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Review article

Targeting autophagy can synergize the efficacy of immune checkpoint inhibitors against therapeutic resistance: New promising strategy to reinvigorate cancer therapy

Mehrdad Hashemi [a,b], Elaheh Mohandesi Khosroshahi [a], Mahsa Tanha [c], Saloomeh Khoushab [a], Anahita Bizhanpour [a], Farnaz Azizi [a], Mahsa Mohammadzadeh [a,b], Arash Matinahmadi [d], Zeinab Khazaei Koohpar [e], Saba Asadi [a], Hengameh Taheri [a], Ramin Khorrami [f], Marzieh Ramezani Farani [g], Mohsen Rashidi [h,i,**], Mahdi Rezaei [j,***], Eisa Fattah [k,****], Afshin Taheriazam [a,l,*****], Maliheh Entezari [a,b,*]

[a] Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[b] Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[c] Department of Biological Sciences, University of Alabama, Tuscaloosa, AL, United States
[d] Department of Cellular and Molecular Biology, Nicolaus Copernicus University, Torun, Poland
[e] Department of Cell and Molecular Biology, Faculty of Biological Sciences, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran
[f] Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
[g] Department of Biological Sciences and Bioengineering, Nano Bio High-Tech Materials Research Center, Inha University, 100 Inha-ro, Michuhol-gu, Incheon, 22212, Republic of Korea
[h] Department Pharmacology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[i] The Health of Plant and Livestock Products Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[j] Health Research Center, Chamran Hospital, Tehran, Iran
[k] School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[l] Department of Orthopedics, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

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ABSTRACT

Immune checkpoints are a set of inhibitory and stimulatory molecules/mechanisms that affect the activity of immune cells to maintain the existing balance between pro- and anti-inflammatory signaling pathways and avoid the progression of autoimmune disorders. Tumor cells can employ these checkpoints to evade immune system. The discovery and development of immune

* Corresponding author. Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
** Corresponding author. Department Pharmacology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
*** Corresponding author.
**** Corresponding author.
***** Corresponding author. Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
E-mail addresses: dr.mohsenrashidi@yahoo.com (M. Rashidi), dr.mrezaei98@gmail.com (M. Rezaei), eesa.fat@gmail.com (E. Fattah), a.taheriazam@iautmu.ac.ir (A. Taheriazam), mentezari@iautmu.ac.ir (M. Entezari).

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Tumor escape
Therapy resistance

checkpoint inhibitors (ICIs) was thereby a milestone in the area of immuno-oncology. ICIs stimulate anti-tumor immune responses primarily by disrupting co-inhibitory signaling mechanisms and accelerate immune-mediated killing of tumor cells. Despite the beneficial effects of ICIs, they sometimes encounter some degrees of therapeutic resistance, and thereby do not effectively act against tumors. Among multiple combination therapies have been introduced to date, targeting autophagy, as a cellular degradative process to remove expired organelles and subcellular constituents, has represented with potential capacities to overcome ICI-related therapy resistance. It has experimentally been illuminated that autophagy induction blocks the immune checkpoint molecules when administered in conjugation with ICIs, suggesting that autophagy activation may restrict therapeutic challenges that ICIs have encountered with. However, the autophagy flux can also provoke the immune escape of tumors, which must be considered. Since the conventional FDA-approved ICIs have designed and developed to target programmed cell death receptor/ligand 1 (PD-1/PD-L1) as well as cytotoxic T lymphocyte-associated molecule 4 (CTLA-4) immune checkpoint molecules, we aim to review the effects of autophagy targeting in combination with anti-PD-1/PD-L1- and anti-CTLA-4-based ICIs on cancer therapeutic resistance and tumor immune evasion.

1. Introduction

Despite multiple developments in cancer therapy, the expansion of therapeutic resistance is still a major obstacle in achieving long-term remedies [1–3]. In recent years, many researchers as well as oncologists have sought such novel approaches to overcome therapy resistance and boost the efficacy of conventional cancer treatments [4–9]. A promising opened up avenue in this area of research involves the conjugation of two potential therapeutic strategies; i.e. targeting autophagy and utilizing ICIs, combined.

Autophagy is a cellular process that facilitates the degradation and restoration of damaged proteins and organelles, by which supporting the cellular homeostasis [10–13]. Thereby, deregulation of the autophagy flux can result in the onset and progression of multiple cancers by deteriorating the therapy resistance and tumor growth [14–18]. On the other hand, ICIs have transfigured the process of cancer therapy by forcing the body's immune system to fight tumor cells [19–22]. In depth, these inhibitors have the ability of blocking immune checkpoints, as particular molecules and mechanisms accounting for the suppression of immune responses, which in turn uncover the immune system's abilities to perceive and eradicate cancer cells [23–25]. PD-1/PD-L1 and CTLA-4 molecules and their related mechanisms are the best studied immune checkpoint pathways in maintaining standard immune activities that can be blocked by specific ICIs [26–30]. Although ICIs have represented considerable degrees of therapeutic success in a number of patients, a significant proportion still experience therapeutic failure [31–34].

Understanding the intricate interplay between autophagy and immune checkpoint pathways can provide new horizons to combination therapies that hold promise in overcoming therapeutic resistance [35,36]. Mounting evidence suggests that targeting autophagy has the potential of sensitizing cancer cells to ICIs, leading to improvement of treatment outcomes and patient survival rates [37]. Preclinical studies have demonstrated that inhibition of autophagy synergized with immune checkpoint blockade boosts immune responses against tumors and promotes tumor cell death [38,39]. By disrupting autophagy, cancer cells become more vulnerable to immune-mediated killing, allowing ICIs to exert their full potential [40]. This observed synergy between autophagy targeting and immune checkpoint blockade offers a novel approach to counteract molecular mechanisms by which treatment resistance is developed, and also enhance the efficacy of approved immunotherapeutic interventions [41].

Clinical findings are limited in this field and ongoing clinical trials are investigating the safety and efficacy of autophagy-ICIs combination regimens in various cancer types. Still, the obtained results from preclinical evaluations are encouraging and highlight the potential of the above-stated therapeutic strategy to extend the benefits of ICIs to a broader spectrum of cancer-suffering patients and overcome therapy resistance [36,42].

The current review aims to highlight the complex crosstalk between autophagy and the immune system to pave the road for more effective and personalized treatment procedures. As ongoing analyses further clarify the concealed mechanisms and optimize the ordinary therapeutic strategies, the potential of revolutionizing cancer remission and improving patient survival is within reach.

2. Autophagy and therapeutic response

2.1. The autophagy machinery at a glance

Autophagy is a tightly regulated flux that is responsible for the degradation of defective organelles and aggregates of misfolded proteins, getting assistance from lysosomes [43–45]. Although the autophagy was first narrated in the 1960s, the recognition of autophagy-related genes (Atgs) was arisen in the 1990s, propelling significant innovations in elucidating the mechanistic convolutions of autophagy [10,46]. Autophagy initiates with the formation of a double-membrane vesicle, autophagosome that is originated from a phagophore, which is regulated by the mTOR (mammalian target of rapamycin) [47–50]. Phagophore formation is further controlled by the activation of the PI3K, the class III phosphatidylinositol 3-kinase, a.k.a. vacuolar protein sorting 34 (Vps34) that is responsible for triggering the conversion of PI to PI3P. For developing the elongation of the autophagic membrane, the Vps34 targets the newly generated membranes through linking to Atg14, and the PI3P effector proteins are then recruited by PI3P into the phagophore sites

[51–53]. The Atg12-Atg5 complex and light chain 3 (LC3) are necessary systems to control the membrane elongation. Atg12 is first activated by Atg7 to bind to Atg10 in order to be conjugated with Atg5. The newly formed Atg12-Atg5 complex connects to Atg16L, and thus the multimeric Atg12-Atg5-Atg16L is generated. In an Atg16L-dependent manner, the corresponding complex is transferred to the outer membrane of phagophore until the elongation is completed [54–56]. On the other hand, the cytosolic isoform of LC3, i.e. LC3-I, is conjugated to phosphatylethanolamine (PE) to be reconstructed into LC3-II, depending on the presence of Atg3 and Atg7. This LC3-II that is located in both inner and outer membranes of the phagophore, specifically controls the elongation step [57]. The expansion of phagophore eventually results in the formation of the autophagosome [58,59].

The autophagosome, containing detrimental organelles and macromolecules, will then be merged with a lysosome to from the autolysosome for further degradation mediated by lysosomal hydrolases [49]. The development of autophagosome-lysosome fusion is facilitated by lysosomal-associated membrane proteins 1 and 2 (LAMP-1 and LAMP-2) [60]. Although both LAMPs participate in the fusion step, LAMP-2 has been found to be the predominant protein in this context, as its deficiency causes more adverse effects [15,61]. Beyond these lysosomal associated proteins, Rab-7, as a small GTPase Ras-associated protein, also contributes to the maturation process [62,63]. Ultimately, the autophagosomal cargos are degraded and recycled to nutritionally support the cell (Fig. 1) [64]. It is worth noting that the autophagosomal degradation process is not on the basis of random choice, and is a selective removal process relying on the existence of p62/sequestosome-1 (SQSTM1) multi-adaptor molecule and the BAG3 co-chaperone [65,66].

2.2. Autophagy and cancer

Since autophagy-mediated recycling of defected organelles and macromolecules is highly conserved, it would undesirably affect genomic integrity and cellular homeostasis if becomes deregulated, thus being involved in the pathogenesis of a wide spectrum of disorders from neurodegenerative diseases to multiple cancers [15,67–69]. By serving as a quality control machinery through starvation as well as other subcellular stress circumstances, autophagy is involving in cell survival; thereby, once it is inhibited, detrimental ingredients are no longer removed, resulting in an oversensitivity against cell death progression. Furthermore, accumulating evidence has shown that uninterrupted activation of the autophagy flux can stimulate the autophagic cell death [65,70,71]. In the case of tumorigenesis and tumor development, autophagy has a dual role as it functions as a tumor suppressor at the commencement to support genomic integrity, while acts as an oncogenic flux in the later stages of tumor progression [72]. Thus, the beneficial or harmful effects of autophagy are context-dependent and indeed it is considered a double-edged sword in oncogenesis and cancer progression.

Autophagy can also provoke the expression of tumor suppressor genes/proteins or oncogenes/-proteins. Tumor suppressor contributors, which can be silenced by mTOR and AMP-activated protein kinase (AMPK), stimulate the autophagy and subsequent inhibition of tumorigenesis [73–75]. Whilst, oncogenes have been found to be switched on by mTOR, class I PI3K, and protein kinase B (Akt) to block autophagy and further progression of oncogenesis [76,77]. Literally, the mutation of key ATGs decelerates or even ceases the tumor development. It is exemplified by Bax-interacting factor 1 protein (BIF-1) that is mutated or abnormal in many cancer species [78,79]. Also, UV radiation resistance-associated protein (UVRAG), which is an autophagy modulator in relation to BECN1, can suppress autophagy in its mutated from, leading to a provoked cancer cell proliferation [80]. A huge number of Ras-associated

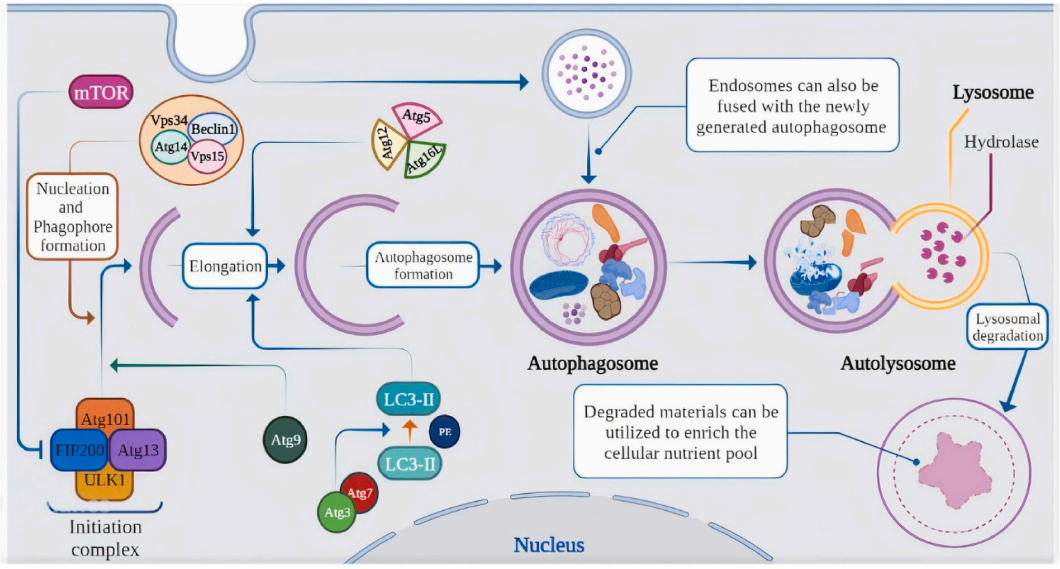

Fig. 1. Autophagy flux; from beginning to end. The initiation step of autophagy, i.e. phagophore formation, is provoked by the initiation complex ULK1/2- Atg13-FIP200-ATG101, which can be inhibited by mTOR. In the next step, Vps34 is activated and connects to Beclin1, Vps15, and Atg14 to conduct the nucleation process and further progression of the phagophore formation. The newly generated phagophores are elongated to form autophagosomes under the regulation of LC3-II and Atg12-Atg5-Atg16L complex. In the following, autophagosomes can fuse with either endosomes or lysosomes to degrade and remove subcellular debris, and thus provide an enriched cellular nutrient pool.

malignancies have also been reported with high basal-level of autophagy [81]. Taken together, either suppression or activation of autophagy can be potential approaches to eradicate cancer (Fig. 2).

2.3. Mechanisms linking autophagy and therapeutic resistance

As a process of cellular self-degradation, autophagy has been found to play a complex role in cancer therapy resistance. Whilst autophagy can promote cell survival during stress conditions, it can also contribute to cell death under certain circumstances [82,83]. The interplay between autophagy and therapeutic resistance in cancer involves several mechanisms; for instance, autophagy can be activated in cancer cells as a survival mechanism in response to various stresses induced by cancer therapies, such as chemotherapy, radiation, or targeted therapies. In other words, it assists cancer cells remove damaged organelles and proteins, maintain energy homeostasis, and promote cell survival during treatment [84].

The activation of protective autophagy is a principal mechanism in association with the success rate of chemotherapy as well as the development of chemoresistance [85]. In this context, the efficacy of 5-Fluorouracil (5-FU), which is a thymidylate synthetase-inhibiting chemo-drug to cure solid tumors, is limited as a consequence of protective autophagy stimulation [86]. Among multiple mechanisms described to explain the interplay between protective autophagy and 5-FU chemoresistance, Beclin 1-mediated conversion of LC3-I to LC3-II, JNK-facilitated phosphorylation of Bcl-2, and over-activation of the autophagy machinery are reported to be more responsible [65]. Temozolomide (TMZ) is another chemotherapeutic agent that acts by alkylating DNA to combat gliomas [87], and the induction of protective autophagy unfortunately attenuates its efficacy, as well [88]. Mechanistically, the up-modulation of the AMPK-ULK1 signaling, the extracellular signal-regulated kinase (ERK) cascade, mitochondrial and endoplasmic reticulum (ER) stress, and reactive oxygen species (ROS) generation are the major mechanisms leading to autophagy activation following the TMZ therapy [65,88]. The response to other chemotherapeutics such as cisplatin, paclitaxel, etc., an also be regulated by the induction of protective autophagy through a vast array of molecular mechanisms and signaling pathways related to autophagy [65].

In the case of radiation therapy, autophagy has been found to be inversely correlated with radioresistance. In other words, autophagy suppression can positively regulate the radiosensitivity in cancer cells, proposing the clinical application of autophagy inhibitors in cancer therapy [89]. In a group of solid tumors, such as osteosarcoma, the activated autophagy reduces post-irradiation ROS production, resulting in radioresistance [90]. Additionally, in glioblastoma (GBM), as well as head and neck carcinoma, the dual inhibitor of PI3K/mTOR, i.e. NVP-BEZ235, triggers radiosensitivity [91]. Cancer stem cells (CSCs) typically represent high degrees of radioresistance and autophagy blockade might help these cells become vulnerable to irradiation [92–94]. In line with this fact, radioresistant GBM stem-like cells (SLGCs) have been reported to have increased basal level autophagy in comparison to sensitive SLGCs [95,96]; thus, silencing the autophagy with an ATG5 small interfering RNA (siRNA) and a PI3K inhibitor such as 3-methyladenine (3-MA) enhances the radiosensitivity in GBM cells, particularly after the inhibition of signal transducer and activator of transcription 3 (STAT3) [97,98]. 3-MA-mediated inhibition of autophagy was also found to be beneficial in increasing the efficacy of radiotherapy in cell culture model of esophageal squamous carcinoma principally by potentiating the apoptotic flux [99].

As the other method of cancer therapy, targeted therapy, which focuses on specific targeting of tumor cells with the lowest degrees of adverse effects on non-cancerous tissues, is also in correlation with protective autophagy [16,100,101]. From this perspective, protective autophagy has been realized to be induced by bevacizumab, an angiogenic-inhibiting monoclonal antibody, to control ROS production, and thereby supporting cell survival in hepatocellular carcinoma (HCC) [102]. Autophagy-dependent resistance to HER2 inhibitors is another example, which provokes cell death evasion in breast cancer [103]. Given the other types of targeted therapeutics,

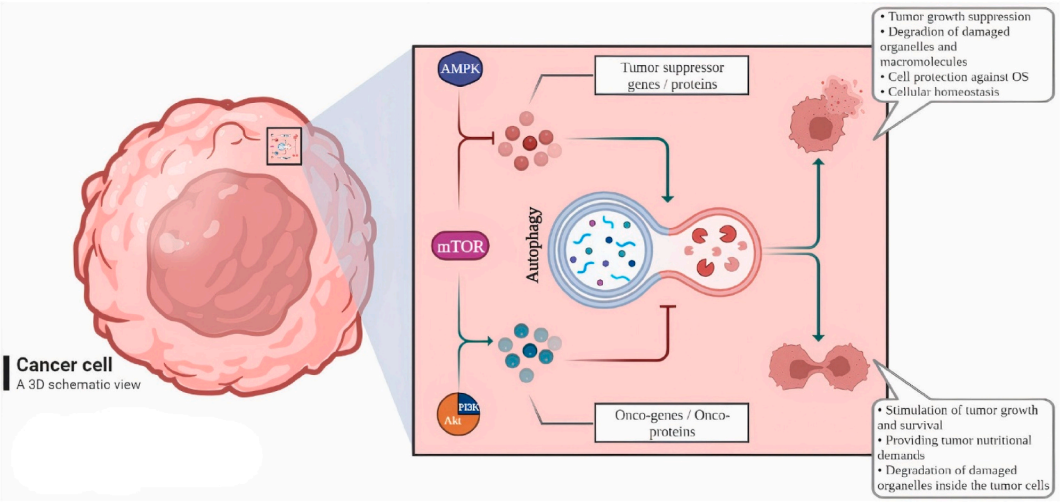

Fig. 2. Dual role of autophagy in cancer. In a tumor cell, autophagy can be activated by tumor suppressor genes/proteins or be inhibited by oncogenes/onco-proteins. In this context, autophagy activation may desirably fight tumor cell, while the inhibited autophagy can result in tumor progression. mTOR and AMPK inhibit the corresponding tumor suppressors, and the same mTOR along with PI3K/Akt stimulate oncogenic factors.

namely small molecule inhibitors (SMIs), autophagy induction may restrict their efficacy; epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are a well-studied group of SMIs that are mechanistically affected by the stimulated autophagy, developing therapeutic resistance [104,105]. TKIs prescribed to combat chronic myeloid leukemia (CML) by interfering with the BCR/Abl oncogene have also been found to trigger protective autophagy in an intracellular calcium-dependent manner [16]. Moreover, sensitivity to the multi-TKI sorafenib can be restored through directing the protective autophagy to death-inducing autophagy in Akt-inhibited sorafenib-resistant HCC cells [106]. In the instance of the interplay between autophagy and hormonal therapy, the therapeutic effectiveness highly depends on the induction of protective autophagy, as well; a hypothesis that was evidenced by the LAMP3-mediated induction of autophagy in tamoxifen-resistant breast cancer [107]. Hence, the up-modulation of protective autophagy is significantly responsible for the expansion of resistance against targeted therapy in a wide variety of cancer models.

Considering the preceding paragraphs, it can be summarized that the efficacy of different cancer therapies is negatively affected by the induction of undesirable protective autophagy, and thus could be overcome by targeting the multiple levels of the autophagy flux, especially in combination with other effective therapeutics, such as immunotherapeutic approaches. Among different types of immunotherapies, using ICIs have clarified promising horizons in cancer eradication. Like all cancer therapeutic methods, ICI therapies encounter various limitations that can be removed or at least attenuated by parallel using of other effective procedures, a.k.a. combination therapies. Targeting autophagy is a potential proceeding in this framework that is specifically highlighted in the following sections.

3. Autophagy and immune checkpoint inhibitors

3.1. Immune checkpoint inhibitors, game-changers in cancer therapy

Under physiological circumstances, a set of immune checkpoints that are known as inhibitory and stimulatory mechanisms affecting the activity of immune cells, have been introduced to maintain the existing balance between pro- and anti-inflammatory signaling cascades as well as conserving the self-tolerance to principally avoid the onset and progression of autoimmune defects [108–110]. Nevertheless, these checkpoints can be employed by tumor cells to evade immune-related eradication [111–115]. Literally, malignant cells suppress tumor antigen expression, trigger T cell tolerance, and release immune suppressive cytokines to turn on inhibitory immune checkpoints [116]. By targeting these checkpoints, ICIs block their inhibitory signals to help the immune system identify and attack tumor cells; in other words, ICI drugs make the immune responses stronger to combat cancer and cancer cells [117–120]. The discovery and approval of ipilimumab was a milestone in ICI therapy and introduced ICIs as new powerful therapeutic weapons to fight a variety of cancers. Unlike the conventional cytotoxic therapeutics, ICIs have improved the efficacy of the host immunity against malignancies [23].

Programmed cell death receptor-1 (PD-1), programmed cell death receptor-1 ligand (PD-L1), and cytotoxic T lymphocyte-

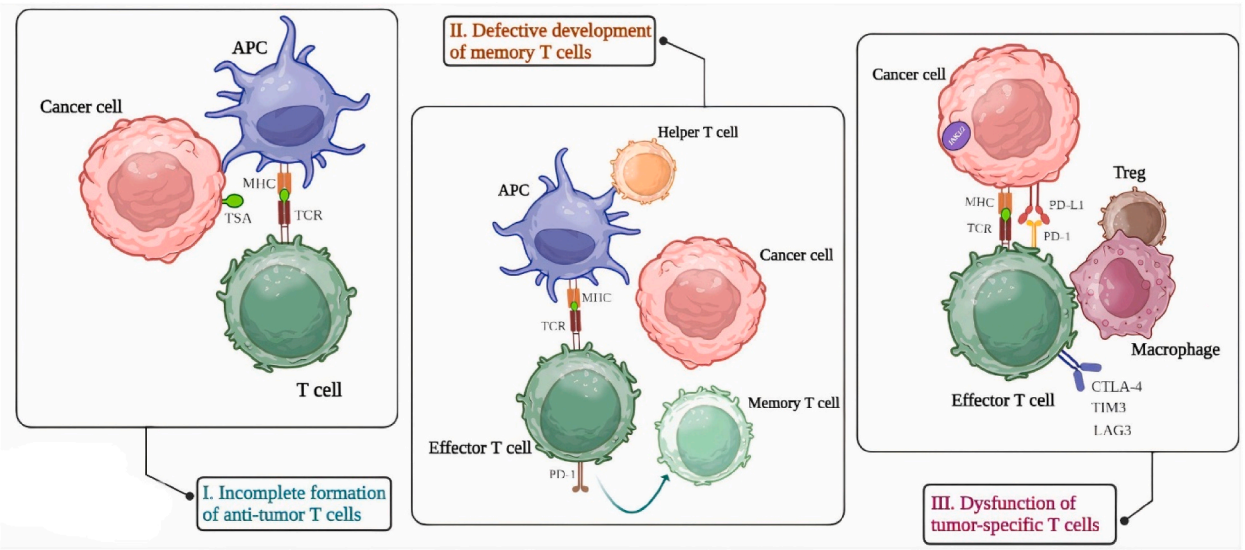

Fig. 3. Underlying mechanisms by which ICI-related therapeutic response and/or resistance can be developed. Innate or acquired resistance against ICIs is developed due to incomplete formation of anti-tumor T cells, defective expansion of memory T cells, and/or dysfunction of tumor-specific T cells. The absence of appropriate neo-antigens, disordered presentation of tumor antigens, and disrupted immune infiltration inside the tumor are considered the major contributors to incomplete T cell generation (Left). In the case of defective development of memory T cells, T cell epigenetic alterations and T cell exhaustion have been realized to be responsible (Middle). Ultimately, defects in IFN signaling, the presence of immune suppressive cells, and alternate immune checkpoints can result in tumor-specific T cell dysfunction (Right). It should be noted that this figure has illustrated the mechanisms related to ICI therapeutic response.

associated molecule-4 (CTLA-4) are the best known immune checkpoints to date [121]. PD-1, which can be up-modulated on activated T cells, attaches to PD-L1 as its ligand, and then restricts the activation of T cells by conducting an inhibitory signal [122]. CTLA-4, as another overexpressed molecule on activated T cells, also blocks the over-stimulation of T cells through T cell receptors (TCRs); in depth, in a competition with the TCR co-stimulatory receptor, CD28, CTLA-4 struggles to link to B7-1/2 ligands for further prevention of CD28-dependent T cell activation [122,123]. Since the oncogenic trait of the tumor microenvironment (TME) depends on the up-regulation of the above-stated molecules, their inhibition could result in the expansion of immune-related anti-tumor responses [124]. For a better understanding, ipilimumab (an anti-CTLA-4 monoclonal antibody) can be exemplified; as the first FDA-approved ICI, ipilimumab was being administered for those with advanced melanoma [125]. Later, anti-PD-1 and anti-PD-L1 drugs, including nivolumab, pembrolizumab, atezolizumab, avelumab, etc., were approved for a wide spectrum of solid and hematologic neoplasms [122,126,127]. Although these ICIs have promoted therapeutic responses, their effectiveness is limited and sometimes they encounter some degrees of resistance [128,129].

According to previous observational studies and clinical trials, there are three different patient populations in response to ICI therapies: responders, which primarily respond and continue to respond; patients with innate resistance that do not respond at all; and those with acquired resistance that respond at first but then develop cancer progression [130–134]. Due to the partial comprehension of the full aspects of clinical, molecular, and immunologic parameters related to clinical response to ICI therapy, the underlying mechanisms by which innate and acquired resistance are developed are not fully elucidated [130]. The central dogma of innate and acquired resistance will be more clarified by reviewing the horizons of the model of response-to-ICI, including the substantial steps that can be suppressed, bypassed, or even blocked in a tumor-dependent manner, or co-selected by stromal and immune ingredients of the TME.

Unsuccessful ICI therapy is principally caused by incomplete production of anti-tumor T cells, dysfunction or inadequate function of tumor-specific T cells, and/or defective expansion of T cell memory [130,133,134] (Fig. 3). In summary, incomplete formation of anti-tumor T cells is developed due to the absence of appropriate neoantigens, disrupted neoantigen processing, or weakened presentation of the antigens [133]. On the other front, various tumor-intrinsic and -extrinsic immune suppressive constituents of the TME are the processes explaining T cell dysfunction [131]. Intending to boost the response to ICI therapy, combination strategies, such as co-administration of anti-CTLA-4 drugs and anti-PD-1/PD-L1 agents, have been employed as one of the promising approaches. Despite the effectiveness of these strategies, the extent of toxicities is challenging [124]. In this regard, over-stimulation of the immune system causes side effects with an autoimmune pattern that may negatively impact diverse organs, leading to hospitalization and cessation of using drugs [135,136]. Furthermore, the next-generation of ICIs that have been designed and developed to target lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin-3 (TIM-3), B7-H3 and B7-H4 molecules, A2aR and CD73, natural killer group protein 2A (NKG2A), and poliovirus receptor-related immunoglobulin domain containing (PVRIG)/poliovirus receptor-related 2 (PVRL2) are being evaluated to enhance the efficacy of current ICI therapies [23,137,138]. Still, some limitations are predicted to disrupt the process of ICI therapy even with the next-generation inhibitors [138]. Thus, more effective and less toxic strategies should be applied to conquer the existing challenges attributed to ICI therapy.

The role of autophagy has been investigated in cancer, and a large number of studies have proposed that autophagy suppression may sensitize tumors to ICIs by releasing T cell-attracting chemokines along with other immunoregulatory mechanisms [139–141]. Thereby, targeting autophagy in conjugation with ICI therapies might improve the efficacy of conventional therapeutics to overcome therapy resistance.

3.2. Impact of autophagy on immune cell function, immune evasion and response

In tumor immunity, tumor cells serve as alloantigens, especially when they are planning to provide antigenic signals to T cells. The recognition of these malignant cells by TCRs on cytotoxic T lymphocytes (CTLs) is facilitated by major histocompatibility complex I (MHC-I) molecules expressed on the surface of the corresponding cells; the molecules that contain tumor-related antigenic peptides. Unfortunately, genetic mutations along with epigenetic alterations can disrupt MHC-I-antigen molecules, leading to cancer cell escape from the immune recognition. Antigen presentation in tumor cells or dendritic cells (DCs) is also affected by autophagy [142,143]. In this regard, T cell immunoglobulin- and mucin domain-containing molecule-4 (TIM-4) link to AMP-activated protein kinase α1 (AMPKα1) as well as activated autophagy-mediated removal of cancer cells, decreasing antigen presentation, impairing CTL responses, and enhancing immune tolerance [144]. Also, malignant cells might serve as antigen presenting cells (APCs), complicating the contribution of autophagy to endogenous antigen processing. Secretory autophagy, in which autophagosomes fuse with plasma membrane instead of lysosomes, can also transmit tumor-specific antigen signals, modulating the immune cells function. Dribbles (defective ribosomal products in blebs) are autophagosomes originated from tumor cells with a content of diverse molecules from DNA to proteins that can be considered hazardous signals [145]. When peripheral blood mononuclear cells (PBMCs) are experimentally loaded with Dribbles come from CMV-pp65 antigen-expressing tumor cells, virus-specific human memory T cells can efficiently be activated [145]. In addition, DRibbles isolated from APCs activate inflammasomes by supplying signals needed for the production of interleukin-1β (IL-1β). B lymphocytes loaded with DRibbles were found to present anti-tumor effects by triggering specific naive $CD8^+$ T cell response [146,147]. Autophagosomes can also act as antigen carriers, which can be utilized in therapeutic cancer vaccination [148]. Considering the impact of autophagosomes derived from cancer cells on immune cell function, the secreted autophagosomes are proposed to affect stromal cells or adjacent tumor cells; a hypothesis that may uncover the immunological role of these autophagosomes to elucidate how secretory autophagy can participate in tumor immunity.

Beyond the effects of autophagy on immune cell function, it can substantially involve in the shaping process of both innate and adaptive immune systems. In this context, the under-expression of MHC-I was recently found to be regulated by an autophagy-

dependent mechanism in pancreatic ductal adenocarcinoma [149–151]. Neighbor of BRCA1 gene 1 (NBR1) autophagy receptor conducts the MHC-I to be targeted to the lysosome, and thus total MHC-I levels were restored following the suppression of autophagy, NBR1, or the lysosome in in vitro and *in vivo* models of PDA [151]. The inhibition of progranulin, as a highly conserved regulator of lysosomal function, was also recognized to be responsible for the restoration of MHC-I expression in PDA cells principally through the suppression of autophagy [152]. Thereby, immune recognition and cancer cell eradication are strongly mediated by the autophagy-lysosome network (Fig. 4). Autophagy-mediated modulation of MHC-I is a specific process, arising from the recognition of aberrant posttranslational modifications (PTM) and is not translatable to MHC-II as well as the other cell surface markers [152,153]. Notwithstanding, further analyses such as global cell surface proteomics are needed to determine the full set of cell surface proteins affected by autophagy. Once autophagy is pharmacologically or even genetically inhibited across multiple cancer cell species, it sensitizes them to immune-mediated eradication [154]. Inflammatory cytokines, such as CCL5, CXCL5, and CCL10 have been found to mediate anti-tumor immune responses in autophagy deficient cancers [155,156]; an interesting finding that supports the hypothesis entitled autophagy inhibition may increase the apparentness of tumors by immune cells. More interestingly, the role of autophagy inhibition in triggering the tumor necrosis factor α (TNFα)-regulated T cell-mediated elimination of tumor cells has also been uncovered by a vast array of genome-wide CRISPR investigations [157–159]. Thoroughly, all these findings focused on the obscure involvement of autophagy in cessation of immune-mediated tumor eradication.

In the case of connection between autophagy and immune response, the autophagy flux can either negatively or positively modulate immune reactions in response to cancer cells. Autophagy triggers T cell survival, and thus maintains ER homeostasis by controlling the content of calcium ions inside the T cells, while autophagy blockade promotes T cell death. Once autophagy is activated, the antigen presentation of DCs and T cell priming is enhanced, resulting in tumor growth deceleration [90]. In response to radiation therapy, as a conventional therapeutic approach to fight cancer cells, autophagy begins to deplete natural ligands of mannose-6-phosphate receptor (MRP), leading to its translocation to the cell surface and subsequent triggering of T cell-mediated eradication together with CTLA-4 immunotherapy in B16F10-bearing tumor model [160]. In response to temozolomide (TMZ) chemo-drug in GL261 glioma cells, autophagy activation can enhance T cell activity. Besides the autophagy-mediated T cell activation, autophagy stimulation also gives rise to NK cell-dependent elimination through homeobox containing 1 (HMBOX1) modulation in HepG2 cells or p53 activation in breast cancer cells [160,161]. In detail, CP31398-mediated reactivation of mutant p53 induces autophagy in breast cancer cells. CP31398 actually prevents lysosomes and autophagosomes to be fused. It also blocks the degradation of granzyme B, as a substantial determinant of NK cell killing [161].

Unlike the aforementioned findings, a group of studies believe that autophagy induction blocks T cell activation in response to chemotherapy [162], as well as epithelial-to-mesenchymal transition (EMT), which results in tumor growth and progression due to disordered T cell-mediated eradication [144,163]. In the absence of APC-associated antigen presentation, T cells priming is disrupted, and further induction of autophagy in macrophages or DCs triggers lysosomal antigen degradation, diminishing T cell killing that promotes tumor growth [144,163]. Chemo-treated cancer cells release danger-associated molecular patterns (DAMPs) to up-regulate TIM-4 on the surface of macrophages and DCs, and TIM-4 itself interacts with AMPKα1 following the autophagy activation. Using chloroquine, as a well-known autophagy inhibitor, causes an increase in $CD8^+$ T cell-mediated killing of colon cancer cells as well as $CD4^+$ T cell-mediated elimination of lung cancer cells. SKI-like proto-oncogene (SKIL)/tafazzin (TAZ)-induced autophagy can block the stimulator of interferon genes (STING) pathway-related immune responses against tumor cells. In parenthesis, SKIL enhances the stability of TAZ protein through down-modulation of LATS2 to induce autophagy in lung cancer. Furthermore, SKIL/TAZ/autophagy cascade suppresses the release of CXCL10, CCL5, and IFN-β, as pro-inflammatory cytokines to activate the STING pathway-triggered immune response against tumor [93,164]. Concurrent with autophagy activation, IL-1β release is decreased, directing the IL-1/Toll-like receptor/nuclear factor κB (IL-1/TLR/NF-κB)-mediated secretion of pro-inflammatory cytokine to be blocked in

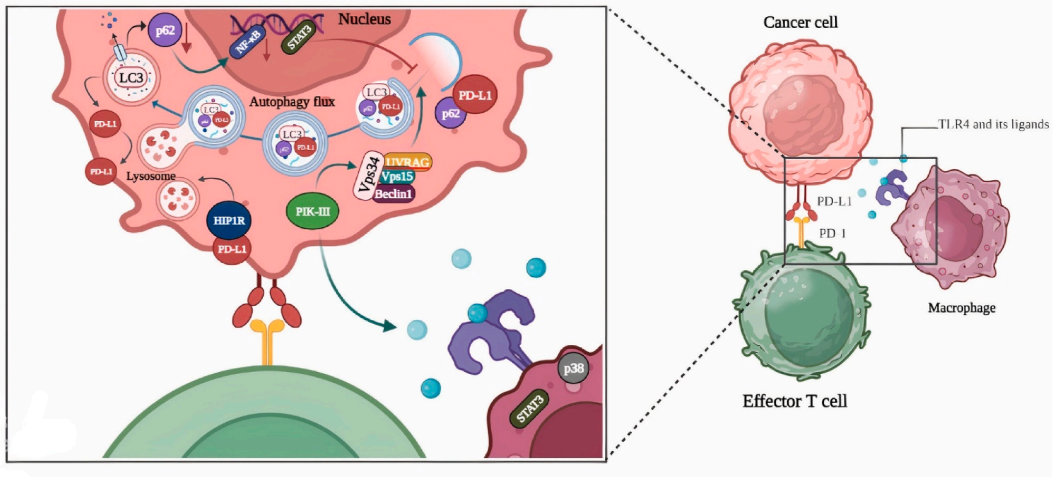

Fig. 4. A schematic view of how autophagy correlates with immune evasion of tumor cell.

macrophages and DCs, which in turn causes an impaired γδ T cell activation [165–167]. Chloroquine can also be used in combination with IL-2 to boost IL-1 immunotherapy in metastatic model of liver cancer [168]. In consequence, autophagy has the ability of repressing pro-inflammatory response-mediated immunotherapy against tumors. Above the autophagy-related down-modulation of T cells, CLL5 is over-stimulated in the absence of autophagy activation, leading to NK cell infiltration followed by tumor growth deceleration in melanomas [169]. Under the hypoxic conditions caused by breast cancer, *in vitro* activated autophagy initiates the degradation of granzyme B to cause an undesirable resistance against NK cell-mediated killing. Together, once autophagy is triggered in APCs or tumor cells, it impedes the activity of immune cells, whose their functions conduct processes such as antigen presentation or granzyme B degradation. Hence, it can be concluded that autophagy induction not only regulates immune responses in a positive manner but also may negatively modulate anti-tumor immune responses.

Surprisingly, autophagy has been found to synergize with dual ICIs therapy (i.e. anti-PD1 and anti-CTLA4 antibodies) to improve the immune responses against cancer cells by up-regulating the MHC-I molecules [162,170]. In the following section, the ambiguous aspects of the existing crosstalk between autophagy and immune checkpoint molecules/mechanisms will be uncovered to highlight the possible effectiveness of autophagy-ICIs combination therapies.

3.3. Interplay between autophagy and immune checkpoint pathways

Regarding the rationale of combination autophagy inhibitors with ICIs, it should be noted that cancer cells are not solitary units; they are in constant interaction with the intricate network of cells and substances that make up their immediate environment [171]. The TME is pivotal at various cancer stages, including its onset, spread, resistance to therapy, and interaction with the immune system [172]. It plays a significant role in both the immune system's monitoring of the tumor and the tumor's evasion of immune detection [173–176]. The TME hosts a variety of immune cells, such as $CD8^+$ and $CD4^+$ T cells, Tregs, B cells, neutrophils, TAMs, NK cells, and DCs. These cells are essential in the dynamic between the tumor and the immune system. Cancer cells present various markers on their surface, including immune checkpoint molecules, which are crucial for self-tolerance and immune regulation, thus enabling the immune system to combat tumors. Nevertheless, cancer cells may utilize these molecules to escape immune detection [177,178]. Two primary mechanisms facilitate immune evasion by cancer cells: One, the disruption of the bond between the MHC molecules on APCs and the TCR impedes antigen presentation and T cell activation [179], and two, the interruption of pathways controlled by co-stimulatory and co-inhibitory molecules, known collectively as immune checkpoints, can also result in immune evasion. Many cancers exhibit a reduction in MHC-I presentation, a vital element for effective antigen presentation, correlating with a negative prognosis [180]. Additionally, the interaction of specific co-inhibitory receptors on T cells, such as CTLA-4 and PD-1, with their respective ligands (B7-1/B7-2 for CTLA-4 and PD-L1 for PD-1) on cancer cells, can inhibit T cell activation and restrict their ability to target tumor cells [181–183].

In the past few decades, ICIs have become a notable strategy in cancer treatment by blocking the inhibitory signals from cancer cells to T cells, thus revitalizing the immune system's attack on tumors [184–186]. Various ICIs targeting CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab, and cemiplimab), and PD-L1 (atezolizumab, avelumab, durvalumab) have been approved for treating more than 50 cancer types [128]. These ICIs can be used alone or in conjunction with chemotherapy, as either primary or secondary treatment options.

Emerging research indicates that autophagy significantly influences the immune response [187–190]. Autophagy can aid immune evasion by targeting MHC-I molecules for degradation [141], a process facilitated by the autophagy cargo receptor NBR1, resulting in reduced MHC-I presentation on cancer cells, thus obstructing antigen presentation and T cell cytotoxicity. Moreover, autophagy can affect the functionality of different immune cells within the TME. For instance, a lack of autophagy in tumor cells can increase PD-L1 expression and dampen T cell-mediated cytotoxicity [191]. On the other hand, inhibiting PPT1, an enzyme involved in autophagic

Table 1
The crosstalk between autophagy and immune checkpoint mechanisms based on *in vitro* evaluations.

Immune checkpoint molecule/mechanism	Target gene/protein/ signaling pathway	Autophagy status	Type of cancer	Cancer-related outcome	Reference
PD-L1 ↓	p62/SQSTM1/NF-κB	Inhibited	Gastric cancer	Tumor progression	[202,203]
PD-L1 ↓	p62	Inhibited	Ovarian epithelial cancer	Platinum chemo-resistance	[225]
PD-L1 ↓	STAT3	Activated	NSCLC	–	[206]
PD-L1 ↓	HIP1R	Activated	NS	Immune-mediated eradication of tumor cells	[208,209]
PD-L1 ↑	SIGMA I	Inhibited	TNBC Prostate cancer	Cancer progression	[210–212]
PD-1/PD-L1	Vps34	Activated	NS	Tumor immune evasion	[140,213]
PD-L1 ↑	ATG7	Activated (degrades FOXO3)	Bladder cancer	Tumor invasion	[214]
CTLA-4 ↑	PI3K/Akt/mTOR	Inhibited	Melanoma	Therapeutic resistance against anti-CTLA-4 Ab	[226]
CTLA-4 ↑	PI3K/Akt/mTOR	Inhibited in DCs	NS	Disruption of antigen presentation and T cell activation	[227]

NS: Not specified.

degradation, can boost T cell priming by encouraging IFN-β release from macrophages and the transition from M2 to M1 phenotype [192]. Inhibiting autophagy also seems to improve the performance of NK cells and DCs in the TME, leading to greater infiltration and cytotoxicity against cancer cells [169,193]. Moreover, blocking autophagy may reprogram TAMs from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype, thereby strengthening the overall anti-tumor immune response [194].

The swift sanctioning of ICIs for oncological applications, favored for their superior risk-to-benefit ratio over conventional treatments, does not guarantee universal effectiveness [180]. Solo ICI treatments have yielded limited success, with response rates seldom surpassing 40 % in specific malignancies. Moreover, ICI-based combination therapies have been linked to an increase in immune-related complications [131]. Such constraints have catalyzed investigations into synergistic approaches, particularly incorporating autophagy blockers to amplify ICI efficacy.

PD-L1, as the PD-1 ligand, is a molecule with immunosuppressive capacities that is expressed on the surface of cancer cells as well as the membrane of immune cells. Immunosuppressive effects of PD-L1 are unveiled when the molecules are bound to their receptor, PD-1, on the surface of T cells, which in turn block the proliferation of these immune cells [195]. Both *in vitro* and *in vivo* assessments have confirmed that autophagy can down-regulate the PD-L1. By degrading immune checkpoints as well as controlling the cytokine release, autophagy can modulate immunotherapy (Table 1). As one of the accepted mechanisms, autophagy decides to degrade damaged DNA, disordered proteins, and expired organelles to sustain standard cell conditions for triggering anti-tumor immunity. Negatively, autophagy also has negative roles in the induction of tumor cell monitoring [196,197], as it provokes immune evasion of cancer cells due to the blockade of mTOR signaling, which leads to autophagy activation.

The autophagy-mediated regulation of PD-L1 expression is orchestrated through multiple mechanisms with the participation of diverse genes and proteins. P62/SQSTM1 is one of those proteins with multifaceted activities that modulates cell vital processes such as signal transduction, survival, and apoptosis [198,199]. P62 that is intrinsically known as a ubiquitin-binding protein, has been observed to be responsible for the regulation of several signaling pathways, as well as the autophagy flux. Through the autophagy, p62 is degraded inside the cytoplasm and is accumulated concurrent with autophagy dysfunction. Indeed, p62 is a reflector of autophagy activity and is inversely correlated with degradative capacity of autophagy [200,201]. Following the p62-induced autophagy, a variety of tumor-provoking pathways such as NF-κB signaling are activated; in gastric cancer, it has been demonstrated that PD-L1 expression is modulated through the p62/SQSTM1-/NF-κB signaling. Using autophagy inhibitors and small interfering RNA (siRNA), PD-L1 can be overexpressed, leading to p62 accumulation and NF-κB over-activation. The accumulated p62 still trigger tumor progression by subsequent activation of NF-κB and other downstream mechanisms. As a consequence, autophagy and p62 can form a cooperative network to support tumor growth and development. The corresponding network can also orchestrate the chemotherapeutic response; for instance, platinum-resistant ovarian epithelial cancer cells have been reported with high expression levels of p62, which is under-expressed when an autophagy stimulator is applied, sensitizing the tumor cells to platinum [202,203]. Therefore, targeting autophagy with subsequent modulation of p62 can be considered an approach to autophagy-ICI combination therapy [204].

In line with the findings reviewed about p62, STAT3 is also of great significance in modulating the nexus between autophagy and PD-1/PD-L1 immune checkpoint pathway. In response to tumor-stimulating signals, STAT3 is up-regulated to switch on target genes for subsequent induction of tumor growth [205]. The mentioned up-modulation of STAT3 has been shown to increase PD-L1 expression, to help cancer cells escape from the immune killing. STAT3 is inversely correlated with tumor autophagy, as its over-stimulation blocks the autophagy flux, and *vice versa*; whilst it can activate autophagy if becomes dephosphorylated [201]. According to the study conducted by Tang et al., miRNA-3127-5p-mediated phosphorylation of STAT3 that results in autophagy inhibition, specifically through blocking the autophagosome generation, over-activate PD-L1 in cell culture model of non-small cell lung carcinoma (NSCLC) [206], suggesting the pivotal role of this miRNA in lung cancer chemotherapeutic resistance with the contribution of STAT3-autophagy-PD-L1 nexus. Accumulating evidence suggests that PD-L1 is also expressed on the Golgi apparatus (GA) and related vesicles other than the cancer cell surface [207]. PD-L1 molecules that are located on the surface of tumor cells are responsible for the repression of immune escape and stimulation of the oncogenic processes. Huntingtin-interacting protein 1-related protein (HIP1R), which is a PD-L1-binding autophagy receptor, targets the PD-L1 to be degraded by the autophagy-lysosome pathway, which in turn potentiates the immune killing effects of immune cells. In the absence of HIP1R, autophagy is down-modulated, while PD-L1 is overexpressed [208,209]. There are a group of proteins that can stabilize PD-L1 by blocking its autophagic lysosomal degradation. SIGMA I (integrated membrane scaffold protein) is one of those proteins that interacts with glycosylated PD-L1 to increase PD-L1 content in *in vitro* models of triple-negative breast cancer (TNBC) and prostate cancer [210,211]. RNAi-mediated silencing of SIGMA I results in PD-L1 under-expression. This event is also caused by using the SIGMA inhibitor, IPAG [1-(4-chlorophenyl)-3-(2-adamantyl) guanidine]. In detail, IPAG stimulates autophagy, up-regulates LC3B, suppresses the PD-L1 expression, and over-activates T-cells, suggesting the autophagy-mediated degradation of PD-L1 [212].

The process of autophagosome formation, which is central to the whole autophagy, is controlled by a type III PI3K (PIK3C3), Vps34, in a complex network with Vps15/Atg14/UVRAG/Beclin1 (Fig. 1); thus, the initiation step of autophagy substantially depends on the presence of Vps34 [140]. Regarding the considerable role of Vps34 in autophagy progression, it can be targeted for autophagy blockade to cease the process of tumor immune efficacy of PD-1/PD-L1 immune checkpoint disruption [213]. Since immune cell dysfunction in the TME triggers the immune evasion of cancer cells, Vps34 inhibition could recruit immune cells by promoting the expression and release of particular chemokines (i.e. CCL5 and CXCL10) from tumor cells and tissues [140]. In this context, combining antibodies to PD-1 and PD-L1 with Vps34 inhibitors represented more efficient therapeutic effects in a mouse model of tumorigenesis.

In bladder cancer, ATG7 overexpression can result in autophagy-mediated removal of forkhead box transcription factor O3 (FOXO3) and the subsequent inhibition of miR-145, which in turn up-regulates the PD-L1 [214]. Literally, once miR-145 is under-expressed, it is no longer linked to the 3′-UTR of PD-L1 mRNA, which leads to stabilization of the corresponding mRNA. The stabilized and over-expressed PD-L1 protein then increases the invasiveness of bladder cancer cells [214].

Research indicates that NSCLC patients with liver kinase B1 (LKB1) mutations respond inadequately to anti-PD-1 therapy. This lack of response may stem from heightened autophagic activity in LKB1-deficient tumors, which leads to the breakdown of antigen-processing systems and diminished MHC presentation. Deng and colleagues found that obstructing ULK1 (via MRT68921) or lysosomal operations hinders the autophagic destruction of immunoproteasome elements, thereby reinstating antigen presentation and bolstering T cell presence in LKB1-mutant NSCLC mouse models, culminating in a bettered reaction to anti-PD-1 therapy [215].

Amaravadi et al. observed that merging hydroxychloroquine (HCQ) with anti-PD-1 therapy curtails tumor expansion and prolongs survival in melanoma rodent models [192]. Chemically impeding PPT1, a controller of autophagy, shifts macrophages from an immunosuppressive M2 type to a cancer-destroying M1 form, enhancing T-cell-driven toxicity. Moreover, PPT1 blockade considerably lessens the infiltration of myeloid-derived suppressor cells within the TME. Additionally, PPT1-lacking DCs seem to better prime naive $CD8^+$ T cells during viral immune reactions, hinting at improved DC functionality post-autophagy inhibition [193].

Recent findings also underscore the promise of merging the PPT1 blocker GNS561 with anti-PD-1 therapy to rejuvenate the immune response in a genetically modified, immunocompetent HCC mouse model [216]. This duo elevates MHC-I expression on cancerous cells, prompting the reoccupation of the tumor locale by cytotoxic T cells. Presently, a phase 2 clinical trial (NCT05448677) is underway to gauge the safety and effectiveness of GNS561 in conjunction with atezolizumab and bevacizumab for the initial management of inoperable HCC, marking the inaugural clinical evaluation of an autophagy inhibitor (PPT1 blocker) in synergy with immunotherapy.

The other immune checkpoint is CTLA-4, whose role in tumor immunity and autophagy has been confirmed in melanoma. Anti-CTLA-4 antibodies can potentiate anti-tumor immune responses. The PI3K/AKT/mTOR signaling pathway that accounts for autophagy inhibition, is undesirably activated in several cancers, and thereby provokes cancer progression [217,218]. CTLA-4 has the ability of triggering the aforementioned signaling to suppress the transcription of proteins required for autophagosome formation, thus blocking the autophagy, while increasing T cell survival. Accordingly, CTLA-4 inhibition by particular antibodies (i.e. anti-CTLA-4 ICIs) reverses the activation of PI3K/AKT/mTOR by down-regulating the ATGs. It has been proposed that autophagy is correlated with CTLA-4 receptor and ligand in an autophagy-PD-L1-like manner [218,219]. In CTLA-4 inhibitor-resistant but not PD-1 inhibitor-resistant melanoma, autophagy inhibition is strongly correlated with cancer-related germline antigens. As a consequence, autophagy inhibition principally contributes to therapeutic resistance against CTLA-4 ICIs. Thus, targeting autophagy in conjugation with CTLA-4 inhibition might provide more efficient therapies against diverse tumors [220]. Consistently, pharmacological inhibition of PI3Kβ has been found to boost the efficacy of anti-PD-1 as well as anti-CTLA-4 therapies, which indicates synergistic effects between ICIs and PI3K-AKT-mTOR signaling. On the other hand, PI3K/Akt/mTOR stimulation caused by CTLA-4 can suppress autophagy in DCs, disrupting the process of antigen presentation and T cell activation. Owing to this finding, a possible connection can be explained between FOXP3+ Tregs and DCs presenting antigens in a CTLA-4-dependent manner, which in turn modifies the autophagy flux. In clinical settings, autophagosome formation is blocked following the treatment of DCs with CTLA-4 antibodies, and thereby autophagy is attenuated [221]. Together, autophagy-CTLA-4 ICI combination therapy may provide more potent anti-tumor T cell immunity.

The Yamamoto group discovered that CQ administration bolsters MHC antigen display in PDAC models. This improvement leads to increased $CD8^+$ T cell growth, activation, and malignant cell eradication. Although CQ alone did not markedly affect tumor size, its use in tandem with anti-PD-1 and anti-CTLA4 treatments resulted in a combined anti-cancer effect and intensified immune response against tumors in rodents [141].

Recently, different approaches are developed for further potentiation of autophagy to increase immunogenic cell death (ICD). Within this context, using low-dose chemotherapeutics in combination with rapamycin, as an autophagy stimulator, has been determined to induce T-cell immunity against tumors. Low-dose rapamycin therapy also enhances neoantigen-specific immune cell responses, accompanied by the modification of the TME [222]. ATG5 silencing declines the release of high mobility group box 1 protein (HMGB1), and the subsequent early inhibited autophagy decreases ICD, while late inhibition can increase ICD, depending on the response of secretory autophagy. Co-administration of ICD stimulator and autophagy inhibitor positively increases the ICD-dependent immunity against multiple malignancies, such as colon cancer [223,224]. This combining strategy has opened up new avenues to cancer immunotherapy. Advantages of ICI-autophagy inhibitor convergence include diminished exhaustion of cytotoxic T cells, transition of TAMs from M2 to M1 phenotype, refined antigen presentation, and strengthened immune response against tumors. Albeit preclinical trials signal potential in the ICI-autophagy inhibitor alliance, extensive clinical trials are essential to substantiate these preliminary outcomes [180].

4. Preclinical evidence: autophagy inhibitors in combination with ICIs

One of the most common circumstances leading to ICI resistance is cold TME that is characterized by the lack of T cells with tumor-infiltrating features as well as the engagement of immunosuppressive cells. As mentioned previously, targeting autophagy facilitates the remodeling of TME to regulate tumor-killing immune responses. It is a fact that supports the significance of combination therapies to increase ICIs efficacy.

Among a variety of *in vitro* and *in vivo* assessments to confirm the effectiveness of autophagy-ICI combination therapies, Sharma et al. revealed that chloroquine in conjugation with dual ICI therapy could significantly increase the potential of immune cells to eradicate tumors [224]. Furthermore, co-administration of SIRPα-Fc and chloroquine was found to disrupt the CD47/SIRPα axis to suppress the protective autophagy in tumor cells, then increased the phagocytosis of macrophages, and finally triggered $CD8^+$ T cell-mediated immunity against cancer cells [228,229]. Above that, hydroxychloroquine and rapamycin co-treatment inhibits autophagy along with the under-expression of CD47 and SIRPα, to increase the phagocytosis of tumor-associated macrophages. Concurrent utilization of hydroxychloroquine and rapamycin also enhance the efficacy of anti-PD-1 therapy through converting the M2-like

macrophages into M1-like cells [230]. In this framework, palmitoyl protein thioesterase 1 (PPT1) is a newly identified autophagy modulator that boosts cancer-eradicating immune responses through the aforementioned macrophage switching and enhancing T cell-mediated cytotoxicity [231].

By repressing the ATGs, including Beclin1 and Vps34, CCL5 and CXCL10 pro-inflammatory cytokines are released into the melanoma and colon cancer-related TME by modulating the STAT1/IRF7 signaling, which causes immune effector cells to be infiltrated. Using Vps34 inhibitors can sensitize *in vitro* models of melanoma and colon cancer to PD-1/PD-L1 ICI, and also produce active immune TMEs [232]. Researchers found a promising autophagy inhibitor, ESK981, which sensitizes prostate cancer cells to ICIs. It has been determined that ESK981 acts by releasing CXC10 to draw T cells [233].

In metastatic NSCLC, the conventional PEM/CDDP chemotherapy was not effective in combination with ICIs, while the combination with mitogen-activated protein kinase kinase inhibitor (MEKi) suppressed the autophagy flux and triggered the recruitment of CTLs for further eradication of tumor cells [234]. In tumor models with mutated LKB1, the production of immune peptides is inhibited; the suppression of Unc-51-like kinase 1 (ULK1), as an autophagy modulator, can reverse these conditions by enhancing the immunoproteasome expression [235]. Together, autophagy inhibitors make CTLs to be infiltrated into the TME, resulting in an improved ICI therapy.

Considering the novel approaches of combination therapies, a group of cancers have been recognized to benefit from CTL activation caused by ICI over-stimulation [236]. Learning to how manipulate immune checkpoint mechanisms has revolutionized the immunotherapy of solid tumors and the development of conventional ICIs was a milestone in this context.

Later, autophagy inhibitors, such as chloroquine, which had been confirmed as anti-tumor agents, were found to be more effective against tumors when used in combination with mono- or dual ICI therapy by inhibiting the autophagy-mediated elimination of MHC-I [237,238]. Although there are no clinical evaluations confirming the co-administration of autophagy modulators and ICIs, it has been suggested that targeting autophagy combined with chemo-immunotherapy, especially using MNPs as integrative multifunctional nanoparticles, provides high degrees of stability, biocompatibility, and encapsulation efficiency [239,240], to enhance the therapeutic efficacy and overcome the existing resistance against individual therapies.

5. Limitations and future directions

Inhibiting autophagy is increasingly recognized as a viable approach in oncology, especially when used in tandem with other therapeutic modalities. Early-stage research with various autophagy-blocking agents has yielded promising outcomes, demonstrating significant anti-tumor effects and low toxicity at reduced dosages. Nonetheless, the transition from preclinical success to clinical application has been challenging, with some trials showing adverse effects and limited effectiveness [180].

The primary obstacle has been the lack of specificity in previously tested autophagy blockers, as they were not originally developed for this purpose. However, recent advancements have introduced a new wave of autophagy inhibitors, specifically engineered for cancer therapy, which are currently undergoing clinical evaluation. These novel inhibitors show great potential, particularly when paired with ICIs, to reactivate cytotoxic T cells and modify the behavior of TAMs to combat cancer. Presently, GNS561 is the only autophagy inhibitor under phase 2 clinical investigation in conjunction with atezolizumab and bevacizumab [180].

The combination of autophagy inhibitors and immune checkpoint inhibitors in cancer therapy is a complex strategy that aims to enhance the effectiveness of treatment. However, there are several challenges and limitations associated with this approach, including the presence of few T cells (“immune-cold” tumors) and a high number of immunosuppressive cells in the TME can limit the effectiveness of combination therapy, primary and secondary resistance to single-agent immunotherapy often results in treatment failure, and only a minority of patients experience long-term benefits, novel strategies need to be investigated for subgroups of patients with low expression of PD-L1, as there is a lack of overall survival benefit of immune checkpoint inhibitor–based regimens in the first-line setting versus chemotherapy alone. The challenge and development of targeting cytoprotective autophagy as a cancer therapeutic approach in clinical application need further study. Furthermore, autophagy plays a role in therapeutic resistance, and the limitations of available autophagic inhibitors in cancer treatment need to be addressed [241–244].

MEK inhibitors (MEKi), akin to ICIs, have demonstrated encouraging preclinical efficacy but have fallen short in clinical settings [245]. Intriguingly, inhibiting the KRAS-RAF-MEK-ERK signaling cascade has been found to induce autophagy, thereby shielding cancer cells from the adverse effects of KRAS pathway disruption [246]. DCC-3116, a molecule designed to counteract this autophagy upsurge, has shown potential in augmenting the anti-cancer effects of trametinib (a MEKi) in laboratory studies [247], underscoring the prospective synergy of autophagy blockers with MEKi in clinical research (NCT04892017).

Despite being in the nascent stages, the strategy of targeting autophagy in cancer therapy remains persuasive, more so when integrated with targeted treatments and MEKi. Emerging research avenues have also come to light. Recent breakthroughs in understanding autophagosome genesis have pinpointed TMEM41B deficiency as a factor in disrupted autophagy initiation and lipid utilization [248,249]. Moreover, ATG9A and ATG2A have been identified as key players in autophagosome construction during the elongation phase [250].

Recent findings emphasize the critical role of protein phosphorylation in autophagy regulation. The phosphorylation of VTI1B by PTPN9 [251]and syntaxin 17 by TBK1 [252] is vital for the growth of autophagic structures and the formation of the ULK1 complex, which governs autophagosome creation. Furthermore, Klionsky and colleagues have demonstrated that ATG14 not only activates the ULK1 complex but also oversees the fusion of autophagosomes with lysosomes, highlighting the intricate functions of autophagy-related protein variants and the therapeutic potential of targeting specific variants [180].

The advent of proteolysis-targeting chimeras (PROTACs) marks an innovative direction for crafting autophagy inhibitors [253]. This approach holds the promise of engaging previously intractable proteins, offering advantages such as reversibility, heightened

specificity, and reduced dosage needs [254]. Despite ongoing developmental challenges, particularly their substantial molecular size, PROTACs present considerable potential for modulating autophagy and other pivotal pathways in cancer treatment and immune cell activation [180].

The pursuit of autophagy as a target in cancer therapy continues to be a dynamic field of study, with the advent of more precise autophagy inhibitors, combined regimens with ICIs and MEKi, and the exploration of innovative methods like PROTACs, paving the way for surmounting existing barriers and forging more efficacious cancer treatments.

6. Conclusions

Despite the effectivity of ICIs in immunotherapeutic cessation of cancers, they represent degrees of insufficiency as tumors may evade the immune system and do not respond to conventional therapies due to their intrinsic or acquired resistance. Many combination therapies have been proposed and evaluated by clinical trials to minimize or even eradicate tumor resistance against ICIs, however most of them were not so beneficial. In recent years, researchers noticed that targeting autophagy in combination with applying conventional ICIs, including anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, can boost the potential and efficacy of theses immunotherapies in fighting different malignancies. Within the context, autophagy induction has been found to be a promising tool to improve tumor immunotherapy based on the autophagic elimination of PD-L1. Thus, the immune checkpoint PD-L1 is almost completely blocked and tumor cells have no longer access to those molecules. Furthermore, the stimulation of autophagy also accelerates the blockade of CTLA-4, as it undergoes recycling to the cell surface and is packaged for further lysosomal degradation. Autophagy activation affects the antigen production and T cell activation, as well. Notwithstanding, no approved autophagy-ICI combination therapy has been introduced to cure a particular cancer type, and also some investigations believe that autophagy can undesirably cause tumor immune evasion. Thus, further experimental studies as well as clinical trials are still needed to confirm possible benefits of using ICIs in combination with autophagy regulators in treating ICI-resistant tumors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AMPK	AMP-activated protein kinase
APC	Antigen presenting cell
ATG	Autophagy-related protein
Atg	Autophagy-related gene.
BAG3	Bcl2-associated athanogene 3

BIF Bax-interacting factor
CML Chronic myeloid leukemia
CRC Colorectal cancer
CSC Cancer stem cell
CTL Cytotoxic T lymphocyte
CTLA-4 Cytotoxic T lymphocyte-associated molecule 4
DAMP Danger-associated molecular pattern
DC Dendritic cell
Dribbles Defective ribosomal products in blebs
EGFR-TKIs Epidermal growth factor receptor – tyrosine kinase inhibitor
EMT Epithelial-to-mesenchymal transition
ER Endoplasmic reticulum
ERK Extracellular signal-regulated kinase
FOXO3 Forkhead box O3
GA Golgi apparatus
GBM Glioblastoma
HCC Hepatocellular carcinoma
HIP1R Huntingtin-interacting protein 1-related protein
HMBOX1 Homeobox containing protein 1
HMGB1 High mobility group box 1 protein
ICD Immunogenic cell death
ICI Immune checkpoint inhibitor
IFN-β Interferon β
IL-1β Interleukin 1β
LAG-3 Lymphocyte activation gene 3
LAMP Lysosomal-associated membrane protein
LATS2 Large tumor suppressor kinase 2
LC3 Light chain protein 3
LKB1 Liver kinase B1
MEKi Mitogen-activated protein kinase kinase inhibitor
MHC Major Histocompatibility complex
MNP Magnetic nanoparticle
MRP Mannose-6-phosphate receptor
mTOR Mammalian target of rapamycin
NBR1 Neighbor of BRCA1 gene 1
NF-κB Nuclear factor κB
NKG2A Natural killer group protein 2A
NSCLC Non-small cell lung cancer
OS Oxidative stress
PBMC Peripheral blood mononuclear cell
PD-1 Programmed cell death receptor-1
PDA Pancreatic ductal adenocarcinoma
PD-L1 Programmed cell death ligand-1
PE Phosphatidylethanolamine
PI3K Phosphoinositide 3-kinase
PPT1 Palmitoyl protein thioesterase 1
PTM Post-translational modifications
PVRIG Poliovirus receptor-related immunoglobulin domain containing
PVRL2 Poliovirus receptor-related 2
SIRPα Signal-regulatory protein α
SKIL SKI-like proto-oncogene
SLGC Stem-like glioma cells
SMI Small molecule inhibitor
SQSTM1 Sequestosome-1
STAT Signal transducer and activator of transcription
STING Stimulator of interferon genes
TAM Tumor-associated macrophage
TAZ Tafazzin
TCR T cell receptor
TIM T cell immunoglobulin
TLR Toll-like receptor

TME	Tumor microenvironment
TMZ	Temozolomide
TNBC	Triple negative breast cancer
TNFα	Tumor necrosis factor-α
TSA	Tumor-specific antigen
ULK1	Unc-51-like kinase 1
UTR	Untranslated region
UVRAG	UV radiation resistance-associated protein
Vps34	Vacuolar protein sorting 34

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