Molecular Cancer

REVIEW

Open Access

Autophagy in tumor immune escape and immunotherapy

Huan Wang[1], Peng Sun[1], Xijing Yuan[1], Zhiyong Xu[2], Xinyuan Jiang[2], Mingshu Xiao[2], Xin Yao[1*] and Yueli Shi[2*]

Abstract

The immunotherapy targeting tumor immune escape mechanisms has become a critical strategy in anticancer treatment; however, the challenge of immune resistance remains significant. Autophagy, a cellular response to various stressors, involves the degradation of damaged proteins and organelles via lysosomal pathways, maintaining cellular homeostasis. This process not only supports tumor cell survival but also profoundly impacts the efficacy of cancer immunotherapies. The modulation of autophagy in tumor cells or immune cells exerts dual effects on tumor immune escape and immunotherapy. However, the mechanistic details of how autophagy influences the immune system and therapy remain inadequately understood. Given this complexity, a deeper understanding of the role of autophagy in the tumor-immune landscape could reveal novel therapeutic avenues. By manipulating autophagy appropriately, it may be possible to overcome immune resistance and enhance the effectiveness of immunotherapeutic strategies. This article summarizes the role of autophagy in tumor immunity, its relationship with immunotherapy, and the potential therapeutic benefits of targeting autophagy to strengthen antitumor immune responses and optimize the outcomes of immunotherapy.

Keywords Autophagy, Immune escape, Immune resistance, Tumor immune microenvironment, Cancer

Introduction

Cellular autophagy, a fundamental process of material recycling metabolism in eukaryotic organisms, involves the encapsulation of damaged proteins or organelles within double-membraned autophagic vesicles, which are subsequently transported to lysosomes for degradation [1, 2]. It has been widely reported that autophagy plays a pivotal role in the pathogenesis and therapeutic treatment of a variety of diseases, including tumors [3, 4]. Autophagy exhibits a dual impact on tumor progression, whereby the modulation of autophagy in distinct types of cells results in variable effects on tumor growth [5, 6]. Thus, proper regulation of autophagy may be a potential pathway for tumor treatment.

The tumor immune microenvironment (TIME) is a complex and dynamical network that significantly influences tumor progression. Tumor cells achieve immune escape by evading immune surveillance through various mechanisms, including deletion or down-regulation of tumor antigens to reduce their immunogenicity and suppression of immune responses [7, 8]. Regulation of immune function exerts significant influence on tumorigenesis and development, with immunotherapy gradually emerging as a key strategy in anti-tumor therapy [9]. Currently, the main classes of immunotherapeutic agents in clinical use are immune checkpoint inhibitors, specifically those targeting the programmed cell death ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) axis and cytotoxic T-lymphocyte-associated protein 4

*Correspondence:
Xin Yao
yaoxin@njmu.edu.cn
Yueli Shi
shiyueli@zju.edu.cn
[1] Department of Respiratory & Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China
[2] Department of Respiratory and Critical Care Medicine, Center for Oncology Medicine, the, Fourth Affiliated Hospital of School of Medicine, and Internation School of Medicine, International Institutes of Medicine, Zhejiang University, Yiwu 322000, China

(CTLA-4) [10–13]. The utilization of immune checkpoint inhibitors alone or in conjunction with cytotoxic drugs and targeted therapies has demonstrated enhanced therapeutic efficacy in tumor management, extending patient survival durations and ameliorating quality of life [14, 15]. However, the clinical benefits of immunotherapy are not universal. Challenges such as immune resistance and severe adverse effects impeding its widespread clinical utility [16]. Recent studies suggest that autophagy plays a pivotal role in modulating immune responses and the efficacy of antitumor immunotherapy by regulating the function of tumor cells or immune cells, as well as the production of cytokines [17–20]. This study presents a comprehensive review elucidating the critical role of autophagy in shaping tumor immunity and influencing immunotherapeutic responses.

Cellular autophagy

Cellular autophagy, a vital process of eliminating dysfunctional cellular components and recycling metabolic byproducts, mainly occurred within lysosomes [21]. It can be categorized into three primary types: macroautophagy, microautophagy, and chaperone-mediated autophagy, with macroautophagy being the most extensively studied pathway [22] (Fig. 1). As a fundamental regulatory mechanism, autophagy allows organisms to adapt to environmental stress and maintains a balance between cell survival and death [23]. The initiation phase of autophagy is primarily orchestrated by the ATG1/ULK1 complex, composed of ATG1/ULK1, ATG13, FIP200, and ATG101 proteins [21]. mTOR kinase serves as a critical regulatory in this process, inhibiting the activity of the ULK complex through the phosphorylation of ULK1 and ATG13, thereby suppressing the onset of autophagy [21]. AMPK and p53 signaling promote autophagy by negatively regulating mTOR activity. Additionally, conditions such as starvation and cellular stress enhance autophagy by inhibiting mTOR [21]. The nucleation phase is primarily driven by the VPS34 (PIK3C3)—VPS15—Beclin-1 complex [24]. There exist two functionally different VPS34—VPS15—Beclin-1 complexes. In the case of complex I, ATG14 binds to the complex and stimulates the synthesis of PI3P, along with the recruitment of other autophagy-associated proteins, thereby promoting autophagosome formation. Complex II, on the other hand, is a complex that contains UVRAG mainly involved in promoting autophagosome maturation, endocytosis, and cytokinesis [25]. It is important to note that the Bcl-2 protein can prevent the initiation of autophagy by inhibiting Beclin-1 activity; alleviating this inhibition activates autophagy [21, 24]. Subsequently, ATG genes regulate the elongation and completion/

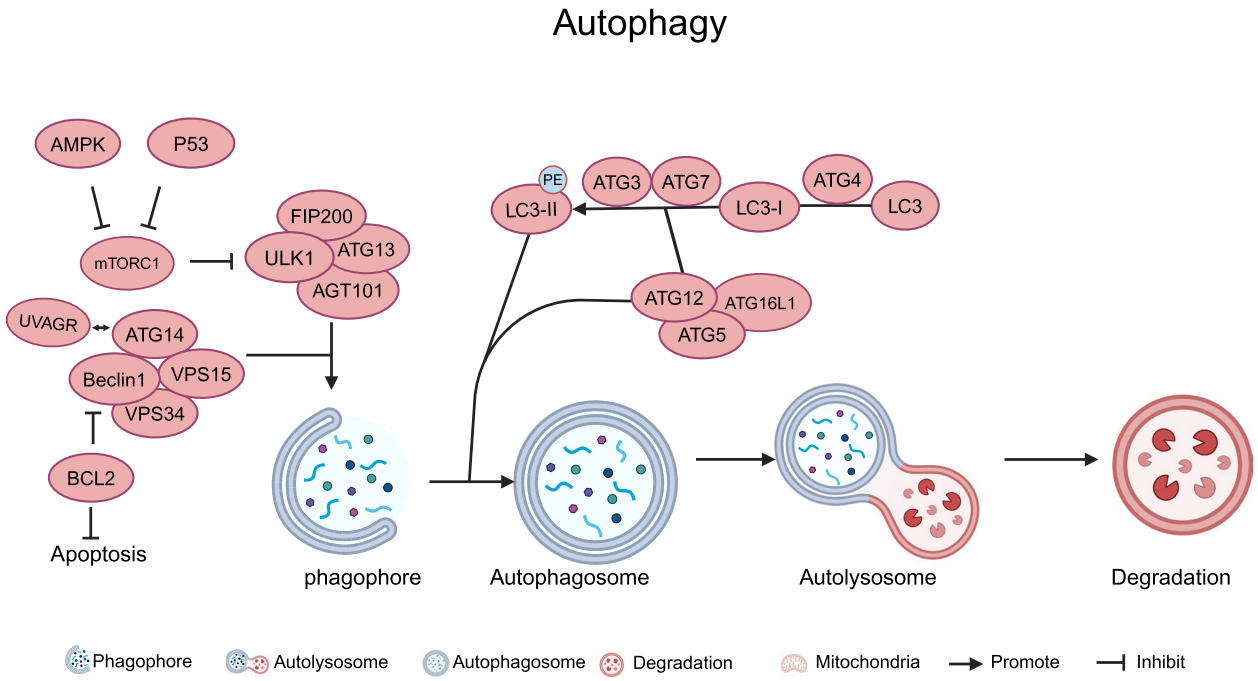

Fig. 1 The brief process of autophagy. Autophagy is regulated by signaling pathways such as AMPK and mTOR. It involves the assembly of the ULK and VPS34 complexes, which facilitate the formation of double-membrane phagophores that subsequently mature into autophagosomes. These structures then fuse with lysosomes to form autolysosomes, where the contents are degraded, allowing for the recycling of cellular components. (Created in https://BioRender.com)

closure of autophagosome. ATG8/LC3 is cleaved by ATG4 to produce LC3-I, which is then activated by ATG7 and translocated to ATG3, and finally modified by phosphatidylethanolamine to form LC3-II with the help of the ATG12-ATG5- ATG16L1 complex [26, 27]. The lipidated form, LC3-II, associates with autophagosome membranes, promoting autophagosome formation [21, 28]. In this process, p62, which acts as a bridge linking LC3 and polyubiquitinated proteins, is selectively wrapped into the autophagosome, after which it is degraded by proteohydrolases in the autophagic lysosome [21, 28]. Thus, the amount of p62 is negatively correlated with autophagic activity [26]. Afterward, nascent autophagosomes fuse with vesicles that originate from endolysosomal compartments prior to the formation of degradative autolysosomes, and this process is called autophagosome maturation. This stage is mainly regulated by the cooperative actions of ATG8 family members, tethering factors, Rab proteins and SNARE complexes [21, 24, 29].

Furthermore, mitophagy, a specialized form of autophagy targeting damaged mitochondria for degradation, plays a pivotal role in maintaining mitochondrial homeostasis [30]. The molecular mechanisms of mitophagy involve both ubiquitin-dependent pathways (such as the PINK1/Parkin and non-Parkin ubiquitin-dependent pathways) and ubiquitin-independent pathways (like the NIX, BNIP3, and FUNDC1 pathway) [30]. The various molecular pathways of mitophagy interact intricately to control mitochondrial quantity and cellular metabolic homeostasis. Apart from the traditional mitophagy mechanism, numerous studies in recent years have confirmed regulatory methods that are different from the classic pathways. For example, Jose et al. found that NDP52 binds to the ULK1 complex through its interaction with FIP200 and initiates autophagy in an LC3-independent manner [31]. OPTN can bind to ATG9A to induce mitophagy, and blocking this binding will lead to a reduction in mitophagy [32]. Moreover, OPTN can also initiate mitophagy by binding to the PI3K complex with the help of TBK1 in a ULK1/2-independent manner [33]. In addition, apart from the well-known LC3, NIX and BNIP3 can initiate autophagy by directly binding to WIPIs [34, 35]. These studies have revealed more mechanisms of how different proteins cooperate to regulate mitophagy, deepening our understanding of this process.

Autophagy undergoes dynamic changes at different stages of tumor development [36–39]. It is generally accepted that autophagy exerts a tumor suppressor role in the early stages of tumorigenesis by inhibiting tissue damage and inflammatory responses. And as the tumor growth, autophagy is enhanced due to inadequate vascularization and limited nutrient supply, forcing cancer cells to rely on autophagy for sustenance [40]. To leverage autophagy effectively for tumor therapy, an in-depth comprehension of the molecular mechanisms governing autophagy during tumor initiation and progression is imperative for designing targeted treatment strategies [37].

Tumour immune escape and immune therapies resistance

The immune system plays a crucial role in maintaining human health and resisting the occurrence and progression of tumors. Under normal circumstances, immune cells in the immune system, including T cells, neutrophils, dendritic cells (DCs), natural killer (NK) cells, macrophages, and B cells, work together in a precise manner to identify tumor-specific antigens and produce cytotoxic factors, effectively eliminating cancer cells and preventing tumor formation and expansion. However, tumor cells can evade immune system surveillance to avoid recognition and attack. This immune evasion is primarily achieved through alterations in the tumor cells themselves and changes in the immune microenvironment, which include: (1) reduced immunogenicity; (2) antigen modulation or loss; (3) low expression of major histocompatibility complex (MHC) class molecules; (4) prevention of apoptosis; (5) lack of costimulatory molecules; (6) recruitment of immunosuppressive cells; and (7) secretion of immunosuppressive factors.

In light of the understanding of immune evasion mechanisms, tumor immunotherapy has rapidly developed in recent years, aiming to effectively kill tumor cells by activating or enhancing the immune system. Current major immunotherapeutic approaches include immune checkpoint inhibitors, adoptive cell therapy, and tumor vaccines. Among these, immune checkpoint inhibitors, such as PD-1/PD-L1 and CTLA-4 blockers, are the most widely used in clinical applications and have demonstrated significant efficacy [10]. For example, studies such as KEYNOTE-189 and KEYNOTE-407 have indicated that the combination of PD-1 monoclonal antibody pembrolizumab with standard chemotherapy results in improved overall survival in patients with non-small cell lung cancer (NSCLC), in comparison to single-agent chemotherapy [12]. Additionally, Cadonilimab, a PD-1/CTLA-4 dual monoclonal antibody, has shown promising objective response rates and safety profiles in solid tumors [13]. However, there are still issues with low efficiency and immune resistance [41]. Immune resistance can be classified into primary resistance and acquired resistance, making the overcoming of immune resistance a pressing issue that needs to be addressed [42].

Autophagy is deemed a significant factor in both immune evasion and immune resistance [21]. Autophagy

Table 1 Effects of autophagy modulation on tumor cell

Compound/taget	Modulation of autophagy	Tumor types	Related mechanisms	Outcome	Ref
PPARγ	PD-L1 selective autophagy	NSCLC	reduce PD-L1 expression	immune activation	46
mTOR inhibitors	Autophagy induction	HCC	reduce PD-L1 expression	immune activation	47
/	Autophagy inhibition	Gastric cancer	promote PD-L1 expression	immune inhibition	48
TRIM14	PD-L1 selective autophagy	Breast cancer	promote PD-L1 expression	immune inhibition	49
CXCL12	Autophagy inhibition	Bladder cancer	promote PD-L1 expression	immune inhibition	50
IL-7A	Autophagy inhibition	NSCLC	promote PD-L1 expression	immune inhibition	51
miR-34a	Autophagy inhibition	Bladder cancer	promote PD-L1 expression	immune inhibition	52
TSPO	Autophagy inhibition	HCC	promote PD-L1 expression	immune inhibition	53
5HT1aR	Autophagy induction	Lung cancer	promote PD-L1 expression	immune inhibition	19
ATG7	Autophagy induction	Bladder cancer	promote PD-L1 expression	immune inhibition	54
Sunitinib	PD-L1 selective autophagy	Melanoma,NSCLC	reduce PD-L1 expression	immune activation	55
Andrographolide	PD-L1 selective autophagy	NSCLC	reduce PD-L1 expression	immune activation	56
Zosuquidar	PD-L1 selective autophagy	CRC	reduce PD-L1 expression	immune activation	57
Curcumin	Autophagy induction	Breast cancer	reduce PD-L1 expression	immune activation	58
Temsirolimus	Autophagy induction	Breast cancer	reduce PD-L1 expression	immune activation	59
Sigma1 inhibitors	ER stress-associated autophagy	Breast and prostate cancer	reduce PD-L1 expression	immune activation	58
Vemurafenib	Golgi-mediated autophagy	Ovarian cancer; lung cancer	reduce PD-L1 expression	immune activation	60
Amlodipine	PD-L1 selective autophagy	Breast cancer; CRC	reduce PD-L1 expression	immune activation	61
Rigosertib	PD-L1 selective autophagy	CRC	reduce PD-L1 expression	immune activation	62
USP24-i-101	Autophagy induction	NSCLC	reduce PD-L1 expression	immune activation	63
Celastrol	Autophagy induction	Renal cell carcinoma	reduce PD-L1 expression	immune activation	64
Cinchonine	Autophagy inhibition	NSCLC	promote PD-L1 expression	NA	65
Chloroquine/ Bafilomycin A1	Autophagy inhibition	Bladder cancer	promote PD-L1 expression	immune inhibition	52
Aspartame potassium	Autophagy inhibition	HCC	promote PD-L1 expression	immune inhibition	66
PINK1-PARK2 loss	Mitophagy	Pancreatic Cancer	reduce PD-L1 expression	immune inhibition	67
NBR1	Autophagy induction	Pancreatic Cancer	reduce MHC-I expression	immune inhibition	71
NDRG1 depletion	Autophagy induction	Pancreatic Cancer	reduce MHC-I expression	immune inhibition	72
Progranulin	Autophagy induction	Pancreatic cancer	reduce MHC-I expression	immune inhibition	73
CH25H loss	Autophagy induction	Pancreatic Cancer	reduce MHC-I expression	immune inhibition	74
HIF1A-AS2	Autophagy induction	Head and Neck Cancer	reduce MHC-I expression	immune inhibition	75
RIPK2	Autophagy induction	Pancreatic Cancer	reduce MHC-I expression	immune inhibition	76
CXCL1	Autophagy induction	CRC	reduce MHC-I expression	immune inhibition	77
IRGQ	Autophagy induction	HCC	reduce MHC-I expression	immune inhibition	78
LSD1 inhibition	Autophagy inhibition	NSCLC	promote MHC-I expression	immune activation	79
PACSIN1 deficiency	Autophagy inhibition	Gastric cancer	promote MHC-I expression	immune activation	80
Berbamine	Autophagy inhibition	Melanoma	promote MHC-I expression	immune activation	81
Radition	Autophagy induction	NSCLC	promote MHC-I expression	immune activation	82
IFN-γ	Autophagy induction	Melanoma	promote MHC-I expression	immune activation	83

Table 1 (continued)

Compound/taget	Modulation of autophagy	Tumor types	Related mechanisms	Outcome	Ref
/	Autophagy inhibition	Pancreatic cancer	increase tumor antigen and LAG3 expression	immune activation	84
/	Autophagy inhibition	NSCLC	upregulate human leukocyte antigens-I expression	immune activation	85
V9302	Autophagy induction	Breast cancer	reduce B7H3 expression and promote granzyme B production	immune activation	86
Radiation	Autophagy induction	Melanoma	promote mannose-6-phosphate receptors expression	immune activation	87
Glycolytic restriction	Autophagy induction	Triple-Negative Breast Cancer	reduce the GM-CSFand CSF expression	immune activation	89
Beclin1 loss	Autophagy inhibition	Melanoma	release CCL5 cytokine	immune activation	90
Rocaglamide	Autophagy inhibition	NSCLC	restored the level of NK cell-derived granzyme B	immune activation	91
ARID1A deficiency	Autophagy inhibition	NSCLC	enhance type I interferon production	immune activation	92
Short-chain fatty acids	Autophagy induction	Prostate cancer	promote CCL20 expression and M2 macrophage polarization	immune inhibition	93,94
F. nucleatum	Autophagy induction	Oral squamous cell carcinoma	promote GLUT1 expression; driving TAMs formation	immune inhibition	95
IFN-γ	Autophagy induction	Cervical cancer	upregulate IDO-1 expression	immune activation	96
Methionine enkephalin	Autophagy induction	Cutaneous squamous cell carcinoma	promote DMAPs emission; promote DC activation	immune activation	100
OBP-702	Autophagy induction	Pancreatic cancer	enhance HMGB1 release	immune activation	101
Piceatannol	Autophagy induction	Fibrosarcom	enhance calreticulin and HMGB1 release	immune activation	102
Thiostrepton	Autophagy induction	Osteosarcoma	enhance ATP and HMGB1 release	immune activation	103
Oncolytic Adenovirus With Temozolomide	Autophagy induction	Prostate cancer	elevated calreticulin, ATP, and HMGB1 release	immune activation	104
Brucine	Autophagy inhibition	CRC	enhance calreticulin and HMGB1 release	immune activation	105
Imipramine	Autophagy induction	Glioblastoma	enhance cAMP levels	immune activation	106
FuFangChangTai Decoction	Autophagy induction	CRC	activate macrophages and increase expression of CD86 and CD40	immune activation	107
PTEN loss	Autophagy inhibition	Melanoma	induce tumor cells to evade T cell killing	immune inhibition	108
SKIL	Autophagy induction	NSCLC	inhibit the STING pathway	immune inhibition	109
TRABID	Autophagy induction	Melanoma	inhibit the STING pathway	immune inhibition	110
FUNDC1	Mitophagy	HCC	suppresse the production of ROS and IL-1β	immune activation	111
MEK inhibitor	Mitophagy	NSCLC	CXCL10 and CD8+T cells increased	immune activation	112
Icaritin	Mitophagy	HCC	stimulate ICD and thus activate T cells	immune activation	113

**CSF* colony stimulating factor; *TAMs* tumor-associated macrophages; *DAMPs* damage-associated molecular patterns; *HMGB1* high mobility group box 1; *ICD* immunogenic cell death; *NSCLC* non-small cell lung cancer; *HCC* hepatocellular carcinoma; *CRC* colorectal cancer; *PD-L1* programmed cell death ligand 1; *MHC* major histocompatibility complex

can have dichotomous roles: on one hand, it may enhance anti-tumor immune responses through autophagy in T cell subsets and support tumor antigen presentation in tumor cells, thereby assisting in tumor immune therapy [37]. On the other hand, autophagy may facilitate tumor cell survival, degrade tumor antigens, enhance regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby contributing to tumor immune escape and drug resistance [3]. Thus, appropriate modulation of autophagy to reduce immune escape, improve immunotherapy efficacy and overcome drug resistance may eventually leads to beneficial clinical outcomes.

Autophagy and cancer cells (Table 1)

Autophagy and its regulatory role in PD-L1 expression in tumor cells (Fig. 2)

PD-L1, also known as B7-H1, is a prominent member of the B7 family, frequently expressed on the surface of various tumor cells. Its interaction with the PD-1 receptor on

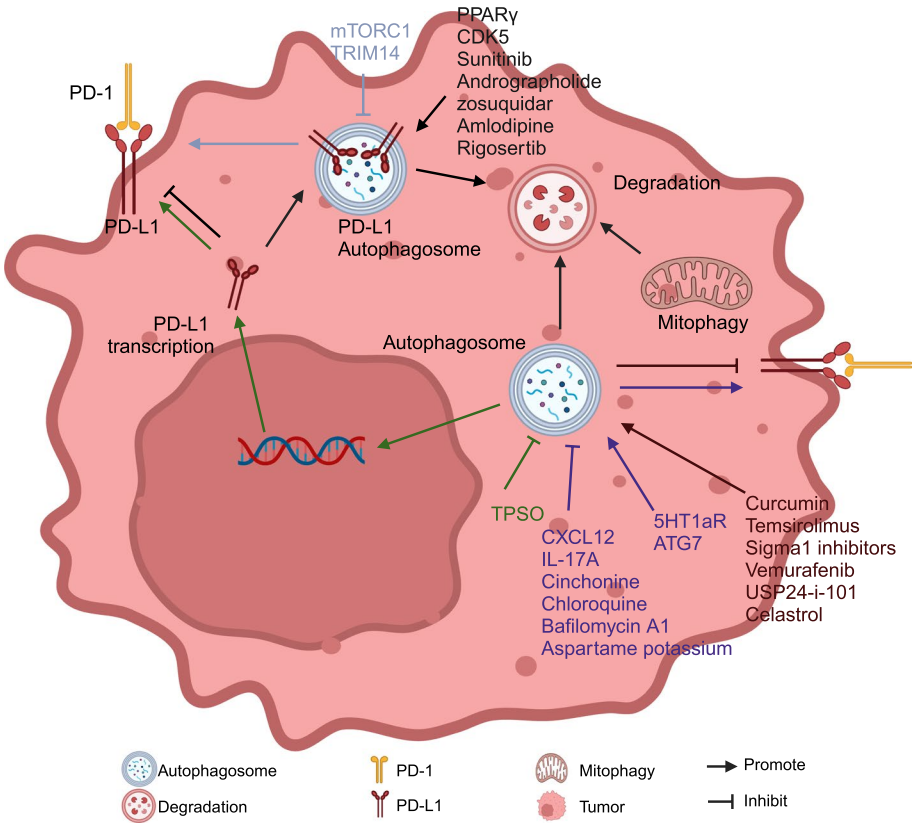

Fig. 2 Autophagy and Its Regulatory Role in PD-L1 Expression in Tumor Cells. Autophagy plays a crucial regulatory role in the expression of PD-L1 in tumor cells. On one hand, autophagy regulates the translation and transcription of PD-L1, with mediators or drugs such as TPSO, CXCL12, and 5HT1aR, as well as curcumin, influencing this pathway. On the other hand, processes involving the autophagic degradation of PD-L1 are mediated by key factors such as mTORC1, TRIM14, and PPARγ, along with specific drugs (e.g., sunitinib, andrographolide) that regulate this pathway. The interaction between autophagy and PD-L1 expression is essential for understanding the mechanisms of immune evasion in tumors and highlights potential therapeutic interventions targeting these processes. (Created in https://BioRender.com)

T cells induces T-cell apoptosis, dysfunction, and exhaustion, thereby inhibits T cells activation and proliferation, which ultimately facilitates tumor immune evasion [43, 44]. Clinically, immune checkpoint inhibitors that target PD-1 and PD-L1 have emerged as the most popular therapeutic options, aimed at enhancing the immune system's ability to attack tumors by restoring T-cell activity [45].

Recent studies reveal that the autophagic degradation of PD-L1 within tumor cells can enhance anti-tumor immunity, augment T-cell cytotoxicity, and inhibit immune evasion. For instance, PPARγ contains a microtubule-associated protein 1A/1B-LC3 interacting region motif, which facilitates the autophagic degradation of PD-L1 in lysosomes, subsequently enhancing T-cell activity against NSCLC [46]. Similarly, mTORC1 inhibition has been shown to induce PD-L1 autophagic degradation in p53-deficient hepatocellular carcinoma (HCC), thus, combining mTOR inhibitors and PD-L1 monoclonal antibodies can enhance anti-tumor efficiency [47]. Accordingly, it is conceivable that inhibition of autophagy can inhibit PD-L1 degradation leading to its up-regulation. Indeed, study has shown that inhibition of selective autophagic degradation mediated by the p62 pathway leads to PD-L1 accumulation [48]. TRIM14 recruits the deubiquitinating enzyme USP14, USP14 deubiquitylated PD-L1 and thus prevents its recognition as cargo by p62 for autophagic degradation [49]. Additionally, CXCL12 mediates immune escape in bladder cancer by upregulating PD-L1 through autophagy inhibition; the combined application of a CXCL12 receptor blocker and PD-1/PD-L1 blockers has shown a more pronounced effect in inhibiting PD-L1 expression and enhancing the anti-tumor immune response [50]. Furthermore, IL-17A inhibits autophagy via the ROS/Nrf2/p62 pathway, thereby promoting PD-L1 expression in cancer cells and driving NSCLC progression [51]. Whereas overexpression of miR-34a in bladder cancer cells could prevent the autophagy blockade-induced PD-L1 upregulation [52]. Apart from preventing PD-L1 degradation, autophagy inhibition can also enhance PD-L1 transcription. For

example, TSPO mediates autophagy inhibition through interaction with p62, leading to its accumulation; this accumulation competes with KEAP1 to prevent Nrf2 degradation, thereby promoting Nrf2-mediated transcriptional upregulation of PD-L1 [53].

However, there are studies suggesting that autophagy activation can also upregulate PD-L1. In lung cancer patients with depression, activation of the 5HT1aR can upregulate PD-L1 expression by activating tumor autophagy and p-STAT3 signaling, contributing to an immunosuppressive environment [19]. The overexpression of ATG7 primarily enhances PD-L1 protein levels by promoting autophagy-mediated degradation of FOXO3a, resulting in the downregulation of miR-145, which stabilizes PD-L1 mRNA [54].

Several pharmacological agents have been identified that inhibit PD-L1 expression by promoting autophagy. For example, Sunitinib, Andrographolide, and zosuquidar enhance p62-dependent selective autophagic degradation of PD-L1, thereby boosting anti-tumor immunity [55–57]. Curcumin, a well-known compound, can induce autophagy to suppress PD-L1 expression, enhancing nucleolin-mediated T-cell activity in triple-negative breast cancer [58]. Additionally, temsirolimus inhibits the secretion of small extracellular vesicle PD-L1and cellular PD-L1 expression in breast cancer cells by activating autophagy, thereby stimulating anti-cancer immunity through increased numbers and activation of $CD4^+$ and $CD8^+$ T cells [59]. Moreover, Sigma1 inhibitors act as potential novel immune modulators by sequestering and eliminating PD-L1 through autophagy in both of breast and prostate cancer cells [58]. Vemurafenib suppresses PD-L1 expression on tumor cells via Golgi-mediated autophagy which increases T lymphocyte infiltration and enhances anti-tumor immune responses [60]. Additionally, amlodipine induces autophagic degradation of PD-L1 by blocking calcium flux, thereby counteracting PD-L1-dependent tumor immune evasion [61]. Rigosertib activates AMPK-ULK1, promotes autophagy-dependent PD-L1 degradation, and synergizes with CTLA-4 antibody in colorectal cancer (CRC) therapy [62]. The compound USP24-i-101 inhibits the expression of ABCG2 and PD-L1 via autophagy induction, thereby suppressing drug resistance in lung cancer [63]. Celastrol exerts antitumor effects on clear cell renal cell carcinoma by activating autophagy to downregulate PD-L1 expression and inducing immunogenic cell death (ICD) [64]. Likewise, pharmacological inhibition of autophagy can upregulate PD-L1 expression. Our study has shown that cinchonine upregulates PD-L1 expression in lung cancer cells by inhibiting autophagy, and combined administration of anti-PD-L1 inhibitors and cinchonine significantly reduces tumor growth [65]. In bladder cancer cells, autophagy inhibitors such as Chloroquine (CQ) and Bafilomycin A1 inhibit autophagy, leading to increased PD-L1 expression and immune suppression via the ERK-JNK-c-Jun signaling pathway [52]. What's more, aspartame potassium upregulates PD-L1 expression through autophagic inhibition, mediating immune evasion in HCC [66].

Mitophagy in tumor cells can influence PD-L1 expression through the autophagy pathway, thereby affecting the immune response. The distribution pattern of PD-L1 is regulated by the ATAD3A-PINK1 axis, wherein PINK1 recruits PD-L1 to mitochondria for degradation via mitophagy [67].

Regulation of immune checkpoints MHC-I expression in tumor cells by autophagy (Fig. 3)

MHC molecules, also known as human leukocyte antigens, are expressed on the surface of cells that recognize and bind antigens, which are then presented to T cells to initiate and regulate immune responses [68]. MHC molecules are divided into two major classes: MHC class I (MHC- I) is widely expressed in a wide variety of cells, whereas MHC class II (MHC- II) is found predominantly on the surface of antigen-presenting cells [68]. During tumor progression, the MHC antigen-presenting process is impaired by different means, leading to tumor immune escape [69]. Restoring the function of MHC molecules, thereby enhancing the specific recognition and attack of T cells against tumors, is currently the direction of many immunotherapeutic strategies [70].

Most current findings below suggest that promotion of autophagy leads to downregulation of MHC-I expression, thereby inhibiting the immune response. In approximately 60% of pancreatic cancers, MHC class I molecules are found at lower-than-normal levels or are completely absent, primarily due to autophagy-induced degradation [71]. Treatments involving progranulin, depletion of NDRG1 or CH25H all reduce MHC-I expression and antigen presentation through autophagy induction in pancreatic cancers [72–74]. Mechanistic studies have shown that autophagy cargo receptor NBR1 induces MHC-1 degradation by binding to MCH-1 and recruiting it to autophagic vesicles in pancreatic cancers [71]. Further studies have shown that MHC-1 is degraded in this mechanism-dependent manner in a variety of tumors, and that HIF1A-AS2, RIPK2 and LC3 all can regulate MHC-1 expression by modulating this mechanism [75, 76]. In CRC, CXCL1 promotes immune evasion through enhancing autophagy-mediated MHC-I degradation [77]. IRGQ promotes tumor immune evasion by directing misfolded MHC-I molecules to the lysosome for degradation, a process that relies on the interaction of IRGQ with autophagy-related proteins GABARAPL2 and LC3-II

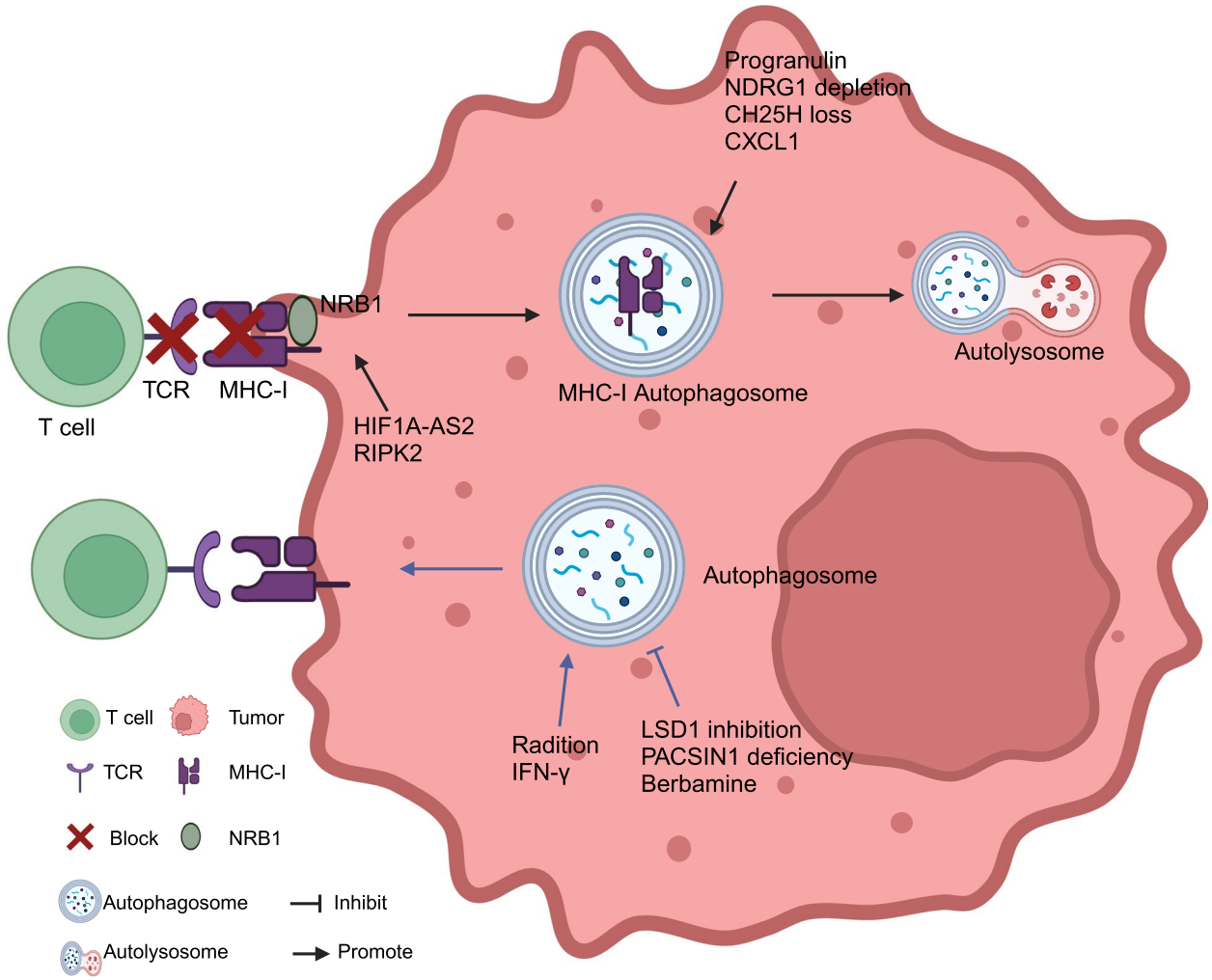

Fig. 3 Regulation of Immune Checkpoints MHC-I Expression in Tumor Cells by Autophagy. Most studies have shown that promotion of autophagy downregulates MHC-I expression and suppresses the immune response. Autophagy cargo receptor NBR1 binds MCH-I and recruits it to autophagic vesicles to induce degradation, and this mechanism can be used by HIF1A-AS2, RIPK2, etc. Treatments such as CXCL1 and progranulin can also induce autophagy to reduce the level of MCH-I. However, autophagy regulates MHC-I expression in a bidirectional manner, for example, autophagy induced by radiotherapy can increase MHC-I expression in a dose-dependent manner. (Created in https://BioRender.com)

[78]. Inhibiting of LSD1 activity can suppress autophagy, leading to an increase in the expression of MHC-I molecules, thereby improving the TIME in NSCLC [79]. Deficiency of PCSIN1 inhibits gastric cancer progression by upregulating MHC-I through the autophagy inhibition [80]. Berbamine has been shown to enhance MHC-I expression by inhibiting autophagy in malignant melanoma, thereby restraining the tumor's immune evasion [81]. However, it has also been shown that autophagy plays a positive or bidirectional role in regulating MHC expression. For example, autophagy induced by radiation increases MHC-I expression and increased $CD8^+$ T cell infiltration during a single radiation dose from 2 to 20 Gy in a dose-dependent manner [82]. Moreover, in melanoma cells, autophagy negatively regulates MHC-I antigen expression; however, this process can be reversed with the presence of IFN-γ [83].

Tumor cell autophagy modulates the immune response in a variety of other ways (Fig. 4)

Autophagy modulates immune responses in tumor cells by influencing the expression of various surface molecules beyond PD-L1 and MHC. For instance, studies in pancreatic cancer have shown that autophagy inhibition leads to tumor antigen accumulation, which activates DCs; however, it also induces the expression of immune checkpoint LAG3 and leads to $CD8^+$ T cell exhaustion

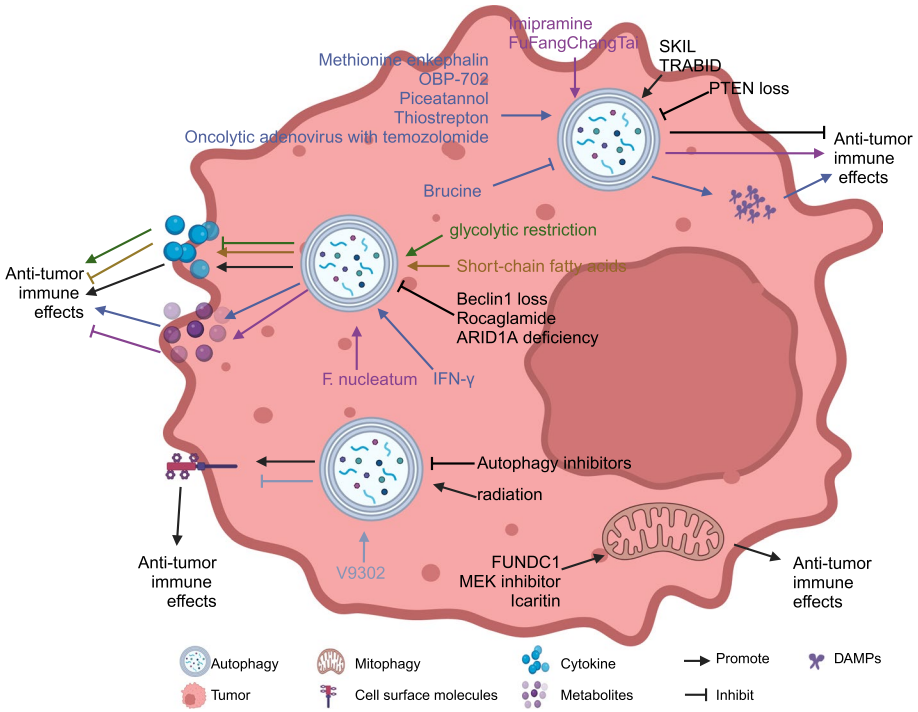

Fig. 4 Autophagy and its role in immunoregulation in tumor cells through other modalities. Autophagy regulates tumor immunity by modulating the expression of other tumor cell surface molecules, influencing cytokine expression, and regulating metabolite secretion; in addition, a variety of substances can modulate the immune response by influencing autophagy to regulate the release of DAMPs. (Created in https://BioRender.com)

[84]. In NSCLC, autophagy inhibition upregulates human leukocyte antigens-I expression, enhancing the cytotoxicity of activated T cells [85]. Additionally, the glutamine metabolism inhibitor V9302 has been found to reduce B7H3 expression and promote granzyme B production in $CD8^+$ T cells through autophagy promotion [86]. In melanoma, radiotherapy boosts anti-CTLA-4 immunotherapy efficacy by facilitating autophagy-induced translocation of mannose-6-phosphate receptors to the cell surface [87].

Cytokines are important mediators of intercellular signaling and can regulate immune cell functions in many ways, such as proliferation, migration, and differentiation [88]. Autophagy can regulate cytokine expression in tumor cells, influencing tumor immunity. In the 4T1 and Py8119 mouse models, glycolytic restriction inhibited LAP expression through activation of AMPK-ULK1 and autophagy, and down-regulation of LAP decreased G-colony stimulating factor (CSF) and GM-CSF expression and thus MDSCs recruitment, which, in turn, enhanced the anti-tumor activity of T cells and inhibited tumor proliferation and metastasis [89]. Loss of the autophagy gene Beclin1 in tumors drives elevated CCL5 expression, recruiting cytotoxic NK cells that inhibit tumor growth [90]. By inhibiting ULK1, Rocaglamide inhibits autophagy, thereby restoring NK cell-derived GZMB (granzyme B) levels in NSCLC cells, which in turn enhances NK-mediated killing [91]. In EGFR-mutant LUAD, ARID1A deficiency suppresses autophagy, promoting type I interferon production and improving ICIs response [92]. What's more, gut microbiota-derived short-chain fatty acids activate cancer cell autophagy, increasing CCL20 chemokine levels, which polarizes macrophages toward the pro-tumor M2 phenotype, facilitating prostate cancer progression [93, 94].

In addition to cytokines, autophagy affects tumor immunity by modulating metabolite secretion. In oral squamous cell carcinoma, F. nucleatum binding to GalNAc triggers autophagy, downregulating TBC1D5 and causing GLUT1 accumulation on the plasma membrane; this promotes lactate secretion, driving tumor-associated macrophages (TAMs) formation and cancer progression [95]. In cervical cancer, IFN-γ treatment upregulates IDO-1 expression, leading to kynurenine accumulation, which induces autophagy that further promotes phagocytic activity and activation of macrophages [96].

ICD refers to the process whereby tumor cells transition from non-immunogenic to immunogenic states upon death, thus inducing an anti-tumor immune response [97]. During ICD, damage-associated molecular patterns (DAMPs) are released, such as High Mobility Group Box 1 (HMGB1), ATPs, and heat shock proteins

(HSP70, HSP90), along with the exposure of calreticulin on the cell surface [98]. These DAMPs play a crucial role in activating anti-tumor immunity. Autophagy, apoptosis, necrosis, and other forms of cell death, collaborate within the ICD process to ensure effective immune activation [99]. Methionine enkephalin, oncolytic adenovirus OBP-702, Piceatannol, Thiostrepton and Oncolytic adenovirus with temozolomide, have all been reported to induces autophagy and promote the secretion of DAMPs, thereby amplifying the immune response [100–104]. However, it's also reported that Brucine induced the release of DAMPs through autophagy inhibition, regulating the TIME of CRC [105].

Emerging studies further highlight autophagy's involvement in tumor immunomodulation. Imipramine promotes T-cell recruitment by activating autophagy, and VEGF inhibitors provide a more suitable environment for T-cell activation; therefore, the combination of both can efficiently activate immunity and inhibit the growth of glioblastoma [106]. In CRC, FuFangChangTai decoction activates autophagy to promote the secretion of autophagosomes, leading to the activation of macrophages toward M1 [107]. PTEN loss in melanoma cells induces tumor cells to evade T cell killing by inhibiting autophagy [108]. In NSCLC, SKIL upregulates TAZ, which induces autophagy and inhibits the STING pathway, promoting immune evasion and tumor growth [109]. Similarly, TRABID activation of autophagy reduces Tbk1 and Irf3 phosphorylation, suppressing cGAS/STING-dependent anti-tumor immunity [110].

Targeting mitophagy also offers potential in tumor immunity. FUNDC1 mediated mitophagy to suppress the production of ROS and IL-1β and regulate immunosuppression [111]. MEK inhibitors have shown promise by promoting mitophagy and TLR9 activation, leading to CXCL10 expression and $CD8^+$ T cell recruitment [112]. Icaritin induces both mitophagy and cell apoptosis, stimulating ICD and thus activate T cells, which contribute to a more effective anti-tumor response [113].

Autophagy and immune cells (Table 2)

Tumor-infiltrating immune cells include T cells, macrophages, NK cells, MDSCs, DCs, B cells and neutrophils [114]. Among these immune cells, autophagy plays an important role in anti-tumor immunity by influencing proliferation, activation and differentiation [115]. We will review the functions of autophagy in immune cells below. It is worth mentioning that many of the relevant studies were not performed in tumor models, but we still list them because we believe that the immune regulatory mechanisms are connected. Fully interpreting these studies will help us to modify immune cells by targeting autophagy in the future to enhance anti-tumor immunity (Fig. 5).

Autophagy in T cells

Cytotoxic T Lymphocytes ($CD8^+$ T cells) are the cornerstone of anti-tumor immunity, directly eliminating tumor cells by recognizing tumor-specific antigens [116]. Helper T Cells (Th, $CD4^+$ T cells) support this response by secreting cytokines. Studies involving autophagy-related genes such as ATG3, ATG5, ATG7, Beclin-1, and PI3K-deficient T cells and mouse models have demonstrated that autophagy defects lead to increased cell apoptosis and ineffective T cell proliferation, ultimately impairing the T cell immune response [116]. Specifically, autophagy deficiency can prevent the degradation of CDKN1B (a major negative regulator of the T cell cycle) following TCR stimulation, resulting in the inability of $CD8^+$ T cells to progress into the S phase [117]. In TIME, oxysterols induce T cell cholesterol deficiency through inhibiting the SREBP2 pathway and activating of the LXR pathway, which in turn inhibits T cell proliferation and triggers autophagy-mediated cell apoptosis, resulting in T cell depletion and dysfunction [118]. In ovarian cancer patients and tumor-bearing mice, tumor-produced lactate inhibits the expression of FIP200, resulting in autophagy defects in naïve T cells, excessive activation of mitochondria, and elevated levels of ROS, thereby promoting T cell apoptosis and immune evasion [119]. Additionally, BCL10 interacts with p62 to mediate selective autophagy in effector T cells and regulate the TCR signaling pathway towards the NF-κB signaling pathway to maintain T-cell homeostasis and function [120].

In addition to regulating proliferation and apoptosis, autophagy affects T cell differentiation, activation, stemness, infiltration, and other aspects. Unlike the previously mentioned, Xu et al. identified that ATG5 or ATG7 depletion has no significant impact on effector T cells function, but impairs the formation of memory T cells [121]. Other studies showed that T cells with ATG5 deficiency undergo a marked shift to an effector memory phenotype, secreting increased amounts of IFN-γ and TNF-α [116, 121]. Furthermore, autophagy inhibition due to ATG5 deficiency induces $CD8^+$ T cell glucose metabolism, which promotes anti-tumor immunity of $CD8^+$ T cells [122]. Liver-resident $CD8^+$ T cells exhibit a higher basal autophagy rate, and inhibiting autophagy could result in the accumulation of depolarized mitochondria, promoting $CD8^+$ T cell exhaustion [123]. Additionally, IL-15 in primary liver cells may induce $CD8^+$ T autophagy and tissue residency [123]. Moreover, it has been discovered that the activation of effector T cells requires the induction of autophagy to supply energy, and restoration of autophagy (even temporarily) has been shown to sustain T cell infiltration [115].Elevated K^+ levels trigger a starvation response in $CD8^+$ T cells, reducing nutrient utilization and inducing

Table 2 Effects of autophagy modulation on immune cell

Compound/taget	Codulation of autophagy	Cells of autophagy	Tumor types	Related mechanisms	Outcome	Ref
Low cholesterol	Autophagy induction	T cell	Tumor	inhibit T cell proliferation and triggers autophagy-mediated cell apoptosis	immune inhibition	118
Lactate	Autophagy inhibition	T cell	Ovarian cancer	promote T cell apoptosis	immune inhibition	119
ATG5 deficiency	Autophagy inhibition	T cell	Breast and prostate, tumors; CRC	induces CD8+ T cell glucose metabolism	immune activation	122
ATG3 or ATG5 deficiency	Autophagy inhibition	T cell	Melanoma; CRC	decrease the differentiation into Th9 cells	immune activation	127
/	Autophagy inhibition	Treg	Melanoma	resistance to CTLA-4 blockade	immune inhibition	134
/	Autophagy inhibition	TAM	HCC	M2 polarization	immune inhibition	138
TRAF2	Autophagy inhibition	TAM	Renal cell carcinoma	M2 polarization	immune inhibition	140
RNF126	Autophagy inhibition	TAM	Nasopharyngeal carcinoma	M2 polarization	immune inhibition	141
Nod1	Autophagy induction	TAM	CRC	M2 polarization	immune inhibition	142
Cryptotanshinone	Autophagy induction	TAM	Breast cancer	reset TAMs from the M2 to the M1 macrophage	immune activation	143
/	Autophagy inhibition	TAM	HCC	activate CCL20-CCR6 signaling	immune inhibition	145
Asparaginase	Autophagy inhibition	TAM	Tumor	reduce MHC-II expression	immune inhibition	148
Recombinant human arginase I	Autophagy inhibition	TAM	Tumor	reduce MHC-II expression	immune inhibition	149
Gemcitabine	Autophagy inhibition	TAM	Tumor	reduce MHC-II expression	immune inhibition	150
TIM-4	Autophagy induction	TAM	Melanoma	reduction in antigen presentation	immune inhibition	152
Hydroxyproline	Autophagy inhibition	Monocyte	THP1	promote PD-L1 expression	immune inhibition	157
ER stress	Autophagy inhibition	Monocyte	Melanoma	inhibit the generation of Ly6Clow anti-tumor type macrophages	immune inhibition	158
MARCH1 E3 inhibition	Autophagy induction	MDSCs	Melanoma	reduce MHC-II expression	immune inhibition	160
HMGB1	Autophagy induction	MDSCs	Breast cancer	/	immune inhibition	161
β2-AR	Autophagy induction	MDSCs	Breast cancer	promote the release of the immunosuppressive mediator PGE2	immune inhibition	162
SOCS3 loss	Autophagy inhibition	MDSCs	Breast cancer	/	immune inhibition	163
LCL521	Autophagy inhibition	MDSCs	Tumor	culminates in MDSCs death	immune activation	164
β-Glucan	Autophagy induction	DC	Tumor	promote MHC-II expression	immune activation	171
Docosahexaenoic acid	Autophagy induction	DC	Multiple myeloma	enhance process and presentation of tumor antigens	immune activation	172
Exosomes form gastric cancer	Autophagy induction	Neutrophil	Gastric cancer	/	immune inhibition	174
Soluble factors	Autophagy induction	Neutrophil	HCC	low cleaved caspase-3	immune inhibition	175
Beclin-1 loss	Autophagy inhibition	Neutrophil	Pre-B acute lymphoblastic lymphoma	promote PD-L1 expression	immune inhibition	176

**NSCLC* non-small cell lung cancer; *HCC* hepatocellular carcinoma; *CRC* colorectal cancer; *DCs* dendritic cells; *MDSCs* myeloid-derived suppressor cells; *PD-L1* programmed cell death ligand 1; *MHC* major histocompatibility complex

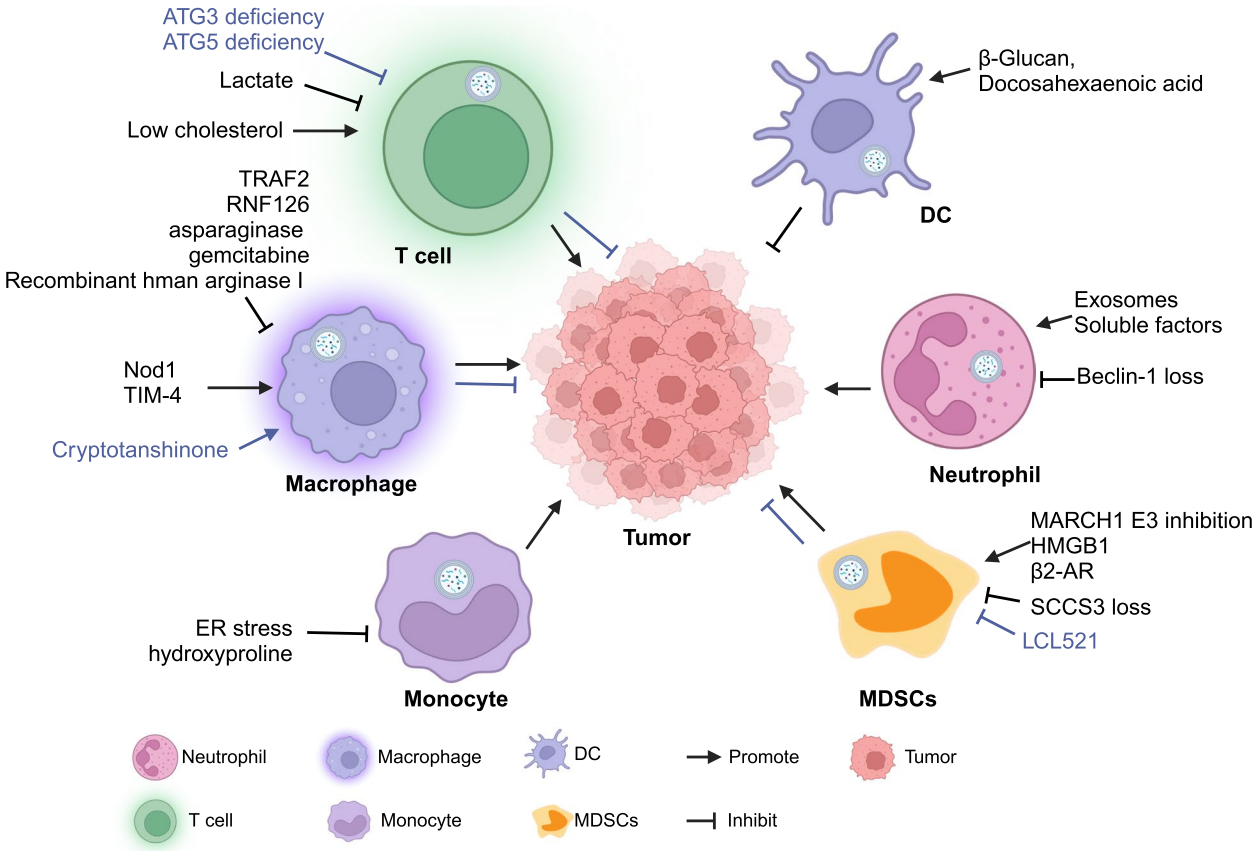

Fig. 5 The Autophagy Occurred in Immune Cells. Autophagy plays a complex role in various immune cells within the tumor microenvironment, including T cells, macrophages, monocytes, DCs, neutrophils, and myeloid-derived suppressor cells MDSCs. For example, ER stress and hydroxyproline inhibit autophagy in monocytes, leading to immunosuppressive effects. Conversely, stimulants like β-glucan and docosahexaenoic acid promote DCs autophagy, resulting in immune activation. This regulation underscores the significant interplay between autophagy and immunity, highlighting potential therapeutic strategies in cancer treatment. (Created in https://BioRender.com)

autophagy, which in turn triggers T cell stemness [124]. Decreased mitophagy activity in $CD8^+$ T cells leads to the accumulation of depolarized mitochondria, pushing $CD8^+$ T cells towards exhaustion [125]. As a key participant in autophagy, PIK3C3/VPS34 deficiency decreases active mitochondria levels in activated T cells, resulting in reduced glycolysis in $CD4^+$ T cells and inhibiting their differentiation into Th1 cells [126]. $CD4^+$ T cells lacking ATG3 or ATG5 show selective repression of their differentiation into Th9 cells due to autophagy blockade, while this blockade enhances the anticancer functions of Th9 cells in vivo [127].

Tregs play a significant role in tumor immune evasion and resistance to immunotherapy through their immunosuppressive effects [128]. It's reported that autophagy is active in Tregs, and the absence of essential autophagy genes such as ATG5 and ATG7 results in dysfunctional Tregs [129, 130]. Mechanistically, defective autophagy in Tregs can upregulate the upstream autophagy signal mTORC1, MYC function, and glycolytic metabolism, resulting in Tregs dysfunction [130]. The mTORC1/C2 inhibitor AZD8055 inhibits autophagy levels and enhances the mitochondrial stress response in Tregs, leading to mitochondrial dysfunction, inhibition of Tregs proliferation, and attenuation of their immune suppressive function [131]. Moreover, CTLA-4, highly expressed on Tregs plays a crucial role in mediating immune suppression capabilities [11, 128, 132, 133]. Studies suggests that autophagy suppression contributes to resistance to CTLA-4 blockade in melanoma, proposing the potential therapeutic synergy of autophagy induction with CTLA-4 inhibitors [134]. Research also indicated that CTLA-4 in Tregs can be degraded through the autophagy-lysosome pathway, with autophagy inhibitors like CQ identified as inhibitors of CTLA-4 degradation [135]. In conclusion, the expression levels of CTLA-4 are closely related to autophagy, which have an impact on the TIME and immune responses.

Autophagy in macrophages

Macrophages are specialized phagocytes capable of presenting antigens by phagocytosis [136]. TAMs are mainly derived from peripheral blood monocytes and tissue-resident macrophages [137]. They can be polarized by the TIME into two distinct phenotypes: pro-inflammatory and anti-cancer M1 types and anti-inflammatory and pro-cancer M2 types [137]. Autophagy played a pivotal role in regulating macrophage polarization. For instance, the inhibition of macrophage autophagy deactivated the NF-κB pathway by promoting the ubiquitination degradation of TAB3, thereby facilitating M2-like polarization of macrophages and promoting HCC progression [138]. Similarly, the activation of the autophagy inhibitor mTOR encourages M2 phenotype. TSC2, as a negative regulator of mTOR signaling, knockdown also causes TAMs M2 polarization, thus promoting tumor angiogenesis [139].What's more, TRAF2 also been reported as a M2 polarization inducer by inhibiting TAMs autophagy [140]. Tumor cell-derived exosomal RNF126, an E3 ubiquitin ligase, mediates PTEN ubiquitination degradation in macrophages to activate the PI3K/AKT signaling and inhibit autophagy, thus promoting macrophage migration and M2 polarization [141]. In contrast, the activation of Nod1 promotes autophagy-dependent reprogramming of macrophages toward an alternative phenotype, facilitating CRC progression [142]. Cryptotanshinone has been shown to remodel TAM from M2 to M1 by downregulating the TRAF6-mediated ASK1/JNK/autophagy signaling pathway [143]. Sorafenib induces macrophage autophagy, thus suppressing the expression of the M1 marker CD80 and phagocytosis [144].

Autophagy also influences macrophage aggregation; study has reported that inhibition of autophagy promotes macrophage self-recruitment through activation of CCL20-CCR6 signaling for HCC progression [145]. In addition, Cucurbitacin IIa enhanced macrophage autophagy induced by LPS, suppressing macrophage proliferation and migration [146]. However, it's also found that recombinant capsid protein VP1 stimulates macrophage migration by autophagy induction via WIPI1and WIPI2 [147].

Furthermore, autophagy modulates the antigen presentation function of macrophages. Asparaginase activates AKT/mTOR and suppresses ERK1/2 signaling to suppress autophagy thus deterring macrophage phagocytosis, cytokine secretion, and MHC-II expression [148]. Recombinant human arginase I and Gemcitabine downregulate autophagy that impairs macrophage functions such as proliferation, phagocytosis and MHC-II expression, leading to immune suppression [149, 150]. Pb was found to increase MHC-II surface expression and induce autophagy in macrophages, which in turn modulates the immune response [151]. In contrast, TIM-4 activates autophagy in macrophages after the uptake of apoptotic tumor cells, leading to a reduction in antigen presentation [152].

In addition to these roles, autophagy influences macrophage cytokine secretion. ATG12-ATG3 interactions are essential for autophagosome formation, and compounds that target this interaction can attenuate IL-1β secretion by macrophages [153].

Autophagy in monocytes

The differentiation of monocytes into macrophages was a caspase-dependent process triggered by CSF-1 [154]. Research has shown that CSF-induced differentiation of monocytes into macrophages is autophagy-dependent, and that knockdown of autophagy-related genes (such as ATG5, ATG7, and Beclin-1) or pharmacological inhibition of autophagy impedes this differentiation process [154, 155]. Additionally, CSF can induce autophagy by activating MAPK/JNK to mediate the disassociation of Beclin-1 from BCL2, promoting monocyte survival and differentiation into macrophages [156]. Therefore, inhibiting autophagy could effectively hinder CSF-induced monocyte differentiation into macrophages, offering a potential approach for clearing macrophages in tumor treatment [156]. Additionally, research has shown that hydroxyproline enhances PD-L1 expression through autophagy inhibition [157]. However, autophagy activation also has the potential to promote monocyte differentiation to anti-tumorigenic macrophages. ER stress increases the expression of CD244 in monocytes and subsequently inhibits the generation of Ly6Clow anti-tumor type macrophage by suppressing autophagy, while CD244 deficiency activates monocyte autophagy, which promotes the generation of anti-tumor macrophages [158].

The autophagy regulation of MDSCs

MDSCs are immunosuppressive cells derived from the myeloid lineage, classified into monocytic MDSCs (M-MDSCs) and granulocytic MDSCs (G-MDSCs) [159]. MDSCs are closely related to tumor progression and metastasis, and emerging evidence indicates that autophagy within MDSCs significantly influences tumor immune responses [159]. Targeting MARCH1 E3 ubiquitin ligase in autophagy-deficient M-MDSC leads to significant upregulation of MHC-II on its surface, which reduces the suppressive activity of M-MDSC and results in significant tumor shrinkage [160]. Additionally, HMGB1 contributes to tumor progression by boosting MDSCs viability through autophagy induction [161]. β2-AR signaling enhances autophagy in MDSCs

and activates the arachidonic acid cycle, which promotes the release of the immunosuppressive mediator PGE2 [162]. Furthermore, SOCS3-deficiency activates the Wnt/mTOR pathway, leading to autophagy repression that arrests early-stage MDSCs differentiation in the myeloid lineage [163]. It has been found that LCL521 targets lysosomes to activate cathepsin B and cathepsin D, resulting in interrupted autophagy and ER stress that culminated in MDSC death [164]. In general, cathepsin B and cathepsin D activation promotes autophagy [165]. The reason for this contrasting outcome is not clear, we speculate that it may be related to the different activation times of the two proteins, or it may be due to the interaction with mTOR, PI3K-Akt and other signaling pathways after its activation. Continuous optimization of experimental conditions and analysis of signaling pathways using a multi-omics system may help to clarify the cause of this discrepancy. Interestingly, G-MDSCs exhibit autophagy upregulation when exposed to LPS [166]. Under such circumstances, inhibiting autophagy promotes the activation of STAT-3 signaling, thereby facilitating the accumulation and immunosuppressive functions of G-MDSCs [166].

Autophagy regulation in DCs

DCs are considered the most powerful antigen-presenting cells. Autophagy plays a crucial role in antigen processing and presentation within DCs, thereby influencing the immune response to tumor cells. Foxp3$^+$ Tregs promote the activation of the PI3K/AKT/mTOR axis and inhibit autophagy in DCs through a CTLA-4-dependent manner, affecting antigen presentation and effectively ameliorates autoimmune responses in vivo [167]. ATG5-mediated autophagy is also essential for DCs loading of extracellular microbial antigens onto MHC-II [168]. Moreover, treatment with IL-4 during DCs differentiation promotes MHC-II-mediated endogenous antigen presentation by inducing autophagic flux through regulation of mTORC1 signaling and upregulation of RUFY4 [169]. Knockdown of TFEB or TFE3 exacerbates autophagy inhibition in arsenic-exposed DCs while simultaneously reducing the expression of antigen-presenting molecules MHC I and MHC II [170]. Additionally, β-glucan-induced autophagy in DCs is a key mechanism for their maturation; it enhances the expression of MHC-II, CD80, and TNF-α secretion, while increasing iNOS production; this process promotes the priming and differentiation of Th1 and cytotoxic T lymphocytes in vitro [171]. Docosahexaenoic acid has been shown to activate autophagy in PBMCs and DCs, thus potentially acting as immune stimulator and enhancing processing and presentation of tumor antigens by DCs [172]. However, study also showed that LC3-II lipidation mediates AAK1 binding to MHC- I, leading to endocytosis and autophagic degradation of MHC-I in DCs thus suppressing T cell immune responses, whereas deletion of ATG5 and ATG7 inhibits its MCH-I internalization by disrupting AAK1 binding to MHC-I [173]. In addition, it has been suggested that autophagy was prominent only in DCs subtypes specialized for cross-presentation, with its effects more pronounced when the antigen was a soluble protein, while being negligible for cell-associated antigens or those delivered through receptor-mediated endocytosis [18].

Autophagy of neutrophils

Neutrophils are the most abundant leukocytes in the human innate immune system and play a bidirectional role in tumor progression. The role of neutrophil autophagy in this context is similarly dual-faceted. Exosomes derived from gastric cancer cells have been shown to induce autophagy in neutrophils through the HMGB1/TLR4/NF-κB signaling pathway, thereby promoting the metastasis and progression of gastric cancer [174]. Additionally, soluble factors produced by HCC cells promote neutrophil survival by increasing autophagy, subsequently facilitating cancer cell metastasis [175]. Conversely, low expression levels of Beclin-1 in human neutrophils have been significantly correlated with upregulated PD-L1 levels in patients with pre-B acute lymphoblastic lymphoma [176]. In this context, Beclin-1 deficiency induces autophagy inhibition that suppresses CD8$^+$ T cell function, illustrating a potential immunosuppressive mechanism [176]. In recent years, researchers have discovered that neutrophils can capture and kill pathogens by forming neutrophil extracellular trapping networks (NETs), a process known as NETosis [177]. Neutrophil autophagy is essential for NETs formation; inhibiting autophagy can impair NETosis and lead to neutrophil apoptosis [177]. Similarly, mTOR inhibitors can enhance the formation of neutrophil autophagosomes and facilitate the release of NETs [178]. Previous studies have shown that NETs can envelop and adhere to tumor cells, promoting tumor dissemination and metastasis [177, 179]. Therefore, inhibiting autophagy and, consequently, NETs production emerges as a promising anti-tumor strategy.

Autophagy of NK cells

As innate immune cells, NK cells exert anti-tumor effects through three primary mechanisms: (1) direct cytotoxicity against tumor cells (2) cytokine production (3) antibody dependent cellular cytotoxicity [180]. Several studies have reported that the inhibition of autophagy (e.g., ATG5 and ATG7 deletion) induces mitochondrial damage and elevated ROS, leading to apoptosis

in NK cells and a compromised innate immunity [181, 182]. Further research shows that FOXO1 can induce autophagy by binding to ATG7 in an mTOR signal independent manner in NK cells, thereby promoting NK cell development [181]. Similarly, genetic deletion of TRPML1 in the lysosomes of NK cells inhibits autophagy, resulting in the accumulation of damaged mitochondria, increased ROS and decreased ATP, consequently damaging NK cells migration [183]. Furthermore, NK cells with autophagy defects show a significant reduction in the expression of critical cytokines such as IL-4 and IFN-γ, which are vital for immune responses [184].Overall, the current studies agree that autophagy is a positive regulator for NK cells in terms of their anti-tumor effects.

Autophagy of B cells

Although B cells are traditionally considered to have a primary function of producing antibodies and supporting immune memory, their role in tumor immunity is complex [185]. Autophagy is critical for the development and proliferation of B cells [186]. Studies have shown that while deletion of the ATG5 gene has minimal effects on B cell differentiation, it is essential for maintaining normal peripheral B cell counts, which is crucial for sustaining long-term autoimmune responses [186]. Memory B cells display elevated levels of autophagy, and the absence of ATG7 in B cells inhibited the occurrence of autophagy, resulting in desensitization of memory B cells [187]. Furthermore, the pro-oxidant adaptor p66SHC promoted B cell mitophagy by disrupting mitochondrial integrity and recruiting LC3-II, mediating the survival and differentiation of B cells [188].

In conclusion, the autophagy pathway is integral to the regulation of the immune response in tumors. Investigating the diverse roles of autophagy in tumor cells and immune cells may facilitate the identification of potential therapeutic targets, thereby offering new perspectives for advancing anti-tumor immunity and refining immunotherapeutic approaches.

Advances in targeting autophagy in clinical trials of tumor immunotherapy

Given the important role of autophagy in modulating immune responses, several clinical trials have been initiated to explore the activation of anti-tumor immunity by targeting autophagy. Currently, CQ and hydroxychloroquine (HCQ) are the most frequently utilized autophagy inhibitors in clinical settings. Owing to its minimal side effects and favorable dosing profile, HCQ is often selected as a candidate drug for clinical trials [189]. Consequently, international clinical trials examining the combination of HCQ with immunosuppressants for the treatment of various solid tumors are currently underway; however, preliminary results have yet to be disclosed. Moreover, a phase III trial found that a multi-targeted receptor tyrosine kinase inhibitor Sunitinib can induce p62-mediated PD-L1 autophagy degradation, thus facilitating antitumor immunity in breast cancer patients with metastasis [55]. Induction and collection of tumor-derived autophagosomes from tumor cells into a novel anti-tumor vaccine (DRibbles) that can effectively activate naïve T cells by upregulating MHC-I on DCs. Preliminary results are now available from a clinical trial against DRibbles. The study showed that six patients received treatment with doxorubicin in conjunction with DRibbles, with only one patient exhibiting a tumor-specific immune response. Researchers have postulated that the limited immune response may be attributed to the advanced stage of the patients enrolled in the trial, which complicates disease management. Furthermore, the insufficient number of patients enrolled in the trial impeded the thorough evaluation of the vaccine's efficacy in tumors. The feasibility of the research plan was deemed low due to the extended preparation time required for DRibbles in advanced-stage patients [190]. The clinical translation of autophagy targeting to enhance immunotherapy is expected to be a protracted and challenging endeavor, with numerous unresolved issues that demand immediate attention (Table 3).

Conclusion

Autophagy plays an important and complex role in regulating tumor immunity, and its activation or inhibition is shown to counteract the activation or inhibition of tumor immunity. The bidirectional role of autophagy in regulating tumor immunity is cell- and microenvironment-dependent. For example, autophagy in NK cells promotes anti-tumor immunity, whereas autophagy in tumor cells may suppress anti-tumor immunity by inhibiting antigen presentation. Currently, most cellular and animal experiments targeting autophagy in combination with immunotherapy have shown that combination therapy is more effective than monotherapy. This underscores the promising applications of combination strategies, although significant challenges remain. The same therapeutic strategy may yield diametrically opposed outcomes due to the varying roles of autophagy in different tumors, the diverse signaling that regulating autophagy, and the distinct effects of autophagy on various immune cell subpopulations. Additionally, the interplay between autophagy and the immune system is characterized by both positive and negative feedback mechanisms. This raises the question: does immunity influence autophagy, and how does autophagy in turn affect immune function? Key considerations for the optimal utilization of autophagy to enhance

Table 3 The ongoing clinical trials about the combinations of immunotherapy with autophagy targeted drugs

NCT Number	Cancer Types	Interventions	Sponsor	Phases	Enrollment
NCT04841148	Breast Cancer	HCQ/Avelumab + Palbociclib	Abramson Cancer Center at Penn Medicine	II	96
NCT04464759	Melanoma	Nivolumab/Ipilimumab + HCQ	Ravi Amaravadi, MD	I/II	94
NCT04787991	Metastatic Pancreatic Adenocarcinoma	HCQ/Nivolumab + Ipilimumab + Nab-paclitaxel/Gemcitabine	Parker Institute for Cancer Immunotherapy	I	45
NCT05448677	HCC	Ezurpimtrostat + Atezolizumab/Bevacizumab	University Hospital, Grenoble	II	196
NCT03344172	Pancreatic Cancer Resectable	Gemcitabine + Nab-Paclitaxel + hydroxychloroquine + Avelumab	Nathan Bahary, MD	II	32
NCT01550367	Metastatic Renal Cell Carcinoma	Hydroxychloroquine + IL-2	Leonard Appleman	I/II	30
NCT04214418	Gastric cancer	Cobimetinib + Hydroxychloroquine + Atezolizumab	Columbia University	I/II	175
NCT05576896	Stage IV CRC	Hydroxychloroquine + Encorafenib + Cetuximab/Panitumumab	Northwestern University	II	43
NCT00850785	NSCLC	DRibble vaccine	Providence Health & Services	I	6
NCT01909752	NSCLC	Cyclophosphamide + DRibble vaccine + HPV vaccine + Imiquimod/GM-CSF	UbiVac	II	12
NCT03057340	NSCLC	Dribble vaccine	Second Affiliated Hospital, School of Medicine, Zhejiang University	I	30
NCT02234921	Adenocarcinoma of the Prostate	Cyclophosphamide + DRibble Vaccine + HPV Vaccine + Imiquimod	UbiVac	I	3
NCT00798135	Breast Neoplasms (Metastasis)	Itraconazole	Indiana University	NA	13

**NSCLC* non-small cell lung cancer; *HCC* hepatocellular carcinoma; *CRC* colorectal cancer; *HCQ* hydroxychloroquine; *CSF* colony stimulating factor

future immunotherapy strategies include: whether the sensitizing impact of autophagy inhibitors or activators are tumor-specific or stage-specific; which components of the autophagic signaling pathway are targeted; the specific cell types selected for autophagy disruption; the optimal timing for interfering with autophagy—whether before, during, or after immunotherapy; the most effective dosages of autophagy inhibitors or activators when used in combination with immunotherapy; the duration of treatment with autophagy inhibitors or activators; and the potential clinical side effects associated with autophagy inhibition.

To address these questions, we must deepen our understanding of how autophagy systematically regulates tumor cells, immune cells, and stromal cells to influence tumor progression. Deciphering these mechanisms and developing temporally and spatially targeted strategies for autophagy flux regulation will be the key to effectively targeting autophagy in improving immunotherapeutic sensitivity and anti-tumor efficacy.

Abbreviations

TIME	Tumor immune microenvironment
PD-L1	Programmed cell death ligand 1
PD-1	Programmed cell death protein 1
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DCs	Dendritic cells
NK	Natural killer
MHC	Major histocompatibility complex
NSCLC	Non-small cell lung cancer
Tregs	Regulatory T cells
MDSCs	Myeloid-derived suppressor cells
HCC	Hepatocellular carcinoma
CRC	Colorectal cancer
ICD	Immunogenic cell death
CQ	Chloroquine
MHC- I	MHC class I
MHC- II	MHC class II
CSF	Colony stimulating factor
TAMs	Tumor-associated macrophages
DAMPs	Damage-associated molecular patterns
HMGB1	High mobility group box 1
Th	Helper T cells
M-MDSCs	Monocytic MDSCs
G-MDSCs	Granulocytic MDSCs
NETs	Neutrophil extracellular trapping networks
HCQ	Hydroxychloroquine

Authors' contributions

H.W. and Yl.S. contributed to the study design. P.S. Xj.Y. contributed to the implementation, manuscript discussion and critical revision. H.W., Yl.S., Zy.X., Xy.J. and Ms.X. collected and interpreted the data. All the authors read and approved the final manuscript.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 32300753).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 3 December 2024 Accepted: 24 February 2025
Published online: 19 March 2025

References

1. Jiang GM, Tan Y, Wang H, et al. The relationship between autophagy and the immune system and its applications for tumor immunotherapy. Mol Cancer. 2019;18:17.
2. Ahn CH, Jeong EG, Lee JW, et al. Expression of beclin-1, an autophagy-related protein, in gastric and colorectal cancers. APMIS. 2007;115:1344–9.
3. Xia H, Green DR, Zou W. Autophagy in tumour immunity and therapy. Nat Rev Cancer. 2021;21:281–97.
4. Gao W, Wang X, Zhou Y, et al. Autophagy, ferroptosis, pyroptosis, and necroptosis in tumor immunotherapy. Signal Transduct Target Ther. 2022;7:196.
5. Katheder NS, Khezri R, O'Farrell F, et al. Microenvironmental autophagy promotes tumour growth. Nature. 2017;541:417–20.
6. Kiyono K, Suzuki HI, Matsuyama H, et al. Autophagy is activated by TGF-beta and potentiates TGF-beta-mediated growth inhibition in human hepatocellular carcinoma cells. Cancer Res. 2009;69:8844–52.
7. Chen K, Wang S, Chen B, et al. Gene therapy in solid tumors: trends in trials in China and beyond. Drug Discov Today. 2021;26:296–300.
8. Maj T, Wang W, Crespo J, et al. Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor. Nat Immunol. 2017;18:1332–41.
9. Zhao H, Wu L, Yan G, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther. 2021;6:263.
10. Yamaguchi H, Hsu JM, Yang WH, Hung MC. Mechanisms regulating PD-L1 expression in cancers and associated opportunities for novel small-molecule therapeutics. Nat Rev Clin Oncol. 2022;19:287–305.
11. Sobhani N, Tardiel-Cyril DR, Davtyan A, et al. CTLA-4 in Regulatory T Cells for Cancer Immunotherapy. Cancers (Basel). 2021;13:1440.
12. Yi M, Zheng X, Niu M, et al. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Mol Cancer. 2022;21:28.
13. Gao X, Xu N, Li Z, et al. Safety and antitumour activity of cadonilimab, an anti-PD-1/CTLA-4 bispecific antibody, for patients with advanced solid tumours (COMPASSION-03): a multicentre, open-label, phase 1b/2 trial. Lancet Oncol. 2023;24:1134–46.
14. Vaddepally RK, Kharel P, Pandey R, et al. Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with the Level of Evidence. Cancers (Basel). 2020;12:738.
15. Walsh RJ, Sundar R, Lim JSJ. Immune checkpoint inhibitor combinations-current and emerging strategies. Br J Cancer. 2023;128:1415–7.
16. Tan S, Li D, Zhu X. Cancer immunotherapy: Pros, cons and beyond. Biomed Pharmacother. 2020;124: 109821.
17. Li CW, Lim SO, Chung EM, et al. Eradication of Triple-Negative Breast Cancer Cells by Targeting Glycosylated PD-L1. Cancer Cell. 2018;33:187-201.e110.
18. Mintern JD, Macri C, Chin WJ, et al. Differential use of autophagy by primary dendritic cells specialized in cross-presentation. Autophagy. 2015;11:906–17.
19. Liu Y, Zhang H, Wang Z, et al. 5-Hydroxytryptamine1a receptors on tumour cells induce immune evasion in lung adenocarcinoma patients with depression via autophagy/pSTAT3. Eur J Cancer. 2019;114:8–24.
20. Lv T, Xiong X, Yan W, et al. Targeting of GSDMD sensitizes HCC to anti-PD-1 by activating cGAS pathway and downregulating PD-L1 expression. J Immunother Cancer. 2022;10:e004763.
21. Debnath J, Gammoh N, Ryan KM. Autophagy and autophagy-related pathways in cancer. Nat Rev Mol Cell Biol. 2023;24:560–75.
22. Nie T, Zhu L, Yang Q. The Classification and Basic Processes of Autophagy. Adv Exp Med Biol. 2021;1208:3–16.
23. Qin C, Lu Y, Bai L, Wang K. The molecular regulation of autophagy in antimicrobial immunity. J Mol Cell Biol. 2022;14:mjac015.
24. Vargas JNS, Hamasaki M, Kawabata T, et al. The mechanisms and roles of selective autophagy in mammals. Nat Rev Mol Cell Biol. 2023;24:167–85.
25. Russell RC, Tian Y, Yuan H, et al. ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase. Nat Cell Biol. 2013;15:741–50.
26. Mohan J, Moparthi SB, Girard-Blanc C, et al. ATG16L1 induces the formation of phagophore-like membrane cups. Nat Struct Mol Biol. 2024;31:1448–59.
27. Lystad AH, Carlsson SR, Simonsen A. Toward the function of mammalian ATG12-ATG5-ATG16L1 complex in autophagy and related processes. Autophagy. 2019;15:1485–6.
28. Xu Y, Wan W. Acetylation in the regulation of autophagy. Autophagy. 2023;19:379–87.
29. Zhao YG, Zhang H. Autophagosome maturation: An epic journey from the ER to lysosomes. J Cell Biol. 2019;218:757–70.
30. Palikaras K, Lionaki E, Tavernarakis N. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. Nat Cell Biol. 2018;20:1013–22.
31. Vargas JNS, Wang C, Bunker E, et al. Spatiotemporal Control of ULK1 Activation by NDP52 and TBK1 during Selective Autophagy. Mol Cell. 2019;74:347-362.e346.
32. Yamano K, Kikuchi R, Kojima W, et al. Critical role of mitochondrial ubiquitination and the OPTN-ATG9A axis in mitophagy. J Cell Biol. 2020;219:e201912144.
33. Nguyen TN, Sawa-Makarska J, Khuu G, et al. Unconventional initiation of PINK1/Parkin mitophagy by Optineurin. Mol Cell. 2023;83:1693-1709.e1699.
34. Bunker EN, Le Guerroué F, Wang C, et al. Nix interacts with WIPI2 to induce mitophagy. Embo j. 2023;42: e113491.
35. Adriaenssens E, Schaar S, Cook ASI et al. Reconstitution of BNIP3/NIX-mediated autophagy reveals two pathways and hierarchical flexibility of the initiation machinery. bioRxiv 2024.
36. Sheen MR, Marotti JD, Allegrezza MJ, et al. Constitutively activated PI3K accelerates tumor initiation and modifies histopathology of breast cancer. Oncogenesis. 2016;5: e267.
37. Mulcahy Levy JM, Thorburn A. Autophagy in cancer: moving from understanding mechanism to improving therapy responses in patients. Cell Death Differ. 2020;27:843–57.
38. Niu X, You Q, Hou K, et al. Autophagy in cancer development, immune evasion, and drug resistance. Drug Resist Updat. 2025;78: 101170.
39. Yang X, Yu DD, Yan F, et al. The role of autophagy induced by tumor microenvironment in different cells and stages of cancer. Cell Biosci. 2015;5:14.
40. Sun K, Deng W, Zhang S, et al. Paradoxical roles of autophagy in different stages of tumorigenesis: protector for normal or cancer cells. Cell Biosci. 2013;3:35.
41. He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. Cell Res. 2020;30:660–9.
42. Kou L, Xie X, Chen X, et al. The progress of research on immune checkpoint inhibitor resistance and reversal strategies for hepatocellular carcinoma. Cancer Immunol Immunother. 2023;72:3953–69.
43. Carvajal-Hausdorf D, Altan M, Velcheti V, et al. Expression and clinical significance of PD-L1, B7–H3, B7–H4 and TILs in human small cell lung Cancer (SCLC). J Immunother Cancer. 2019;7:65.
44. Zou W, Wolchok JD, Chen L. PD-L1 (B7–H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Sci Transl Med. 2016;8:328rv324.
45. Gou Q, Dong C, Xu H, et al. PD-L1 degradation pathway and immunotherapy for cancer. Cell Death Dis. 2020;11:955.
46. Gou Q, Che S, Chen M, et al. PPARγ inhibited tumor immune escape by inducing PD-L1 autophagic degradation. Cancer Sci. 2023;114:2871–81.

47. Yu J, Ling S, Hong J, et al. TP53/mTORC1-mediated bidirectional regulation of PD-L1 modulates immune evasion in hepatocellular carcinoma. J Immunother Cancer. 2023;11:e007479.
48. Wang X, Wu WKK, Gao J, et al. Autophagy inhibition enhances PD-L1 expression in gastric cancer. J Exp Clin Cancer Res. 2019;38:140.
49. Liu D, Li M, Zhao Z, et al. Targeting the TRIM14/USP14 Axis Enhances Immunotherapy Efficacy by Inducing Autophagic Degradation of PD-L1. Cancer Res. 2024;84:2806–19.
50. Zhang Z, Yu Y, Zhang Z, et al. Cancer-associated fibroblasts-derived CXCL12 enhances immune escape of bladder cancer through inhibiting P62-mediated autophagic degradation of PDL1. J Exp Clin Cancer Res. 2023;42:316.
51. Liao H, Chang X, Gao L, et al. IL-17A promotes tumorigenesis and upregulates PD-L1 expression in non-small cell lung cancer. J Transl Med. 2023;21:828.
52. Tsai TF, Chang AC, Chen PC, et al. Autophagy blockade potentiates cancer-associated immunosuppression through programmed death ligand-1 upregulation in bladder cancer. J Cell Physiol. 2022;237:3587–97.
53. Zhang D, Man D, Lu J, et al. Mitochondrial TSPO Promotes Hepatocellular Carcinoma Progression through Ferroptosis Inhibition and Immune Evasion. Adv Sci (Weinh). 2023;10: e2206669.
54. Zhu J, Li Y, Luo Y, et al. A Feedback Loop Formed by ATG7/Autophagy, FOXO3a/miR-145 and PD-L1 Regulates Stem-Like Properties and Invasion in Human Bladder Cancer. Cancers (Basel). 2019;11:349.
55. Li H, Kuang X, Liang L, et al. The Beneficial Role of Sunitinib in Tumor Immune Surveillance by Regulating Tumor PD-L1. Adv Sci (Weinh). 2021;8:2001596.
56. Wang XR, Jiang ZB, Xu C, et al. Andrographolide suppresses non-small-cell lung cancer progression through induction of autophagy and antitumor immune response. Pharmacol Res. 2022;179: 106198.
57. Ding L, Guo H, Zhang J, et al. Zosuquidar Promotes Antitumor Immunity by Inducing Autophagic Degradation of PD-L1. Adv Sci (Weinh). 2024;11:e2400340.
58. Maher CM, Thomas JD, Haas DA, et al. Small-Molecule Sigma1 Modulator Induces Autophagic Degradation of PD-L1. Mol Cancer Res. 2018;16:243–55.
59. Park SS, Kim JI, Lee CH, et al. Temsirolimus Enhances Anti-Cancer Immunity by Inducing Autophagy-Mediated Degradation of the Secretion of Small Extracellular Vesicle PD-L1. Cancers (Basel). 2022;14:4081.
60. Liang J, Wang L, Wang C, et al. Verteporfin Inhibits PD-L1 through Autophagy and the STAT1-IRF1-TRIM28 Signaling Axis. Exerting Antitumor Efficacy Cancer Immunol Res. 2020;8:952–65.
61. Li C, Yao H, Wang H, et al. Repurposing screen identifies Amlodipine as an inducer of PD-L1 degradation and antitumor immunity. Oncogene. 2021;40:1128–46.
62. Zhou X, Fu D, Yang H, et al. Rigosertib promotes anti-tumor immunity via autophagic degradation of PD-L1 in colorectal cancer cells. Cancer Lett. 2023;577: 216422.
63. Young MJ, Wang SA, Chen YC, et al. USP24-i-101 targeting of USP24 activates autophagy to inhibit drug resistance acquired during cancer therapy. Cell Death Differ. 2024;31:574–91.
64. Li HF, Zhu N, Wu JJ, et al. Celastrol Elicits Antitumor Effects through Inducing Immunogenic Cell Death and Downregulating PD-L1 in ccRCC. Curr Pharm Des. 2024;30:1265–78.
65. Wang H, Shi Y, Ma D, et al. Cinchonine exerts anti-tumor and immunotherapy sensitizing effects in lung cancer by impairing autophagic-lysosomal degradation. Biomed Pharmacother. 2023;164: 114980.
66. Kim DH, Kwon EJ, Park KG, et al. Acesulfame potassium upregulates PD-L1 in HCC cells by attenuating autophagic degradation. Biochem Biophys Res Commun. 2024;711: 149921.
67. Xie XQ, Yang Y, Wang Q, et al. Targeting ATAD3A-PINK1-mitophagy axis overcomes chemoimmunotherapy resistance by redirecting PD-L1 to mitochondria. Cell Res. 2023;33:215–28.
68. Pishesha N, Harmand TJ, Ploegh HL. A guide to antigen processing and presentation. Nat Rev Immunol. 2022;22:751–64.
69. Yang K, Halima A, Chan TA. Antigen presentation in cancer - mechanisms and clinical implications for immunotherapy. Nat Rev Clin Oncol. 2023;20:604–23.
70. Garrido F, Aptsiauri N. Cancer immune escape: MHC expression in primary tumours versus metastases. Immunology. 2019;158:255–66.
71. Yamamoto K, Venida A, Yano J, et al. Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. Nature. 2020;581:100–5.
72. Zhang Z, Song B, Wei H, et al. NDRG1 overcomes resistance to immunotherapy of pancreatic ductal adenocarcinoma through inhibiting ATG9A-dependent degradation of MHC-1. Drug Resist Updat. 2024;73: 101040.
73. Cheung PF, Yang J, Fang R, et al. Progranulin mediates immune evasion of pancreatic ductal adenocarcinoma through regulation of MHCI expression. Nat Commun. 2022;13:156.
74. McBrearty N, Cho C, Chen J, et al. Tumor-Suppressive and Immune-Stimulating Roles of Cholesterol 25-hydroxylase in Pancreatic Cancer Cells. Mol Cancer Res. 2023;21:228–39.
75. Liao TT, Chen YH, Li ZY, et al. Hypoxia-Induced Long Noncoding RNA HIF1A-AS2 Regulates Stability of MHC Class I Protein in Head and Neck Cancer. Cancer Immunol Res. 2024;12:1468–84.
76. Sang W, Zhou Y, Chen H, et al. Receptor-interacting Protein Kinase 2 Is an Immunotherapy Target in Pancreatic Cancer. Cancer Discov. 2024;14:326–47.
77. Kong J, Xu S, Zhang P, Zhao Y. CXCL1 promotes immune escape in colorectal cancer by autophagy-mediated MHC-I degradation. Hum Immunol. 2023;84: 110716.
78. Herhaus L, Gestal-Mato U, Eapen VV, et al. IRGQ-mediated autophagy in MHC class I quality control promotes tumor immune evasion. Cell. 2024;187:7285-7302.e7229.
79. Tang F, Lu C, He X, et al. E3 ligase Trim35 inhibits LSD1 demethylase activity through K63-linked ubiquitination and enhances anti-tumor immunity in NSCLC. Cell Rep. 2023;42: 113477.
80. Liu Z, Li X, Muhammad A et al. PACSIN1 promotes immunosuppression in gastric cancer by degrading MHC-I. Acta Biochim Biophys Sin (Shanghai) 2024.
81. Xian J, Gao L, Ren Z, et al. Inhibition of Autophagy by Berbamine Hydrochloride Mitigates Tumor Immune Escape by Elevating MHC-I in Melanoma Cells. Cells. 2024;13:1537.
82. Zeng H, Zhang W, Gong Y, Xie C. Radiotherapy activates autophagy to increase CD8(+) T cell infiltration by modulating major histocompatibility complex class-I expression in non-small cell lung cancer. J Int Med Res. 2019;47:3818–30.
83. Li B, Lei Z, Lichty BD, et al. Autophagy facilitates major histocompatibility complex class I expression induced by IFN-γ in B16 melanoma cells. Cancer Immunol Immunother. 2010;59:313–21.
84. Oyama K, Nakata K, Tsutsumi C, et al. Combined Autophagy Inhibition and Dendritic Cell Recruitment Induces Antitumor Immunity and Enhances Immune Checkpoint Blockade Sensitivity in Pancreatic Cancer. Cancer research. 2024;84:4214–32.
85. Xanthopoulou E, Lamprou I, Mitrakas AG, et al. Autophagy Blockage Up-Regulates HLA-Class-I Molecule Expression in Lung Cancer and Enhances Anti-PD-L1 Immunotherapy Efficacy. Cancers (Basel). 2024;16:3272.
86. Li Q, Zhong X, Yao W, et al. Inhibitor of glutamine metabolism V9302 promotes ROS-induced autophagic degradation of B7H3 to enhance antitumor immunity. J Biol Chem. 2022;298: 101753.
87. Kim S, Ramakrishnan R, Lavilla-Alonso S, et al. Radiation-induced autophagy potentiates immunotherapy of cancer via up-regulation of mannose 6-phosphate receptor on tumor cells in mice. Cancer Immunol Immunother. 2014;63:1009–21.
88. Altan-Bonnet G, Mukherjee R. Cytokine-mediated communication: a quantitative appraisal of immune complexity. Nat Rev Immunol. 2019;19:205–17.
89. Li W, Tanikawa T, Kryczek I, et al. Aerobic Glycolysis Controls Myeloid-Derived Suppressor Cells and Tumor Immunity via a Specific CEBPB Isoform in Triple-Negative Breast Cancer. Cell Metab. 2018;28:87-103.e106.
90. Noman MZ, Berchem G, Janji B. Targeting autophagy blocks melanoma growth by bringing natural killer cells to the tumor battlefield. Autophagy. 2018;14:730–2.
91. Yao C, Ni Z, Gong C, et al. Rocaglamide enhances NK cell-mediated killing of non-small cell lung cancer cells by inhibiting autophagy. Autophagy. 2018;14:1831–44.
92. Sun D, Qian H, Wang J, et al. ARID1A deficiency reverses the response to anti-PD(L)1 therapy in EGFR-mutant lung adenocarcinoma by enhancing autophagy-inhibited type I interferon production. Cell Commun Signal. 2022;20:156.

93. Liu Y, Zhou Q, Ye F, et al. Gut microbiota-derived short-chain fatty acids promote prostate cancer progression via inducing cancer cell autophagy and M2 macrophage polarization. Neoplasia. 2023;43: 100928.
94. Duan H, Wang L, Huangfu M, Li H. The impact of microbiota-derived short-chain fatty acids on macrophage activities in disease: Mechanisms and therapeutic potentials. Biomed Pharmacother. 2023;165: 115276.
95. Sun J, Tang Q, Yu S, et al. F. nucleatum facilitates oral squamous cell carcinoma progression via GLUT1-driven lactate production. EBioMedicine. 2023;88:104444.
96. Yang SL, Tan HX, Niu TT, et al. The IFN-γ-IDO1-kynureine pathway-induced autophagy in cervical cancer cell promotes phagocytosis of macrophage. Int J Biol Sci. 2021;17:339–52.
97. Kroemer G, Galassi C, Zitvogel L, Galluzzi L. Immunogenic cell stress and death. Nat Immunol. 2022;23:487–500.
98. Krysko DV, Garg AD, Kaczmarek A, et al. Immunogenic cell death and DAMPs in cancer therapy. Nat Rev Cancer. 2012;12:860–75.
99. Hou W, Zhang Q, Yan Z, et al. Strange attractors: DAMPs and autophagy link tumor cell death and immunity. Cell Death Dis. 2013;4: e966.
100. Bai X, Cao X, Qu N, et al. Methionine enkephalin activates autophagy and stimulates tumour cell immunogenicity in human cutaneous squamous cell carcinoma. Int Immunopharmacol. 2021;96: 107733.
101. Araki H, Tazawa H, Kanaya N, et al. Oncolytic virus-mediated p53 overexpression promotes immunogenic cell death and efficacy of PD-1 blockade in pancreatic cancer. Mol Ther Oncolytics. 2022;27:3–13.
102. Wang S, Wang G, Wu W, et al. Autophagy activation by dietary piceatannol enhances the efficacy of immunogenic chemotherapy. Front Immunol. 2022;13: 968686.
103. Kepp O, Kroemer G. Autophagy induction by thiostrepton for the improvement of anticancer therapy. Autophagy. 2020;16:1166–7.
104. Liikanen I, Ahtiainen L, Hirvinen ML, et al. Oncolytic adenovirus with temozolomide induces autophagy and antitumor immune responses in cancer patients. Mol Ther. 2013;21:1212–23.
105. Ishimwe N, Wei P, Wang M, et al. Autophagy Impairment through Lysosome Dysfunction by Brucine Induces Immunogenic Cell Death (ICD). Am J Chin Med. 2020;48:1915–40.
106. Chryplewicz A, Scotton J, Tichet M, et al. Cancer cell autophagy, reprogrammed macrophages, and remodeled vasculature in glioblastoma triggers tumor immunity. Cancer Cell. 2022;40:1111-1127.e1119.
107. Li L, Wang H, Qian J, et al. FuFangChangTai Decoction Activates Macrophages via Inducing Autophagy. Evid Based Complement Alternat Med. 2019;2019:5657035.
108. Peng W, Chen JQ, Liu C, et al. Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy. Cancer Discov. 2016;6:202–16.
109. Ma F, Ding MG, Lei YY, et al. SKIL facilitates tumorigenesis and immune escape of NSCLC via upregulating TAZ/autophagy axis. Cell Death Dis. 2020;11:1028.
110. Chen YH, Chen HH, Wang WJ, et al. TRABID inhibition activates cGAS/STING-mediated anti-tumor immunity through mitosis and autophagy dysregulation. Nat Commun. 2023;14:3050.
111. Li W, Li Y, Siraj S, et al. FUN14 Domain-Containing 1-Mediated Mitophagy Suppresses Hepatocarcinogenesis by Inhibition of Inflammasome Activation in Mice. Hepatology. 2019;69:604–21.
112. Limagne E, Nuttin L, Thibaudin M, et al. MEK inhibition overcomes chemoimmunotherapy resistance by inducing CXCL10 in cancer cells. Cancer Cell. 2022;40:136-152.e112.
113. Yu Z, Guo J, Hu M, et al. Icaritin Exacerbates Mitophagy and Synergizes with Doxorubicin to Induce Immunogenic Cell Death in Hepatocellular Carcinoma. ACS Nano. 2020;14:4816–28.
114. Christofides A, Strauss L, Yeo A, et al. The complex role of tumor-infiltrating macrophages. Nat Immunol. 2022;23:1148–56.
115. Hubbard VM, Valdor R, Patel B, et al. Macroautophagy regulates energy metabolism during effector T cell activation. J Immunol. 2010;185:7349–57.
116. Panahi Meymandi AR, Akbari B, Soltantoyeh T, et al. Crosstalk between autophagy and metabolic regulation of (CAR) T cells: therapeutic implications. Front Immunol. 2023;14:1212695.
117. Jia W, He MX, McLeod IX, et al. Autophagy regulates T lymphocyte proliferation through selective degradation of the cell-cycle inhibitor CDKN1B/p27Kip1. Autophagy. 2015;11:2335–45.
118. Yan C, Zheng L, Jiang S, et al. Exhaustion-associated cholesterol deficiency dampens the cytotoxic arm of antitumor immunity. Cancer Cell. 2023;41:1276-1293.e1211.
119. Xia H, Wang W, Crespo J, et al. Suppression of FIP200 and autophagy by tumor-derived lactate promotes naïve T cell apoptosis and affects tumor immunity. Sci Immunol. 2017;2:eaan4631.
120. Paul S, Kashyap AK, Jia W, et al. Selective autophagy of the adaptor protein Bcl10 modulates T cell receptor activation of NF-κB. Immunity. 2012;36:947–58.
121. Xu X, Araki K, Li S, et al. Autophagy is essential for effector CD8(+) T cell survival and memory formation. Nat Immunol. 2014;15:1152–61.
122. DeVorkin L, Pavey N, Carleton G, et al. Autophagy Regulation of Metabolism Is Required for CD8(+) T Cell Anti-tumor Immunity. Cell Rep. 2019;27:502-513.e505.
123. Swadling L, Pallett LJ, Diniz MO, et al. Human Liver Memory CD8(+) T Cells Use Autophagy for Tissue Residence. Cell Rep. 2020;30:687-698.e686.
124. Vodnala SK, Eil R, Kishton RJ, et al. T cell stemness and dysfunction in tumors are triggered by a common mechanism. Science. 2019;363:eaau0135.
125. Yu YR, Imrichova H, Wang H, et al. Disturbed mitochondrial dynamics in CD8(+) TILs reinforce T cell exhaustion. Nat Immunol. 2020;21:1540–51.
126. Yang G, Song W, Postoak JL, et al. Autophagy-related protein PIK3C3/VPS34 controls T cell metabolism and function. Autophagy. 2021;17:1193–204.
127. Rivera Vargas T, Cai Z, Shen Y, et al. Selective degradation of PU.1 during autophagy represses the differentiation and antitumour activity of T(H)9 cells. Nat Commun. 2017;8:559.
128. Walker LS. Treg and CTLA-4: two intertwining pathways to immune tolerance. J Autoimmun. 2013;45:49–57.
129. Zou W. Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol. 2006;6:295–307.
130. Wei J, Long L, Yang K, et al. Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis. Nat Immunol. 2016;17:277–85.
131. Gedaly R, Orozco G, Ancheta AP, et al. Metabolic Disruption Induced by mTOR Signaling Pathway Inhibition in Regulatory T-Cell Expansion for Clinical Application. Cells. 2023;12:2066.
132. Chikuma S. CTLA-4, an Essential Immune-Checkpoint for T-Cell Activation. Curr Top Microbiol Immunol. 2017;410:99–126.
133. Hosseini A, Gharibi T, Marofi F, et al. CTLA-4: From mechanism to autoimmune therapy. Int Immunopharmacol. 2020;80: 106221.
134. Shukla SA, Bachireddy P, Schilling B, et al. Cancer-Germline Antigen Expression Discriminates Clinical Outcome to CTLA-4 Blockade. Cell. 2018;173:624-633.e628.
135. Cui J, Yu J, Xu H, et al. Autophagy-lysosome inhibitor chloroquine prevents CTLA-4 degradation of T cells and attenuates acute rejection in murine skin and heart transplantation. Theranostics. 2020;10:8051–60.
136. Chen S, Saeed A, Liu Q, et al. Macrophages in immunoregulation and therapeutics. Signal Transduct Target Ther. 2023;8:207.
137. Li C, Xu X, Wei S, et al. Tumor-associated macrophages: potential therapeutic strategies and future prospects in cancer. J Immunother Cancer. 2021;9:e001341.
138. Gao Z, Li XG, Feng SR, et al. Autophagy suppression facilitates macrophage M2 polarization via increased instability of NF-κB pathway in hepatocellular carcinoma. Int Immunopharmacol. 2023;123: 110685.
139. Chen W, Ma T, Shen XN, et al. Macrophage-induced tumor angiogenesis is regulated by the TSC2-mTOR pathway. Cancer Res. 2012;72:1363–72.
140. Xu Y, Li L, Yang W, et al. TRAF2 promotes M2-polarized tumor-associated macrophage infiltration, angiogenesis and cancer progression by inhibiting autophagy in clear cell renal cell carcinoma. J Exp Clin Cancer Res. 2023;42:159.
141. Yu C, Xue B, Li J, Zhang Q. Tumor cell-derived exosome RNF126 affects the immune microenvironment and promotes nasopharyngeal carcinoma progression by regulating PTEN ubiquitination. Apoptosis. 2022;27:590–605.

142. Maisonneuve C, Tsang DKL, Foerster EG, et al. Nod1 promotes colorectal carcinogenesis by regulating the immunosuppressive functions of tumor-infiltrating myeloid cells. Cell Rep. 2021;34: 108677.
143. Yen JH, Huang WC, Lin SC, et al. Metabolic remodeling in tumor-associated macrophages contributing to antitumor activity of cryptotanshinone by regulating TRAF6-ASK1 axis. Mol Ther Oncolytics. 2022;26:158–74.
144. Lin JC, Liu CL, Lee JJ, et al. Sorafenib induces autophagy and suppresses activation of human macrophage. Int Immunopharmacol. 2013;15:333–9.
145. Gao Z, Feng SR, Chen JF, et al. Inhibition of autophagy in macrophage promotes IL-1β-mediated hepatocellular carcinoma progression via inflammasome accumulation and self-recruitment. Biomed Pharmacother. 2023;161: 114560.
146. He J, Wang Y, Xu LH, et al. Cucurbitacin IIa induces caspase-3-dependent apoptosis and enhances autophagy in lipopolysaccharide-stimulated RAW 264.7 macrophages. Int Immunopharmacol. 2013;16:27–34.
147. Liao CC, Ho MY, Liang SM, Liang CM. Recombinant protein rVP1 upregulates BECN1-independent autophagy, MAPK1/3 phosphorylation and MMP9 activity via WIPI1/WIPI2 to promote macrophage migration. Autophagy. 2013;9:5–19.
148. Song P, Wang Z, Zhang X, et al. The role of autophagy in asparaginase-induced immune suppression of macrophages. Cell Death Dis. 2017;8: e2721.
149. Wang Z, Song P, Li Y, et al. Recombinant human arginase I elicited immunosuppression in activated macrophages through inhibiting autophagy. Appl Microbiol Biotechnol. 2019;103:4825–38.
150. Jiang S, Wang R, Han L, et al. Activation of autophagy reverses gemcitabine-induced immune inhibition of RAW264.7 macrophages by promoting TNF-α, IL-6 and MHC-II expression. Immunol Res. 2021;69:352–62.
151. Kerr RP, Krunkosky TM, Hurley DJ, et al. Lead at 2.5 and 5.0 μM induced aberrant MH-II surface expression through increased MII exocytosis and increased autophagosome formation in Raw 267.4 cells. Toxicol In Vitro. 2013;27:1018–24.
152. Baghdadi M, Yoneda A, Yamashina T, et al. TIM-4 glycoprotein-mediated degradation of dying tumor cells by autophagy leads to reduced antigen presentation and increased immune tolerance. Immunity. 2013;39:1070–81.
153. Nuta GC, Gilad Y, Goldberg N, et al. Identifying a selective inhibitor of autophagy that targets ATG12-ATG3 protein-protein interaction. Autophagy. 2023;19:2372–85.
154. Jacquel A, Obba S, Boyer L, et al. Autophagy is required for CSF-1-induced macrophagic differentiation and acquisition of phagocytic functions. Blood. 2012;119:4527–31.
155. Jacquel A, Obba S, Solary E, Auberger P. Proper macrophagic differentiation requires both autophagy and caspase activation. Autophagy. 2012;8:1141–3.
156. Zhang Y, Morgan MJ, Chen K, et al. Induction of autophagy is essential for monocyte-macrophage differentiation. Blood. 2012;119:2895–905.
157. Spangenberg SH, Palermo A, Gazaniga NR, et al. Hydroxyproline metabolism enhances IFN-γ-induced PD-L1 expression and inhibits autophagic flux. Cell Chem Biol. 2023;30:1115-1134.e1110.
158. Kim J, Kim TJ, Chae S, et al. Targeted deletion of CD244 on monocytes promotes differentiation into anti-tumorigenic macrophages and potentiates PD-L1 blockade in melanoma. Mol Cancer. 2024;23:45.
159. Ostrand-Rosenberg S, Beury DW, Parker KH, Horn LA. Survival of the fittest: how myeloid-derived suppressor cells survive in the inhospitable tumor microenvironment. Cancer Immunol Immunother. 2020;69:215–21.
160. Alissafi T, Hatzioannou A, Mintzas K, et al. Autophagy orchestrates the regulatory program of tumor-associated myeloid-derived suppressor cells. J Clin Invest. 2018;128:3840–52.
161. Parker KH, Horn LA, Ostrand-Rosenberg S. High-mobility group box protein 1 promotes the survival of myeloid-derived suppressor cells by inducing autophagy. J Leukoc Biol. 2016;100:463–70.
162. Mohammadpour H, MacDonald CR, McCarthy PL, et al. β2-adrenergic receptor signaling regulates metabolic pathways critical to myeloid-derived suppressor cell function within the TME. Cell Rep. 2021;37: 109883.
163. Zhang W, Li X, Jiang M, et al. SOCS3 deficiency-dependent autophagy repression promotes the survival of early-stage myeloid-derived suppressor cells in breast cancer by activating the Wnt/mTOR pathway. J Leukoc Biol. 2023;113:445–60.
164. Liu F, Li X, Lu C, et al. Ceramide activates lysosomal cathepsin B and cathepsin D to attenuate autophagy and induces ER stress to suppress myeloid-derived suppressor cells. Oncotarget. 2016;7:83907–25.
165. Iwama H, Mehanna S, Imasaka M, et al. Cathepsin B and D deficiency in the mouse pancreas induces impaired autophagy and chronic pancreatitis. Sci Rep. 2021;11:6596.
166. Dong G, Si C, Zhang Q, et al. Autophagy regulates accumulation and functional activity of granulocytic myeloid-derived suppressor cells via STAT3 signaling in endotoxin shock. Biochim Biophys Acta Mol Basis Dis. 2017;1863:2796–807.
167. Alissafi T, Banos A, Boon L, et al. Tregs restrain dendritic cell autophagy to ameliorate autoimmunity. J Clin Invest. 2017;127:2789–804.
168. Lee HK, Mattei LM, Steinberg BE, et al. In vivo requirement for Atg5 in antigen presentation by dendritic cells. Immunity. 2010;32:227–39.
169. Terawaki S, Camosseto V, Prete F, et al. RUN and FYVE domain-containing protein 4 enhances autophagy and lysosome tethering in response to Interleukin-4. J Cell Biol. 2015;210:1133–52.
170. Xu G, Peng H, Yao R, et al. TFEB and TFE3 cooperate in regulating inorganic arsenic-induced autophagy-lysosome impairment and immunodysfunction in primary dendritic cells. Cell Biol Toxicol. 2024;40:4.
171. Ding J, Ning Y, Bai Y, et al. β-Glucan induces autophagy in dendritic cells and influences T-cell differentiation. Med Microbiol Immunol. 2019;208:39–48.
172. D'Eliseo D, Di Renzo L, Santoni A, Velotti F. Docosahexaenoic acid (DHA) promotes immunogenic apoptosis in human multiple myeloma cells, induces autophagy and inhibits STAT3 in both tumor and dendritic cells. Genes Cancer. 2017;8:426–37.
173. Loi M, Müller A, Steinbach K, et al. Macroautophagy Proteins Control MHC Class I Levels on Dendritic Cells and Shape Anti-viral CD8(+) T Cell Responses. Cell Rep. 2016;15:1076–87.
174. Zhang X, Shi H, Yuan X, et al. Tumor-derived exosomes induce N2 polarization of neutrophils to promote gastric cancer cell migration. Mol Cancer. 2018;17:146.
175. Li XF, Chen DP, Ouyang FZ, et al. Increased autophagy sustains the survival and pro-tumourigenic effects of neutrophils in human hepatocellular carcinoma. J Hepatol. 2015;62:131–9.
176. Tan P, He L, Xing C, et al. Myeloid loss of Beclin 1 promotes PD-L1hi precursor B cell lymphoma development. J Clin Invest. 2019;129:5261–77.
177. Remijsen Q, Vanden Berghe T, Wirawan E, et al. Neutrophil extracellular trap cell death requires both autophagy and superoxide generation. Cell Res. 2011;21:290–304.
178. Itakura A, McCarty OJ. Pivotal role for the mTOR pathway in the formation of neutrophil extracellular traps via regulation of autophagy. Am J Physiol Cell Physiol. 2013;305:C348-354.
179. Yang LY, Luo Q, Lu L, et al. Increased neutrophil extracellular traps promote metastasis potential of hepatocellular carcinoma via provoking tumorous inflammatory response. J Hematol Oncol. 2020;13:3.
180. Yang G, Driver JP, Van Kaer L. The Role of Autophagy in iNKT Cell Development. Front Immunol. 2018;9:2653.
181. Wang S, Xia P, Huang G, et al. FoxO1-mediated autophagy is required for NK cell development and innate immunity. Nat Commun. 2016;7:11023.
182. Salio M, Puleston DJ, Mathan TS, et al. Essential role for autophagy during invariant NKT cell development. Proc Natl Acad Sci U S A. 2014;111:E5678-5687.
183. Clement D, Szabo EK, Krokeide SZ, et al. The Lysosomal Calcium Channel TRPML1 Maintains Mitochondrial Fitness in NK Cells through Interorganelle Cross-Talk. J Immunol. 2023;211:1348–58.
184. Pei B, Zhao M, Miller BC, et al. Invariant NKT cells require autophagy to coordinate proliferation and survival signals during differentiation. J Immunol. 2015;194:5872–84.
185. Syeda MZ, Hong T, Huang C, et al. B cell memory: from generation to reactivation: a multipronged defense wall against pathogens. Cell Death Discov. 2024;10:117.
186. Arnold J, Murera D, Arbogast F, et al. Autophagy is dispensable for B-cell development but essential for humoral autoimmune responses. Cell Death Differ. 2016;23:853–64.

187. Fribourg M, Ni J, Nina Papavasiliou F, et al. Allospecific Memory B Cell Responses Are Dependent on Autophagy. Am J Transplant. 2018;18:102–12.
188. Onnis A, Cianfanelli V, Cassioli C, et al. The pro-oxidant adaptor p66SHC promotes B cell mitophagy by disrupting mitochondrial integrity and recruiting LC3-II. Autophagy. 2018;14:2117–38.
189. Nirk EL, Reggiori F, Mauthe M. Hydroxychloroquine in rheumatic autoimmune disorders and beyond. EMBO Mol Med. 2020;12: e12476.
190. Sanborn RE, Ross HJ, Aung S, et al. A pilot study of an autologous tumor-derived autophagosome vaccine with docetaxel in patients with stage IV non-small cell lung cancer. J Immunother Cancer. 2017;5:103.

Publisher's Note