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The Functions of Autopahgy at the Tumor-Immune Interface

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Abstract

Autophagy is frequently induced in the hypoxic tumor microenvironment. Accumulating evidence reveals important functions of autophagy at the tumor-immune interface. Herein, we propose an update on the roles of autophagy in modulating tumor immunity. Autophagy promotes adaptive resistance of established tumors to the cytotoxic effects of natural killer cells (NKs), macrophages, and effector T cells. Increased autophagic flux in tumors dampen their immunogenicity and inhibits the expansion of cytotoxic T lymphocytes (CTLs) by suppressing the activation of STING-type-I interferon signaling (IFN-I) innate immune sensing pathway. Autophagy in suppressive tumor-infiltrating immune subsets maintains their survival through metabolic remodeling. On the other hand, autophagy is involved in the antigen processing and presentation process, which is essential for anti-tumor immune responses. Genetic deletion of autophagy induces spontaneous tumors in some models. Thus, the role of autophagy is context dependent. In summary, our review has revealed the dichotomous roles of autophagy in modulating tumor immunity. Broad targeting of autophagy may not yield maximal benefits. The characterization of specific genes regulating tumor immunogenicity and innovation in targeted delivery of autophagy inhibitors into certain tumors are among the most urgent tasks to sensitize cold cancers to immunotherapy.

Keywords: Autophagy; Tumor cell; Immune cell; Tumor immunity

Background

Autophagy serves as an evolutionarily conserved physiological phenomenon to maintain cellular homeostasis and survival during nutrient deprivation. The initiation of autophagic response is briefly presented as the encapsulation of excessive or damaged cellular components and organelles into autophagosome leading to

enzymatic degradation.[1, 2] According to the various delivering routes and contents to lysosomes, autophagy is generally categorized into macroautophagy (predominant form generally termed as autophagy), microautophagy and chaperon-mediated autophagy.[3] Autophagy is also frequently altered under pathological circumstances, namely hypoxia, endoplasmic reticulum (ER) stress, nutrient deficiency, radiation and chemotherapy.[4-6] Aside from its direct effect on cancer cell response to environmental challenges, recent studies show that autophagy in cancer cells regulates tumor-immune interactions, depending upon the context of cancer types, metabolic alterations in the tumor microenvironment (TME), and the stage of cancers.[7] Genetic evidence showed that autophagy is a critical mechanism suppressing tumor initiation,[8] however, in established tumors autophagy contributes to adaptive resistance.[9] Of note, mitophagy, another form of autophagy, plays a similar role in regulating tumor development by adjusting tumor immune response.[10] In this review, we seek to summarize recent evidence characterizing the functions of autophagy, including mitophagy, in regulating tumor-immune interactions (Figure 1-3, Table 1).

Autophagy in established tumors promote evasion from innate and adaptive immune surveillance

Autophagy could directly or indirectly exert its effect on the innate immunity mediated by natural killer (NK) cells, dendritic cells (DCs), and macrophage population. First, autophagy of tumor cells promotes adaptive resistance to NK-induced tumor lysis. NK cells, which are considered as the first-line defense against tumors, releasing perforin, and granzyme B for the lysis of tumor cells.[11, 12] Its anti-cancer role has been validated in malignancies, such as gastric cancer [13] and lung cancer.[14] By exploiting the *in vivo* and *in vitro* breast cancer models, Baginska et al. observed that the autophagy provoked by the hypoxic TME is involved in the degradation of granzyme B originated from NK into cancer cells, thus counteracting the apoptotic cell death effect induced by NK cells.[12] Besides, several studies also suggest additional mechanisms that contribute to the low tumor immunosurveillance

and cytotoxicity of NK cells for cancers. Gap junctions (GJs) are interacting channels that mediate the exchange of the small molecules between cells composed by connexin subunits, among which Connexin 43 (Cx43) is uncovered as the major GJ protein located at the immunological synapse and bridging the interplay between immune cells and cancer cells.[15] Hypoxia-induced autophagic flux results in the degradation of Cx43 in melanoma cells and impairs the cytotoxic effects of NK cells upon cancer cells. In agreement, elevated Cx43 expression levels in tumor cells are beneficial to enhance the efficacy of NK-based immunotherapy.[15] Inositol 1,4,5-trisphosphate receptor, type 1 (ITPR1), as one ligand-gated channel of ion for managing calcium release from the endoplasmic reticulum, is reported to be able to induce autophagy.[16] Messai's study regarding clear cell renal cell carcinomas (CCRCC) indicated that the elevated expression of ITPR1 evoked by HIF-2α initiated the autophagic degradation of granzyme B and abolished the NK-induced killing effect on tumor cells. In agreement with that, they implanted the tumors in mice and observed reduced tumor growth by inhibiting ITPR, while the depletion of NK cells reverted the tumor suppression.[17] As another line of evidence of autophagy-mediated immune resistance, depletion of autophagy-promoting Beclin 1 (BECN1) leads to increased intensity of chemokine (C-C motif) ligand 5 (CCL5) expression within melanoma cells and redirects massive NK cells into the tumor microenvironment, thus leading to tumor suppression.[18]

Macrophages may also exert innate immune surveillance in the TME through their phagocytic functions.[19-21] A glioblastoma study employing a combinatorial treatment to target both VEGF and CD47, the latter of which inhibited the phagocytic effect of macrophages, revealed that it could trigger autophagy of cancer cells which attenuated the phagocytosis and cytotoxicity of macrophage population. Inhibition of various signaling pathways, including Akt/mTOR and Erk, was responsible for the enhanced autophagy.[21] The same group also demonstrated that the combination of anti-CD47 therapy with autophagy inhibitor would robustly improve the therapeutic efficacy against non–small cell lung cancer (NSCLC).These results suggest that autophagy originated from tumor cells could impede the phagocytic function of

macrophages.[22] Zhang et al. found that autophagy occurring in glioblastoma cells could mitigate the immunotherapeutic efficacy of anti-CD47-SIRPα treatment, displaying as the reduced macrophages-derived phagocytosis and subsequent attenuation of $CD8^+$ T cell cytotoxicity.[23] Notably, macrophages may be regulated by tumor cell-released autophagosomes (TRAPs) and affect the cytotoxic T-lymphocytes (CTLs).[24] TRAPs are a type of double-membrane vesicles released into the TME by tumor cells, which escape from the lysosome fusion stage of classical autophagy.[25] Wen and colleagues uncovered that within several tumor models, the TRAPs could skew macrophages into M2-phenotype with higher levels of PD-L1 and IL-10 via Toll-like receptor 4 (TLR4)-MyD88-p38-STAT3 pathway, therefore resulting in suppression of CTL function and reduced IFN-γ secretion.[24]

Moreover, tumor-associated autophagy also contributes to evasion from adaptive immunity. For example, the response rate of head and neck squamous cell carcinoma (HNSCC) to immunotherapy remains less than 15%, for which low immunogenicity and a poor infiltration of CTLs were indicated as the possible reason.[26, 27] Type-I interferon (IFN-I) signaling promotes anti-tumor effects by mediating the recruitment and maturation of antigen-presenting cells (APCs). Stimulator of IFN genes (STING) is a pivotal adaptor protein that could activate the IFN-I pathway.[28,29] Nonetheless, STING is frequently inhibited in TME, contributing to tumor escape from innate immune sensing. Recent studies identified previously unknown functions of oncogenes in suppressing the STING-IFN-I innate immune sensing pathway.[30,31] Specifically, SOX2, previously known as a cancer stemness gene, was correlated with immunosuppression.[30, 32, 33] *SOX2* amplification in tumor cells lead to an increased autophagic influx, which promoted the turnover of STING in HNSCC cells. Inhibition of autophagy could rescue SOX2-potentiated suppression of STING. In addition, the results of *in vivo* experiment suggested that SOX2-expressing tumors contained lower numbers of $CD8^+$ CTLs and that those infiltrating T-cells expressed higher levels of PD-1 than SOX2-negative tumors.[30] HPV^+ HNSCC is driven by a distinct etiology, with different immune infiltration patterns from HPV^- tumors. Interestingly, HPV^+ HNSCCs contain less T-cell receptor richness, in contrast to its usually heavy immune

infiltration.[34] IFN-I is essential for tumor-specific CTL expansion. A recent study showed that HPV16 E7 could contribute to the autophagic degradation of STING by binding to NLRX1, which was shown to promote autophagosome formation. [5, 31,35, 36] NLRX1 deficiency in the tumor cells promoted $CD8^+$ CTL expansion located in the tumor-draining lymph nodes and reduces CTL exhaustion in the TME.[31] In agreement, additional studies also found that high-risk HPV subtypes utilize a number of strategies to antagonize IFN-I induction;[37-39] Gariglio and colleagues observed that HPV E7 could attenuate the IFN-I activation in HPV-transformed cells via epigenetic silencing of sensor genes including RIG-I, cGAS and STING in an SUV39H1-dependent manner.[37] NLRX1 has an LC3-interacting region and can directly interact with LC3. Such interaction underpins an NLRX1-mediated mitophagy process. Depletion of NLRX1 promotes mitochondria-derived reactive oxygen species , which arguably amplifies the production of Th1 cytokines.[40] The role of autophagy in inhibiting IFN-I was also corroborated using a transgenic FIP200 (FAK family-interacting protein of 200 kDa)-deficient mouse model. *FIP200* is an essential autophagy gene, in the absence of which mammary tumorigenesis is suppressed. The study found that inhibition of autophagy promoted the activation of IFN-I signaling as well as its downstream chemokines such as CXCL10, subsequently inducing $CD8^+$ CTL expansion in the TME.[41] Of interest, Yamamoto and colleagues recently reported that autophagy is responsible for the degradation of MHC-I in pancreatic ductal adenocarcinoma by employing the autophagy cargo receptor NBR1, resulting in the tumor immune evasion.[42] Thus, modulating selective autophagy represents a non-tapped approach to fine-tune host immune responses.

Additional evidence implies that autophagy is also responsible for tumor immune escape by stimulating signal transducer and activator of transcription 3 (STAT3) signaling, an oncogenic pathway. The STAT3 pathway has been an important link between tumor and immune cells.[7, 43] Wang et al. reported that STAT3 activation occurring in tumor cells could significantly reduce the production of pro-inflammatory cytokines and chemokines critical for APC maturation and its recruitment to the tumor bed.[44] Autophagy has been shown to increase STAT3

phosphorylation in multiple tumor models.[45-47] Autophagy may also inhibit adaptive immunity by dampening the immunogenic cell death (ICD)-induced immune killing. ICD can be triggered by several anti-cancer treatments such as chemotherapy, radiotherapy,[48,49] and hypericin-based photodynamic therapy (Hyp-PDT).[50] This phenomenon is predominantly represented as the calreticulin (CRT) exposure on the cellular surface, the secretion of high mobility group box 1 (HMGB1) along with adenosine triphosphate (ATP). [51-53] These are pivotal to the proper processing of antigen by APCs, and these molecules, including CRT, HMGB1, and ATP were defined as damage-associated molecular patterns (DAMPs).[54] Garg et al. reported that by genetically blocking autophagy in the tumor model under Hyp-PDT, an increase in CRT and ICD-caused immune reaction was detected. This was elucidated as the upregulation of IL6-producing mature DCs and CTLs along with IFN-γ. [50]

In addition to tumor-intrinsic autophagy, immune cell-inherent autophagy may also deliver resistance to immune killing. Myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) are the dominant subsets in the TME to promote tumor immune escape.[55,56] HMGB1-induced autophagy was found essential for maintaining the survival of MDSCs in the TME.[57] Autophagy could also induce the lysosomal breakdown of MHC II and repress the anti-tumor effect of $CD4^+$ T cells.[58] As a critical adaptive mechanism in a nutrient-poor environment, autophagy in the MDSCs and Tregs is essential to maintain their survival and sustained production of transforming growth factor-β (TGF-β), which dampens the activation of CTLs. [56, 59, 60]

The protective role of autophagy in promoting neoantigen presentation

Compelling evidence demonstrates that the functions of autophagy in tumor initiation and established tumor response to therapy are different. One of the examples is that the genetic deletion of *BECN1* enhances spontaneous tumor formation.[61] A recent study suggests that such autophagy-mediated protection depends on immune surveillance. Autophagy promotes the processing and presentation of neoantigens from transforming cells to CTLs, leading to the elimination of target cells.[62] Under the circumstances of compromised proteasomal function, autophagy is central for the

assembly of neoantigens with MHC-I complex in APCs to facilitate its cross-presentation to $CD8^+$ T cells.[4, 63, 64] In addition, autophagy in transforming cells facilitates antigen presentation to $CD8^+$ T cells.[65, 66] Here we summarize some evidence for the above notion and other potential mechanisms of autophagy that contribute to anti-tumor immunity.

The efficient uptake and presentation of tumor antigen is essential to subvert the immunosuppressant TME. Li and colleagues showed that tumor cell autophagy triggered by the synthetic Nano-DOX contributed to the increased immunogenicity of glioblastoma. These are presented as the elevated expression of MHC-I complex and antigen-presentation on tumor cells, the activation of DCs, and the transmission of DAMPs into extracellular TME.[67] Michaud et al. observed that autophagy of colon cancer cells could promote ICD, including the ATP release followed by IL1-β released from activated DCs, and the latter cytokine might enhance DC functions.[53] Additionally, the autophagosome extruded by tumor cells, called TRAPs could also implicate in this process. One study indicated that TRAPs produced by alpha-tocopheryloxyacetic acid (a-TEA) treatment in breast and lung cancer models might boost the potential of DCs to intake and present antigens, then inducing the activation of $CD8^+$ T cells.[65] Autophagy-mediated reduction of lysosomal integrity could potentiate MHC-I presentation and augment the cross-dressing of MHC-antigen complexes to DCs, contributing to significant $CD8^+$ T cell activation.[68] To address the tumor-stage-dependent dichotomous roles of autophagy, genetically engineered mouse models offer a robust tool. For example, in the early stage of carcinogenesis of $KRas^{G12D}$ murine lung cancer, autophagy inhibited Treg infiltration through suppressing adenosinergic signaling and repressed tumor growth.[61] However, the autophagy at later stage potentiated tumor progression via dampening oxidative stress as well as inhibiting the DNA damage response. [61]

Similar to the observation in tumor cells, autophagy in macrophages was shown to promote the surface expression of MHC-II.[69] In a diethylnitrosamine-induced hepatocellular carcinoma model, autophagy in macrophages was essential for their intratumoral infiltration.[70] Another study reported that autophagy of T cells induced

by metformin in a breast cancer model of mice could substantially enhance the functional $CD8^+$ T cell response by maintaining T cell function; Meanwhile, the autophagy of $CD8^+$ memory T cells is considered indispensable to maintain their survival and sustain tumor immunosurveillance after tumor resection.[71]

The crucial role of mitophagy in regulating tumor immune response

Autophagy-mediated turnover of aged and/or damaged mitochondria is known as mitophagy.[72,73] The role of mitophagy in modulating the tumor immunity is emerging. On one side, Ziegler and colleagues shows that mitophagy promotes anti-tumor immunity. Increased mitophagy in intestinal epithelial cells triggers iron accumulation-induced lysosomal membrane permeabilization, which promotes the release of of proteases into the cytosol and augments of MHC class I presentation.[68] Besides, in the hepatocellular carcinoma (HCC) model, mitophagy could be induced upon the icaritin treatment, which subsequently triggers ICD and augments anti-tumor immunity.[74] On the other hand, mitophagy can also suppress inflammation. FUN14 domain-containing 1 (FUNDC1), one mitophagy receptor that initiates the mitophagy, suppresses inflammasome activation and related immune responses.[73] In addition, Xia and colleagues uncovered that in mice ovarian cancer models with peritoneal metastasis, the infiltrating Tim4+ tumor-associated macrophages (TAMs) exhibited higher mitophagy activity, thereby inhibiting the T cell-mediated antitumor immunity and facilitating tumor progression.[10] Thus, mitophagy may regulate different inflammatory pathways where mitochondria maintains their homeostasis.[75] Its role in tumor cells and immune cells likely impose different impacts on anti-tumor immunity (Figure 3). Future different studies using genetically engineered models, syngeneic models and human material are needed to better refine the role of mitophagy of different cell types in regulating tumor immunogenecity.

Upstream regulators of autophagy involved in the tumor immune response

In TME, autophagy can be induced by several stress factors, including hypoxia, endoplasmic reticulum (ER) stress, nutrient deprivation, extracellular matrix (ECM) disassociation, and DAMPs.[57, 76-79] Hypoxia is revealed in approximately 50-60% tumors, and several hypoxia-mediated pathways are reported to induce autophagy.[80,

[81] HIF1α translocates into nucleus under hypoxic conditions, resulting in increased adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) and its interacting partner BNIP3L. The BNIP3-BNIP3L complex promotes autophagy by in a BECN1-dependent fashion.[82] In relation to that, another study found that NANOG could transcriptionally improve the level of BNIP3L, thereby inducing autophagy and abolishing the CTL-mediated tumor lysis.[80] With the increased ratio of ADP:ATP within the hypoxic TME, adenosine monophosphate-activated protein kinase (AMPK) could be activated to stimulate autophagy via attenuation of the mammalian target of rapamycin (mTOR) pathway. [83, 84]

Another process closely associated with hypoxia, Epithelial to Mesenchymal Transition (EMT) is another inducer of autophagy in TME, which confers tumor resistance to CTL killing. EMT of cancer cells accompanied with Snail homolog 1 (SNAI1) overexpression upregulates BECN1, leading to increased autophagy.[85, 86] EMT could activate autophagy through regulating genes of DAPK1, PTEN, and CDKN2A, enabling the cancer evasion from CTL cytotoxicity. [47]

HMGB1, as an inducer of ICD, can trigger autophagy in TME. A co-culture study revealed that HMGB1 could induce autophagy in colon cancer cells in an ER stress-JNK phosphorylation-dependent manner [78]. Another study implied that HMGB1, similar to BNIP3, dissociated Bcl2 from BECN1, which in turn triggered autophagy.[79]

Mitophagy in tumors may be modulated by other upstream modulators. For instance, the STAT3 status, the FUNDC1 expression and the icaritin treatment implicate in regulating mitophagy and tumor immunity;[68,73,74] In addition, high expression levels of arginase-1 suppress mTORC1 activation, which then contributes to enhanced mitophagy level in TAMs.[10]

Conclusions

In summary, despite the dichotomous functions of autophagy in regulating anti-tumor immune responses, its predominant function is likely dependent on cancer stages, cancer types, immune infiltration profiles, and modeling methods. Autophagy in immune cells is an essential protective mechanism by facilitating tumor neoantigen

presentation. However, autophagy in cancer cells may promote adaptive resistance to immune killing by dampening IFN-I-mediated immune sensing and rapid turnover of cytotoxic effector molecules. Global inhibition of autophagy may not yield the maximal benefits due to its interference with the antigen presentation machinery in the APCs; even such inhibition may sensitize tumors to immune killing. Thus, the characterization of specific genes regulating tumor immunogenicity and innovation in targeted delivery of autophagy inhibitors into tumor cells are among the most urgent tasks to sensitize cold cancers to immunotherapy.

Authors' Contribution Statement

Conception and design: XL, YQ, YLL, QC; Writing: XL, YQ, PD, WG; Review, and/or revision of the manuscript: XL, YQ, LJ, XF, JL,YJ, YLL, QC. All authors read and approved the final manuscript.

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Conflict of Interest Statement

The authors declare no potential conflicts of interest.

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Table 1: Summary of literatures regarding tumor or immune cell-intrinsic autophagy in the modulation of tumor immunity

Mechanisms involved in regulating tumor immunity	Tumor type	Source of autophagy	Authors	Year	The impact of autophagy on tumors
HPV16 E7-STING and IFN-I ↓ -CTLs suppression	HNSCC	HNSCC	Luo et al[31]	2020	Tumor-promoting
MHC-I degradation-antigen presentation ↓ - CTL ↓	Pancreatic cancer	Pancreatic cancer	Yamamoto et al[42]	2020	Tumor-promoting
Mitophagy-CTL inhibition	Ovarian cancer	Tim-4+ macrophages	Xia et al[10]	2020	Tumor-promoting
Mitophagy-ICD- CTL and DC activation ↑	Hepatocellular carcinoma	Hepatocellular carcinoma	Yu et al[74]	2020	Tumor-inhibiting

p-STAT3 ↑ -PD-L1 ↑ -CTL inhibition	Lung adenocarcinoma	Lung adenocarcinoma	Liu et al[46]	2019	Tumor-promoting
MHC-I and antigen presentation ↑ -DC activation	Glioblastoma	Glioblastoma	Li et al[67]	2019	Tumor-inhibiting
Mitophagy-inflammasome activation ↓	Hepatocellular carcinoma	Hepatocellular carcinoma	Li et al[73]	2019	Tumor-inhibiting
M2 macrophage-TLR4-mediated MyD88 ↑ -p38 ↑ -STAT3 ↑ -PD-L1,IL10 ↑ -CTL ↓	Melanoma	TRAPs	Wen et al[24]	2018	Tumor-promoting
SOX2-STING ↓ -IFN-I ↓ -CD8+ T cells ↓	HNSCC	HNSCC	Tan et al[30]	2018	Tumor-promoting

Macrophage phagocytosis and cytotoxicity ↓	Glioblastoma	Glioblastoma	Zhang et al[21]	2018	Tumor-promoting
Macrophage phagocytosis and cytotoxicity ↓ and CD8+ T cells ↓	Glioblastoma	Glioblastoma	Zhang et al[23]	2018	Tumor-promoting
Maintain function of MDSC and MHC-II ↓ ,CD4 T cells inhibition	Melanoma	MDSC	Alissafi et al[58]	2018	Tumor-promoting
Mitophagy-MHC-I and antigen presentation by DCs ↑	Colorectal cancer	Colorectal cancer	Ziegler et al[68]	2018	Tumor-inhibiting

Macrophage phagocytosis and cytotoxicity ↓	NSCLC	NSCLC	Zhang et al[22]	2017	Tumor-promoting
Tumor-derived CCL5 ↓ -NK cell infiltration ↓	Melanoma	Melanoma	Mgrditchian et al[18]	2017	Tumor-promoting
Maintaining memory T cell-CD8+ T cells ↑ upon stimulation	Breast cancer	CD8+ T cells	Curry et al[71]	2017	Tumor-inhibiting
Inhibiting mTORC1 and c-Myc function and glycolytic metabolism-maintaining Treg function	Colon adenocarcinoma	Treg	Wei et al[56]	2016	Tumor-promoting
Maintain survival and	Breast cancer	MDSC	Parker et al[57]	2016	Tumor-promoting

function of MDSCs					
Cx43 in tumor cells ↓ -NK cells ↓	Melanoma	Melanoma	Tittarelli et al[15]	2015	Tumor-promoting
Maintain survival and function of neutrophils	Hepatocellular carcinoma	Neutrophils	Li et al[60]	2015	Tumor-promoting
Autophagy sensor ITPR1 ↑ -NK-derived granzyme B degradation	Renal cancer	Renal cancer	Messai et al[17]	2014	Tumor-promoting
Adenosinergic signaling ↓ -Treg ↓ in early phase of tumorigenesis	NSCLC	NSCLC	Rao et all[61]	2014	Tumor-inhibiting
Granzyme B released into tumor cells by NK cells ↓	Breast cancer	Breast cancer	Baginska et al[12]	2013	Tumor-promoting

CTL cytotoxicity ↓	Breast cancer	Breast cancer	Akalay et al[47]	2013	Tumor-promoting
Calreticulin ↓ -maturation of IL-6 secreting DCs,IFNγ released by CTLs ↓	Bladder cancer, cervical cancer and melanoma	Tumor cells	Garg et al[50]	2013	Tumor-promoting
Antigen presentation of myeloid cells ↓ -CTL ↓	Colon cancer, melanoma	Myeloid cells	Baghdadi et al[59]	2013	Tumor-promoting
Infiltrated M2 macrophage ↓	Hepatocellular carcinoma	Macrophage	Lin et al[70]	2013	Tumor-inhibiting
Antigen presentation by DCs ↑ -CD8+ T cells ↑	Breast cancer and lung cancer	TRAPs	Li et al[65]	2012	Tumor-inhibiting
p-STAT3 ↑ -tumor susceptibility to	Lung cancer and melanoma	Lung cancer and melanoma	Noman et al[45]	2011	Tumor-promoting

CTL-mediated lysis ↑ IFN-I↓ -CD8+ T cells ↓ , CXCL10 ↓	Breast cancer	Breast cancer	Wei et al [41]	2011	Tumor-promoting
ICD ↑ -ATP release into TME ↑ -IL-1β from DCs ↑ -Tumor lysis-DC phagocytosis and antigen presentation ↑ -CTL activation ↑	Colon cancer	Colon cancer	Michaud et al[53]	2011	Tumor-inhibiting
p-STAT3 ↑ -DC maturation ↓ -CTL cytotoxicity ↓	Melanoma and lung cancer	Melanoma and lung cancer	Yu et al[43]	2007	Tumor-promoting

Abbreviations: HNSCC: Head and neck squamous cell carcinoma; IFN-I: Type I interferon; CTL: cytotoxic T lymphocytes; TRAPs: Tumor cell-released autophagosomes; TLR4:Toll-like receptor 4; STAT3:Signal transducer and activator of transcription 3; PD-L1:Programmed death-ligand 1; DC: Dendritic cell; CCL5: Chemokine (C-C motif) ligand 5; NK: Natural killer cells; NSCLC:Non–small cell lung cancer; Cx43:Connexin 43; ITPR1: Inositol 1,4,5-trisphosphate receptor, type 1; MDSC:Myeloid derived suppressor cells; MHC:Major histocompatibility

class; Treg: Regulatory T cells; mTORC1:Mammalian target of rapamycin complex 1; ICD:Immunogenic cell death; ATP:Adenosine triphosphate; TME:Tumor microenvironment.

Figure legends

Figure 1. Schematic presentation regarding the potential mechanisms of tumor cell or immune cell instrinsic autophagy in modulating tumor-immune interplay and the development of tumor.

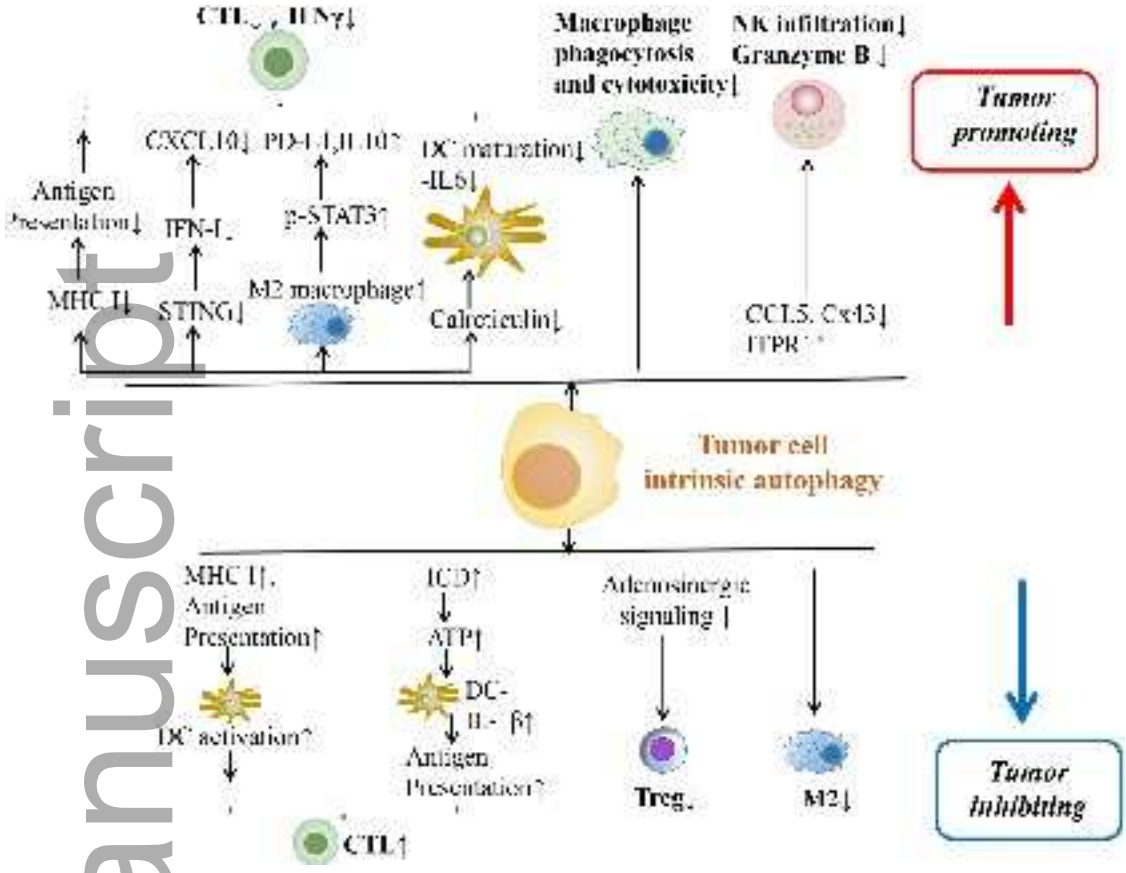
Abbreviations: IFN-I: Type I interferon; CTL: Cytotoxic T lymphocytes; STAT3:Signal transducer and activator of transcription 3; PD-L1:Programmed death-ligand 1; DC: Dendritic cell; CCL5: Chemokine (C-C motif) ligand 5; NK: Natural killer cells; Cx43:Connexin 43; ITPR1: Inositol 1,4,5-trisphosphate receptor, type 1; MHC: Major histocompatibility class; Treg: Regulatory T cells; ICD:Immunogenic cell death; ATP:Adenosine triphosphate.

Figure 2. Schematic diagram indicating the possible mechanisms of immune cell instrinsic autophagy in regulating tumor-immune interplay and the tumor outcome.

Abbreviations: CTL: Cytotoxic T lymphocytes; MDSC:Myeloid derived suppressor cells; MHC: Major histocompatibility class; Treg: Regulatory T cells.

Figure 3. Schematic image demonstrating the potential role of mitophagy in regulating tumor immunity and the tumor outcome.

Abbreviations: CTL: Cytotoxic T lymphocytes; ICD:Immunogenic cell death; DC: Dendritic cell; MHC: Major histocompatibility class.



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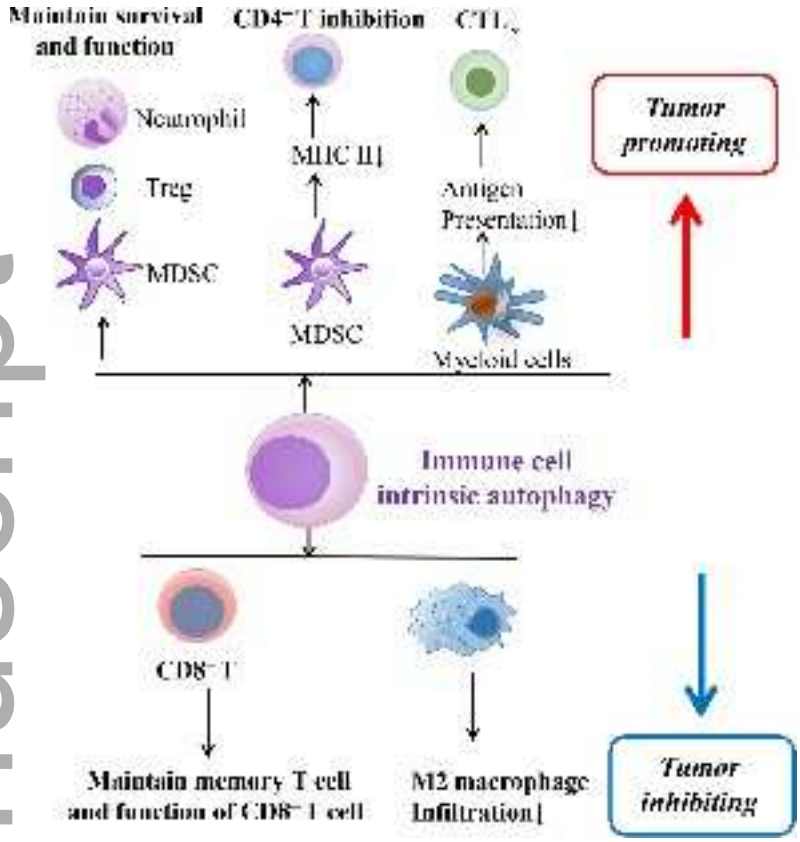

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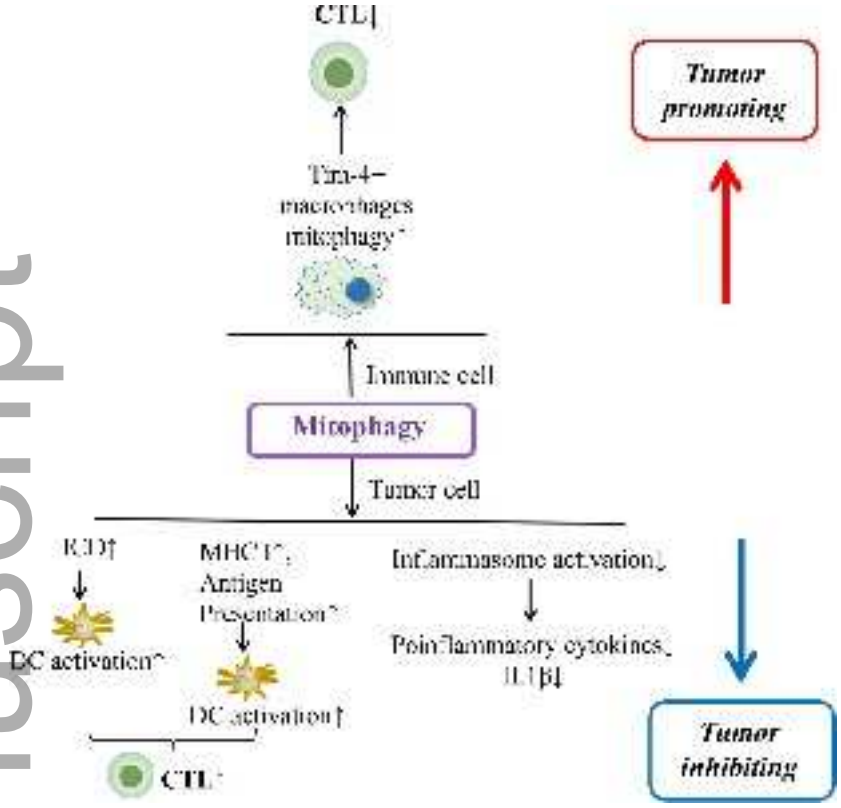

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