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REVIEW

Regulatory roles of non-coding RNAs in programmed cell death pathways and drug resistance in gastrointestinal stromal tumors

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Abstract

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract, primarily driven by KIT or PDGFRA mutations. Programmed cell death (PCD), including apoptosis, autophagy, and ferroptosis, plays a crucial role in GIST pathogenesis, progression, and treatment response. Non-coding RNAs (ncRNAs) have emerged as key regulators of PCD pathways, influencing GIST proliferation, metastasis, and drug resistance, particularly in response to tyrosine kinase inhibitors (TKIs) such as imatinib. Apoptosis suppression is strongly associated with poor prognosis, while autophagy contributes to tumor dormancy and TKI resistance. Ferroptosis, a novel iron-dependent cell death pathway, represents a promising therapeutic target. Recent evidence suggests that ncRNAs modulate these PCD pathways through interactions with key molecular regulators such as miR-494, miR-30a, and lncRNAs, which affect signaling networks including PI3K/AKT, MAPK, and mTOR. Furthermore, ncRNAs have mediated secondary resistance to imatinib by promoting autophagic flux and altering ferroptosis sensitivity. Understanding the molecular interplay between ncRNAs and PCD in GIST provides novel insights into disease mechanisms and offers potential therapeutic strategies to overcome drug resistance. Targeting ncRNA-mediated regulation of apoptosis, autophagy, and ferroptosis may enhance treatment efficacy and improve patient outcomes. Future research should focus on elucidating the mechanistic roles of ncRNAs in PCD pathways to develop innovative diagnostic and therapeutic approaches for GIST.

Keywords Gastrointestinal stromal tumor · Non-coding RNA · Programmed cell death · Autophagy · Ferroptosis

Abbreviations

3'UTRs	3' Untranslated regions
AMA	Autophagy-related genes (ATGs)
AMPK	AMP-activated protein kinase
APAF1	Apoptotic peptidase activating factor 1
CDKIs	Cyclin-dependent kinase inhibitors
circRNAs	Circular RNAs
CMA	Chaperone-mediated autophagy
DD	Death domains
ER	Endoplasmic reticulum
FAT	Fatty acid synthase
FOXOs	Forkhead box proteins
GAS5	Growth arrest-specific 5
GIST	Gastrointestinal stromal tumors
GPX4	Glutathione peroxidase 4
GSH	Glutathione
HIF-1α	Hypoxia-inducible factor-1α
HSP	Heat shock protein
HSPB1	Heat shock protein family B member 1
ICC	Interstitial cells of cajal
IM	Imatinib
LI	Labeling indices
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
mTORC1	Mechanistic target of rapamycin complex 1
ncBAF	Non-classical BAF

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ncRNA	Non-coding RNA
OPN	Osteopontin
PI3P	Phosphatidylinositol-3-phosphate
PCD	Programmed cell death
PGD	6-Phosphogluconate dehydrogenase
PPP	Pentose phosphate pathway
PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SDH	Succinate dehydrogenase
TCA	Tricarboxylic acid
TFRC	Transferrin receptor
TNF	Tumor necrosis factor
TRAIL	TNF-related apoptosis-inducing ligand
TMA	Tissue microarray
TKIs	Tyrosine kinase inhibitors
XIAP	X-linked inhibitor of apoptosis protein

Introduction

Gastrointestinal stromal tumors (GIST) are the most common sarcomas of the gastrointestinal tract, originating from interstitial cells of Cajal (ICC) [1–3]. Despite this, GIST is still considered a rare disease. Its incidence varies across regions and periods, with registry data generally reporting an annual incidence exceeding 12 cases per million [4, 5]. While GIST has a low global incidence, significant regional differences have been observed. For instance, in North America and parts of Europe, the annual incidence can reach 20–30 cases per million [6], whereas in some Asian countries, the reported incidence is lower, ranging from 5 to 10 cases per million [7]. These differences highlight the significant impact of racial and geographical factors on GIST incidence. The primary driver mutations in GIST occur in the KIT (60–70%) and PDGFRA (10–15%) genes [6, 8, 9].

Approximately 15% of GIST cases lack KIT or PDGFRA mutations but exhibit other genetic alterations, such as mutations in succinate dehydrogenase (SDH) subunits (A, B, C, or D), BRAF, KRAS, NF1, or FGFR1. Some cases also show overexpression of IGF1R [10–12]. SDH deficiency promotes the accumulation of succinate, which activates signaling pathways such as PI3K/Akt, MAPK, and mTOR, thereby enhancing GIST cell proliferation, survival, and migration. Activation of these abnormal pathways increases tumor invasiveness and is closely associated with malignancy and poor patient prognosis (Fig. 1). KIT and PDGFRA encode receptor tyrosine kinases, and their driver mutations dysregulate and activate several downstream pathways, including MEK-MAPK, PI3K-AKT, and JAK-STAT [13–15].

In addition, GIST exhibits high levels of ETV1 expression, a transcription factor downstream of the MEK-MAPK pathway. ETV1 is essential for ICC development and its transformation into GIST cells, driving abnormal proliferation and inhibiting apoptosis [16]. The activation of KIT synergizes with ETV1, further promoting aberrant cell proliferation and apoptosis suppression [16]. Other genetic alterations, such as SDH gene silencing and mutations in RAS, BRAF, NF1, and FGFR1, have also been identified in a minority of GIST cases [11, 12]. These genetic changes present potential targets for individualized therapy.

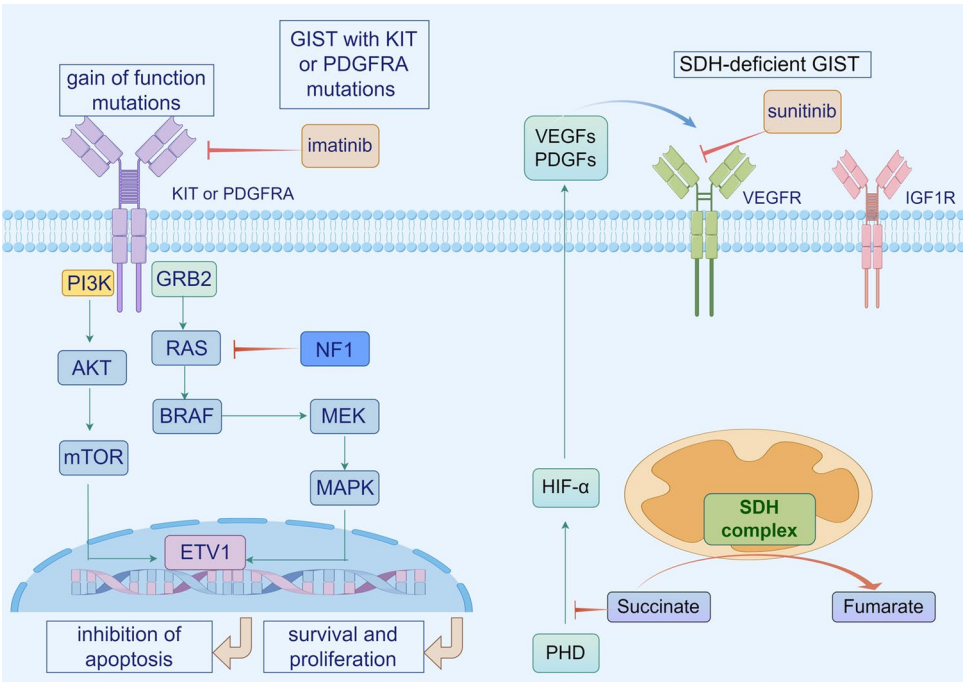

Fig. 1 Tumor Metabolism and Apoptosis Inhibition Mechanisms Driven by SDH Deficiency (Created by BioRender). This figure illustrates the key molecular mechanisms underlying GIST associated with SDH deficiency, observed in approximately 15% of GIST cases. The accumulation of succinate and fumarate affects the PHD and HIF signaling pathways, subsequently activating the MAPK pathway. This process ultimately supports tumor cell survival and proliferation while inhibiting apoptosis

With the advancement of targeted therapy, systemic treatment of GIST has significantly progressed, primarily focusing on tyrosine kinase inhibitors (TKIs) targeting KIT and PDGFRA mutations. However, GIST exhibits considerable molecular heterogeneity. Approximately 5–10% of patients have succinate dehydrogenase (SDH)-deficient GISTs [17], which are more frequently seen in younger individuals and often associated with hereditary syndromes. SDH deficiency leads to succinate accumulation and activation of oncogenic signaling pathways [18]. This subtype responds poorly to conventional TKIs and displays distinct molecular features such as high expression of neural markers, FGFR signaling activation, and epithelial-mesenchymal transition (EMT), indicating the need for alternative therapeutic approaches [19].

In PDGFRA-mutant GISTs, the D842V mutation (exon 18), which accounts for approximately 5% of cases, confers primary resistance to imatinib and sunitinib. The novel TKI avapritinib has demonstrated promising efficacy in this mutation subtype and represents a new direction for precision therapy [20]. Moreover, the efficacy of immune checkpoint inhibitors (ICIs) in GIST remains uncertain. Studies have shown that SDH-deficient GISTs possess an immune-cold microenvironment, which may influence their response to ICIs [19, 21]. In addition, immune-related adverse events (irAEs), such as hearing loss, have been reported during ICI treatment and warrant attention [22]. The neutrophil-to-eosinophil ratio (NER) has recently been proposed as a potential prognostic biomarker. Although its role in GIST is not well-established, it may offer insights for future personalized treatment strategies [23].

KIT and PDGFRA have been identified in treating GIST as type III receptor tyrosine kinases, leading to TKIs such as imatinib (IM). As a targeted therapy, IM has become one of the standard treatments for GIST. It inhibits tumor growth by suppressing the tyrosine kinase activity of KIT and PDGFRA [13, 14]. Over the past two decades, IM has significantly improved the median survival of patients, extending it from 18 months to over 5 years [24, 25].

Although IM remains the first-line therapy for GIST, disease progression typically occurs after a median duration of 20–24 months [26]. The most studied mechanism of IM resistance involves secondary mutations in KIT or PDGFRA and the activation of alternative pathways such as MEK-MAPK and PI3K-AKT. This phenomenon, known as secondary resistance, limits the effectiveness of IM [15]. These mutations primarily occur in the ATP-binding domain (exon 13 or 14 of KIT; exon 14 of PDGFRA) or the activation loop (exon 17 of KIT; exon 18 of PDGFRA) [27–30].

Sunitinib and regorafenib are currently used as standard second and third-line therapies for IM-resistant GIST [31, 32]. However, treating secondary resistance remains challenging, as the molecular mechanisms underlying resistance to these drugs are not fully understood. Studies suggest that IM can induce autophagy, possibly contributing to developing secondary resistance [33, 34]. Additionally, IM has been shown to induce ferroptosis and apoptosis [35–40], highlighting programmed cell death (PCD) as a promising therapeutic target for GIST. Table 1 summarizes the major drugs currently used for GIST treatment, their targets and mechanisms of action.

Overview of the pathogenesis of GIST

PCD pathways and their roles in GIST

PCD encompasses various forms, including classical apoptosis, necroptosis, pyroptosis, autophagy, and ferroptosis, each playing distinct roles in tumor malignancy and therapeutic responses [41–43]. In GIST, apoptosis, autophagy, and ferroptosis are the primary forms of cell death. Table 2 summarizes the key regulatory factors involved in these pathways and their functional impacts on GIST cells. The apoptotic pathway is regulated by p53 and the Bcl-2 family, while autophagy involves Beclin-1, LC3, and the mTOR pathway. Ferroptosis is controlled by glutathione peroxidase 4 (GPX4), ferroportin, and the Fenton reaction. Studies have shown that suppression of apoptosis correlates with poor prognosis in GIST patients, whereas the role of autophagy can vary under different conditions [33, 44–46].

Apoptosis has been reported to correlate with GIST malignancy, while autophagy generally exhibits an inverse relationship with apoptosis. During GIST progression, ferroptosis appears to function similarly to apoptosis, with ferroptosis-related proteins identified as potential targets and predictive markers for TKI therapy [35–37]. As a novel therapeutic target, developing ferroptosis-specific drugs is promising for treating advanced GIST [45, 47, 48]. Apoptosis, one of the most extensively studied forms of PCD, is characterized by cellular shrinkage, an undulated yet intact plasma membrane, nuclear condensation, and fragmentation, indicative of its non-inflammatory nature.

Apoptotic cells exhibit characteristic morphological changes, including the formation of apoptosomes, which consist of apoptotic peptidase activating factor 1 (APAF1) and caspase-9 [49, 50]. The apoptosis pathway is classified into intrinsic and extrinsic pathways and further divided into the mitochondrial pathway [51, 52], death receptor pathway [53], and endoplasmic reticulum (ER) stress pathway [54]. The intrinsic (mitochondrial) and extrinsic pathways are the most extensively studied. The extrinsic pathway is typically triggered by activating tumor necrosis factor (TNF) receptor family members [55].

Table 1 Key drugs, their targets, and signaling pathways in the treatment of GIST

Drug Name	Target	Signaling pathway	Role in GIST treatment
Imatinib	c-Kit, PDGFR	Inhibits the activation of c-Kit and PDGFR, blocking tumor cell proliferation and survival signaling pathways	Effective in the treatment of GIST, especially in patients with c-Kit mutations, inhibiting tumor cell proliferation and survival
Sorafenib	VEGFR, c-Kit, PDGFR	Inhibits VEGFR, c-Kit, and other receptors, suppressing tumor angiogenesis and cell proliferation pathways	In GIST, it inhibits tumor angiogenesis and enhances apoptosis
Lapatinib	EGFR, HER2	Inhibits the activation of EGFR and HER2, disrupting tumor cell proliferation, survival, and metastasis signaling pathways	Exhibits antiproliferative effects on HER2-positive GIST cells, slowing tumor progression
Docetaxel	Microtubules	Inhibits microtubule depolymerization, interfering with cell division and mitosis, promoting apoptosis	Enhances apoptosis of GIST cells and inhibits tumor growth in treatment
Doxorubicin	DNA, Topoisomerase II	Binds to DNA and inhibits topoisomerase II, disrupting DNA replication and repair, inducing cell death	Inhibits GIST cell proliferation and induces apoptosis through DNA damage
Bevacizumab	VEGF	Inhibits VEGF, suppressing tumor angiogenesis and slowing tumor growth	Reduces blood supply to GIST tumors, inhibiting proliferation and metastasis
Cyclophosphamide	DNA, Antigen Presentation	Binds to DNA, inhibits DNA repair, triggers immune responses, and enhances cell death	In adjuvant therapy for GIST, enhances immune system recognition and clearance of tumors
Vemurafenib	BRAF	Inhibits BRAF mutations, suppressing the MAPK pathway, reducing cell proliferation and inducing apoptosis	Primarily used for BRAF-mutant tumors, modulating cell cycle and apoptosis processes

Table 2 Molecular regulators of cell death mechanisms in GIST

Cell Death Type	Regulator	Mechanism of Action	Role in GIST
Apoptosis	p53	p53 upregulates pro-apoptotic genes such as Bax, promoting mitochondrial release of cytochrome C, and activating caspase family members	p53 mutations or inactivation inhibit apoptosis, promoting tumor cell survival
	Bcl-2 Family	Bcl-2 proteins regulate mitochondrial membrane permeability, inhibiting pro-apoptotic signals, and maintaining cell survival	In GIST cells, Bcl-2 expression is upregulated, inhibiting apoptosis
	Caspases	The caspase family is key in executing apoptosis by cleaving various intracellular substrates, leading to cell death	Caspase-3 and other enzymes are inhibited in GIST, reducing apoptosis occurrence
Autophagy	Beclin-1	Beclin-1 is a crucial regulator in the early stages of autophagy, promoting the formation of autophagosomes and initiating autophagy	Beclin-1 is expressed at low levels in GIST, leading to suppressed autophagy
	LC3	LC3 proteins play a pivotal role in autophagosome formation by binding to autophagosomes and facilitating the autophagic process	High expression of LC3-II indicates activation of autophagy in GIST cells
	mTOR	mTOR suppresses the expression of autophagy-related genes, regulating the initiation and progression of autophagy	The mTOR pathway is hyperactivated in GIST cells, inhibiting the autophagy process
Ferroptosis	GPX4	GPX4 removes intracellular lipid peroxides, inhibiting ferroptosis	In GIST, GPX4 expression may be suppressed, promoting ferroptosis
	Ferroportin	Ferroportin is the main protein for cellular iron transport, controlling iron export and regulating intracellular iron levels	Ferroportin expression is decreased in GIST, exacerbating iron accumulation
	Fenton Reaction	Iron ions generate free radicals through the Fenton reaction, leading to oxidative stress and promoting ferroptosis	Excess iron accumulation increases ROS in GIST cells, triggering ferroptosis

The intrinsic pathway is initiated by increased mitochondrial outer membrane permeability (MOMP) and cytochrome c release, leading to apoptosome formation [56]. The Bcl-2 family plays a critical regulatory role in this pathway and is divided into three subfamilies: pro-apoptotic BH3-only proteins (e.g., Bim, Bid, Puma), anti-apoptotic Bcl-2 family members (e.g., Bcl-2, Mcl-1), and effector molecules (e.g., Bax, Bak) [57]. In contrast, the extrinsic pathway is initiated by activating pro-apoptotic death receptors, which are cell membrane proteins, including Fas and TNFR. Death receptors are activated by binding specific ligands, leading to the recruitment of adaptor proteins such as FADD via their death domains (DD) [58–60]. Evasion of apoptosis and the aberrant expression of survival proteins are among the most common alterations during malignant transformation. By avoiding apoptosis, malignant cells enhance their survival and develop drug resistance [61–63]. As understanding of apoptotic mechanisms has advanced, a limited number of FDA-approved anticancer drugs have been developed to directly target apoptosis pathways. Additionally, many FDA-approved anticancer drugs targeting cell survival and proliferation pathways exert their anti-tumor effects by modulating apoptotic signaling pathways [64].

Objectives and innovations of this review

This review examines the molecular functions of PCD pathways in GIST, focusing on their roles in the pathogenesis, malignancy, and responses to TKI therapies. Additionally, we emphasize the significance of non-coding RNAs (ncRNAs) in these pathways, as growing evidence suggests that ncRNAs play critical roles across various pathways. Investigating the interplay between these pathways and ncRNAs may offer new research directions and therapeutic strategies for GIST.

Mechanisms of PCD in GIST

Apoptosis and GIST

Apoptosis plays a key role in the pathogenesis and biology of GIST), particularly in changes in apoptotic signaling and drug resistance following TKI therapy, such as IM. The most common driver mutations in GIST involve the KIT and PDGFRA genes, which activate multiple downstream signaling pathways that regulate cell survival and apoptosis. Overexpression of the transcription factor ETV1 may facilitate the transformation of interstitial cells of Cajal into GIST cells while suppressing apoptosis, contributing to tumor progression. Activating mutations in the c-KIT gene result in constitutive KIT tyrosine kinase activity, which provides continuous proliferative and survival signals—one of the central mechanisms in GIST pathogenesis. While inhibition of apoptosis and dysregulation of the cell cycle are likely early molecular events in GIST, the precise mechanisms remain under investigation.

Mechanisms of apoptosis evasion

Driver mutations in KIT and PDGFRA activate multiple pathways that disrupt the expression and function of apoptotic regulators. Constitutively active KIT signaling enables tumor cells to evade apoptosis. Cyclin D1 is significantly overexpressed in KIT-independent GIST and is associated with antiproliferative and pro-apoptotic responses, indicating a role for cell cycle regulators in the transition from KIT dependence to resistance [65]. Alterations in E2F1, p53, p16, and p27KIP1 are more frequent in malignant GIST, further implicating apoptosis escape in tumor progression [45, 66].

Bcl-2, a classic anti-apoptotic protein, is highly expressed in GIST and correlates with poor prognosis. Cunningham et al. reported shorter survival in patients with high Bcl-2 expression, supporting its role in apoptosis evasion [44]. APAF-1, a core component of the apoptosome, is negatively regulated by KIT expression, suppressing apoptosis in GIST [67]. FAM96A, a tumor suppressor that enhances mitochondria-mediated apoptosis via interaction with APAF1, is significantly downregulated in GIST, suggesting a loss of pro-apoptotic function [68].

FOXO transcription factors, particularly FOXO3a, promote apoptosis by upregulating BIM [69]. Apoptosis evasion supports GIST growth and survival and contributes to resistance. Although IM has strong antiproliferative effects, it fails to induce sufficient apoptosis, pushing cells into a quiescent state, a potential source of resistance [70]. Upregulation of p27(Kip1) and loss of Cyclin A through the APC/CDH1-SKP2-p27(Kip1) axis facilitates apoptosis evasion and quiescence [70].

Apoptosis-related biomarkers

Apoptosis-related proteins are valuable biomarkers for predicting GIST behavior and prognosis. Wang et al. demonstrated a correlation between telomerase activity, apoptotic intensity, and GIST malignancy, noting that apoptosis progressively declines in benign and potentially malignant GIST [71]. Risk stratification based on the Ki-67 index, tumor size, and location helps predict recurrence in IM-naive patients [72, 73].

Nemoto et al. found that high-risk GIST cases exhibit elevated labeling indices (LIs) for Ki-67, ssDNA, Cyclin A, and CDK2,

Survivin (BIRC5), an anti-apoptotic protein, inhibits the extrinsic pathway via interaction with XIAP [53, 74]. Its expression is elevated in GIST and downregulated following KIT inhibition, implying a role in KIT-mediated survival signaling [75]. FOXO proteins activate apoptosis through multiple mechanisms, including the induction of Bcl-2 pro-apoptotic members, expression of death ligands (e.g., FasL), and upregulation of CDK inhibitors [76] (Fig. 2). FOXO1 influences GIST proliferation, apoptosis, and cell cycle through phosphorylation-dependent mechanisms [69].

Imatinib treatment and apoptosis

Apoptosis is essential in determining the response to IM and in the development of drug resistance in GIST. Although IM strongly inhibits proliferation, it often fails to trigger adequate apoptosis, resulting in low pathological complete response rates and high progression rates in metastatic disease [77]. Liu et al. reported that IM induces quiescence in some GIST cells, marked by p27(Kip1) upregulation, Cyclin A loss, and G0-G1 arrest [70]. The DREAM complex also plays a role in maintaining quiescence [78].

IM alters apoptotic protein expression, revealing potential therapeutic targets. Romeo et al. found that p53 and p16 expression independently affect PFS, highlighting the importance of apoptosis/cell cycle balance [39]. Osteopontin, via β-catenin signaling, upregulates Mcl-1, antagonizing IM-induced apoptosis [79]. The FBXW7-Mcl-1 axis regulates IM sensitivity; FBXW7 suppresses Mcl-1 to enhance apoptosis and predict IM response [80]. Inhibiting BRD9 activates PUMA through the TUFT1/AKT/GSK-3β/p65 axis, enhancing IM-induced apoptosis [81].

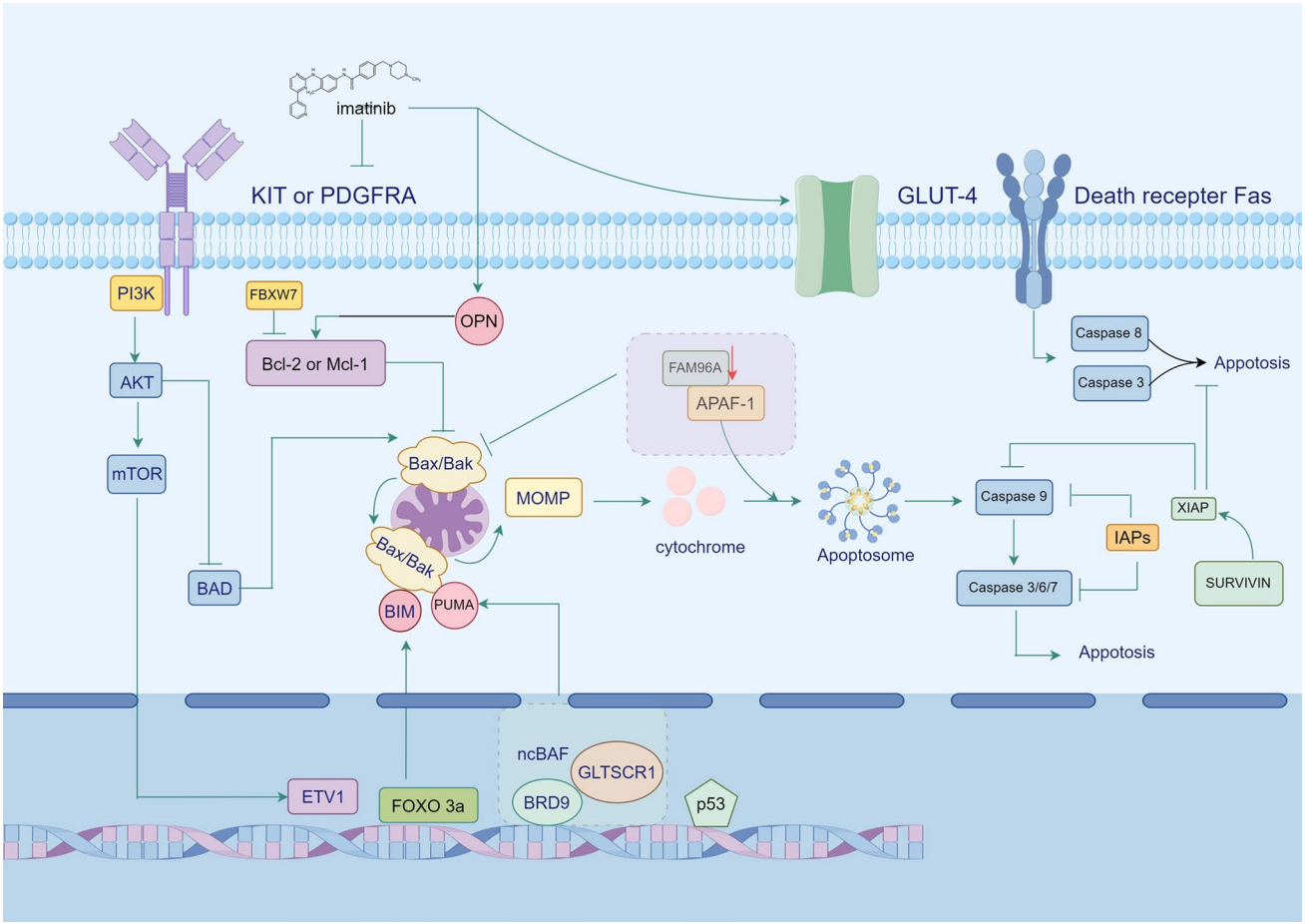

Fig. 2 Fas-Mitochondria-Dependent Apoptosis Pathway (Created by BioRender). This figure depicts how the extrinsic apoptosis pathway mediated by the death receptor Fas intersects with the mitochondrial pathway. Mitochondrial release of cytochrome C forms apoptosomes, activating caspase family enzymes (such as Caspase-9, Caspase-3/6/7), which leads to apoptosis. However, survival inhibits this process

Autophagy and GIST

Overview of autophagy

Autophagy is a tightly regulated lysosome-dependent degradation pathway that ensures cellular homeostasis by eliminating damaged organelles, misfolded proteins, and invading pathogens [82]. It is classified into macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). CMA selectively degrades soluble cytosolic proteins harboring a KFERQ-like motif, mediated by the LAMP-2A receptor and Hsp70 [83–85].

Macroautophagy, the most studied subtype, involves the formation of double-membraned autophagosomes, which engulf cytoplasmic cargo and fuse with lysosomes for degradation. This process is orchestrated by autophagy-related genes (ATGs), evolutionarily conserved from yeast to mammals [86]. Initiation occurs under nutrient deprivation or stress, leading to mTORC1 inactivation and activation of the ULK1/2 complex [87]. The ULK complex, comprising ULK1/2, ATG13, and ATG101, promotes phagophore formation. PI3P production by the VPS34 complex I, modulated by Bcl-2, recruits WIPI proteins and facilitates Atg12-Atg5-Atg16L1 complex formation, driving LC3 lipidation and autophagosome maturation [88, 89].

The dual role of autophagy in the tumor microenvironment

Autophagy exhibits a context-dependent dual role in tumor biology. On the one hand, it functions as a cytoprotective mechanism under metabolic and oxidative stress, enabling tumor cells to sustain viability under hypoxia, nutrient scarcity, or therapeutic insult [90]. In GIST, c-KIT mutations are associated with aberrant autophagy activation, enhancing resistance to apoptosis and contributing to therapeutic resistance [91]. Enhanced autophagic flux under stress conditions delays senescence, facilitates immune evasion, and sustains tumor proliferation [92].

Conversely, persistent or excessive autophagy may elicit autophagic cell death. In GIST, knockout of ATGs such as ATG7 sensitizes tumor cells to IM, highlighting autophagy as a mechanism of drug resistance and a potential therapeutic target [93]. Elevated expression of autophagy markers correlates with unfavorable prognosis in several cancers [94]. Inhibition of autophagy using lysosomal blockers like chloroquine impedes autophagosome-lysosome fusion, potentiating IM-induced cytotoxicity [95]. This dualistic nature of autophagy underscores its therapeutic complexity and offers the potential for context-specific modulation.

The role of autophagy in IM treatment

Research on the therapeutic effects of IM in GISTs has traditionally emphasized its capacity to induce apoptosis. However, apoptosis and autophagy, often initiated by overlapping upstream signaling pathways, engage in distinct and sometimes opposing cellular functions. Apoptosis is widely recognized as a tumor-suppressive mechanism, whereas the role of autophagy remains context-dependent, influenced by tumor stage, oncogenic mutations, and microenvironmental conditions [96]. Emerging evidence suggests that IM resistance may be mediated, at least in part, through autophagy, regulated by various molecular factors, including ncRNAs [97]. Accordingly, elucidating the interplay between TKI-induced autophagy and apoptosis in GISTs may uncover novel strategies to overcome drug resistance (Fig. 3).

A pivotal study by Miselli et al. (2008) examined surgical specimens from 11 GIST patients with confirmed molecular characteristics who received IM therapy, compared to 2 untreated patients. The IM-treated group exhibited elevated expression of the pre-autophagic marker Beclin1/PI3KIII and reduced anti-autophagic Beclin1/Bcl-2 complex levels. Notably, apoptosis-related proteins were undetectable in these samples. These findings suggest that in untreated tumors, IM may induce anti-tumor activity via KIT autophagy, whereas in pretreated tumors, a subset of GIST cells may transition into a quiescent state-retaining proliferative potential upon IM discontinuation or acquisition of resistance mutations [34].

Further supporting this notion, Gupta et al. demonstrated that GIST cell survival and dormancy during IM therapy are associated with a stabilized tumor burden. Despite limited apoptotic induction by IM, autophagic vesicle formation was observed as early as 8 h post-treatment, particularly in IM-sensitive cells. Importantly, a negative correlation between autophagy and apoptosis was established. These findings underscore autophagy's critical role in maintaining GIST cells in a quiescent, reversible, non-proliferative state. This dormancy allows tumor cells to withstand intrinsic vulnerabilities and therapeutic stress, ultimately contributing to recurrence and the development of drug resistance.

The role of autophagy regulatory factors

Autophagy is tightly regulated by several signaling pathways, among which mTOR and AMP-activated protein kinase (AMPK) are the most prominent. The mechanistic target of rapamycin (mTOR) serves as a negative regulator of autophagy by integrating upstream signals such as PI3K/Akt. It suppresses autophagy initiation by phosphorylating ULK1 complex components, including ULK1 and Atg13. In GIST, hyperactivation of mTOR correlates with increased tumor growth, invasiveness, and therapeutic resistance.

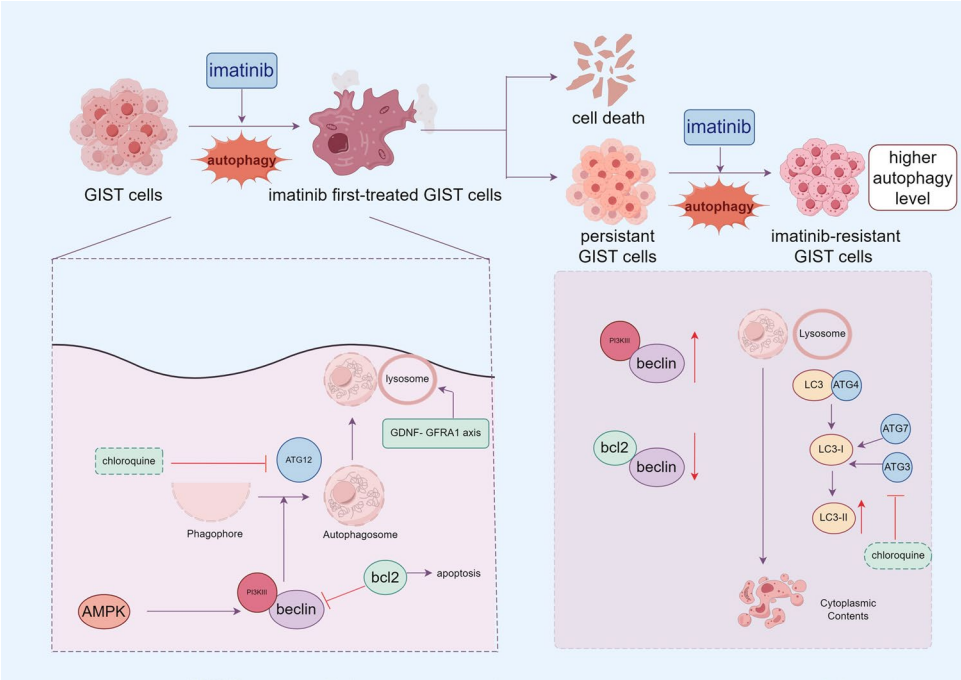

Fig. 3 Role of Autophagy in GIST Cell Drug Resistance (Created by BioRender). This figure explores the response of GIST cells to IM treatment. Autophagy levels significantly increase post-treatment, especially in drug-resistant GIST cells. Chloroquine, an autophagy inhibitor, may promote apoptosis by blocking autophagy, suggesting potential therapeutic effects

Notably, mTOR signaling enhances cellular metabolism and restrains autophagic cell death, contributing to treatment evasion [98]. As a result, mTOR inhibitors like rapamycin have been widely explored as modulators of autophagy and potential anticancer agents. Rapamycin has demonstrated efficacy in suppressing GIST cell proliferation and enhancing chemotherapy sensitivity [99].

Conversely, AMPK functions as a cellular energy sensor and positive regulator of autophagy. Under energy stress, AMPK inhibits mTOR signaling and directly activates autophagy to restore metabolic homeostasis. In GIST, AMPK activation has been shown to inhibit tumor cell proliferation and promote apoptosis while enhancing autophagy and alleviating mTOR-mediated suppression [100]. Beyond autophagy induction, AMPK modulates lipid metabolism and glycolysis, creating a more vulnerable metabolic state in tumor cells. Small-molecule AMPK activators have improved chemotherapeutic responses in preclinical GIST models, highlighting their potential as therapeutic agents [101].

In summary, mTOR and AMPK are opposing autophagy regulators and play critical roles in GIST pathogenesis and drug response. Therapeutically targeting this regulatory axis offers promising opportunities to overcome resistance in GIST and other malignancies.

Potential effects of lysosomal inhibitors in GIST

Silencing of autophagy-related genes ATG7 and ATG12 via RNA interference, or pharmacological inhibition of lysosomes using antimalarial agents, has synergized with IM to induce GIST cell death [46]. Song et al. reported that autophagy activity is significantly elevated in IM-resistant GIST cell lines compared to sensitive ones. Importantly, co-treatment with chloroquine, a lysosomal inhibitor, and IM suppressed autophagy via the MAPK/ERK pathway, enhancing cytotoxicity and overcoming drug resistance [102]. Chloroquine disrupts autophagosome-lysosome fusion, and its combination with IM reduces LC3-II expression, increases chemotherapy sensitivity, and exerts potent tumor-suppressive effects in GIST mouse models [102] (Fig. 3).

Beyond lysosomal inhibition, targeting heat shock proteins (HSPs) has emerged as another promising strategy. As molecular chaperones, HSPs stabilize oncogenic proteins such as mutant KIT. Inhibition of HSP90 using NVP-AUY922 (AUY922) facilitates KIT degradation via proteasomal and autophagic pathways. AUY922 effectively suppresses the growth of both IM-sensitive (GIST882) and IM-resistant (GIST48) cells. However, when autophagy is blocked, the KIT protein accumulates, highlighting the critical role of autophagy in KIT turnover induced by HSP90AA1 inhibition [103].

Subsequent studies demonstrated that rapamycin, an mTOR inhibitor, reduces total and phosphorylated KIT levels in IM-resistant GIST cells. Combined treatment with rapamycin and AUY922 produces a synergistic antiproliferative effect in vitro [104]. Mechanistically, the tyrosine kinase WEE1 promotes KIT degradation by repressing Beclin1 and enhancing the LC3BII/I ratio, thus facilitating autophagic flux [105].

A reciprocal relationship between autophagy and apoptosis has been widely observed in GIST. The X-linked inhibitor of apoptosis protein (XIAP), which suppresses apoptosis, becomes stabilized in IM-treated GIST-882 cells due to decreased ubiquitination. It is accompanied by increased autophagy, suggesting that the ubiquitin–proteasome system may modulate autophagic activity and contribute to secondary resistance [102].

Autophagy regulation also involves post-translational and epigenetic mechanisms. ATG5 is stabilized by the deubiquitinase USP13 in a PAK1-dependent manner, with USP13 is transcriptionally regulated by the methyltransferase METTL3 [47]. In addition, recent studies have uncovered a neurotrophic signaling axis in GIST. The GDNF-GFRA1 pathway interacts with the lysosomal calcium channel MCOLN1, activating Ca^{2+}-dependent TFEB signaling. TFEB subsequently upregulates lysosomal gene expression, amplifies autophagic flux, and inhibits apoptosis under TKI treatment. Dual inhibition of GFRA1 and autophagy demonstrates promising potential for overcoming drug resistance in GIST therapy [106].

Ferroptosis and GIST

Overview of ferroptosis and its pathways

Ferroptosis is a distinct form of PCD characterized by iron-dependent lipid peroxidation and reactive oxygen species (ROS) accumulation. Unlike apoptosis or necrosis, ferroptosis is driven by intracellular iron overload, which catalyzes Fenton reactions to generate hydroxyl radicals that damage polyunsaturated fatty acids (PUFAs) in membrane phospholipids, ultimately leading to cell death [107]. Beyond its role in tumor suppression, ferroptosis is implicated in various pathological conditions, including neurodegenerative, cardiovascular, and hepatic diseases.

A central ferroptosis regulator is glutathione peroxidase 4 (GPX4), which protects cells by reducing lipid peroxides. Inhibition or loss of GPX4 function induces ferroptosis. The small-molecule RSL3 is a well-characterized GPX4 inhibitor that irreversibly inactivates GPX4, promoting lipid peroxidation and cell death. RSL3 has shown potent anti-tumor activity across multiple cancer models and enhances chemotherapy efficacy, particularly in drug-resistant tumors [108]. Co-administration with other ferroptosis inducers, such as FIN56, amplifies tumor cell death [109]. Furthermore, GPX4 inhibitors elevate ROS levels, stimulate T and NK cell activation, and improve tumor immune surveillance [110]. In vivo studies confirm their tolerability and efficacy against solid tumors, including GIST [111].

Ferroptosis induction in GIST is primarily mediated by ROS generated through mitochondrial respiration and the NADPH oxidase (NOX) family. These ROS disrupt membrane integrity, triggering ferroptosis. Their clearance depends largely on the xc^--glutathione (GSH)-GPX4 axis, with additional antioxidant inputs from coenzyme Q10 and tetrahydrobiopterin [112] (Fig. 4). GPX4 utilizes GSH, supplied by cysteine imported through the xc^- cystine/glutamate antiporter system, to neutralize lipid ROS and maintain redox homeostasis.

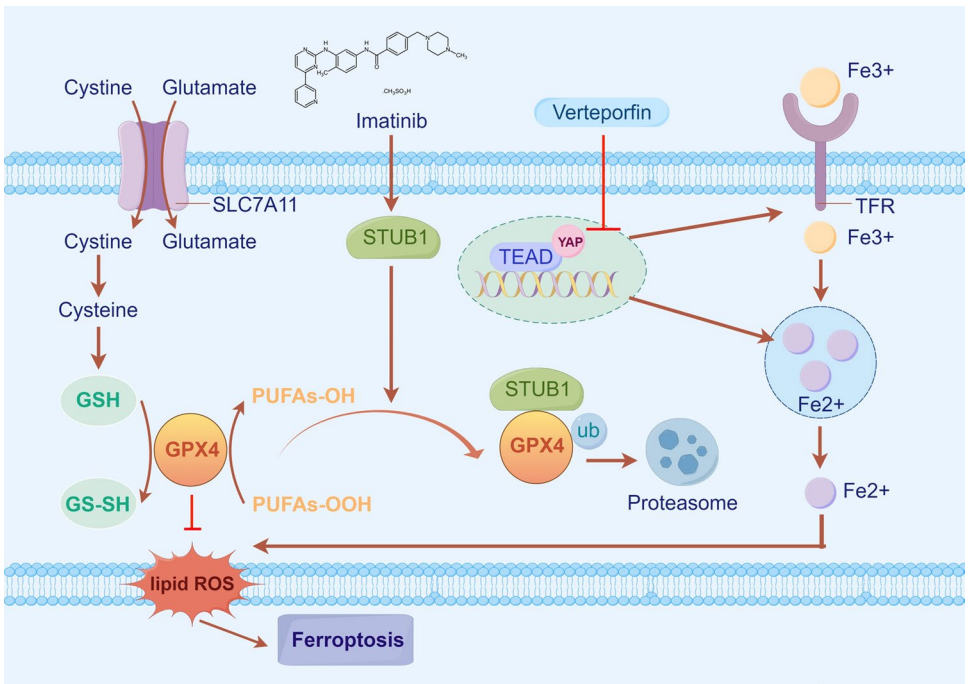

Fig. 4 Metabolic Regulation and Drug Targets in Ferroptosis Pathway (Created by BioRender). This figure outlines the key molecular mechanisms of the ferroptosis pathway, including the interactions between GSH, PUFAs, and iron ions. Drugs such as IM and vorinostat may also enhance anti-tumor effects by modulating ferroptosis-related pathways

The xc^- antiporter consists of SLC7A11 (xCT) and SLC3A2 subunits, which exchange extracellular cystine for intracellular glutamate [113]. These transporters are crucial in regulating redox balance, iron metabolism, and susceptibility to ferroptosis. Targeting GPX4 or SLC7A11 has emerged as a promising strategy to sensitize GIST cells to chemotherapy via ferroptosis induction. Nevertheless, issues such as treatment specificity and resistance remain challenges for future clinical applications.

In addition to GPX4 and SLC7A11, ferroptosis is modulated by proteins involved in iron homeostasis, such as hepcidin and ferritin, which control intracellular iron availability [114]. Increasing evidence highlights ferroptosis as a novel therapeutic avenue, especially in tumors unresponsive to conventional chemotherapy or targeted therapy. Agents like RSL3 activate ferroptosis pathways and effectively inhibit tumor cell proliferation [115]. However, the context-dependent nature of ferroptosis and its specific regulatory mechanisms in different tumor types warrant further investigation.

The role of ferroptosis in GIST

The redox state of intracellular iron significantly influences cellular sensitivity to ferroptosis. Additionally, the cytoskeleton, modulated by phosphorylation of heat shock protein family B member 1 (HSPB1), plays a role in iron uptake and lipid ROS generation [116]. Before the introduction of IM, inhibitors of *HSPs* attracted attention as potential therapeutics. For example, the HSP90 inhibitor IPI-504 was shown to induce KIT degradation, suppress cell proliferation, and reduce tumor burden, highlighting its clinical potential. Since HSP family members may also modulate ferroptosis, further investigation is warranted into their role in GIST ferroptosis.

Ferroptosis has recently emerged as a therapeutic strategy and prognostic marker in GIST. Studies report that some tumor cells evade therapeutic stress by entering a dormant, drug-tolerant state known as "persistence." In these persistent cells, glucose metabolism is downregulated, leading to decreased glutathione (GSH) levels and increased sensitivity to GPX4 inhibitors such as RSL3. RSL3 has demonstrated efficacy against persistent tumor cells in vitro and in vivo. Moreover, inhibitors of YAP, such as verteporfin (VP) and CA3, can further enhance ferroptosis-induced cytotoxicity.

The combination of RSL3 with IM has shown synergistic therapeutic effects in GIST [36]. Sun et al. found that IM treatment increases intracellular Fe^{2+} levels and lipid ROS while depleting GSH. The ferroptosis inhibitor Ferrostatin-1 can partially block these effects. Additionally, STUB1 knockdown or GPX4 overexpression reverses IM-induced ferroptosis. STUB1 was identified as a novel E3 ubiquitin ligase that promotes GPX4 ubiquitination and degradation. Combined treatment with RSL3 and IM significantly enhances ferroptosis and suppresses GIST proliferation both in vitro and in vivo [37]. The ferroptotic process and its key molecular events in GIST cells are illustrated in Fig. 5. Iron accumulation leads to lipid peroxidation and oxidative stress, culminating in ferroptotic cell death. Disruption of iron metabolism is closely linked to this process in GIST.

In addition to its therapeutic potential, ferroptosis is associated with GIST prognosis. Zhuang et al. reported that transferrin receptor (TFRC) expression is significantly upregulated in high-risk GIST patients, as defined by NIH risk criteria. High TFRC expression correlates with increased recurrence risk. Delvaux et al. further validated TFRC as a prognostic biomarker. Tissue microarray (TMA) analysis demonstrated that elevated TFRC levels were associated with increased mitotic activity, greater tumor aggressiveness, and enhanced YAP expression/activation in human GIST specimens [48].

Interaction between ferroptosis, apoptosis, and autophagy

Ferroptosis and apoptosis are two distinct forms of PCD, each governed by different mechanisms but closely interconnected. Ferroptosis is defined by iron accumulation and lipid peroxidation, while apoptosis involves DNA fragmentation, mitochondrial dysfunction, and caspase activation. Recent studies suggest that although these pathways can operate independently, ferroptosis may influence the initiation and progression of apoptosis. For instance, GPX4, a key ferroptosis inhibitor, prevents lipid peroxidation and maintains cell viability. Conversely, iron accumulation can trigger mitochondrial dysfunction through Fenton reactions, leading to a loss of mitochondrial membrane potential and activation of apoptotic cascades [117]. Inactivation of GPX4 promotes lipid peroxidation and activates apoptotic markers like caspase-3, further amplifying cell death [118].

Excessive ROS accumulation, a hallmark of ferroptosis, can activate signaling pathways such as p53, JNK, and MAPK, contributing to apoptosis induction [119]. These interactions highlight a regulatory overlap between ferroptosis and apoptosis, offering new therapeutic insights. Figure 6 illustrates the dynamic crosstalk between ferroptosis, apoptosis, and autophagy.

Ferroptosis also exhibits complex interactions with autophagy, a lysosome-dependent degradation process that removes damaged proteins, organelles, and iron, maintaining cellular homeostasis. Depending on the context, autophagy may either suppress or promote ferroptosis. In some cases, autophagy clears excess iron, reducing Fenton reactions and preventing lipid peroxidation [120]. In contrast, excessive

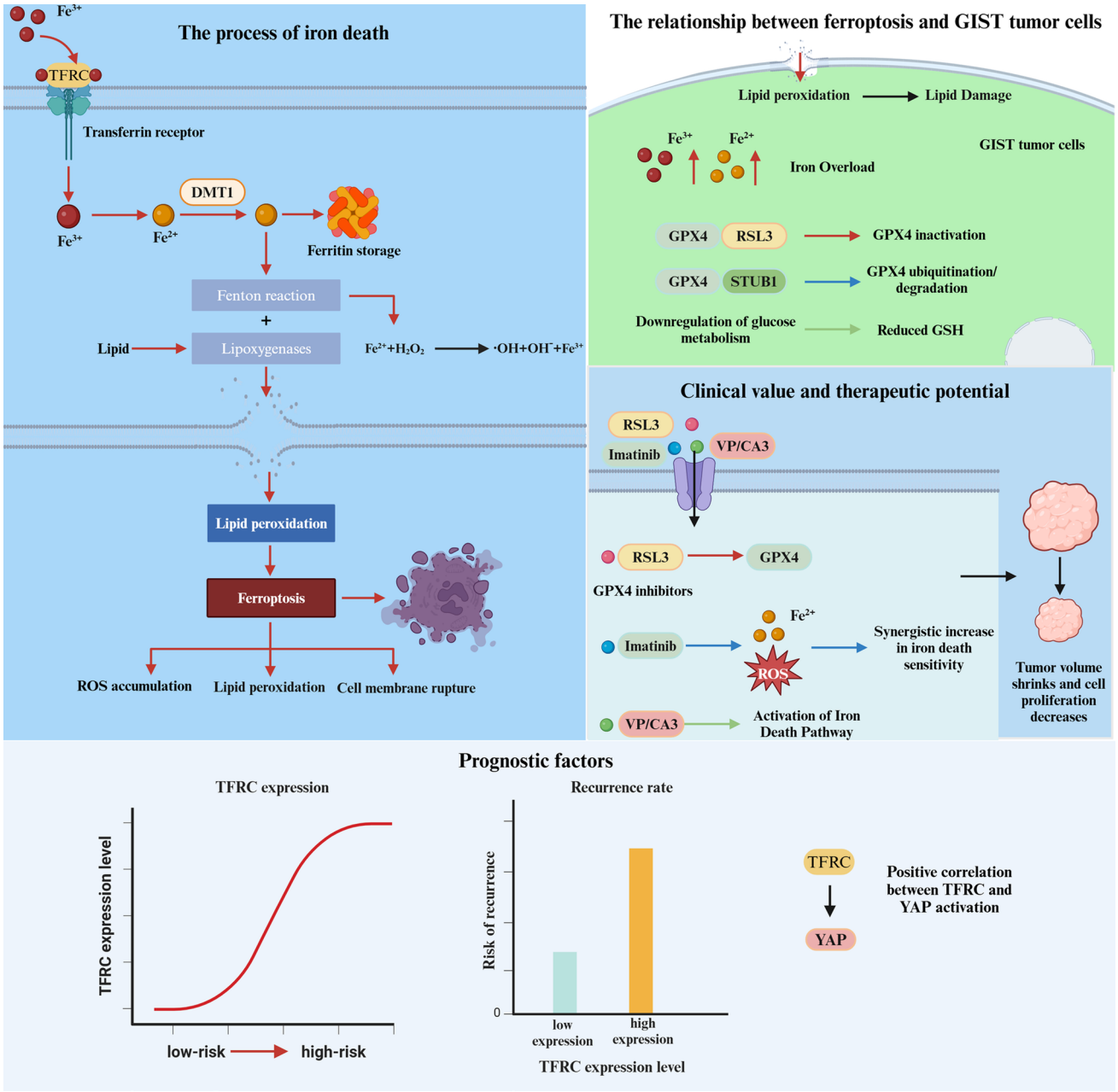

Fig. 5 Mechanisms and clinical potential of ferroptosis in GIST treatment (Created by BioRender)

autophagy may degrade antioxidant proteins like GPX4, sensitizing cells to ferroptosis [121].

Ferroptosis can also modulate autophagy-related pathways by influencing key regulators such as mTOR and Beclin1, thereby affecting cell survival [122]. ROS generated during ferroptosis can also activate autophagy through ATG proteins, forming a feedback loop that intensifies oxidative damage [123]. This bidirectional regulation allows cells to fine-tune their response to stress and determine survival or death.

The crosstalk among ferroptosis, apoptosis, and autophagy reflects a dynamic, multilayered system of cell fate regulation. These interactions are context-dependent and vary across physiological and pathological conditions. In some cancers, ferroptosis regulates cell viability by interacting with apoptosis and autophagy. For example, ferroptosis-induced mitochondrial dysfunction can reduce ATP levels and activate autophagy, while autophagy, in turn, can alleviate ferroptosis by removing damaged mitochondria and iron [124].

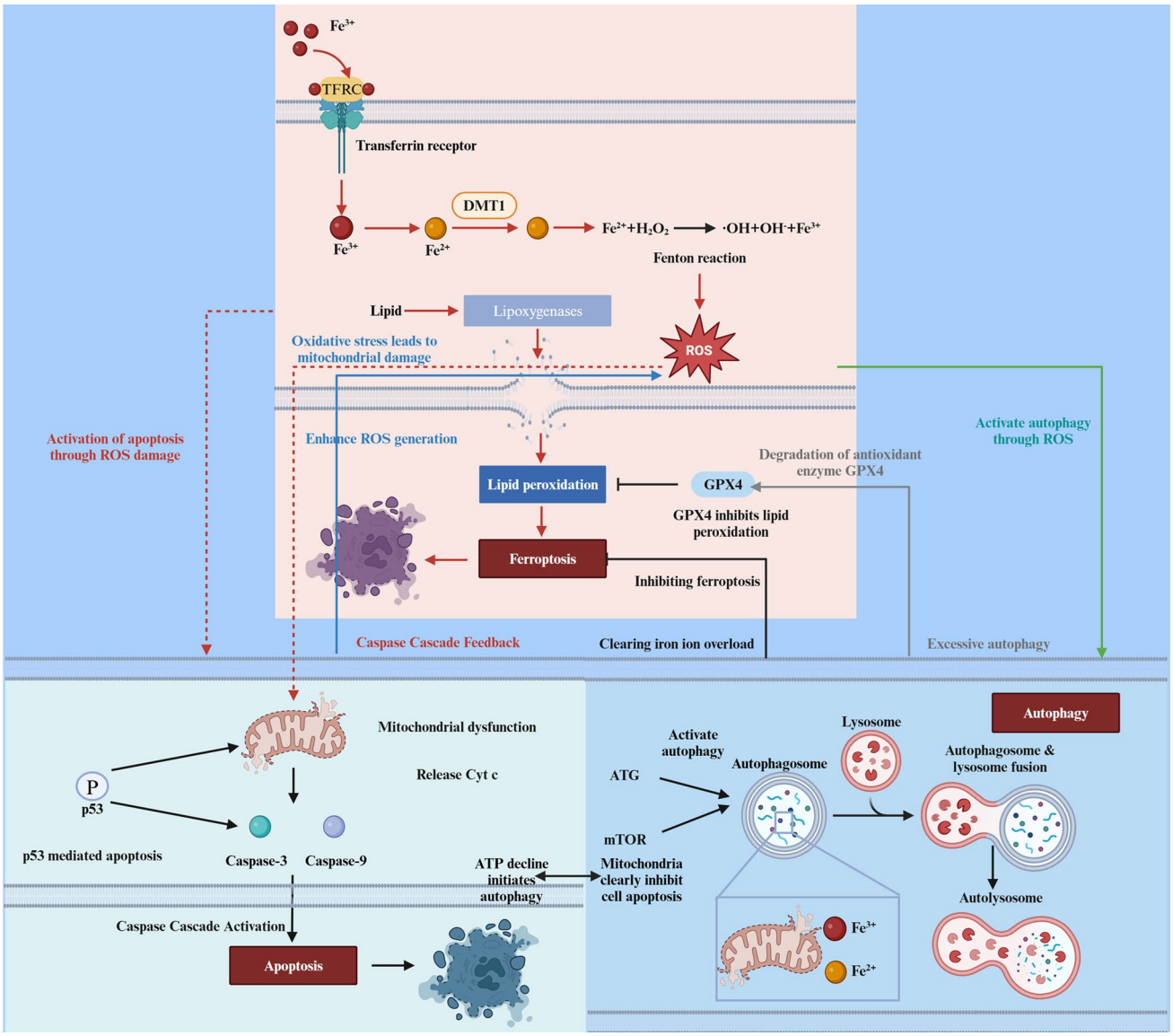

Fig. 6 Interaction mechanisms between ferroptosis, apoptosis, and autophagy (Created by BioRender)

Furthermore, ferroptosis is linked to cell cycle regulation. It can influence key regulators such as p53 and cyclin D through apoptotic interactions, thereby affecting proliferation and cell death [125]. In certain tumor models, ferroptosis modulates chemotherapy resistance through its relationship with autophagy, offering new therapeutic opportunities [126]. The interaction between apoptosis and ferroptosis underscores the critical role of mitochondria in drug resistance and cell death. Collectively, the interplay between ferroptosis, apoptosis, and autophagy provides a comprehensive framework for understanding tumor cell fate and offers novel targets for precision oncology.

ncRNA-regulated cell death mechanisms

Cell death is a complex biological phenomenon crucial in physiological and pathological processes involving apoptosis, necrosis, and autophagy. These processes are vital for maintaining homeostasis and contribute significantly to the onset and progression of various diseases. In recent years, ncRNAs have emerged as key regulatory factors in cell death. ncRNAs are RNA molecules that do not encode proteins but influence gene expression and cellular functions through multiple

mechanisms. The main types of ncRNAs—miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)—regulate cell death via distinct pathways. MiRNAs bind to target mRNAs to inhibit translation or promote mRNA degradation, affecting gene expression in cell death. LncRNAs regulate gene transcription, post-transcriptional modifications, and translation by interacting with DNA, RNA, or proteins, thus influencing cell survival or death. CircRNAs act as molecular "sponges" that sequester miRNAs or other molecules, modulating their functions and impacting the progression of cell death.

Figures 7 and 8 illustrate the regulatory roles of these ncRNAs in cell death pathways, encompassing the actions of different types of ncRNAs. Furthermore, ncRNAs are involved in several aspects of GIST biology. Table 3 lists key ncRNA types, including miRNAs, lncRNAs, and circRNAs, along with their targets and functions. By regulating processes such as cell proliferation, migration, and apoptosis, these ncRNAs play critical roles in the initiation and progression of GIST.

ncRNAs and apoptosis

ncRNAs, including microRNAs (miRNAs), lncRNAs, and circRNAs, are crucial regulators of gene expression and have been increasingly recognized for their roles in apoptosis. In various tumors, including GIST, ncRNAs modulate apoptosis by targeting key genes and signaling pathways, thereby influencing tumor progression and therapeutic response.

miRNAs regulate apoptosis by binding to target genes and modulating the expression of apoptosis-related proteins. In GIST, several miRNAs have been linked to drug

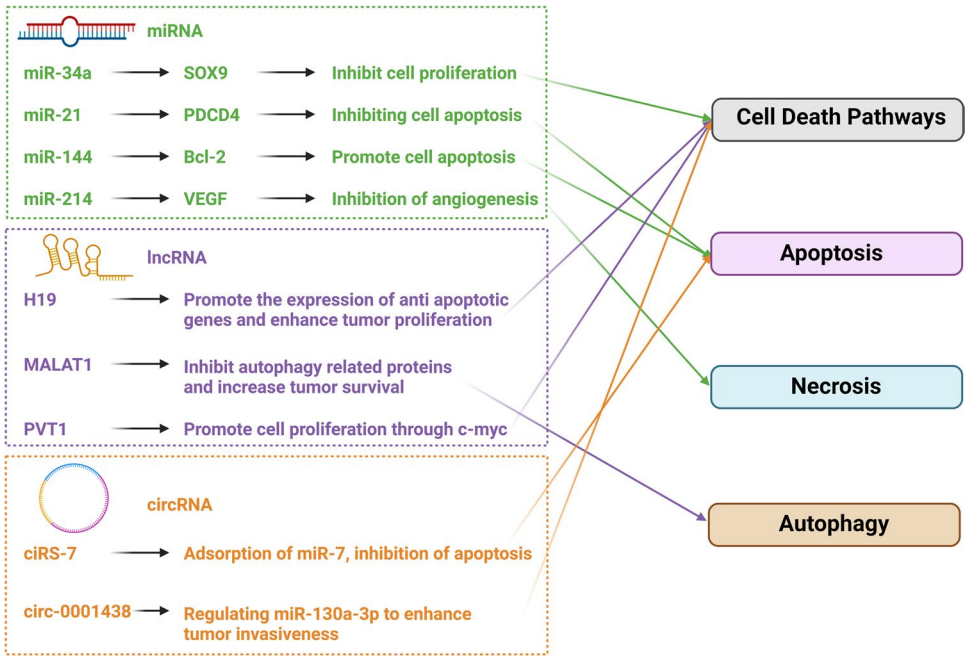

Fig. 7 Network diagram of different ncRNAs regulating cell death pathways

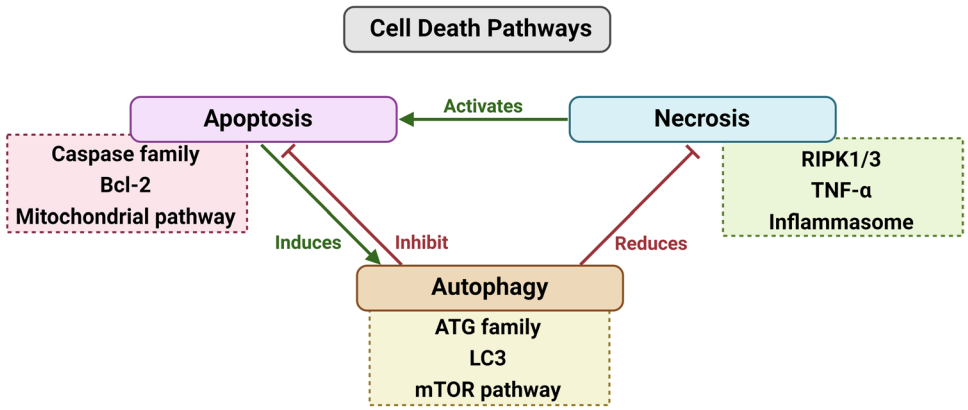

Fig. 8 Interaction mechanisms between cell death pathways

Table 3 Roles of Non-coding RNAs in GIST and their targets and functions

ncRNA Type	Target	Function	Role in GIST
miRNA	SOX9	Regulates cell proliferation, differentiation, migration, and apoptosis	SOX9 is an important oncogene in GIST, and miR-34a inhibits its expression, reducing tumor cell proliferation
	Bcl-2	Inhibits Bcl-2 family proteins, promoting apoptosis	miR-144 regulates Bcl-2 expression, enhancing apoptosis in GIST cells
	VEGF	Involved in angiogenesis and tumor neovascularization	miR-214 targets VEGF to suppress angiogenesis in GIST cells
lncRNA	H19	Regulates the activity of transcription factors, involved in the regulation of cell proliferation and apoptosis	H19 acts as an oncogene in GIST, promoting cell proliferation and anti-apoptotic effects
	MALAT1	Affects cell migration, proliferation, and metastasis, involved in cell cycle regulation	High expression of MALAT1 in GIST is associated with tumor cell invasiveness and metastatic potential
	PVT1	Interacts with c-Myc to promote tumor cell proliferation and anti-apoptosis	Overexpression of PVT1 in GIST enhances tumor growth and resistance to therapy
circRNA	ciRS-7	Competes with miRNAs to inhibit their function, regulating tumor-associated gene expression	ciRS-7 regulates miR-7 in GIST, influencing cell proliferation and apoptosis
	circ-0001438	Modulates miR-130a-3p to affect tumor invasiveness	circ-0001438 promotes GIST progression by enhancing the function of miR-130a-3p
piRNA	PIWIL1	Participates in the regulation of gene transcription, affecting cell proliferation and apoptosis	Overexpression of PIWIL1 is closely associated with GIST cell proliferation and migration

sensitivity and cell death regulation. For instance, miR-21 promotes anti-apoptotic activity by downregulating tumor suppressors such as PDCD4 and PTEN [127]. In contrast, miR-34a acts as a tumor suppressor by enhancing p53 signaling and downregulating Bcl-2 family proteins, activating the mitochondrial apoptotic pathway and inhibiting tumor growth [128]. Similarly, miR-155 enhances apoptosis by suppressing Bcl-2 expression and shows therapeutic potential [129]. In ovarian granulosa cells, miR-484 targets the LINC00958/SESN2 axis to modulate mitochondrial function and promote apoptosis under oxidative stress, offering the potential for translational application [130].

lncRNAs exhibit complex regulatory functions and play important roles in modulating apoptosis in GIST. HOTAIR, a widely studied oncogenic lncRNA, inhibits apoptosis by repressing p21 and p53 via EZH2 binding, contributing to GIST proliferation and drug resistance [131]. MALAT1 suppresses autophagy and enhances GIST cell survival [132], while GAS5 activates the p53 pathway to promote apoptosis and inhibit proliferation and migration [133]. LINC00958 competes with miR-484 to regulate SESN2 expression, influencing mitochondrial function and apoptotic signaling [134]. Furthermore, lncRNA HIF1A-AS2 promotes IM resistance under hypoxic conditions by inhibiting apoptosis and enhancing autophagy. Silencing HIF1A-AS2 restores IM sensitivity and increases apoptosis in GIST cells [135]. These findings suggest that lncRNAs are promising therapeutic targets for modulating apoptosis and overcoming drug resistance in GIST.

circRNAs are structurally stable ncRNAs that play emerging roles in apoptosis regulation. Unlike linear RNAs, circRNAs resist degradation and often function as miRNA sponges to modulate downstream gene expression. In non-small cell lung cancer (NSCLC), circRNA-CPA4 binds competitively to miR-1183, thereby upregulating PDPK1 and promoting proliferation while inhibiting apoptosis [136]. In GIST, circRNA CIRS-7 sequesters miR-7, relieving inhibition on Bcl-2 family members and suppressing apoptosis [137]. In gastric cancer, circRNA ciRS-7 modulates miR-7 and miR-671 to enhance apoptosis and improve chemotherapy sensitivity [138]. These findings highlight circRNAs as novel regulators of apoptosis and potential targets in cancer therapy.

ncRNA and autophagy

Recent studies have highlighted the critical role of ncRNAs in regulating autophagy. ncRNAs modulate autophagy by directly targeting autophagy-related genes and interacting with key signaling pathways that control tumor cell survival and death. In GIST, abnormal expression of ncRNAs has been closely linked to tumorigenesis, progression, and drug resistance. Among them, miRNAs and lncRNAs are the most extensively studied, offering new therapeutic targets for GIST.

miRNAs regulate autophagy primarily by targeting autophagy-related genes such as ATGs, LC3, and Beclin1. Autophagy is commonly initiated by signaling pathways, including mTOR and PI3K/Akt, which are frequent miRNA targets [139]. For instance, the miR-30 family suppresses autophagy by directly targeting mTOR and ATG7 [140],

while miR-101 enhances autophagy through mTOR inhibition, thereby reducing tumor cell proliferation [141].

In GIST, miRNAs may influence autophagy to regulate drug resistance and tumor growth. miR-126 modulates the PI3K/Akt pathway and thereby alters autophagy activity [142], whereas miR-183 suppresses Beclin1, inhibiting autophagy and promoting GIST cell proliferation [143]. Additionally, circRNA circ-CCS is significantly elevated in the serum of IM-resistant GIST patients. Its silencing inhibits proliferation and autophagy while promoting apoptosis. Mechanistic studies revealed that circ-CCS targets miR-197-3p to downregulate ATG10 expression, suggesting a role in autophagy-mediated drug resistance [144].

lncRNAs regulate autophagy by interacting with transcription factors, miRNAs, and autophagy-related proteins. In GIST, altered expression of specific lncRNAs has been linked to autophagy activity and tumor behavior changes. HOTAIR enhances autophagy by modulating the PI3K/Akt/mTOR axis, contributing to tumor proliferation and reduced drug sensitivity [145]. MALAT1, another well-studied lncRNA, binds to autophagy suppressors to inhibit autophagy and promote cell survival and invasion [146]. lncRNA ATB has also been shown to activate autophagy-related proteins, thereby promoting tumor growth and resistance [147].

Autophagy is a protective mechanism under therapeutic stress by removing damaged components and maintaining cellular viability. However, excessive autophagy may lead to treatment resistance. ncRNAs regulate autophagy in this context and influence drug sensitivity. For example, miR-138 suppresses autophagy by targeting ATG5, enhancing chemosensitivity [148]. In contrast, lncRNA NEAT1 promotes resistance by increasing autophagy in GIST cells under targeted therapy [149]. CircRNAs also play a role; circRNA CDR1as functions as a miRNA sponge to regulate ATG7 expression, modulating autophagy activity and drug response in GIST [150].

These findings underscore the significance of ncRNAs in autophagy regulation and drug resistance. Targeting specific ncRNAs that control autophagy pathways may represent a promising strategy for enhancing GIST therapy.

ncRNA and ferroptosis

Growing evidence suggests that ncRNAs, particularly miRNAs and lncRNAs, play crucial roles in regulating ferroptosis. In tumor cells, ncRNAs influence ferroptosis by modulating genes involved in iron metabolism, antioxidant defense, and membrane lipid composition. For example, miRNAs have been shown to regulate ferroptosis by targeting key genes such as GPX4, FTH1, and SLC7A11, thereby affecting tumor cell survival [151]. In gastrointestinal cancers, including gastric and colorectal cancer, miRNAs regulate ferroptosis by modulating iron homeostasis, lipid peroxidation, and oxidative stress responses [152].

miRNAs regulate ferroptosis by binding to target genes' 3' untranslated regions (3'UTRs), influencing iron balance and redox homeostasis. For instance, miR-27a downregulates GPX4, a critical antioxidant enzyme suppressing lipid peroxidation. Reduced GPX4 expression enhances ferroptosis and alters tumor cell proliferation and viability [153]. Similarly, miR-9 targets SLC7A11, a key component of system Xc^-, thereby decreasing intracellular glutathione (GSH) levels and increasing oxidative stress and iron accumulation [154]. These findings highlight the importance of miRNAs in regulating ferroptosis through direct control of iron metabolism and antioxidant capacity.

lncRNAs have also emerged as important regulators of ferroptosis. Unlike miRNAs, lncRNAs typically modulate gene expression by interacting with transcription factors or epigenetic regulators. lncRNA H19, for example, is upregulated in several cancers and influences ferroptosis by targeting miR-675 and regulating iron metabolism genes [155]. Another lncRNA, p53RRA, enhances p53 transcriptional activity, suppresses GPX4 expression, and promotes ferroptosis [156]. These mechanisms suggest that lncRNAs regulate ferroptosis by controlling oxidative stress and iron-related gene expression.

circRNAs, a newly identified ncRNA subtype, regulate ferroptosis primarily through miRNA sponging. In gastric cancer, circ_0000284 binds to miR-29a, reducing its activity. Since miR-29a inhibits FTH1, a ferroptosis suppressor, this sponging effect enhances ferroptosis [157]. Conversely, circRNA CDR1as regulates miR-7 and upregulates FTH1 expression, suppressing ferroptosis and promoting tumor growth and drug resistance [158]. These studies illustrate the dual roles of circRNAs in modulating ferroptosis, either enhancing or inhibiting the process through miRNA regulation.

Targeting ncRNAs presents a promising therapeutic strategy for modulating ferroptosis in cancer. RNA interference and CRISPR/Cas9 technologies have enabled precise manipulation of specific miRNAs and lncRNAs, allowing selective ferroptosis induction in tumor cells. For example, miRNA mimics or inhibitors can regulate ferroptosis-related genes involved in iron metabolism. CRISPR-based approaches offer high specificity and the potential to fine-tune ferroptosis activation without damaging normal cells [159]. These strategies not only improve treatment efficacy but may also enhance anti-tumor immunity. Overall, ncRNA-based modulation of ferroptosis opens up new avenues for precision cancer therapy.

Conclusion and future directions

PCD plays a vital role in preventing uncontrolled proliferation and malignant transformation, while its dysregulation is commonly associated with tumor progression and therapeutic resistance. IM has been shown to induce autophagy, apoptosis, and ferroptosis as a first-line treatment for GIST. The crosstalk among these PCD pathways significantly influences drug sensitivity and is closely linked to metastasis and recurrence. This study systematically explored the regulatory roles of ncRNAs in PCD pathways in GIST, highlighting their key mechanisms in apoptosis, autophagy, and ferroptosis and their potential association with malignancy and drug resistance, thereby providing a theoretical foundation for precision therapy. However, challenges remain in understanding the interactions among different ncRNAs, their roles within the tumor immune microenvironment, and developing efficient and targeted delivery strategies. Future research integrating single-cell sequencing, multi-omics analysis, and functional validation is expected to further elucidate the ncRNA-PCD-GIST regulatory axis. In the next few years, key directions include network-level dissection of ncRNA-PCD regulation, clinical translation of ncRNA biomarkers, development of therapeutic strategies such as ASOs and CRISPR tools, and integration of ncRNA targeting with immunotherapy to optimize treatment paradigms.

Despite the comprehensive analysis of ncRNA-mediated PCD regulation in GIST, several limitations should be acknowledged. The study is largely based on literature synthesis and existing experimental data, lacking in vivo and in vitro validation of specific ncRNAs, making it difficult to define their direct functional roles in PCD. Given the molecular heterogeneity of GIST, ncRNA expression and function may vary across different mutation subtypes, which were not fully addressed here. Moreover, although we discussed ncRNAs as potential therapeutic targets, current ncRNA-based interventions in GIST remain in the early stages. Efficient delivery, stability, and off-target minimization remain major barriers to clinical application. Notably, the role of ncRNAs in shaping the immune microenvironment of GIST is not well understood, although PCD pathways are increasingly recognized to intersect with tumor immune regulation.

Future work should combine single-cell sequencing, integrative multi-omics, and functional studies to systematically unravel the molecular landscape of the ncRNA-PCD-GIST axis and identify critical regulators involved in tumor progression, immune modulation, and drug resistance. Exploration of additional cell death pathways in GIST may expand the therapeutic target pool and contribute to developing a more comprehensive risk stratification model. Such a model could incorporate conventional biological features and PCD-related molecular profiles to support more precise clinical decision-making. Identifying novel PCD-associated prognostic or predictive biomarkers and elucidating their mechanistic roles may accelerate the advancement of personalized therapy in GIST.

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Author contributions Yuxuan Ma, Yuhao Wang, and Shu Wang contributed equally to this work and share first authorship. Yuxuan Ma and Yuhao Wang performed literature review and drafted the manuscript. Shu Wang contributed to data analysis and manuscript revision. Haoyuan Wang and Yan Zhao assisted in data collection and figure preparation. Chaosheng Peng and Xin Liu provided critical insights and helped revise the manuscript. Jianjun Yang conceptualized and supervised the study, acquired funding, and finalized the manuscript. All authors read and approved the final version of the manuscript.

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Data availability All data can be provided as needed.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

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