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The inducible role of autophagy in cell death: emerging evidence and future perspectives

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Abstract

Background Autophagy is a lysosome-dependent degradation pathway for recycling intracellular materials and removing damaged organelles, and it is usually considered a prosurvival process in response to stress stimuli. However, increasing evidence suggests that autophagy can also drive cell death in a context-dependent manner. The bulk degradation of cell contents and the accumulation of autophagosomes are recognized as the mechanisms of cell death induced by autophagy alone. However, autophagy can also drive other forms of regulated cell death (RCD) whose mechanisms are not related to excessive autophagic vacuolization. Notably, few reviews address studies on the transformation from autophagy to RCD, and the underlying molecular mechanisms are still vague.

Aim of review This review aims to summarize the existing studies on autophagy-mediated RCD, to elucidate the mechanism by which autophagy initiates RCD, and to comprehensively understand the role of autophagy in determining cell fate.

Key scientific concepts of review This review highlights the prodeath effect of autophagy, which is distinct from the generally perceived cytoprotective role, and its mechanisms are mainly associated with the selective degradation of proteins or organelles essential for cell survival and the direct involvement of the autophagy machinery in cell death. Additionally, this review highlights the need for better manipulation of autophagy activation or inhibition in different pathological contexts, depending on clinical purpose.

Keywords Autophagy, Cell death, Mammals, Selective degradation, Autophagy machinery components

Introduction

Autophagy is an evolutionarily conserved degradation pathway that plays a critical role in the maintenance of cellular homeostasis, including adaptation to metabolic stress, the removal of extrinsic or intrinsic hazardous substances, and the recycling basic materials and energy [1]. Three forms of autophagy have been identified: macroautophagy, chaperone-mediated autophagy (CMA) and microautophagy [2]. Macroautophagy sequesters the cargo protein into the double-membrane vesicle, which is named as the autophagosome, after which the autophagosome fuses with the lysosome to form the autolysosome [3]. Microautophagy involves the entry of cytosolic cargo into vesicles formed by the invagination

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of lysosomes and late endosomes [4]. In CMA, the KFERQ-like motif-bearing protein is selectively delivered to lysosomes via the chaperone HSC70 and then internalized into the lysosome lumen through the receptor lysosome-associated membrane protein type 2 A (LAMP2A) [5]. The following text focus primarily on macroautophagy (simply referred to as autophagy hereafter).

Autophagy is generally considered a prosurvival process that is triggered in response to multiple endogenous or exogenous stresses/stimuli [6–8]. The self-nourishment and metabolic recycling features of autophagy make the cell resistant to survival pressure under harsh conditions [7]. For example, in response to lipid overaccumulation, autophagy accelerates the turnover of triglycerides and regulates intracellular lipid stores, and its inhibition leads to increased lipid contents [9]. Moreover, systemically abolishing autophagy-related protein 7 (*Atg7*) to inhibit autophagic flux exacerbates the progression of obesity to diabetes [10]. In addition, mice with macrophages deficient in *Atg5* tend to develop severe atherosclerosis, and their macrophages exhibit aggravated apoptosis and oxidative stress [11]. The above evidence shows that functional inhibition of autophagy leads to the progression of various metabolic diseases. Furthermore, many neurodegeneration-related proteins serve as autophagy substrates, and impairment of autophagy in neurons causes the accumulation of protein aggregates and inclusions, thereby leading to neuronal death and promoting the progression of neurodegenerative diseases [12, 13]. And autophagy was also reported to function in the neurodevelopment process, including regulating exon guidance and outgrowth, neuromuscular junction, synapse formation, etc. and autophagy deficiency in neurons could induce neurodevelopmental disorders [14].

Compared to canonically cytoprotective function of autophagy, the inducible role of autophagy in cell death has received less attention. In 1974, the morphological microstructure of cell death was described by Schweichel and Merker via the treatment of prenatal tissue with different embryotoxic substances. Notably, in some cases, cell death is accompanied by the occurrence of many autophagic vacuoles encapsulating cytosolic macromolecules and cellular organelles [15]. Accordingly, autophagy can also disrupt normal cellular functions and bias cell fates toward death. On the basis of the published literature [2, 16–18], the inducible effects of autophagy on cell death can be summarized into two forms: (1) autophagy-dependent cell death, also known as "autosis", where autophagy takes place independently of canonical RCD and autophagy inhibition prevents cell death. (2) autophagy-mediated cell death, where autophagy occurs before cell death and autophagy induction triggers different forms of RCD, including apoptosis, necroptosis, ferroptosis, etc [16].

Recent reviews have multifacetedly discussed autosis, an autophagy-dependent form of cell death, which provides novel insights into the mechanism by which autophagy regulates cell death and highlights the potential feasibility of manipulating autophagy in different pathological conditions [16, 19, 20]. However, a comprehensive understanding of the interaction between autophagy and other forms of RCD is still lack, thereby limiting further depictions of the network involved in autophagy and cell death [21–23]. In this review, we aim to elucidate how autophagy influences other forms of RCD, highlighting mechanistical research. RCD in mammalian cells is the focus of this review because of its relevance to clinical conditions and applications.

Autophagy involvement in cell death induction

Autosis

Autosis is a subtype of autophagy-dependent cell death that was first coined in 2013. Autosis can be induced by nutrient starvation or autophagy-inducing peptide treatment in various cell lines (such as HeLa cells, U2OS cells, mouse embryonic fibroblasts (MEFs), and murine bone marrow-derived macrophages (BMDMs)), or by hypoxia-ischemia treatment in neonatal rat cerebra [17]. Autosis is morphologically characterized by increased adherence between cells and the matrix, fragmentation of the endoplasmic reticulum (ER) structure, and focal swelling of the perinuclear space accompanied by massive autophagic vacuolization [24]. Na^+/K^+-ATPase and Na^+/H^+ exchanger 1 are reported to participate in autosis, which can be prevented by cardiac glycosides (antagonists of Na^+/K^+-ATPase) and empagliflozin (SGLT2 inhibitors), respectively [17, 25]. Notably, the mechanism by which empagliflozin interferes with autosis induced by high glucose is also related to the inhibition of the AMPK/GSK3β pathway, which attenuates excessive autophagy [25]. What's more, the dysregulated accumulation of autophagosomes is common in autophagy-inducing peptide- or ischemia-reperfusion (I/R)-induced cardiomyocyte autosis, which is caused by the upregulation of Rubicon and the nuclear translocation of transcription factor EB (TFEB) [26, 27]. Targeting autosis appears to have potential as a novel approach to cancer treatment because combination of oncolytic virotherapy (myxoma virus) with CAR-T adoptive cell therapy triggers significant autosis in various cancer cells, which is a potent bystander killing mechanism that suppresses antigen escape [28]. Moreover, designated autophagy-inducing peptides, such as Tat-SP4, have been found to cause autosis-like death in triple-negative breast cancer, offering potential for cancer eradication [29].

Defining Autophagy-Mediated cell death

Unlike autosis, autophagy-mediated cell death involves different types of RCD, including apoptosis, necroptosis, ferroptosis, immunogenic cell death, pyroptosis, entosis, and parthanatos. To explicate and define "autophagy-mediated cell death", it is important to first clarify whether autophagy triggers RCD or merely accompanies RCD. Autophagy-mediated cell death should be considered to follow the principle of "autophagic cell death", in which death can be attenuated by the genetic inhibition of at least two autophagic machinery components and possesses the features of specific RCD [30]. Given that cell death initiated by autophagy may involve the canonical autophagy mechanism and that the accumulation of autophagosomes due to impaired autophagic flux also leads to cell death [23, 31], the criterion of autophagy-mediated cell death, which may be context specific, needs to be extend. The core principle is to distinguish autophagy-related proteins or components (including autophagosomes, autophagic vacuoles, and lysosomes) that initiate different forms of RCD via the selective degradation of prosurvival elements (such as proteins or organelles), contribution to the assembly of death-associated complexes, or the release of death-promoting factors. Additional supplements that inhibit autophagy-related proteins or components in both genetic or pharmacological manners are needed to prevent cell death.

Autophagy-Mediated apoptosis

Apoptosis was the first fully described form of programmed cell death, and its hallmarks include cell shrinkage, chromatin condensation, nuclear fragmentation, the formation of apoptotic bodies, and the clearance of cell debris by neighboring phagocytes [23, 32]. The interplay between autophagy and apoptosis is complex and deserves adequate discussion. In contrast to the numerous reports concerning the protective role of autophagy in apoptosis [22, 33–35], we focus on the potential proapoptotic aspects of autophagy. Diverse components of the molecular machinery for autophagy are reported to participate in the execution of apoptosis in MEFs exposed to SKI-I and HeLa cells exposed to interferon-γ (IFN-γ). The self-association of the apoptosis initiator Caspase-8 requires p62 and its self-processing at the Atg16L- and LC3-positive autophagosomal membrane, where Caspase-8 combines with Atg5 through the scaffold protein FADD to form an intracellular death-inducing signaling complex (iDISC) [36, 37]. Other investigations have revealed that iDISC comprises both apoptosis-related and necroptosis-related proteins (FADD, RIPK1, RIPK3, Caspase-8 and MLKL) as well as autophagy-related proteins (Atg5, Atg7 and p62) that localize at phagophore membranes when treating HIV-infected $CD4^+$ T cells with mimetics of DIABLO/SMAC (the mitochondrial protein that can induce apoptosis) [38–41]. In addition, the cleavage of Atg5 by calpain activates apoptosis, which is common in multiple in vitro models (e.g., immature neutrophils, Jurkat cells, HeLa cells, etc.). This mechanism involves the translocation of truncated Atg5 from the cytoplasm to the mitochondria, where it binds with the antiapoptotic protein Bcl-XL and subsequently induces cytochrome c release. Notably, *Atg5* overexpression significantly increases doxorubicin-induced anticancer effect in MDA-MA-231 cells derived xenograft model [42]. The autophagosome biogenesis-related protein Atg4D, which is cleaved by Caspase-3, can also be recruited to mitochondria, leading to mitochondria-mediated apoptosis in HeLa and A431 cells. Hence, Atg4D is recognized as an autophagy regulator that links damaged mitochondria with apoptosis [43]. In additon, two essential components of autophagy ubiquitin-like conjugation system, Atg12 and Atg3, are conjugated and this complex decreases Bcl-XL protein levels during mitochondria-mediated apoptosis in fibroblasts and HeLa cells, which is not observed during canonical autophagy activation by starvation [44]. Moreover, non-conjugated Atg12 is also served as an apoptosis effector that can interact with the antiapoptotic proteins Mcl-1 and Bcl-2, facilitating the release of cytochrome c as well as mitochondria-mediated apoptosis in HeLa cells [45]. Similarly, in cellular model systems (HeLa cells exposed to staurosporine and Ba/F3 cells deprived of IL-3) in which autophagy precedes apoptosis, the autophagy nucleation protein Beclin1 is cleaved by Caspase-3, and the C-terminal fragment is translocated to mitochondria, which sensitizes cells to apoptosis [46, 47] (Fig. 1A).

Autophagy is usually considered to remove protein aggregates, damaged organelles and harmful metabolites [1]; however, in other cases, the selective degradation of pivotal physiological function-sustaining proteins or basic organelles disrupts of cellular homeostasis and promotes apoptosis. For example, the accumulation of palmitic acid in astrocytes induces the autophagic degradation of Caveolin-1 (Cav-1), a fundamental protein for astrocyte survival, and leads to apoptosis [48]. Furthermore, there is strong evidence of the involvement of autophagy in HIV-1-induced apoptosis of uninfected bystander $CD4^+$ T lymphocyte, and the underlying mechanism is related to the selective degradation of the peroxisomal proteins CAT and PEX14 upon exposure to viral envelope glycoproteins [49]. Notably, autophagy plays opposite roles in Fas ligand-induced cell apoptosis, which can occur in two ways, with (Type II) or without mitochondrial permeabilization involvement (Type I), and varies in different cell lines. In Fas Type I cells (such as BJAB and SKW6.4 cells), the selective degradation of Fas-associated phosphatase-1 (Fap-1), which binds to the cytoplasmic tail of Fas and is identified as a negative

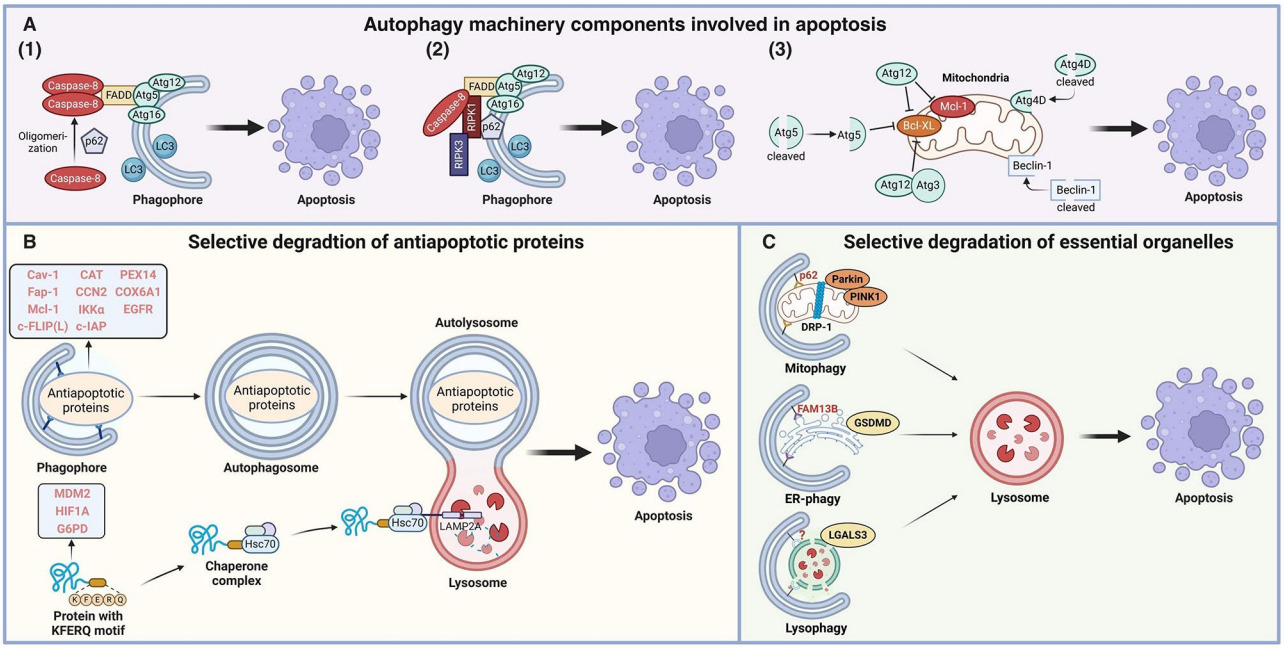

Fig. 1 Autophagy-mediated apoptosis. **A** Autophagy machinery components involved in apoptosis. (1) The protein p62 is required for the oligomerization of Caspase-8 in MEFs exposed to SKI-I and HeLa cells exposed to IFN-γ. The Atg5-Atg12-Atg16 complex serves as the scaffold for the assembly of Caspase-8 and FADD located at the phagophore membrane for subsequent apoptosis activation. (2) When HIV-infected CD4+ T cells are treated with DIABLO/SMAC mimetics, the Atg5-Atg12-Atg16 complex and p62 are considered to provide scaffolds for the assembly of both apoptosis- and necroptosis-related proteins, including Caspase-8, FADD, RIPK1, and RIPK3, that trigger apoptosis. (3) Cleaved Atg5, Atg3-conjugated Atg12, or Atg12 alone antagonizes the antiapoptotic protein family. In addition, cleaved Atg4D and cleaved Beclin-1 translocate to mitochondria, promoting cell apoptosis in different cell or animal models. **B** Autophagy mediates apoptosis by selective degradation of antiapoptotic proteins (Cav-1, CAT, PEX14, Fap-1, CCN2, COX6A1, Mcl-1, IKKα, c-FLIP (L), and c-IAP) via macroautophagy or (MDM2, HIF1A, and G6PD) via CMA in different cell or animal models. **C** Autophagy promotes apoptosis by selectively targeting essential organelle degradation, including mitophagy (p62 serves as the cargo receptor), ER-phagy (FAM13B serves as the cargo receptor), and lysophagy (the cargo receptor has not yet been identified) in different cell or animal models. This figure created in BioRender. Huang, X. (2024) https://BioRender.com/t95c542

regulator of apoptosis, with p62 as the cargo receptor promotes Fas ligand-induced apoptosis, whereas autophagy inhibits apoptosis in Fas Type II cells (such as Jurkat and CEM cells) [50]. The above contradictory conclusion is due to the reason that Fap-1 is expressed in Fas Type I cells but undetectable in Fas Type II cells, and hence, only Type I cells require autophagy for efficient apoptosis through the selective degradation of Fap-1. Notably, in type II cells, apoptosis activation relies on mitochondrial permeabilization; thus, autophagy may play a protective role by clearing damaged mitochondria. However, regarding the effects of autophagy on apoptosis involving mitochondria, other studies have drawn different conclusions when using different cell lines treated with other autophagy activators. The decrease in the cardiomyocyte survival mediator CCN2 by maladaptive autophagy results in mitochondria-mediated apoptosis when cardiomyocytes are exposed to sunitinib, a small-molecule kinase inhibitor [51]. Additionally, the specific autophagic degradation of the antiapoptotic factor COX6A1, mediated by the activation of PLK1 and its further inhibition of mTOR kinase, a negative regulator of autophagy, causes mitochondrial permeabilization and induces hepatocyte apoptosis [52]. Intriguingly, the targeted induction of apoptosis through selective autophagic degradation is a potential method for cancer treatment. In arsenite-treated hepatoma cells, IkappaB kinase alpha (IKKα) can be specifically recognized via the autophagic machinery, which depends on the association between the C-terminal arm of LC3-interacting regions within IKKα and LC3-II [53]. Moreover, researchers have developed and provided a novel PROTAC tool that selectively targets mutant EGFR protein for autophagic degradation to induce the apoptosis of non-small cell lung cancer cells [54]. A novel chalcone derivative, chalcone-24, has been shown to activate the degradation of antiapoptotic proteins, c-FLIP (L) and c-IAPs, via the autophagy-lysosome pathway to sensitize human lung cancer cells to apoptosis [55] (Fig. 1B).

Autophagy-mediated apoptosis involves not only the selective degradation of essential survival proteins but also the specific degradation of important organelles, such as mitochondria, the ER, and lysosomes. The p53 upregulated modulator of apoptosis (PUMA) is reported to induce the selective removal of mitochondria through Bax in Saos2 cells, which is termed mitophagy, and

mitophagy coincides with cytochrome c release as well as apoptosis [56]. Moreover, myoglobin or I/R injury treatment induces apoptosis by activating mitophagy through the PINK/Parkin pathway in renal tubular epithelial cells [57, 58]. PINK/Parkin-mediated mitophagy has also been reported to trigger excessive degradation of normal mitochondria and subsequent apoptosis in hepatocellular carcinoma cells treated with ketoconazole [59]. Additionally, T-2 toxin can induce dynamin-related protein 1 (DRP-1)-dependent mitophagy, leading to hepatic cell apoptosis [60]. Another extensively reported form of autophagy that specifically targets cellular organelles is called ER-phagy, which is considered to participate in doxorubicin-induced cardiomyocyte apoptosis. Mechanistically, increased gasdermin D (GSDMD) by doxorubincin upregulates the activity of ER-phagy receptor, FAM134B, through forming pores on the ER membrane by its N-terminus and activating ER stress. Afterwards, FAM134B interacts with LC3 and promotes ER-phagy, thereby leading to cell apoptosis [61]. Notably, the lysosome is the degradation organelle for autophagy and is susceptible to exogenous stimuli. Both Δ9-tetrahydrocannabinol and periplocin cause lysosome damage by permeabilizing the lysosomal membrane damage as well as causing the release of cathepsin and subsequent apoptosis. In addition, periplocin induces excessive autophagic degradation targeting lysosomes (referred to as lysophagy), leading to the exacerbation of lysosomal damage and ultimately of apoptotic cell death, both in colorectal cancer cell lines and in the corresponding tumor xenograft models [62, 63] (Fig. 1C).

CMA is considered a prosurvival machinery when cells are subjected to prolonged starvation or oxidative stress [5, 64]. However, because of the specific recognition of cargo containing the KFERQ motif by HSC70 and LAMP2A, CMA is particularly characterized by selectivity. It is reasonable that CMA may also play an adverse role in apoptosis via the selective degradation of proteins necessary for survival. The first evidence regarding the negative function of CMA in apoptosis was described in 2010. Hispolon, which is isolated from many *Phellinus species*, can induce apoptosis in breast cancer cells via a mechanism associated with the downregulation of MDM2, the negative regulator of p53, and further studies revealed that hispolon promotes the interaction between LAMP2A and MDM2, resulting in targeted CMA degradation [65, 66]. In recent years, multiple studies have demonstrated the potential ability of CMA to degrade critical proteins involved in tumor resistance, thereby facilitating cancer cell apoptosis. For example, enhancing the binding between HSC70 and HIF1A or between HSC70 and G6PD promotes CMA degradation of the latter proteins and sensitizes hepatoma or small cell lung cancer to apoptosis, respectively [67, 68]. In addition, CMA is reported to mediate glutamate-induced apoptosis in hippocampal neuronal cell line HT22, which can be alleviated by the cysteine protease inhibitor E-64d [69] (Fig. 1B).

Autophagy-mediated necroptosis

Necroptosis is characterized by cell swelling, plasma membrane breakage, and moderate chromatin agglutination. The activation of the RIPK1, RIPK3, and MLKL signaling pathways as well as the formation of necrosomes are involved in necroptosis [24]. Autophagy acts as a double-edged sword during necroptosis [70]. Some studies have demonstrated that autophagy antagonizes necroptosis via autophagic degradation of pronecroptotic factors, such as RIPK1, RIPK3, and TRIF [71, 72]. However, in many other situations, autophagy promotes necroptosis. The inhibition of apoptosis in rhabdomyosarcoma, glucocorticoid-resistant acute lymphoblastic leukemia, or thymic epithelial tumor by obatoclax (GX15-070), a small-molecule inhibitor of Bcl-2, can trigger autophagy-mediated necroptosis, the mechanism of which is related to the accumulation of autophagosomes and the availability of the autophagosomal membrane component Atg5 for interaction with FADD, RIPK1, and RIPK3, which facilitates the assembly of necrosomes on autophagosomes [73–75]. Autophagy serves as a switch between apoptosis and necroptosis and is also reported to be involved in TNF-related apoptosis inducing ligand (TRAIL)-induced cell death. In MAP3K7-intact mouse prostate cells, TRAIL-induced cell death occurs via apoptosis due to the competitive interaction between RIPK1 and MAP3K7, thereby inhibiting the execution of necroptosis; conversely, in MAP3K7-defective mouse prostate cells, TRAIL-induced cell death occurs primarily through necroptosis, whose mechanism involves the recruitment of released RIPK1 by p62 on the autophagosome membrane and the mediation of necrosome assembly with the autophagic machinery. Intriguingly, cell death switches back to apoptosis if autophagy flux is blocked via p62 knockout [76]. The transformation from apoptosis to necroptosis via autophagy can be an attractive way to reverse acquired drug resistance. For example, graphene oxide can cause massive accumulation of autophagosomes and thus lead to necroptosis in non-small-cell lung cancer when combined with the autophagosome-lysosome fusion inhibitor chloroquine [77]. In addition to the above research, other evidence strongly supports the existence of autophagy-mediated necroptosis. The LC3 interacting region domain has been confirmed to be present in RIPK1 and RIPK3, and the interaction between LC3 and RIPK1, as well as between LC3 and RIPK3, mediates necroptosis in hypoxia-treated cardiomyocytes or alcohol-exposed hepatocytes [78, 79]. Either pharmacological or genetic inhibition of Atg7, an

E1-like enzyme necessary for the transformation of LC3-I to LC3-II and the expansion of the phagophore [80, 81], can rescue palmitic acid-induced necroptosis in human umbilical vein endothelial cell line EA.hy926 [82]. In addition, the accumulation of the autophagy cargo protein p62 in aged myocardium has been found to result in the formation of a necrosome complex with RIPK1-RIPK3, which promotes their interaction and exaggerates necroptosis in cultured primary cardiomyocytes followed by hypoxia-reoxygenation (H/R) treatment or I/R-induced myocardial necroptosis in mouse hearts [83] (Fig. 2A).

Like apoptosis, the selective degradation of antinecroptotic factors or certain intracellular organelles contributes to the occurrence of necroptosis. Chalcone-24 extensively induces the degradation of c-IAP1 and c-IAP2, the E3 ubiquitin ligases of RIPK1, thereby facilitating the formation of the ripoptosome (the complex of FADD, RIPK1, and Caspase-8 [84]), resulting in the activation of necrosomes and subsequent necrosis in A549 and UM-UC-3 cells [85] (Fig. 2B). Notably, the specific autophagic degradation of organelles, especially mitophagy, has also been shown to participate in necroptosis [86]. During the progression of chronic obstructive pulmonary disease, cigarette smoke exposure causes mitochondrial dysfunction via the induction of PINK1-mediated mitophagy in pulmonary epithelial cells, which increases the phosphorylation of MLKL and leads to subsequent necroptosis. Mitophagy inhibitors Mdivi-1 and thymoquinone protect against cigarette smoke-induced necroptosis [87, 88]. Moreover, the DRP-1-associated mitophagy is reported to cause a generalized loss of mitochondria in cardiomyocytes from mice heart or melanoma cells (G361 and SK-MEL-28 cells) contributing to necroptosis; however, the function of DRP-1 in these two situations is controversial, which may be attributable to differences between normal cells and cancer cells [89, 90] (Fig. 2C).

Autophagy-mediated ferroptosis

Ferroptosis was first defined by Brent Stockwell as an iron-dependent form of nonapoptotic and nonnecroptotic RCD induced by erastin [91]. The morphological features of ferroptosis include smaller mitochondria, increased rupture of the mitochondrial membrane, and a decreased number of mitochondrial cristae. The induction of ferroptosis is due to lipid membrane damage caused by the accumulation of lipid peroxides and reactive oxygen species (ROS) generated by iron metabolism [24, 92]. According to recent research, ferroptosis is closely associated with autophagy and is also known as an autophagic cell death process [93]. First, whatever in cancer cell lines (HCT116 cells, CX-1 cells, HT1080 cells, etc.) or cancer cell lines derived xenograft models, the autophagy machinery component Beclin1 reportedly blocks cystine/glutamate antiporter system Xc^- activity via direct binding to its central regulatory element SLC7A11 after the phosphorylation of Beclin1 at Ser90/93/96 by AMPK, thereby activating lipid peroxidation and inducing ferroptosis [94, 95] (Fig. 3A). In addition to its ability to inhibit system Xc^- activity, Beclin1, the core component of the PI3K III nucleation complex, can exert proferroptotic effects via the activation of autophagy. In primary human or mouse fibroblastic cells,

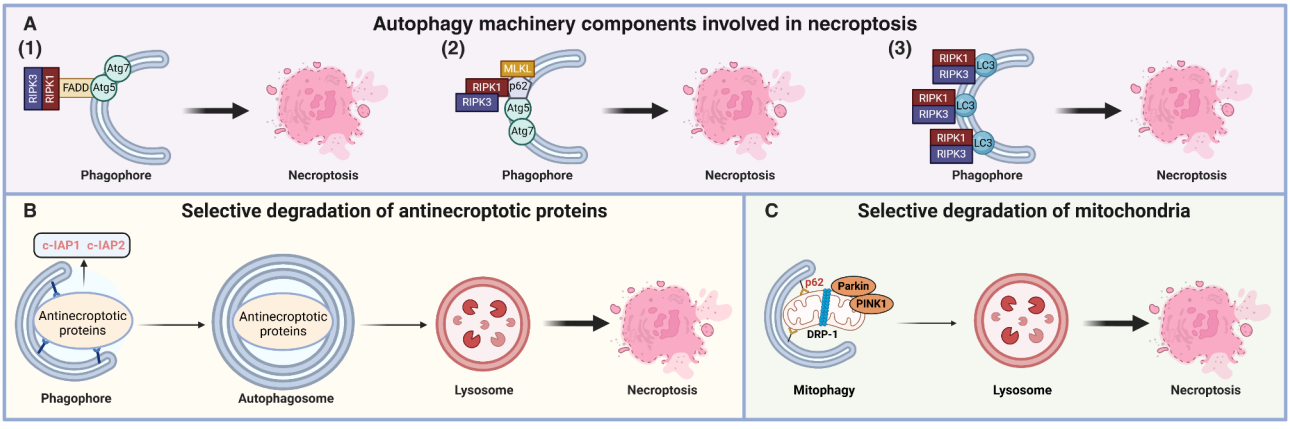

Fig. 2 Autophagy-mediated necroptosis. **A** Autophagy machinery components involved in necroptosis. (1) When apoptosis is inhibited by GX15-070 in rhabdomyosarcomas, glucocorticoid-resistant acute lymphoblastic leukemias or thymic epithelial tumors, Atg5 serves as a scaffold for the interaction of FADD, RIPK1, and RIPK3, promoting necrosome formation and necroptosis. (2) When response to TRAIL in mouse prostate cells, p62 is required for the recruitment of RIPK1, RIPK3, and MLKL to the phagophore membrane for subsequent necroptosis. (3) Under H/R treatment in cultured primary cardiomyocytes or I/R-induced myocardial necroptosis in mouse hearts, LC3 can interact with RIPK1 and RIPK3, thereby triggering necroptosis. **B** Autophagy mediates necroptosis via the selective degradation of antinecroptotic proteins (c-IAP1 and c-IAP2) in A549 and UM-UC-3 cells treated with chalcone-24. **C** Autophagy promotes necroptosis in pulmonary epithelial cell, cardiomyocytes, and melanoma cells by selectively targeting mitochondrial degradation (mitophagy), and p62 serves as the cargo receptor. This figure created in BioRender. Huang, X. (2025) https://BioRender.com/x17x967

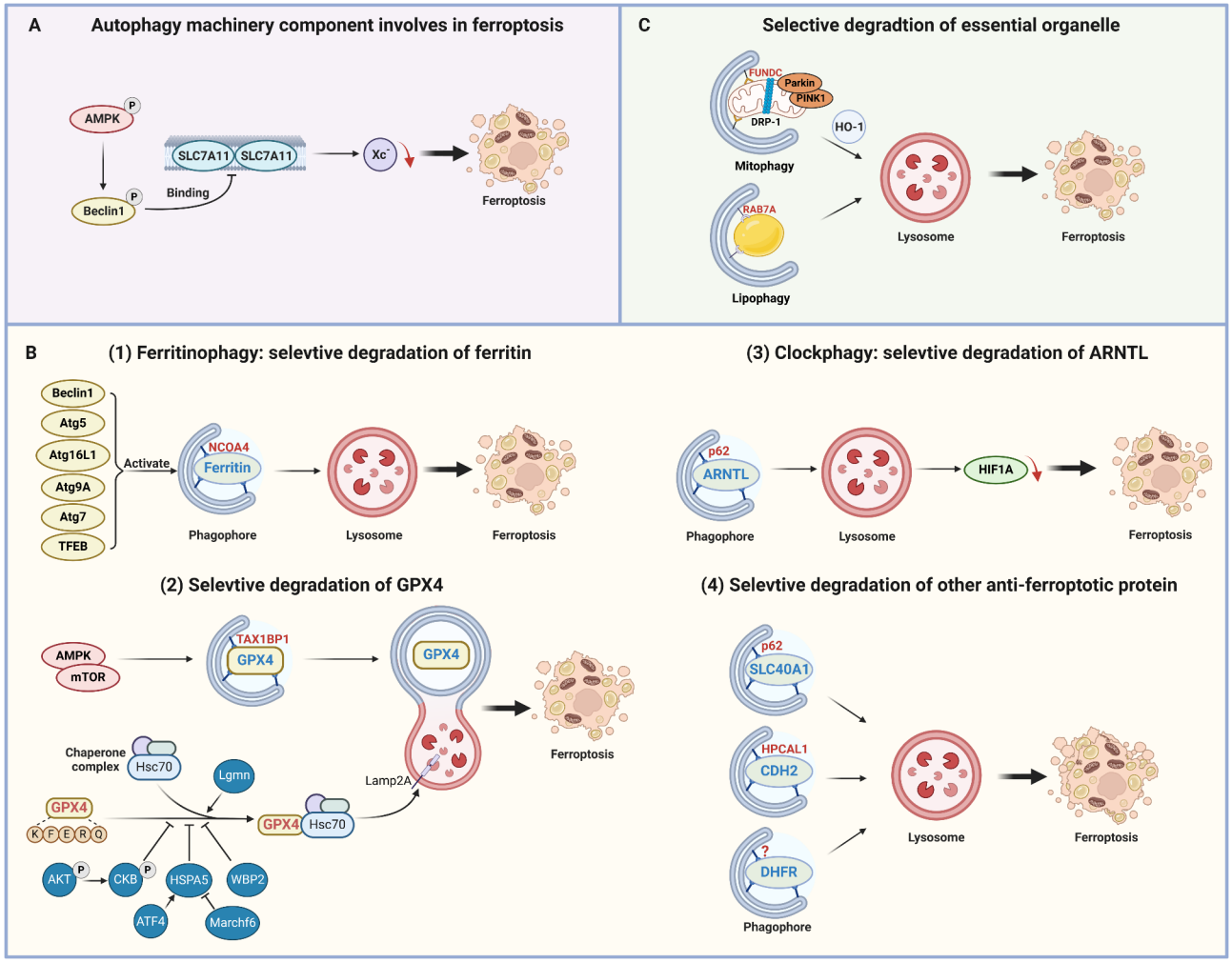

Fig. 3 Autophagy-mediated ferroptosis. **A** Activated AMPK phosphorylates the autophagy machinery component Beclin1, and Beclin1 directly binds to SLC7A11, which leads to the inhibition of Xc^- system activity and mediates ferroptosis. **B** Autophagy mediates ferroptosis via the selective degradation of essential proteins. (1) Ferritinophagy is a term that describes the selective degradation of ferritin, and NCOA4 is considered the cargo receptor. Various autophagy-related proteins are involved in the activation of ferritinophagy. (2) Selective degradation of GPX4 via macroautophagy: TAX1BP1 serves as the cargo receptor, and the AMPK/mTOR signaling pathway regulates this process. Moreover, CMA can mediate the selective degradation of GPX4. CKB, WBP2 and HSPA5 inhibit the recognition of GPX4 by HSC70, which prevents ferroptosis; instead, Lgmn strengthens the interaction between HSC70 and GPX and between LAMP2A and GPX, hence promoting ferroptosis. (3) Clockphagy is a term that describes the selective degradation of ARNTL, and p62 is the cargo receptor. Clockphagy reduces HIF1A (a ferroptosis suppressor), leading to ferroptosis. (4) Selective degradation of other antiferroptotic proteins such as SLC40A1 (p62 serves as the cargo receptor), CDH2 (HPCAL1 serves as the cargo receptor), and DHFR (the relevant cargo receptor has not yet been identified). **C** Autophagy promotes ferroptosis by selectively targeting mitochondria (mitophagy) or lipid droplet degradation (lipophagy), and FUNDC or RAB7A is considered to be the cargo receptor, respectively. The abovementioned mechanisms are shared in different cell or animal models. This figure created in BioRender. Huang, X. (2025) https://BioRender.com/p09w858

autophagy activation leads to the selective degradation of ferritin, also referred to as ferritinophagy, and increases the intracellular labile iron pool, resulting in a bias toward ferroptosis, which can be reversed by Beclin1 knockdown [96]. Moreover, N6-methyladenosine (m^6A) modification is reported to stabilize Beclin1 mRNA to trigger autophagy-mediated ferroptosis, and YTHDF1 has been identified as a key m^6A reader protein of the Beclin1 coding region in hepatic stellate cells [97, 98]. ELAVL1, USP11, USP19 and HMGB1 are also positive regulators that stabilize Beclin1 mRNA to activate autophagy-mediated ferroptosis in various normal and cancer cells [99–104]. Conversely, PCBP1 can bind to CU-rich elements in the 3'-UTR of Beclin1 mRNA, inhibiting autophagy activation and ferroptosis in both HN12 cells and HN12 cells derived tumor xenograft models [105]. Second, the Atg5-Atg12-Atg16L1 conjugation system is believed to participate in autophagy-mediated ferroptosis. The increase in m^6A methylation on Atg5 mRNA, mediated by WTAP in a YTHDC2-dependent manner, clearly triggers ferritinophagy and eventually ferroptosis in hepatocellular carcinoma [106]. The RNA-binding protein

ZFP36 plays a crucial role in Atg16L1-induced ferroptosis in hepatic stellate cells by binding to Atg16L1 mRNA and promoting its decay, which can be impaired by the ubiquitin ligases of ZFP36 and FBXW7 [107]. Importantly, the switch between prosurvival autophagy and prodeath autophagy may depend on upstream regulatory factors affecting the Atg5-Atg12-Atg16L1 complex. Atg9A is required for starvation-induced autophagosome formation, and promotes cell survival via the bulk degradation of cytosolic components; however, in the case of PANC1 pancreatic cancer cells or corresponding xenograft tumors exposed to ferroptosis activators, TMEM164 dominates autophagosome formation, which leads to the specific degradation of antiferroptosis factors [108]. Third, Atg7 is known to participate in autophagy-mediated ferroptosis, which is negatively regulated by the GATA6/miR-193b/Atg7 axis in the cerebral I/R injury rat model or neuronal oxygen-glucose deprivation cell model [109]. Finally, the nuclear translocation of TFEB, the master regulator of autophagy-lysosome biogenesis, specifically induces the degradation of ferritin and lipid droplets, which leads to ferroptosis in rat liver accompanied by iron overload and lipid stress [110] (Fig. 3B).

The most important mechanism underlying autophagy-mediated ferroptosis involves the selective degradation of iron storage proteins, the core components of the antioxidant system, and even critical organelles that respond to cellular stress. As mentioned above, ferritinophagy is a term that describes the selective removal of ferritin (FTH1, FTL, and FTMT) via autophagy [111]. Nuclear receptor coactivator 4 (NCOA4) serves as the major cargo receptor that specifically delivers ferritin to lysosomes for degradation [93, 111–114]. The regulation of NCOA4 via different upstream pathways is reported to influence ferroptosis. For example, the Ser/Thr protein kinase ATM is indispensable for the execution of ferroptosis: it phosphorylates NCOA4 and promotes interaction between NCOA4 and ferritin, thus sustaining ferritinophagy in MEFs, HT-1080, and HCT116 cells [115]. Similarly, in H9C2 cells treated with oleic acid/palmitic acid or mouse cardiac injury caused by a high-fat diet, IL-6/STAT3 signaling has been shown to positively regulate NCOA4 expression after phosphorylation of STAT3, and piperlongumine, a natural compound, can protect cardiomyocytes from ferroptosis by decreasing phosphorylated STAT3 levels [116]. USP14 is another regulator that stabilizes NCOA4 via a deubiquitination process in damaged neurons [117]. In addition to positive regulatory signaling, other factors negatively regulate the protein level of NCOA4. c-MYC binds to NCOA4 mRNA, which directly inhibits its expression, hence endowing ovarian cancer with resistance to ferroptosis, and miR-6862-5P inhibits NCOA4 transcription via the degradation of NCOA4 mRNA, which protects primary human macrophages from ferroptosis under hypoxia [118, 119]. Additionally, TRIM7 reduces ferritinophagy and ferroptosis in human glioblastoma cell lines (A172 and U87MG cells) by binding and ubiquitinating NCOA4 via K48-linked chains, which promotes its proteasomal degradation [120] (Fig. 3B).

Glutathione peroxidase 4 (GPX4), the core component of the antioxidant system, reduces lipid hydroperoxide to a nontoxic lipid alcohol through its enzymatic activity [121]. CMA is known to be involved in the execution of ferroptosis via the selective degradation of GPX4, whose mechanism is associated with the interaction between HSC70 and GPX4 and between LAMP2A and GPX4 by the recognition of the KFERQ motif in GPX4. Both pharmacological and genetic inhibition of CMA can in turn hinder erastin-induced ferroptosis in HT-22 and HT-1080 cells or radiation-induced lung epithelial cell ferroptosis [122, 123]. Moreover, AKT activated by insulin-like growth factor 1 receptor signaling can phosphorylate creatine kinase B at Thr133, which further phosphorylates GPX4 at Ser104, and this phosphorylation prevents GPX4 from binding to HSC70, thus preventing the degradation of GPX4 via CMA and counteracting ferroptosis in hepatocellular carcinoma [124]. WBP2, one of the molecular chaperons, competes with HSC70 for binding with the KFERQ motif of GPX4, increasing the stability of GPX4 and conferring the resistance to ferroptosis in cisplatin-induced acute kidney injury (AKI) [125]. Unlike WBP2, legumain promotes autophagy-mediated ferroptosis by strengthening the interaction between HSC70 and GPX4 and between LAMP2A and GPX4, thereby aggravating AKI induced by I/R or folic acid [126]. Moreover, the activation of transcription factor 4 (ATF4) induces the expression of HSPA5, which binds to GPX4 and protects against GPX4 degradation via CMA in pancreatic ductal adenocarcinoma or glioma [127, 128]. Conversely, the cytosol-retained prohormone proopiomelanocortin (POMC) in neuronal cells (N43/5 cell line or mice neurons specifically expressing POMC) can sequester HSPA5, thus accelerating the degradation of GPX4 by CMA; notably, the E3 ubiquitin ligase Marchf6 regulates the degradation of cytosol-retained POMC, making itself a negative regulator of ferroptosis [129]. CMA is not the only pathway involved in the selective degradation of GPX4; similar selectivity also occurs in macroautophagy. When exogenous copper treatment is applied to various pancreatic ductal adenocarcinoma cell lines or PANC1 cells derived xenograft model, copper binds to GPX4 at Cys107 and Cys148, resulting in GPX4 ubiquitination and the formation of GPX4 aggregates for subsequent delivery to lysosomes with the help of the cargo receptor TAX1BP1 [130]. When experiencing I/R-induced AKI in mice or H/R-induced AKI in HK-2 cells, the deubiquitinase OTUD5 reportedly decreases

the ubiquitination of GPX4, thus protecting GPX4 from TAX1BP1-dependent autophagy [131]. Notably, AMPK/mTOR signaling is important in the activation of macroautophagy-mediated GPX4 degradation in both cancer and normal cells, which can be regulated by SIRT3 and ALOX5 [132–134] (Fig. 3B).

The autophagic degradation of ferritin and GPX4 has been extensively reported to occur in ferroptosis, and other crucial antiferroptotic proteins that can be degraded to promote ferroptosis have received less attention. BMAL1/ARNTL is a central component of the circadian clock, which drives the rhythmic expression of PER as well as CRY and sustains cell homeostasis [135]. The selective degradation of ARNTL, which is referred to as clockphagy, is involved in the execution of ferroptosis in various human tumor cells (Calu-1, HT1080, and HL-60 cells) and HT1080 cells derived xenograft model treated with type 2 ferroptosis inducers (RSL3 and FIN56), via the upregulation of Egln2 and subsequent blockade of the activation of the ferroptosis suppressor HIF1A, ultimately leading to lipid peroxidation and ferroptosis. Notably, p62 has been identified as the specific cargo receptor responsible for the recognition and delivery of ARNTL during clockphagy [136, 137]. Furthermore, the intracellular iron exporter SLC40A1/ferroportin-1 is another substrate protein that can be recognized by p62 and then targeted to lysosomes for degradation, increasing the cellular labile iron concentration and causing ferroptosis following treatment with erastin in HT1080, PANC1 cells, and PANC1 cells derived xenograft model [138]. HPCAL1, a novel cargo receptor for the selective degradation of CDH2, promotes RSL3- and erastin-induced ferroptosis in multiple caners cells, as well as cerulein-induced acute pancreatitis by reducing membrane tension and promoting lipid peroxidation. A study also revealed that protein kinase C theta (PRKCQ)-mediated HPCAL1 phosphorylation at Thr149 is required for the interaction between HPCAL1, CDH2, and LC3, which triggers the autophagic degradation of CDH2 [139]. In addition, the specific recruitment of the TLR4-p62-LC3 complex into autophagosomes mediated by soluble glucose regulated protein 78 (sGRP78) contributes to ferroptosis in myeloid cells exposed to LPS and favors sGRP78-mediated inflammation resolution [140]. Finally, high CD38 expression increases ROS levels, thereby leading to the oxidative degradation of dihydrofolate reductase (DHFR), a negative regulator of ferroptosis. The molecular mechanism involves ROS-mediated sulfonation at Cys7 of DHFR and its subsequent degradation by autophagy as well as by non-canonical proteasome pathways, which sensitize BMDMs to ferroptosis [141] (Fig. 3B).

In addition to the important role of the selective degradation of crucial functional proteins in ferroptosis, organelle-specific autophagy is also widely involved in the execution of ferroptosis. PINK/Parkin-mediated mitophagy is reported to exacerbate cysteine deprivation-, tris (1,3-dichloro-2-propyl) phosphate- and zinc-induced ferroptosis both in cancer cells and normal cells [142–144]. The mitochondrion-targeted H2S donor AP39 can antagonize myocardial ferroptosis via the inhibition of PINK/Parkin-mediated mitophagy, thereby alleviating myocardial fibrosis after myocardial infarction [144]. The underlying mechanism of mitophagy activation may be associated with the compartmentalization of HO-1 into the mitochondria, which leads it to the lysosome for degradation, at least in the context of BAY 11-7085-induced ferroptosis in various cancer cells [145]. The receptor cargo protein FUNDC may mediate selectivity in mitophagy conditionally, and its ablation renders the myocardium resistant to ferroptosis induced by paraquiat [146]. In addition, the targeting of myoferlin by WJ460 has been shown to activate mitophagy and induce ferroptosis in pancreas ductal adenocarcinoma, and this pharmacological effect can be reversed by Mdivi1, a mitophagy inhibitor [147]. In the type 2 diabetic osteoporosis rat model, or human osteoblast cell line hFOB 1.19 treated with high glucose, silencing of mitochondrial ferritin, *Ftmt*, significantly induces mitophagy and ferroptosis, indicating the protective effect of FTMT against autophagy-mediated ferroptosis [148]. In contrast, DRP-1 can exacerbate mitophagy-mediated ferroptosis in melanoma cells treated with BAY 87-2243 [90] (Fig. 3C).

Lipophagy is a selective autophagic process for the degradation of lipid droplets and has important implications for lipid metabolism [9]. Lipophagy promotes RSL3-induced ferroptosis in primary mouse hepatocytes and HepG2 cells via decreased lipid storage, the release of free fatty acids, and lipid peroxidation [149]. Notably, RAB7A is reported to be the common cargo receptor in lipophagy and is also required for the execution of ferroptosis [149–152]. Intriguingly, lipophagy can occur concomitantly with mitophagy in ionizing radiation-induced ferroptosis in PANC1, SW1990, and A549 cells, as well as in B16 and S91 cells derived tumor-bearing models. Ionizing radiation activates mitophagy and causes the formation of lipid droplets near damaged mitochondria, resulting in the autophagic degradation of peridroplet mitochondria and the release of free fatty acids as well as lipid peroxidation [153] (Fig. 3C).

In addition to the selective autophagic degradation of antiferroptotic factors or specific organelles, other pathways are involved in the initiation of ferroptosis via the autophagy machinery. Lysosomal permeability is increased by the iron-mediated Fenton reaction and the leakage of lysosomal contents such as cathepsin B (CTSB), which directly unleashes structural and functional changes in mitochondria or translocates to the

nucleus, causing DNA damage via the cleavage of histone H3, thereby contributing to ferroptosis in PANC1, MIAPaCa2, HT22, and NIH3T3 cells [154–156]. Additionally, increased autophagy promotes the degradation of p62, which can sequester Keap1 to target lysosomes [157], promote Keap1-mediated Nrf2 degradation via the proteasome pathway, and thus decrease the transcription of genes downstream of Nrf2 (including FTH, FPN, and HO-1), thereby promoting erastin-, sorafenib-, or alcohol-induced ferroptosis in hepatocellular carcinoma [158, 159].

Autophagy-mediated immunogenic cell death

Immunogenic cell death (ICD) was first introduced in 2015 and is distinguished from other forms of RCD that induce an antigen-specific immune response involving immunological memory, such as necroptosis, which activates the innate immune response solely, and apoptosis, which elicits active immunosuppression [160]. However, at least in a specific context, stress-induced apoptosis or other tolerogenic cell death can turn into ICD, which can drive an adaptive immune response [24, 161]. The immunogenicity of ICD is dependent on two factors: antigenicity and adjuvanticity. Antigenicity is conferred by the expression and presentation of antigenic peptide-MHC class I or II, which can be recognized by the mature αβ T repertoire [162]. Healthy cells have insufficient antigenicity to drive ICD due to peripheral and central tolerance. In contrast, infected and malignant cells display sufficient antigenicity to initiate adaptive immune responses. Adjuvanticity arises from the coordinated release or exposure of danger signals and are essential for the recruitment and maturation of antigen-presenting cells (APCs), also known as damage-associated molecular patterns (DAMPs) [161]. The reported adjuvants include extracellular ATP, CALR, HMGB1, ANXA1, Type I IFN, and CXCL10, which contributes to ICD in different manners. Extracellular ATP produces a "find me" signal, promoting the recruitment and activation of APCs. CALR serves as an "eat me" signal, which promotes the uptake of dying cancer cell-associated antigens. HMGB1 has been shown to increase the synthesis of various proinflammatory factors, mostly by binding to TLR4 in APCs. ANXA1 functions as a guide for the final process by which APCs collect antigens from dying cancer cells. Type I IFNs synergize with CXCL10 for the recruitment of T cells [163].

Given the requirement of immunogenicity, ICD can serve as a specific avenue to remove malignant cells. Investigations have revealed that ionizing radiation, oncolytic viruses, and certain immunogenic chemotherapeutic agents can induce ICD in cancers via a mechanism that is highly dependent on autophagy [164]. First, autophagy promotes the presentation of both MHC-I and MHC-II antigens and participates in both the trafficking and the ingestion of exogenous antigens inside APCs. The engulfed extracellular antigens are delivered to endosomal/lysosomal compartments, where they are ingested into peptides by cathepsins and loaded onto MHC-II, which is then translocated to the cell membrane for presentation to $CD4^+$ T cells [164–167]. Furthermore, autophagy facilitates the "cross-presentation" of extracellular antigens, with results pertinent to tumor antigens. Autophagy activation in APCs increases the processing of tumor antigens and their subsequent loading onto MHC-I for presentation to $CD8^+$ T cells [164]. In addition, a sustained autophagy flux in antigen donor cells, where autophagosomes serve as efficient antigen carriers, is required for antigen sequestration and delivery to APCs for cross-presentation. Knockdown of Beclin1 or Atg5 in MEFs, B16-F10 cells, and ovalbumin-expressing HEK293T cells weakens the cross-presentation of tumor antigens by dendritic cells (DCs), which are classical APCs [168, 169]. A more detailed study demonstrated that autophagy may increase the antigenicity of early-stage B16-F1 melanoma cells by promoting the generation of MHC-I-binding peptides in response to IFN-γ [170]. Finally, autophagy is required for the survival and proliferation of T lymphocytes [171], and inhibition of autophagy in hepatocytes causes the accumulation of lipid droplets, which ultimately leads to the depletion of $CD4^+$ T cells [164, 172]. Additionally, autophagy is pivotal for plasma cell homeostasis and the maintenance of long-term humoral immunity through the inhibition of ER stress [173] (Fig. 4A).

In addition to endowing dying cancer cells with antigenicity and providing favorable survival conditions for immune cells, autophagy plays an important role in the release of DAMPs, which endow antigen-donor cells with adjuvanticity. Autophagy-intact rather than autophagy-deficient cancers attract DCs and T cells to the tumor bed, triggering the ICD of various cancer cells (U2OS, CT26, and MCA205 cells) both in vitro and in vivo when response to chemotherapy, such as mitoxantrone or oxaliplatin, the mechanism of which is related to the autophagy-dependent release of ATP [174, 175]. ATP is redistributed from lysosomes to autolysosomes upon exposure to ICD inducers and then is secreted by the autophagic machinery, which is involved in LAMP1-PANX1-dependent lysosomal exocytosis [176, 177]. In addition, the release of HMGB1 and CALR can be increased via the activation of autophagy and the accumulation of secretory autophagosomes when induction of ICD in colorectal cancer via thioridazine, in bladder cancer via norcantharidin, or in mesothelioma via carboplatin plus pemetrexed [178–180]. Moreover, combining a MEK inhibitor with pemetrexed and cisplatin chemotherapy triggers CXCL10 secretion in lung adenocarcinoma via the promotion of OPTN-dependent mitophagy,

which can be abolished by mitophagy inhibition [181]. The above conclusion is also supported by clinical findings that cancer patients harboring high immunohistochemical signs of autophagy are correlated with better prognosis [182, 183] (Fig. 4A).

However, autophagy is usually inhibited in malignant cancer cells; therefore, combination with autophagy enhancers that target cancers may be an attractive strategy to enhance ICD-treatment in cancer. Caloric restriction mimetics, including thiostrepton and hydroxycitrate, reportedly stimulate autophagy in various cancers by activating TFEB/transcription factor binding to IGHM enhancer 3 (TFE3), which sensitizes cancers to ICD induced by chemotherapies [184–186]. IGF1R inhibitors such as picropodophyllin and linsitinib, are other potent autophagy inducers that increase the release of ATP and enhance chemotherapy-induced ICD in U2OS, MCA204, and TC1 cells [187, 188]. Piceatannol, a dietary phenolic compound, enhances the oxaliplatin-induced release of DAMPs from U2OS osteosarcoma or MCA205 fibrosarcoma via TFEB/TFE3-dependent autophagy activation [189]. In addition, some natural compounds, such as P2Et or (-)-Guaiol, can directly induce autophagy and ICD in melanoma or non-small cell lung cancer without being combined with traditional chemotherapeutics [190, 191]. The use of oncolytic viruses is an intriguing strategy for cancer treatment. In addition to direct oncolysis, oncolytic viruses have recently been shown to trigger ICD in lung cancer, prostate cancer, and breast cancer and prime antitumor immunity through the autophagic release of ICD determinants [192, 193].

Autophagy-mediated NETosis

NETosis is one of the RCD forms that occurs in neutrophils as well as other leukocytes and culminates in the release of neutrophil extracellular traps (NETs), which are extracellular chromatin structures loaded with granule proteins that can trap and degrade microbes [194, 195]. NETosis was first confirmed in 2004 when using neutrophils treated with phorbol myristate acetate or IL-8, resulting in morphological features including rupture of the plasma membrane and nuclear membrane as well as leakage of chromatin fibers [24, 196]. A mechanistic study revealed that the activation of NETosis involves NADPH oxidase activity, the collapse of the nuclear envelope and most granule membranes, the decondensation of nuclear chromatin and the formation of NETs. Notably, autophagy is required for chromatin decondensation and the formation of NETs, and autophagy inhibition by wortmannin or 3-methyladenine, a classical PI3K III inhibitor, or *ATG5* or *ATG7* deficiency can decrease the NETosis rate of neutrophils and convert NETosis to apoptosis in certain contexts [194, 197–199]. In patients with familial Mediterranean fever, the low basal autophagy level of polymorphonuclear neutrophils protects against crises by alleviating the release of proinflammatory NETs [200]. Moreover, neutrophils from patients with active systemic lupus erythematosus display elevated basal autophagy levels compared with those from healthy individuals, resulting in increased NETosis, which can be prevented by an autophagy inhibitor, hydroxychloroquine, in vitro [201]. The above findings are also supported by a study on asthma in which peripheral blood neutrophils from severe asthma patients presented higher autophagy and NETosis levels than those from patients with nonsevere asthma [202], which could be exacerbated by treatment with IL-8 in vitro. A further mechanistic study revealed that the PI3K/AKT/mTOR pathway plays a crucial role in connecting autophagy and NETosis [203]. In combination with the pharmacological mTOR inhibitor rapamycin, the activation of autophagy can accelerate NETs release in neutrophils induced by formyl-Met-Leu-Phe or diphenyl phosphate as well as in promyelocytes induced by arsenic trioxide [204–206]. However, mTOR-dependent autophagy is not associated with aging-related spontaneous NETosis; in contrast, trehalose, an inducer of mTOR-independent autophagy, significantly increases the spontaneous release of NETs in neutrophils [207]. The underlying molecular mechanism is not completely clear, but selective autophagic degradation of various survival-maintenance proteins is considered to contribute to NETosis. Conditional deletion of Wdfy3, the master regulator of macroselective autophagy, which functions as a recognition and targeting cargo proteins for autophagic degradation, protects neutrophils from NETosis and alleviates IL-17A-mediated epidermal hyperplasia [208]. On the basis of the above conclusions, it is reasonable to regulate NETosis by manipulation of autophagy to achieve different clinical aims. For example, quercetin or hesperetin alleviates the aberrant formation of NETs by suppressing autophagy, which can provide alternative treatments for rheumatoid arthritis or sepsis-induced intestinal barrier injury, respectively [209, 210]. In contrast, the promotion of autophagosome formation by all-trans retinoic acid or arsenic trioxide mediates the NETosis of promyelocytes, providing new insights for the treatment of acute promyelocytic leukemia [199, 205] (Fig. 4B).

Autophagy-mediated pyroptosis

Pyroptosis was first described in 2000 as Caspase-1-dependent lytic programmed cell death initiated by inflammasomes in infected macrophages [211–213]. The morphological features of pyroptosis include membrane bubbling, mild swelling, and ultimately rupture, which leads to the release of cell contents and a subsequent inflammatory response [24, 213]. A recent study revealed that GSDMD is the effector of pyroptosis and forms

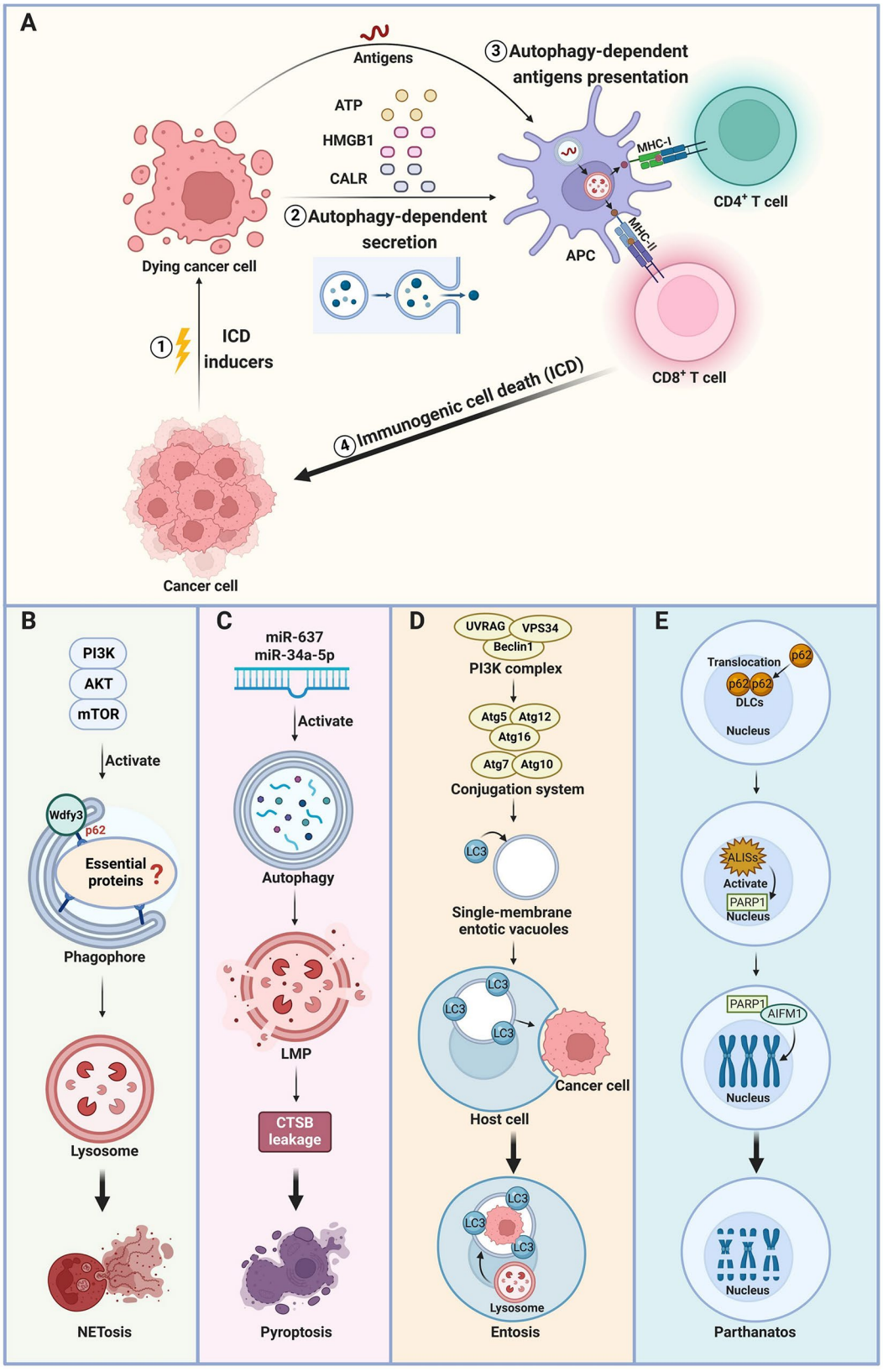

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Fig. 4 Autophagy-mediated other forms of RCD. **A** Autophagy-mediated ICD. ICD inducers initiate the autophagy-dependent secretion of DAMPs (ATP, HMGB1, and CALR) and the release of antigens by cancer cells. DAMPs induce the maturation and activation of APCs and the antigens are subsequently engulfed by APCs where they can be processed via the autophagic machinery for loading onto MHC-I or MHC-II. Then, MHC-I or MHC-II is presented to $CD4^+$ or $CD8^+$ T cells, respectively, after which activated T cells induce ICD in cancer cells. **B** Autophagy-mediated NETosis. The PI3K/AKT/mTOR signaling pathway activates Wdfy3-dependent selective autophagy, which mediates NETosis, but the essential protein has not yet been confirmed. **C** Autophagy-mediated pyroptosis. miR-637 and miR-34a-5p are involved in the activation of autophagy, which leads to LMP and subsequent CTSB leakage, causing NLRP3 inflammasome activation, GSDMD cleavage and ultimately pyroptosis. The abovementioned mechanism is shared in different cell or animal models. **D** Autophagy-mediated entosis. The PI3K complex consists of Beclin1, UVRAG, and VPS34, and activates the downstream autophagy conjugation system, which mediates the recruitment of LC3 into the single-membrane entotic vacuole. Then, the cells are internalized into neighboring host cells via the entotic vacuole and fuses with lysosomes, thus causing internalized cell entosis. **E** Autophagy-mediated parthanatos. When treating HT1080 cells with oxidative stress, the autophagy cargo receptor p62 translocates into the nucleus and forms disulfide-linked conjugates (DLCs). The DLCs further accumulates into p62-based aggresome-like induced structures (ALISs), which hyperactivate PARP1, and activated PARP1 directly binds to AIFM1, leading to its translocation from the mitochondria to the nucleus. Finally, AIFM1 induces parthanatos in the nucleus. This figure created in BioRender. Huang, X. (2025) https://BioRender.com/c37a934

pores in the membrane via its N-terminal domain after cleaved by Caspase-1/11, thereby allowing the secretion of proinflammatory factors, such as mature IL-1β, IL-18, HMGB1, etc [214]. Autophagy seems to serve as a protective process in pyroptosis because of the clearance of inflammasomes and excessively damaged mitochondria thus maintaining intracellular homeostasis during pyroptosis [215]. However, when apoptosis and necroptosis are blocked in $FADD^{-/-}$ $RIPK^{-/-}$ BMDMs or bone marrow-derived dendritic cells, Z-IETD-FMK (a Caspase-8 inhibitor) induces autophagy-mediated pyroptosis, in which cell death can be prevented by autophagy inhibition via 3-methyladenine treatment or genetic knockdown of *Atg5*. A further mechanistic study demonstrated that CTSB mediates inflammasome activation as well as Caspase-1/11 and GSDMD cleavage, thereby contributing to autophagy-dependent pyroptosis [216]. Moreover, in liver injury caused by different contributors (arsenic trioxide, patulin, elaidic acid, and benzo[a]pyrene), autophagy is considered to promote the initiation of pyroptosis by inducing lysosomal membrane permeabilization (LMP) and accompanying CTSB leakage, which results in the activation of the NLRP3 inflammasome and the upregulation of pyroptosis marker proteins in hepatocytes [217–220]. Notably, the autophagy-CTSB-NLRP3 inflammasome-pyroptosis axis can also affect hyperuric acid-mediated renal injury [221]. The regulation of autophagy in pyroptosis may be associated with noncoding RNAs: miR-637 and miR-34a-5p are reported to promote pyroptosis via autophagy in vascular endothelial cells and cardiomyocytes, respectively [222, 223]. Importantly, the activation of autophagy-mediated pyroptosis has potential for cancer treatment, as some natural compounds, including kaempferol, nobiletin and sesamin, have been shown to inhibit growth of glioblastoma, ovarian cancer, and lymphoma respectively via autophagy-mediated pyroptosis [224–226] (Fig. 4C).

Autophagy-mediated entosis

Entosis is a form of cell death involving the invasion of one cell into another and the formation of a cell-in-cell transient state, which was first described in 2005 by Overholtzer et al. [227, 228]. Entosis mostly occurs when epithelial tumor cells internalize into neighboring host cells in response to matrix detachment, glucose starvation, or mitotic stress, which may mediate the clearance of cancer cells [24]. Autophagy promotes lysosome fusion to single-membrane vacuoles, which results in the death of internalized cells. Further mechanistic research has demonstrated that the recruitment of LC3 to single-membrane entotic vacuoles, also called LC3-associated phagocytosis (LAP), is necessary for the execution of entosis. This process depends on the assembly of the class III PI3K complex, which is composed of Beclin-1, UVRAG, and VPS34, and is crucial for the activation of downstream autophagy conjugation systems. Instead, the ULK-Atg13-FIP200 complex, regulated by the early autophagy factor mTOR, is not involved in this process [229, 230]. Moreover, in the case of MCF10A cells phagocytized by neighboring cells or U937 cells phagocytized by J774 macrophages, genetic inhibition of autophagy by knocking down *ATG5* in host but not internalized cells prevents the recruitment of LC3 and partially protects internalized cells from entosis [229]. Interestingly, entosis is also positively regulated by AMPK when treating MCF-7, MDA-MB-231, and MCF-10 A cells with glucose starvation [231], which is similar to autophagy and indicates that autophagy and entosis may share the same mechanism (Fig. 4D).

Autophagy-mediated parthanatos

Parthanatos is a form of the RCD caused by hyperactivation of PARP1, which functions in the repair of DNA single-strand or double-strand breaks. Parthanatos was coined in 2009 to describe a novel mode of cell death in response to oxidative stress-induced DNA damage and chromatinolysis [24, 232]. Hyperactive PARP1 can directly bind to apoptosis-inducing factor mitochondria-associated 1 (AIFM1), which leads to the translocation of AIFM1 from mitochondria to the nucleus, causing parthanatotic chromatinolysis without the formation of apoptotic bodies or small DNA fragments [233, 234].

The autophagy cargo receptor p62 is reported to mediate cefotaxime- and H_2O_2-induced parthanatos in HT1080 cells by a mechanism involving the ability of the probe to respond to oxidative stress via the presence of oxidation-sensitive cysteines (Cys105 and Cys113) and the formation of p62 oligomers designated as disulfide-linked conjugates (DLCs) after cytoplasmic-nuclear shuttling via two nuclear localization signals. Further formation and accumulation of p62-based aggresome-like induced structures (ALISs) in the nucleus hyperactivates PARP1 and ultimately triggers parthanatos, which can be inhibited by *SQSTM1* knockout [235, 236] (Fig. 4E).

Conclusions

(1) We have explained and clarified the definition of autophagy-mediated cell death, in which autophagy does not merely accompany cell death but rather initiates death through multiple mechanisms. Moreover, autophagy-mediated cell death is the transformation from autophagy to different forms of RCD, which is distinguished from autosis.
(2) We describe research on the different forms of RCD mediated by autophagy, such as apoptosis, necroptosis, ferroptosis, etc., and summarize the underlying mechanism behind autophagy-mediated cell death.
(3) Selective degradation of important intracellular elements is considered the core machinery for the initiation of autophagy-mediated cell death, which determines cell death or survival depending on the cargo proteins or organelles. However, the upstream machinery that guides organisms to specifically degrade intracellular elements is unclear; notably, this process depends on the context and still needs to be elucidated.
(4) Autophagy-related machinery components are closely associated with the execution of autophagy-mediated cell death, the mechanism of which is usually not shared with the canonical autophagy process; therefore, this may constitute another watershed that divides cell fate into survival or RCD. However, the molecular mechanism by which these components drive the assembly of death-associated complexes is still highly obscure and deserves further investigation.
(5) We emphasize the deleterious facet of autophagy-mediated cell death in the progression of distinct pathologies, such as chronic obstructive pulmonary disease, acute kidney injury, acute pancreatitis, myocardial infarction, etc., and targeting autophagy seems to be a promising strategy for the treatment of these diseases. However, the mechanism of disease progression is complicated, and the role of autophagy can vary at different stages of a disease and among different cells, even within the same stage. Hence, there is still a long way to go before autophagy can be precisely manipulated for clinical disease treatment.
(7) We hope that future studies will aim to resolve the abovementioned questions and elucidate the network involved in the regulation of cell death by autophagy. Moreover, most studies referenced rely on experiments using cell lines treated with autophagy and/or cell death inhibitors, which may not accurately reflect the physiological and pathological mechanisms for autophagy involvement in cell death pathways. Additional in vivo models, which are more closely associated with physiological and pathological phenotypes, should be applied to the current field to facilitate the interpretation and manipulation of autophagy under both physiological and pathological conditions.

Abbreviations

RCD	Regulated cell death
CMA	Chaperone-mediated autophagy
LAMP2A	Lysosome-associated membrane protein type 2 A
Atg7	Autophagy-related protein 7
MEFs	Mouse embryonic fibroblasts
BMDMs	Murine bone marrow-derived macrophages
I/R	Ischemia-reperfusion
TFEB	Transcription factor EB
IFN	γ-Interferon-γ
ER	Endoplasmic reticulum
iDISC	Intracellular death-inducing signaling complex
Cav	1-Caveolin-1
Fap	1-Fas-associated phosphatase-1
IKKα	IkappaB kinase alpha
PUMA	p53 upregulated modulator of apoptosis
DRP	1-Dynamin-related protein 1
GSDMD	Gasdermin D
TRAIL	TNF-related apoptosis inducing ligand
H/R	Hypoxia-reoxygenation
ROS	Reactive oxygen species
m^6A	N6-methyladenosine
NCOA4	Nuclear receptor coactivator 4
GPX4	Glutathione peroxidase 4
AKI	Acute kidney injury
ATF4	Transcription factor 4
POMC	Cytosol-retained prohormone pro-opiomelanocortin
PRKCQ	Protein kinase C theta
sGRP78	Soluble glucose regulated protein 78
DHFR	Dihydrofolate reductase
ICD	Immunogenic cell death
APCs	Antigen-presenting cells
DAMPs	Damage-associated molecular patterns
DCs	Dendritic cells
TFE3	Transcription factor binding to IGHM enhancer 3
NETs	Neutrophil extracellular traps
LMP	Lysosomal membrane permeabilization
CTSB	Cathepsin B
LAP	LC3-associated phagocytosis
AIFM1	Apoptosis-inducing factor mitochondria-associated 1
DLCs	Designated disulphide-linked conjugates
ALISs	Aggresome-like induced structures

Author contributions

Conceptualization, X. H., P. L. and Q. H.; Original Draft Preparation, X. H., H. Y., P. L. and Q. H.; Visualization and figures, X. H., H. Y. and Z. X.; Supervision, B. Y., P. L. and Q. H. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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