation of calcium-activated potassium channel, subfamily M subunit α-1 predicts poor survival (74); and high insulin receptor tyrosine kinase substrate expression

associates with unfavorable prognosis (75). Additional regulators, including serine protease 23, gastrokine-2, estrogen-related receptor α, and non-coding RNAs (ncRNAs), such as miR-216 and circ-DONSON, modulate the survival-death balance and are associated with clinical features such as TNM stage (45,76-78). Taken together, apoptosis-related molecules link mechanistic insights with clinical application and support the development of precision and personalized therapies in GC.

Inflammation-related cell death. Unlike canonical apoptosis, inflammation-related cell death features loss of plasma membrane integrity, release of inflammatory mediators, and sustained activation of innate immune signaling. These processes reshape the TME and influence immune surveillance, therapeutic response and disease progression (79). In GC, these cell death modalities show marked context dependence and bidirectional regulation. They can promote tumor progression through chronic inflammation or enhance antitumor immunity by amplifying immune activation. This dual role underscores their mechanistic importance and translational potential (Fig. 2).

Necroptosis

Mechanism of necroptosis in GC. Necroptosis is a regulated form of necrotic cell death characterized by mixed lineage kinase domain-like protein (MLKL)-mediated membrane permeabilization and typically occurs when death receptor or innate immune signaling is activated but caspase-8-dependent apoptosis is limited. In the TNFα-TNFR1 pathway, the ubiquitination status of RIPK1 determines signaling output. Ubiquitinated RIPK1 promotes NF-κB- and MAPK-driven survival signaling. By contrast, deubiquitinated RIPK1 with kinase activity engages RIPK3 through RIP homotypic interaction motif (RHIM) domains to form the necrosome, which activates RIPK3 and drives MLKL phosphorylation, oligomerization and membrane translocation, leading to membrane rupture and damage-associated molecular patterns (DAMPs) release that amplify inflammatory and immune responses (80,81). RHIM-mediated amyloid-like assembly stabilizes this platform and enhances signal propagation (82). Moreover, caspase-8 and c-FLIP function as a checkpoint that regulates the balance between apoptosis and necroptosis. During execution, ion flux and cellular content release further activate inflammasomes and PANoptosis networks, linking membrane disruption to amplified inflammatory cascades (83). Consequently, necroptosis exerts context-dependent effects in tumors. It can enhance antitumor immunity through DAMP-driven antigen presentation and $CD8^+$ T cell activation. It can also promote tumor progression by sustaining inflammatory signaling, recruiting immunosuppressive myeloid cells and supporting metastatic niche formation (84-86). In GC, necroptosis is regulated by threshold mechanisms and can be reactivated under therapeutic or oxidative stress. HUHS1015 induces RIPK1-dependent membrane-disruptive cell death, whereas chelerythrine promotes ROS accumulation and shifts cell fate toward necroptosis (87,88). Endogenous regulators further modulate this pathway. miR-204-3p suppresses RIPK1 and MLKL activation while enhancing mitochondrial apoptosis, whereas Clofoctol induces TNF-dependent necroptosis in stem-like cells, indicating a targetable vulnerability within this axis (89,90). Spatial and single-cell transcriptomic analyses indicate that necroptosis-associated DAMP signaling contributes to metastatic niche remodeling and immunosuppressive microenvironment formation, suggesting that necroptosis functions as a dynamic regulator of tumor-immune interactions rather than a simple cell death program (91). Overall, necroptosis in GC is a RIPK1-RIPK3-MLKL-driven membrane-disruptive process regulated by caspase-8 checkpoints and redox and proteostasis stress, providing both an alternative route to overcome apoptosis resistance and a modulatable inflammatory output that shapes immune responses and therapeutic sensitivity (81,92).

Clinical implications of necroptosis in GC. The clinical relevance of necroptosis in cancer stems from its pathway activity and inflammatory output, which reshape the TME and influence tumor classification, prognosis and therapeutic response. In hepatocellular carcinoma models, activation of the RIPK3-MLKL axis associates with specific cytokine profiles and drives transition toward a cholangiocarcinoma-like phenotype. By contrast, inhibition of RIPK1 or MLKL alters tumor progression and histological features, indicating that necroptosis-related signaling can serve as a molecular readout for tumor stratification and risk assessment (93). In immunotherapy settings, induction of RIPK3-dependent necroptosis promotes mitochondrial DNA release and activates the cGAS-STING pathway, which enhances type I interferon production and dendritic cell cross-presentation. This response amplifies the efficacy of radiotherapy or cisplatin combined with anti-PD-1 therapy and associates with favorable immune infiltration and treatment outcomes (94). Consistently, pharmacological activation of RIPK1 and MLKL enhances intratumoral $CD8^+$ T cell function and increases sensitivity to immune checkpoint blockade (95). However, necroptosis-associated inflammation can also drive tumor progression in certain contexts. In pancreatic cancer, MLKL-associated programs associate with increased liver metastasis and promote pro-metastatic niche formation through myeloid cell recruitment and immunosuppressive signaling (96). In GC, necroptosis-related gene signatures are incorporated into prognostic and therapeutic stratification models. Analyses of The Cancer Genome Atlas and Gene Expression Omnibus datasets show that high-risk groups have poorer overall survival and retain independent predictive value in multivariate models. These groups also display distinct patterns of immune infiltration, immune checkpoint expression, tumor mutational burden (TMB) and TIDE scores, linking necroptosis-associated transcriptional programs to immune exclusion or dysfunction and potential immunotherapy response (97,98). A validated six-gene model further shows that high-risk tumors associate with advanced stage, higher grade, and immunosuppressive features, whereas low-risk tumors exhibit increased $CD8^+$ T cell and Th1 activity and greater drug sensitivity. Single-cell communication analyses indicate that necroptosis-related signaling is activated through TNF pathways in myeloid cells and couples with glycolytic reprogramming, linking inflammation, metabolism, and prognosis (99). Incorporation of necroptosis into the broader PANoptosis framework further connects prognosis, immune contexture and chemotherapy sensitivity, supporting therapy selection based on cell death network states (100). In conclusion, necroptosis-related pathways

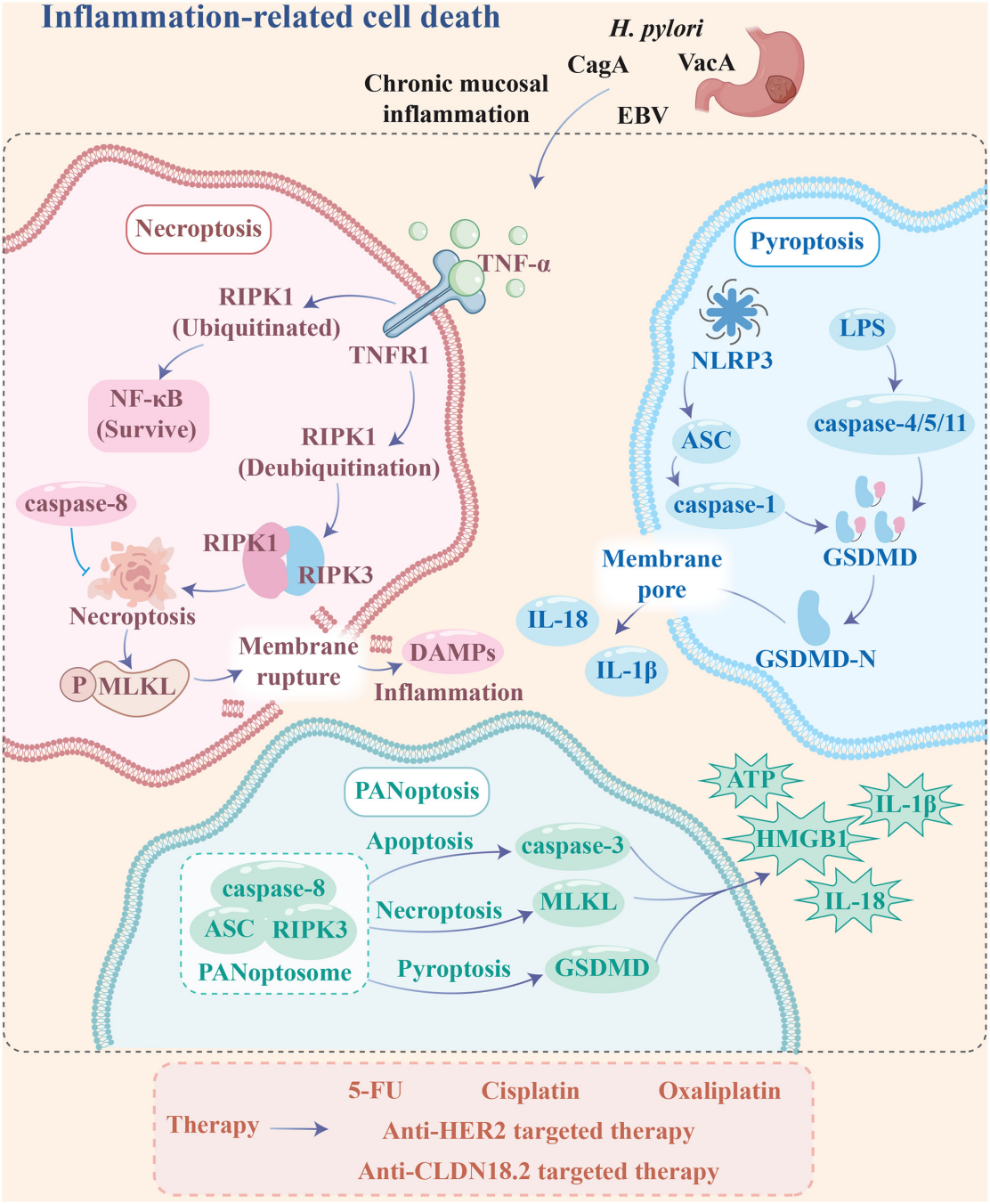

Figure 2. Integrated regulatory network of inflammation-related cell death in gastric cancer. Inflammation-related cell death in gastric cancer primarily includes necroptosis, pyroptosis and PANoptosis, which are interconnected through shared signaling nodes and inflammatory outputs. Gastric cancer-specific etiological factors, including *H. pylori* infection and its virulence factors CagA and VacA, EBV infection and chronic mucosal inflammation, provide upstream inflammatory and cellular stress contexts that can modulate these cell death programs. Necroptosis is typically initiated by TNF-α/TNFR1 signaling. Ubiquitinated RIPK1 mainly promotes NF-κB-mediated survival signaling, whereas deubiquitinated RIPK1 interacts with RIPK3 to form the necrosome, leading to MLKL phosphorylation, membrane rupture, release of DAMPs, and inflammatory amplification. Caspase-8 functions as an important checkpoint regulating the balance between apoptosis and necroptosis. Pyroptosis is mediated through canonical inflammasome signaling or noncanonical LPS sensing pathways. Activation of NLRP3 promotes assembly of the inflammasome complex containing ASC and caspase-1, resulting in GSDMD cleavage and generation of membrane pores through GSDMD-N oligomerization. In parallel, intracellular LPS activates caspase-4/5/11 to induce noncanonical pyroptotic signaling. These processes facilitate membrane permeabilization and release of inflammatory cytokines such as IL-1β and IL-18. PANoptosis represents an integrated inflammatory cell death program that coordinates apoptosis, necroptosis, and pyroptosis through PANoptosome complexes containing molecules such as caspase-8, RIPK3, and ASC. Concurrent activation of caspase-3, MLKL and GSDMD amplifies inflammatory and immunogenic outputs, including ATP, HMGB1, IL-1β and IL-18 release. DAMPs, damage-associated molecular patterns; EBV, Epstein-Barr virus; TNFR1, TNF receptor 1; RIPK1, receptor-interacting serine/threonine-protein kinase 1; MLKL, mixed lineage kinase domain like pseudokinase; LPS, lipopolysaccharide; GSDMD, gasdermin D; HMGB1, high mobility group box 1.

act as indicators of inflammation-immunity-metabolism coupling and as targets for immunotherapy sensitization and combination strategies, with clinical utility dependent on tumor subtype and microenvironmental context in GC.

Pyroptosis

Mechanism of pyroptosis in GC. Pyroptosis is a lytic form of RCD driven by Gasdermin (GSDM)-mediated pore formation in the plasma membrane. In the canonical pathway, pattern recognition receptors such as NLRP3 and AIM2 sense pathogen-associated molecular patterns or DAMPs and assemble inflammasomes that activate caspase-1 and cleave GSDMD, leading to cell swelling, membrane rupture, and release of inflammatory mediators such as IL-1β and IL-18, whereas in the non-canonical pathway, cytosolic lipopolysaccharide (LPS) directly activates caspase-4, caspase-5 or caspase-11 and similarly converges on GSDMD cleavage (101,102). In tumors, pyroptosis arises through additional mechanisms, as caspase-3 or caspase-8 cleave GSDMC, and cytotoxic lymphocytes release granzymes that target GSDMB or GSDME, thereby linking immune cytotoxicity to pyroptotic execution (103-106). Pyroptotic activity is further regulated by GSDM stability and cellular stress states, with USP48 stabilizing GSDME through deubiquitination to increase pyroptotic sensitivity, whereas the IRE1α-RIDD axis limits chemotherapy-induced NLRP3-GSDMD pyroptosis by degrading double-stranded RNA (107,108). In GC, pyroptosis shows marked context dependence, acting as an antitumor effector under therapeutic stress, where agents such as 5-FU, oxaliplatin and cisplatin activate caspase-3 and cleave GSDME, shifting cell death from apoptosis to a more immunogenic pyroptotic form accompanied by membrane blebbing and lactate dehydrogenase release (109-111), while ROS accumulation and NF-κB activation further promote NLRP3 inflammasome assembly and caspase-1 activation to enhance GSDMD- or GSDME-mediated pyroptosis (112,113). Conversely, GC cells suppress pyroptosis through multilayered regulation, including GSDME promoter hypermethylation, ALKBH4-mediated reduction of H3K4me3 enrichment and EBV-associated epigenetic silencing that limit GSDME expression, as well as METTL3-PFKFB3-driven metabolic reprogramming and HIC1 downregulation that inhibit the NLRP3-GSDMD pathway or reduce GSDMD transcription (114-117). Notably, under chronic inflammatory conditions, persistent *H. pylori* infection activates inflammasome and GSDMD signaling through virulence factors such as VacA and CagA, contributing to sustained mucosal inflammation and tumor initiation (118,119). Collectively, GC cells dynamically regulate pyroptotic output by modulating GSDM expression, inflammasome activation thresholds and metabolic states, enabling pyroptosis to function either as an effector of therapy-induced tumor killing or as a driver of tumor-promoting inflammation in chronic inflammatory settings.

Clinical implications of pyroptosis in GC. The therapeutic value of pyroptosis in cancer lies in its dual role as a quantifiable stratification marker and a reactivatable effector pathway. Pan-cancer studies show that GSDM-dependent pyroptosis influences both chemotherapy sensitivity and the conversion of treatment-induced inflammatory signals into effective immune recruitment and tumor clearance. In several tumor models, low GSDME expression or suppression of the NLRP3-caspase-1-GSDMD axis associates with poor therapeutic response, whereas restoration of pyroptotic execution enhances cytotoxicity and antitumor immunity, supporting its potential as both a companion biomarker and a combinatorial therapeutic target (120,121). In GC, pyroptosis contributes to clinical management in three main ways. First, pyroptosis-related signatures derived from genes, ncRNAs, or PANoptosis features associate with overall survival, immune infiltration, TMB, MSI and immune checkpoint expression, supporting their potential utility for risk stratification and prediction of immunotherapy response, including in neoadjuvant settings (122-124). Second, pyroptosis provides an entry point for chemosensitization and reversal of drug resistance, as agents such as BIX-01294 or lens protein with glutamine synthetase domain inhibition can activate GSDME- or NLRP3-GSDMD-dependent pathways to enhance responses to cisplatin, 5-FU and oxaliplatin, suggesting that redirecting resistant or stem-like tumor cells toward the pyroptotic threshold may reduce relapse (125,126). Third, pyroptosis-related molecules themselves show therapeutic relevance, with elevated caspase-1, IL-1β and IL-18 reflecting activation of the pyroptotic inflammatory axis and GSDMD linking tumor growth, immune contexture and treatment sensitivity (127,128). However, pyroptosis is not uniformly beneficial, as its inflammatory output may also sustain chronic inflammation, promote stromal remodeling, and drive immunosuppressive microenvironments (129). In summary, pyroptosis in GC is transitioning from a mechanistic concept to a clinically relevant framework for stratification, response prediction and combination therapy design, although further prospective validation and standardized assessment remain necessary.

PANoptosis. PANoptosis is an integrated cell death program coordinated by shared signaling nodes and defined by the coordinated activation of pyroptosis, apoptosis and necroptosis within common sensing and execution platforms, accompanied by robust inflammatory and immunogenic outputs (130-132). Pan-cancer studies support this framework, as sterile α motif and HD domain-containing protein 1 deficiency in diffuse large B-cell lymphoma induces cytosolic double stranded (ds)DNA accumulation and activates STING, promoting formation of CASP8-, RIPK3- and ASC-containing complexes and triggering GSDME cleavage, caspase-3 activation and MLKL phosphorylation (133), while deoxyribonuclease 1L3 in hepatocellular carcinoma enhances dsDNA accumulation and AIM2-dependent PANoptosome assembly, shifting sorafenib-induced cell death toward stronger PANoptotic output with enhanced antitumor immunity (134). These findings position PANoptosis as a convergence point linking multiple death pathways with therapeutic sensitization and immune remodeling. Direct evidence in GC remains limited but is supported by functional studies, as Jolkinolide B induces PANoptotic death through caspase-8 activation with concurrent increases in cleaved caspase-3/7, GSDMD-N, and phosphorylated RIPK1 and MLKL, and this effect is partially reversed by caspase-8 inhibition, indicating a central integrative role (135); similarly, a nanoparticle-based photodynamic system (CJP-TiN) amplifies PANoptosis via ROS accumulation and caspase-8 activation, enhances cleaved caspase-3/7/8, GSDME-N and p-MLKL signaling, and promotes release of ATP, HMGB1, IL-1β and IL-18, demonstrating coordinated activation of multiple

death pathways and immunostimulatory outputs (136). By contrast, GC cells suppress PANoptosis to sustain survival and drug resistance, as Y-box binding protein 1 (YBX1) is upregulated in oxaliplatin-resistant cells and restricts activation of apoptosis, necroptosis, and pyroptosis through a PPM1B-YBX1-USP10 regulatory axis that modulates platinum sensitivity (137), while high heat shock protein β-1 expression suppresses RIPK3, cleaved caspase-1, NLRP3 and cleaved caspase-3, and its silencing reduces proliferation, invasion and tumorigenicity, supporting a tumor-suppressive role for PANoptosis (138). Clinically, PANoptosis in GC is mainly characterized through transcriptomic stratification and risk modeling, where high PANoptosis activity associates with stronger immune signaling, higher tumor mutational burden or MSI-H status, increased effector immune cell infiltration, and improved survival, whereas low activity is associated with epithelial-mesenchymal transition, extracellular matrix remodeling, TGF-β signaling, enrichment of cancer-associated fibroblasts (CAFs) and M2 macrophages, and immune evasion phenotypes (100,139), and PANoptosis-based risk scores further show prognostic value and may predict responses to immune checkpoint inhibitors, chemotherapy, and targeted therapies (140-143). In conclusion, PANoptosis in GC functions as an integrative framework linking cell death programs, immune heterogeneity, and therapeutic response, although its regulatory mechanisms and translational potential require further systematic investigation.

Metabolism-dependent cell death. Tumor cells continuously reprogram metabolic networks to sustain rapid proliferation and adapt to a complex microenvironment. This reprogramming, centered on lipid, amino acid and energy metabolism, supports growth and sets the threshold for tolerating metabolic stress. Cell death driven by metabolic imbalance has therefore emerged as a key process. It is triggered by disruptions in redox homeostasis, abnormal metal ion accumulation or loss of proteostasis. GC cells can delay or evade this process through adaptive metabolic rewiring. When these compensatory mechanisms fail, metabolic stress converts into lethal signaling. Metabolism-dependent cell death thus reflects tumor metabolic plasticity and provides an opportunity to overcome therapeutic resistance and improve treatment efficacy (Fig. 3).

Autophagy

Mechanism of autophagy in GC. Autophagy is a multistep degradative process triggered by nutrient deprivation, oxidative stress, endoplasmic reticulum stress, infection or energy imbalance and regulated by AMPK-unc-51-like autophagy-activating kinase (ULK)1 and PI3K-Akt-mTOR signaling. It proceeds through phagophore nucleation via the Beclin1-VPS34 complex, autophagosome formation mediated by the ATG5-ATG12-ATG16L system and LC3 lipidation and substrate degradation after fusion with lysosomes (144,145). In GC, autophagy primarily functions as a context-dependent adaptive process rather than an autonomous cell death program, exhibiting either cytoprotective or tumor-suppressive effects depending on disease stage and cellular context. During early *H. pylori*-associated lesions, it acts as a protective mechanism that limits oncoprotein accumulation, buffers oxidative stress and maintains genomic stability. For example, VacA activates ROS-dependent Akt-MDM2-p53 signaling to induce autophagy and promote CagA degradation in normal gastric epithelial cells, whereas elevated xCT-mediated GSH in CD44v9-positive stem-like cells suppresses autophagy and permits CagA accumulation (146). Moreover, *H. pylori* induced nuclear translocation of low-density lipoprotein receptor-related protein 1-isocitrate dehydrogenase (IDH) promotes lysosomal-associated membrane protein 1 transcription and autophagolysosome formation, while capping actin protein of muscle z-line subunit α 1 upregulation disrupts this process and facilitates CagA persistence (147). Sustained infection further impairs autophagy, leading to p62 accumulation and Rad51 degradation, which compromises DNA repair and promotes tumorigenesis (148). In established GC, autophagy primarily supports adaptive survival. E2 transcription factor 4 activates ATG2A and ULK2 to promote growth and invasion, SEC23A is induced by STAT3 under endoplasmic reticulum stress and enhances autophagy via annexin A2 membrane translocation to buffer stress and reduce 5-FU-induced apoptosis, c-Jun upregulates protein phosphatase 1 regulatory subunit 15A under glucose deprivation to sustain autophagosome formation, and latent membrane protein 2A activates the PI3K/Akt-NRF1-CXCR4-ZEB1-ATG7 axis to maintain autophagy and viral persistence (149-152). However, under specific experimental conditions, sustained or excessive autophagy has been reported to suppress tumor progression and may contribute to cell death-associated phenotypes, although direct evidence for autophagy-dependent cell death remains limited in GC. Death-associated protein kinase 3 phosphorylates ULK1 at Ser556 to promote autophagy initiation and suppress proliferation and metastasis, BDH2 induces ROS accumulation and inhibits Akt/mTOR signaling to trigger autophagy with enhanced apoptosis, and glucose deprivation-induced autophagy promotes sequestosome-1/LC3-dependent degradation of N-acetyltransferase 10 to suppress hexokinase 2-driven glycolysis and tumor growth (49,153,154). Dysregulation in GC often occurs at the level of autophagic flux rather than initiation. VacA impairs lysosomal function by inhibiting transient receptor potential mucolipin 1 and blocks autophagosome maturation and substrate clearance, whereas polypyrimidine tract binding protein 1 deficiency increases thioredoxin-interacting protein and ROS levels, disrupts lysosomal integrity and prevents autophagosome-lysosome fusion, autophagosome accumulation, lysosomal dysfunction and subsequent cell death, although the death phenotype may not be exclusively mediated by autophagy itself (155,156). Overall, autophagy in GC is therefore a dynamic and context-dependent process, with biological effects determined by disease stage and cellular state. According to current consensus, autophagy should not be considered synonymous with autophagy-dependent cell death, unless cell death is demonstrated to rely directly on the autophagic machinery.

Clinical implications of autophagy in GC. The clinical relevance of autophagy in GC depends on its function across disease stages and molecular contexts. During persistent *H. pylori* infection and premalignant lesions, autophagy acts as a protective mechanism that limits oncoprotein accumulation, maintains genomic stability and modulates inflammation, thereby supporting risk stratification and early intervention. IFN-γ induces Beclin-1-dependent autophagy

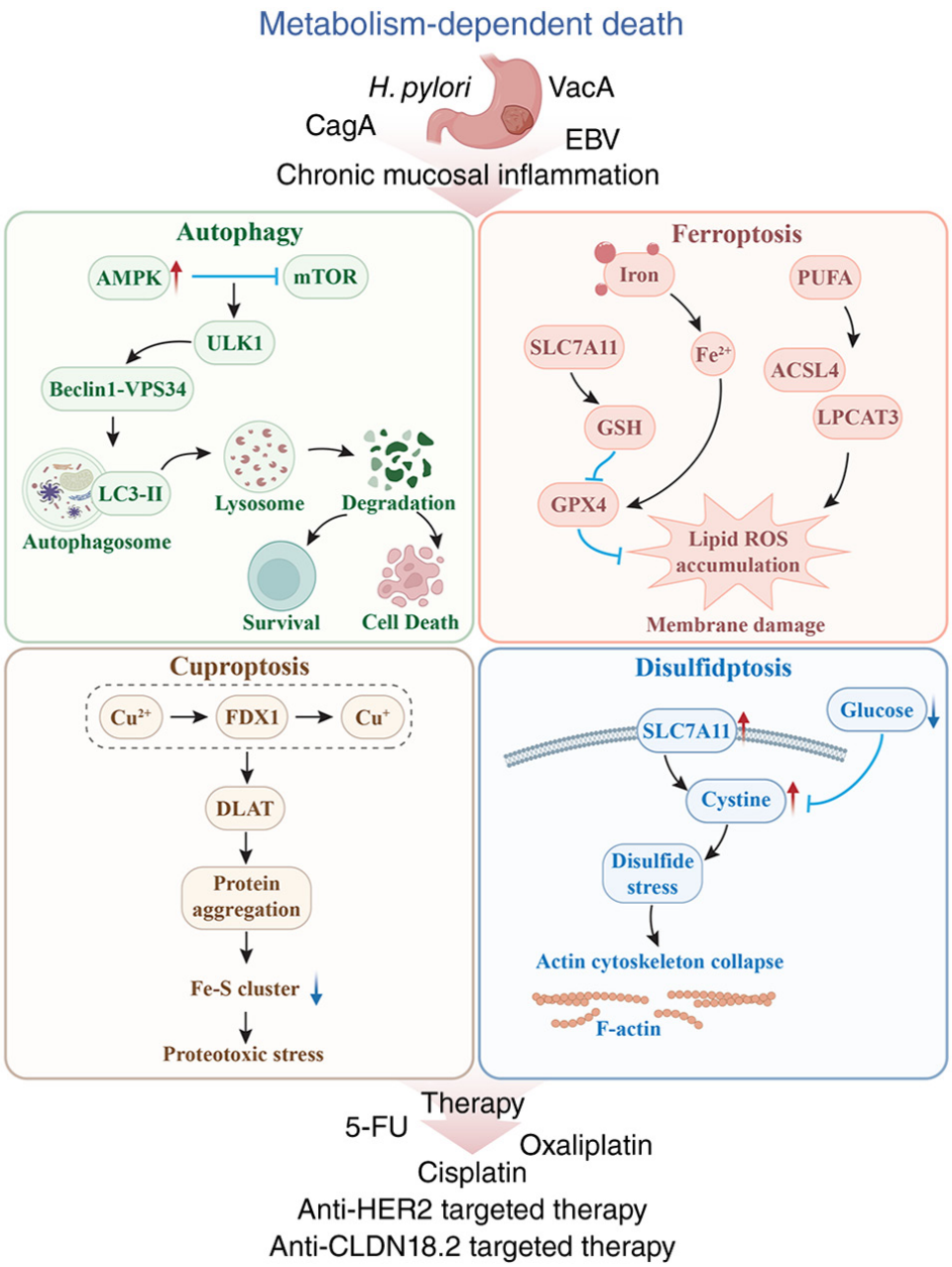

Figure 3. Metabolism-dependent cell death pathways and metabolic vulnerabilities in gastric cancer. Metabolism-dependent cell death in gastric cancer is closely linked to nutrient sensing, redox homeostasis, mitochondrial metabolism, and lipid remodeling, and mainly includes autophagy, ferroptosis, cuproptosis, and disulfidptosis. Autophagy is primarily regulated through the AMPK-mTOR-ULK1 axis. Under nutrient deprivation or metabolic stress, AMPK activation and mTOR inhibition promote ULK1 activation and Beclin1-VPS34-mediated autophagosome formation, followed by lysosomal fusion and substrate degradation, thereby contributing either to stress adaptation and survival or, under excessive activation, to autophagy-associated cell death. Ferroptosis is driven by iron-dependent lipid peroxidation. Iron accumulation together with ACSL4- and LPCAT3-mediated incorporation of PUFAs into membrane phospholipids promotes lipid ROS generation and membrane damage, whereas the SLC7A11-GSH-GPX4 antioxidant system counteracts lipid peroxide accumulation and suppresses ferroptotic execution. Cuproptosis is a mitochondrial metabolism-associated cell death process triggered by intracellular copper overload. FDX1-mediated reduction of Cu^{2+} to Cu^{+} facilitates abnormal aggregation of lipoylated proteins such as DLAT, disrupts Fe-S cluster homeostasis, and induces proteotoxic stress. Disulfidptosis is induced under conditions of high SLC7A11 expression and glucose deprivation, in which excessive cystine uptake and impaired reducing capacity result in intracellular disulfide stress, actin cytoskeleton collapse, and F-actin contraction. Clinically relevant therapeutic stresses in gastric cancer, including 5-FU, cisplatin, oxaliplatin anti-HER2 targeted therapy, and anti-CLDN18.2 targeted therapy, may further modulate these metabolic vulnerabilities and influence cell death susceptibility and therapeutic response. EBV, Epstein-Barr virus; UNKL, Unc-51-like autophagy-activating kinase 1; PUFAs, polyunsaturated fatty acids; VPS34, phosphatidylinositol 3-kinase; LPCAT3, lysophosphatidylcholine acyltransferase 3; GSH, glutathione; GPX4, GSH peroxidase 4; FDX1, ferredoxin 1; DLAT, dihydrolipoamide S-acetyltransferase.

to suppress inflammation-driven tumorigenesis and reduce abnormal epithelial proliferation and progenitor expansion (157,158). In established GC, autophagy primarily supports adaptation to metabolic and therapeutic stress and influences responses to chemotherapy and targeted therapy. Numerous agents induce protective autophagy that attenuates cell death signaling, whereas inhibition of autophagy enhances treatment efficacy. For example, quercetin induces HIF-1α-associated autophagy, and chloroquine treatment or knockdown of ATG5 or Beclin-1 increases apoptosis (159).

In HER2-positive GC, GSDMB promotes Rab7-dependent autophagosome maturation and contributes to anti-HER2 resistance, indicating that autophagy-related markers may identify patients who benefit from combination therapy (160). Under specific experimental conditions, excessive or sustained autophagy has been associated with tumor cell death or enhanced therapeutic efficacy. However, because definitive evidence for autophagy-dependent cell death remains limited, these observations should be interpreted cautiously as autophagy-associated cell death processes rather than autonomous execution by autophagy. The compound w09 enhances autophagic flux and triggers caspase-dependent apoptosis, and 8-paradol activates PINK1/Parkin-dependent mitophagy to induce mitochondrial damage and apoptosis, supporting modulation of mitophagy as a potential therapeutic strategy (161,162). Clinically, autophagy-related markers and signatures are used for prognostic stratification. Immunophenotypes defined by LC3A/B, Beclin-1 and AMBRA-1 associate with tumor grade and survival, and gene-based risk models consistently stratify patients by prognosis and immune features, including immune infiltration, checkpoint expression and treatment response (163-167). Autophagy also regulates immunotherapy response. Its inhibition increases programmed death-ligand 1 (PD-L1) expression through the p62/NF-κB axis and alters sensitivity to immune checkpoint blockade (168). Autophagy-targeted delivery and combination strategies, including nanomedicine approaches, are under development to enhance chemosensitivity and drug accumulation, although most remain preclinical (169-171). Taken together, autophagy primarily functions as a context-dependent regulator of tumor adaptation and therapeutic response in GC, while its direct role as an execution mechanism of cell death requires further experimental validation.

Ferroptosis

Mechanism of ferroptosis in GC. Ferroptosis in GC is a regulated oxidative stress-driven process determined by the balance between lipid peroxidation and antioxidant capacity and occurs when lipid peroxide accumulation exceeds cellular detoxification thresholds and causes irreversible membrane damage (172,173). At the execution level, Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 promote incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids and expand the pool of oxidizable substrates. Transferrin receptor-mediated iron uptake and nuclear receptor coactivator 4-dependent ferritinophagy increase labile iron and amplify Fenton reactions, which accelerate lipid peroxidation (172,174). Antioxidant systems counteract this process through System Xc^--mediated cystine import and the GSH-GSH peroxidase 4 (GPX4) axis, together with ferroptosis suppressor protein 1 (FSP1)-CoQ, DHODH-CoQ and GCH1-BH4 pathways that detoxify lipid peroxides and determine ferroptosis sensitivity (174-176). In GC, this network is not lost but reprogrammed to raise the threshold for lethal lipid peroxidation (174,177). Tumor-intrinsic signaling pathways regulate this balance. In cisplatin-resistant cells, activation of the NRF2/xCT axis increases GSH levels, whereas loss of activating transcription factor 3 (ATF3) stabilizes antioxidant defenses; restoration of ATF3 suppresses NRF2 and SLC7A11 and restores ferroptosis sensitivity (178). Wnt/β-catenin signaling similarly upregulates GPX4 through transcription factor 4, reduces lipid ROS and attenuates ferroptosis, thereby promoting drug resistance (20). The TME further increases ferroptosis tolerance. Under hypoxia, HIF-1α-induced long non-coding RNA (lncRNA) PMAN stabilizes SLC7A11 mRNA through ELAV-like protein 1 translocation to maintain GSH and support peritoneal dissemination, whereas lncRNA CBSLR reduces cystathionine β-synthase expression via YTHDF2 and destabilizes ACSL4, limiting PUFA-PE substrate availability and promoting ferroptosis resistance and chemoresistance (179,180). Stromal interactions also suppress lipid peroxidation. CAF-derived exosomal miR-522 downregulates arachidonate 15-lipoxygenase, and chemotherapy activates the ubiquitin-specific peptidase 7-hnRNPA1 axis in fibroblasts to sustain miR-522 secretion and maintain low lipid peroxide levels in tumor cells (181). Ferroptosis also interacts with immune regulation. CAFs alter iron export and induce natural killer (NK) cell ferroptosis through follistatin-like protein 1 (FSTL1) signaling, while tumor-derived L-kynurenine triggers ferroptosis in NK cells and reduces their infiltration, indicating that ferroptosis can both eliminate tumor cells and impair antitumor immunity (182,183). Notably, ferroptosis is not uniformly suppressed in GC. *H. pylori* CagA enhances ether lipid synthesis and expands PUFA-containing phospholipid pools, which increases sensitivity to xCT or GPX4 inhibition (184). Metabolic adaptations observed in CIN and GS subtypes may create distinct vulnerabilities to ferroptotic induction. The therapeutic potential of ferroptosis therefore depends on biological context and treatment timing, and effective strategies should maximize tumor cell killing while limiting immunosuppression and off-target toxicity (185).

Clinical implications of ferroptosis in GC. The clinical relevance of ferroptosis in GC centers on biomarker development, risk stratification and therapeutic sensitization. Ferroptosis networks contribute to tumor biology and provide measurable features for patient classification and treatment optimization. Multi-omics models show that ferroptosis-related gene signatures stratify patients by survival and associate with immune contexture and treatment response, supporting their use in postoperative management and therapy selection (186). These associations extend across disease stages. In premalignant lesions, ferroptosis-related genes support diagnostic and risk assessment models. During tumor progression, adaptations in the lymph node lipid microenvironment and PPARγ-FABP1-related metabolism promote ferroptosis tolerance. In peritoneal metastasis, stromal-targeted ferroptosis induction combined with imaging shows therapeutic potential, indicating that ferroptosis signaling spans tumor evolution (187-189). Targeting ferroptosis resistance has emerged as a sensitization strategy. ATF2 stabilizes SLC7A11 and reduces sorafenib-induced ferroptosis, whereas its inhibition restores drug sensitivity (190). STAT3 suppresses ferroptosis and promotes chemoresistance, and its inhibition induces ferroptosis-dependent antitumor effects in organoid and PDX models and improves chemosensitivity (191). Small molecules such as the Jiyuan oridonin A derivative a2 induce ferroptosis and suppress tumor growth, with GPX4 serving as a potential sensitivity marker (192). Ferroptosis also interacts

with immune regulation. Cadherin 19 functions as both a stratification marker and a predictor of immunotherapy response (193). Inhibition of ferroptosis in tumor-associated neutrophils reduces immunosuppressive lipid peroxidation and enhances responses to anti-PD-1 therapy, highlighting the need to balance tumor cell killing with preservation of antitumor immunity (194). Overall, ferroptosis thus provides a framework for understanding tumor heterogeneity and offers opportunities for clinical translation in GC.

Cuproptosis

Mechanism of cuproptosis in GC. Cuproptosis in GC is an RCD process driven by mitochondrial metabolism and protein lipoylation, rather than by copper accumulation alone. It depends on ferredoxin 1 (FDX1)-mediated reduction of Cu^{2+}, maintenance of lipoylated proteins by lipoyl synthase (LIAS) and lipoyltransferase 1, and subsequent aggregation of lipoylated tricarboxylic acid cycle proteins with disruption of Fe-S cluster homeostasis (195-197). This mechanism is conserved across cancers. Excess copper preferentially targets lipoylated proteins such as dihydrolipoamide S-acetyltransferase (DLAT) and dihydrolipoamide S-succinyltransferase (DLST), induces their oligomerization and triggers proteotoxic stress, whereas enhanced glycolysis, hypoxia adaptation, increased copper efflux or preserved Fe-S assembly reduce susceptibility (198,199). In GC, methyltransferase-like protein 16 (METTL16) undergoes K229 lactylation under high copper conditions, increases m6A methyltransferase activity, stabilizes FDX1 mRNA and amplifies cuproptosis (200). Tumor cells attenuate this pathway through multiple mechanisms. Kynureninase downregulates LIAS through a non-canonical mechanism and reduces protein lipoylation, which increases resistance (201). In peritoneal metastases, polypyrimidine tract-binding protein 3 alters COX11 splicing, reduces mitochondrial copper accumulation, and limits FDX1-dependent DLAT aggregation (202). In diffuse-type GC, high integrin β-1 expression associates with reduced expression of FDX1, DLAT, DLST and pyruvate dehydrogenase E1 component subunit α-1 and with lower cuproptosis scores, indicating that integrin-driven metabolic reprogramming maintains a low-sensitivity state (203). Similar regulatory patterns occur in other cancers. In esophageal squamous cell carcinoma, lactate-induced nudix hydrolase 21 lactylation suppresses FDX1 expression and promotes resistance, whereas ATP7A-mediated copper efflux reduces cuproptosis susceptibility in KRAS-mutant lung adenocarcinoma and glioblastoma stem cells (204-206). Cuproptosis sensitivity can also be restored. In GC, mitochondrial uncoupling increases FDX1 and DLAT expression and enhances elesclomol-copper-induced DLAT oligomerization and Fe-S protein loss and punicalagin further promotes DLAT aggregation by targeting FDX1, thereby increasing cuproptotic responses (207,208). Cross-talk with other metal-dependent cell death pathways further shapes this process. Metal-regulatory transcription factor 1 coordinates iron homeostasis and Fe-S cluster assembly and limits synergy between ferroptosis and cuproptosis (209). Cuproptosis therefore represents a targetable metabolic vulnerability in GC driven by the coupling of copper homeostasis and mitochondrial metabolism.

Clinical implications of cuproptosis in GC. Research on cuproptosis in GC is transitioning from mechanistic studies to translational evaluation and currently focuses on prognostic stratification, immune characterization and prediction of therapeutic response. Multi-cohort analyses show that risk models based on copper-binding proteins or cuproptosis-related genes have independent prognostic value, with high-risk groups showing poorer survival and increased disease progression (210,211). These molecular features reflect both metabolic states and immune contexture. Low-risk patients show higher $CD8^+$ T cell infiltration, increased tumor mutational burden or MSI, and more active antitumor immunity, whereas high-risk groups show enrichment of immunosuppressive cells and stromal remodeling (212,213). Accordingly, cuproptosis-based metrics can support immunotherapy stratification. Low-risk patients are more likely to benefit from PD-1 blockade, whereas high-risk patients display immune-excluded or dysfunctional phenotypes. Cuproptosis also influences chemotherapy response. FDX1 expression correlates with sensitivity to cisplatin and 5-FU, indicating that mitochondrial metabolism affects platinum efficacy (214). Differences in drug sensitivity across risk groups further support its role in treatment selection (215). Cuproptosis-related gene signatures also distinguish tumor from normal tissue and support diagnostic model development (216). Meanwhile, therapeutic strategies targeting this pathway are emerging. Nanoparticle-based systems that increase intratumoral copper can induce cuproptosis and enhance cisplatin efficacy in preclinical models with acceptable safety (217). Evidence from other cancers shows that cuproptosis-related features contribute to tumor stratification, radiosensitization, and immune microenvironment remodeling, supporting their relevance in GC (218-220). Overall, cuproptosis represents a clinically relevant pathway with growing translational potential in GC.

Disulfidptosis. Disulfidptosis is an RCD process linked to cystine metabolism and cytoskeletal integrity. It arises in cells with high SLC7A11 expression under glucose deprivation or limited reducing capacity, where cystine reduction to cysteine fails and intracellular disulfides accumulate. These changes induce aberrant disulfide bonding in actin cytoskeletal proteins and drive F-actin contraction. The process depends on RAC1-WRC-mediated branched actin networks and reflects cytoskeletal instability under defined metabolic conditions rather than nonspecific oxidative damage (221-223). In GC, evidence supports the presence of disulfidptosis-associated states, although canonical execution pathways remain incompletely defined. Cohort studies show dysregulation of SLC7A11, SLC3A2, ribophorin 1 and NCK-associated protein 1 (NCKAP1), which associate with actin dynamics, GTPase signaling, invasion, migration and immune infiltration. These changes sustain tumor survival through enhanced cystine uptake and antioxidant capacity but create dependence on glucose and NADPH, which increases vulnerability to disulfide stress when redox balance fails (224,225). Mechanistically, SLC7A11 controls cystine influx and reductive burden, whereas NCKAP1 and related proteins link disulfide stress to cytoskeletal instability, indicating coordinated regulation by metabolic supply and structural control. This state also relates to metabolic reprogramming and microenvironmental adaptation. NRP1 may buffer disulfide stress through glutamine metabolism, while subtype analyses show that high-risk

tumors associate with hypoxia, angiogenesis and stromal remodeling, whereas low-risk tumors display oxidative phosphorylation and improved treatment response (226-228). lncRNA studies further connect MYH10, tight junctions, and actin regulation, reinforcing the role of cytoskeletal dynamics (229). Disulfidptosis sensitivity is also shaped by the thioredoxin system, endoplasmic reticulum stress, and DNA repair. Endoplasmic reticulum stress partially buffers high-SLC7A11 cells, whereas cell cycle arrest and DNA repair defects increase susceptibility (230,231). Clinically, gene- and lncRNA-based models stratify patients and associate with MSI, TMB, TIDE and immune infiltration, supporting their use in predicting immunotherapy response and chemotherapy sensitivity (232-234). However, disulfidptosis is not restricted to tumor cells. Exhausted $CD8^+$ T cells may also undergo this process, which can impair antitumor immunity (235,236). In conclusion, disulfidptosis represents an emerging metabolism-dependent vulnerability with potential for therapeutic targeting in GC.

Other cell death. NETosis in GC represents a pathological program linked to metastatic dissemination, immune remodeling and systemic inflammation rather than a simple consequence of neutrophil infiltration. Circulating neutrophil extracellular trap (NET) levels increase with tumor stage and associate with lymph node and distant metastasis. Primary tumors induce systemic NET formation in the absence of infection or surgical stress, and NET levels decline after tumor resection, indicating that tumor burden drives NETosis (236). Mechanistically, NETs promote adhesion and retention of circulating tumor cells in distant microvascular beds, particularly in liver sinusoids, thereby facilitating metastasis. Pan-cancer studies further show that tumor-derived chemokines, complement activation, exosomes and therapy-related stress induce NETosis, which proceeds through ROS accumulation, nuclear translocation of neutrophil elastase and myeloperoxidase, chromatin decondensation and release of DNA-protein networks (237,238). These structures capture circulating tumor cells, promote extravasation and colonization and restrict interactions with cytotoxic T lymphocytes and NK cells through spatial sequestration. They also drive epithelial-mesenchymal transition, reactivation of dormant cells, and formation of pre-metastatic niches (239,240). In GC, NETosis-related signatures associate with hypoxia, stromal remodeling, and increased immune checkpoint expression and associate with poor prognosis. This inflammatory state does not improve immunotherapy response. Instead, it coincides with neutrophil enrichment, increased M2 macrophages and reduced effector lymphocyte activity (241,242). Additionally, in highly aggressive disease with bone marrow metastasis and disseminated intravascular coagulation, NETosis presents as a systemic neutrophil program, where immature yet activated neutrophils expand and amplify complement-coagulation cascades and immunosuppression (243).

Parthanatos is a caspase-independent cell death program driven by PARP1 hyperactivation and characterized by collapse of cellular energy metabolism. Excessive DNA damage and ROS trigger rapid poly (ADP-ribose) synthesis, deplete NAD^+ and ATP, and induce apoptosis-inducing factor (AIF) translocation to the nucleus, leading to large-scale DNA fragmentation and a death outcome distinct from apoptosis (244). In GC, glucose deprivation elevates ROS, disrupts NADPH/$NADP^+$ balance, and activates PARP1, resulting in PAR accumulation and AIF nuclear translocation; olaparib reverses these effects, confirming PARP1 dependence. Lactate metabolism counteracts this process through the lactate dehydrogenase B-IDH1 axis, which enhances NADPH production, buffers oxidative stress, and limits PARP1 overactivation, thereby suppressing Parthanatos under metabolic stress (245). Beyond this core pathway, Parthanatos shows mechanistic plasticity. It engages not only the canonical PAR-AIF-MIF axis but also ROS amplification, Ca^{2+} imbalance, JNK signaling, and RIP1-associated pathways, and integrates with glycolytic inhibition and energy crisis to determine cell fate (246-248). At the tissue level, multi-omics analyses reveal marked single-cell and spatial heterogeneity of Parthanatos-related gene networks in GC, involving tumor epithelial, myeloid, and proliferative cell populations. Across molecular subtypes, these networks consistently associate with extracellular matrix remodeling, TGF-β and WNT signaling, CAF enrichment, reduced tumor purity and increased immune checkpoint expression (249,250).

In addition to NETosis and Parthanatos, several non-canonical cell death-related processes contribute to GC biology. Entosis is a non-apoptotic process in which a viable cell actively invades a neighboring homotypic cell to form a cell-in-cell structure. This process relies on cadherin-mediated adhesion and RhoA-ROCK-actomyosin contractility. The internalized cell may undergo lysosomal degradation, escape, survive, or divide within the host cell (251-253). In GC, cell-in-cell structures are enriched in high-grade dysplasia and early-stage tumors and associate with CDC20 overexpression and cell competition, supporting a role in clonal selection and tumor evolution during malignant transformation. Similar morphologies do not always indicate entosis. Tumor cells can engulf apoptotic neutrophils, a process consistent with cannibalism rather than active invasion (254). Moreover, GC cells also undergo caspase-independent death. Phenoxazine derivatives induce TUNEL-positive, z-VAD-fmk-insensitive cell death, indicating alternative lethal pathways (255). Excessive macropinocytosis provides another route to cell death. Jaspine B induces large single-membrane vacuoles and disrupts cytoplasmic architecture, producing a methuosis-like phenotype distinct from apoptosis or autophagy (256).

Collectively, these processes indicate that cell death in GC operates as a dynamic network rather than a single pathway. This network integrates metabolic reprogramming, inflammatory signaling, immune regulation and therapeutic stress, thereby shaping tumor progression and informing patient stratification and treatment strategies. Given the heterogeneous nature of the available evidence, mechanistically validated findings are distinguished from bioinformatic associations throughout the following sections, with representative studies and their evidence levels summarized in Table I. Notably, for the drug delivery systems, natural products and multi-component interventions discussed in the present review, the currently available evidence remains entirely preclinical, with no established clinical evidence supporting these cell death-targeting strategies in GC to date.

Table I. Levels of evidence supporting regulated cell death mechanisms in GC.

Cell death pathway	Key regulators	Main finding	Evidence source	Experimental validation	Evidence level	(Refs.)
Apoptosis	ROS/Ca2+-ER stress-eIF2α/GADD153-calpain/caspase-12-Bcl-2/Bax axis	ApoG2 induces ER stress-associated apoptosis and suppresses GC growth through ROS and Ca2+ accumulation, activation of eIF2α/GADD153 and calpain/caspase-12 signaling, and modulation of Bcl-2/Bax	GC cell line + xenograft mouse model	*in vitro* + *in vivo* validation	Experimentally supported	(70)
	ASC (PYCARD)-caspase-1-IL18-NF-κB-caspase-8/caspase-3 axis	ASC inflammasome–derived IL18 suppresses caspase-8-mediated apoptosis of GC cells through an inflammation-independent, tumor cell-autonomous mechanism	Human GC specimens + TCGA-STAD + human GC cell lines (AGS, MKN1) + gp130F/F spontaneous intestinal-type GC mouse model	Extensive *in vitro* + *in vivo* + human tissue validation	Mechanistically validated	(51)
	GKN2/Hsc70/NF-κB/JNK/ROS/caspase-9/caspase-3	GKN2 promotes oxidative stress-induced mitochondrial dysfunction and apoptosis in GC cells through interaction with Hsc70, leading toNF-κB inhibition and JNK activationAu-	GC cell lines + xenograft mouse models + human GC tissues/clinical cohort	Extensive in vitro + *in vivo* + human tissue/clinical validation	Mechanistically validated	(45)
	ROS-MAPK/PI3K-AKT-p53/DNA damage signaling	Apt-TPE@Zn, a novel multifunctional nanomaterial, mediates photothermal therapy and induces apoptosis in GC cells through ROS overproduction and modulation of MAPK, PI3K/AKT, p53, and DNA damage signaling	SGC-7901 GC cells + SGC-7901 xenograft mouse model	*in vitro* + *in vivo* validation	Experimentally supported	(71)
	BCL-2, MCL-1, caspase-3, PARP; YAP1/SOX9	The pan-BCL-2 inhibitor AT-101 induces apoptosis in GC cells and sensitizes GC cells to docetaxel, accompanied by suppression of BCL-2/MCL-1 and CSC-associated YAP1/SOX9 signaling	Human GC tissues + GC cell lines + xenograft models + clinical trial	Extensive *in vitro* + *in vivo* + human tissue/clinical validation	Experimentally supported	(65)
	lncRNA ABL / cytochrome c/ IGF2BP1/METTL3	m6A-stabilized lncRNA ABL binds APAF1 to block apoptosome assembly and caspase	GC tissues/cohorts + RNA-seq/TCGA + GC cell lines + patient-derived GC	Extensive *in vitro* + organoid +	Mechanistically validated	(52)

Table I. Continued.

Cell death pathway	Key regulators	Main finding	Evidence source	Experimental validation	Evidence level	(Refs.)
		activation, thereby promoting multidrug resistance in GC	xenograft mouse models	*in vivo* + human tissue/clinical cohort validation		
	TRIM17/BAX/ ubiquitin-proteasome system/Caspase-3/ PARP	TRIM17 promotes BAX ubiquitination and degradation, thereby suppressing apoptosis and promoting GC progression and drug resistance	TCGA/GSEA + human GC tissue microarray + GC cell lines + xenograft mouse models	Extensive *in vitro* + *in vivo* + human tissue validation	Mechanistically validated	(43)
	EGFR, GRP78, PERK, eIF2α, ATF4, CHOP, caspase-9, TRIM21	Pyrotinib induces ER stress-mediated apoptosis via the EGFR-GRP78-PERK/eIF2α/ATF4/CHOP axis and promotes GRP78 degradation, thereby enhancing oxaliplatin sensitivity in GC	Primary human GC cells + GC cell lines + xenograft models	Extensive *in vitro* + *in vivo* validation	Experimentally supported	(66)
	DNPB/DHODH-UMP-NR4A1-Bcl-2-cytochrome c-caspase-3/7 axis	UMP suppresses NR4A1-mediated apoptosis, while pyrimidine depletion promotes NR4A1 mitochondrial translocation and NR4A1-Bcl-2-dependent apoptosis in GC	Human GC tissues/ metabolomics + TCGA + scRNA-seq + RNA-seq/ ChIP-seq + GC cell lines + PDX-derived organoids + CDX/PDX + orthotopic and metastatic GC mouse models	Extensive *in vitro* + organoid + *in vivo* + human tissue/ multi-omics validation	Mechanistically validated	(47)
Apoptosis/Anoikis	NNT-NADPH/GSH-ROS axis	NNT maintains NADPH-dependent redox homeostasis and limits ROS accumulation, thereby protecting GC cells from oxidative stress-induced apoptosis and anoikis and promoting tumor growth and metastasis	Human GC tissues + GC cell lines (mainly HGC27 and BGC823) + cell line-derived xenografts + GC PDX models	Extensive *in vitro* + *in vivo* + human tissue validation	Mechanistically validated	(44)
Necroptosis	AMID (AIFM2/FSP1), RIP1	HUHS1015 induces necroptosis and caspase-independent apoptosis in GC cells through Nec-1-sensitive signaling and AMID nuclear translocation	Human GC cell lines: MKN28 and MKN45; mechanistic experiments mainly in MKN28	*in vitro* only	Experimentally supported	(87)
	Necroptosis-related genes	A necroptosis-related 11-gene signature stratifies patients with GC by prognosis, immune landscape and predicted therapeutic response	TCGA-STAD + GSE84437	None	Bioinformatic association	(97)

Table I. Continued.

Cell death pathway	Key regulators	Main finding	Evidence source	Experimental validation	Evidence level	(Refs.)
	AXL, RAI14, NOX4	A three-gene necroptosis-related prognostic score predicts prognosis, tumor immune characteristics, and potential immunotherapy response in GC	TCGA + multiple GEO cohorts + clinical GC tissues	Human tissue validation only	Bioinformatic association	(98)
	TXNRD1/Sec498-ROS-ER stress-RIPK1	Chelerythrine inhibits TXNRD1 by targeting its Sec498 residue, inducing ROS accumulation and ER stress and ultimately triggering necroptosis in GC	GC cell lines + NCI-N87-derived 3D tumor spheroids	Extensive *in vitro* mechanistic validation	Mechanistically supported	(88)
	Clofoctol (CFT)-RanBP2-TNF-RIPK1/MLKL	CFT induces TNF-mediated necroptosis in GC stem cells by directly binding to RanBP2	GC cell lines, GCSCs, patient-derived GC organoids, xenograft models, RNA-seq/scRNA-seq	Extensive *in vitro* + *in vivo*	Mechanistically validated	(90)
	CHMP3; DAMPs; MDK-NCL	Necroptosis is enriched during GC lymph node metastasis, with CHMP3 and MDK-NCL signaling associated with an immunosuppressive microenvironment	ScRNA-seq + spatial transcriptomics + TCGA + human tissue	Human tissue validation only	Bioinformatic association	(91)
Pyroptosis	GSDMC; pyroptosis-related genes	Pyroptosis-related patterns and scores are associated with prognosis, immune infiltration, and therapeutic response in GC	TCGA-STAD + GSE15459 + GSE34942 + GSE57303 + GSE62254 + human GC tissues	Human tissue validation only	Bioinformatic association	(123)
	LGSN/Vimentin/NLRP3/Caspase-1/GSDMD	LGSN maintains GCSC stemness and chemoresistance by suppressing NLRP3/caspase-1/GSDMD-mediated pyroptosis, while LGSN depletion restores chemosensitivity	Patient-derived GCSCs + GC cell lines + human GC tissues/TMA + TCGA/GEO + xenograft mouse models	Extensive *in vitro* and *in vivo*	Mechanistically validated	(126)
	GSDMD, CASP1, GSDME, CASP3; BATF2, PTPRJ, RGS1, VCAN	Higher pyroptotic activity is associated with favorable prognosis and improved immunotherapy response in GC, with a pyroptosis risk score predicting treatment benefit	TCGA/GEO + bulk RNA-seq/WES + scRNA-seq + human GC tissues + multicenter clinical cohorts	Human tissue validation only	Bioinformatic association	(299)

Table I. Continued.

Cell death pathway	Key regulators	Main finding	Evidence source	Experimental validation	Evidence level	(Refs.)
	Jab1, HIC1, GSDMD	HIC1 transcriptionally activates GSDMD-mediated pyroptosis and antitumor immunity, while Jab1 promotes HIC1 degradation to suppress pyroptosis in GC	Human GC tissues + MKN45/HGC27 GC cells + *in vivo* GC mouse models + bioinformatic analyses	Extensive *in vitro* + *in vivo* + human tissue	Mechanistically validated	(117)
PANoptosis	YBX1, PPM1B, USP10	YBX1 suppresses PANoptosis and promotes oxaliplatin resistance, while PPM1B promotes YBX1 degradation and restores PANoptosis in GC	GC cell lines + xenograft mouse models + human GC tissues/clinical cohort	Extensive *in vitro* + *in vivo* + human tissue/ clinical validation	Mechanistically validated	(137)
	Jolkinolide B-Caspase-8 axis	Jolkinolide B induces PANoptosis in GC cells through Caspase-8 activation, simultaneously activating apoptotic, pyroptotic, and necroptotic pathways, thereby suppressing GC growth	GC cell lines (AGS and MKN45) + RNA-seq + MKN45 xenograft mouse model	Extensive *in vitro* + *in vivo*	Mechanistically validated	(135)
	ROS-Caspase-8-GSDME/Caspase-3/7/ MLKL axis	CJP-TiN induces ROS/Caspase-8-mediated PANoptosis, integrating pyroptosis, apoptosis, and necroptosis while enhancing antitumor immunity in GC	GC cell lines (AGS and MKN45) + RNA-seq + human GC tissues + MKN45-CDX and MFC-615 mouse models	Extensive *in vitro* + *in vivo* + human tissue validation	Mechanistically validated	(136)
	HSPB1, RIPK3, p-MLKL, NLRP3	HSPB1 promotes GC progression by suppressing PANoptosis; HSPB1 silencing activates apoptosis, necroptosis, and pyroptosis and inhibits GC	GEO/TCGA datasets + human GC tissues + GC cell lines + xenograft models	Extensive *in vitro* + *in vivo* + human tissue validation	Mechanistically validated	(138)
PANoptosis/ Apoptosis	PANoptosis-related genes	APOD knockdown reduces proliferation, migration and invasion and increase apoptosis	CGA-STAD + GSE62254	Human tissue validation only	Bioinformatic association	(143)
Autophagy	GRID2, ATG4D, GABARAPL2, CXCR4	A four-gene autophagy-related signature comprising GRID2, ATG4D, GABARAPL2, and CXCR4 predicts overall survival in GC, with the derived risk score serving as an independent prognostic factor	TCGA-STAD + GSE62254	Human tissue validation only	Bioinformatic association	(164)

Table I. Continued.

Cell death pathway	Key regulators	Main finding	Evidence source	Experimental validation	Evidence level	(Refs.)
	BDH2, Keap1, Nrf2, ROS, PI3K/Akt/mTOR	BDH2 promotes Nrf2 degradation and ROS accumulation, thereby suppressing PI3K/Akt/mTOR signaling and inducing apoptosis and pro-death autophagy in GC	Oncomine/UALCAN datasets + human GC tissues + GC cell lines + xenograft mouse model	Extensive *in vitro* + *in vivo* + human tissue validation	Mechanistically validated	(49)
	LMP2A, PI3K/AKT, NRF1, CXCR4, ZEB1, ATG7	LMP2A activates PI3K/AKT-NRF1-CXCR4 signaling to induce ZEB1/ATG7-mediated autophagy, thereby suppressing apoptosis and promoting EBVaGC survival	GEO dataset + human EBVaGC tissues + EBVaGC cell lines	Extensive *in vitro* + human tissue validation	Mechanistically validated	(152)
	8-paradol; PINK1; Parkin	8-paradol induces excessive PINK1/Parkin-mediated mitophagy, leading to mitochondrial dysfunction in GC cells	Human gastric adenocarcinoma AGS cells + AGS xenograft mouse model	Extensive *in vitro* + *in vivo* validation	Mechanistically validated	(162)
	ER stress-JAK2/STAT3-SEC23A-ANXA2	JAK2/STAT3-induced SEC23A promotes ANXA2-dependent autophagy, thereby suppressing ER stress-induced apoptosis and enhancing 5-FU resistance in GC	GC cell lines + human GC tissues + *in vivo* xenograft models	Extensive *in vitro* + *in vivo* + human tissue validation	Mechanistically validated	(150)
	c-Jun-PPP1R15A	Glucose deprivation induces c-Jun-dependent PPP1R15A expression; PPP1R15A activates autophagic flux and enables GC cells to adapt to energy stress	Human GC cell lines + human GC tissues + TCGA/GEO datasets + xenograft model	Extensive *in vitro* + *in vivo* + human tissue/clinical validation	Mechanistically validated	(151)
	FAM117B-KEAP1/NRF2-ROS/AMPK/mTOR	WSGC@MS, a novel multifunctional nanomaterial, promotes KEAP1-dependent NRF2 degradation and ROS accumulation, activating AMPK/mTOR-mediated autophagy to induce apoptosis and enhance chemosensitivity in GC	GC cell lines + chemoresistant GC cell lines + transcriptomic analysis + xenograft/liver metastasis models	Extensive *in vitro* + *in vivo*	Mechanistically validated	(170)

Table I. Continued.

Cell death pathway	Key regulators	Main finding	Evidence source	Experimental validation	Evidence level	(Refs.)
Ferroptosis	ATF3-Nrf2/Keap1-xCT	ATF3 induces ferroptosis by suppressing Nrf2/Keap1/xCT signaling, thereby sensitizing cisplatin-resistant GC cells to cisplatin	GC cell lines + cisplatin-resistant GC cell lines + public GC patient datasets	Extensive *in vitro*	Mechanistically validated	(178)
	STAT3-GPX4/SLC7A11/FTH1 axis	STAT3 transcriptionally activates GPX4, SLC7A11, and FTH1 to suppress ferroptosis; STAT3 inhibition induces ferroptosis and restores 5-FU sensitivity in GC	GC cell lines + 5-FU-resistant GC cells + human GC tissues + TCGA/GTEx/GEO datasets + organoids + xenograft/PDX models	Extensive *in vitro* + organoid + *in vivo* + human tissue/clinical validation	Mechanistically validated	(191)
	CDH19-ACSL4/GPX4/SLC7A11 axis	CDH19 knockdown promotes ferroptosis by increasing iron and ROS and regulating ACSL4, GPX4, and SLC7A11, thereby suppressing GC progression	Bioinformatic + experimental evidence	Extensive *in vitro* validation	Experimentally supported	(193)
	FAPI-MSPION/CDDP-Fe2+/Fe3+-ROS-GPX4-LPO axis	FAPI-targeted MSPION/CDDP induces ferroptosis in GC cells and CAFs through ROS accumulation and GPX4 suppression, thereby inhibiting GC peritoneal metastasis	Experimental + single-cell evidence	Extensive *in vitro* + *in vivo* + human tissue validation	Experimentally supported	(189)
	USP29-FSP1/SMURF1-FSP1 axis	USP29 stabilizes FSP1 to suppress ferroptosis and promote chemoresistance, whereas SMURF1 promotes FSP1 degradation to enhance ferroptosis and chemosensitivity in GC	GC cell lines, cisplatin-resistant GC cells, human GC clinical cohort, mouse xenograft models, GC patient-derived organoids, and PDX models	Extensive *in vitro* + *in vivo* + clinical cohort + PDO + PDX validation	Mechanistically validated	(269)
Cuproptosis	PTBP3-COX11 alternative splicing axis	PTBP3 promotes exon 4 skipping of COX11 and increases the short COX11 isoform, thereby reducing mitochondrial copper accumulation and enabling GC cells to evade cuproptosis	Experimental + bioinformatics + clinical tissue evidence	Extensive *in vitro* + PDO + *in vivo* validation	Mechanistically validated	(202)
Cuproptosis/Ferroptosis	MTF1-FTH1 / MTF1-TRIM31-NCOA4/MTF1-ISCA2 axis	MTF1 suppresses ferroptosis-cuproptosis synergy through FTH1, TRIM31/NCOA4, and ISCA2-	Experimental + bioinformatics + clinical tissue evidence	Extensive *in vitro* + *in vivo* +	Mechanistically validated	(209)

Table I. Continued.

Cell death pathway	Key regulators	Main finding	Evidence source	Experimental validation	Evidence level	(Refs.)
		mediated iron homeostasis, thereby promoting GC survival		human tissue validation		
Disulfidptosis	GAMT; disulfidptosis-related genes	Disulfidptosis-related subtypes predict prognosis and therapeutic response in GC, while GAMT promotes GC cell proliferation, migration, and chemoresistance	Bioinformatic + experimental evidence	*in vitro* only	Bioinformatic association	(227)
NETosis	NETosis-related genes	NETosis-related subtypes are associated with prognosis, immune infiltration, and therapeutic response in GC	Bioinformatic evidence	None	Bioinformatic association	(242)
Parthanatos	COL8A1; parthanatos-related genes	Parthanatos-related subtypes predict prognosis and therapeutic response, while COL8A1 promotes GC cell proliferation and migration	Bioinformatic + experimental evidence	*in vitro* only	Bioinformatic association	(250)

GC, gastric cancer; ROS, reactive oxygen species; ER, endoplasmic reticulum; PD, patient derived xenograft; miRNA, microRNA; eIF2α, eukaryotic translation initiation factor 2 subunit alpha; GADD15, growth arrest and DNA Damage-inducible protein 15; ASC, apoptosis-associated speck-like protein containing a CARD; TCGA, The Cancer Genome Atlas; GKN2, gastrokine 2; lncRNA, long non-coding RNA; IGF2BP1, insulin-like growth factor 2 binding protein 1; METTL3, methyltransferase-like 3; seq, sequencing; sc, single cell; ChIP, chromatin immunoprecipitation; NNT, nicotinamide nucleotide transhydrogenase; DHODH, dihydroorate dehydrogenase; GSH, glutathione; AMID, apoptosis-inducing factor-homologous mitochondrion-associated inducer of death; AIFM1, apoptosis-inducing factor 1, mitochondrial; FSP1, ferroptosis suppressor protein 1; RIP1/RIPK1, receptor-interacting serine/threonine-protein kinase 1; RAI14, retinoic acid-induced protein 14; NOX4, NADPH oxidase 4; TXNRD1, thioredoxin reductase 1; STAD, stomach adenocarcinoma; CFT, clofoctol; DAMPs, damage-associated molecular patterns; GCSC, gastric cancer stem cells; CHMP3, charged multivesicular body protein 3; MDK, midkine; MLKL, mixed lineage kinase domain-like protein; CAPG, capping actin protein gelsolin-like; LGSN, lengsin; LRP3, lipoprotein receptor-related protein 3; GEO, gene expression omnibus; WES, whole exome sequencing; ARID1A, AT-rich interactive domain-containing protein 1A; THBS1, thrombospondin-1; Jab1, Jun activation domain-binding protein 1; HIC1, hypermethylated in cancer 1; LDH, lactate dehydrogenase; YBX1, Y-box binding protein 1; PPM1B, protein phosphatase 1B enzyme; USP10, ubiquitin-specific peptidase 10; HSPB1, heat shock protein beta-1; APOD, apolipoprotein D; CCL2, C-C motif chemokine ligand 2; SQSTM1, sequestosome-1; GRID2, glutamate ionotropic receptor delta-2 subunit; ATG4D, autophagy-related cysteine endopeptidase 4; GABARAPL2, Gamma-aminobutyric acid receptor-associated protein-like 2; CXCR4, C-X-C chemokine receptor type 4; BDH2, 3-hydroxybutyrate dehydrogenase type 2; Keap1, Kelch-like ECH-associated protein 1; LMP2A, latent membrane protein 2A; ZEB1, zinc finger e-box binding homeobox 1; ATG7, autophagy related protein 7; ANXA2, annexin 2; PPP1R15A, protein phosphatase 1 regulatory subunit; ATF3, activating transcription factor 3; GPX4, GSH peroxidase 4; ACTL6A, actin-like protein 6A; GCLC, glutamate-cysteine ligase catalytic subunit; PDO, patient-derived organoids; USP7, ubiquitin-specific peptidase 7; SCD, stearoyl-CoA desaturase; CDH19, cadherin-19; ACSL4, acyl-CoA synthetase long-chain family member 4; FAPI, fibroblast activation protein inhibitor; CDDP, cisplatin; LPO, lactoperoxidase; FSP1, ferroptosis suppressor protein 1; FDX1, ferredoxin 1; LIAS, lipoyl synthase; MTF1, metal-regulatory transcription factor 1; PTBP3, polypyrimidine tract-binding protein 3; CIAO1, cytosolic iron-sulfur assembly component 1; FTH1, ferritin heavy chain 1; NCOA4, nuclear receptor coactivator 4; ISCA2, iron-sulfur cluster assembly 2; GPC3, glypican 3; GAMT, guanidinoacetate N-methyltransferase; COL8A1, collagen alpha-1(VIII) chain.

3. Molecular regulation and crosstalk of cell death in GC

In GC, cell death is not governed solely by tumor cell-intrinsic signaling but is shaped by multi-level regulatory inputs. These include stromal and immune components of the TME, intercellular signaling networks and systemic metabolic and inflammatory states. Together, these inputs determine the activation threshold, execution efficiency, and functional outcomes of RCDs. Accordingly, cell death pathways do not act independently; they are co-regulated under stress and interact through signaling crosstalk that produces compensatory or amplifying effects. This coordinated regulation defines tumor cell survival and influences therapeutic response.

TME regulation. The TME in GC functions as an active regulatory system rather than a passive backdrop. It comprises immune cells, fibroblasts, endothelial cells, extracellular matrix components and conditions such as hypoxia, inflammation and metabolic stress, which collectively shape tumor cell survival, death thresholds and therapeutic sensitivity (257,258). Accordingly, targeting the TME has become an important therapeutic strategy, as modulation of immune pressure, inflammatory signaling and metabolic states can lower death thresholds and restore impaired cell death programs, thereby enhancing treatment efficacy (259). Mechanistically, this regulation can be understood through four interconnected processes: Immune suppression, stromal interaction, metabolic adaptation and spatial niche remodeling, which together determine the activation, execution, and outcomes of RCD. Immunosuppressive conditions impair antitumor effector function, with regulatory T cell expansion and IL-10 signaling reducing $CD8^+$ T cell cytotoxicity, while tumor-derived kynurenine, CAF-mediated iron export and FSTL1 signaling induce ferroptosis in NK cells and oxidized lipids released from ferroptotic neutrophils further suppress T cell activity (183,194,260). In parallel, CAFs act as active regulators rather than structural support; they induce apoptosis through DR4-caspase-8 signaling, yet vesicles released from apoptotic cells promote CAF migration and facilitate invasion and lymphatic dissemination (261), and CAF- and neutrophil-derived exosomes further enhance tumor cell resistance to ferroptosis, thereby weakening chemotherapy-induced clearance (262,263). The metabolic microenvironment also constrains cell death by buffering lethal stress, as redox balance and lipid homeostasis limit effective execution of stress-induced death programs; although glucose deprivation can trigger parthanatos through ROS accumulation and PARP1 activation, lactate metabolism counteracts this process via the LDHB-IDH1-NADPH axis (245), and in lipid-rich niches, GC cells evade ferroptosis by restricting polyunsaturated fatty acid availability or altering cholesterol metabolism, thereby promoting metastasis and drug resistance (188). In addition, inflammatory signals and spatial constraints can redirect cell death toward pro-metastatic outcomes, with primary tumors inducing systemic NETosis to enhance circulating tumor cell adhesion and metastatic seeding (264), while entosis under detachment and nutrient stress contributes to clonal selection and tumor evolution. By contrast, when immunogenic cell death effectively activates the microenvironment, it promotes antitumor immunity; for example, pyroptosis mediated by the HIC1-GSDMD axis enhances $CD8^+$ T cell infiltration, and activation of the cGAS-STING-IFN axis drives macrophage polarization and tumor clearance (265). Overall, the TME regulates not only whether cell death occurs but also which cells undergo death, how it is executed, and what signals are released, thereby shaping immune responses, therapeutic outcomes, and the evolution of resistance and metastasis.

Notably, epigenetic regulation serves as a key interface linking external stress signals, gene expression programs and the execution threshold of cell death in GC. It operates across multiple layers, including DNA and histone modifications, epitranscriptomic regulation, ncRNA networks and post-translational modifications, which together determine whether tumor cells under therapeutic pressure, metabolic imbalance and oxidative stress survive, develop resistance or undergo cell death. At the epitranscriptomic and chromatin levels, METTL3/IGF2BP2-dependent m6A modification stabilizes SUV39H2 transcripts, thereby promoting H3K9me3-mediated silencing of dual specificity phosphatase 6, enhancing DNA damage repair, and suppressing cisplatin-induced apoptosis, which establishes a coordinated regulatory axis between RNA modification and histone methylation (266,267). Under elevated copper and lactate conditions, METTL16 undergoes lactylation, which increases its m6A methyltransferase activity, upregulates FDX1 and promotes cuproptosis (200). In addition, ncRNAs broadly RCD programs; microRNAs (miRNAs), lncRNAs and circular RNAs modulate apoptosis, autophagy and therapy-related death thresholds through ceRNA networks, mRNA stability and translational control. For example, circCUL2 suppresses protective autophagy and enhances cisplatin-induced apoptosis via the miR-142-3p/ROCK2 axis, indicating that post-transcriptional regulation directly shapes cell death outcomes under therapeutic stress (268). Moreover, post-translational modifications provide rapid and direct control over death thresholds; TRIM17-mediated ubiquitination of BAX reduces mitochondrial apoptosis, whereas USP29 and SMURF1 regulate ferroptosis suppressor protein 1 stability to determine ferroptosis sensitivity and chemoresistance (43,269). Together, epigenetic and post-transcriptional mechanisms coordinate how GC cells integrate stress signals and execute cell death programs, thereby influencing tumor progression and therapeutic response.

Systemic regulation. Unlike the TME, which reflects local cellular interactions and stromal organization, the tumor macroenvironment captures the sustained influence of systemic host states on tumor biology. This influence arises from integrated signals that shape inflammatory tone, immune clearance capacity, redox balance, nutrient and lipid availability and organelle homeostasis, thereby defining cell death thresholds and outcomes in both tumor and non-tumor cells (270-272). In GC, this regulation is most evident in infection-associated contexts, particularly chronic inflammation driven by persistent *H. pylori* colonization. Chronic infection maintains a high-turnover state marked by epithelial loss, compensatory proliferation and accumulated DNA damage. Reactive oxygen and nitrogen species, together with Th1-skewed cytokines, promote epithelial apoptosis, whereas concurrent activation of NF-κB, EGFR and AKT pathways supports survival and antioxidant responses, allowing damaged

cells to evade clearance and facilitating precancerous progression (273-275). Notably, these effects extend beyond apoptosis. CagA-positive *H. pylori* increases PUFA-ether phospholipid content and sensitizes cells to ferroptosis induced by RSL3 or erastin (184); under different metabolic and redox conditions, it suppresses ferroptosis through the NOX4/NRF2/GPX4 axis (276). These context-dependent effects indicate that the macroenvironment does not simply enhance or inhibit a specific pathway but biases cell fate toward distinct death outcomes. Viral factors exert similar control. EBV-encoded miRNAs suppress BAD expression, inhibit mitochondrial apoptosis and confer resistance to 5-FU and docetaxel (277), while EBV-mediated promoter hypermethylation of GSDME reduces baseline pyroptosis but permits a shift from apoptosis to pyroptosis when GSDME expression is restored under therapeutic stress (115). Systemic metabolic and nutritional states represent another major regulatory axis. Glucose deprivation induces apoptosis and cell cycle arrest; however, GC cells activate JUN-PPP1R15A-dependent protective autophagy to maintain energy homeostasis and partially offset lethal stress (151). Under severe nutrient deprivation, ULK1 directly activates GSDMA to trigger pyroptosis, indicating that metabolic stress can initiate lytic cell death (278). Lipid availability further modulates death susceptibility. Mesenchymal-type GC, with elevated elongation of very long chain fatty acids protein 5 and fatty acid desaturase 1 expression, maintains abundant arachidonic acid (AA) and adrenic acid lipid pools and shows increased ferroptosis sensitivity, whereas intestinal-type tumors exhibit ferroptosis resistance due to epigenetic silencing of these enzymes, which can be partially reversed by exogenous AA supplementation (279). Obesity and aging extend this regulation at the systemic level. Palmitate-induced endothelial senescence releases SLC1A5-enriched exosomes that suppress ferroptosis through the EGFR/SRC/YAP1/GPX4 axis and promote invasion and metastasis (280). Neuroendocrine signaling also contributes to cell death of GC. Serotonin acting through 5-hydroxytryptamine receptor 2B remodels lipid metabolism via the Fyn/PI3K/Akt/mTOR/HIF1α/ABCD1 pathway, reduces ROS and lipid peroxidation, and enhances tumor cell survival by suppressing ferroptosis (281). Moreover, the macroenvironment affects host immune cells as well as tumor cells. Untreated patients with GC exhibit systemic oxidative stress, mitochondrial dysfunction and increased apoptosis in peripheral blood mononuclear cells across multiple immune subsets, indicating impaired immune clearance capacity (282). Environmental exposures such as microplastics and nanoplastics further contribute by inducing ROS accumulation, activating NLRP3 and MAPK signaling and disrupting mitochondrial and barrier function, thereby establishing a chronic high-damage, low-clearance state that may impair cell death efficiency (283). Collectively, the tumor macroenvironment integrates infection, metabolism, immunity and stress signals to regulate the balance between cell survival and death, thereby influencing GC initiation, progression and therapeutic response.

Crosstalk among cell death pathways. Accumulating evidence indicates that tumor cell death is not governed by a single program but by multiple modalities operating under shared stress and metabolic constraints. Rather than functioning as isolated pathways, these death programs form an interconnected network through convergence on shared stress signals, bifurcation or switching at common regulatory nodes and compensatory regulation of death thresholds. These pathways converge on common upstream processes, including oxidative stress, mitochondrial dysfunction, lipid remodeling and inflammatory signaling, which provide a common stress landscape from which different death programs can be activated in parallel or sequentially (284). In GC, several consistent patterns of crosstalk have emerged, most notably between apoptosis and ferroptosis. Diverse therapeutic stimuli can simultaneously induce mitochondrial apoptosis and lipid peroxidation-driven ferroptosis via ROS accumulation, disruption of lipid homeostasis or mTOR inhibition, and blocking either pathway only partially restores cell viability, indicating parallel contributions to cell clearance (285,286). This interaction arises from a shared stress framework in which lipid peroxidation and antioxidant collapse amplify mitochondrial damage and apoptotic signaling, whereas mitochondrial dysfunction and ROS accumulation further enhance ferroptotic susceptibility, forming a self-reinforcing loop. Ferroptosis and cuproptosis represent another example of stress convergence, as both can be co-amplified through redox imbalance, mitochondrial dysfunction and disruption of metal-dependent metabolic homeostasis. Thus, oxidative, mitochondrial and metabolic stress can function as upstream hubs that converge on multiple death pathways rather than exclusively committing cells to a single mode of death.

In contrast to pathway convergence, other forms of crosstalk are determined by fate-decision nodes that redirect signaling from one execution program to another. Apoptosis and necroptosis are primarily linked through conditional switching at bifurcation nodes, with RIPK1 acting as a central checkpoint that directs signaling toward apoptosis when caspase-8 is active and toward RIPK3-MLKL-dependent necroptosis when it is inhibited. Accordingly, miR-148a/152-mediated RIPK1 downregulation suppresses both pathways and promotes chemoresistance, whereas severe stress can co-activate them to enhance cytotoxicity (287). Apoptosis and pyroptosis are connected more directly, as caspase-3 not only executes apoptosis but also cleaves GSDME to trigger membrane-lytic pyroptosis, thereby altering inflammatory output (288). This caspase-3-GSDME axis enables an initially apoptotic signal to switch toward a lytic and inflammatory mode of cell death. PANoptosis further extends this concept by coordinately engaging apoptotic, pyroptotic and necroptotic machinery through shared regulatory nodes rather than simply activating three independent pathways. By contrast, autophagy exerts context-dependent effects, as it can limit mitochondrial damage and ROS accumulation to suppress apoptosis and reduce treatment efficacy (289), or accompany non-apoptotic death without serving as a primary driver. Autophagy therefore acts mainly as a threshold-modulating process within the death network: its stress-buffering capacity can delay the activation of other death programs, whereas failure or overwhelming of this capacity may facilitate their execution.

Beyond these relatively well-defined interactions, additional connections among metabolic and inflammatory death pathways are beginning to emerge. Ferroptosis can synergize

with pyroptosis to enhance antitumor immunity and improve immunotherapy responses, linking lipid peroxidation-driven stress with inflammatory cell death and immune activation (209). Although evidence for disulfidptosis and other metabolic death programs in GC remains limited, their reliance on the SLC7A11-GSH-GPX4 axis, mitochondrial metabolism and redox homeostasis suggests potential integration into this framework. However, these emerging relationships should be interpreted cautiously, because some are supported by direct functional experiments, whereas others are inferred from shared therapeutic responses or transcriptomic associations rather than demonstrated pathway switching. At the systems level, integrated analyses show that combined signatures of multiple death pathways outperform single-pathway markers in predicting prognosis, immune infiltration and therapeutic response (290,291). Such transcriptomic co-occurrence should not itself be considered evidence of mechanistic crosstalk. Collectively, cell death crosstalk in GC can therefore be understood as a dynamic network governed by shared stress hubs, fate-decision nodes, and compensatory mechanisms that collectively determine whether death pathways converge, diverge, or switch under different cellular contexts. This framework also suggests that targeting upstream stress regulators or shared fate-decision nodes may provide greater therapeutic leverage than targeting a single terminal execution pathway.

4. Translational implications of cell death in GC

Cell death in GC constitutes the final effector through which most anticancer therapies achieve tumor clearance. The efficacy of chemotherapy, targeted therapy and immunotherapy depends on their ability to induce and complete specific cell death programs in tumor cells. Therapeutic resistance arises when these programs are attenuated or delayed at multiple regulatory levels. Distinct modes of cell death differ in signal input, execution mechanisms and inflammatory output, which results in context-dependent activation under therapeutic pressure. Reframing treatment response and resistance through the lens of cell death and identifying actionable regulatory nodes with translational relevance therefore represent a key direction in GC research.

Conventional therapies and drug resistance. Conventional treatment for GC is based on surgery, chemotherapy and radiotherapy, with strategies determined by disease stage. Early-stage disease is managed by endoscopic resection or radical gastrectomy, whereas locally advanced tumors are treated with perioperative therapy plus surgery, with the FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) as a standard approach. For recurrent, unresectable or metastatic disease, fluoropyrimidine- and platinum-based regimens form the backbone of systemic therapy, and radiotherapy is used in selected cases to improve local control (1). Despite this framework, clinical responses remain heterogeneous, with frequent progression from initial sensitivity to acquired resistance, limited durability and reduced efficacy upon retreatment. These limitations reflect not only pharmacokinetic variability or single resistance mechanisms but also a broader shift in cell fate determination under therapeutic stress. In DNA damage-based treatments, including radiotherapy and platinum compounds, cytotoxicity requires effective activation of apoptotic execution; impairment of p53 signaling, checkpoint adaptation or disruption of mitochondrial apoptosis allows survival despite damage and reduces treatment sensitivity (292). In parallel, some tumor cells rely on adaptive programs such as autophagy, metabolic buffering and redox homeostasis to withstand therapeutic stress, making autophagy an active contributor to cisplatin and oxaliplatin resistance rather than a passive response (293). Reduced susceptibility to ferroptosis further weakens treatment efficacy, as tumor cells and their microenvironment remodel lipid peroxidation, cystine metabolism, GSH buffering and mitochondrial function to limit oxidative damage under 5-FU or platinum-based therapy (294,295). Similarly, impaired pyroptosis alters both the magnitude and form of therapy-induced cell death, further shaping treatment response (296). Resistance is also enriched in stem-like populations, metabolically adaptable subclones and microenvironment-protected cell states, which sustain survival and drive relapse under prolonged treatment pressure (297). Thus, the primary challenge in conventional therapy lies not in insufficient drug potency but in the progressive establishment of adaptive survival programs, including redistribution among cell death pathways, metabolic and redox reprogramming, microenvironmental protection and persistence of resistant cell subsets (191,298). Reframing treatment resistance through cell death regulation provides a basis for therapeutic optimization by prioritizing suppressed death pathways and targeting the mechanisms that sustain tumor cell survival.

Emerging therapeutic approaches. Beyond conventional treatments, emerging strategies are expanding therapeutic options in GC and shifting the focus from increasing cytotoxic intensity to mechanism-driven interventions guided by molecular subtypes, tumor ecology and cell death vulnerabilities. Notably, the level of evidence supporting these approaches varies considerably. Immune checkpoint inhibitors and selected targeted therapies have entered routine clinical practice or late-stage clinical evaluation, whereas most nanomedicine-based platforms, natural products and organelle-targeted strategies remain supported predominantly by preclinical evidence. Immunotherapy represents a key component of this transition. PD-1/PD-L1 blockade is now widely used in advanced disease, but its efficacy varies and depends on both the immunogenic state of the TME and the capacity of tumor cells to execute cell death programs. Tumors with higher pyroptotic activity show increased effector T cell infiltration, enhanced immune activation and improved responses to neoadjuvant immunotherapy, whereas IL-1β-driven inflammatory conditions reinforce metabolic buffering and iron homeostasis, suppress ferroptosis sensitivity and reduce responsiveness to PD-1 blockade (299,300). These observations suggest that therapeutic outcomes depend not only on inflammatory status but also on whether tumor cells engage immunostimulatory forms of cell death. In parallel, targeted therapy is moving from single-receptor inhibition toward refined patient stratification and combination strategies. HER2- and CLDN18.2-directed therapies exemplify this shift, while antibody-drug conjugates, bispecific antibodies and CAR-T platforms further extend precision

treatment (2,301). These approaches not only introduce new targets but also help overcome apoptosis resistance, pro-survival signaling and microenvironmental protection, thereby restoring susceptibility to tumor cell clearance. Drug delivery systems have emerged as promising platforms for modulating cell death pathways by enhancing intratumoral drug exposure and optimizing drug release. However, current evidence is derived predominantly from cell lines and animal models. Clinical translation remains limited by challenges including pharmacokinetic variability, systemic toxicity, insufficient *in vivo* delivery efficiency, manufacturing complexity and the lack of prospective clinical validation. Current strategies can be grouped into three categories. Biomarker-guided nanodelivery systems concentrate agents in defined contexts such as HER2-positive tumors and induce apoptosis or autophagy-related death (302). Integrated platforms combine nucleic acid therapy, photothermal treatment and immune activation to amplify local cytotoxic and immune effects (303,304). Sustained or rhythm-controlled systems, including injectable hydrogels and biomimetic nanoparticles, enhance ROS accumulation, mitochondrial damage, ferroptosis or thermal sensitivity while limiting systemic toxicity (305). Rather than replacing existing drugs, these systems optimize the spatial and temporal delivery of lethal signals and support combination therapy. Natural products and multi-component interventions have shown promising activity in modulating cell death pathways and enhancing therapeutic sensitivity in experimental GC models. However, their current translational value should be interpreted cautiously, as most evidence is limited to preclinical studies and challenges related to bioavailability, pharmacokinetic properties, target specificity and clinical validation remain to be resolved. For example, resveratrol restores apoptotic execution and suppresses epithelial-mesenchymal transition-associated phenotypes in doxorubicin-resistant GC, whereas baicalin, Yiqi Jiedu formulations and alkannin enhance the efficacy of 5-FU and platinum drugs by weakening antioxidant defenses and lipid metabolic adaptation (285,306). Emerging physical and organelle-targeted approaches further broaden this landscape. Rotating magnetic field-driven nanoparticles induce mitochondrial apoptosis and ferroptosis in GC stem-like cells, and mitochondrial transfer reprograms metabolic state and stress adaptation to enhance 5-FU sensitivity (307,308). Taken together, these strategies emphasize patient stratification, optimized delivery and diversified death induction, which together restore suppressed clearance pathways and provide a rational basis for combination therapy.

Imaging-based clinical applications. In addition to drug development and combination strategies, imaging has emerged as a distinct translational direction in cell death research. Its value lies not in improved visualization of tumor lesions but in converting treatment-induced cell death into functional signals that can be detected earlier, monitored dynamically and used to guide clinical decisions. Because most anticancer therapies ultimately rely on tumor cell clearance, while conventional CT and MRI capture delayed anatomical changes, cell death-oriented imaging can shift response evaluation from structural endpoints to mechanistic readouts. Current strategies fall into three main categories. One approach targets molecular events associated with cell death; probes recognizing phosphatidylserine externalization enable early detection of apoptosis in GC models and, when combined with photoacoustic imaging, support lesion localization, localized intervention and response monitoring, indicating that cell death signals can precede tumor shrinkage (71). A second approach integrates imaging modalities, including MRI, near-infrared fluorescence, ultrasound and CT, with photothermal therapy, photodynamic therapy, chemotherapy or gene delivery to establish theranostic platforms. These systems assess intratumoral accumulation and distribution, guide intervention timing, and achieve tumor clearance through apoptosis, ferroptosis or related programs. Although validation still depends largely on histological and molecular endpoints, this strategy shows that imaging can inform treatment timing, local dose modulation and dynamic response assessment rather than serving as a static comparator (309-311). The development of ferroptosis-oriented platforms further extends imaging beyond apoptosis by enabling functional interrogation of lipid peroxidation, ROS amplification and metabolic vulnerabilities (310). A third approach focuses on indirect imaging of microenvironmental and molecular states that determine death thresholds. Fibroblast activation protein inhibitor-based imaging improves detection of CAF-rich primary tumors and peritoneal metastases and complements conventional metabolic imaging in stromal-dominant GC. Although it does not directly visualize cell death execution, it captures conditions associated with apoptosis resistance, ferroptosis tolerance and therapeutic failure, thereby maintaining relevance to cell death-oriented translation (312). Additional advances include MRI-responsive platforms that simultaneously target tumor cells and CAFs to induce dual ferroptosis, linking microenvironmental remodeling, therapeutic delivery and real-time monitoring within a unified framework (189). Preclinical studies using 3D spheroids and live-cell imaging further show that apoptosis can be continuously and quantitatively tracked, supporting translation from *in vitro* systems to *in vivo* and clinical functional imaging (313). Collectively, cell death-centered imaging represents a promising strategy for functional assessment of therapeutic response. Nevertheless, most imaging platforms remain at the preclinical or early translational stage, and further prospective clinical studies are required before routine clinical implementation.

Overall, the translational maturity of cell death-targeted strategies varies considerably. Conventional chemotherapy, immune checkpoint blockade and selected targeted therapies are supported by robust clinical evidence, whereas nanomedicine, natural products, organelle-targeted interventions and most imaging-based approaches remain largely investigational and are supported predominantly by preclinical studies. Despite encouraging progress, their broader clinical application continues to face important challenges, including suboptimal pharmacokinetic properties, systemic toxicity, limited tumor-specific delivery efficiency, manufacturing complexity, tumor heterogeneity and the lack of prospective randomized clinical trials. Future advances will depend on molecular stratification, biomarker-guided patient selection, optimization of drug delivery systems, and well-designed

clinical studies to translate these promising strategies into routine clinical practice.

5. Conclusion and future perspectives

Rather than viewing cell death in GC as a set of independent molecular pathways, it is better understood as a dynamically regulated process of cell fate determination reshaped by sustained stress and adaptation. GC cells do not lose the capacity for cell death; instead, they adjust the transmission and execution of death signals at multiple levels, which favors survival under damage, metabolic stress and immune attack. Meanwhile, the local microenvironment and systemic host state continuously redefine the conditions under which these processes occur, producing distinct outcomes even under similar stimuli. This perspective explains the variability in therapeutic responses and indicates that cell death is not a single downstream event but a constraint operating throughout treatment. This variability extends beyond the occurrence of cell death to include its magnitude, kinetics and completeness of clearance. When these processes are delayed or interrupted, cells persist in a damaged yet uncleared state, which supports resistance and relapse. Despite these insights, several limitations remain. Most evidence derives from single models or isolated pathway analyses and does not capture the coexistence and dynamic switching of multiple death programs in tumors. In addition, numerous emerging forms of cell death lack *in vivo* validation, and their functional roles in GC remain unclear. The consequences of cell death are also context-dependent and bidirectional; they can promote tumor clearance but may also exacerbate inflammation, immune suppression or metastatic progression, which limits direct therapeutic translation. Current assessments rely on endpoint measurements or static molecular markers and do not capture dynamic changes, which restricts clinical application. Future research should adopt an integrative approach that evaluates different death programs in physiologically relevant tumor contexts and links them to molecular subtypes, metabolic states and immune landscapes. It is also necessary to develop dynamic indicators of cell death to guide treatment selection and response assessment.

In conclusion, alterations in cell death are not secondary events in GC progression but key determinants of tumor behavior and therapeutic outcomes. A systematic understanding of these processes may improve treatment response and delay resistance within current therapeutic frameworks. More importantly, translating fragmented molecular insights into actionable principles can inform clinical decision-making and promote more consistent and predictable management of GC.

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Authors' contributions

ML wrote the original draft, conducted the literature search and curated the relevant literature and data. ZW curated the literature and contributed to the organization and synthesis of the evidence and visualization. QC conducted the literature search, verified the extracted information and contributed to the review framework. WN provided resources and contributed to literature verification and critical evaluation of the evidence. YC contributed to evidence synthesis and visualization and curated the relevant literature and data. YZ conducted the literature search, verified the extracted information and provided resources. YC contributed to the development of the review framework, literature organization and evidence synthesis. HA and YL supervised the study and reviewed and edited the manuscript. HA acquired the funding. All authors read and approved the final version of the manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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