Selective autophagy in hepatocellular carcinoma: Mechanisms, roles and therapeutic implications (Review)

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Abstract. Selective autophagy, which is the targeted degradation of specific cellular components through lysosomes, serves a complex role in hepatocellular carcinoma (HCC). The present review explores the following 10 distinct selective autophagy pathways in HCC: Mitophagy, lysophagy, reticulophagy, pexophagy, nucleophagy, ribophagy, lipophagy, glycophagy, ferritinophagy and fluidophagy. In HCC, mitophagy can support therapy resistance by clearing damaged mitochondria, whereas lysophagy maintains lysosomal homeostasis through receptor recycling, such as coiled-coil domain containing 50. Reticulophagy, mediated by family with sequence similarity 134 member B (FAM134B), protects HCC cells from ferroptosis during kinase inhibitor treatment. Ferritinophagy, driven by nuclear receptor coactivator 4, regulates iron availability and sensitivity to ferroptotic cell death. Lipophagy has dual functions, where it provides energy substrates for tumor survival whilst potentially suppressing tumor growth through BCL2-interacting protein 3-mediated mechanism in fatty livers. Altogether, these aforementioned pathways offer therapeutic opportunities through inhibition, activation or synthetic lethality approaches. Promising strategies include combining ferroptosis inducers with autophagy inhibitors, targeting specific receptors, (such as FAM134B) and modulating mitophagy regulators (such as dynamin-related protein 1). In addition, autophagy-related biomarkers (sequestosome 1, LC-3B and beclin-1) are associated with clinical outcomes and may guide patient stratification. Given the bidirectional nature of selective autophagy in HCC, personalized approaches based on tumor context, specific pathway dependencies and disease stage are essential for effective therapeutic intervention.

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Abbreviations: AMPK, AMP-activated protein kinase; BNIP3, BCL2 interacting protein 3; CCDC50, coiled-coil domain containing 50; CQ, chloroquine; DRP1, dynamin-related protein 1; ER, endoplasmic reticulum; FAM134B, family with sequence similarity 134 member B; HCC, hepatocellular carcinoma; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; PINK1, phosphatase and tensin homolog-induced kinase 1; PPT1, palmitoyl-protein thioesterase 1; PTBP1, polypyrimidine tract-binding protein 1; ROS, reactive oxygen species; SQSTM1, sequestosome 1 (p62); STBD1, starch-binding domain-containing protein 1

Key words: selective autophagy, hepatocellular carcinoma, ferritinophagy, mitophagy, therapeutic targeting

Contents

1. Introduction

Hepatocellular carcinoma (HCC) was the third leading cause of cancer-related mortality in 2020, with ~905,000 new cases and 830,000 deaths worldwide (1). The incidence remains the highest in East Asia and Africa, but is increasing in Western nations. In total, ~54% cases are caused by chronic hepatitis B infection, whereas 15% are caused by hepatitis C. Alcohol abuse, aflatoxin, non-alcoholic steatohepatitis and metabolic syndrome-related diabetes are also contributing factors (2,3). The male predominance (2-3:1) in hepatocellular carcinoma (HCC) suggests gender-specific differences in exposure to risk

factors like chronic viral infections and alcohol consumption, which may contribute to the higher incidence in men (2).

Autophagy is a cellular self-digestion process that serves to maintain homeostasis by degrading damaged organelles and macromolecules through the lysosomes. In cancer, autophagy serves complex, context-dependent roles, suppressing tumor initiation by removing harmful cellular components, but can also promote the survival of established tumors under stress (4,5). Starvation-induced non-selective macroautophagy randomly engulfs the cytoplasm and generates nutrients through indiscriminate lysosomal breakdown (5). Selective autophagy uses cargo receptors containing LC3-interacting regions, such as sequestosome 1 (p62), nuclear dot protein 52 kDa or nuclear receptor coactivator 4 (NCOA4), to bind ubiquitin-tagged substrates (such as damaged mitochondria, ferritin and aggregates) and recruit phagophores exclusively to them. This receptor-guided precision allows for organelle-specific quality control whilst minimizing biomass loss and can be adjusted independently of bulk autophagy (6,7). HCC frequently exhibits dysregulated autophagy (4,5). Selective autophagy involves the autophagic targeting of specific intracellular organelles or materials. Key forms of autophagy (Table I) include mitophagy (mitochondria) (8-11), lysophagy (lysosomes) (10,12), reticulophagy [endoplasmic reticulum (ER)] (9,13), pexophagy (peroxisomes) (14), nucleophagy (nucleus) (15), ribophagy (ribosomes) (16,17), lipophagy (lipid droplets) (11,17-19), glycophagy (glycogen) (19,20), ferritinophagy (ferritin/iron) (13,21) and fluidophagy (autophagy of phase-separated liquid condensates (18-22). Each of the aforementioned processes has been implicated in the pathogenesis and therapeutic response in HCC. Target regulators and therapeutic agents unique to each type of selective autophagy are shown in Fig. 1.

In this review work, PubMed and Google Scholar were searched for entries added between January 2015 and March 2025 with Boolean strings combining 'selective autophagy', 'hepatocellular carcinoma' and each pathway name (such as 'mitophagy' and 'ferritinophagy') for a narrative-review approach. In addition, the reference lists of the retrieved articles were hand-screened. The inclusion criteria were as follows: English-language primary data or systematic reviews detailing mechanisms, biomarkers or therapeutic manipulation of selective autophagy in HCC or liver models. The exclusion criteria were non-HCC cancers, conference abstracts without the full text, studies lacking mechanistic details and commentaries. Two authors independently screened titles/abstracts, and any disagreements were resolved by a third reviewer. Data on the pathway effectors, experimental design and translational relevance were extracted and tabulated to ensure consistency.

2. Mitophagy in HCC

Mitophagy is the selective autophagic removal of mitochondria that is critical for mitochondrial quality control. This is primarily mediated by the phosphatase and tensin homolog-induced kinase 1 (PINK1)/Parkin pathway, wherein PINK1 accumulates in depolarized mitochondria and recruits Parkin to tag the mitochondria for autophagy (23,24). In HCC, Parkin expression is frequently lost or reduced (downregulated in ~50% HCC tumors) (25). Previous studies have identified siah E3 ubiquitin protein ligase 1 (SIAH1) as a key Parkin substitute in HCC. Specifically, SIAH1 can cooperate with PINK1 to ubiquitinate mitochondrial proteins and initiate mitophagy (26,27).

Sorafenib-induced mitophagy serves as a cytoprotective mechanism, clearing drug-damaged mitochondria and preventing the excess accumulation of reactive oxygen species (ROS) (26). Sorafenib actively induces mitophagy as a defense mechanism against HCC, by inducing PINK1 accumulation and Parkin recruitment to damaged mitochondria, in turn activating mitophagy in HCC cells. Inhibition or silencing of PINK1 or SIAH1 has been found to suppress mitophagy and increase sorafenib-induced cell death, confirming their role as a cytoprotective component (28,29). In orthotopic Huh7 xenografts, combining sorafenib with the dynamin-related protein 1 (DRP1) inhibitor mdivi-1 (50 mg/kg) was observed to cut tumor volume by 63 vs. 41% for sorafenib monotherapy, indicating that blocking mitophagy can magnify sorafenib lethality (30). Consequently, HCC cells can survive more readily after sorafenib treatment when mitophagy remains intact. Although basal mitophagy can prevent liver tumor initiation by removing dysfunctional ROS-producing mitochondria in established HCC, it frequently promotes tumor cell metabolism and therapy resistance (5). Chemotherapy (such as cisplatin) has been reported to induce mitophagy in surviving HCC cells through DRP1-mediated mitochondrial fission (31). Inhibiting DRP1 with mdivi-1 can block this mitophagy and increase the apoptosis of cisplatin-treated HCC cells (31).

Excessive mitophagy activation has been explored as a therapeutic strategy for inducing HCC cell death (Table II). The iron chelator deferiprone triggers PINK1/Parkin-independent mitophagy in liver cells and slows HCC tumor growth in mice, presumably by forcing mitochondrial turnover and compromising tumor bioenergetics (8). Chronic hepatitis B virus infection, a major etiological factor of HCC, can influence mitophagy (32,33). Hepatitis B virus X protein has been shown to induce NIP3-like protein X-dependent mitophagy in liver cells, which reprograms metabolism towards glycolysis to enhance cancer stem cell properties (34).

In summary, mitophagy in HCC appears to have a dual role. It can either protect cells by clearing damaged mitochondria (limiting oxidative stress and cell death) or enable tumor survival under treatments, such as kinase inhibitors or chemotherapy (5,31). Therapeutically, mitophagy can be manipulated by inhibition (to prevent tumor cells from escaping apoptosis during therapy) or overactivation (to induce metabolic crisis in tumors) (8,31).

3. Lysophagy in HCC

Lysophagy is the selective removal of lysosomes damaged by autophagy. When lysosomal membranes are compromised, cells can target these leaky lysosomes for autophagic degradation to prevent the release of hydrolytic enzymes into the cytosol (9). The process involves damage recognition by cytosolic galectins (whereby galectin-3/8 binds to exposed luminal glycans on ruptured lysosomes) and the ubiquitination of lysosomal membrane proteins, followed by the recruitment of autophagy receptors (35,36).

Table I. Experimental findings in selective autophagy in HCC.

Autophagy type	Key experimental findings	(Refs.)
Mitophagy	• PINK1/Parkin inhibition leads to dysfunctional mitochondria and increased apoptosis	(8)
	• High mitophagy gene expression correlates with worse survival	(8)
	• Parkin-mediated mitophagy supports cancer stem cells and neutralizes p53	(8)
Lysophagy	• Sorafenib-resistant HCC cells rely on lysophagy; polyphyllin D disrupts this process, causing cell death	(12)
	• UBE2QL1 knockdown leads to damaged lysosome accumulation, sensitizing cells to lysosomal death	(12)
Reticulophagy	• Sorafenib activates FAM134B-mediated ER-phagy, protecting against ferroptosis	(34)
	• FAM134B knockdown enhances ferroptotic cell death	(9)
	• circFAM134B silencing enhances lenvatinib-induced ferroptosis	(34)
Pexophagy	• Oxidative stress triggers peroxisomal protein ubiquitination and p62/NBR1-mediated clearance	(14)
	• Blocking autophagy leads to dysfunctional peroxisome accumulation and DNA oxidation	(14)
	• HCC cells may use pexophagy to shift metabolism toward mitochondria	(14)
Nucleophagy	• Autophagy degrades micronuclear DNA via cGAS-LC3 interaction, reducing STING signaling	(15)
	• Autophagy inhibition increases cytosolic DNA and interferon signaling (15)	
	• cGAS-STING can trigger autophagy-dependent cell death under severe telomere damage (15)	
Ribophagy	• Nutrient starvation/mTORC1 inhibition relocates NUFIP1 to ribosomes, driving degradation	(17)
	• Blocking autophagy during nutrient deprivation reduces HCC cell survival	(17)
	• Ribophagy may help cells remove stalled ribosomes and adapt to stress	(17)
Lipophagy	• Autophagy dysfunction leads to lipid accumulation and HCC development	(18)
	• Blocking autophagy causes lipid droplet buildup and energy depletion	(19)
	• BNIP3-driven lipophagy restrains tumor growth; low BNIP3 yields lipid-rich tumors	(30)
Glycophagy	• STBD1/PTG loss sensitizes HCC cells to glucose withdrawal	(19)
	• Autophagy inhibition reduces glucose output during fasting	(20)
	• G6PC deficiency impairs glycophagy, leading to adenomas/HCC	(64)
Ferritinophagy	• NCOA4 releases iron from ferritin, enabling ferroptosis	(13)
	• NCOA4 overexpression increases labile iron and slows tumor growth	(49)
	• PTBP1 silencing upregulates NCOA4 and sensitizes tumors to sorafenib	(13)
Fluidophagy	• Optineurin/NDP52 form droplets on damaged mitochondria to facilitate clearance	(22)
	• p62 forms liquid droplets that sequester ubiquitinated proteins	(22)
	• In autophagy-deficient tumors, p62 aggregates activate NRF2, promoting tumorigenesis	(18)

AMPK, AMP-activated protein kinase; BNIP3, BCL2 interacting protein 3; CCDC50, coiled-coil domain containing 50; CQ, chloroquine; DRP1, dynamin-related protein 1; ER, endoplasmic reticulum; FAM134B, family with sequence similarity 134 member B; HCC, hepatocellular carcinoma; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; PINK1, phosphatase and tensin homolog-induced kinase 1; PPT1, palmitoyl-protein thioesterase 1; PTBP1, polypyrimidine tract-binding protein 1; ROS, reactive oxygen species; SQSTM1, sequestosome 1 (p62); STBD1, starch-binding domain-containing protein 1.

Recently, coiled-coil domain containing 50 (CCDC50) was identified as a dedicated lysophagy receptor in human melanoma cells (9). CCDC50 can bind to galectin-3-decorated K63-ubiquitinated lysosomes and facilitate their clearance through autophagy (9). In HCC, CCDC50 serves a tumor-promoting role by sustaining lysosomal homeostasis. It was previously shown that CCDC50 expression is upregulated in HCC tumors and cell lines, where its high expression associates with more aggressive tumor features and worse patient prognosis (9).

Functionally, CCDC50 loss led to the accumulation of broken lysosomes in HCC cells, impaired autophagic flux, elevated ROS levels and cell death (9). In mouse models, CCDC50 deficiency was found to significantly suppress HCC tumor growth, presumably due to the cytotoxic buildup of dysfunctional lysosomes and oxidative damage (9). Therapeutically, inhibiting lysophagy could harm cancer cells by allowing lysosomal damage to accumulate. Polyphyllin D has been observed to cause lysosomal membrane permeabilization in HCC cells, resulting in the loss of lysophagy and spillage of enzymes to trigger cell death (37). Lysosome-targeting agents, such as chloroquine or the palmitoyl-protein thioesterase 1 (PPT1) inhibitor GNS561, can effectively kill HCC cells by overwhelming the lysosomal system (38). GNS561 (ezurpimtrostat) showed potent anti-tumor activity in preclinical HCC models and has since entered clinical trials (39).

Overall, these aforementioned findings suggest that lysophagy allows HCC cells to maintain the functionality

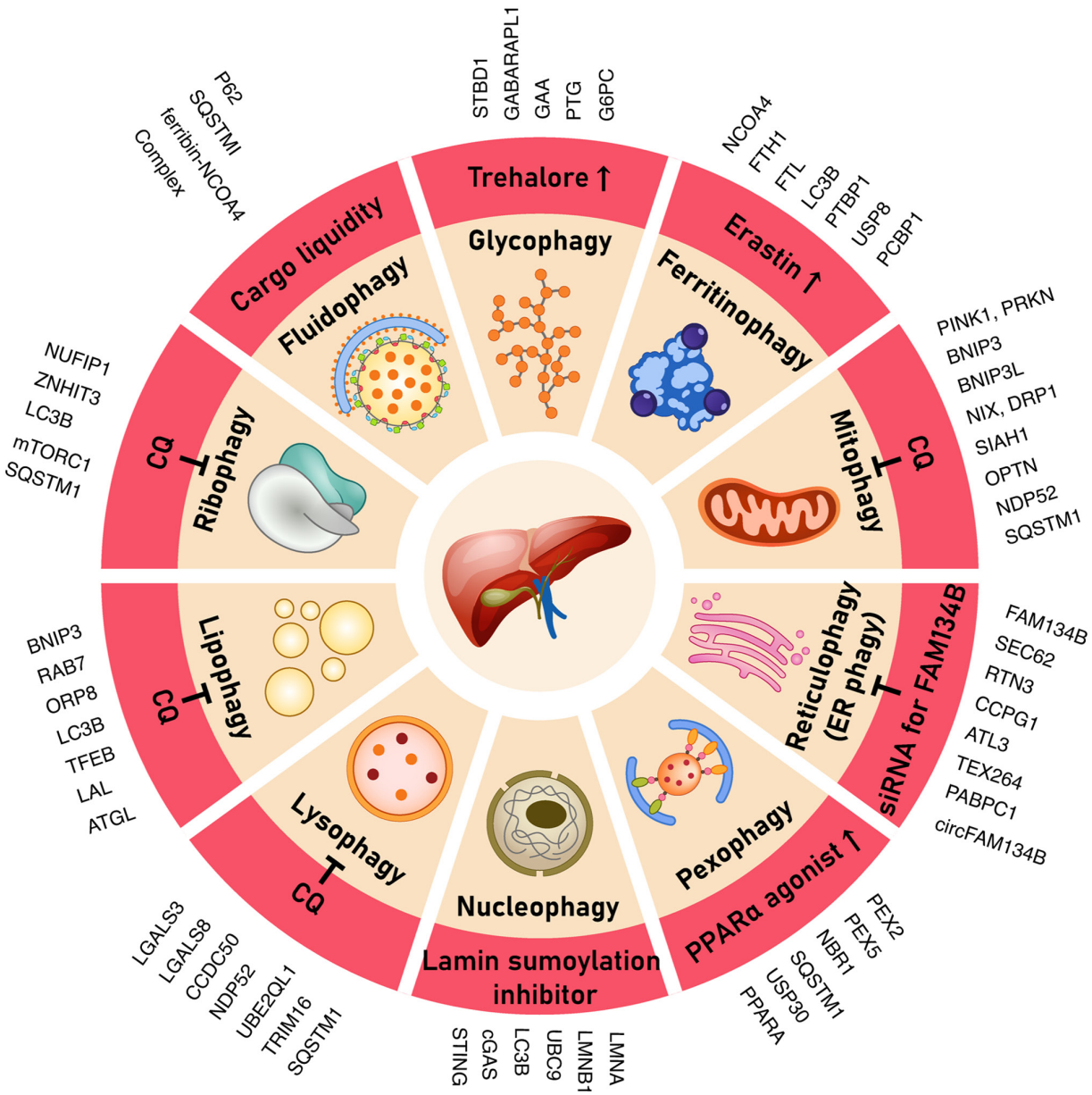

Figure 1. Target regulators and therapeutic agent unique to each selective autophagy type in hepatocellular carcinoma.

of their digestive organelles. Disruption of lysophagy (either genetically or with lysosomotropic drugs) will likely cause catastrophic lysosomal failure and tumor suppression (9,37).

4. Reticulophagy (ER-phagy) in HCC

Reticulophagy is the selective autophagic degradation of portions of the ER. Several ER-resident receptor proteins [family with sequence similarity 134 member B (FAM134B), SEC62 homolog, preprotein translocation factor (SEC62), reticulon 3 (RTN3) and cell cycle progression 1 (CCPG1)] can mediate reticulophagy by binding LC3/γ-aminobutyric acid receptor-associated protein (GABARAP), a type B autophagy-related gene 8 family protein receptor, to form autophagosomes and capture ER fragments (40). FAM134B is a critical ER-phagy receptor that binds to LC3 through a conserved LIR motif and selectively fragments the ER membrane for autophagic engulfment (40).

Sorafenib induces ER stress and activates FAM134B-dependent reticulophagy (41). Liu *et al* (41) reported that sorafenib can stimulate ER-phagy through FAM134B, potentially mitigating the cytotoxicity of sorafenib. FAM134B knockdown blocked ER-phagy and enhanced sorafenib-induced ferroptosis in HCC cells (40). Intact FAM134B-mediated reticulophagy was protective because it contains ER components, including misfolded proteins, calcium-overloaded ER fragments, and damaged ER membranes, along with oxidized lipids and proteins generating ROS, that contribute to oxidative stress and ferroptosis (40).

A recent study on the circular (circ)RNA of the FAM134B gene (circFAM134B) showed that this circRNA increases FAM134B expression and promotes ER-phagy, leading to the suppression of ferroptosis in HCC cells treated with lenvatinib. Silencing circFAM134B increased the sensitivity of HCC cells to Lenvatinib (40). From a therapeutic perspective, inhibiting FAM134B-mediated ER-phagy may be beneficial

Table II. Therapeutic strategies for selective autophagy in HCC.

Autophagy type	Therapeutic targets/strategies	Mechanism/rationale	(Refs.)
Mitophagy	• Parkin/PINK1 pathway inhibition	• Increases dysfunctional mitochondria, ROS and apoptosis	(8)
	• Chloroquine/Hydroxychloroquine	• Prevents autolysosome formation, increases mitochondrial ROS	(10)
	• AMPK activators (Metformin)	• Removes damaged mitochondria, reduces steatosis	(11)
	• BNIP3 upregulation	• Triggers excessive mitophagy and cell death	(9)
Lysophagy	• ASM inhibitors (Desipramine)	• Destabilizes lysosomes, mimicking polyphyllin D effects	(10,12)
	• Lysosomal BH3 mimetics (BMH-21)	• Activates autophagy to overwhelm lysosomes	(10)
	• TFEB activators (Trehalose)	• Increases lysosome biogenesis, generates autophagy trap	(10)
	• Lysosomal pH alkalinizers	• Impairs degradation, causing substrate accumulation	(10)
Reticulophagy	• FAM134B inhibition	• Enhances sorafenib-induced ferroptosis	(9)
	• PABPC1 inhibitors	• Reduces FAM134B translation and ER-phagy	(9)
	• Ferroptosis inducers + autophagy inhibitors	• Prevents ferroptosis mitigation via ER-phagy	(9)
Pexophagy	• USP30 inhibitors	• Increases peroxisome ubiquitination and clearance	(14)
	• ROS inducers + autophagy inhibitors	• Forces peroxisome damage accumulation	(14)
	• PPARα agonists + autophagy inhibitors	• Increases peroxisome load then blocks turnover	(14)
Nucleophagy	• STING agonists + autophagy inhibitors	• Amplifies innate immune activation by sustaining STING signals	(15)
	• Immune checkpoint inhibitors + autophagy inhibitors	• Promotes immunogenic cell death via DNA release	(15)
	• p53 reactivators + mTOR inhibitors	• Induces death in genomically unstable cells	(15)
Ribophagy	• mTORC1 inhibitors	• Induces autophagy including ribophagy	(16)
	• Dual PI3K/mTOR inhibitors + autophagy blockers	• Traps non-functional ribosomes in autophagosomes	(16)
	• NUFIP1/ZNHITE3 disruptors	• Prevents ribosome clearance during stress	(17)
Lipophagy	• Autophagy inhibitors in NAFLD-HCC	• Blocks fat mobilization, causing energy deficit	(17-19)
	• AMPK activators + autophagy inhibitors	• Creates autophagy trap during peak lipid mobilization	(11)
	• DGAT1/2 inhibitors + autophagy blockers	• Prevents triglyceride formation, increasing toxic free fatty acids	(11)
Glycophagy	• Glycogen phosphorylase inhibitors + autophagy blockers	• Redirects to lysosomal route then blocks it, causing energy crisis	(19)
	• STBD1 stabilizers	• Increases glycogen autophagy beyond handling capacity	(19)
	• Glucose restriction/SGLT2 inhibitors	• Forces tumors to consume internal glycogen	(19,20)
Ferritinophagy/ Ferroptosis	• NCOA4 upregulation	• Increases iron release from ferritin	(13)
	• Ferroptosis inducers	• Promotes iron-dependent lipid peroxidation	(13)
	• Iron mobilizers	• Primes cells for ferroptosis	(13,21)

AMPK, AMP-activated protein kinase; ASM, acid sphingomyelinase; BNIP3, BCL2 interacting protein 3; DGAT1/2, diacylglycerol O-acyltransferase 1/2; HCC, hepatocellular carcinoma; mTORC1, mechanistic target of rapamycin complex 1; NAFLD, non-alcoholic fatty liver disease; NUFIP1, nuclear FMR1 interacting protein 1; PABPC1, poly(A) binding protein cytoplasmic 1; PI3K, phosphatidylinositol 3-kinase; PINK1, phosphatase and tensin homolog-induced kinase 1; PPARα, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; SGLT2, sodium-glucose cotransporter 2; STBD1, starch-binding domain-containing protein 1; STING, stimulator of interferon genes; TFEB, transcription factor EB; USP30, ubiquitin specific peptidase 30; ZNHITE3, zinc finger HIT domain-containing protein 3.

by eliminating ferroptosis in tyrosine kinase inhibitor-treated tumors (40). This hypothesis is based on the observation that FAM134B knockdown potentiated sorafenib and lenvatinib lethality in preclinical models (40).

5. Pexophagy in HCC

Pexophagy is the selective autophagic degradation of peroxisomes. Peroxisomes are vital organelles involved in lipid metabolism, ROS detoxification, biosynthesis of bile acids and plasmalogens (42). Quality control of peroxisomes is essential because dysfunctional peroxisomes can produce excessive ROS and toxic byproducts. Pexophagy removes surplus or damaged peroxisomes to maintain the cellular redox balance (5).

Pexophagy malfunction leads to peroxisomal accumulation, which is associated with oxidative stress and inflammation in the liver (43). In catalase-knockout mice, extended fasting triggered excessive pexophagy and hepatocyte cell death (44). This suggests that under conditions of high oxidative stress burden, pexophagy may be activated to the point of cell death, a mechanism potentially relevant in chronic liver disease and HCC development (5).

To the best of our knowledge, direct studies of pexophagy in HCC are sparse. However, analyses of HCC tissues have revealed the dysregulation of peroxisomal proteins and redox imbalance, which could be partly due to altered pexophagic activity (5). Pexophagy in HCC remains underexplored therapeutically. Peroxisome proliferator-activated receptor-α agonists (such as clofibrate) can induce peroxisome proliferation and subsequent pexophagy in the liver, such that they trigger pexophagy in fatty liver contexts (45). Another approach is to target autophagy adapters, such as neighbor of BRCA1 gene 1 protein which, along with p62, can act as receptors for ubiquitinated peroxisomes to enhance the efficiency of pexophagy (46).

6. Nucleophagy in HCC

Nucleophagy is the selective autophagic degradation of nuclear material. In mammalian cells, nucleophagy is less common but has been observed during senescence and after DNA damage (21). One key mechanism described in cancer cells is DNA damage-induced nucleophagy through lamin tagging (21). Nucleophagy excises and degrades damaged nuclear constituents when chromatin breaks or lamin scaffolds become irreparable. During this process, SUMO-modified lamin A/C binds to LC3, allowing autophagosomes to sequester micronuclei or ruptured envelope fragments for lysosomal digestion (47). In hepatocytes, inhibiting lamin A/C SUMOylation increases γ-H2AX foci and micronuclei, reflecting elevated DNA damage. Activation of nucleophagy mitigates this damage by removing damaged nuclear components, thereby preserving genome stability. However, this protective process may allow tumor cells to survive genotoxic stress. Cells do not necessarily die immediately, because nucleophagy selectively engulfs and digests damaged nuclear material, maintaining nuclear integrity and cellular viability despite persistent DNA lesions. Consequently, nucleophagy functions as a double-edged sword, limiting DNA-damage signaling while potentially promoting tumor cell survival (21).

Li *et al* (21) demonstrated that when DNA damage causes small fragments of DNA to leak from the nucleus, the cell responds by SUMOylating nuclear lamin A/C through the E2 enzyme ubiquitin-conjugating enzyme E2 I. SUMOylation creates a signal that recruits LC3, effectively bridging the nuclear lamina to the autophagosome (21). In the context of HCC, direct evidence of nucleophagy is limited. However, the liver tumor environment such as DNA-damaging chemotherapeutic agents, metabolic stress or lamina deformations, trigger nucleophagy in HCC. HCC cells are frequently exposed to genotoxic stress, which can result in double-stranded DNA breaks and micronucleus formation (21,47).

From a therapeutic standpoint, targeting nucleophagy is challenging because it is not well defined and can harm normal cells. One potential angle is that inhibiting SUMOylation can block nucleophagy and perhaps make HCC cells more prone to accumulating nuclear damage, leading to cell death.

7. Ribophagy in HCC

Ribophagy involves the selective autophagic degradation of ribosomes. During nutrient starvation, cells degrade their ribosomes to recycle amino acids and nucleotides (48). Autophagy-dependent degradation of ribosomal RNA has been shown to be crucial for maintaining nucleotide pools during development (13). During metabolic stress, ribophagy dismantles superfluous or stalled ribosomes to recycle nucleotides and amino acids. Starvation or mTOR1 inhibition drives nuclear FMR1-interacting protein 1 (NUFIP1) from the nucleoplasm to the 60S subunits, where its LC3-interacting region, aided by zinc finger HIT domain-containing protein 3, targets ribosomes to autophagosomes, whereas concurrent p62 recruitment clears ubiquitinated ribosomal proteins (49). Suppressing NUFIP1 in nutrient-deprived HCC cells heightens proteotoxic stress, ATP depletion and apoptosis, underscoring the role of ribophagy in balancing translation load and energy supply (49). Direct studies on the role of ribophagy in HCC are lacking. However, given that solid tumors frequently experience nutrient-poor and hypoxic microenvironments, it is conceivable that HCC cells can invoke ribophagy as an adaptive mechanism. A study has previously shown that blocking late-stage autophagy with chloroquine similarly impaired ribophagic recycling in HCC cells (22). From a functional standpoint, ribophagy in HCC could contribute to therapy resistance, where when exposed to metabolic stress (such as glycolysis inhibitors or anti-angiogenic therapy), HCC cells may digest ribosomes and survive longer.

8. Lipophagy in HCC

Lipophagy is the autophagic degradation of lipid droplets. In liver cells, lipophagy is crucial for mobilizing stored triglycerides and cholesterol esters, delivering them to lysosomes where lipases break them down to free fatty acids (50). This process is central to energy homeostasis. In the context of liver disease and HCC, lipophagy has significant implications in counteracting lipid accumulation (51).

In HCC tumors, lipophagy appears to have a context-dependent role. Cancer cells can use lipophagy to tap into lipid droplet reserves to meet energy demands (4). During starvation or therapy-induced nutrient stress, HCC cells can upregulate factors, such as CCAAT/enhancer binding protein α, enhancing lipophagy to release fatty acids from lipid droplets to sustain ATP production (4).

Conversely, lipophagy can act as a tumor-suppressive mechanism by preventing excessive lipid accumulation

and lipotoxicity. Preventing lipotoxicity suppresses tumors because BCL2-interacting protein 3 (BNIP3)-mediated lipophagy tethers lipid droplets to autophagosomes, ensuring their degradation. By clearing excess lipids, this process avoids lipid-driven energy supply and toxic lipid accumulation, restraining tumor growth. Loss of BNIP3 leads to lipid-rich tumors and poorer survival, underscoring lipophagy's tumor-suppressive role. Chen *et al* (34) previously showed that BNIP3 can tether lipid droplets to autophagosomes through LC3 binding in a process termed 'mitolipophagy', which restrained HCC development. In a genetic HCC mouse model, loss of BNIP3 led to the earlier development of larger tumors that contained markedly more lipid droplets (51).

In human HCC specimens, low BNIP3 expression has been associated with higher lipid content in tumors and poor patient survival (51). These findings indicate that insufficient lipophagy (at least in part due to BNIP3 inactivation) can promote HCC progression by allowing lipids to accumulate and fuel tumor growth (51). Therapeutically, there are two potential strategies: Inhibition of lipophagy to starve HCC cells or enhancement of lipophagy to induce lipotoxic stress in tumors. It has been previously demonstrated that combining an autophagy inhibitor (e.g., chloroquine or its analog hydroxychloroquine) with a metabolic stressor increased lipid accumulation and cell death in HCC (22,38).

9. Glycophagy in HCC

Glycophagy is the selective autophagy of glycogen. The liver is the main storage site for glycogen, where in addition to canonical cytosolic glycogenolysis, hepatocytes possess a lysosomal route to degrade glycogen. This pathway is mediated by starch-binding domain-containing protein 1, which binds glycogen and recruits it to the autophagosome by interacting with γ-aminobutyric acid receptor-associated protein-like 1 (52). Inside lysosomes, glycogen is broken down by acid α-glucosidase (52).

In HCC, the role of glycophagy is not well characterized but is likely relevant, given that numerous HCC cells exhibit metabolic flexibility and the ability to store glucose as glycogen (53). HCC cells may invoke glycophagy when extracellular glucose is scarce. During transarterial embolization therapy, which induces acute nutrient starvation in the tumor region, cancer cells can survive by consuming their glycogen through autophagy (53). Previous studies have shown that depriving HCC cells of glucose triggers autophagy activation (26,53). Therapeutically, targeting glycophagy is challenging. A conceivable approach during transarterial embolization or fasting-mimicking diet therapy for HCC is to add an agent that stimulates glycophagy to rapidly deplete tumor glycogen, thereby rendering the nutrient cut-off more lethal to cancer cells.

10. Ferritinophagy in HCC

Ferritinophagy is the selective autophagy of ferritin, a cellular iron storage complex. This process is mainly mediated by the cargo receptor NCOA4, which binds to ferritin and delivers it to autophagosomes (54). Through ferritinophagy, iron stored in ferritin can be released upon lysosomal degradation, increasing the labile iron pool within the cell (54). Ferritinophagy links autophagy to iron homeostasis and ferroptosis, which is a form of cell death caused by iron-dependent lipid peroxidation.

Aberrant iron metabolism is common in HCC. Previous studies have indicated that ferritinophagy serves a role in HCC cell death and survival (10,55). The induction of ferritinophagy can kill HCC cells by ferroptosis. NCOA4 mediates ferritinophagy, targeting ferritin for lysosomal degradation to release stored iron. This NCOA4-driven iron liberation expands the cellular labile iron pool, providing redox-active Fe^{2+} that catalyzes ROS generation through Fenton chemistry (56). The resulting oxidative stress triggers the peroxidation of polyunsaturated fatty acids in membranes, which is a hallmark of ferroptosis (10). Mechanistically, NCOA4-mediated ferritinophagy sensitizes cells to ferroptosis by elevating catalytic iron and accelerating lethal lipid peroxide accumulation. Consistently, inducing ferritinophagy (such as by caryophyllene oxide) increases free Fe^{2+} and malondialdehyde levels (a lipid peroxidation product), whereas NCOA4 knockdown or interfering with NCOA4-ferritin binding prevents iron release and protects cells from ferroptotic damage (42). In addition, suppression of NCOA4 or its regulator, polypyrimidine tract-binding protein 1 (PTBP1), can reduce the labile iron pool and lipid peroxidation, blunting ferroptotic death (43). Therefore, NCOA4-driven ferritinophagic iron release is a pivotal trigger of ferroptosis through labile iron accumulation and subsequent ROS-mediated lipid peroxidation. In an *in vitro* study, caryophyllene-oxide treatment (20 μM; 6 h) doubled the extent of NCOA4-ferritin co-localization in Hep3B cells, raised calcein-quenchable Fe^{2+} by 42% and increased malondialdehyde by 2.5X. By contrast, NCOA4 knockdown abolished iron release and rescued 60% cells from cell death (54).

Another study by Yang *et al* (57) identified a pathway involving PTBP1 that can regulate ferritinophagy and ferroptosis in HCC. Specifically, PTBP1 can bind to NCOA4 mRNA to enhance its translation, where the knocking down PTBP1 expression in sorafenib-treated HCC cells led to lower NCOA4 levels, reducing free iron and malondialdehyde levels whilst increasing glutathione levels, suppressing ferroptosis (57). Simultaneously, PTBP1 depletion lowered NCOA4 by 48 %, shrank the labile iron pool by 35 % and suppressed erastin-induced ferroptosis in MHCC-97H xenografts (57). However, ferritinophagy may also help HCC cells survive under certain conditions by providing iron for essential enzymes. A recent report on pancreatic cancer has shown that NCOA4-mediated ferritinophagy is required for tumor growth by supplying iron to the proliferating cells (58).

Induction of excessive ferritinophagy appears to be a promising therapeutic approach for HCC, essentially pushing cells into ferroptosis, which is a lethal oxidative form of cell death that cancer cells cannot easily reverse. Various compounds, such as artesunate, sorafenib and caryophyllene oxide, can induce ferroptosis, at least partly by increasing free iron levels either through ferritinophagy or direct iron import (54).

11. Fluidophagy in HCC

Fluidophagy is a relatively novel term, describing the autophagic degradation of fluid-like, phase-separated

intracellular condensates (59). Cells contain numerous non-membrane-bound organelles that behave as liquid droplets. A number of biophysical studies have previously shown that the 'wetting' properties of droplets on autophagosome membranes are crucial (60-62). This process of droplet autophagy has been named 'fluidophagy' (59,63). At present, fluidophagy is a mechanistic insight into selective autophagy, rather than a distinct pathway with unique regulators.

For HCC, the biophysical state of the cargo (solid aggregates vs. liquid droplets) can affect autophagic clearance. In particular, the NCOA4-ferritin complex, which can form liquid condensates in the cytosol, helps concentrate ferritin into such droplets, which are then autophagically consumed (63). In addition, the autophagic degradation of p62/sequestosome 1 (SQSTM1) bodies is another possible example of fluidophagy (59).

In HCC, fluidophagy likely underlies the removal of certain protein aggregates or storage complexes from the cells. HCC cells frequently accumulate aggregates of p62 and ubiquitinated proteins (p62 is commonly elevated in HCC and is used as a marker of autophagic flux) (11).

12. Therapeutic targeting

Dysregulated selective autophagy contributes to HCC progression and resistance to therapy, making the components of these pathways attractive therapeutic targets. Strategies to modulate autophagy in cancer are two-fold: Inhibition (to prevent tumor cells from recycling organelles and evading death) and activation (to drive cancer cells into lethal self-digestion).

Inhibiting pro-survival autophagy. HCC has been a prime candidate for autophagy inhibition trials. Chloroquine (CQ) and hydroxychloroquine, which inhibit lysosomal acidification and late-stage autophagy, have been tested in preclinical HCC models and in early clinical studies (38,39). Combining CQ with chemotherapeutic oxaliplatin led to more pronounced tumor suppression in HCC xenografts compared with chemotherapy alone (38). Newer lysosome-targeted agents, such as GNS561, show even greater potency. GNS561, a PPT1 inhibitor, accumulates in the lysosomes and blocks autophagy at a late stage, causing cancer cell death (12). In HCC models, GNS561 not only killed bulk tumor cells but was also active against cancer stem cell populations (56). One previous clinical trial tested hydroxychloroquine with the mTOR inhibitor everolimus in HCC according to the 'simultaneous activation and blockade' strategy, with disease control reaching 67% (with 6% partial responses) and 45% of patients had ≥6-month progression-free survival (14). Additionally, nutrient modulation, such as ketogenic or fasting-mimicking diet to induce autophagy in tumors, followed by autophagy inhibitor administration, is another reported experimental approach aiming to catch cancer cells in a vulnerable state ('autophagy trap') (15).

Targeting specific autophagy pathways. A more tailored approach is to target regulators unique to the selective autophagy types on which HCC depends. The role of DRP1 in mitophagy in HCC has been proposed. DRP1-driven mitophagy allows HCC cells to survive chemotherapy, since inhibiting DRP1 with mdivi-1 was found to sensitize tumors to cisplatin in mice (31). Another proposed lysophagy target is CCDC50. Since CCDC50 knockdown causes HCC cell death and tumor suppression by blocking lysophagy (9), a drug that inhibits CCDC50 may mimic this tumor-suppressive effect. In the ER-phagy arena, FAM134B and its regulator circFAM134B are potential targets to enhance ferroptosis in tumors resistant to tyrosine kinase inhibitors. An antisense oligonucleotide against circFAM134B was found to decrease FAM134B levels, impairing ER-phagy and promoting lenvatinib-induced ferroptosis (40). For lipophagy, one approach is to restore BNIP3 function in HCC. BNIP3 is frequently silenced epigenetically in cancers. Therefore, demethylating the BNIP3 promoter or delivering BNIP3 by gene therapy may reinstate autophagic clearance of lipid droplets, potentially slowing tumor growth in steatotic HCC (51).

Exploiting ferritinophagy and ferroptosis. This is a promising novel direction. Ferroptosis inducers (including sorafenib, sulfasalazine or experimental agents, such as erastin and RSL3) can be combined with strategies to increase ferritinophagy. Furthermore, various drugs, such as caryophyllene oxide, may upregulate NCOA4 and drive ferritinophagy, since they have shown efficacy in HCC models (54).

Precision considerations. Whether a given autophagy process is inhibited or induced depends on the tumor context. Early-stage, well-differentiated HCC may be more vulnerable to autophagy induction to trigger cell death, whereas late-stage, therapy-resistant HCC may require autophagy inhibition to remove its survival crutch (4,5). Biomarkers are being investigated: For instance, a 'mitophagy gene signature' stratifies patients with HCC and correlates with immune microenvironment differences (16). The mitophagy gene signature is an eight-gene score derived from core mitophagy regulators (e.g., optineurin and ATG12). By calculating a composite expression score and splitting at the median, it divides patients with HCC into high-risk and low-risk groups for survival. High scores indicate aggressive disease and are associated with immunosuppressive tumour microenvironments-characterised by increased infiltration of certain immune cells (B cells, CD4/8 T cells, dendritic cells, NK cells and macrophages) and altered cytokine gene expression. Thus, the signature not only predicts prognosis but also reflects differences in immune cell infiltration patterns (16).

13. Biomarkers of autophagy in HCC

Several autophagy-related biomarkers have been documented to serve prognostic and predictive values for HCC (Table III).

p62/SQSTM1. p62/SQSTM1 frequently accumulates in HCC cells with defective autophagy. High p62 levels are associated with larger tumor size, venous invasion and poorer overall survival (17). In addition, p62 can serve as an oncoprotein through nuclear factor erythroid 2-related factor 2 activation (18).

LC3B. Increased LC3B expression is associated with increased differentiation and smaller tumor size. A meta-analysis has previously indicated that positive LC3B immunostaining predicts longer survival in patients with HCC (19).

Table III. Autophagy-related biomarkers in HCC.

Biomarker	Clinical findings	(Refs.)
p62/SQSTM1	• Accumulates in autophagy-defective HCC • High levels associate with larger tumors, venous invasion and poor survival • Acts as oncoprotein through NRF2 activation	(18,65,66)
LC3B	• Increased expression associates with superior differentiation and smaller tumors • Positive staining predicts longer survival • Context-dependent: Sometimes indicates high autophagic flux in advanced HCC	(16,67)
Beclin-1	• Frequently downregulated in HCC (17q loss or low transcription) • Preserved expression associates with favorable OS and DFS • Low levels associate with poor differentiation and vascular invasion	(68-70)
BNIP3	• Frequently silenced in HCC, especially in fatty liver-associated cases • Low expression associates with high lipid content and worse prognosis • Higher expression associated with lower microvascular invasion	(44)
NCOA4	• Emerging biomarker with higher expression in some HCC tissues • May predict response to ferroptosis-inducing therapy • Prognostic value unclear; correlation with iron load needed	(13,49)
p62/LC3 ratio	• High p62/low LC3 indicates autophagy-deficient tumors with poor RFS • Low p62/high LC3 associated with less aggressive tumors • Dual staining used to gauge autophagy flux	(66,67)
Autophagy gene signatures	• 8-gene mitophagy score (such as optineurin and ATG12) stratifies HCC prognosis • Multiple predictive signatures (6-13 genes) correlate with outcomes • High autophagy gene expression indicates aggressive disease	(72,74)
Immune-autophagy markers	• High LC3 in surrounding tissue but low in tumor correlates with recurrence • Circulating HMGB1 may predict immunotherapy response • Links autophagy status to tumor microenvironment	(10,15)

ATG12, autophagy related 12; BNIP3, BCL2 interacting protein 3; DFS, disease-free survival; HCC, hepatocellular carcinoma; HMGB1, high mobility group box 1; LC3B, microtubule-associated protein 1A/1B-light chain 3B; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; OS, overall survival; RFS, recurrence-free survival; SQSTM1, sequestosome 1.

Beclin-1. This protein is downregulated in HCCs due to the monoallelic loss of 17q or low transcription. Patients with preserved Beclin-1 expression tend to have a more favorable overall survival and disease-free survival (20).

BNIP3. It is frequently silenced or have its expression reduced in HCC, particularly in fatty liver-associated HCC. Low BNIP3 expression is associated with high intracellular lipid levels and poor prognosis (51).

NCOA4. Initial data have suggested higher NCOA4 mRNA levels in HCC tissues compared with those in adjacent tissues. It has been hypothesized that NCOA4-high tumors respond with superior efficacy to ferroptosis-inducing therapies (51).

p62/LC3 ratio. The combination of high p62 and low LC3 levels in HCC tumor tissues indicates autophagy-deficient tumors, which are associated with shorter recurrence-free survival (64).

Autophagy gene signatures. Several prognostic signatures using autophagy-related genes have been developed to predict recurrence and overall survival (65). An eight-gene mitophagy score containing optineurin, ATG12 and related genes that stratifies patients into high- and low-risk groups and a series of predictive signatures using 6-13 autophagy genes or gene pairs (e.g., LC3B/p62/BNIP3). These signatures correlate with recurrence or overall survival, and higher autophagy-gene expression generally signifies more aggressive disease (65).

14. Clinical implications and future directions

Understanding selective autophagy in HCC has important clinical implications because HCC cells frequently co-opt organelle-specific recycling to survive hypoxia, metabolic stress and chemotherapy (51,66). The autophagy status may serve as a stratification tool to identify patients who can benefit from autophagy modulation. Tumors with high autophagic flux may be more vulnerable to autophagy inhibition, whereas those with impaired autophagy may benefit from strategies that overcome their compromised degradation systems. Furthermore, late-stage agents, such as hydroxychloroquine or the lysosomotropic inhibitor GNS561, can be used to exploit this vulnerability by arresting lysophagy and bulk flux. GNS561 was found to achieve durable disease control in a previous phase I clinical study and is advancing to phase II (30). Targeted inhibition of pro-survival mitophagy may enhance drug efficacy. Mdivi-1, genetic PINK1 or PRKN (the

Parkin gene) knockdown was found to boost sorafenib-induced apoptosis by >30 % in xenografts (67).

Conversely, activating death-linked pathways is equally promising. Agents that stimulate NCOA4-dependent ferritinophagy (such as caryophyllene oxide) can enlarge the labile-iron pool, intensifying lipid peroxidation to synergize with ferroptosis inducers, achieving tumor shrinkage without added systemic toxicity (54,68). ER-phagy modulation offers precision, where circFAM134B silencing can disable reticulophagy, magnifying lenvatinib-triggered ferroptosis in resistant HCC models (40). Finally, autophagy gene signatures (LC3B, p62 and BNIP3) are emerging prognostic tools for stratifying patients according to combination regimens (69). Collectively, these data support a future in which pathway-specific autophagy modulators, paired with existing systemic or locoregional therapies can be used to drive personalized HCC management whilst sparing normal hepatocytes (70,71).

The concept of 'synthetic lethality' is particularly relevant, identifying genetic or metabolic vulnerabilities in HCC that, when coupled with autophagy manipulation, can lead to tumor cell death (53,55,72,73). HCC tumors with BNIP3 deficiency (and thus impaired mitophagy/lipophagy) may be particularly sensitive to treatments that increase lipid or oxidative stress (41,51,74).

Future directions in this field include the following: i) Development of selective autophagy inhibitors, moving beyond chloroquine to more targeted agents against specific autophagy receptors or regulators (4); ii) biomarker-guided therapy, where autophagy signatures can be used to guide treatment decisions (such as which patients should receive autophagy inhibitors in addition to conventional therapy) (75); iii) Combined metabolic and autophagic targeting, by exploiting the dependence of HCC on autophagy for metabolic adaptation by simultaneously targeting metabolic pathways and autophagy (76); iv) local delivery technologies, by developing liver-targeted delivery systems for autophagy modulators to minimize systemic effects (77); and v) integration with immunotherapy, by understanding how selective autophagy influences tumor immune microenvironments and exploring combinations with immune checkpoint inhibitors (78).

15. Limitations of the review

The present narrative review has several limitations that readers should consider. No formal systematic review methodology with structured database queries or predefined inclusion/exclusion criteria was applied, which introduced potential selection bias in the literature citations. Given the breadth of the field, certain relevant studies may have been inadvertently omitted, particularly since the primary focus was on English-language publications in common databases, such as PubMed. In addition, research on certain selective autophagy pathways in HCC, such as nucleophagy and ribophagy, is limited, requiring analogies to be drawn from other contexts or rely on preliminary data. the majority of the evidence discussed is also only preclinical, derived from cell lines or animal models rather than from clinical trials. Although ongoing trials were mentioned, the proposed therapeutic strategies using autophagy modulators lack proven clinical efficacy for HCC treatment. These limitations establish appropriate interpretive boundaries, ensuring the scope of the present review is within the current preclinical landscape whilst highlighting areas that require further investigation.

16. Conclusion

The selective autophagy pathways in HCC are emerging as druggable nodes. By understanding whether a given type of autophagy supports or hinders tumor growth, interventions can be designed to tip the balance against cancer. The complexity of autophagy in HCC highlights the need for personalized approaches. Some tumors rely on specific autophagy pathways for survival, whereas others may be suppressed by the same pathways. Therefore, characterizing the autophagy dependence of individual tumors is crucial for effective therapeutic interventions. The bidirectional nature of autophagy, both tumor-promoting and tumor-suppressing, necessitates careful consideration of the context, timing and specific pathways when designing therapeutic strategies. As understanding deepens, selective autophagy modulation promises to become an important component of personalized HCC treatment. As research progresses, a promising approach may be to first stress cancer cells with conventional treatments and then disable their selective autophagy defenses, thereby driving them into irrecoverable failure.

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Competing interests

The author declares that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J and Finn RS: Hepatocellular carcinoma. Nat Rev Dis Primers 7: 6, 2021.
3. Ker CG: Hepatobiliary surgery in Taiwan: The past, present, and future. Part I; biliary surgery. Formosan J Surg 57: 1-10, 2024.
4. Alim Al-Bari A, Ito Y, Thomes PG, Menon MB, García-Macia M, Fadel R, Stadlin A, Peake N, Faris ME, Eid N and Klionsky DJ: Emerging mechanistic insights of selective autophagy in hepatic diseases. Front Pharmacol 14: 1149809, 2023.
5. Nguyen TH, Nguyen TM, Ngoc DTM, You T, Park MK and Lee CH: Unraveling the janus-faced role of autophagy in hepatocellular carcinoma: Implications for therapeutic interventions. Int J Mol Sci 24: 16255, 2023.
6. Klionsky DJ, Abdel-Aziz AK, Abdelfatah S, Abdellatif M, Abdoli A, Abel S, Abeliovich H, Abildgaard MH, Abud YP, Acevedo-Arozena A, *et al*: Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). Autophagy 17: 1-382, 2021.
7. Vainshtein A and Grumati P: Selective autophagy by close encounters of the ubiquitin kind. Cells 9: 2349, 2020.
8. Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, Cookson MR and Youle RJ: PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol 8: e1000298, 2010.
9. Youle RJ and Narendra DP: Mechanisms of mitophagy. Nat Rev Mol Cell Biol 12: 9-14, 2011.
10. Wang F, Denison S, Lai JP, Philips LA, Montoya D, Kock N, Schüle B, Klein C, Shridhar V, Roberts LR and Smith DI: Parkin gene alterations in hepatocellular carcinoma. Genes Chromosomes Cancer 40: 85-96, 2004.
11. Feng J, Zhou J, Wu Y, Shen HM, Peng T and Lu GD: Targeting mitophagy as a novel therapeutic approach in liver cancer. Autophagy 19: 2164-2165, 2023.
12. Szargel R, Shani V, Elghani FA, Mekies LN, Liani E, Rott R and Engelender S: The PINK1, synphilin-1 and SIAH-1 complex constitutes a novel mitophagy pathway. Hum Mol Genet 25: 3476-3490, 2016.
13. Zhou J, Feng J, Wu Y, Dai HQ, Zhu GZ, Chen PH, Wang LM, Lu G, Liao XW, Lu PZ, *et al*: Simultaneous treatment with sorafenib and glucose restriction inhibits hepatocellular carcinoma in vitro and in vivo by impairing SIAH1-mediated mitophagy. Exp Mol Med 54: 2007-2021, 2022.
14. Luo P, An Y, He J, Xing X, Zhang Q, Liu X, Chen Y, Yuan H, Chen J, Wong YK, *et al*: Icaritin with autophagy/mitophagy inhibitors synergistically enhances anticancer efficacy and apoptotic effects through PINK1/Parkin-mediated mitophagy in hepatocellular carcinoma. Cancer Lett 587: 216621, 2024.
15. Zhang S, Wang Y, Cao Y, Wu J, Zhang Z, Ren H, Xu X, Kaznacheyeva E, Li Q and Wang G: Inhibition of the PINK1-parkin pathway enhances the lethality of sorafenib and regorafenib in hepatocellular carcinoma. Front Pharmacol 13: 851832, 2022.
16. Ma M, Lin XH, Liu HH, Zhang R and Chen RX: Suppression of DRP1-mediated mitophagy increases the apoptosis of hepatocellular carcinoma cells in the setting of chemotherapy. Oncol Rep 43: 1010-1018, 2020.
17. Aman Y, Cao S and Fang EF: Iron out, mitophagy in! A way to slow down hepatocellular carcinoma. EMBO Rep 21: e51652, 2020.
18. Kim SJ, Khan M, Quan J, Till A, Subramani S and Siddiqui A: Hepatitis B virus disrupts mitochondrial dynamics: Induces fission and mitophagy to attenuate apoptosis. PLoS Pathog 9: e1003722, 2013.
19. Li Y and Ou JJ: Regulation of mitochondrial metabolism by hepatitis B virus. Viruses 15: 2359, 2023.
20. Chen YY, Wang WH, Che L, Lan Y, Zhang LY, Zhan DL, Huang ZY, Lin ZN and Lin YC: BNIP3L-dependent mitophagy promotes HBx-induced cancer stemness of hepatocellular carcinoma cells via glycolysis metabolism reprogramming. Cancers (Basel) 12: 655, 2020.
21. Jia P, Tian T, Li Z, Wang Y, Lin Y, Zeng W, Ye Y, He M, Ni X, Pan J, *et al*: CCDC50 promotes tumor growth through regulation of lysosome homeostasis. EMBO Rep 24: e56948, 2023.
22. Eapen VV, Swarup S, Hoyer MJ, Paulo JA and Harper JW: Quantitative proteomics reveals the selectivity of ubiquitin-binding autophagy receptors in the turnover of damaged lysosomes by lysophagy. Elife 10: e72328, 2021.
23. Hoyer MJ, Swarup S and Harper JW: Mechanisms controlling selective elimination of damaged lysosomes. Curr Opin Physiol 29: 100590, 2022.
24. Wang Y, Wang Z, Sun J and Qian Y: Identification of HCC subtypes with different prognosis and metabolic patterns based on mitophagy. Front Cell Dev Biol 9: 799507, 2021.
25. Ding ZB, Hui B, Shi YH, Zhou J, Peng YF, Gu CY, Yang H, Shi GM, Ke AW, Wang XY, *et al*: Autophagy activation in hepatocellular carcinoma contributes to the tolerance of Oxaliplatin via reactive oxygen species modulation. Clin Cancer Res 17: 6229-6238, 2011.
26. Brun S, Bestion E, Raymond E, Bassissi F, Jilkova ZM, Mezouar S, Rachid M, Novello M, Tracz J, Hamaï A, *et al*: GNS561, a clinical-stage PPT1 inhibitor, is efficient against hepatocellular carcinoma via modulation of lysosomal functions. Autophagy 18: 678-694, 2022.
27. Bi T, Lu Q, Pan X, Dong F, Hu Y, Xu Z, Xiu P, Liu Z and Li J: circFAM134B is a key factor regulating reticulophagy-mediated ferroptosis in hepatocellular carcinoma. Cell Cycle 22: 1900-1920, 2023.
28. Liu Z, Ma C, Wang Q, Yang H, Lu Z, Bi T, Xu Z, Li T, Zhang L, Zhang Y, *et al*: Targeting FAM134B-mediated reticulophagy activates sorafenib-induced ferroptosis in hepatocellular carcinoma. Biochem Biophys Res Commun 589: 247-253, 2022.
29. Wu H, Liu Q, Shan X, Gao W and Chen Q: ATM orchestrates ferritinophagy and ferroptosis by phosphorylating NCOA4. Autophagy 19: 2062-2077, 2023.
30. Wei X, Manandhar L, Kim H, Chhetri A, Hwang J, Jang G, Park C and Park R: Pexophagy and oxidative stress: Focus on peroxisomal proteins and reactive oxygen species (ROS) signaling pathways. Antioxidants (Basel) 14: 126, 2025.
31. Dutta RK, Maharjan Y, Lee JN, Park C, Ho YS and Park R: Catalase deficiency induces reactive oxygen species mediated pexophagy and cell death in the liver during prolonged fasting. Biofactors 47: 112-125, 2021.
32. Ohshima K, Hara E, Takimoto M, Bai Y, Hirata M, Zeng W, Uomoto S, Todoroki M, Kobayashi M, Kozono T, *et al*: Peroxisome proliferator activator α agonist clofibrate induces pexophagy in coconut oil-based high-fat diet-fed rats. Biology (Basel) 13: 1027, 2024.
33. Deosaran E, Larsen KB, Hua R, Sargent G, Wang Y, Kim S, Lamark T, Jauregui M, Law K, Lippincott-Schwartz J, *et al*: NBR1 acts as an autophagy receptor for peroxisomes. J Cell Sci 126: 939-952, 2013.
34. Li Y, Jiang X, Zhang Y, Gao Z, Liu Y, Hu J, Hu X, Li L, Shi J and Gao N: Nuclear accumulation of UBC9 contributes to SUMOylation of lamin A/C and nucleophagy in response to DNA damage. J Exp Clin Cancer Res 38: 67, 2019.
35. Papandreou ME and Tavernarakis N: Nucleophagy: From homeostasis to disease. Cell Death Differ 26: 630-639, 2019.
36. Cebollero E, Reggiori F and Kraft C: Reticulophagy and ribophagy: Regulated degradation of protein production factories. Int J Cell Biol 2012: 182834, 2012.
37. Liu Y, Zou W, Yang P, Wang L, Ma Y, Zhang H and Wang X: Autophagy-dependent ribosomal RNA degradation is essential for maintaining nucleotide homeostasis during C. elegans development. eLife 7: e36588, 2018.
38. Wyant GA, Abu-Remaileh M, Frenkel EM, Laqtom NN, Dharamdasani V, Lewis CA, Chan SH, Heinze I, Ori A and Sabatini DM: NUFIP1 is a ribosome receptor for starvation-induced ribophagy. Science 360: 751-758, 2018.
39. Xu F, Tautenhahn HM, Dirsch O and Dahmen U: Blocking autophagy with chloroquine aggravates lipid accumulation and reduces intracellular energy synthesis in hepatocellular carcinoma cells, both contributing to its anti-proliferative effect. J Cancer Res Clin Oncol 148: 3243-3256, 2022.
40. Xu C and Fan J: Links between autophagy and lipid droplet dynamics. J Exp Bot 73: 2848-2858, 2022.
41. Berardi DE, Bock-Hughes A, Terry AR, Drake LE, Bozek G and Macleod KF: Lipid droplet turnover at the lysosome inhibits growth of hepatocellular carcinoma in a BNIP3-dependent manner. Sci Adv 8: eabo2510, 2022.
42. Koutsifeli P, Varma U, Daniels LJ, Annandale M, Li X, Neale JPH, Hayes S, Weeks KL, James S, Delbridge LMD and Mellor KM: Glycogen-autophagy: Molecular machinery and cellular mechanisms of glycophagy. J Biol Chem 298: 102093, 2022.

43. Gade TPF, Tucker E, Nakazawa MS, Hunt SJ, Wong W, Krock B, Weber CN, Nadolski GJ, Clark TWI, Soulen MC, *et al*: Ischemia induces quiescence and autophagy dependence in hepatocellular carcinoma. Radiology 283: 702-710, 2017.
44. Xiu Z, Zhu Y, Han J, Li Y, Yang X, Yang G, Song G, Li S, Li Y, Cheng C, *et al*: Caryophyllene oxide induces ferritinophagy by regulating the NCOA4/FTH1/LC3 pathway in hepatocellular carcinoma. Front Pharmacol 13: 930958, 2022.
45. Wang G, Li J, Zhu L, Zhou Z, Ma Z, Zhang H, Yang Y, Niu Q and Wang X: Identification of hepatocellular carcinoma-related subtypes and development of a prognostic model: A study based on ferritinophagy-related genes. Discov Oncol 14: 147, 2023.
46. Zhou B, Liu J, Kang R, Klionsky DJ, Kroemer G and Tang D: Ferroptosis is a type of autophagy-dependent cell death. Semin Cancer Biol 66: 89-100, 2020.
47. Subburayan K, Thayyullathil F, Pallichankandy S, Cheratta AR, Alakkal A, Sultana M, Drou N, Arshad M, Palanikumar L, Magzoub M, *et al*: Tumor suppressor Par-4 activates autophagy-dependent ferroptosis. Commun Biol 7: 732, 2024.
48. Yang H, Sun W, Bi T, Wang Q, Wang W, Xu Y, Liu Z and Li J: The PTBP1-NCOA4 axis promotes ferroptosis in liver cancer cells. Oncol Rep 49: 45, 2023.
49. Santana-Codina N, del Rey MQ, Kapner KS, Zhang H, Gikandi A, Malcolm C, Poupault C, Kuljanin M, John KM, Biancur DE, *et al*: NCOA4-Mediated ferritinophagy is a pancreatic cancer dependency via maintenance of iron bioavailability for iron-sulfur cluster proteins. Cancer Discov 12: 2180-2197, 2022.
50. Yang Z, Yoshii SR, Sakai Y, Zhang J, Chino H, Knorr RL and Mizushima N: Autophagy adaptors mediate Parkin-dependent mitophagy by forming sheet-like liquid condensates. EMBO J 43: 5613-5634, 2024.
51. Agudo-Canalejo J, Schultz SW, Chino H, Migliano SM, Saito C, Koyama-Honda I, Stenmark H, Brech A, May AI, Mizushima N and Knorr RL: Wetting regulates autophagy of phase-separated compartments and the cytosol. Nature 591: 142-146, 2021.
52. Mangiarotti A, Sabri E, Schmidt KV, Hoffmann C, Milovanovic D, Lipowsky R and Dimova R: Lipid packing and cholesterol content regulate membrane wetting and remodeling by biomolecular condensates. Nat Commun 16: 2756, 2025.
53. Mangiarotti A, Chen N, Zhao Z, Lipowsky R and Dimova R: Wetting and complex remodeling of membranes by biomolecular condensates. Nat Commun 14: 2809, 2023.
54. Ohshima T, Yamamoto H, Sakamaki Y, Saito C and Mizushima N: NCOA4 drives ferritin phase separation to facilitate macroferritinophagy and microferritinophagy. J Cell Biol 221: e202203102, 2022.
55. Cerda-Troncoso C, Varas-Godoy M and Burgos PV: Pro-tumoral functions of autophagy receptors in the modulation of cancer progression. Front Oncol 10: 619727, 2021.
56. Brun S, Pascussi JM, Gifu EP, Bestion E, Macek-Jilkova Z, Wang G, Bassissi F, Mezouar S, Courcambeck J, Merle P, *et al*: GNS561, a new autophagy inhibitor active against cancer stem cells in hepatocellular carcinoma and hepatic metastasis from colorectal cancer. J Cancer 12: 5432-5438, 2021.
57. Shalhoub H, Gonzalez P, Dos Santos A, Guillermet-Guibert J, Moniaux N, Dupont N and Faivre J: Simultaneous activation and blockade of autophagy to fight hepatocellular carcinoma. Autophagy Rep 3: 2326241, 2024.
58. Qian R, Cao G, Su W, Zhang J, Jiang Y, Song H, Jia F and Wang H: Enhanced sensitivity of tumor cells to autophagy inhibitors using fasting-mimicking diet and targeted lysosomal delivery nanoplatform. Nano Lett 22: 9154-9162, 2022.
59. Liu C, Wu Z, Wang L, Yang Q, Huang J and Huang J: A mitophagy-related gene signature for subtype identification and prognosis prediction of hepatocellular carcinoma. Int J Mol Sci 23: 12123, 2022.
60. Umemura A, He F, Taniguchi K, Nakagawa H, Yamachika S, Font-Burgada J, Zhong Z, Subramaniam S, Raghunandan S, Duran A, *et al*: p62, Upregulated during preneoplasia, induces hepatocellular carcinogenesis by maintaining survival of stressed HCC-initiating cells. Cancer Cell 29: 935-948, 2016.
61. Saito T, Ichimura Y, Taguchi K, Suzuki T, Mizushima T, Takagi K, Hirose Y, Nagahashi M, Iso T, Fukutomi T, *et al*: p62/Sqstm1 promotes malignancy of HCV-positive hepatocellular carcinoma through Nrf2-dependent metabolic reprogramming. Nat Commun 7: 12030, 2016.
62. Meng YC, Lou XL, Yang LY, Li D and Hou YQ: Role of the autophagy-related marker LC3 expression in hepatocellular carcinoma: A meta-analysis. J Cancer Res Clin Oncol 146: 1103-1113, 2020.
63. Qiu DM, Wang GL, Chen L, Xu YY, He S, Cao XL, Qin J, Zhou JM, Zhang YX and Qun E: The expression of beclin-1, an autophagic gene, in hepatocellular carcinoma associated with clinical pathological and prognostic significance. BMC Cancer 14: 327, 2014.
64. Lin CW, Chen YS, Lin CC, Lee PH, Lo GH, Hsu CC, Hsieh PM, Koh KW, Chou TC, Dai CY, *et al*: Autophagy-related gene LC3 expression in tumor and liver microenvironments significantly predicts recurrence of hepatocellular carcinoma after surgical resection. Clin Transl Gastroenterol 9: 166, 2018.
65. Cao J, Wu L, Lei X, Shi K and Shi L: A signature of 13 autophagy-related gene pairs predicts prognosis in hepatocellular carcinoma. Bioengineered 12: 697-707, 2021.
66. Wang S, Cheng H, Li M, Gao D, Wu H, Zhang S, Huang Y and Guo K: BNIP3-mediated mitophagy boosts the competitive growth of Lenvatinib-resistant cells via energy metabolism reprogramming in HCC. Cell Death Dis 15: 484, 2024.
67. Bassissi F, Jílková Z, Brun S, Courcambeck J, Tracz J, Kurma K, Roth GS, Khaldi C, Chaimbault C, Quentin B, *et al*: Abstract 5124: GNS561 a new quinoline derivative inhibits the growth of hepatocellular carcinoma in a cirrhotic rat and human PDX orthotopic mouse models. Cancer Res 77 (Suppl 13): 5124, 2017.
68. Miao Y, Yin Q, Ping L, Sheng H, Chang J, Li W and Lv S: Pseudolaric acid B triggers ferritinophagy and ferroptosis via upregulating NCOA4 in lung adenocarcinoma cells. J Cancer Res Ther 19: 1646-1653, 2023.
69. Zhu J, Wang M and Hu D: Development of an autophagy-related gene prognostic signature in lung adenocarcinoma and lung squamous cell carcinoma. PeerJ 8: e8288, 2020.
70. Rahdan F, Abedi F, Dianat-Moghadam H, Sani MZ, Taghizadeh M and Alizadeh E: Autophagy-based therapy for hepatocellular carcinoma: from standard treatments to combination therapy, oncolytic virotherapy, and targeted nanomedicines. Clin Exp Med 25: 13, 2024.
71. Zai W, Chen W, Han Y, Wu Z, Fan J, Zhang X, Luan J, Tang S, Jin X, Fu X, *et al*: Targeting PARP and autophagy evoked synergistic lethality in hepatocellular carcinoma. Carcinogenesis 41: 345-357, 2020.
72. Qian M, Wan Z, Liang X, Jing L, Zhang H, Qin H, Duan W, Chen R, Zhang T, He Q, *et al*: Targeting autophagy in HCC treatment: Exploiting the CD147 internalization pathway. Cell Commun Signal 22: 583, 2024.
73. Macleod K: Abstract 4984: BNip3 suppresses hepatocellular carcinoma (HCC) growth by limiting lipogenesis. Cancer Res 77 (Suppl 13): 4984, 2017.
74. Zai W, Chen W, Liu H and Yuxuan H: MO1-5-3-Compromised autophagy sensitizes hepatocellular carcinoma to PARP inhibition. Ann Oncol 30: vi91-vi2, 2019.
75. Sadagopan N and He AR: Recent progress in systemic therapy for advanced hepatocellular carcinoma. Int J Mol Sci 25: 1259, 2024.
76. Byrnes K, Blessinger S, Bailey NT, Scaife R, Liu G and Khambu B: Therapeutic regulation of autophagy in hepatic metabolism. Acta Pharm Sin B 12: 33-49, 2022.
77. Allaire M, Rautou PE, Codogno P and Lotersztajn S: Autophagy in liver diseases: Time for translation? J Hepatol 70: 985-998, 2019.
78. Martini G, Ciardiello D, Paragliola F, Nacca V, Santaniello W, Urraro F, Stanzione M, Niosi M, Dallio M, Federico A, *et al*: How immunotherapy has changed the continuum of care in hepatocellular carcinoma. Cancers (Basel) 13: 4719, 2021.