Ferroptosis, pyroptosis and necroptosis in hepatocellular carcinoma immunotherapy: Mechanisms and immunologic landscape (Review)

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Abstract. Hepatocellular carcinoma (HCC), one of the leading causes of cancer-related mortality worldwide, is challenging to identify in its early stages and prone to metastasis, and the prognosis of patients with this disease is poor. Treatment options for HCC are limited, with even radical treatments being associated with a risk of recurrence or transformation in the short term. Furthermore, the multi-tyrosine kinase inhibitors approved for first-line therapy have marked drawbacks, including drug resistance and side effects. The rise and breakthrough of immune checkpoint inhibitors (ICIs) have provided a novel direction for HCC immunotherapy but these have the drawback of low response rates. Since avoiding apoptosis is a universal feature of cancer, the induction of non-apoptotic regulatory cell death (NARCD) is a novel strategy for HCC immunotherapy. At present, NARCD pathways, including ferroptosis, pyroptosis and necroptosis, are novel potential forms of immunogenic cell death, which have synergistic effects with antitumor immunity, transforming immune 'cold' tumors into immune 'hot' tumors and exerting antitumor effects. Therefore, these pathways may be targeted as a novel treatment strategy for HCC. In the present review, the roles of ferroptosis, pyroptosis and necroptosis in antitumor immunity in HCC are discussed, and the relevant targets and signaling pathways, and the current status of combined therapy with ICIs are summarized. The prospects of targeting ferroptosis, pyroptosis and necroptosis in HCC immunotherapy are also considered.

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Abbreviations: HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TME, tumor microenvironment; ICD, immunogenic cell death; TIME, tumor immune microenvironment; Cys, cysteine; ROS, reactive oxygen species; GSH, glutathione; PL, phospholipid; GPX4, glutathione peroxidase 4; Sec, selenocysteine; SLC7A11, solute carrier family 7 member 11; PFD, pore-forming domain; RD, repressor domain; CCP, cancer cell pyroptosis; CTL, cytotoxic T lymphocyte; PRR, pattern recognition receptor; TLR, toll-like receptor; LPS, lipopolysaccharide; TRADD, tumor necrosis factor receptor 1-associated death domain protein; RIPK, receptor-interacting protein kinase; FADD, Fas-associated death domain; MLKL, mixed lineage kinase domain-like pseudokinase; RHIM, RIP homotypic-interacting motif; SOR, sorafenib; HSC, hepatic stellate cell; miR, microRNA; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; PYS, pyroptosis-score

Key words: ferroptosis, pyroptosis, necroptosis, HCC, immunotherapy

Contents

1. Introduction

Liver cancer is the sixth most frequently diagnosed cancer worldwide and the third most common cause of cancer-related death, with ~906,000 new cases and 830,000 deaths worldwide in 2020 (1). In addition, the incidence and mortality rates of liver cancer are generally higher in men than in women (1). Hepatocellular carcinoma (HCC) accounts for the largest proportion of cases among all liver cancer types, is heterogeneous and imposes a large global socio-economic burden (2). HCC can occur either due to the dedifferentiation of hepatocytes or due to the development of intrahepatic stem cells (3-5), is characterized by difficulties in early detection, is prone to metastasis and is associated with poor prognosis (6). The aggressiveness of HCC is closely related to its degree of differentiation, microvascular infiltration, intrahepatic metastases and satellite lesions, and poorly differentiated HCC is associated with earlier recurrence and poorer prognosis compared with well-differentiated HCC (7).

HCC therapy options include surgical excision, liver transplantation, radiofrequency ablation and microwave ablation for early-stage HCC (8-10). However, 40% of patients already have advanced HCC when they are first diagnosed (11), resulting in limited treatment options, and even radical treatment can still result in recurrence or transformation within a short period, commonly within 1-3 years (12). Although treatments with multi-tyrosine kinase inhibitors (TKIs) have been demonstrated to prolong the overall survival (OS) of patients with HCC (13,14), drug resistance and side effects limit the effect of TKIs (15,16).

The rise in immune checkpoint inhibitors (ICIs) and breakthroughs in immunology studies have sparked an expanding interest in cancer immunotherapy, especially in antibodies against programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) (17). Anti-PD-1 drugs, such as nivolumab and pembrolizumab, are efficient and well-tolerated in patients with advanced HCC and are currently recognized as second-line treatment options for patients with HCC (18,19). A clinical study, IMBrave150, revealed that atezolizumab (anti-PD-L1) in combination with bevacizumab (anti-vascular endothelial growth factor) was more beneficial than sorafenib (SOR) in patients with advanced HCC, and prolonged the median OS time of patients with unresectable HCC (uHCC) (20,21). Compared with SOR, the combination immunotherapy of durvalumab (anti-PD-L1) and tremelimumab (anti-cytotoxic T-lymphocyte associated protein 4) administered in the HIMALAYA study, which likely exerted antitumor effects by activating T cells, exhibited an improved therapeutic effect for uHCC (17,22). In addition, immunotherapy drugs have the advantage that they do not need to be metabolized by the liver, which marks a significant advancement in the management of advanced HCC (23,24). Nevertheless, ICI therapy for HCC still has shortcomings such as a low response rate, high tumor tolerance to ICI therapy and multiple side effects (25-28), leading to the use of ICI therapy in combination with various other therapies.

It has been confirmed that, during the development and progression of HCC, the balance between regulatory cell death (RCD) and cell survival serves a crucial function, and resistance to apoptosis and evasion of cell death is one of the hallmarks of HCC (29). Overcoming or delaying TKI resistance increases tumor cell death (30,31), and inducing inflammatory forms of cell death may enhance the tumor response to ICI treatment (32). Therefore, cell death has emerged as a popular research topic in the treatment of HCC. Notably, considering that resistance to apoptotic RCD is a general characteristic of cancer, non-apoptotic RCD (NARCD) serves a more crucial role during the development of HCC and its response to therapy (29). TKIs and ICIs are both tightly associated with the regulation of NARCD pathways (33,34).

At present, ferroptosis, pyroptosis and necroptosis are three highly studied types of NARCD in HCC development and treatment, and these influence the fate of cells in the liver (35-40). There are some differences and similarities among these three types of NARCD, and the key features of ferroptosis, pyroptosis and necroptosis, including the morphological and biochemical features, key regulators, and related drugs are shown in Table I. Furthermore, the roles of these NARCD pathways in the tumor microenvironment (TME) and tumor immune microenvironment (TIME) are gradually being recognized. Treatments targeting these NARCD pathways in combination with TKI treatments (41-43) or ICI therapies (44-46) exhibit synergistically enhanced anticancer activity compared with single treatment. Treatments targeting these NARCD pathways could exert anticancer effects even in cancer types resistant to TKIs and ICIs (34,47,48). Only a few patients exhibit a response to TKI or ICI treatment alone, while triggering ferroptosis, necroptosis or pyroptosis can alter this response status and improve the response rate of therapy (32,49). Furthermore, ferroptosis, pyroptosis and necroptosis, as three potential novel mechanisms of immunogenic cell death (ICD) (50,51), have been suggested to transform immune 'cold' tumors into immune 'hot' tumors, increasing the sensitivity to ICI therapy, activating $CD8^+$ T cell adaptive immunity and maintaining durable immune memory so that the body gains long-term antitumor immunity (52). Thus, ferroptosis, pyroptosis and necroptosis are considered three novel potential therapeutic targets to improve the treatment outcomes of HCC (49).

The present review first investigates the role of ferroptosis, pyroptosis and necroptosis in the TME and TIME of HCC and summarizes the related novel targets and signaling pathways. Subsequently, the current status of targeting ferroptosis, pyroptosis and necroptosis in combination with multiple HCC treatment modalities is described. In particular, the potential applications of targeting ferroptosis, pyroptosis and necroptosis in combination with ICIs to enhance immune efficacy are discussed.

2. Mechanism of ferroptosis

Originally conceptualized in 2012, ferroptosis is considered a lipid peroxidation-driven, iron-dependent and non-apoptotic form of cell death (53). Morphologically, the cellular microstructure after ferroptosis is characterized by organelle expansion, rupture of the plasma membrane and moderate chromatin condensation, and the mitochondrial ultrastructure showing abnormalities including contraction, fracture, enlargement of cristae, increased membrane density and rupture of the outer membrane (53-56). Mechanically,

Table I. Morphological and biochemical features, key regulators and related drugs of ferroptosis, pyroptosis and necroptosis (46,49,54,83,107).

RCD type	Morphological features	Biochemical features	Positive regulators	Negative regulators	Related drugs
Ferroptosis	Cell membrane rupture and exfoliation, smaller mitochondria, decreased mitochondrial cristae, increased mitochondrial membrane densities, mitochondrial membrane disruption and normal-size nuclei without chromatin condensation	Intracellular iron accumulation, SLC7A11/GSH/GPX4 pathway inhibition, cysteine deprivation and lipid peroxidation	TFR1, TFRC, DMT1 and ACSL4	GPX4, SLC7A11, NRF2 and p53	Sulfasalazine, glutamate, SOR, cisplatin, statins, trigonelline, artesunate, doxorubicin and iron
Pyroptosis	Cell swelling, membrane rupture, chromatin condensation and cytoplasmic content release	Induction of inflammatory cytokines, activation of caspases, GSDM cleavage, formation of inflammasome, IL-18 and IL-1β release, and regulation of caspase-dependent pathways	Caspase-1, caspase-4, caspase-5, caspase-11 and GSDM	ESCRT-III and GPX4	Cisplatin, metformin, anthocyanin, DHA, paclitaxel and doxorubicin
Necroptosis	Cell swelling, plasma membrane rupture, chromatin condensation, organelle expansion and cytoplasmic content release	RIPK1/RIPK3-mediated phosphorylation and ubiquitination of RIPK1/RIPK3/MLKL, assembly of necrosome, and release of inflammatory cytokines	RIPK1, RIPK3 and MLKL	AURKA and ESCRT-III	Iron, 5-FU,resibufogenin, shikonin, artesunate and SOR

5-FU, 5-fluorouracil; ACSL4, acyl-CoA synthetase long chain family member 4; AURKA, aurora kinase A; DHA, docosahexaenoic acid; DMT1, divalent metal transporter 1; ESCRT-III, endosomal sorting complex required for transport III; GPX4, glutathione peroxidase 4; GSDM, gasdermin; GSH, glutathione; MLKL, mixed lineage kinase domain-like pseudokinase; NRF2, nuclear factor erythroid 2-related factor 2; RCD, regulatory cell death; RIPK, receptor-interacting protein kinase; SLC7A11, solute carrier family 7 member 11; SOR, sorafenib; TFR1, transferrin receptor 1; TFRC, transferrin receptor.

ferroptosis is driven by iron-dependent phospholipid (PL) peroxidation, and regulated by multiple cellular metabolic pathways, including redox homeostasis, iron handling, mitochondrial activity, and metabolism of amino acids, lipids and sugars (Fig. 1) (53,57).

Iron and lipid peroxides are important regulators of ferroptosis (53,57). Unstable iron metabolism drives lipid peroxidation to increase susceptibility to ferroptosis, which is in turn closely linked to the inability to store iron during ferritin depletion (58,59). A study suggests that iron storage also requires poly (RC) binding protein 1 to deliver the GSH-iron complex to ferritin, thus repressing ferritinophagy-mediated ferroptosis (60). Furthermore, iron uptake, utilization, storage, and secretion are primarily the responsibility of the liver, which is consequently a central player in iron homeostasis (60,61). Therefore, abnormal iron metabolism is strongly linked to ferroptosis in liver diseases.

Unsaturated fatty acids in cell membranes, such as polyunsaturated fatty acids (PUFAs), are mainly affected by lipid peroxidation driven by free radicals (62). The key characteristic of PUFAs driving ferroptosis is their ability to bind to PLs in membranes upon PUFA activation (62). Arachidonate lipoxygenase and cytochrome P450 oxidoreductase act as regulators of lipid peroxidation, mediating PUFA peroxidation to promote ferroptosis (54,63).

GSH peroxidase 4 (GPX4) acts as a key inhibitor of ferroptosis and is regulated via several mechanisms. For example, ferroptosis inducing 56 can induce degradation of GPX4 to induce ferroptosis (Fig. 1) (64) or covalently binds to the selenocysteine (Sec) site of GPX4 to induce GPX4 inactivation (65). GSH depletion also inactivates GPX4, and thus, drives ferroptosis, while both GSH-related enzymes and the multidrug resistance protein 1, promote GSH depletion (66,67). As research has progressed, a number

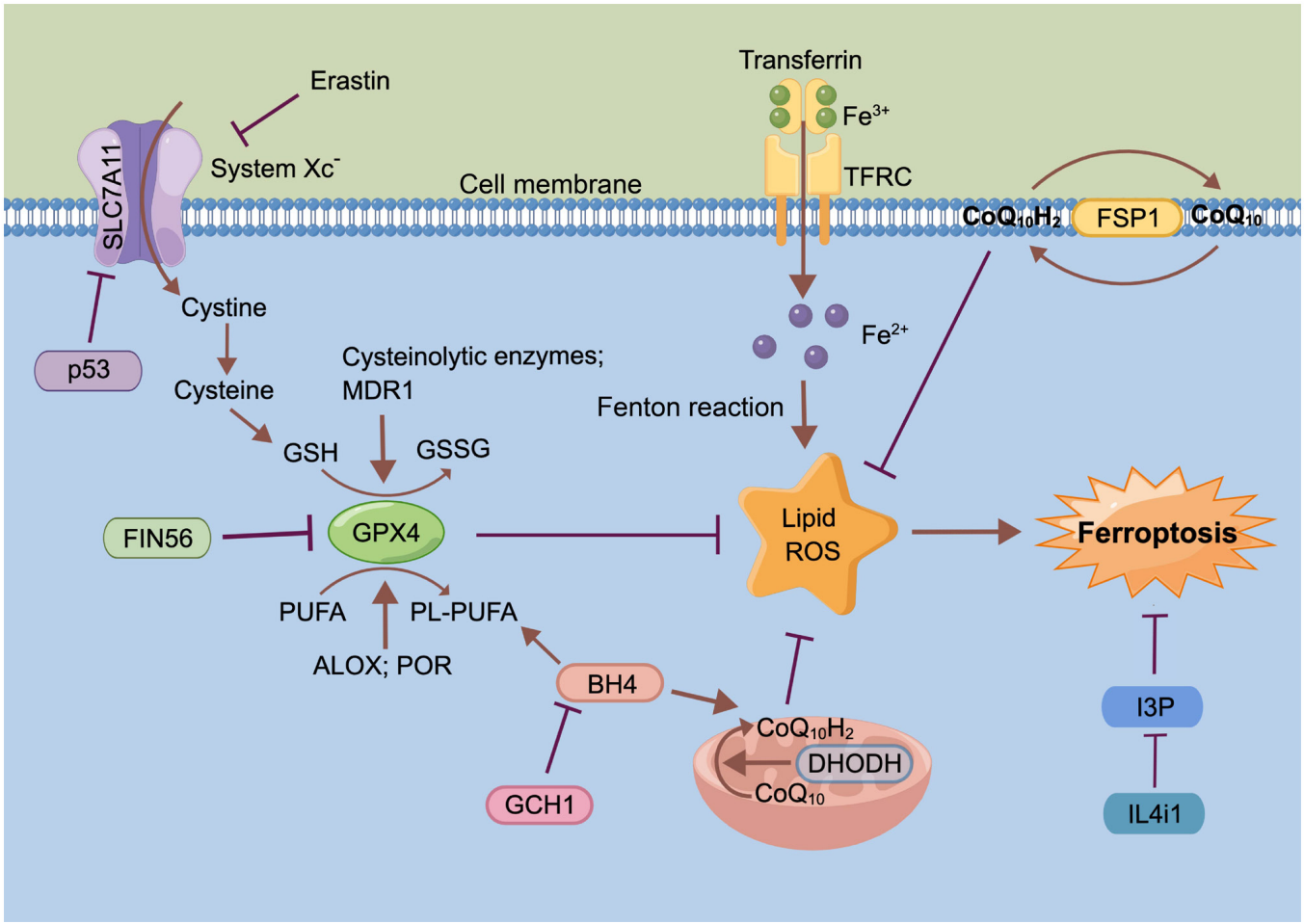

Figure 1. Overview of the molecular mechanisms of ferroptosis. The figure was drawn using Figdraw (www.figdraw.com). ALOX, arachidonate lipoxygenase; BH4, tetrahydrobiopterin; CoQ_{10}, coenzyme Q10; $CoQ_{10}H_2$, ubiquinol; DHODH, dihydroorotate dehydrogenase; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclic hydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, glutathione disulfide; I3P, indole-3-pyruvate; IL4i1, IL-4-induced-1; MDR1, multidrug resistance 1; PL, phospholipid; POR, cytochrome P450 oxidoreductase; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TFRC, transferrin receptor.

of novel ferroptosis-inducing mechanisms independent of GPX4 have been identified, such as ferroptosis suppressor protein 1 and dihydroorotate dehydrogenase inhibiting ferroptosis by producing ubiquinol ($CoQ_{10}H_2$) in the cell cytomembrane and inner mitochondrial membranes, respectively (68,69).

Mitochondria serve a diversified role in the process of ferroptosis, iron metabolism and the oxidative phosphorylation pathway, and reactive oxygen species (ROS) are highly involved in ferroptosis (70). It has been demonstrated that the typical metabolic activities of the mitochondria, including tricarboxylic acid cycle and electron transport chain activities, are required for cellular lipid peroxide production in ferroptosis induced by cysteine (Cys) deprivation, but not in that induced by inhibiting GPX4 (57,71).

System Xc^-, encoded by the solute carrier family 7 member 11 (SLC7A11) gene, is also a key inhibitor of ferroptosis, and the small molecule erastin and its analogs specifically inhibit cystine uptake through system Xc^-, leading to the consumption of GSH and inducing ferroptosis (71). In addition, p53 can also trigger ferroptosis by repressing expression of SLC7A11 and inhibiting cystine uptake through system Xc^- (72).

GTP cyclic hydrolase 1 improves ferroptosis sensitivity by inhibiting generation of the antioxidant tetrahydrobiopterin and increasing the abundance of $CoQ_{10}H_2$ and PL-PUFA (73,74). IL-4-induced-1 stimulates ferroptosis by inhibiting production of the metabolite indole-3-pyruvate and limiting the activation of cytoprotective gene expression programs (75).

3. Mechanism of pyroptosis

Pyroptosis is a type of programmed cell death mediated by gasdermin (GSDM) (Fig. 2) (76,77). The GSDM family includes GSDMA, GSDMB, GSDMC and GSDMD, as well as two extended family members, GSDME (also referred to as DFNA5) and deafness, autosomal recessive 59 (DFNB59; also referred to as PJVK) (78). Among them, GSDMD, an immediate target of inflammatory caspases and an executor of immune cell pyroptosis, consists of an N-terminal pore-forming domain (PFD) and a C-terminal repressor domain (RD) (76,79,80). N-terminal PFD oligomerization and cell membrane pore formation are regulated by the C-terminal RD (76).

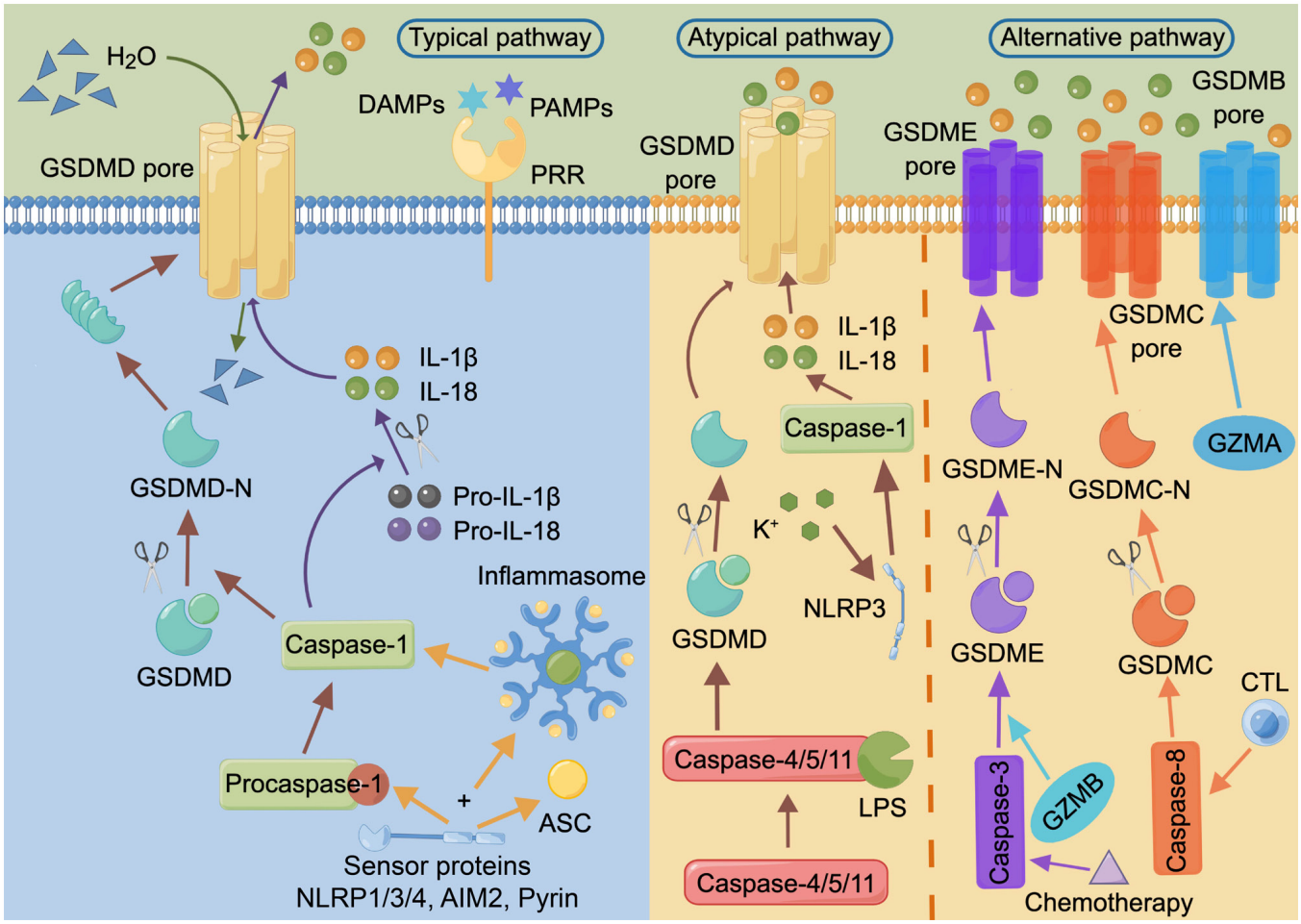

Figure 2. Summary of three molecular mechanisms of pyroptosis, including the typical, atypical and alternative pathway. The figure was drawn using Figdraw (www.figdraw.com). AIM2, absent in melanoma 2; ASC, apoptosis associated dot like protein; CTL, cytotoxic T lymphocyte; DAMP, damage-associated molecular pattern; GSDM, gasdermin; GZM, granzyme; LPS, lipopolysaccharide; -N, N terminal; NLRP, NOD-like receptor family pyrin domain containing; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor.

The typical pathway of pyroptosis is that, upon host stimulation, GSDMD is cleaved by caspase-1, followed by oligomerization and the formation of functional pores in the cell membrane, leading to the release of inflammatory molecules such as IL-1β and IL-18, disruption of osmotic pressure, water influx, and thus, cell swelling, formation of membrane vesicles with bubble-like protrusions (also known as scorch bodies) and plasma membrane cleavage, and ultimately pyroptosis (80-83).

The atypical pathway of pyroptosis is a process not reliant on inflammasome sensors, and involves the lytic apoptosis of GSDMD cleaved by caspase-4/5/11 interacting with stimulators such as lipopolysaccharide (LPS). The subsequently released K^+ activates NOD-like receptor family pyrin domain containing 3 (NLRP3), which in turn activates caspase-1, and thus, indirectly induces IL-1β and IL-18 production (84-86).

In addition, there are alternative pathways of pyroptosis, such as via activated caspase-3/8, that can mediate the cleavage of GSDME or GSDMC, releasing the N-terminal PFD and eventually inducing pyroptosis (87-91). Alternatively, granzyme B from lymphocytes induces pyroptosis by activating caspase-3 and subsequent GSDME cleavage or by directly cleaving GSDME (92,93). Most GSDMs (except DFNB59) have an N-terminal PFD and a C-terminal RD (81), and thus, also have the potential to undergo cellular scorching, with GSDMB, GSDMC and GSDME being the executors of cancer cell pyroptosis (CCP) (78). For example, GSDME can be cleaved by small molecule kinase inhibitors or following the chemotherapy-induced activation of caspase-3, resulting in pyroptosis and the improvement of lung cancer and melanoma treatments (87,94). GSDMC can be cleaved by caspase-8 to trigger CCP, including in lung and liver cancer (88). GSDMB can be cleaved directly by granzyme A released from natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) independently of caspases, contributing to the necrosis of murine cancer cells (95).

In the induction of pyroptosis, inflammasomes are oligomeric complexes composed of sensor proteins, bridging proteins and effector caspases (96,97), and similarly serve as molecular platforms for the activation of inflammatory caspases (97). Pattern recognition receptors (PRRs) can act as sensor proteins, recognizing the relevant molecular patterns that initiate inflammasome activation (98). Among them, NLRP1/3/4, absent in melanoma 2 and pyrin can recruit the adapter apoptosis-associated speck-like protein containing a caspase recruitment domain and/or pro-caspase-1 to assemble

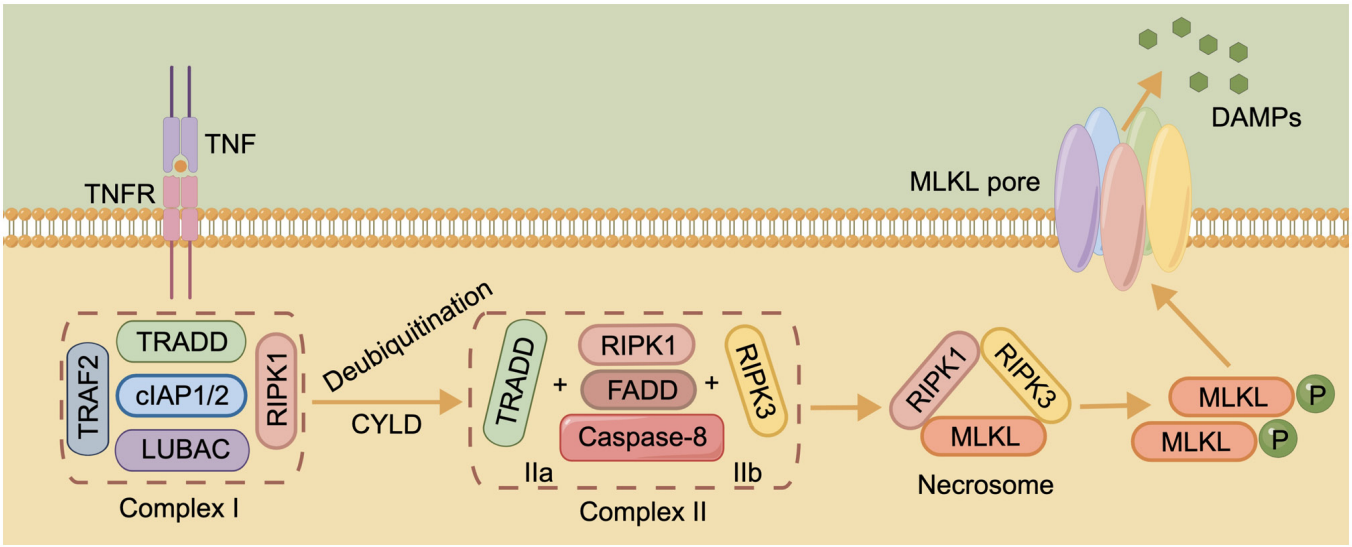

Figure 3. Core molecular mechanisms of necroptosis. The figure was drawn using Figdraw (www.figdraw.com). cIAP1/2, cellular inhibitor of apoptosis protein 1/2; CYLD, cylindromatosis; DAMP, damage-associated molecular pattern; FADD, Fas-associated death domain; LUBAC, linear ubiquitin chain assembly complex; MLKL, mixed lineage kinase domain-like pseudokinase; P, phosphate group; RIPK, receptor-interacting protein kinase; TNFR, tumor necrosis factor receptor; TRADD, TNFR1-associated death domain protein; TRAF2, TNF receptor-associated factor 2.

into inflammasomes and thereby activate caspase-1, which in turn induces IL-1β and IL-18 processing (99,100).

4. Mechanism of necroptosis

The initiation of necroptosis relies on specific death receptors (DRs), including FAS, tumor necrosis factor receptor 1 (TNFR1) and TNF-related apoptosis-inducing ligand (TRAIL) receptors TRAIL-R1 and TRAIL-R2, or PRRs, such as toll-like receptor (TLR)3, to recognize unfavorable signals from the intra- and extracellular microenvironment (101). TNF is a major stimulus in necroptosis, delivering cell death signals via binding to DRs (102). This process is associated with complex I, consisting of TNFR1-associated death domain protein (TRADD), linear ubiquitin chain assembly complex, TNF receptor-associated factor 2 (TRAF2), cellular inhibitor of apoptosis protein (cIAP)1/2 and receptor-interacting protein kinase (RIPK)1 (103). When cylindromatosis deubiquitinates RIPK1, A20, ubiquitin-specific peptidase (USP)21 or USP20, complex I becomes unstable, and TRADD and RIPK1 are isolated and assembled with Fas-associated death domain (FADD) protein and caspase-8 to form complex IIa, or RIPK3 replaces TRADD to form complex IIb with the other components (104,105). Inactivation of caspase-8 and cIAP induces the conversion of complex IIb into a necrosome, triggering DR-induced necroptosis (106,107).

The necrosome is formed by binding of RIPK3 and RIPK1 via the RIP homotypic-interacting motif (RHIM) domain at first, followed by recruitment of mixed lineage kinase domain-like pseudokinase (MLKL) after the formation of the complex (108). Phosphorylated MLKL, the main executor of necroptosis, later oligomerizes and migrates to the plasma membrane, damaging it and releasing potential damage-associated molecular patterns to trigger necroptosis (Fig. 3) (109,110). Another TLR containing RHIM, TIR domain-containing adapter-inducing interferon-β enables direct RHIM-dependent signaling, initiating necrosis via receptor interacting protein 3 and MLKL (111). A recent study found that extracellular osmotic pressure was also a stimulus for the induction of necroptosis and that the activation of RIPK3 by the Na^+/H^+ exchanger solute carrier family 9 member A1 increased the cytosolic pH, and this is a pathway that does not depend on the RHIM structural domain to activate the downstream effector MLKL (112).

5. Ferroptosis in HCC

As research regarding ferroptosis progresses, more ferroptosis-related drugs and targets are being identified for HCC treatment. As a type of TKI, SOR also induces ferroptosis to augment anti-HCC benefits (113,114). Furthermore, SOR attenuates the binding of beclin-1 to MCL1 by modulating the Src homology region 2 domain-containing phosphatase-1/STAT3 axis, whilst enhancing the binding to SLC7A11 and thereby inhibiting system Xc^- activity (115). In addition, glutaminase 2 exerts anti-HCC effects by depleting glutamine, and thus, promoting ferroptosis (116). Using CRISPR screening, phosphatidylserine-transfer RNA kinase depletion has been identified to interfere with Sec and Cys synthesis, leading to GSH depletion and GPX4 inactivation, thus inducing ferroptosis and enhancing the sensitivity to targeted chemotherapy in HCC treatment (117). The long non-coding RNA HEPFA promotes erastin-induced ferroptosis by mediating the destabilization of SLC7A11 through ubiquitination, causing its depletion and the consequent accumulation of ROS and iron (118). In addition, suppressor of cytokine signaling 2 can enhance the degradation of K48-linked polyubiquitinated SLC7A11, and thus, promote ferroptosis to enhance the sensitivity of HCC radiotherapy (119). Ferroptosis inducer erastin and photosensitizer are ultrasonically treated with CD47-transfected donor cells to form engineered exosomes

to cause ferroptosis in HCC and avoid phagocytosis by the mononuclear phagocyte system for improved anticancer effects (120). In a previous study, since arsenic trioxide (ATO) could induce ferroptosis, the therapeutic effect of ATO was enhanced by the construction of arsenic-loaded mimetic iron oxide nanoparticles, specifically magnetic nanoparticles containing ATO that were camouflaged with HCC cell membranes (121). In another study, a novel cascade of copper-based nanocatalysts, which can result in ferroptosis alone, also enhanced the HCC treatment effects of cyclooxygenase-2 inhibitor meloxicam and SOR (122). It has also been reported that the pH sensitivity of liposomal vesicles is enhanced following incubation with amphiphilic dendrimers, thereby improving the delivery of the anticancer drug SOR and the ferroptosis inducer hemin in the acidic TME, synergistically treating the induction of ferroptosis and apoptosis (123).

In addition to the previous understanding that SOR induces the death of hepatoma cells, investigations have also revealed that SOR could trigger ferroptosis in hepatic stellate cells (HSCs), as demonstrated in an analysis of liver tissue HSCs from patients with advanced fibrotic HCC treated with SOR monotherapy (124,125). Liver fibrosis is a frequent pathological process that numerous chronic liver diseases undergo before progressing to cirrhosis and HCC, and the conversion of quiescent, vitamin A-storing cells into proliferating, fibrotic myofibroblasts by activated HSCs is a critical step in the development of hepatic fibrosis; therefore, targeted removal of HSCs is of great therapeutic significance (126). ELAV-like RNA binding protein 1, zinc finger protein 36 and N6-methyladenosine can act as regulators of SOR-induced ferroptosis in HSCs (124,125,127). In addition, artesunate reduces hepatic fibrosis by triggering ferroptosis in activated HSCs (128). Furthermore, SOR and artesunate induce ferroptosis through different pathways, and their combined use greatly improves the therapeutic effect in HCC (128). With the rising development of ICIs, SOR has often been used to assess the effectiveness of ICIs in treating HCC, such as in the phase III IMbrave150 and HIMALAYA trials, which demonstrated that the efficacy of ICI combination therapy was comparable to or better than that of SOR in patients with advanced HCC (21). Furthermore, clinical trials of ICIs in combination with SOR (such as NCT03439891 and NCT02988440) are underway and may provide novel perspectives on the administration of ICIs in combination with TKIs.

Given the notable anticancer effect of SOR, there has been an increasing number of studies on the association between ferroptosis and SOR resistance in HCC. For instance, it has been found that Yes1 associated transcriptional regulator (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) and activating transcription factor 4 (ATF4) drive resistance to SOR in HCC by increasing SLC7A11 expression and preventing ferroptosis, and knockdown of YAP/TAZ expression helped to overcome the SOR resistance in HCC (30). Additionally, in SOR-resistant HCC cells, ETS proto-oncogene 1 increases the transcription of microRNA (miR)-23a-3p, which could directly target the 3'-untranslated region of acyl-CoA synthetase long chain family member 4 (ACSL4), the key positive regulator of ferroptosis (47). The co-delivery of ACSL4 small interfering RNA and miR-23a-3p inhibitor abolishes the SOR response (47). Furthermore, metallothionein-1G has been found to facilitate SOR resistance through inhibition of ferroptosis (129). The genetic and pharmacological inhibition of MT-1G enhances the anticancer activity of SOR by inducing ferroptosis of HCC cells (129). A novel photoactive SOR-ruthenium (II) complex, is irradiated to reduce SOR resistance in HCC by inducing ferroptosis and disrupting purine metabolism (31). It has also been found that treatment of HCC with SOR induces macropinocytosis, which replaces ferroptosis-depleted Cys, and thus, promotes resistance to SOR, while amiloride can target micropinocytosis (130).

The proliferation of cancer cells depends on lactic acid, which is produced following glucose consumption via aerobic glycolysis to provide energy and is closely associated with ferroptosis (131). For instance, the glycolytic enzyme α-enolase 1 protects cancer cells from ferroptosis by reducing mitochondrial iron accumulation through inhibition of the iron regulatory protein 1/mitoferrin-1 pathway (132). Monocarboxylate transporter 1 (MCT1)-mediated lactic acid uptake promotes ATP production and AMP-activated protein kinase inactivation in HCC, which in turn upregulates downstream stearoyl-coenzyme A desaturase-1 to enhance the production of anti-ferroptosis monounsaturated fatty acids (133). Hypoxia-inducible factor-1α also drives resistance to ferroptosis in solid tumors by promoting lactate production (134).

Nuclear factor erythroid 2-related factor 2 (NRF2) has long been known to influence tumor progression as a pivotal regulator of the antioxidant response (135,136). Nuclear accumulation of NRF2 has been found to activate ferroptosis-associated proteins, while Kelch-like ECH-associated protein 1 (Keap1), an adaptor of the Cul3-ubiquitin E3 ligase complex, is responsible for the degradation of NRF2; in turn, phosphorylated p62 binds Keap1 with high affinity, thus targeting the p62/Keap1/NRF2 pathway increases the anticancer activity of elastin and SOR, a process that is facilitated by disulfiram/Cu (137-139). The GSH S-transferase Z1/NRF2/GPX4 axis and the leukemia inhibitory factor receptor/NF-κB/lipocalin-2 axis can also be targeted to promote ferroptosis, thereby enhancing the sensitivity to SOR in HCC treatment (140,141).

6. Pyroptosis in HCC

Miltirone, a phenanthrene derivative from the roots of *Salvia miltiorrhiza* Bunge, and ATO nanoparticles (142) have both been demonstrated to induce GSDME-associated HCC pyroptosis by activating caspase-3, while cannabidiol from the plant *Cannabis sativa* inhibits aerobic glycolysis via the ATF4/insulin-like growth factor binding protein 1/Akt signaling pathway (143). GSDMD is a common executor of pyroptosis, and mallotucin D activates caspase-9 and caspase-3 in HepG2 cells, inducing GSDMD cleavage and ultimately causing pyroptosis (144). NLRP3, a member of the PRR family, induces inflammasome activation and thus pyroptosis, while metformin indirectly activates NLRP3 and thus pyroptosis in HCC by upregulating FOXO3 (145).

The small nucleolar RNA hostgene 7/miR-34a/sirtuin 1 signaling pathway also induces NLRP3-dependent pyroptosis in HCC (146). In addition, 17β-estradiol, alpine ginseng flavonoid and hepatitis C virus infection in Huh-7.5 cells can induce caspase-1-dependent pyroptosis via activation of the NLRP3 inflammasome (147-149). Cisplatin-induced activation of the NLRP3 inflammasome can be inhibited by incomplete radiofrequency ablation-induced upregulation of heat shock protein (HSP) 70, which leads to cisplatin resistance in HCC (150).

7. Necroptosis in HCC

Necroptosis serves an important role in HCC development. According to a previous study, the hepatic microenvironment epigenetically shapes lineage commitment of liver tumorigenesis, and abnormal activation of hepatocyte oncogenes can lead to cholangiocarcinoma if adjacent hepatocytes undergo necroptosis, but hepatocytes regulated by the same oncogenic factors can develop into HCC cells if they are surrounded by apoptotic hepatocytes (151). Deletion of RIPK1, a central element of necroptosis, in hepatocytes induces downregulation of TRAF2, leading to impaired caspase-8 activation and NF-κB activation; therefore, the RIPK1/TRAF2/caspase-8 pathway has a notable influence on the development of HCC (152). As confirmed by a previous study, the NF-κB signaling pathway is an important player in necroptosis (153). Apigetrin and deferasirox exert anti-HCC effects by inhibiting the NF-κB signaling pathway to induce necroptosis (43,154). HSP90α has been found to bind with the necrosome complex and promotes chaperone-mediated autophagy degradation, which leads to necroptosis blocking and results in SOR resistance (48). The HSP90 inhibitor 17-allylamino demethoxygeldanamycin could inhibit HSP90α activity and reverse SOR resistance in HCC by activating necroptosis (48). FADD, RIPK1, RIPK3 and MLKL are key signaling molecules in necroptosis, and miR-675 could target FADD to induce necroptosis and inhibit HCC progression via the RIPK3/MLKL axis (155), and rapamycin could induce HCC cell necroptosis via the RIPK1/RIPK3/MLKL signaling pathway (156). A recent study has found that, as the liver progressively ages, necroptosis increases, which in turn continuously exacerbates chronic liver inflammation, thus exacerbating the HCC transition (157). This necroptosis-mediated liver inflammation process may be prevented by β-carotene and heterogeneous nuclear ribonucleoprotein A1 (158,159). In addition, excess sorbitol dehydrogenase (SORD) in HCC cells could inhibit tumor growth and stemness by enhancing necroptosis signaling, and treatment with human recombinant SORD controlled HCC cell growth and regulated macrophage polarization in the tumor microenvironment (160). Nuclear protein 1 (NUPR1) and Linc00176 are also associated with HCC cell necroptosis, and inhibition of NUPR1 with small compound ZZW-115 and deletion of Linc00176 could induce necroptosis and exert anti-HCC effects (161,162). In addition, connexin 32 has been found to bind to Src and then mediate the inactivation of caspase 8 to trigger necroptosis in HCC cells, which could be used as an anticancer target to enhance the function of necroptosis inducers (163).

8. Ferroptosis, pyroptosis, necroptosis and tumor immunity

During the treatment of tumors, ferroptosis, pyroptosis and necroptosis are closely associated with the immune response (50,95,164). It has been found that immunotherapy-activated $CD8^+$ T cells could induce ferroptosis of tumor cells by downregulating the expression of SLC3A2 and SLC7A11, and ferroptosis inducers in combination with checkpoint blockade synergistically enhanced antitumor efficacy (164). Similarly, $CD8^+$ T cells have also been found to trigger tumor clearance through activation of the GSDM granzyme axis to induce pyroptosis (95,165), as have NK cells (93,95). Furthermore, necroptotic tumor cells can release damage-associated molecular patterns such as heat shock proteins, being more immunogenic than naïve tumor cells, to activate the immune system with the participation of $CD8^+$ T cells, NK cells and dendritic cells (DCs) (166-168), which may be related to the activation of NF-κB (50). Necrotic tumor cells, as well as fibroblast vaccination, contribute to the induction of antitumor immunogenicity by necrotic apoptotic cells (50,167,169), which enhances the antitumor efficacy of ICI treatments (167).

9. Ferroptosis and tumor immunity in HCC

The relationship between ferroptosis and the tumor immune response is complicated. It has been demonstrated that GPX4-associated ferroptotic hepatocyte death could cause a HCC-suppressive immune response, characterized by a C-X-C motif chemokine ligand 10-dependent infiltration of cytotoxic $CD8^+$ T cells that is counterbalanced by PD-L1 upregulation on tumor cells, as well as by a marked high mobility group box 1-mediated myeloid derived suppressor cell (MDSC) infiltration (170). A triple combination of the ferroptosis-inducing natural compound withaferin A, the C-X-C motif chemokine receptor 2 inhibitor SB225002 and α-PD-1 contributed to improved treatment of HCC compared with single treatment or dual combinations (170). In addition, inhibition of phosphoglycerate mutase 1 promotes ferroptosis and downregulates PD-L1 expression in HCC cells, further enhancing the infiltration of $CD8^+$ T cells, and thereby exerting antitumor effects (36). Furthermore, TLR2 agonist Pam3CSK4 could promote polarization of MDSCs into DCs and macrophages and recovery of T cell function by downregulating the expression of RUNX family transcription factor 1 (RUNX1), and TLR2 and RUNX1 may exert a regulatory effect on MDSCs by increasing ROS, which is related to the ferroptosis pathway (171).

Tumor-associated macrophages (TAMs), a key tumor-infiltrating immune cell type in the TME, encourage tumor invasion and metastasis by switching from the pro-inflammatory and antitumor type M1 TAMs to the anti-inflammatory and pro-tumor type M2 TAMs (172). Previous studies have demonstrated that TAMs generally exhibit a pro-tumor phenotype and inhibit CTLs by expressing PD-L1, thereby inducing immune escape and tolerance (173-175). Inhibition of apolipoprotein C1 can reverse the M2 phenotype to the M1 phenotype in TAMs via the ferroptosis pathway, enhancing the effect of anti-PD-1 immunotherapy and exerting anti-HCC effects (176). Injection of dextran chitosan hydrogel can induce

the repolarization of macrophages to the M1-like phenotype, and promote the maturation and activation of DCs, and combined treatment with PD-1 immunotherapy can effectively treat the peritoneal dissemination of advanced HCC and malignant ascites (37). A recent study also revealed that inhibition of the heavy chain subunit from system Xc^- encoded by the SLC7A11 gene (xCT) could induce ferroptosis of TAMs via the GPX4/ribonucleotide reductase regulatory subunit M2 signaling pathway and inhibit M2-type polarization via the suppressor of cytokine signaling 3/STAT6/peroxisome proliferator-activated receptor (PPAR)-γ pathway (35). Furthermore, this xCT inhibition-mediated macrophage ferroptosis increased PD-L1 expression in macrophages and improved the antitumor efficacy of anti-PD-L1 therapy (35).

10. Pyroptosis and tumor immunity in HCC

TKIs can remodel the TME of HCC and alter the immunosuppressive microenvironment, which is closely connected to pyroptosis, NK cells, T cells and regulatory T cells (177). Among them, SOR is a multi-target kinase inhibitor that directly modulates immunity, causing HCC cell death by inducing macrophage pyroptosis and activating cytotoxic NK cells (41). A study has found that the pyroptosis-score (PYS) could be used to assess the prognosis of patients with HCC due to hepatitis B virus (HBV-HCC), as a higher PYS in patients with HBV-HCC was associated with a worse prognosis, and these patients were more likely to receive anti-PD-L1 therapy (178). In addition, a risk score model related to pyroptosis can be constructed to predict the prognosis and immunological characteristics of HCC (38).

11. Necroptosis and tumor immunity in HCC

The interaction of necroptosis and the immune response is considered to be important in HCC development and treatment because necroptosis is a primary cause of liver inflammation and upregulates not only proinflammatory M1 TAMs, but also proinflammatory cytokines and chemokines, ultimately leading to chronic liver disease (179). However, a study has reported that RIPK3 is not expressed in hepatocytes, and MLKL does not depend on RIPK3 alone to regulate endoplasmic reticulum (ER)-mitochondrial Mg^{2+} dynamics (108). Defective MLKL inhibits mitochondrial Mg^{2+} absorption and ER Mg^{2+} release, and the resulting metabolic stress, in turn, induces parthanatos [a form of ICD associated with antitumor immunity (180)], activates anticancer immune responses and increases the therapeutic impact of ICIs, inhibiting HCC progression and immune escape (181). Similarly, RIPK3 defects in TAMs activate PPAR and promote fatty acid metabolism, which in turn induces the accumulation and polarization of M2 TAMs and ultimately promotes HCC progression (182). In addition, higher expression levels of RIPK1, RIPK3 and MLKL, are associated with good prognosis in HCC and are especially positively associated with $CD3^+$ and $CD8^+$ T cells in HCC (183). However, monoclonal antibodies targeting CD147 structural domain 1 can induce atypical necroptosis independent of RIPK (184). Furthermore, both senescence and SORD induce necroptosis in HCC cells and promote M1 TAM polarization (157,160).

12. Conclusion

In conclusion, induction of ferroptosis, pyroptosis and necroptosis is a novel avenue for killing HCC cells, providing novel targets and signaling pathways for drug discovery, increasing treatment effectiveness of immunotherapy, and possibly addressing drug resistance. The combination of ferroptosis, pyroptosis and necroptosis targets with ICIs may improve the therapeutic effect and prognosis in patients with advanced HCC. However, some problems still remain. First, although several compounds or drugs that induce ferroptosis, pyroptosis and necroptosis have been identified, clinical studies to assess their feasibility and safety are lacking. Therefore, more research should be performed in the future to improve the safety and personalized treatment options of this treatment avenue. Second, clinical studies of novel drugs or therapies for HCC are usually long and costly, which makes it difficult to develop novel medicines and treatments based on ferroptosis, pyroptosis and necroptosis. Third, the significance and mechanisms of ferroptosis, pyroptosis and necroptosis in HCC still need to be elaborated in further detail.

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Authors' contributions

RJL and XDY wrote the manuscript. RJL drew the figures. SSY and ZWG participated in the conception of the manuscript. XBZ and YSZ revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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