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REVIEW

Autophagy-based therapy for hepatocellular carcinoma: from standard treatments to combination therapy, oncolytic virotherapy, and targeted nanomedicines

Fereshteh Rahdan[1] · Fatemeh Abedi[2] · Hassan Dianat-Moghadam[3,4] · Maryam Zamani Sani[5] · Mohammad Taghizadeh[6] · Effat Alizadeh[1]

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Abstract

Human hepatocellular carcinoma (HCC) has been identified as a significant cause of mortality worldwide. In recent years, extensive research has been conducted to understand the underlying mechanisms of autophagy in the pathogenesis of the disease, with the aim of developing novel therapeutic agents. Targeting autophagy with conventional therapies in invasive HCC has opened up new opportunities for treatment. However, the emergence of resistance and the immunosuppressive tumor environment highlight the need for combination therapy or specific targeting, as well as an efficient drug delivery system to ensure targeted tumor areas receive sufficient doses without affecting normal cells or tissues. In this review, we discuss the findings of several studies that have explored autophagy as a potential therapeutic approach in HCC. We also outline the potential and limitations of standard therapies for autophagy modulation in HCC treatment. Additionally, we discuss how different combination therapies, nano-targeted strategies, and oncolytic virotherapy could enhance autophagy-based HCC treatment in future research.

Keywords Autophagy · Drug resistance · Immunotherapy · Nanocarrier · Oncovirus therapy · Targeted therapy

Introduction

Autophagy may play a part in organelle and protein turnover as well as metabolic control and cell quality control [1]. Under normal circumstances, the basic level of autophagy is necessary, but its stimulation can be mediated by metabolic adjustments [2], oxidative stress [3], endoplasmic reticulum stress [4], mechanical damage [5], and an accumulation of misfolded proteins [6]. Autophagy preserves cellular homeostasis and recovers amino acids and macromolecules for the creation of proteins and ATP [7]. The sequential steps of autophagy are initiation, elongation, autophagosome synthesis, fusion with lysosomes, and destruction [8]. Autophagy-related genes (Atgs) regulate autophagy and their roles well demonstrated by investigations using specific *Atg*-deletion in the liver models [9]. The processes of autophagy are (i) the adenosine monophosphate-activated protein kinase (AMPK), UNC51-like kinase 1 (ULK1), and mammalian target of rapamycin complex 1 (mTORC1) complex regulate the initiation stage. The primary inhibitor of ULK1-induced autophagosome formation is mTORC1. When there is a shortage of nutrients, such as glucose,

✉ Hassan Dianat-Moghadam
dianat.h@med.mui.ac.ir

✉ Effat Alizadeh
alizadehe@tbzmed.ac.ir

1 Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

2 Clinical Research Development, Unit of Tabriz Valiasr Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

3 Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan 8174673461, Iran

4 Pediatric Inherited Diseases Research Center, Isfahan University of Medical Sciences, Isfahan 8174673461, Iran

5 Department of Biochemistry and Clinical Laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

6 Department of Molecular Medicine, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

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at first, mTORC1 is inhibited by active AMPK, and then active AMPK directly phosphorylates ULK1 and initiates autophagy [10]; (ii) nucleation of the phagophore is mediated by the Beclin-1-class III phosphatidylinositol 3-kinase (PI3K) complex that includes Beclin-1, Vps34 (class II PI3K), p150 (homolog of Vps15), Atg14L/Barkor, and Ambra-1 [11]; (iii) elongation of the phagophore into a complete autophagosome is regulated by two ubiquitin-like protein conjugated complexes: Atg5-Atg12-Atg16L1 and LC3-II. These processes require the mediation of several Atgs, including E1-like protein, Atg7, E2-like protein, and Atg10 [12]. The primary mammalian homologue of Atg8 is LC3. Following the fusion of autophagosomes and lysosomes, LC3-1 is changed into LC3-II and then destroyed [13]. LC3-II is therefore regarded as an autophagosome marker [14]. Microautophagy can consume cargo either randomly or intentionally (by individually targeting each cargo molecule) [15]; and (iv) autophagic degradation is the last stage (Fig. 1).

During the onset and progression of a disease, internal and external factors cause autophagy to adapt cells to the new conditions. The pathophysiology of various human cancers has been linked to the autophagy mechanism [16]. Autophagy also controls other cellular processes and can either trigger or suppress apoptosis [17], and photodynamic treatment for cancer may be more effective when autophagy is inhibited [18]. Hepatocellular carcinoma (HCC) is the predominant form of liver cancer, accounting for more than 80% of cases. Both environmental and genetic factors interact to cause the development of HCC. Important risk factors for the development of HCC include liver cirrhosis, infection with the hepatitis B (HBV) and c (HCV) viruses, excessive alcohol use, ingesting aflatoxin B1, and nonalcoholic steatohepatitis (NASH) [19]. Due to its high rate of recurrence and poor prognosis, liver cancer is the third most common cause of cancer-related death worldwide [20]. For patients with very early-stage HCC, surgical resection is currently advised after chemo/radiotherapy. However, HCC is still prone to recurrence and metastasis after surgery, and there is still no viable treatment for patients with advanced, metastatic, or drug-resistant HCC [21]. Therefore, determining the mechanisms underlying carcinogenesis, metastasis, and drug resistance in HCC is crucial for deployment of effective therapeutic approaches and prognostic biomarkers.

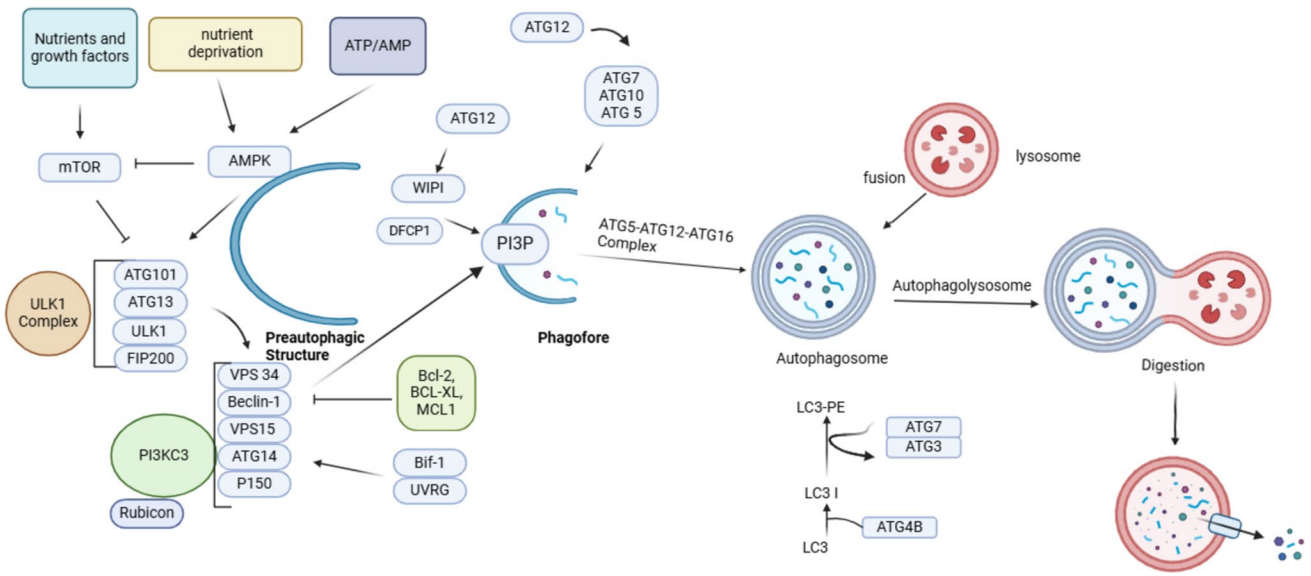

Fig. 1 Regulation of mammalian autophagy is influenced by nutrients and growth factors. Target of rapamycin drug (mTOR) is a negative regulator of autophagy initiation. It inhibits the formation of the ULK1 initiation complex (including ATG13, FIP200 ULK1, and ATG101) by phosphorylation of the ATG13 subunit. When the cell is under nutritional conditions, AMPK is activated. It detects altered levels of the ATP/AMP ratio, leading to the inhibition of mTOR interactions and activation of ULK1 initiation complex. ULK1 complex activates the phosphatidylinositol kinase 3 enzyme (which includes Beclin-1, ATG14, VPS 34, VPS15 and p150), leading to phagophore nucleation. Positive regulators (UVRAG, Bif-1, and Rubicon) and negative regulators (Bcl-2, Bcl-XL, and Mcl-1) regulate the PI3KC3 complex. Activation of the PI3KC3 complex by the interaction of DFCP1 and PI3P with WIPI ultimately positively regulates PI3P, activating the ubiquitin-like conjugation system. During initial stage, the ATG12-ATG5 system interacts with the ATG16L1 protein, forming the ATG5-ATG12-ATG16 complex. The ubiquitin-like conjugation system is further regulated by LC3. Activation of PI3KC3 increases PI3P, enhancing its interaction with WIPI and DFCP1. Elongation and maturation involve two conjugation systems such as ubiquitin. ATG4B proteases perform a proteolytic cleavage in LC3, forming LC3-I. Finally, mediated by ATG12-ATG5-ATG16 and ATG7, ATG3 conjugates LC3-I-PE to form LC3-II, leading to phagophore closure. Lysosomal membranes in contact with autophagosomes form autophagolysosomes during fusion. The contents of the autophagosome are then digested with hydrolytic enzymes, and the decomposed cellular components are transferred from the lumen of the lysosome to the cytosol

Activated autophagy plays a significant role in the development and incidence of fatty liver disease and malignancies [22]. Autophagy regulation is tightly correlated with HCC cell survival and proliferation. Overexpression of 3-hydroxybutyrate dehydrogenase 2 (BDH2) inhibits the development of HCC cells by promoting apoptosis and suppressing autophagy. However, upon HCC progression, BDH2 expression is downregulated, which is associated with tumor cells growth, indicating a pro-survival function of this protein [23]. Impaired autophagy in macrophages causes overexpression of programmed death-ligand 1 (PD-L1) and immunosuppression in HCC, further promoting the tumor progression [24].

Another drawback of the studies is that some of them failed to look at how autophagy and apoptosis interact in both healthy and HCC conditions. They found that autophagy can occasionally block apoptosis [25]. The inactivation of autophagy-specific genes such as Beclin 1 causes tumorigenesis in mice. Therefore, decreased autophagy activity may initially contribute to HCC cancer development [26]. On the other hand, the overexpression of autophagic LC3-II is positively associated with malignant development and predicts poor prognosis in HCC. Autophagy may provide the materials and energy for progress and survival of cancer cells in the tumor microenvironment, which may include nutrient deficiency, hypoxia, and therapeutic stress [27]. Herein, we present how autophagy aids in cancer cell survival, promotes metastasis, and increases resistance to treatment. We also discuss difficulties of current treatments and explore the potential for improving HCC treatments through autophagy targeting.

Autophagy: promotion or regulation of hepatocellular carcinoma?

Autophagy regulate tumorigenesis

According to experimental data, autophagy prevents the malignant transition of normal cells into cancer cells in the early stages of cancer formation (Fig. 2a). Autophagy's ability to clean damaged mitochondria, eliminate aberrant and mutant proteins and protein aggregates, and specifically eliminate proteins associated with proliferation may all have a protective effect against cancer [28]. Reactive oxygen species (ROS) levels rise as a result of disruptions in autophagic activity, making cells more vulnerable to genomic instability and DNA damage [29]. First, cells' ROS burden is increased by protein aggregation buildup and damaged mitochondria. Additionally, there are additional antioxidant processes linked to autophagy. For instance, autophagy controls the activation of NRF2, a crucial transcription factor

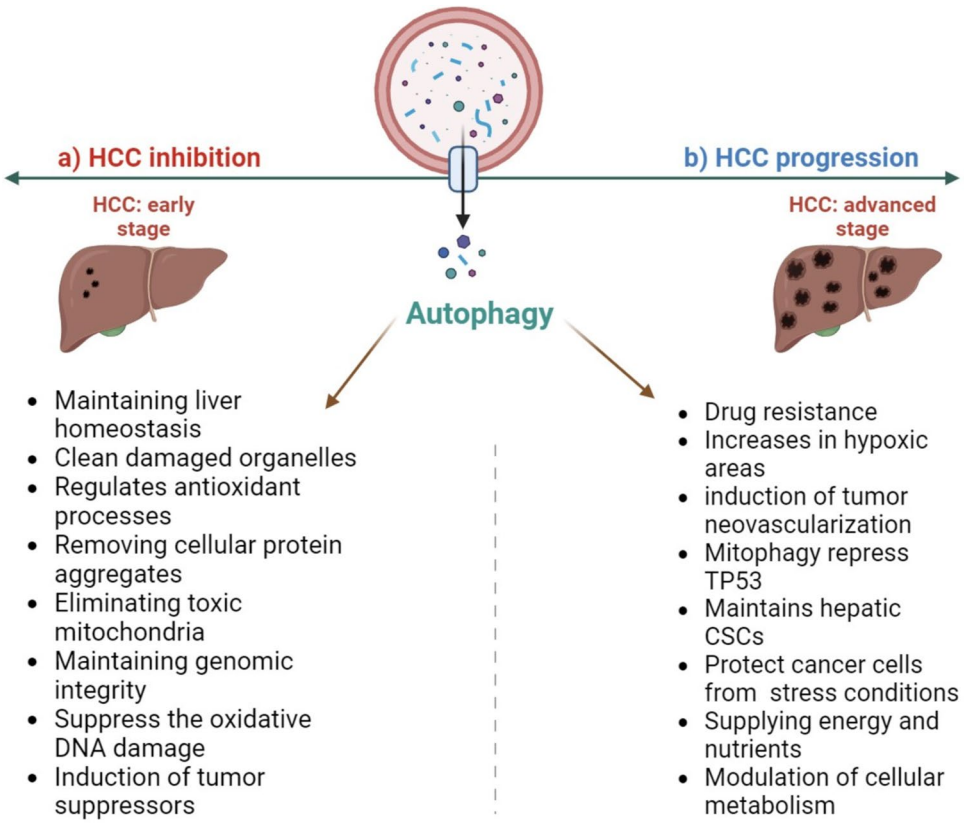

Fig. 2 Bifunctional autophagy in **a** early stage and **b** advanced stage of HCC

in antioxidant defense [30]. Keap1, an adapter protein of the Cullin-3 ubiquitin ligase, normally enables the ubiquitination and destruction of NRF2. As ROS build up, Keap1 is oxidized and separates from NRF2, which causes it to stabilize and migrate to the nucleus. Selective autophagy is another method of Keap1 elimination. NRF2 is activated by the competitive binding of the autophagy receptor p62 to Keap1, followed by their preferential autophagic destruction, which opens a transcriptional route for antioxidants [31].

In the autophagy pathway, ATG6/BECN1 (Beclin 1) is a crucial gene. Between 40 and 75% of human cancers show BECN1 deletion. Intriguingly, mice with a heterozygous deletion of *atg6/becn1* showed an increase in tumorigenesis across a liver tissue [32]. The importance of the *atg6/becn1* gene in the development of liver cancer is further highlighted by the fact that *becn1* deletion accelerated HCCs linked to the hepatitis B virus (HBV) [33]. As a factor in cellular homeostasis, ubiquitin-specific protease 24 (USP24) has decreased expression in HCC. In a study by Cao et al., the role of USP24 in inhibiting HCC was investigated. The results demonstrated an intrinsic relationship between USP24 and Beclin1. Mechanistically, USP24 prevents Beclin1 degradation by reducing K48-linked ubiquitination. Therefore, overexpression of USP24 induces autophagy along with ferroptosis and reduces sorafenib resistance in HCC [34]. Furthermore, Deng et al. studied the molecular role of the non-coding RNA lncSNHG16 in HCC both in vitro and in vivo. The findings revealed that overexpression of lncSNHG16 inhibits autophagy and apoptosis by upregulating STAT3. This overexpression is also associated with disease relapse, making it potential therapeutic target [35].

The deletion of other autophagy genes, such as *atg5* and *atg7*, resulted in the development of benign liver adenomas in mouse models [36]. Furthermore, liver-specific *atg7* deletion causes hepatomegaly and hepatic failure. Surprisingly, further p62 deletion in an atg7-specific background reduced tumor burden, demonstrating that autophagy plays a crucial role in this situation by removing cellular protein aggregates in a p62-dependent way [37]. Mice with *Uvrag* gene deletion were more susceptible to developing HCC [38]. Therefore, maintaining liver homeostasis and preventing the emergence of HCC are critical functions of autophagy-related proteins and the autophagy pathway in liver cells.

Autophagy contributes to preserving genome integrity in liver cells and preventing malignant transformation by eliminating toxic mitochondria and damaged liver cells, as well as maintaining liver homeostasis [20]. However, knockout (KO) of important autophagy genes *Atg5* and *Atg7* causes an accumulation of defective organelles and proteins in liver cells [36] as well as hepatomegaly and other metabolic liver problems in mice liver [39]. Using BECLIN1 KO mice, direct proof of the tumor-suppressing function of autophagy in HCC was obtained [33]. Thus, it has been established that autophagy suppresses HCC carcinogenesis in its early stages.

The BECLIN1 molecule has two distinct roles, tumor suppression and autophagy regulation [40]. Mice with heterozygous disruption of BECLIN1 displayed decreased autophagy activity and a propensity to develop HCC and other spontaneous malignant lesions [33]. Studies revealed a correlation between BECLIN1 expression levels and HCC grade, supporting the potential use of BECLIN1 as an HCC prognostic biomarker [41]. Specific KO of *ATG5* impeded autophagy in the liver, caused oxidative DNA damage, and resulted in the growth of benign hepatic tumors with no discernible carcinoma [36]. The induction of tumor suppressors like TP53, TP16, TP21, and TP27, which negatively regulate the progression of tumorigenesis when autophagy is impaired, displayed features of mitochondrial swelling, p62 accumulation, oxidative stress, and genomic damage responses, was linked to the inability to develop HCC [42]. In addition, liver-specific *ATG7* KO mice had hepatic tumors that were reduced in size after TP62 deletion, demonstrating that the buildup of p62 brought on by a lack of autophagy contributes to the development of tumors [36].

Autophagy support HCC progression

Autophagy plays a role in several stages of cancer spread and progression (Fig. 2b). Both upregulation and downregulation of autophagy have been observed in malignancies, indicating that it has both oncogenic and tumor-suppressor capabilities during malignant transformation [20]. Particularly, autophagic activity has been linked to the survival of fast-growing tumors. There is also a significant body of literature linking autophagy to medication resistance [43]. Several autophagy mouse model systems have shown liver cancer formation. For instance, basal autophagy is increased in hypoxic areas of various solid tumor types and has been demonstrated to play a crucial role in the survival of tumor cells in vivo [44]. A uniform vessel network may not always be produced by tumor neovascularization, and regions with restricted access to nutrients and oxygen are common, particularly in rapidly expanding tumors [45]. As a result, compared to cells that are normally developing in these areas, cancer cells may be more dependent on autophagy to supports the formation of HCC [46]. Moreover, the development of benign hepatic tumors into malignant HCC requires autophagy to retain hepatic cancer stem cells (CSCs) and encourage hepatocarcinogenesis. Additionally, mitophagy is necessary to repress TP53 and activate the expression of the transcription factor NANOG [47]. Thus, despite acting as an antitumor pathway preventing early stages of cancer development in established tumors, autophagy may protect

cancer cells from various stress conditions and contribute to the growth and spread of cancerous cells [48].

Autophagy contributes to cancer metabolism by providing energy and nutrients for cancer cell survival and growth. In addition to recycling cellular components, autophagy can also supply lipids and amino acids for biosynthesis by modulating cellular metabolism [49]. For instance, glutamine metabolism is frequently required for the survival and growth of cancer cells. Autophagy provides glutamine by breaking down intracellular proteins in cancer cells. Inhibiting autophagy can lead to reduced glutamine levels and increased sensitivity to metabolic stress [50, 51]. Consequently, autophagy acts as a tumor suppressor in the early stages of tumor cell growth. However, after establishment of HCC, autophagy becomes crucial for cancer cell survival in the hypoxic areas of solid tumors [52]. Additionally, autophagy is necessary to induce carcinogenesis by sustaining oxidative metabolism or facilitating glycolysis [53].

Autophagy and HCC metastasis

More than 90% of cancer-related deaths are due to tumor metastasis. Under oxygen and nutrient deprivation, cancer cells that have grown in close proximity to the main tumor might separate and form metastatic nodules [54]. Activated autophagy is crucial for tumor metastasis because it provides tumor cells with energy, enhancing their ability to survive and promoting their migration [55]. Additionally, autophagy can alter cell adhesion signals and encourage the invasion and migration of tumor cells [56]. A more focused inhibition of FAK (focal adhesion kinase), activates SRC kinase and prevents autophagy [57]. In turn, SRC-driven metastatic tumor cells cannot migrate when autophagy is inhibited [56]. The accumulation of paxillin (PXN), a crucial component of focal adhesions, is the reason why focal adhesions reduce the amount of autophagic flux [58]. Due to its pro-survival function, autophagy may aid in the spread of HCC. Lentivirus-mediated silencing of the *BECN1* and *Atg5* genes effectively inhibited autophagy of HCC cell lines and in a tissue-specific manner in vivo, suppressing HCC metastasis by promoting anoikis resistance and lung colonization of HCC cells [59]. Furthermore, there is much more LC3 expression in metastases than in patients with primary HCC, suggesting that autophagy is more advanced in HCC metastases [60]. Starvation-induced autophagy enhances the expression of epithelial-mesenchymal transition (EMT) markers and invasion in HCC cells, which is mediated by TGF-β/Smad3 signaling SPS:refid::bib61(61). Finally, autophagy enhances HCC cells glycolysis along with an increase in monocarboxylate transporter 1 (MCT1) expression through activating Wnt/β-catenin signaling related to the metastasis of HCC cells [62].

Signaling pathways that modulate autophagy in *cancer* cells

Multiple signaling pathways and cellular processes are involved in the intricate and multidimensional control of autophagy in cancer cells [63]. In cancer cells, the mTOR pathway plays a crucial role in controlling autophagy. A serine/threonine kinase called mTOR, which is activated in response to nutrient-rich environments, blocks the crucial autophagy initiator ULK1 by phosphorylating it. In contrast, when nutrients are scarce, mTOR is suppressed, which activates ULK1 and triggers autophagy [64, 65]. Cancers with a poor prognosis and chemoresistance have overactive mTOR. Rapamycin or its analogs can induce autophagy and make cancer cells more susceptible to chemotherapy by inhibiting mTOR [65, 66].

The AMP-activated protein kinase (AMPK) pathway is an important mechanism that controls autophagy in cancer cells. The serine/threonine kinase AMPK promotes autophagy by phosphorylating and activating ULK1 [67]. In contrast, AMPK is suppressed in energy-rich environments, which inhibits ULK1 and autophagy. Activation of the AMPK pathway by metformin triggers autophagy and makes cancer cells more susceptible to chemotherapy [67–69]. The p53 tumor suppressor can control autophagy by altering the expression of autophagy-related genes, such as DRAM1 and TP53INP1, [70]. p53 can also prevent autophagy through the inhibition of ULK1 expression. Therefore, p53 mutations can cause dysregulation of autophagy in cancer and the emergence of chemoresistance. Restoring p53 function can make tumor cell susceptible to treatment [64].

Cancer cells' autophagy can be modified by the endoplasmic reticulum (ER) stress pathway, which is activated in response to cellular stresses like chemotherapy [71, 72]. ER stress stimulates the PERK-eIF2α-ATF4 pathway, which encourages the production of genes associated with autophagy. ER stress can also suppress autophagy by activating the IRE1α pathway, which promotes the degradation of autophagy-related mRNAs [71, 73]. ER stress driving autophagy increases chemoresistance in cancer cells, and inhibiting ER stress using small molecules or genetically silencing ER stress-related genes can decrease autophagy and make cancer cells more susceptible to chemotherapy [74].

The NF-κB pathway, the lysosomal pathway, the Wnt/β-catenin pathway, the MAPK pathway, and the PI3K/Akt pathway are other signaling pathways and biological functions that affect autophagy in cancer cells [75]. For instance, the PI3K/Akt pathway can inhibit autophagy by phosphorylating and suppressing ULK1. Inhibiting PI3K/Akt pathway with small-molecules or genetically knocking down of PI3K or Akt can promote autophagy and make cancer cells more susceptible to chemotherapy [76]. The lysosomal pathway

can also influence autophagy by regulating the fusion of autophagosomes with lysosomes. The NF-κB pathway can stimulate autophagy by upregulating the expression of genes relevant to autophagy [76, 77]..

Autophagy inhibitors

Small molecules known as autophagy inhibitors have the ability to prevent the development or degeneration of autophagosomes. Clinical trials for the treatment of cancer have used a number of autophagy inhibitors, including chloroquine and hydroxychloroquine [78]. These inhibitors make cancer cells more sensitive to chemotherapy by preventing chemotherapeutic agents from degrading and fostering apoptosis. However, autophagy inhibitors may only be partially effective in treating cancer because they can also prevent damaged organelles and proteins from being degraded by their own cells, resulting in cellular stress and chemotherapy resistance [79]. Hence, it is important to carefully assess the efficacy of autophagy inhibitors in treating cancer.

For the treatment of HCC, lysosomotropic agents, such as chloroquine and hydroxychloroquine prevent the acidification of lysosomes, which inhibits the body's ability to undergo autophagy [80]. In experimental models of HCC, sorafenib, doxorubicin, and cisplatin have been shown to be more effective when combined with chloroquine and hydroxychloroquine. Autophagy is inhibited by lysosomal inhibitors like bafilomycin A1 and concanamycin A, which prevent the fusion of autophagosomes [81]. In the phase I/ II clinical trial, patients with advanced HCC were shown to be healthy and well-tolerated when given hydroxychloroquine and sorafenib or bafilomycin A1 and sorafenib. The combination therapy also demonstrated promising antitumor activity, with a 54% disease control rate [82, 83].

Inhibitors like Spain-1 and 3 methyladenine (3- MA) prevent autophagy by targeting ATGs [84]. The Beclin-1-VPS34 complex inhibits autophagy, which can be targeted by spautin-1 to improve sorafenib and doxorubicin's efficacy in vivo [85, 86]. Sporting-1 and sorafenib were combined in the phase I clinical trial to demonstrate their safety and well-tolerance in patients with advanced HCC. With a 71% disease control rate, the combination therapy also demonstrated promising antitumor activity. Rapamycin blocks the mTOR pathway and in preclinical models of HCC, mTOR inhibitors have been shown to improve sorafenib and cisplatin's efficacy [87]. Rapamycin and sorafenib were shown to be safe and well-tolerated in patients with advanced HCC in a phase I/ II clinical trial. Other autophagy inhibitors like verteporfin and tunicamycin have also demonstrated promising efficacy as a therapeutic approach to HCC in preclinical models [88]. Photosensitizer verteporfin targets autophagy regulators such as YAP/ TAZ and improves sorafenib and doxorubicin's efficacy pathway in preclinical models [89, 90]. Protein glycosylation is inhibited by tunicamycin, which can cause autophagy and endoplasmic reticulum stress. In preclinical models of HCC, tunicamycin has been shown to improve sorafenib and cisplatin's efficacy [91].

Autophagy and resistant HCC to conventional therapies

Autophagy in chemotherapy-resistant HCC

Cancer cell subpopulations undergo mutations that make them less sensitive to chemotherapy drugs [92, 93]. Cancer cells are able to escape from chemotherapy and resistance to chemo drugs leads to the ultimate failure of cancer treatment [94]. Autophagy is one of the cellular factors that may contribute to the resistance of cancer cells to chemotherapy drugs (Fig. 3). However, there is a lot of evidence about the contradictory role of autophagy in the process of various anticancer therapeutic strategies.

On one hand, autophagy, by creating a protective role, creates an acquired resistance phenotype in cancer cells to chemotherapy drugs. On the other hand, it induces a form of cell death that differs from apoptosis as programmed cell death [95, 96]. Autophagy can contribute to the metabolism of cancer cells in various ways. Among them, damaged cellular components caused by chemotherapy drugs such as damaged DNA, damaged organelles and misfolded proteins may be converted into substances that support the survival of HCC cells [22].

Autophagy causes resistance mechanisms by increasing the basal autophagic flux or gradually developing acquired drug resistance by increasing the autophagic flux. Despite these conditions, the increase in autophagic flux in some cases leads to the death of cancer cells, creating many ambiguities and contradictions in studies [97]. Therefore, better understanding of the role of autophagy in the creation of chemotherapy resistance helps to create more effective treatment strategies.

Autophagy also promotes chemoresistance by sending drugs to autophagosomes or lysosomes for destruction [98]. In this process, cisplatin-induced autophagy promotes the removal of damaged mitochondria and inhibits the buildup of toxic metabolites, both of which are beneficial for cancer cell survival [99, 100]. Autophagy also causes the degradation of doxorubicin and the emergence of chemoresistance. Doxorubicin's anticancer efficacy can be increased by genetically or chemically inhibiting autophagy [101, 102]. Chemotherapy drugs can induce DNA damage and oxidative stress, leading to cancer cell apoptosis. However, by eliminating damaged organelles and proteins and supplying energy and nutrients for cell survival, autophagy can

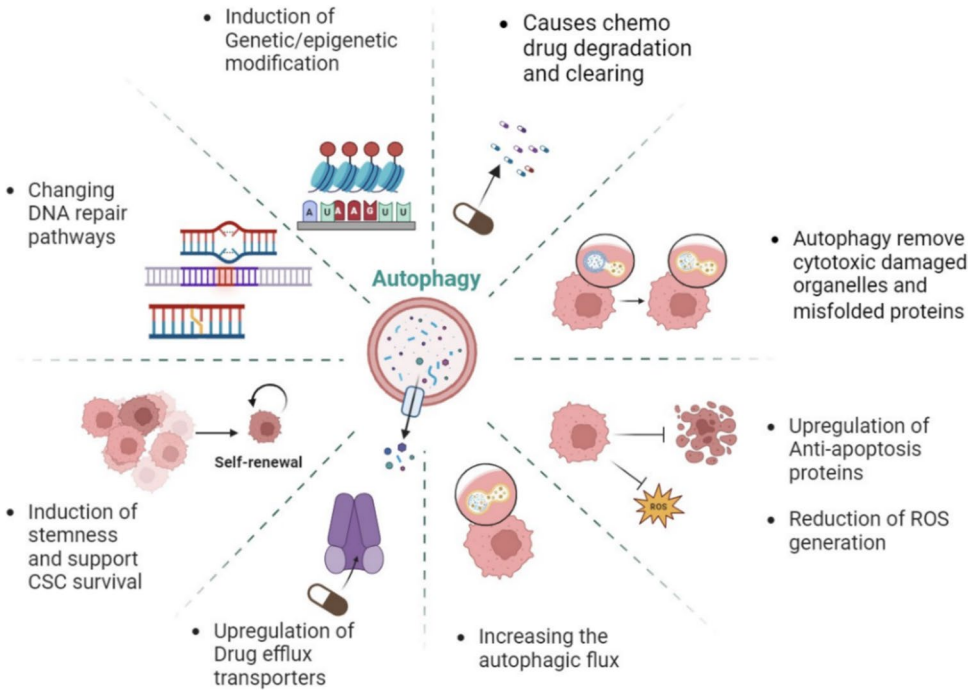

Fig. 3 The overall mechanisms by which autophagy modulates chemoresistance in HCC

support the survival of cancer cells under certain conditions [103, 104]. Additionally, autophagy can stop the buildup of dangerous compounds that trigger apoptosis. For instance, Gemcitabine-induced autophagy promotes the removal of damaged mitochondria and inhibits the buildup of toxic metabolites, both of which are beneficial for cancer cell survival. Gemcitabine's anticancer activity can therefore be increased by genetically reducing ATGs or inhibiting autophagy with small compounds [105] (Table 1).

Regarding the roles of autophagy in chemotherapy-resistant cancer, targeting autophagy has emerged as a promising strategy for overcoming chemoresistance in cancer [77]. Sorafenib can increase the overall survival of HCC patients, however, resistance to sorafenib occur due to the activation of alternative signaling pathways (AKT/mTOR, HGF/MET, Notch), an increase in the activity of drug efflux pumps, and changes in the TME [75, 126]. Combining sorafenib with DOX and cisplatin can increase tumor cell death and prolong

Table 1 The molecular mechanisms of autophagy in chemo/radio/PTT -resistant HCC

Mechanism	Description	References
Activation of autophagy	The autophagy system in HCC cells can be activated by chemotherapy to promote tumor cell survival and resistance to radio- and chemotherapy	[64, 106, 107, 108]
Regulation of drug efflux pumps	In HCC cells responding to chemotherapy, autophagy can control drug efflux pumps such as P-glycoprotein, which can increase chemotherapy resistance	[109]
Regulation of DNA repair	In response to chemotherapy, autophagy can control DNA repair pathways in HCC cells to enhance the repair of DNA damage, which is linked to tumor cell survival and therapeutic resistance	[110–112]
Regulation of cell death	By inhibiting cell death pathways and fostering resistance to cancer treatment, active autophagy regulates cell death mechanisms like apoptosis and necroptosis	[113–116]
Regulation of the immune response	Autophagy can influence the immunological response to therapies in HCC and foster immune therapy resistance by controlling the release of damage-associated molecular patterns (DAMPs) and fostering antigen presentation	[67, 117, 118]
Regulation of hypoxia-inducible factor (HIF)	In response to cancer treatments, autophagy can increase the expression of HIF in HCC cells to promote tumor cell survival and resistance to chemotherapy	[119–122]
Regulation of reactive oxygen species (ROS)	The activation of autophagy improved the scavenging of ROS in HCC cells in response to radio/chemotherapy	[123–125]

overall survival in HCC animal models. There are active clinical trials examining the effectiveness of combination therapy in HCC [127].

More importantly, personalized therapy based on the molecular profile of the tumor has become a potentially effective method for treating HCC patients who have developed resistance to chemotherapy. Clinical trials investigating the effectiveness of personalized treatment for HCC are still ongoing [109, 128].

Autophagy and radio-resistant HCC

Radiation therapy (RT) for the treatment of HCC has been limited due to livers low tolerance to radiation. However, depending on the stage of the disease, RT has shown effectiveness with the development of modern advances such as image-guided radiotherapy (IGRT), intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) [129]. Several studies have been conducted using different therapeutic methods to inhibit or stimulate autophagy in cancer treatment. However, the relationship between the mechanism of autophagy and radiotherapy has not been deeply investigated. Cancer treatment with radiotherapy is stressor that can activate autophagy in both cancer and normal cells [130]. RT also affects autophagy through the mTOR pathway and ER stress in relation to cell death [131]. HCC has showed resistance to ionizing radiation (IR) due to autophagic response. 3-MA enhanced the effect of radiation therapy by inhibiting the expression of LC3 and increasing cell death [132].

The effect of early growth response factor (Egr-1) was studied in relation to autophagy and resistance to IR in HCC cell lines. Egr-1 induces resistance to IR by affecting autophagy. Suppressing the function of Egr-1 inhibits Atg4B gene expression and following inhibition of autophagy, sensitivity to radiation therapy increases [133].

Additionally, the role of nuclear enriched abundant transcript 1 (NEAT1) type 1 (NEAT1v1) in relation to radiation therapy sensitivity and autophagy was investigated in CSCs of HCC patients. NEAT1 as a long non-coding RNA increases the expression of gamma-aminobutyric acid receptor-related protein (GABARAP) and GABARAP in turn increases autophagy and resistance to radiotherapy through autophagosome-lysosome fusion. Gene deletion using short hairpin RNAs was performed in HCC cell lines and it was observed that knockdown of NEAT1 increases the sensitivity to radiation therapy while inhibiting autophagy [107]. A metalloprotease (ADAM) 9 increases autophagy by decreasing Nrf2 expression levels and reduces sensitivity to radiation therapy. Knockdown of ADAM9 in HCC cell line showed increased sensitivity to radiation therapy by inhibiting autophagy [134]. Hexokinase 2 (HK2) is a key enzyme in glycolysis that can act as an oncogene and increases autophagy through autophagic lysosome-dependent degradation (Fig. 4) and decreases apoptosis by binding to the pro-apoptotic protein aminoacyl tRNA synthetase, thereby creating resistance to radiotherapy in HCC. In this study, ketoconazole was used as an HK2 inhibitor along with RT. The results showed that these two act synergistically and increase sensitivity to radiotherapy [135]. Overall, RT is used along with other systemic treatments in pre-clinic and clinical setting, including treatment methods in the first line of fight in HCC patients. Radio resistance causes specific changes in biological traits, including autophagy, and it seems that mainly by inhibiting autophagy, the resistance to radiotherapy is eliminated and the hope of treatment increases in HCC patients.

Autophagy and PDT/PPT -resistant of HCC

Phototherapy (PTT) has been recognized as a promising strategy for the treatment of malignant cancer. In this method, photosensitizers are stimulated by near-infrared (NIR) laser radiation and cause cell death by producing heat. PTT has been reported to prevent migration to lymph nodes and metastasis by killing HCC cells in the primary tumor in this way [136].

In a study, a nanoparticle system composed of NIR dye IR780 was designed with NIR laser irradiation at 808 nm wavelength and chemotherapy drug paclitaxel (PTX). The results of this study showed inhibition of cell growth and apoptosis in HCC cells [137, 138]. In addition, autophagy inhibitor chloroquine diphosphate and branched Au–Ag nanoformulations coated with polydopamine (PDA) were used together with PTT using an 808 nm laser. The results showed that autophagy inhibition combined with PTT-induced extensive photothermal cytotoxicity against applied HCC cells and a HepG2 mouse xenograft model [139].

Synthesized Au@PDA nanoparticles are suitable for near-infrared stimulated PTT therapy. This platform was investigated in an HCC cell line and in vivo, and the results showed that PTT based on Au@PDA-RGD NPs affects the mitochondrial-lysosomal and autophagy pathways and increases the expression of integrin receptor aVb3, which leads to HCC cell death [140].

Photodynamic therapy (PDT) is form of photochemical therapy used in cancer treatment (Fig. 5). This method involves using unique wavelengths of light to trigger reactions and produce cytotoxic ROS such as free radicals and singlet oxygen, in combination with light-sensitive drugs for treating cancers [141]. PDT has been approved as a combination therapy for treating HCC [142]. Several PDT-mediated mechanisms have been implicated to interfere with cell biological programs including autophagy. PDT targets the mitochondria to increase ROS production near the mitochondrial membrane. This leads to

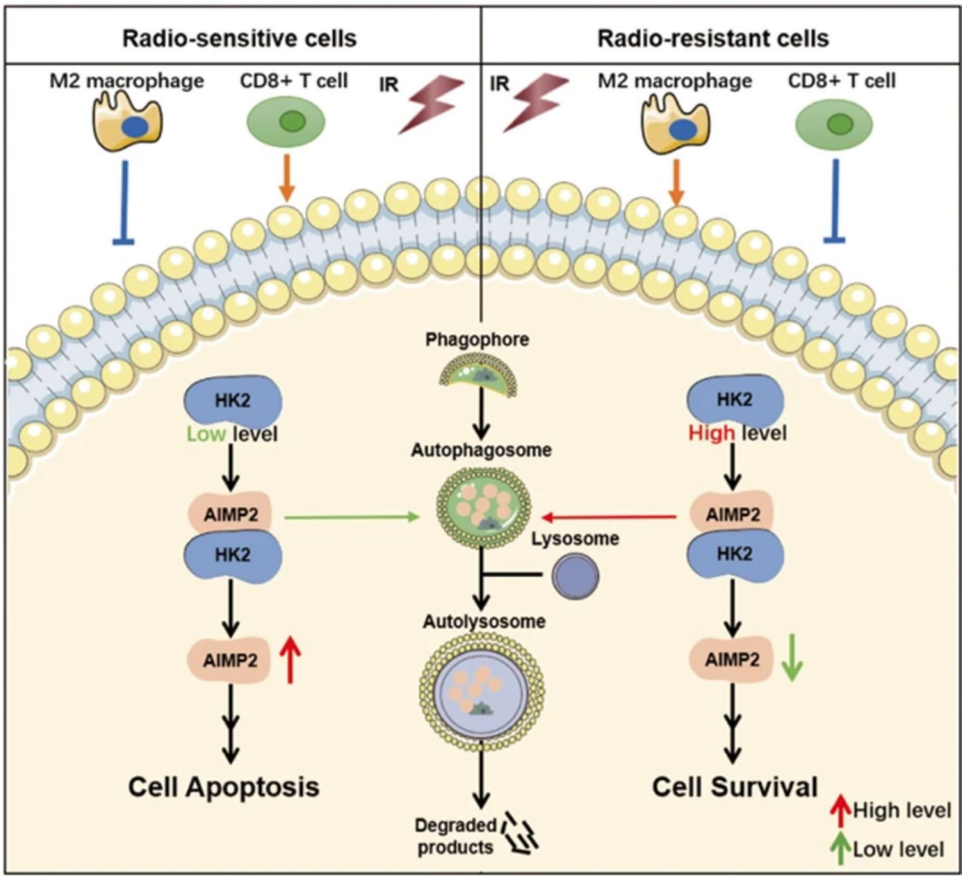

Fig. 4 Hexokinase 2 (HK2), an oncogene, may interact with AIMP2 to induce lysosomal-dependent autophagy, thereby reducing radiation-mediated apoptosis. Upregulation of HK2 is associated with immunosuppression and progression of HCC. [135] Reproduced from reference

the mitochondrial membrane potential, causing releasing cytochrome c from the mitochondria and inducing apoptosis in cancer cells. At this time, another pathway of cell death, which is autophagy, is also induced. For this purpose, Domagala et al. sensitized and killed cancer cells by inhibiting autophagy through photoferrin-based PDT [143, 144]. In addition, knocking down the *Atg7* gene significantly increases the therapeutic effectiveness of PDT in HCC model [143]. In a study, a multifunctional platform MnO2-SOR-Ce6@PDA-PEG-FA, MSCPF was synthesized. Sorafenib (SOR) as a first-line chemotherapy drug, chlorine 6 (Ce6) as a photosensitizing agent, MnO2 as a photothermal and other agents have been used in this platform. MSCPF plays the role of an oxygen generator, thereby generating a large amount of ROS, and also induces cell death termed ferroptosis. This platform improve the combined and synergistic chemotherapy/PDT/PTT SOR treatment in HCC patients [145]. Therefore, the positive synergistic effects of PDT/PTT with other therapeutic strategies such as chemotherapy drugs, nanoparticles, and the important role of autophagy in creating resistance to treatment, there are also effective strategies for obtaining the best and most effective treatments for HCC patients with this method of treatment is forthcoming.

Autophagy and immune evasion or immunotherapy resistant HCC

Immunotherapy is utilized to activate the host immune system to identify and eliminate cancer cells. Autophagy can be triggered by immunotherapy as a defense against therapy-induced cell death (Fig. 6). As a result, inhibiting autophagy in addition to immune therapy may increase the therapy's antitumor efficacy [147–149]. The control of the TME is one of the primary mechanisms of autophagy in immune treatment resistance in HCC. The creation of an immunosuppressive TME is a key factor in immune treatment resistance. Autophagy has the ability to control TME by influencing immune checkpoint protein expression, cytokine and chemokine secretion, and CSCs survival, a subpopulation of cancer cells with stem cell-like characteristics that are crucial for the growth and metastasis of tumors [150]. Through the provision of nutrients and energy during stressful situations, autophagy has been demonstrated to support the survival of CSCs in HCC [151]. For instance, autophagy inhibitors like chloroquine and hydroxychloroquine can prevent CSCs from surviving and self-renewing [152]. NF-κB is essential for controlling inflammatory processes and immunological reactions. NF-κB signaling pathway activation can cause the release of cytokines and

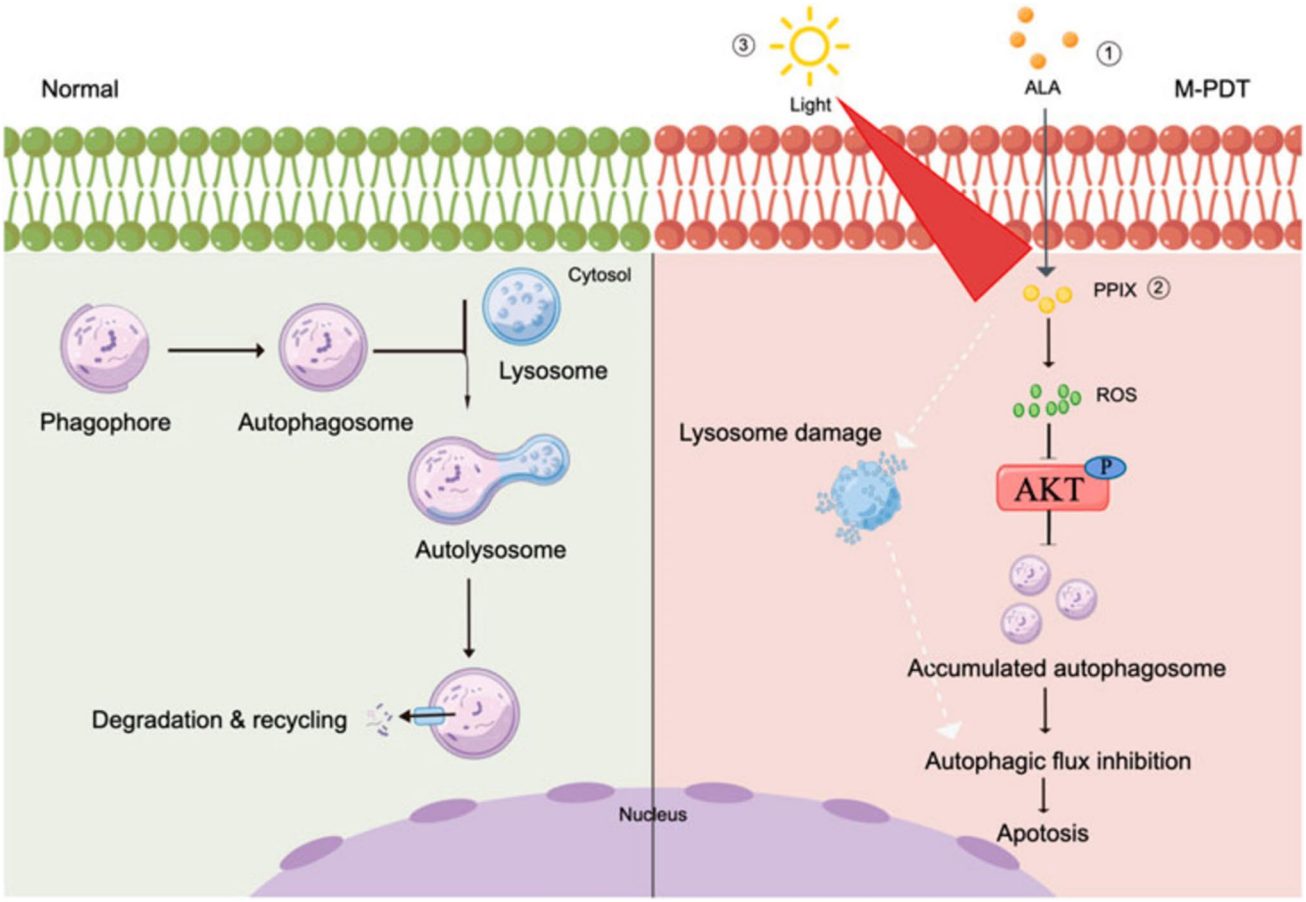

Fig. 5 (5-aminolevulinic acid photodynamic therapy (ALA-PDT) inhibits ROS-mediated Akt, thereby preventing autophagic flux, which contributes to suppressing cell viability. Consequently, the accumulated autophagosomes induce inhibition of cell viability. In addition, PDT causes lysosomal dysfunction in a ROS-independent manner. [146] Reproduced from reference

chemokines that aid in immune evasion and tumor growth [153]. Autophagy can modify the release of cytokines and chemokines by controlling the NF-κB signaling pathway's activation [154, 155]. Autophagy also controls the activity of NF-κB by encouraging the degradation of the NF-κB inhibitor IκBα and thus enhances immune treatment resistance [153, 156]. For instance, NF-κB signaling pathway inhibitors like bortezomib and curcumin have been demonstrated in preclinical trials to limit cytokine and chemokine release and boost the antitumor immune response. The effectiveness bortezomib and ICI combination in HCC is being studied in ongoing clinical trials [157].

Immune checkpoint proteins such as PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are regulators of T cell activation, can be produced through autophagy, and induce resistance to immune treatment [154, 158]. HCC can be treated using ICBs, and chloroquine and hydroxychloroquine can increase the effectiveness of ICIs by suppressing the expression of PD-L1 and CTLA-4, as are being tested in clinical trials to determine their efficacy in treating HCC [159]. In addition, the regulatory function of dendritic cells (DCs) is a crucial component of autophagy [160, 161], and autophagy inhibitors like chloroquine and hydroxychloroquine improve DC and cytotoxic T cell activities in vivo [9, 10].

During cisplatin chemotherapy, autophagy can help cancer cells evade the immune system by destroying MHC-I molecules, which are necessary for antigen presentation to T cells [162, 163]. Therefore, inhibiting autophagy can increase MHC-I expression and make cancer cells more susceptible to T cell-mediated eradication. Of note, autophagy can facilitate DCs' cross-presentation of tumor antigens, an important step in the activation of cytotoxic T lymphocytes [164, 165]. Furthermore, autophagy regulates the activity, metabolism, and expression of activation markers and cytokines in immune cells involved in antitumor responses such as T cells and natural killer (NK) cells. This can increase resistance to immune treatment [166, 167], but chloroquine and hydroxychloroquine can improve the functionality of T cells and NK cells [168].

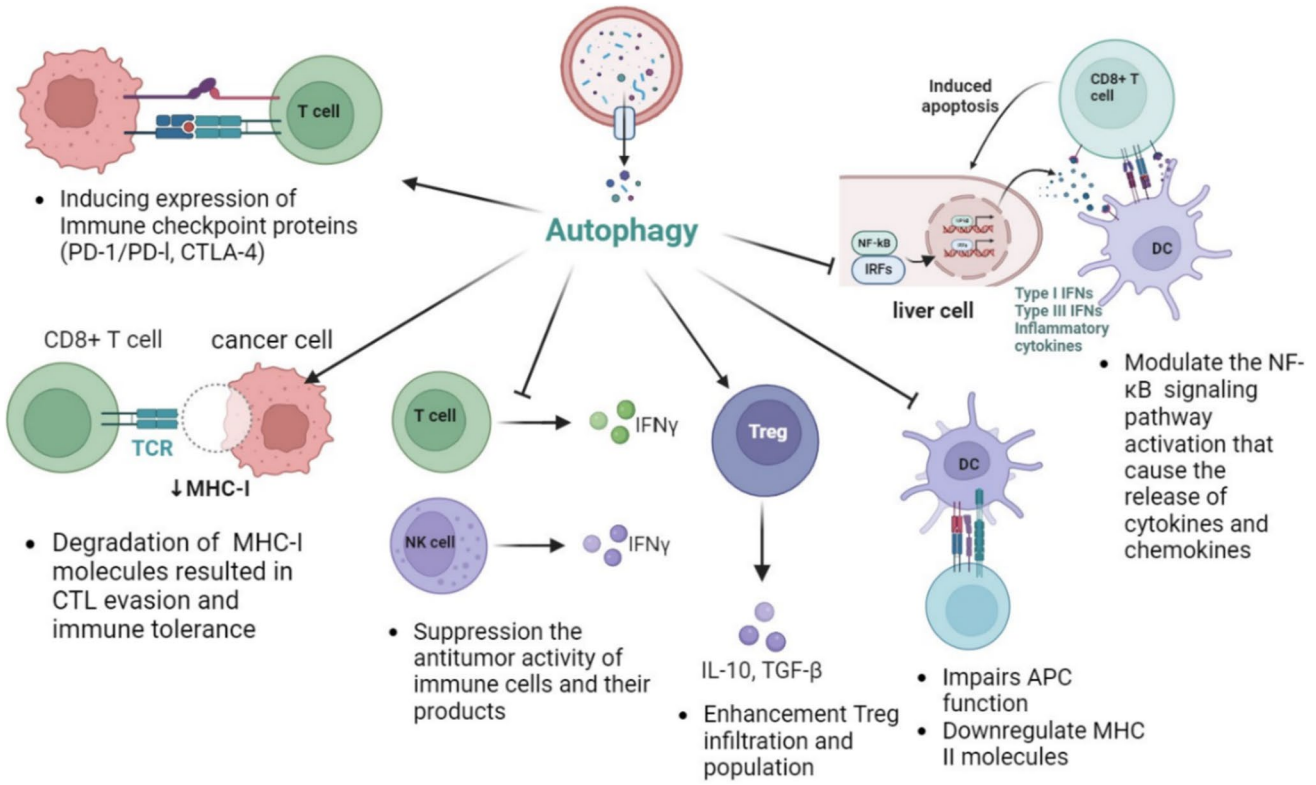

Fig. 6 The overall mechanisms by which autophagy modulates the immune responses in the of progression HCC

Perspective approaches for improving autophagy-based HCC

HCC treatment has great potential for improving tumor lethality by targeting autophagy, while having less of an effect on normal tissue cells [39]. Autophagy plays dual role in cancer inhibition and progression, acting as suppressor in tumorigenesis of HCC, and as an oncogenic factor in advanced HCC [169]. This provides a basis for promising targeted therapy in both early and advanced stages of HCC by stimulating and inhibiting autophagy, respectively. It is crucial to develop more efficient and economically feasible approaches. Efficient methods that not solely rely on traditional cytotoxicity profiles are necessary to provide a more targeted, effective, and improved form of cancer therapy [170–172].

Combined therapy

The combination of two or more therapies to precisely target cells that sustain or promote cancer pathways is a foundation of cancer therapy [173, 174]. One of these methods is the combination of two or more chemotherapy drugs to increase the effectiveness of drugs and reduce drug resistance by targeting autophagy in the treatment of HCC [175]. For example, sorafenib temporarily keeps HCC patients alive for several months by suppressing the activity of Raf kinase and VEGF receptor (VEGFR) and platelet-derived growth factor receptor-beta (PDGF-β). The combination therapy of sorafenib with DOX being investigated in a randomized phase III trial [176]. DOX induces cell death by upregulating the MEK/ERK pathway, while sorafenib has the opposite effect on the same cascade. Their co-treatment inhibits cell cycle progression, reduces autophagy, and increases survival. Indeed, sorafenib suppresses DOX-induced ERK1/2 activation and targeting ERK with the selective inhibitor U0126 impaired DOX-induced toxicity. By disrupting the simultaneous effects of the two drugs, the survival of cancer cells can be enhanced. The use of MEK/ERK inhibitors like U0126 in combination with chemotherapy drugs to enhance the anticancer effect and remove possible antagonistic effects is being considered [176].

Metformin targets the MAPK pathway and the AMPK/mTOR complex 1 pathway. Combined treatment of metformin and sorafenib strongly inhibits the mTOR pathway and stimulated apoptosis in HCC [177]. Activation of Akt is predicted to be the responsible mediator of acquired resistance to sorafenib. GDC0068, an Akt inhibitor, synergize with sorafenib to reverse acquired resistance by switching autophagy from a cell-protective role to a death-promoting mechanism in HCC cells [178].

Dysregulation of the poly(ADP-ribose) polymerase 1 (PARP1)/high mobility box 1 (HMGB1) signaling pathway is an important mechanism involved in resistance to cisplatin. Combined treatment of cisplatin and murine hydrate effectively reverses HepG2DR cell resistance through the suppression of PARP1-mediated autophagy. Murine hydrate binds to cisplatin and inhibits cisplatin-mediated induction of autophagy, increasing the sensitivity of HepG2DR cells to cisplatin toxicity [100].

FDA-approved linifanib and sorafenib induce MEK/kinase signaling pathways and activate autophagic flux. Combination therapy using hydroxychloroquine, chloroquine, and verteporfin with linifanib and sorafenib significantly inhibits autophagy and cell death in HCC patient-derived tumors and mouse xenograft model [98, 179, 180] (Fig. 7).

In clinical trials, cisplatin or oxaliplatin have shown limited and moderate effects in the treatment of advanced HCC, may by inducing cell-protective autophagy. Using chloroquine in combination with cisplatin leads to lysosomal destruction or inhibits the formation of autophagosomes, increasing the level of ROS and thus increasing tumor cell sensitivity in HCC patients [181, 182].

Regarding to the dual role of autophagy, abnormal or excessive autophagy can induce programmed cell death in the forms of non-apoptotic cell death (PCD), known as autophagic cell death or PCD type II [183, 184]. Therefore, in the case of defects in cell apoptosis and resistance to chemotherapy drugs that target apoptosis, modulation of autophagy is necessary for cell death [185]. Sorafenib in combination with the antifolate drug pemetrexed synergistically increased autophagy and cell death. Simultaneously knocking down Beclin 1 suppressed the cytotoxic interaction between sorafenib and pemetrexed, inhibiting autophagy. In contrast to Beclin 1 knockdown, pemetrexed induced MEK/ERK-mediated cell-protective autophagy, indicating autophagy stimulation via a p53- independent or dependent mechanism in HCC [186, 187]. The use of 3-methyladenine as an autophagy blocker along with celecoxib, a cyclooxygenase-2 inhibitor called OSU-03012, causes autophagic cell death in HCC [188].

The combination of sorafenib and modified FOLFOX(m), leucovorin and oxaliplatin was investigated in a phase II clinical trial for treating advanced HCC, which was effective but had moderate toxicity [189]. In addition, radiofrequency ablation (RFA) combined with sorafenib was performed on HCC patients, resulting in enhanced overall survival (OS) [190]. Combined therapy using RFA and transcatheter arterial chemoembolization (TACE) was evaluated in patients with unresectable HCC patients that increased local success and patient survival [191]. TACE was also used in combination with Licartin in 341 patients with stage III/IV HCC and the results showed that the effect of radiopharmaceuticals in the primary endpoint including overall survival in stage III compared to stage IV and the secondary endpoint including time to progression, and side effects [192]. Triple

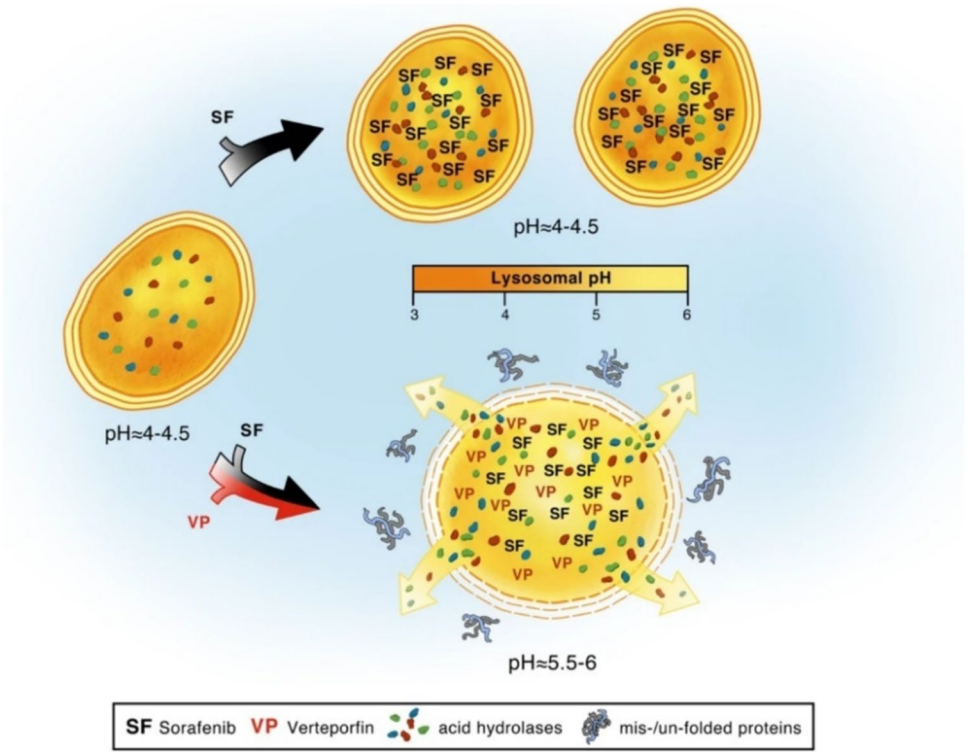

Fig. 7 Co-administration of sorafenib and verteporfin. Sorafenib reduces the distribution and concentration of SF at the target site by passively accumulating in the acidic lumen of lysosomes. Verteporfin creates an alkaline environment inside the lumen, which increases lysosomal membrane permeability. This lead to instability inside the lysosome, disrupting autophagic flux and causing a proteotoxic effect. Reprinted from reference [98]

combination therapy of anti-PD-1 antibodies, lenvatinib, and TACE was evaluated in the clinical phase of HCC patients with unresectable tumor, which showed tumor resection with controllable toxicity [193]. Given the relative success of combined treatments in the clinical phases of HCC patients, combined therapeutic methods targeting autophagy can be a good solution for the treatment of HCC. However, the dual role of autophagy must be carefully considered.

Combination therapies of gene targeting and chemo agents

Another method of combination therapy involves using engineered structures to combine autophagy inhibitor genes with drugs to have a synergistic effect in cancer treatment. For example, resistance to EGFR inhibitor treatment is often observed in human HCC due to the induction of autophagy. Co-treatment with Er and C-225 (EGFR inhibitors) plasmids that overexpress 57 can synergistically target EGFR and contribute to the treatment of HCC [194]. E2F1/USP11 modulates autophagy by regulating the ERK/mTOR pathway, leading to HCC cell proliferation and metastasis. Lipofectamine containing plasmids encoding Flag-USP11 and pCMV-E2F1, along with CQ drug, can simultaneously inhibit autophagy. This approach greatly reduced the tumor size in an HCC mouse model [195].

Combination of miRNAs with other therapeutic agents has been suggested to overcome drug resistance. Transfection of pcDNA/miR-142-3p plasmid constructs-targeting *ATG5/ATG16L1* genes enhanced sensitivity of HCC cancer cells to sorafenib in an animal model [196] (Fig. 8). Small core RNA host gene 16 (SNHG16) belongs to the long non-coding RNA (LncRNA) family and has been shown to induce HCC tumorigenesis by increasing autophagy and causing sorafenib resistance. Conversely, low expression of miR-23b-3p with high expression of SNHG16 was observed in HCC. The SNHG16 target gene was anticipated to be miR-23b-3p, which targets EGR1 gene expression. Silencing of *SNHG16* gene inhibited autophagy and increased the expression of miR-23b-3p by reducing the level of EGR1 through expression vectors. This mechanism inhibited autophagy, used sorafenib, and increased sensitivity to this drug in vivo [197]. Overexpression of LncRNA HANR is another factor in sorafenib resistance by promoting autophagy. miR-29b targeting ATG9A and HANR function inhibited autophagy and reduced sorafenib resistance in HCC cells [198]. Overall, miRNAs and LncRNAs are involved in drug resistance through autophagy and combination therapy with chemotherapy drugs is a promising therapeutic strategy to improve clinical outcomes in HCC patients.

Nanotechnology improved targeting autophagy

The initiation, progression, and metastasis of HCC involve multigene process and genes, making gene therapy using pcDNA, microRNA or siRNA as therapeutic agents an attractive approach for HCC treatment [199–201]. Furthermore, combining chemotherapy with gene therapy can result in synergistic effects on HCC through various mechanisms and has shown some achievement in HCC

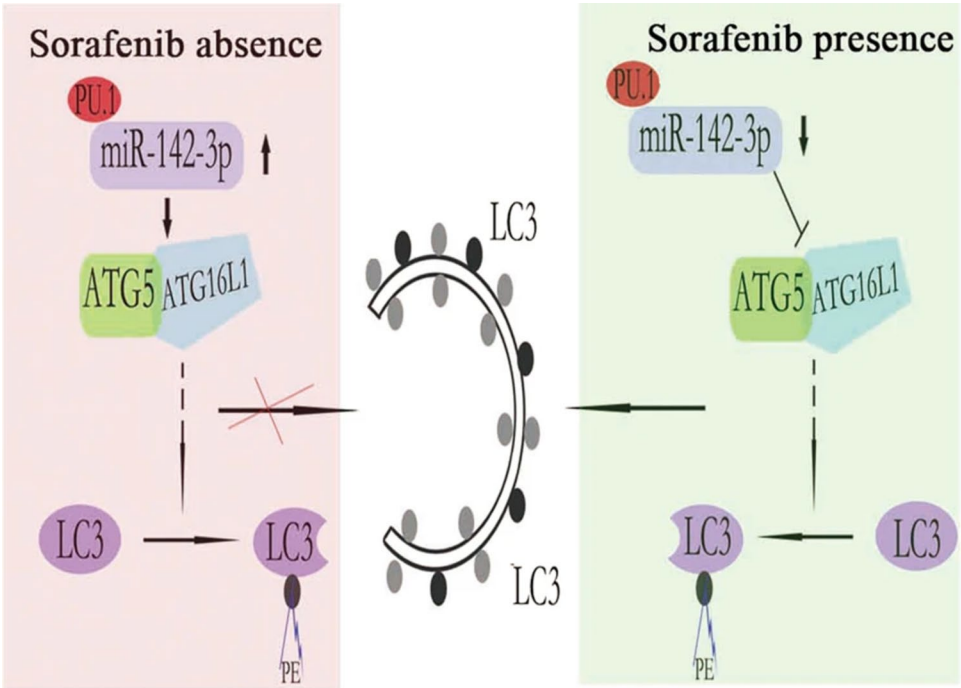

Fig. 8 Schematic overview of miR-142-3p regulatory signaling and its effect on autophagy genes through the miR-142-3p/ATG5/ATG16L1 axis, the presence or absence of sorafenib. Reprinted from reference [196]

therapy [202, 203]. However, development of combination therapies require the creation of an efficient and safe carrier system for the simultaneous delivery of drugs and genes to overcome obstacles such as ineffective gene packaging, low drug solubility, tumor non-specificity, and others [204]. Multifunctional nanocarriers have been designed that can be intended to deliver therapeutic agents for inducing apoptosis, inhibiting autophagy, and interfering with cancer cell growth (Fig. 9). For example, lipid-coated calcium carbonate nanoparticles loaded with sorafenib and miR-375 as an autophagy inhibitor, miR-375/Sf-LCC NPs, have be shown to suppress sorafenib-induced autophagosome formation in HCC cells and tumor tissues, enhancing the antitumor effect in vivo [205]. In comparison with traditional chemotherapies, FTY720 may be a promising anticancer drug due to its lower toxicity and improved oral bioavailability. Calcium phosphate NPs loaded with Beclin 1 siRNA or ATG 5 siRNA and FTY720 have demonstrated increased systemic stability of siRNAs in bloodstream, increased autophagy inhibition, reduced cytotoxicity, and enhanced drug sensitivity and apoptosis in HCC [206].

The self-assembled and biocompatible micelle system was designed to deliver the AMPK activator narcyclazine (Narc) along with a siRNA that targets ULK1. This therapeutic approach targets both the AMPK and autophagy pathways to synergistically promote programmed cell death in vitro and in the animal model. Result have showed that their efficiency of transfection into cells and their ability to release the drug or siRNA cargo and facilitate drug release in the acidic TME, preventing protective autophagy and inhibiting tumor growth [207].

Multidrug resistance is a challenge in HCC treatment that can be associated with autophagy. Research findings indicate that miR-26b expression decreases following DOX treatment in human HCC tissues. Autophagy induced by doxorubicin intensifies resistance to this drug. miR-26b increases doxorubicin sensitivity in HCC cells, but in Hep3B cells, this effect occurs in the absence of p53, which ubiquitination of p53 causes doxorubicin drug resistance. The impact of sp94dr/miR-26b nanowires on HCC cancer cells showed that the combined treatment of miR-26b and DOX increases the sensitivity of HCC cells to DOX by reducing USP9X-mediated p53 deubiquitination and inhibiting autophagy [208].

The results of other studies have shown that inhibition of autophagy cannot always inhibit cancer. For example, when using an amphiphilic copolymer of poly(ethylenimine)-glycyrrhetinic acid (PEI-GA) loaded with DOX and shAkt1, the expression of LC3B-II protein increased, resulting in cell apoptosis in HepG2 cell line and animal mouse model [209]. Overall, compared to monotherapy methods, therapeutic strategies based on nanotechnology have been developed in preclinical stages to act as both drug carriers and delivery system for genes and small compounds effective in specific targeting autophagy pathways. In this way, in a synergistic and targeted manner, they help increase drug sensitivity and improve the efficiency of HCC treatment.

Oncolytic virotherapy

Recent advances in genetic engineering technologies have introduced a new generation of oncolytic viruses (OVs) with acceptable safety and potency for the treating various cancers [210]. Recombinant OVs with therapeutic purposes can target and kill selective tumor cells without affecting healthy cells. In addition, modulated OVs induce antitumor immune responses by lysing tumor cells and

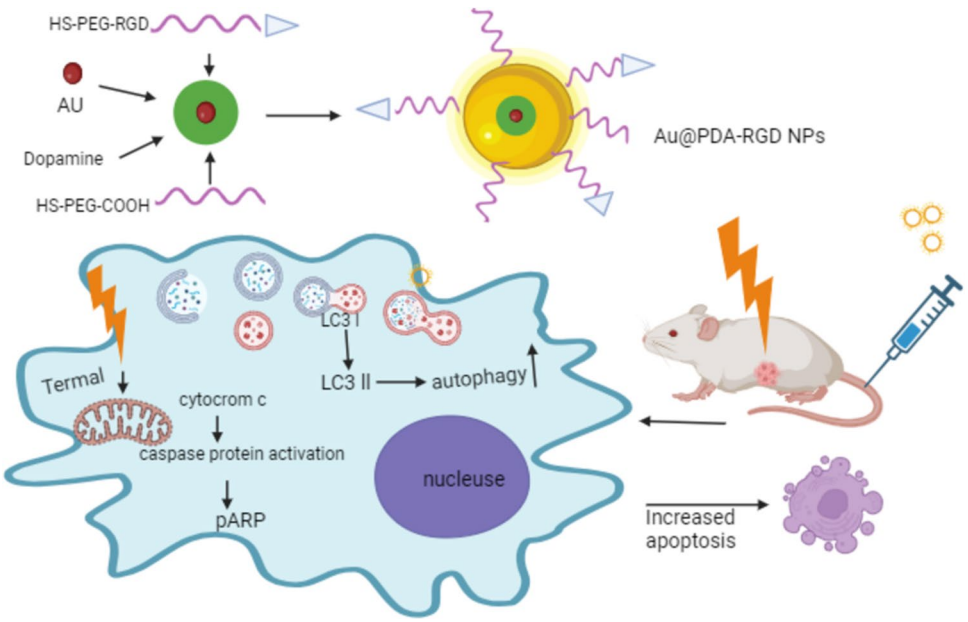

Fig. 9 The Arg-Gly-Asp (RGD) peptide-conjugated polydopamine-coated gold nanostars (Au@PDA-RGD NPs) mediated Photothermal therapy (PTT) induces HCC cell death through the mitochondrial-lysosomal and autophagy pathways. [140] Reproduced from reference

releasing damage-associated molecular patterns (DAMPs), tumor-associated antigens (TAAs), and pathogen-associated molecular patterns (PAMPs). These products are often activated and processed by APCs to stimulate adaptive antitumor immune responses, thereby reducing damage to healthy organs [211, 212]. OV-mediated cancer virus therapy has emerged as a new and successful cancer treatment strategy. The antitumor ability of OVs depends on natural interactions between the immune system, viruses, and cancer cells. Moreover, targeted OVs can be used to express TME-specific genes or carry gene encoding TAAs, antibodies, and cytokines, all of which strengthen the antitumor arm of the immune system or enhance the ability of OVs to combat cancer cells [213, 214] (Fig. 10).

During infection, viruses develop an autophagy system that can play a critical role in preventing the viral life cycle or promoting pathogenicity [215, 216]. Oncolytic virus therapy can interfere with the cellular autophagic mechanism [217, 218]. In regards to oncolytic adenoviruses having a targeted killing effect on HCCcells, Jian Zhang et al. designed an engineered oncolytic adenovirus with dual regulation of Ad. Wnt E1A (△24bp)-TSLC1. This targets the Rb and Wnt signaling pathways individually and transfers the tumor suppressor gene, TSLC1. Results have shown that Ad.wnt-E1A(△24bp)-TSLC1 induces autophagic death effectively and apoptosis in liver CSC-xenografted mice [219] (Fig. 11).

Deficiency of the post-translational modification (PTM) enzyme arginine N-methyltransferase 6 (PRMT6) was reported in HCC. PRMT6 deficiency promotes autophagy through methylation of BAG5 to support cell survival and tumorigenesis in the aggressive TME of HCC. PRMT6 shRNA was cloned into cells using lentiviral cloning vectors. This therapeutic approach of genetic manipulation along with simultaneous treatment with the chemotherapy drug sorafenib was also investigated in an in vivo model. According to the results, targeting BAG5 suppressed autophagy and induced sensitivity of HCC cells to sorafenib for HCC treatment [220].

Addressing autophagy and chemoresistance, decreased expression of miR-125b in HCC leads to oxaliplatin resistance. Transmembrane protein 166 (TMEM166, or EVA1A) is a lysosomal and ER-associated protein that can facilitate autophagy. EVA1A has been identified as a target gene of miR-125b. In this study, the human miR-125b precursor and human EVA1A coding sequence were cloned into the mammalian pcDNA3 vector and pCDH lentiviral vector, and packaging plasmids were used to transfect cells.

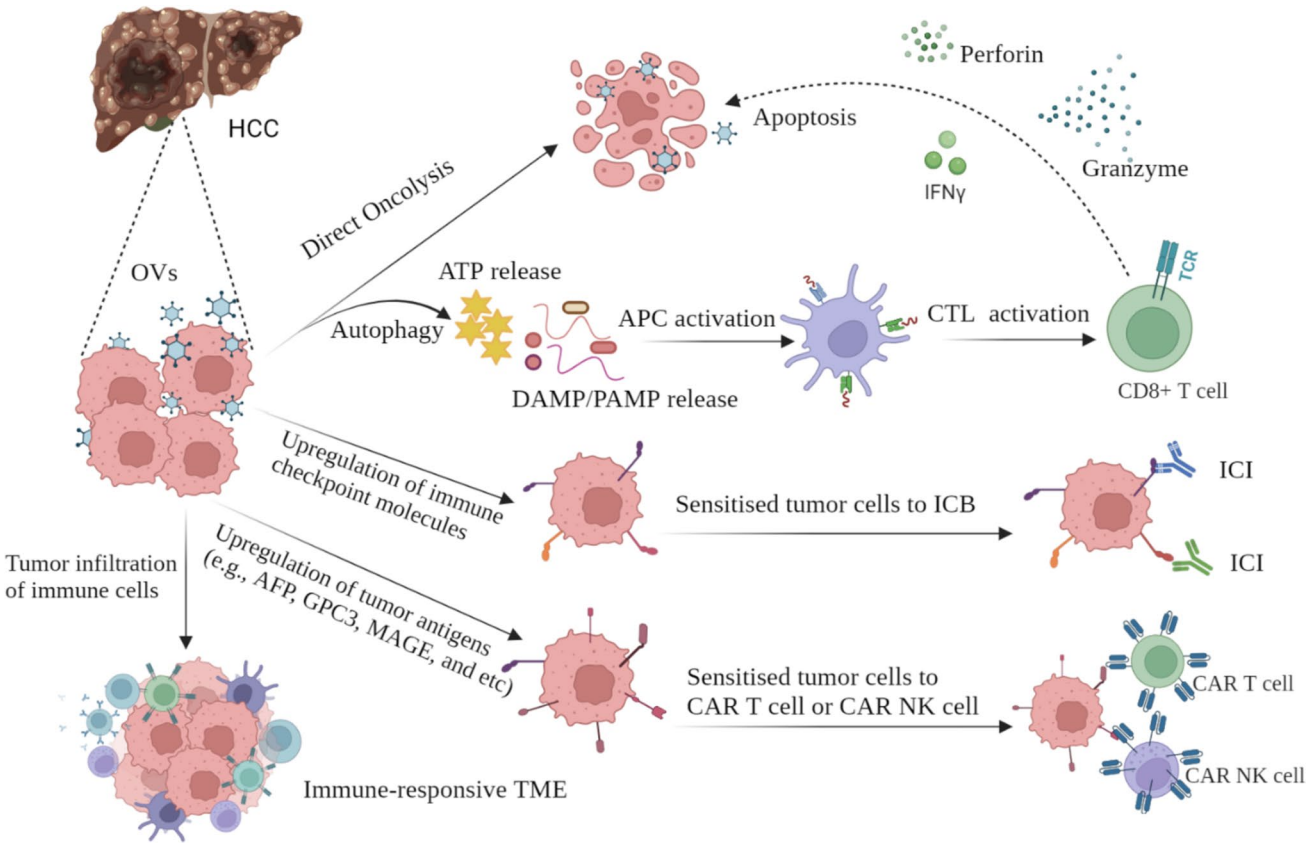

Fig. 10 Major mechanisms by which OVs improve immune responses and immunotherapy in HCC

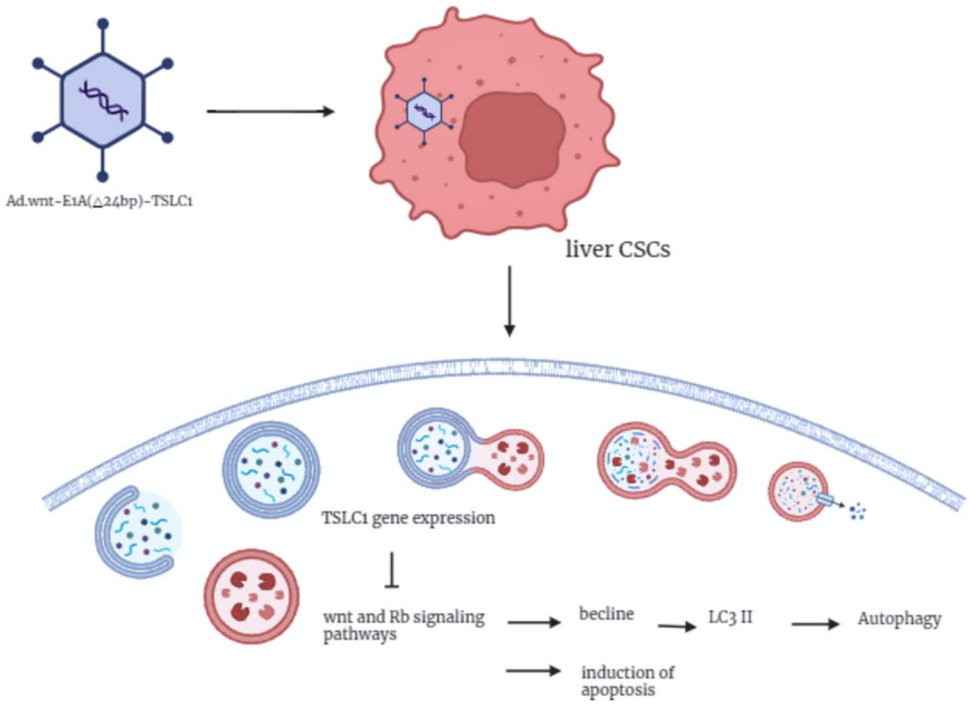

Fig. 11 Ad.wnt-E1A(△24bp)-TSLC1 induces apoptosis and autophagic death in liver cancer stem cells (CSCs) by downregulating the Wnt and Rb signaling pathways

Results showed that miR-125b reversed the EVA1A-induced increase in the LC3-II/LC3-1 ratio, Beclin-1 upregulation, p62 downregulation, and autophagy. It inhibits EVA1A and greatly reduces resistance to oxaliplatin treatment in a mouse model [221].

Hypoxia and nutrient deficiency induce autophagy, which contributes to chemoresistance in HCC, and is also associated with the low expression of Bad and Bim proteins. The engineering and transfection of the lentiviral vector pLSLG carrying the oligonucleotide sequences encoding specific shRNAs for Bad and Bim resulted in the overexpression of Bad and Bim. Combined treatment with mitomycin increased cell death despite the protective effect of LH-induced autophagy [222].

Infection and replication of OVs in cancer cells stimulate host antitumor immune responses and lead to cell death. This mechanism forms the basis for combining OVs with FDA-approved immunotherapies, showing promising synergistic efficacy in improving HCC treatment. Overall, the synergistic effect of OVs in combination with targeted therapy, radiation therapy, chemotherapy and immunotherapy drugs can be more effective than single drug treatments by targeting autophagy in the treatment HCC. Therefore, understanding the mechanism of this interaction in developing combination therapy with autophagy targets for HCC is crucial. To achieve this goal, the role of the virus and cell type in stimulating and inhibiting autophagy should be carefully investigated.

There are challenges in oncolytic virotherapy, such as possibility of those drugs, genes, and other molecule involved in autophagy targeting non-autophagic targets, and complexity of prescribing time or order for autophagy modulators. In the case of HCC, this treatment method is still in the preclinical stages of in vitro and in vivo testing (212, 219).

Conclusion

Autophagy has dual, competitive, and context-dependent effects in cancer. Therefore, a therapeutic approach solely targeting the enhancement or inhibition of the autophagy to cure cancer will not be successful. However, the influence of autophagy in different conditions on the process of cancer development is inevitable, and current clinical treatments for cancer affect autophagy. In addition, physiological stimuli, such as nutrient deprivation or hypoxia, also alter autophagy in tumors. This means that the effects of these changes on the development or inhibition of cancer must be identified and understood to implement appropriate intervention measures in specific situation. Initially, these actions are likely to inhibit autophagy. Therefore, determining which patients will benefit from autophagy inhibition treatment is vital. In order to increase the treatment efficiency, combined methods have been used in different dimensions for the treatment of HCC. Clinical trials have shown the synergistic role of sorafenib, leucovorin, and oxaliplatin with other drugs and small molecules, as well as in combination with other treatment methods, which increases patient survival. Certainly,

these drugs directly or indirectly affect autophagy and play a role kin treatment.

However, drug toxicity and off-target/side effects have limited the efficacy of combined treatments and patient survival. As a result, new biological tools are being researched in the preclinical stages to increase sensitivity to current therapies through the inhibition or modulation of autophagy. These methods involve the use of genetic engineering, expression cloning, nanomedicine, and oncolytic viruses to improve the treatment of HCC patients by strengthening and synergizing the treatment.

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Availability of data and materials No datasets were generated or analyzed during the current study.

Declarations

Competing interest The authors declare no competing interests.

Ethics approval and consent to participate Not applicable.

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