The regulatory role of autophagy between TAMs and tumor cells

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Abstract

Cancer has become a global public health problem and its harmful effects have received widespread attention. Conventional treatments such as surgical resection, radiotherapy and other techniques are applicable to clinical practice, but new drugs are constantly being developed and other therapeutic approaches such as immunotherapy are being applied. In addition to studying the effects on individual tumor cells, it is important to explore the role of tumor microenvironment (TME) on tumor cell development since tumor cells do not exist alone but in the tumor microenvironment. In the TME, tumor cells are interconnected with other stromal cells and influence each other, among which tumor-associated macrophages (TAMs) are the most numerous immune cells. At the same time, it was found that cancer cells have different levels of autophagy from normal cells. In cancer therapy, the occurrence of autophagy plays an important role in promoting tumor cell death or inhibiting tumor cell death, and is closely related to the environment. Therefore, elucidating the regulatory role of autophagy between TAMs and tumor cells is an important breakthrough, providing new perspectives for further research on anti-tumor immune mechanisms and understanding the efficacy of cancer immunotherapy.

Review

The regulatory role of autophagy between TAMs and tumor cells

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List of abbreviations:

TME, tumor microenvironment

TAMs, tumor-associated macrophages

IL-6, interleukin-6

IL-12, interleukin-12

TNF-α, tumor Necrosis Factor-α

IL-10, interleukin-10

TGF-β, transforming growth factor-β

IL-13, interleukin-13

PD-L1, Programmed cell death 1 ligand 1

PD-L2, Programmed cell death 1 ligand 2

IL-8, interleukin-8

STAT3, signal transducer and activator of transcription 3

PDAC, pancreatic ductal adenocarcinoma

CXCL8, C-X-C motif ligand 8

MMP-9, Matrix Metalloproteinase-9

VEGF, vascular endothelial growth factor

CMA, chaperone-mediated autophagy

Hsp70, heat-shock protein 70

LAMP-2A, lysosomal-associated membrane protein-2A

MVBs, multivesicular bodies

IL-1β, interleukin-1β

HMGB1, high mobility group box 1

Th1, T helper 1

CXCL9, C-X-C motif ligand 9

CXCL10, C-X-C motif ligand 10

IL-10, interleukin-10

OXPHOS, oxidative phosphorylation

OSCC, Oral squamous cell carcinoma

GLUT1, Glucose transporter 1

CCL5, C-C chemokine ligand 5

NK, natural killer cell

DC, Dendritic Cells

Mcoln1, mucolipin-1

TFEB, transcription factor EB

TLR2, toll-like receptor 2

NOX2, NADPH oxidase 2

ROS, reactive oxygen species

MPE, malignant pleural effusions

TMZ, temozolomide

ASK1, apoptosis signal-regulating kinase 1

FFAs, free fatty acids

IL-33, interleukin-33

ST2, suppressor of tumorigenicity 2

PGE2, prostaglandin E2

Tregs, regulatory cells

IL-17, interleukin-17

GDNF, glial cell line-derived neurotrophic factor

GFRA1, Anti-GDNF Family Receptor Alpha 1

GC, gastric cancer

FUT4, fucosyltransferase IV

EMT, Epithelial-mesenchymal transition

Gal-1, Galectin 1

HCC, Hepatocellular Carcinoma

PPT1, palmitoyl protein thioesterase 1

PDA, pancreatic ductal adenocarcinoma

TRAF2, TNF receptor-associated factor 2

Abstract: Cancer has become a global public health problem and its harmful effects have received widespread attention. Conventional treatments such as surgical resection, radiotherapy and other techniques are applicable to clinical practice, but new drugs are constantly being developed and other therapeutic approaches such as immunotherapy are being applied. In addition to studying the effects on individual tumor cells, it is important to explore the role of tumor microenvironment (TME) on tumor cell development since tumor cells do not exist alone but in the tumor microenvironment. In the TME, tumor cells are interconnected with other stromal cells and influence each other, among which tumor-associated macrophages (TAMs) are the most numerous immune cells. At the same time, it was found that cancer cells have different levels of autophagy from normal cells. In cancer therapy, the occurrence of autophagy plays an important role in promoting tumor cell death or inhibiting tumor cell death, and is closely related to the environment. Therefore, elucidating the regulatory role of autophagy between TAMs and tumor cells is an important breakthrough, providing new perspectives for further research on anti-tumor immune mechanisms and understanding the efficacy of cancer immunotherapy.

Keywords: TME, TAMs, autophagy, immunotherapy, cancer

Introduction

Cancer poses a serious threat to human life and health. Aata from GLOBOCAN 2020[1] show that 19.3 million new cancer cases and 9.9 million cancer deaths occurred worldwide in 2020, with a disease and death rate of 51.3%. The number of cancer cases in China reached 4.57 million, accounting for 24% of the total number of new cancers worldwide, of which the top five cancer types diagnosed were lung, colorectal, gastric, breast, and liver cancers; the number of deaths was about 3 million, accounting for 30% of the total cancer deaths, and the top five cancers leading to death were lung, liver, gastric, esophageal, and colorectal cancers. It is noteworthy that China ranks first in the world in terms of both new cancer incidence and deaths. It is estimated that in 2022, China will have approximately 4.82 million new cancer cases and 3.21 million cancer deaths[2]. However, the form of cancer diagnosis and treatment in China is not optimistic, mainly surgical resection of lesions with radiotherapy and chemotherapy as adjuvant means, but incomplete surgical resection and postoperative recurrence and metastasis may occur, resulting in poor prognosis. Most of the research on cancer focuses on the tumor itself. In fact, the drugs targeting tumors cannot eliminate

all the tumor cells in the body, and the remaining part of tenacious tumor cells can further promote the immune microenvironment of the tumor, which eventually leads to the recurrence and metastasis of the tumor. Importantly, tumor cells do not exist alone, but are in a collection known as the TME. The tumor microenvironment[3] is composed of lymphocytes, endothelial cells, tumor-associated macrophages (TAMs), cancer-associated fibroblasts, myeloid-derived suppressor cells, local and bone marrow-derived stem cells, and surrounding stroma, which have an important influence on the growth, proliferation, and metastasis of tumor cells. In the TME, cell-cell interactions and cell-matrix interactions, both directly contacted and indirectly regulated, constitute a complex network system that allows tumor cells to respond to them, such as antitumor immune response and immune escape. Recent studies have clarified the important role of the TME in carcinogenesis and progression, where a series of immunosuppressive cell subsets, inflammatory molecules and signaling pathways mediate immunosuppressive effects, induce tolerance and promote tumor proliferation, invasion and metastasis[4]. Therefore, the study of the role of TME will be an important breakthrough to change the current situation of symptomatic treatment"[5].

In the tumor microenvironment, TAMs are an abundant and active class of infiltrative inflammatory cells, accounting for 50% of infiltrating tumor stromal cells[6], and play an important role in promoting tumorigenesis, metastasis and invasion, angiogenesis, and drug resistance through the secretion of cytokines and chemokines[7-9]. TAMs have two functional states due to the stimulatory signals of the particular microenvironment in which they reside[10], M1 type can secrete pro-inflammatory cytokines, increase tumor antigen presentation, and directly kill tumor cells through phagocytosis, which leads to immune activation, for example, M1 TAM exert anti-tumor immune effects by secreting inflammatory mediators such as IL-6, IL-12, and TNF-α[11]; M2 type promote angiogenesis and tumor development by producing anti-inflammatory cytokines such as IL-10, TGF-β, and IL-13, promote angiogenesis and tumor development, and exert immunosuppressive effects by directly inhibiting cytotoxic T cell function through the expression of programmed cell death ligands PD-L1 and PD-L2[6, 11]. In pancreatic ductal adenocarcinoma, increased secretion of IL-8 by TAMs promotes PDAC cell motility in vitro and metastasis in vivo via the STAT3 pathway, which mediated epithelial-mesenchymal transition in cancer cells[12]. The infiltration of TAMs is significantly increased in patients with bladder cancer, and the secretion of CXCL8 by TAMs promotes the expression of MMP-9, VEGF and E-cadherin in bladder cancer cells, which causes alterations in the migration, invasion and pro-angiogenic capacity of bladder cancer cells, leading to the progression of bladder cancer[13]. For the treatment of breast cancer, TAMs-targeted therapy may improve the efficacy of breast cancer chemotherapy, reverse tumor cell resistance to chemotherapeutic agents, as well as enhance the efficacy of immune checkpoint inhibition in preclinical breast cancer models, while TAM repolarization may also be a potential strategy to improve the efficacy of breast cancer radiation therapy[14]. Apart from that, in the context of relevant cancer studies, TAM PD-1 expression not only negatively correlated with M1 polarization and phagocytosis of tumors by tumor-associated macrophages, but also inhibited neighboring T cells by promoting M2 macrophage polarization in the tumor microenvironment, thereby suppressing neighboring effector T cells and thus impairing anti-tumor immunity[15-17]. In conclusion, TAMs play an important role in tumor development, immunosuppression and mediating therapeutic resistance, and research targeting tumor-associated macrophages holds great promise. Notably, macrophages as immune cells are the first line of defense against infection and have a crucial role in many physiological processes, and the two polarization states of TAMs also play different anti-tumor and tumor-promoting roles in the tumor microenvironment, therefore, antagonizing the tumor-promoting effector molecules produced in TAMs and blocking the signaling pathways would be feasible approaches.

Recently, autophagy has been shown to play a key role in almost all diseases, especially in cancer[18, 19]. Tumor cells always maintain higher levels of basal autophagy compared to normal cells and play an important role in tumor cell survival. Importantly, the role of autophagy in cancer is complex and highly context-dependent[20]. During cancer development and tumorigenesis, autophagy has been found to play a double-edged role in the molecular mechanisms of cancer, i.e., promoting apoptosis or inhibiting apoptosis, thereby affecting tumor cell growth, proliferation, and metastasis, etc. Some studies have established that the dual role of autophagy in tumor progression is closely related to microenvironmental stress and immune system

conditions[21]. Therefore, further understanding of the role of autophagy in the tumor microenvironment in cancer is crucial for the corresponding cancer therapy. Autophagy, a process of intracellular degradation, has three main modes of action, namely macroautophagy, microautophagy and molecular chaperone-mediated autophagy (CMA). Macroautophagy, the process of which is achieved by wrapping associated misfolded proteins and damaged organelles within the cell to form autophagic vesicles, which then fuse with lysosomes to achieve degradation, thus allowing the cell to reach homeostasis[22]. Microautophagy refers to the direct uptake of cytoplasmic material into invaginations in the lysosomal and endosomal limiting membrane, which are then pinched off and released as vacuoles to the lumen[23]. CMA is unique as its substrates are not transported to the lysosome by vacuolar import, but by the binding of selected proteins expressing specific targeting motifs to the ubiquitous cytoplasmic protein Hsp70 (heat-shock protein 70) and dock directly onto lysosomal-associated membrane protein-2A (LAMP-2A), which is its unique receptor in the lysosomal membrane for import across the lysosomal membrane and degradation[24]. However, instead of being degraded, some cargo proteins can be secreted through autophagy[25, 26]. Both degradative and secretory autophagy utilize various chemical processes and active substances (e.g. autophagosome formation, ubiquitin), but secretory autophagy does not degrade its cargo through lysosomes; the proteins in the autophagosomes are secreted out after their fusion with the multivesicular bodies (MVBs) to form amphisomes, which are then fused to secretory lysosomes or direct to the plasma membrane to secrete proteins[27], and secretory autophagy mediates the secretion of IL-1β, IL-6, CXCL8,TGF-β, HMGB1, but their regulatory mechanisms need further investigation and will contribute to therapeutic development to counteract the disease and enhance normal physiological functions[27, 28]. However, the results of many in vivo and in vitro experiments have shown that antitumor drugs induce cytoprotective, cytotoxic and cytostatic forms of autophagy in various cancer models, which is an important mechanism leading to the development of drug resistance[29]. And what can be seen is that the multiple roles of autophagy in cancer therapy are of great interest. In this review, we summarize the regulatory role of autophagy in the interaction between TAMs and tumor cells and outline the various signaling molecules and molecular pathways through which these processes occur in order to further understand their significance in cancer, their impact on cancer development, and to provide additional ideas for cancer research.

Characteristics of TAMs

TAMs are the most abundant immune cells in the TME with phenotypic heterogeneity and functional diversity, the phenotype and exact role of TAMs are still controversial. What is certain is that M1 killer-like TAMs trigger inflammation and direct T cells towards T helper 1 (Th1) tumoricidal responses; M2 repair-like TAMs promote cancer progression, not only by promoting tumor survival and proliferation, vascular generation and metastasis, but also suppress anti-tumor immune responses[6, 8, 30]. The polarization of M1-like macrophages is characterized by decreased phagocytosis, NF-ϰB signaling activation and release of pro-inflammatory cytokines including IL-1β, IL-6, CXCL9, TNF-α and CXCL10 to promote inflammation and exacerbate tissue damage[31, 32]. During tumor development, pro-inflammatory effects are exerted through M1 macrophages to inhibit tumor progression[33]. M2 macrophages are essentially characterized by elevated levels of arginase-1 (Arg-1) and using phagocytosis to repair damaged tissues, can lead to the vascularization of solid tumor tissues, thus promoting tumor cell proliferation in cancer angiogenesis with anti-inflammatory effects and promote tumor cell proliferation[34], and can aid in tumor metastasis, promote regeneration by making tumor cells resistant to chemotherapy and promote immunosuppressive signaling in tumors by inhibiting cytotoxic T cells[33, 35, 36]. Notably, TAMs secrete molecules such as Arg1, IL-10 and TGF-β1, forming paracrine and autocrine loops[37]. $Arg1^+$ macrophages are more abundant in tumors, and Arg1 release is influenced by autophagy[38, 39]. IL-10 directly suppresses T cell function, while TGF-β1 exerts immunosuppression, promotes cancer cell proliferation, and induces epithelial to mesenchymal transition and cancer stem cell generation[40, 41]. Interestingly, M1 macrophages exhibit a metabolic profile dominated by aerobic glycolysis, similar to the Warburg effect in tumor cells; in contrast, M2 macrophages use OXPHOS as the main metabolic method[42]. Autophagy was shown to contribute to macrophage polarization toward the pro-inflammatory and more glycolytic M1 phenotype, but not the OXPHOS phenotypic M2 polarization[43]. However, exceptions have been observed, where the major subtype of the TAMs might be the anti-tumor M1

macrophages instead of M2. Meanwhile, M1 macrophages might contribute to tumor malignancy as well[44]. Therefore, clarifying the phenotype and function of TAMs and elucidating the specific differences between M1 and M2 types are crucial for tumor research and treatment (Table 1).

Table 1. The basic characteristics between M1 and M2

M1	M1	M1	M2	M2	M2
Stimulation	Secretion	Markers	Stimulation	Secretion	Markers
LPS[42, 45]	IL-6[11, 31, 32]	iNOS[42]	TGF-β1[46]	IL-10[11]	CD163[33, 44, 47]
IFN-γ[34, 42]	TNF-α[11, 31, 32]	CD86[44]	IL-4[37, 42, 44]	IL-1β[48]	CD206[33, 49]
	IL-1β[32]	$CD68^{+}CD80^{+}$[44]	IL-13[42, 44]	IL-17[33, 50]	Arg-1[42]
	CXCL9[32]	MHC-II[51]	CSF-1[52]	CCL18[44]	
	CXCL10[32]			MRC1[44]	
	NO[34]			Arg-1[34]	
	IL-23[34]				
	IL-12[34, 35]				
	iNOS[53]				
	ROS[54]				

Infiltration of TAMs and autophagy

High infiltration of TAM usually has a poor prognosis in most human tumor diseases[55]. It has been shown that the infiltration of immune cells into tumors is orchestrated by cytokines and chemokines released from the tumor microenvironment acting in autocrine and/or paracrine manner(s), thus facilitating the communication between several types of cells within the TME in order to control and shape tumor growth[56]. Among them, TAMs, as the main tumor-infiltrating immune cell population, are usually induced as "accomplices" by tumor cells to promote tumor immune escape, angiogenesis, tumor growth and metastasis[57]. It was demonstrated that inhibition of tumor-associated macrophages-induced autophagy in hepatocellular carcinoma enhances the cytotoxicity of the chemotherapeutic agent oxaliplatin against hepatocellular carcinoma cells[58]. *F. nucleatum* was found to be a major oncogenic bacterium that drives TAMs formation and induces infiltration. The main mechanisms are manifested in, *F. nucleatum*was able to bind to membrane proteins on the surface of OSCC cells to activate autophagy, leading to GLUT1 aggregation in the plasma membrane and extracellular lactate deposition, thereby increasing extracellular acidification and M2-like TAM formation. Inhibition of both autophagy signaling and GLUT1 can effectively reduce the formation of TAMs and inhibit the progression of OSCC cells[49, 59]. This provides a theoretical basis to further investigate the complex relationship between TAM infiltration, autophagogenesis, and tumor cell development. Notably, one study found that high M1 macrophage infiltration correlated with better treatment profiles in cancer patients. Increased secretion of the pro-inflammatory factors CCL5 and CXCL10 in TME of melanoma and CRC tumor cells when induced with the autophagy inhibitor VPS34 inhibitor (SB02024 or SAR405), which in turn promoted major immune effector cells (NK cells, $CD8^{+}$T and $CD4^{+}$T cells, DC cells and M1 macrophages) infiltration increased, and thus reversed resistance to anti-PD-1/PD-L1 therapy in melanoma and colorectal cancer tumor models[60]. In summary, these studies suggest that autophagy exerts a pro- or oncogenic effect on the accumulation of TAMs in TME, but the interaction between autophagy and the infiltration of such cytotoxic effector immune cells is largely understudied.

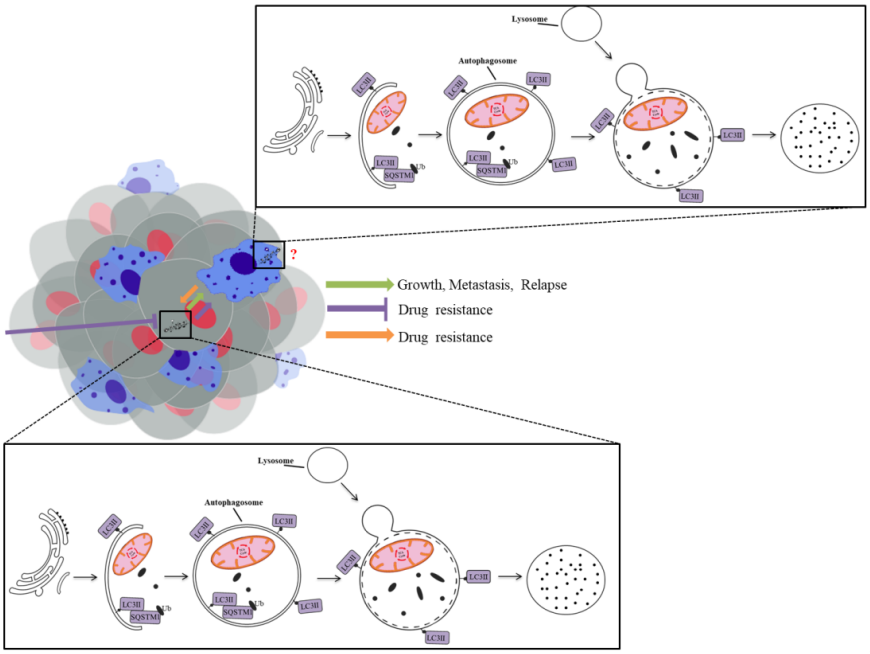


Figure 1. Relationship between TAMs infiltration and autophagy. Autophagy of tumor cells occurs to promote TAM infiltration, which promotes the processes of tumor cell, including growth, metastasis and recurrence; inhibition of autophagy of tumor cells can promote M1 macrophage infiltration and inhibit drug resistance of tumor cells; TAM infiltration promotes autophagy occurs of tumor cells, which makes the tumor resistant to drugs.

Polarization of TAMs and autophagy

Balancing macrophage polarization has been called the "holy grail" of macrophage-targeted therapy[51]. Since different phenotypes of macrophages maintain plasticity, TAMs in the TME can switch between phenotypes according to different stimulation signals, regulating the polarization status of macrophages in the TME has become one of the current therapeutic research strategies. There is evidence for an important role of autophagy in TAMs polarization and tumor progression[61]. Importantly, M2 macrophages are more affected by autophagy-regulated metabolic responses than M1 macrophages, and therefore autophagy inhibitors will likely serve as a class of drugs used as repolarizing agents for TAMs, thereby improving tumor development[62]. The study indicates a correlation between autophagy inhibition and TAM repolarization, in the Hep-2 laryngeal tumor model in mice, autophagy inhibitor CQ converted the M2-dominated TAM population to an M1-dominated TAM population, and LC3-II expression analysis demonstrated that the TAM repolarization in vivo was associated with a significant reduction of the autophagy level in the tumor tissue[63]. To elucidate how M1 macrophages can be polarized by inhibiting autophagy, Chen et al[64] found that following the administration of the autophagy inhibitor CQ, an increase in macrophage lysosomal pH was measured, and causing $Ca2^{+}$ release via the lysosomal $Ca2^{+}$ channel mucolipin-1 (Mcoln1), which induces the activation of p38 and NF-$\varkappa$B and transcription factor EB (TFEB), thus polarizing TAMs to M1 phenotype and reprograming the metabolism of TAMs from oxidative phosphorylation to glycolysis. Similar to CQ, HCQ is a class of autophagy inhibitors that promotes the conversion of M2 macrophages to M1 macrophages and enhances the sensitivity of tumor cells to chemotherapeutic agents when HCQ is used in combination with chemotherapeutic agents. Meanwhile, Li et al[65]demonstrated that HCQ can induce $CD8^{+}$T cell infiltration into tumor sites to exert anti-tumor effects by increasing the lysosomal pH in cancer cells and fostering the transition of M2-TAMs to M1 macrophages. Notably, when the autophagy inducer rapamycin and the autophagy inhibitor HCQ were combined, M2-like TAM were reprogrammed

to an M1-like phenotype by modulating the ratio between the two, and the results showed that decreased macrophage polarization in M2 in vitro and enhanced the intra-tumoral M1/M2 ratio in the intracranial GL261 tumor model after RQ treatment were evident [66]. Through tumor-derived signaling within TME, TAMs can be polarized into a pro-tumor phenotype with immunomodulatory effects. Hepatocellular-derived HMGB1 stimulates NADPH NOX2-reactive oxygen species (ROS) production via TLR2, which triggers autophagy formation and leads to lysosomal degradation of NF-ϰB p65, thereby maintaining M2 macrophage polarization[67]. H-GDEs induce autophagy of TAMs and promote M2-like macrophage polarization, thereby promoting glioma proliferation and migration in vitro and in vivo[68]. KDELC2, which can stimulate angiogenic factor expression and thus promote tumor neovascularization, mainly by increasing autophagy of glioblastoma cells to promote tumor angiogenesis, and by inducing TAM polarization into M2 macrophages to promote tumor angiogenesis. Inhibition of KDELC2 expression increases TAM activity, which mainly tends to differentiate into M1 macrophages and inhibits glioblastoma angiogenesis[69]. However, the Chinese herbal medicine XSD, in vitro and in vivo, was found to promote the polarization of M2 TAMs to the M1 phenotype by enhancing autophagy in MPE, resulting in the expansion of M1 macrophages and reduction of M2 macrophages, and thus improving clinical symptoms and the quality for life of patients[70]. HMGB1, a secretory autophagy protein, increased secretion from glioblastomas in response to the chemotherapeutic drug temozolomide and promoted M1-like polarization of TAMs, thereby enhancing glioblastoma cell sensitivity to TMZ as well as inhibiting glioblastoma growth[71]. CPT, a drug studied in triple-negative breast cancer, induces autophagy to reset the phenotype of tumor-associated M2 macrophages to the M1 phenotype and ameliorates tumor proliferation via the apoptosis signal-regulating kinase 1 (ASK1) pathway and promotes anaerobic glycolysis in M2 macrophages[72]. This also provides a theoretical basis for further studies on the complex relationship between autophagy, the polarization of tumor-associated macrophages that occur and tumor cell development. It illustrates that the level of autophagy may be an important factor affecting repolarization of TAMs, and cannot promote M2 polarization or M1 repolarization by absolutely inhibiting or inducing autophagy, thus exerting anti-tumor effects. In addition to that,macrophage polarization is not only associated with phenotypic changes (surface markers, cytokines and enzymes) but also reprograms their metabolic patterns. Autophagy promotes mitochondrial respiration, maintains mitochondrial health and provides free fatty acids, M2 macrophages require increased breakdown of FFAs and mitochondrial oxidative phosphorylation to differentiate, whereas M1 macrophages are committed to aerobic glycolysis[62]. It has been reported that the IL-33/ST2 pathway promotes enhanced cellular oxidative phosphorylation through regulation of mitochondrial autophagy to remodel macrophage metabolism, further increasing the expression of M2 polarization genes thereby enhancing M2 polarization in macrophages and ultimately promoting tumor growth[73].

Accumulated studies have demonstrated that targeted TAMs to undergo autophagy-induced changes in polarization status as the primary means, so what effect would autophagy have on TAMs if it is tumor cells that undergo autophagy, and consequently, what effect would it have on tumor progression? It has been shown that autophagosomal TRAP released from tumor cells promotes suppression of T-cell-mediated anti-tumor immune response by inducing M2-like macrophages to promote tumor progression. In Beclin1 knockdown tumor-bearing mice, TAMs with significantly decreased expression of CD206 and PD-L1, as well as slightly increased expression of CD86 and MHC-II, suggesting that inhibition of tumor cell autophagy leads to reprogramming of TAMs from an immunosuppressive M2-like phenotype to an inflammatory M1-like phenotype[74]. It is important to regulate the polarization state of TAMs rather than depleting them in the TME on tumor cell progression, in which the level of autophagy plays a key role and provides ideas and directions for further research.

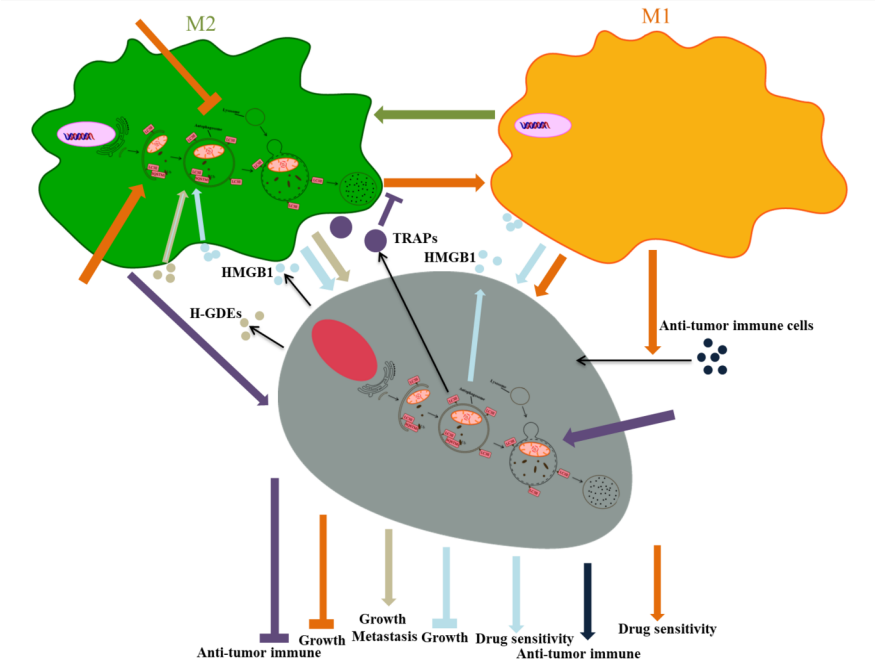
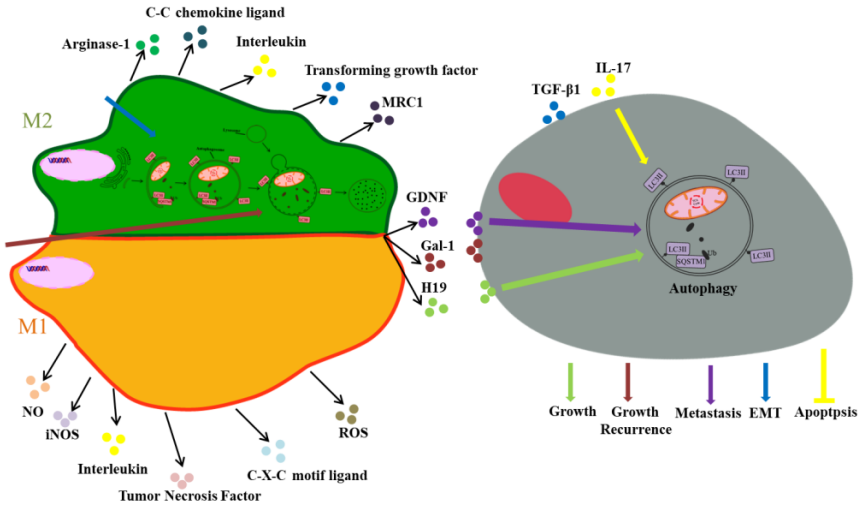


Figure 2. Interaction between TAMs polarization and autophagy. Inhibition of autophagy in M2 macrophages promotes repolarization of M1 macrophages, which promotes sensitivity of tumor cells to chemotherapeutic agents and/or infiltration of anti-tumor immune cells for anti-tumor immune response; HMGB1 secreted by tumor cells induces autophagy in M2 macrophages and promotes polarization of M2 macrophages, which promotes sensitivity of tumor cells to drugs; autophagy in tumor cells H-GDEs induce autophagy in TAM, which promotes M2 macrophage polarization and tumor cell proliferation and migration; induce autophagy in M2 macrophages and promote M1 macrophage repolarization, which inhibits tumor cell growth; promote the release of the autophagosome TRAP by tumor cells; promote the release of the autophagosome TRAP by tumor cells; promote the release of the autophagosome TRAP by tumor cells; and promote the release of the autophagosome TRAP by tumor cells. cells to release the autophagosome TRAP, which induced M2 macrophage polarization and inhibited M1 macrophage repolarization, thereby suppressing anti-tumor immune responses.

Secretion of TAMs and autophagy

TAMs can secrete various immunosuppressive molecules, such as IL-10, TGF-β, and prostaglandin E2 (PGE2), into TME, which results in the induction of immunosuppressive Tregs and facilitates T cell suppression and further suppress antitumor immunity[75]. Based on the secretion of various growth factors, cytokines, chemokines, and extracellular vesicles, TAMs can exert antitumor immune effects and immunosuppressive effects through multiple pathways[76, 77]. Certain substances secreted by TAMs promote autophagy in tumor cells. Research showed that M2 macrophages would secrete IL-17 to stimulate chaperon-mediated autophagy in tumor cells to help them avoid apoptosis[50]. Ni[78] et al. indicated that GDNF secreted by TAMs can regulate lysosomal function and autophagic flux through the GDNF-GFRA1 axis to enhance autophagy levels in GC cells, thus helping TAM colonization and survival in the metastasis. TAMs-exosome H19, because of the increased LC3-II expression and decreased levels of p62, significantly enhanced the autophagy of BC cells by stabilizing the expression of ULK1[79]. This suggests that the secretion of TAMs contained the regulatory effector of autophagy process in cancer cells. The activation of autophagy in TAMs promotes the secretion of inflammatory cytokines and thus increases the tumor-associated inflammatory response, aiding tumor progression[61]. Wang[80] et al. found that induction of autophagy in TAMs, promoting TGF-β1

secretion through the FUT4/p-ezrin pathway and induced EMT in co-cultured lung adenocarcinoma cells. However, some cargo proteins can be secreted through autophagy[25, 26]. For example, Gal-1, a soluble pro-tumor factor widely expressed in TAMs. TAMs can regulate Gal-1 secretion via TLR2-mediated secretory autophagy to facilitate HCC growth in mice and correlates with the poor prognosis of HCC patients[81]. In summary, Autophagy-regulated TAM can promote tumorigenesis and progression by mediating interactions with tumor cells through autocrine or paracrine, activating inflammatory cells, disrupting cytokine networks, and evading immune surveillance.



Φιγυρε 3. Ιντεραστιον βετωεεν TAMς σεςρετιον ανδ αυτοπηαγψ. M1 μαςροπηαγες σεςρετε NO, ιNOΣ, ΙΛ-6, ΙΛ-23, ΙΛ-12, ΤΝΦ-α, ΙΛ-1β, "Ξ"Λ9, "Ξ"Λ10, ΡΟΣ· M2 μαςροπηαγες σεςρετε Αργ-1, ""Λ18, ΙΛ-10, ΙΛ-1β, ΙΛ-17, ΜΡ"1· ΙΛ-17 σεςρετεδ βψ M2 μαςροπηαγες ινδυςες αυτοπηαγψ ανδ ινηιβιτς αποπτοσις· βψ ινηιβιτινγ τηε Bψ ινηιβιτινγ τηε αυτοπηαγψ οφ M2 μαςροπηαγες, ιτ προμοτες τηε σεςρετιον οφ ΤΓΦ-β1, ωηιςη προμοτες τηε οςςυρρενςε οφ EMT ιν τυμορ ςελλς· TAM ςαν σεςρετε ΓΔΝΦ το ινδυςε αυτοπηαγψ ανδ τηυς προμοτε τηε μεταστασις οφ τυμορ ςελλς· TAM ςαν σεςρετε H19 το ινδυςε τηε οςςυρρενςε οφ αυτοπηαγψ ανδ προμοτε τηε γροωτη οφ τυμορ ςελλς· ι-νηιβιτινγ τηε αυτοπηαγψ οφ TAM ςαυσες TAM το σεςρετε Γαλ-1, ωηιςη προμοτες τηε γροωτη ανδ μεταστασις οφ τυμορ ςελλς.

Immunotherapy based on autophagy and TAMs

Clarifying how TAMs in TME support or inhibit tumor progression could lead to the development of more effective therapies. and there is abundant evidence that it not only has tumoricidal effects but also adapts and promotes tumorigenesis and metastasis[82, 83]. In fact, the TME could be simply characterized into cold (non T cell inflamed) or hot (T cell inflamed), the ability of immunosuppressive cells, including M2 macrophages, to infiltrate highly into TME is one of the characteristics of "cold" TME, also known as "immune rejection" TME[84, 85]. "hot" TME are enriched in CD8 lymphocytes and M1 TAMs and characterized by T cell infiltration and molecular signatures of immune activation, all of which contribute to an enhanced response to immunotherapy[84, 85]. Reprogramming immunosuppressive TME to an immunostimulatory phenotype can enhance the sensitivity of tumor responses to immunotherapy. Many current tumor immunotherapies

are based on T cells, B cells, NK cells, etc., and exploring TAMs-related immunotherapy then becomes a new direction and a breakthrough in the treatment of cancer. Therefore, targeting TAMs will be considered as a promising strategy for cancer immunotherapy.

Autophagy appears to be one of the most common processes in cancer immunotherapy, playing a bidirectional role in immunotherapy. Although the direct link between autophagy and immunotherapy has not been explored completely, there is growing evidence that autophagy may have a differential impact, enhancing or attenuating the efficiency of immunotherapy, on tumor response to immunotherapy, making autophagy a key factor and potential target for improving the efficiency of immunotherapy. On the one hand, autophagy contributes to antitumor immunity. Enhanced autophagy for cancer cell death triggers autocrine or paracrine ATP signaling, which may serve as a strong mediator of pro-inflammatory responses by macrophages in the tumor microenvironment, thereby enhancing anti-tumor immune responses[86]. The autophagosomes isolated from cancer cells can induce strong T cell responses, promoting adaptive immune responses against tumor cells and mediating tumor regression[87]. On the other hand, autophagy promote immune evasion in tumor cells by major mechanisms including impaired antigen presentation[88, 89], inhibition of infiltration of anti-tumor immune cells such as T-lymphocytes[90, 91] and targeting of tumor-associated immune regulatory cells to immunogenic cells that promote tumor rejection[92], leading to antitumor immunotherapy intrinsic resistance. Several recent studies using genome-wide CRISPR screens have identified autophagy is a key conserved mechanism in the tumor microenvironment that protects tumor cells from T-cell killing and drives immune evasion of cancer cells[93-95]. Notably, since autophagy inhibition produces different effects on different immune cells, when inhibiting autophagy to enhance the antitumor immune response, it is important to determine the effect of autophagy inhibition on the respective immune cells and the antitumor immune response [96]. Based on the fact that induction or inhibition of autophagy contributes to the efficacy of immunotherapy, exploring autophagic targets and their modifiers to control autophagy in the tumor microenvironment is an emerging strategy to promote cancer immunotherapy.

In fact, autophagy level and TAMs both regulate cytotoxic T cell activity[97]. Sharma[98] et al. found that targeted inhibition of palmitoyl protein thioesterase 1 (PPT1), a novel regulator of autophagy in cancer cells, enhances antitumor immune responses by converting the M2 phenotype of macrophages to the M1 phenotype while increasing T cell-mediated cytotoxicity in combination with anti-PD-1 therapy. Autophagy is able to lead to poor antigen presentation in TAM by downregulating MHC expression on macrophages, thus limiting the ability of T cells and immunotherapy to kill tumors[61]. When autophagy is blocked, polarization of TAMs into M1 macrophages improves immunosuppressive TME and thus enhances immunotherapy for cancer[33, 36, 51]. In a more intuitive way, direct use of autophagy inhibitors, HCQ blockade of autophagy converts M2 macrophages to M1 and promotes the sensitivity of tumor cells to chemotherapeutic agents, killing most of the tumor cells, and the killed tumor cells release tumor antigens to promote antitumor immunity. At the same time, CD8+ T cells are recruited into the TME, subjecting tumor cells to a second strike and inducing more effective tumor killing[99]. The combination treatment with HCQ and rapamycin also increases the M1/M2 ratio in the intracranial glioblastoma tumor model by reprogramming the M2-like TAM to an M1-like phenotype, decreasing the macrophage polarization of M2, and enhancing T cell-mediated cytotoxicity to improve anti-PD-1 therapy[36]. It has even been reported that if MEK inhibitors are used in combination with autophagy inhibitors to activate TAM to convert to an immunogenic M1-like phenotype via the STING/type I interferon pathway in tumor cells, this is an attractive therapeutic approach for PDA immunotherapy development[100]. These studies indicate that a blockade of autophagy can ameliorate immunosuppressive TME through M1 macrophage polarization, which may enhance the immunotherapy of cancer. However, it was recently shown that a Listeria-based HCC vaccine can induce autophagy in TAM via the TLR2/Myd88/NF-ϰB pathway, which leads to repolarization of macrophages from the M2 phenotype to the M1 phenotype and recruitment of increasing amounts of antitumor cytokines. Moreover, the vaccine induced a robust antitumor response by reshaping the tumor immune microenvironment through binding PD-1 blockade[101]. Tan[102] et al. revealed that the natural compound baicalin, a potential immunotherapeutic candidate for hepatocellular carcinoma, promoted the activation of TRAF2 degradation-related RelB/p52 pathway through the induction of autophagy, initiating the reprogramming of TAM to M1 macrophages,

thereby exerting an inhibitory effect on hepatocellular carcinoma cells. In addition, TAM induced autophagy in HCC cells and attenuated the toxic effects of oxaliplatin. This autophagy-mediated drug resistance mechanism provides a new therapeutic strategy[103]. Overall, a large body of evidence suggests that autophagy and TAMs play a crucial role in the tumor cell stress response and that targeting autophagy is able to reset TAMs for immunotherapy of cancer. Targeting autophagy regulation and/or TAMs therapy may be a viable means and a key breakthrough to increase the effectiveness of immunotherapy.

Conclusions and prospects

Autophagy and TAMs have a dual role in cancer, intricately intertwined with tumorigenesis, tumor progression, and chemotherapeutic drug sensitivity, all depending on tumor characteristics and TME, and more studies are needed for a comprehensive assessment to determine how to use autophagy modulators and TAMs strategies appropriately. It has been suggested, first, that inhibition of autophagy regulates infiltration of TAMs thereby improving drug resistance in tumor cells. However, knowledge remains limited compared to other autophagic pathways, and many challenges remain to be addressed. Is the increase or decrease of TAMs infiltration associated with changes in the number of peripheral macrophages, allowing for changes in the immune response? Does it increase infiltration of other stromal cells in the TME and modulate the antitumor immune response? Second, targeting autophagy of TAMs or tumor cells can regulate repolarization of TAMs and ameliorate tumor development, and there are multiple mechanistic studies to support this, but are the autophagy regulation of TAMs and tumor cells consistent? Can targeting TAMs or tumor cell autophagic processes promote antitumor effects more efficiently? In addition to this, new studies have found that M1-type macrophages also promote malignancy. Does this suggest that there is a balance between M2 depletion, M1 repolarization and M1/M2 ratio that can make the TME unfavorable for tumor cell development? Then, autophagy in TAMs is activated to promote the secretion of multiple immune mediators, which regulates the autophagy of tumor cells to occur and cause tumor development. However, can these secreted substances be markers of TAMs or/and TME that have some potential significance in judging the therapeutic effect of tumor patients? Again, from the study of TME, TAMs may play a key role in transforming immune "cold" tumors into "hot" tumors, and autophagy is also one of the common processes in immunotherapy, so can the two be rationally linked? Is there a potential role in improving the efficacy of immunotherapy for malignant tumors by modulating the level of autophagy between TAMs and tumor cells? Finally, autophagy plays an important role in the infiltration, polarization, and secretion of TAMs for the development of tumor cells. Can the synergistic occurrence of these three aspects be promoted to improve the sensitivity of tumor cells to anti-tumor immune responses? In the course of this review, two key points were identified: autophagy regulation does not correspond to the state of TAMs and the development of tumor cells in a single way, and is this related to the different levels of autophagy in different cells? M1 macrophages have metabolic characteristics more similar to tumor cells, and M2 macrophages are closer to the metabolic state of normal cells. So is there competition between M1TAM and tumor cells and between M2 TAM and normal cells? Therefore, we need to investigate more deeply the molecular regulatory mechanisms of autophagy between TAMs and tumor cells, and this knowledge will open a new window for the study of autophagy and TME and, more importantly, will provide new opportunities for the treatment of related cancers. However, the application of this strategy to different cancer types and different stages of cancer development remains context-specific.

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