Targeting the TME-Autophagy Axis to Overcome Cancer Drug Resistance

Yaoyang Gong

Department of Applied Biology and Chemical Technology Hong Kong Polytechnic University, 710048 Hong Kong, China

22097617d@connect.polyu.hk

Abstract. The tumor microenvironment (TME), as an essential ecological niche for tumor cell survival, is composed of stromal cells, immune cells, extracellular matrix, and signaling molecules. It not only provides metabolic support for tumors but also promotes their proliferation, invasion, and treatment resistance through dynamic regulation. Autophagy, a key mechanism in cellular homeostasis, plays a dual role in tumors: early on, it inhibits malignant transformation by clearing damaged organelles, while later it supports tumor survival through metabolic adaptation. Recent studies have revealed extensive interactions between TME and autophagy. For example, hypoxia and nutrient deprivation can activate autophagy pathways, while autophagy-derived metabolites can reshape the components of the TME. This mechanism plays a crucial role in tumorigenesis and its drug resistance characteristics. However, most current drugs (such as autophagy inhibitors or anti-angiogenesis drugs) target single pathways, failing to block the autophagy-TME interaction, which forms a resistance network. This review will analyze the mechanisms of the autophagy-TME interaction in the development of drug resistance during different stages of cancer and discuss strategies that may improve the therapeutic efficacy of cancer treatments.

Keywords: Tumor microenvironment, cellular autophagy, metabolic reprogramming, drug resistance, Targeted therapy.

1. Introduction

The tumor microenvironment (TME), as an essential ecological niche for tumor cell survival, consists of stromal cells, immune cells, extracellular matrix, and signaling molecules. It not only provides metabolic support for tumors but also promotes their proliferation, invasion, and therapeutic resistance through dynamic regulation. Autophagy, a key mechanism for maintaining cellular homeostasis, has a dual role in tumors: early on, it suppresses malignant transformation by clearing damaged organelles, while in later stages, it assists tumor survival through metabolic adaptation. Recent studies have shown extensive interactions between TME and autophagy, such as how hypoxia and nutrient deprivation can activate autophagy pathways, while autophagy-derived metabolites can reshape TME components. However, existing therapeutic strategies often target only autophagy or TME regulatory factors individually, failing to integrate the cooperative network of both, leading to limited clinical efficacy (e.g., clinical trials of autophagy inhibitors such as hydroxychloroquine have not met expectations). This highlights the urgent need to elucidate the autophagy-TME interaction mechanism. This review will systematically explain the regulatory interactions between TME and autophagy in tumor progression, focusing on how microenvironmental factors like metabolic stress, immune remodeling, and mechanical stress drive the functional transition of autophagy, and critically evaluate the limitations of existing therapeutic strategies. Based on the molecular features of the autophagy-TME interaction network, we will further propose combined treatment strategies targeting dual regulatory nodes, providing new research directions for overcoming tumor adaptive resistance.

2. Autophagy and Tumor Microenvironment Concept

Autophagy, as a core mechanism for cellular clearance of damaged components and maintenance of homeostasis, participates in energy stress response, genome stability, and inflammation regulation through the degradation of abnormal macromolecules. Recent studies have revealed that autophagy

not only plays a key role in tumor cell autonomous survival but also forms a dynamic interaction network with the tumor microenvironment (TME): It helps tumors adapt to hypoxic/nutrient-deprived TME through metabolic reprogramming, while also releasing exosomes and other mediators to remodel the immunosuppressive microenvironment, driving immune evasion, metastasis, and treatment resistance. Although therapies targeting autophagy or TME regulators have entered clinical practice, they often fail to deliver expected outcomes due to the neglect of the synergistic mechanisms between the two, leading to limited efficacy or even compensatory deterioration. For example, anti-angiogenesis drugs may inadvertently activate autophagy metabolism by exacerbating the hypoxic microenvironment; therapies aimed at inhibiting chronic inflammation may have limited efficacy due to the immune-suppressive TME remodeling mediated by autophagy; even strategies targeting nutrient supply may fail to achieve the desired effect due to the autophagy-dependent recycling of substrates (as shown in Table 1).

Table 1. Autophagy-TME Interaction in Drug Resistance

Targeting dimension	Representative Drug	Target/Mechanism of Action	Autophagy-TME Interaction Resistance Mechanism
Anti-angiogenesis	Bevacizumab	Inhibits VEGF, blocks angiogenesis	PD-L1 inhibitor, blocks PD-1/PD-L1 signaling
Anti-Chronic Inflammation	Etanercept	Neutralizes TNF-α, inhibits chronic inflammation drivers	Mitochondrial autophagy → PI3K-AKT activation
Anti-Metabolic Reprogramming	Everolimus	mTOR inhibitor, rapamycin analog	mTOR inhibition → autophagy → Metabolic circuit remodeling
Reducing Tumor Nutrient Utilization	Rapamycin	mTOR inhibitor, reduces tumor nutrient utilization	mTOR inhibition promotes autophagy → Nutrient replenishment
Inhibiting Immune Evasion	Pembrolizumab	PD-1 inhibitor, activates T-cell anti-tumor immunity	Autophagy degrades MHC-I + PD-L1 membrane cycling

This contradiction underscores the central role of the autophagy-TME interaction as a "barrier" in tumor drug resistance — single-dimensional targeted interventions are insufficient to overcome the adaptive survival network constructed by their cooperation. Therefore, systematically analyzing the mechanisms of the autophagy-TME interaction at different stages of tumor progression has significant translational value in optimizing therapeutic strategies.

3. Interactive Regulatory Mechanisms Between TME and Autophagy

3.1. Early Tumor Formation

In the early stages of tumorigenesis, autophagy suppresses malignant transformation through dual mechanisms: on one hand, it clears dysfunctional mitochondria to prevent ROS-mediated genomic damage (such as oncogene activation); on the other hand, it constructs a "autophagy-TME-inflammation" triad regulatory network to maintain immune homeostasis. When core autophagy genes (such as Atg5, Beclin 1) are defective, necrotic cell death increases, leading to the release of molecules such as HMGB1 (DAMPs), which activate stromal cells via the RAGE/TLR4-NF-κB axis, driving the secretion of pro-tumor factors like IL-6 and TNF-α. Additionally, autophagy defects result in mitochondrial quality control imbalance, with abnormal accumulation of mt ROS, which activates the NLRP3 inflammasome and promotes the maturation of IL-1β/IL-18, forming a cascade-amplified pro-inflammatory microenvironment. This inflammatory reprogramming marks the transition of the TME from immune surveillance to a pro-cancer phenotype.

The inflammatory microenvironment remodeling induced by autophagy defects not only directly promotes tumor progression but also leads to therapeutic resistance by activating compensatory survival signals. For example, Etanercept, a TNF-α neutralizing agent, theoretically reduces tumor-related inflammation and delays carcinogenesis by blocking the interaction between TNF-α and its receptors. However, in autophagy-deficient tumors, the efficacy of this drug is significantly limited due to the activation of the compensatory "mitophagy-PI3K/AKT survival axis." The activation of the PI3K/AKT pathway leads to the activation of NF-κB and STAT3 in cancer cells [1], which in turn promotes further tumor cell proliferation, thus reducing the therapeutic efficacy of Etanercept [2].

3.2. Tumor Progression

3.2.1 The Cooperative of Autophagy and Angiogenesis in Drug Resistance

In the development of malignant tumors, tumor cells dynamically remodel the microenvironment to create a unique survival niche. When the tumor diameter exceeds 2 mm, a hypoxic (oxygen pressure <5%) and nutrient-deprived stress microenvironment gradually forms within, and this dual pressure activates hypoxia-inducible factor HIF-1α, driving a cooperative adaptation mechanism between autophagy and angiogenesis [3]. HIF-1α, as a core regulatory hub, activates BNIP3/BNIP3L gene expression on one hand, destabilizing the Beclin1/Bcl-2 complex, thereby inducing mitochondrial autophagy to remove ROS-overloaded damaged mitochondria; on the other hand, it directly binds to the hypoxia-responsive element of the VEGF gene, increasing its expression 5-20 times, in conjunction with fibroblast growth factor (FGF2) to promote pathological angiogenesis. This HIF-1α-driven "autophagy-angiogenesis" axis not only maintains metabolic homeostasis in tumor cells but also establishes a leaky vascular network, laying the foundation for pre-metastatic niches.

Most current anti-angiogenesis drugs focus on inhibiting VEGF and VEGFR2 growth factors to suppress angiogenesis [4]. However, studies have shown that these drugs often have limited therapeutic effects due to the resistance networks formed by the autophagy-TME interaction being overlooked. For example, bevacizumab, a drug that targets VEGF and blocks angiogenesis, can initially inhibit the formation of new blood vessels and achieve therapeutic effects. However, research indicates that in clinical treatments for glioblastoma and other cancers, high concentrations of bevacizumab show limited efficacy [4]. This is because, while inhibiting VEGF and similar molecules significantly alters the tumor microenvironment, the related cancer cells, in response to the dramatic changes in the microenvironment, undergo autophagy via stress responses and produce HIF-1α, which greatly reduces the anti-angiogenesis effects of the drug [5]. Another class of anti-angiogenesis drugs, such as apatinib, blocks endothelial cell proliferation signals, leading to the release of large amounts of HMGB1 into the microenvironment under hypoxic conditions. This activates the TLR4/Beclin1 signaling axis to promote autophagosome formation, improving the hypoxic environment to aid tumor growth, which undoubtedly reduces the therapeutic efficacy of the drug [6].

3.2.2 Nutrient Support and Metabolic Reprogramming

During the progression of solid tumors, the nutrient-deprived microenvironment forces tumor cells to reconfigure their metabolic networks through autophagy to maintain survival. This autophagy activation is regulated by multiple layers of metabolic sensing: amino acid metabolism imbalance (e.g., glutamine deamination activating autophagy, branched-chain amino acid depletion inhibiting mTORC1-induced autophagy) and glucose depletion (via dual pathways involving ATP shortage and ROS accumulation) together form core inductive factors. Additionally, advanced glycation end products (AGEs) receptors (RAGE) can enhance autophagic activity by inhibiting the mTOR pathway, significantly improving cancer cell (such as pancreatic cancer) adaptive survival under extreme nutritional stress, thereby creating a vicious cycle of metabolic reprogramming and TME interaction. This interaction mechanism is particularly evident in the development of resistance to the mTOR inhibitor rapamycin (Rapamycin). As an mTORC1 inhibitor, rapamycin suppresses tumor

proliferation by blocking nutrient-sensing signals. However, simultaneous inhibition of mTOR also releases the negative regulation on autophagy, promoting tumor cells to recycle amino acids, fatty acids, and other metabolic substrates via autophagy [7]. The activation of autophagy leads tumor cells to form a "metabolic escape cycle" under rapamycin treatment—by degrading intracellular components, replenishing TCA cycle intermediates (e.g., α-ketoglutarate), maintaining energy supply, and driving drug resistance.

In summary, autophagy confers a remarkable plasticity to tumor cells under nutritional stress by dynamically regulating the degradation of metabolic enzymes and the recycling of substrates. However, metabolic-targeting drugs (e.g., rapamycin) often overlook the autophagy-TME interaction, thereby activating compensatory metabolic cycles, sharing a common resistance pattern with anti-angiogenesis drugs (e.g., bevacizumab) and anti-inflammatory drugs (e.g., etanercept): therapeutic stress → autophagic compensation → pathway reprogramming. Future strategies should focus on "metabolism-autophagy dual-targeting" approaches to break through the tumor adaptive survival network.

3.3. Tumor Invasion and Dissemination Stage

In the tumor microenvironment (TME), autophagy plays a pivotal role in immune system regulation, serving as a critical hub in tumor immune evasion and progression. On one hand, autophagy influences immune surveillance efficiency by modulating antigen-presenting pathways: tumor cells can degrade MHC class I molecules through an autophagy-dependent mechanism, such as the ubiquitination modification of MHC I molecules mediated by the NBR1 receptor in pancreatic cancer cells, promoting their entry into the lysosome for degradation via classical autophagy, thus reducing the tumor antigen presentation capacity and weakening CD8+ T cell recognition and cytotoxicity [8]. On the other hand, autophagy dynamically regulates the immune cell trafficking pattern. Tumor cells with intact autophagy function secrete chemokines such as CXCL5 and CXCL12 to recruit myeloid-derived suppressor cells (MDSCs) and M2 macrophages, constructing an immunosuppressive niche that impacts the immune system's ability to kill cancer cells [9].

At the effector immune cell functional level, autophagy directly interferes with anti-tumor immune responses through metabolic stress mechanisms. Hypoxia-induced tumor autophagy can degrade granzyme B released by NK cells and suppress the phosphorylation of the STAT3 signaling pathway, thus weakening the cytotoxic functions of NK cells and CD8+ T cells.

Current research shows that autophagy inhibitors (e.g., chloroquine) can enhance anti-tumor immunity through multiple mechanisms, such as restoring MHC class I expression, increasing CXCL9/CXCL10 secretion, and blocking granzyme B degradation. However, the efficacy of these inhibitors may vary depending on the tumor type and immune infiltration status. Therefore, understanding how autophagy regulates the cross-talk between immune checkpoints, metabolic reprogramming, and cell death pathways in specific TME contexts will be crucial in developing combined immunotherapy strategies.

Currently, immune checkpoint inhibitors (e.g., pembrolizumab and atezolizumab) have shown significant progress in the treatment of various tumors, but autophagy enhances PD-L1 expression and inhibits antigen presentation, limiting the efficacy of these drugs [10]. In the treatment of bladder cancer, the efficacy of atezolizumab (anti-PD-L1) is significantly influenced by autophagy-mediated PD-L1 degradation. Research has shown that while atezolizumab can extend the median survival of patients with high PD-L1 expression, the effect is only 4.3 months [11]. Therefore, overcoming tumor autophagy-mediated immune evasion may be key to improving immunotherapy efficacy. In the future, combining autophagy inhibitors with immune checkpoint inhibitors may help restore anti-tumor immune responses, especially in tumors with high autophagy activity.

In summary, the role of autophagy in tumor immune evasion is multifaceted: it directly suppresses immune therapy efficacy by reducing antigen presentation and enhancing PD-L1 surface expression and further promotes immune evasion by modulating immune cells and the metabolic responses of the tumor microenvironment. Therefore, in-depth study of the relationship between autophagy and

immune evasion, along with the development of corresponding combination therapies, will provide new directions for enhancing the effectiveness of tumor immunotherapy.

4. Mechanisms and Case Studies of Targeted Drug Combination with Autophagy Inhibitors/Inducers to Overcome Resistance

Based on the dynamic interaction network between the tumor microenvironment (TME) and autophagy, the core of targeted therapy resistance mechanisms lies in the activation of compensatory autophagy or TME remodeling. Therefore, the combined use of chemotherapeutic agents and autophagy inhibitors has become a necessary strategy to overcome resistance. Existing studies show that the synergistic effect of autophagy inhibitors and targeted drugs can significantly enhance anti-tumor efficacy. For example, the combination of the anti-metabolic drug everolimus with the MC-4 inhibitor can simultaneously target the PI3K/Akt/PKM2 and mTORC1 pathways, co-inhibiting tumor cell proliferation and blocking autophagy-dependent survival, thereby overcoming resistance to mTOR inhibitors in advanced renal cell carcinoma (RCC) patients [12].

Autophagy inhibitors, such as chloroquine (CQ) and hydroxychloroquine (HCQ), have been widely used in clinical practice. These inhibitors block autophagic flux by inhibiting lysosomal function, significantly enhancing the efficacy of various targeted drugs. Studies have confirmed that CQ/HCQ can synergistically enhance the effects of etanercept (TNF-α neutralizing agent) to inhibit TNF-α-mediated inflammatory signals [13], reverse compensatory autophagy induced by mTOR inhibition when combined with rapamycin [14] or restore T-cell immune responses when combined with pembrolizumab [15].

In recent years, the development of novel autophagy modulators has further expanded combination therapy strategies. For example, metformin enhances metabolic stress by activating the AMPK pathway, synergizing with rapamycin to inhibit mTORC1 signaling, while VPS34 inhibitor SAR405 blocks autophagosome formation, significantly enhancing the targeting efficiency of PD-L1 inhibitor atezolizumab [16]. These studies highlight the pivotal role of the autophagy-TME interaction in cross-therapy resistance and demonstrate that combined interventions can precisely dismantle the tumor adaptive survival network.

Future research should focus on the following areas: First, developing dual-target drugs (e.g., bispecific antibodies targeting both PD-L1 and ULK1) to simultaneously block immune checkpoint and autophagy pathways; second, exploring dynamic sequential treatment regimens, adjusting drug timing based on TME hypoxia levels or autophagy activity; third, establishing patient stratification systems based on biomarkers (e.g., LC3B, HIF-1α) for precise treatment. By integrating the multidimensional regulation of the "autophagy-TME-therapy axis," it is expected that tumor resistance barriers can be overcome, leading to a paradigm shift in cancer treatment from single-target interventions to ecological niche regulation.

5. Conclusion

In this review, we explored the mechanisms by which autophagy interacts with the tumor microenvironment (TME) at different stages of cancer, addressing the question of how autophagy transitions from a “guardian” that suppresses cancer to a “promoter” that facilitates cancer initiation and progression. The study approached this issue from the perspective of dynamic microenvironmental evolution, integrating four key dimensions: chronic inflammation activation, metabolic reprogramming, neo angiogenesis, and immune evasion. We deeply analyzed how tumor cells, under microenvironmental stress, establish adaptive survival strategies through autophagy-mediated compensatory mechanisms, and discussed how the activation of these compensatory pathways could contribute to the formation of a resistance network, affecting the therapeutic efficacy of chemotherapy drugs.

Autophagy, as a core regulatory node in the tumor microenvironment, exhibits a "double-edged sword" nature, serving both as a challenge in therapy and as an opportunity for breakthroughs. Future research should shift from static mechanism analysis to dynamic network intervention, combining systems biology and precision medicine strategies to decode the autophagy-mediated adaptive survival code, ultimately achieving a paradigm shift from "tumor resistance" to "treatment enhancement.

References

[1] Li D, Ji H, Niu X, et al. Tumor-associated macrophages secrete CC-chemokine ligand 2 and induce tamoxifen resistance by activating PI3K/Akt/mTOR in breast cancer. Cancer science, 2020, 111 (1): 47-58.

[2] Shirmohammadi E, Ebrahimi S E S, Farshchi A, et al. The efficacy of etanercept as anti-breast cancer treatment is attenuated by residing macrophages. Bmc Cancer, 2020, 20: 1-10.

[3] Mihalache C C, Yousefi S, Conus S, et al. Inflammation-associated autophagy-related programmed necrotic death of human neutrophils characterized by organelle fusion events. The Journal of Immunology, 2011, 186 (11): 6532-6542.

[4] Huang H, Song J, Liu Z, et al. Autophagy activation promotes bevacizumab resistance in glioblastoma by suppressing Akt/mTOR signaling pathway. Oncology letters, 2018, 15 (2): 1487-1494.

[5] Guo X, Li D, Sun K, et al. Inhibition of autophagy enhances anticancer effects of bevacizumab in hepatocarcinoma. Journal of Molecular Medicine, 2013, 91: 473-483.

[6] Yang Q K, Chen T, Wang S Q, et al. Apatinib as targeted therapy for advanced bone and soft tissue sarcoma: a dilemma of reversing multidrug resistance while suffering drug resistance itself. Angiogenesis, 2020, 23: 279-298.

[7] Klionsky D J, Petroni G, Amaravadi R K, et al. Autophagy in major human diseases. The EMBO journal, 2021, 40 (19): e108863.

[8] Yamamoto K, Venida A, Yano J, et al. Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. Nature, 2020, 581 (7806): 100-105.

[9] Görgülü K, Diakopoulos K N, Ai J, et al. Levels of the autophagy-related 5 protein affect progression and metastasis of pancreatic tumors in mice. Gastroenterology, 2019, 156 (1): 203-217. e20.

[10] Koustas E, Sarantis P, Papavassiliou A G, et al. The resistance mechanisms of checkpoint inhibitors in solid tumors. Biomolecules, 2020, 10 (5): 666.

[11] Petrylak D P, Loriot Y, Shaffer D R, et al. Safety and clinical activity of atezolizumab in patients with metastatic castration-resistant prostate cancer: a phase I study. Clinical Cancer Research, 2021, 27 (12): 3360-3369.

[12] Son J Y, Yoon S, Tae I H, et al. Novel therapeutic roles of MC-4 in combination with everolimus against advanced renal cell carcinoma by dual targeting of Akt/pyruvate kinase muscle isozyme M2 and mechanistic target of rapamycin complex 1 pathways. Cancer medicine, 2018, 7 (10): 5083-5095.

[13] Gros F, Muller S. Pharmacological regulators of autophagy and their link with modulators of lupus disease. British journal of pharmacology, 2014, 171 (19): 4337-4359.

[14] Chi K H, Ko H L, Yang K L, et al. Addition of rapamycin and hydroxychloroquine to metronomic chemotherapy as a second line treatment results in high salvage rates for refractory metastatic solid tumors: a pilot safety and effectiveness analysis in a small patient cohort. Oncotarget, 2015, 6 (18): 16735.

[15] Haynes J, Manogaran P. Mechanisms and Strategies to Overcome Drug Resistance in Colorectal Cancer. International Journal of Molecular Sciences, 2025, 26 (5): 1988.

[16] Pasquier B. SAR405, a PIK3C3/Vps34 inhibitor that prevents autophagy and synergizes with MTOR inhibition in tumor cells. Autophagy, 2015, 11 (4): 725-726.