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Autophagy-Lysosome Dysfunction in Cancer: Molecular Mechanism and Therapeutic Prospects

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Abstract. The autophagy-lysosomal pathway constitutes a fundamental intracellular degradation system that recycles cellular components and eliminates damaged organelles through both non-selective and selective mechanisms. Selective autophagy is mediated by specific receptors that target substrates for degradation, including mitochondria (mitophagy), the endoplasmic reticulum (ER-phagy), lipid droplets (lipophagy), and intracellular pathogens (xenophagy), collectively forming a network that maintains cellular homeostasis. In tumors, autophagy-lysosomal dysfunction plays a dual role: on the one hand, it suppresses malignant transformation during early tumorigenesis by maintaining genomic stability and limiting oxidative stress; on the other hand, it drives the progression of established tumors by enhancing metabolic adaptation, promoting therapeutic resistance and facilitating immune evasion. This functional shift is driven by metabolic reprogramming within the tumor microenvironment, ferroptosis inhibition, inflammasome activation and spatiotemporal heterogeneity. Recent therapeutic strategies have evolved from broad-spectrum inhibitors toward precision interventions, including nanodrug delivery systems, patient stratification guided by single-cell and spatial multi-omics and targeted protein degradation. Technologies such as proteolysis-targeting chimeras and lysosome-targeting chimeras offer promising approaches for selectively modulating protein degradation pathways. The integration of these approaches with immune checkpoint blockade and epigenetic modulators has opened new avenues for overcoming drug resistance and improving clinical outcomes. This review systematically explores the molecular mechanisms, dual functions and therapeutic implications of autophagy-lysosomal dysfunction in cancer, emphasizing the shift from non-selective inhibition toward selective precision targeting.

Keywords: Autophagy-Lysosome Dysfunction, Selective Autophagy, Mitophagy, Ferroptosis, Cancer Therapy

1. Introduction

Autophagy is a lysosome-dependent degradation pathway that mediates the recycling of intracellular materials and the clearance of damaged organelles through either non-selective or selective mechanisms. The core process of autophagy initiates with the formation of a phagophore, which subsequently expands to engulf cytosolic materials and eventually closes to form an autophagosome.

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The autophagosome then fuses with a lysosome to form an autolysosome, within which the enclosed materials are degraded by lysosomal enzymes and subsequently recycled [1]. Selective autophagy is mediated by specific receptor proteins that recognize distinct substrates and direct mitophagy, endoplasmic reticulum autophagy (ER-phagy), lipophagy, and xenophagy. Mitophagy primarily eliminates damaged mitochondria through the PTEN-induced putative kinase 1 (PINK1)/Parkin RBR E3 ubiquitin protein ligase (Parkin) pathway but it can also be achieved via mechanisms mediated by BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3)/BNIP3-like protein X and FUN14 domain-containing protein 1. ER-phagy clears endoplasmic reticulum fragments through receptors such as family with sequence similarity 134 member B, testis-expressed protein 264 (TEX264), SEC62 homolog, preprotein translocation factor, reticulon-3L, cell cycle progression protein 1, and atlastin GTPase 3, thereby maintaining endoplasmic reticulum homeostasis. Lipophagy degrades lipid droplets to release free fatty acids and produce energy. Xenophagy targets ubiquitin-labeled pathogens. Pathogens are recognized by receptors including sequestosome 1 (p62/SQSTM1), nuclear dot protein 52, BRCA1 gene neighbor 1, and optineurin and are degraded through the autophagic pathway [2]. These selective autophagy pathways constitute an integrated organelle quality control network that maintains cellular homeostasis under various stress conditions [3]. These findings have transformed the understanding of autophagy from a non-selective bulk degradation process into a highly selective system, laying the foundation for modern autophagy research.

Under normal physiological conditions, the autophagy-lysosomal pathway serves as a central hub for substance metabolism, metabolic regulation, and cellular quality control. It also maintains intracellular homeostasis by degrading and recycling damaged or superfluous proteins and organelles. The lysosomes function not only as degradative structures but also as signaling transduction centers that sense and integrate signals derived from nutrient status, metabolic stress, and pathogens, thereby coordinating processes such as cell growth, autophagy, immune responses, and cell death. In cancer, the autophagy-lysosomal pathway plays dual roles: on the one hand, it suppresses early tumorigenesis by maintaining genomic integrity and limiting oxidative stress; on the other hand, it accelerates the progression of established tumors by promoting metabolic adaptation, therapeutic tolerance, and immune evasion [4]. Relevant therapeutic strategies have shifted from nonspecific autophagy inhibitors to biomarker-based precision modulation.

This review systematically summarizes the molecular mechanisms and regulatory networks of the autophagy-lysosomal pathway, with particular emphasis on the dual roles and spatiotemporal heterogeneity of selective autophagy in tumorigenesis and antitumor therapy. It further reviews therapeutic strategies targeting selective autophagy, including nanomedicine delivery systems, targeted protein degradation technologies such as proteolysis-targeting chimeras (PROTACs) and lysosome-targeting chimeras (LYTACs), and patient stratification guided by single-cell multi-omics and spatial transcriptomics, and highlights the shift from nonspecific inhibition toward context-dependent precision targeting. These efforts provide an integrated reference for understanding the complex role of autophagy-lysosomal dysfunction in cancer and offer directions for future research on selective autophagy-targeted drugs and combination therapies.

2. Core molecular mechanisms and regulatory networks of the autophagy-lysosomal pathway

The core molecular mechanism of autophagy-lysosomal pathway is shown in Figure 1. Figure 1 (A) shows the formation process of autophagosomes: the autophagosomes of the bilayer membrane encapsulate the cytoplasmic components, and the microtubule-associated protein 1 light chain 3 (LC3)/γ-aminobutyric acid receptor-associated protein (GABARAP) is anchored on the membrane;

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the cargo receptor p62/SQSTM1 binds to the ubiquitinated substrate and LC3/GABARAP by virtue of its LC3 interacting region (LIR) motif, thereby achieving selective capture of specific substrates. After that, autophagosomes and lysosomes fuse to form autolysosomes, in which the encapsulated substances are degraded and recovered. Figure 1 (B) is mitophagy. The damaged mitochondria are selectively encapsulated by autophagosomes and transported to lysosomes for degradation. Figure 1 (C) is lipophagy. Lipid droplets are selectively encapsulated by autophagosomes and sent to lysosomes. After degradation, free fatty acids are released for energy. Figure 1 (D) is ER-phagy. Endoplasmic reticulum (ER) fragments are specifically recognized by receptors residing in the endoplasmic reticulum and transported to lysosomes for degradation by autophagosomes to maintain endoplasmic reticulum homeostasis. On this basis, Section 2.1 further analyzed the interaction network between selective autophagy receptors and LC3/GABARAP.

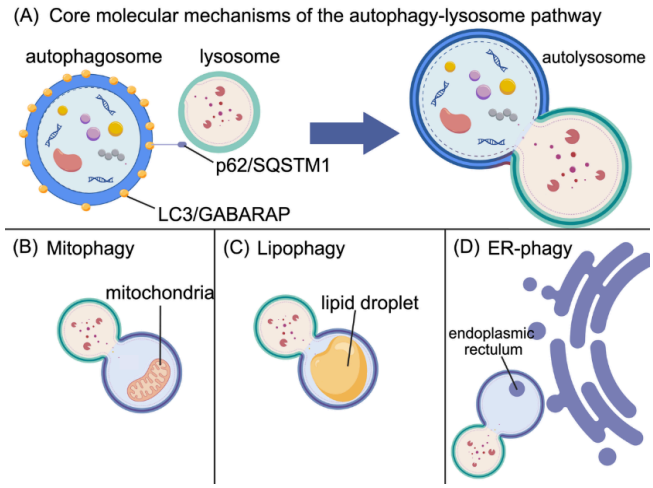


Figure 1. Core molecular mechanisms of the autophagy-lysosomal pathway

2.1. Core recognition mechanism: interaction network between selective autophagy receptors and LC3/GABARAP

The establishment of selective autophagy fundamentally depends on a class of receptor proteins that recognize the substrate to be degraded and accurately deliver it to the autophagy-related protein 8 (ATG8) family members and LC3/GABARAP on the autophagosome membrane, thereby completing the isolation and degradation of the substrate. The key to this network is the binding between the LIR domain receptor and the ATG8 protein, and it is this binding process that distinguishes selective autophagy from non-selective autophagy [5] (Figure 1 (A)). Different types of receptors recognize different targets, including damaged organelles, protein aggregates, or invading pathogens. In DNA damage repair, TEX264 acts as a selective autophagy receptor that senses the topoisomerase 1 cleavage complex (TOP1cc) that is blocked in the DNA replication fork. Under the action of MRE11 nuclease and ataxia telangiectasia mutation and Rad3-associated (ATR) kinase, TEX264 transports TOP1cc to lysosomes for degradation, thereby promoting cancer cell survival. This mechanism is highly conserved in evolution and is associated with the clinical characteristics of colorectal cancer patients [6]. In terms of immune quality control, the immune-related GTPase family Q protein (IRGQ) specifically binds to γ-aminobutyric acid receptor-associated protein-like 2 (GABARAPL2)/microtubule-associated protein 1 light chain 3 beta (LC3B) to accurately recruit autophagosomes. IRGQ is not involved in systemic autophagy, and its role is limited to identifying abnormal major histocompatibility complex (MHC) class I molecules in

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the ER, such as free heavy chains or unassembled dimers, encapsulating them into autophagosomes, which are transported to lysosomal degradation through GABARAPL2/LC3B-mediated pathways. When IRGQ is deficient, abnormal MHC I molecules that should have been cleared escape quality control, accumulate in the cell and transport to the cell surface. It is worth noting that these non-classical conformational MHC I molecules can effectively activate cluster of differentiation 8 (CD8)-positive ($CD8^+$) T cells, and significantly enhance the anti-tumor immune response. This mechanism has been fully verified in human and mouse hepatocellular carcinoma models: knockout of IRGQ can significantly increase the expression level of MHC class I molecules on the surface of tumor cells, enhance the infiltration, activation and killing function of $CD8^+$ cells, and ultimately significantly prolong the survival time of tumor-bearing mice, and this effect is completely dependent on $CD8^+$ cells [7].

2.2. Regulatory pathways and molecular switches of mitophagy (PINK1/Parkin and non-dependent pathways)

Mitophagy is the core mechanism for selective removal of damaged or redundant mitochondria (Figure 1 (B)). Its regulatory network forms precise molecular switches in different tissues and under various stress conditions through multiple dependent and independent pathways. In the PINK1/Parkin axis, PINK1 regulates the balance of substrate ubiquitination, promotes the recruitment and activation of Parkin on the outer surface of mitochondria, drives the ubiquitination of mitochondrial outer membrane proteins, and is finally recognized and degraded by autophagy receptors. Ubiquitin-specific peptidase 30 is a mitochondrial deubiquitinase. Inhibition of its activity can activate ubiquitin-mediated mitophagy, which provides an intervention idea for reducing the level of mutant mitochondrial DNA [8]. Independent approach also cannot be ignored. The decrease of cytosolic acetyl-coenzyme A (acetyl-CoA) level can trigger mitophagy mediated by NLR family member X1 (NLRX1). When NLRX1 does not bind to acetyl-CoA, its leucine-rich repeat domain dissociates from NAIP, CIITA, HET-E and TP1 (NACHT) domains, exposing the binding sites that can directly interact with LC3, thereby initiating mitophagy. This pathway also plays an important role in the formation of drug resistance induced by KRAS inhibitors [9].

2.3. ER-phagy and the receptor classification of the stress regulatory network

ER-phagy is a selective degradation process of the ER membrane and its contents (Figure 1(D)), it plays a crucial role in maintaining ER homeostasis and responding to unfolded protein stress. The receptor network involved in ER-phagy exhibits a regulatory pattern capable of adapting to specific cellular states and stress conditions. In ER-phagy, PINK1 promotes the process by modulating Kelch-like ECH-associated protein 1 (Keap1), the Keap1-Cullin3 complex collaborates with receptor proteins reticulon-like 1 and atlastin to mediate the clearance of ER membranes. Under proteotoxic stress conditions, such as when ubiquitin-specific protease 39 gene deletion leads to abnormal assembly of the splicing complex, the accumulation of misfolded proteins may trigger ER stress. At this point, the ubiquitin-proteasome system and selective autophagy work synergistically to eliminate these toxic proteins to alleviate ER stress and maintain cell survival [10]. As a core component of the protein homeostasis network, ER-phagy, together with mitophagy, constitutes an organ-specific organelle degradation pathway whose dysfunction is closely associated with cancer initiation and progression [11].

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3. Autophagy-lysosome dysfunction as a dual mechanism in tumor development and progression

For a long time, autophagy has been regarded as a non-selective batch degradation process. Today's understanding is more refined. Selective autophagy mediated by specific receptor proteins makes metabolic reprogramming and organelle quality control possible. This distinction has clinical significance-inhibiting non-selective autophagy affects all autophagy substrates, while targeting selective autophagy retains its beneficial functions. In tumors, the role of the autophagy-lysosomal pathway is dual and is deeply affected by the tumor microenvironment. In this chapter, the anti-tumor mechanism and tumor-promoting mechanism are discussed respectively.

3.1. Mechanisms of tumor suppression: genome guardian role and programmed cell death induced by excessive activation

In the early stages of tumor development, the autophagy-lysosomal pathway plays a key role in inhibiting tumor progression. The anti-cancer mechanism of autophagy-lysosomal dysfunction is shown in Figure 2. Figure 2 (A) is the genome-guarding effect: at the stalled replication fork, TEX264 recognizes TOP1cc and mediates its lysosomal degradation by p97 ATPase, MRE11 and ATR to maintain genome stability. Figure 2 (B) is the p53-tuberous sclerosis complex 2 (TSC2) - transcription factor EB (TFEB) tumor suppressor pathway: p53 activates TSC2, which inhibits mTORC1 and promotes TFEB nuclear accumulation, inducing cell senescence; senescent cells recruit macrophages, causing cancer cells to be engulfed. Figure 2 (C) is programmed cell death induced by excessive autophagy: excessive autophagy causes mitochondrial dysfunction and reduces the accumulation of reactive oxygen species (ROS), triggering apoptosis, autophagy-dependent death and ferroptosis. Figure 2 (D) is macrophage phagocytic cell death: excessive phagocytosis/nutrient uptake of macrophages by early cancer cells leads to non-apoptotic macrophage phagocytic cell death.

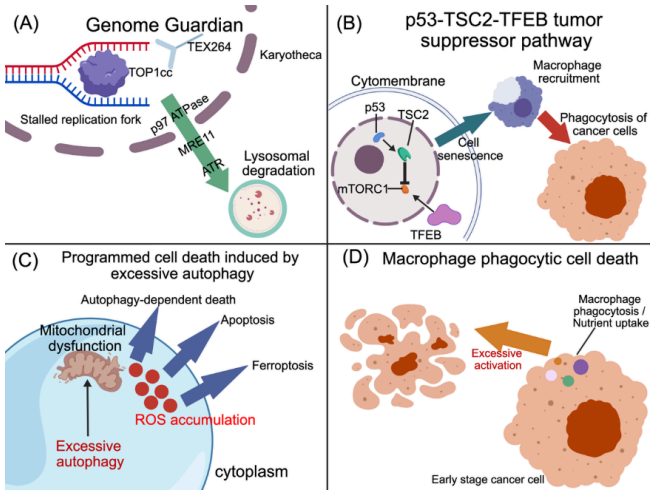


Figure 2. Anti-cancer mechanisms of autophagy-lysosome dysfunction

The autophagy-lysosomal pathway maintains genomic stability and clears damaged organelles. The loss of autophagy function will promote the malignant transformation of tumors, and effective autophagy response can quickly remove aggregation proteins and damaged mitochondria, and prevent the accumulation of oxidative stress and DNA damage. The TEX264 receptor senses

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TOP1cc and transports it to lysosomes for degradation through p97 (valosin-containing protein) ATPase. This process depends on MRE11 enzyme and ATR kinase and is of significant importance for maintaining genomic stability and cell survival (Figure 2(A)). P53 can activate TSC2, thereby inhibiting the rapamycin mechanism target complex 1 (mTORC1) and promoting the accumulation of TFEB in the nucleus, thereby initiating the lysosomal gene expression program and inducing autophagy and cell senescence. Senescent cancer cells then secrete a variety of factors that recruit macrophages and trigger phagocytosis, leading to tumor regression (Figure 2 (B)). This cascade reaction reveals the mechanism of p53-induced tumor regression [12]. On the other hand, excessive activation of autophagy may exceed the cell survival threshold and trigger programmed cell death. The metabolic activity of cancer cells is enhanced, and the level of ROS is increased. Moderate oxidative stress promotes tumor development by inducing DNA damage and genomic instability. Excessive ROS can destroy the antioxidant defense system and induce oxidative stress-related programmed cell death, including autophagy-dependent cell death and ferroptosis (Figure 2 (C)) [13]. In addition, tumor cells often use macrophage phagocytosis to meet metabolic needs when they are nutritionally deficient, but excessive activation of macrophage phagocytosis may lead to their own phagocytic cell death, suggesting that disruption of the lysosomal degradation pathway may also translate into anti-tumor effects (Figure 2 (D)) [14]. It can be seen that the autophagy-lysosomal network plays a role in both gene protection and programmed cell death regulation in tumorigenesis. However, the function of autophagy depends on the context, and its activity is affected by multiple factors such as tumor type, genetic background and tumor microenvironment, which also increases the difficulty of generalization of research conclusions and its clinical application.

3.2. Mechanisms promoting tumor initiation and progression: metabolic reprogramming, stemness maintenance, invasion, and metastasis

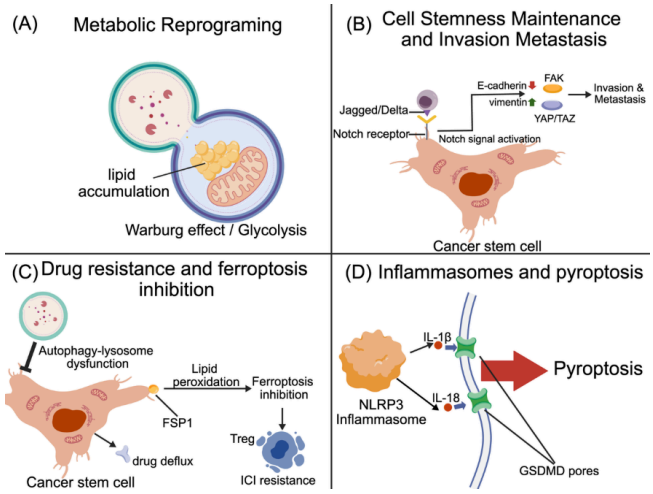


Figure 3. Pro-cancer mechanisms of autophagy-lysosome dysfunction

Autophagic-lysosomal pathway function remodeling constitutes a core driving factor for tumor cells' acquisition of metabolic adaptability, maintenance of stem cell-like properties and achievement of invasion and metastasis. The pro-cancer mechanisms of autophagy-lysosome dysfunction are summarized in Figure 3. Figure 3(A) shows metabolic reprogramming: autophagy-lysosome dysfunction promotes lipid accumulation and the Warburg effect/glycolysis. Figure 3(B) shows cell stemness maintenance and invasion/metastasis: Jagged/Delta–Notch receptor signaling activation upregulates vimentin and downregulates E-cadherin, and activates focal adhesion kinase

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(FAK) and Yes-associated protein (YAP)/WW domain-containing transcription regulator 1 (TAZ), promoting invasion and metastasis in cancer stem cells. Figure 3(C) shows drug resistance and ferroptosis inhibition: autophagy-lysosome dysfunction leads to drug efflux, ferroptosis suppressor protein 1 (FSP1)-mediated inhibition of lipid peroxidation and ferroptosis, and regulatory T cell-mediated immune checkpoint inhibitor (ICI) resistance. Figure 3(D) shows inflammasomes and pyroptosis: NLR family pyrin domain containing 3 (NLRP3) inflammasome activation releases interleukin-1β (IL-1β) and interleukin-18 (IL-18) and induces gasdermin D pore formation and pyroptosis.

In clear cell renal cell carcinoma (ccRCC), reprogramming of lipid metabolism cooperate with ferroptosis tolerance to promote tumorigenesis, through which tumor cells facilitate growth and evade ferroptosis through lipid accumulation. This reflects the intimate association between metabolic reprogramming and evasion of immunogenic cell death (Figure 3(A)) [15]. Pancreatic ductal adenocarcinoma (PDAC) is highly dependent on autophagy and lysosomal activity. Phosphatidylinositol kinase containing a FYVE-type zinc finger domain (PIKfyve) as a key lipid kinase for lysosomal function, when inhibited, it can trigger transcription and metabolic reprogramming of tumor cells and promote de novo lipid synthesis. Simultaneous blockade of PIKfyve and the KRAS-mitogen-activated protein kinase (MAPK) pathway can produce a synthetic lethal effect, thereby eliminating tumor burden [16]. The abnormal activation of the mTORC1 pathway suppresses metabolic stress-induced autophagy, leading to energy crisis and aspartate depletion, ultimately resulting in cell death. Coexistence of p62 accumulation and eukaryotic translation initiation factor 4E-binding protein 1 phosphorylation can predict poor prognosis in breast cancer patients, revealing metabolic vulnerability arising from suppressed autophagy [17]. Glycolytic enzymes not only provide energy but also regulate autophagy, cell aging and tumor microenvironment remodeling through non-classical functions, directly integrating metabolic networks with tumor progression [18]. At the post-transcriptional level, circRAPGEF5 (derived from the RAPGEF5 gene) in lung adenocarcinoma can bind insulin-like growth factor 2 mRNA-binding protein 2 to stabilize nucleoporin 160 mRNA, thereby inhibiting autophagic flux and promoting tumor proliferation, migration and invasion. This pro-metastatic function has been validated in in vivo models [19]. Exosomes in the tumor microenvironment can deliver bioactive molecules to cells, driving metabolic reprogramming, further promoting proliferation, invasion, metastasis and the establishment of drug resistance in cancers such as thyroid cancer [20]. In gastrointestinal tumors, cancer-associated fibroblasts (CAFs) activate signaling pathways including YAP/TAZ and integrin/FAK by secreting cytokines and exosomes. These processes interact with autophagy regulation to promote metabolic changes and treatment tolerance between cancer cells and CAFs in advanced tumors (Figure 3 (B)) [21]. The tumor microenvironment also further amplifies this dysfunction by spatial and microenvironment heterogeneity. Taking PDAC as an example, extracellular matrix (ECM) senses and regulates autophagy level through integrin α3-Hippo-YAP1 axis, resulting in heterogeneity: tumor cells with low autophagy level proliferate actively, while cells with high autophagy level show stronger tolerance to chemotherapy [22]. Hypoxia, oxidative stress and nutritional deficiency in the tumor microenvironment trigger endoplasmic reticulum stress and activate the unfolded protein response (UPR), which not only promotes tumorigenesis, metastasis and therapeutic resistance, but also suppresses anti-tumor immunity [23]. As a quality control mechanism for selective removal of endoplasmic reticulum fragments, ER-phagy plays a tumor-promoting role in the process of tumor microenvironment adapting to stress. Its imbalance may aggravate endoplasmic reticulum stress signals and support the survival and invasion of tumor cells. The interaction between cells in the tumor microenvironment

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further aggravates the heterogeneity of autophagy-lysosomal function : melanoma and non-small cell lung cancer (NSCLC) cells can transfer mitochondria carrying mutant mitochondrial DNA (mtDNA) to tumor-infiltrating lymphocytes (TILs), making the mitochondria of TILs unable to carry out mitophagy normally, causing metabolic abnormalities and cell senescence, impairing T cell effector function and memory formation ability, and ultimately weakening the anti-tumor immune response. This effect is associated with poor prognosis after treatment with immune checkpoint inhibitors [24]. This autophagy dysfunction mediated by mitochondrial transfer in immune cells reflects the spatial transmission mode of autophagy heterogeneity in tumor microenvironment. Single-cell and spatial omics technologies provide a new perspective for analyzing this heterogeneity, which is helpful to identify cell markers and autophagy regulatory nodes related to drug resistance [25]. The above-mentioned multi-layer regulatory network shows that autophagy-lysosomal dysfunction systematically drives malignant tumor progression by reshaping metabolic flow, stabilizing stem cell phenotype and destroying invasion barrier.

3.3. Molecular pathways mediating tumor treatment resistance, inhibition of ferroptosis, activation of inflammasomes and pyroptosis

Autophagy-lysosomal dysfunction plays a key role in tumor treatment resistance, which is mainly manifested in the inhibition of ferroptosis and the regulation of inflammatory cell death pathways. Ferroptosis is driven by lipid peroxidation and dependent on iron ions. It is a kind of programmed cell death, which is of great significance in tumor inhibition. Induction of ferroptosis can not only directly kill cancer cells, but also enhance the immune response and overcome the resistance of existing therapies [26]. However, tumor cells suppress ferroptosis through a variety of mechanisms to survive. Lung adenocarcinoma cells are highly sensitive to ferroptosis, but FSP1 can protect tumor cells from the accumulation of lipid peroxidation in vivo. Its high expression is related to disease progression and poor prognosis of patients, and drug inhibition of FSP1 can significantly inhibit tumorigenesis (Figure 3 (C)) [27]. In the tumor microenvironment, tumor cells can uptake itaconic acid produced by tumor-associated macrophages through solute carrier family 13 member 3, and then activate the nuclear factor erythroid 2-related factor 2 (NRF2) -solute carrier family 7 member 11 (SLC7A11) pathway to resist immune-mediated ferroptosis [28]. Regulatory T cells likewise maintain survival advantages in non-small cell lung cancer by resisting ferroptosis, and dominate immunosuppression under hypoxia and nutritional deficiency conditions, which limits the continuous efficacy of immune checkpoint inhibitors [29]. There is a two-way, cell context-dependent regulatory relationship between autophagy and ferroptosis. On the one hand, autophagy can promote ferroptosis through ferritin autophagy, that is, selective autophagy degradation of ferritin: this process releases unstable iron, expands the intracellular redox active iron pool, and then enhances lipid peroxidation and ferroptosis cell death. In addition, autophagy-mediated lipophagy can release polyunsaturated fatty acids and provide substrates for lipid peroxidation. On the other hand, autophagy can also inhibit ferroptosis through the p62/SQSTM1-NRF2 axis: autophagic degradation of p62 releases NRF2 from Keap1-mediated inhibition, inducing NRF2 to up-regulate the expression of antioxidant genes including SLC7A11 and glutathione peroxidase 4, thereby enhancing cell resistance to ferroptosis; mitochondrial autophagy can also remove damaged mitochondria, which are the main source of reactive oxygen species, and indirectly limit the initiation of ferroptosis. These pathways have some functional redundancy and tissue-specific expression advantages, which increases the complexity of targeted therapy. This two-way interaction shows that when regulating autophagy to overcome ferroptosis-related treatment resistance, a context-dependent intervention strategy should be adopted. In addition to ferroptosis, this process is

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also regulated by epigenetic and post-translational modifications that affect the sensitivity of cancer cells to ferroptosis and promote cancer progression and metastasis [30]. Inflammasomes are multiprotein complexes in the innate immune system that recognize pathogenic signals and cellular stress, and trigger the release of inflammatory cytokines. Among them, the NLRP3 inflammasome plays a key role in immune response and cancer progression. The activation of NLRP3 complex not only promotes the maturation and release of pro-inflammatory cytokines, but also induces pyroptosis. Pyroptosis is a soluble, pro-inflammatory programmed cell death mediated by the gasdermin protein family. Upon inflammasome activation, inflammatory caspases (such as caspase-1 in the classical pathway) cleave the gasdermin protein, releasing the N-terminal pore-forming domain from the C-terminal autoinhibitory domain. The released N-terminal fragments oligomerize and insert into the plasma membrane, forming pores, which leads to cell swelling, membrane rupture, and the release of pro-inflammatory cytokines including IL-1β and IL-18. The interaction between autophagy and pyroptosis is bidirectional and context-dependent. Autophagy can inhibit pyroptosis by degrading inflammasome components (such as NLRP3), eliminating mitochondrial reactive oxygen species or damaged mitochondria through mitophagy. Excessive or dysregulated autophagy may promote pyroptosis through lysosomal rupture and cathepsin release, which activates the NLRP3 inflammasome. In the tumor microenvironment, pyroptosis has a dual role. Gasdermin E (GSDME)-mediated pyroptosis can enhance anti-tumor immunity by releasing immunogenic damage-associated molecular patterns and recruiting $CD8^+$ T cells. However, in most solid tumors, GSDME is often silenced due to promoter hypermethylation, and its abnormal overexpression in certain cancers (such as hepatocellular carcinoma) can promote immune suppression and resistance to programmed death-1 (PD-1) therapy through pyroptosis-independent mechanisms [31].

4. Anti-tumor therapeutic strategy based on targeted selective autophagy

4.1. Cross-network study of autophagy regulation and DNA damage repair, as well as immune remodeling of the tumor microenvironment

There is a close connection among the autophagy-lysosome pathway, DNA damage repair, and immune remodeling of the tumor microenvironment, which jointly determine the fate of tumor cells and their response to treatment. In terms of maintaining genomic stability, selective autophagy senses and degrades the TOP1cc through the receptor TEX264. This process does not rely on the proteasome and involves the p97 ATPase, MRE11 nuclease, and ATR kinase. In the early stage of tumor development, autophagy plays the role of a genomic guardian, while established tumors utilize autophagy to maintain metabolic adaptability and treatment resistance. This functional transformation is regulated by tumor genotypes and microenvironmental factors. In terms of immune remodeling, autophagy interacts with various components in the tumor microenvironment. CAFs regulate autophagy through the transforming growth factor-β/interleukin-6/ROS signaling pathway and AMP-activated protein kinase/signal transducer and activator of transcription 3/nuclear factor kappa B, mechanistic target of rapamycin (mTOR), etc., and interact with cancer cells to promote immune evasion and treatment resistance. In follicular lymphoma, purine-rich box-1 regulates autophagy through the PD-1/programmed death-ligand 1 (PD-L1) and tumor necrosis factor receptor superfamily member 9 /tumor necrosis factor ligand superfamily member 9 pathways and affects the infiltration and maturation of dendritic cells [32]. Autophagy also regulates the redox balance of the tumor immune microenvironment. Changes in reactive oxygen species levels can trigger immunogenic cell death, and the sensitivity of effector T cells to oxidative stress constitutes a

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key mechanism for immune evasion [33]. In hepatocellular carcinoma, lipid metabolism-related ATP-binding cassette transporter A1 stabilizes the mRNA of scavenger receptor class B member 1, inhibits lipid droplet autophagy, promotes cholesterol uptake, and polarizes M2 macrophages, thereby reshaping the immunosuppressive microenvironment [34]. Targeting the YAP pathway can increase the infiltration of cluster 4 and CD8 T cells, but at the same time induce the expression of PD-1 in T cells. When combined with anti-PD-L1 treatment, tumor regression was significantly enhanced [35]. The combination of autophagy inhibitors and mTOR inhibitors can remove minimal residual lesions and significantly improve the recurrence-free survival rate of breast cancer patients, which indicates that targeted autophagy can cooperate with immune surveillance to remove residual tumor cells [36]. The above findings suggest that autophagy-lysosomal dysfunction not only regulates DNA damage response, but also shapes immunosuppressive microenvironment, which plays a pivotal role in tumorigenesis, progression and treatment tolerance. Precise intervention in this cross-network is expected to achieve synergy between synthetic lethal effect and immune activation.

4.2. Application of nanomedicine delivery systems in precise targeted autophagy-lysosome pathway and combined delivery

Nanomedicine delivery systems are gradually achieving precise regulation of the autophagy-lysosomal pathway, providing multi-level interventions for anti-tumor therapy. One idea is to design and synthesize a biomimetic nano-receptor targeting mutant p53-enhance the autophagic degradation of mutant p53 with the help of mutant p53 binding peptide. This method has shown therapeutic potential in both in vitro experiments and xenograft ovarian cancer models. Another idea is to encapsulate phosphatidylinositol 4-phosphate in titanium nitride nanodots to block the fusion of autophagosomes and lysosomes to form stable nanodots encapsulating autophagosomes, which can escape to lymph nodes, promote cross-presentation of tumor antigens, activate tumor-specific T cells, and achieve long-term immune surveillance [37]. Lipid nanoparticles (LNPs) have been used to deliver mRNAs encoding immunomodulatory factors, activate antigen-presenting cells after intratumoral or intravenous administration, and significantly enhance the anti-tumor $CD8^+$ T cell response. When combined with antigen mRNA vaccine, the immune enhancement effect is about ten times [38]. In addition, a customizable mRNA nanomedicine platform (TITUR, integrating tumor-customizable ionizable lipids and tumor-specific untranslated regions) uses tumor-specific ionizable lipids and non-coding regions to achieve tumor-specific mRNA expression, effectively induce immunogenic cell death, and reshape the tumor microenvironment. When combined with immune checkpoint inhibitors, it can inhibit the growth of primary tumors and metastases [39]. Nanomaterials and biomimetic strategies for lysosomes use the acidic microenvironment of lysosomes to achieve lysosomal escape, and enhance efficacy and overcome drug resistance through targeted membrane permeability. Mitochondrial nanoinducers promote autophagy-mediated mitochondrial degradation, thereby enhancing the recognition and killing of cancer cells by $CD8^+$ T cells, providing a promising auxiliary strategy for autologous T cell therapy and chimeric antigen receptor T cell therapy [40]. In terms of combination therapy, stimuli-responsive nanomedicines that respond to pathological abnormalities in the tumor microenvironment can overcome the biological barriers faced by conventional nanoparticles and achieve space-time controllable co-delivery of multiple drugs [41]. Through surface engineering strategies such as non-covalent modification, engineered nanoparticles can accurately regulate the transport from the injection site to the subcellular destination, and multi-level targeting design optimizes tumor accumulation and cell internalization [42].

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By precisely targeting autophagosome formation, autophagosome-lysosomal fusion or lysosomal function, and integrating with immunotherapy, chemotherapy, phototherapy and other means, the above nano-delivery systems are promoting the shift of autophagy regulation from broad-spectrum inhibition to precise control depending on the situation. PROTACs and LYTACs are two targeted protein degradation technologies with different mechanisms, both of which remove pathogenic proteins through their respective pathways. PROTACs use the ubiquitin-proteasome system to degrade intracellular proteins, with significant clinical progress [43]. LYTACs employ lysosome-targeting receptors (such as cation-independent mannose-6-phosphate receptor) and the lysosomal degradation pathway to clear extracellular and membrane-associated proteins (e.g., PD-L1, epidermal growth factor receptor), thereby enhancing the anti-tumor immune response [44]. Although LYTACs are still in the early stage of development, they offer a strategy complementary to PROTACs for targeting previously "undruggable proteins" and overcoming the resistance of traditional drugs, thus expanding the scope of precision cancer treatment. Despite these advances, clinical translation of nanomedicine-based autophagy regulation still faces obstacles, including limited tumor penetration in desmoplastic tumors, off-target effects and immunogenicity of nanoparticle carriers, and safety concerns of systemic autophagy regulation. Therefore, tumor-specific delivery systems and tissue-selective autophagy modulators remain a priority for future research.

4.3. Mechanistic in-depth analysis based on single-cell multi-omics and spatial transcriptomics, and cross-system model validation

Single-cell multi-omics and spatial transcriptomics provide novel tools for analyzing the spatiotemporal heterogeneity of autophagy-lysosome dysfunction in the tumor microenvironment. The spatial transcriptomics algorithm Gradient Analysis of Spatial Transcriptomics with Optimal Normalization can perform unsupervised identification of spatial regions and gradient patterns in tissue sections, revealing continuous gradient changes in metabolism and immune activities in the tumor microenvironment [45]. In follicular lymphoma, spatial analysis techniques have revealed tumor-specific features in patients with early recurrence, including changes in stromal fibrosis and follicular growth patterns. These microenvironmental features have already appeared approximately 20 months before the initial progression [46]. The spatial analysis characteristics observed in follicular lymphoma are closely related to the autophagy-lysosome dysfunction in the tumor microenvironment. In a large number of follicular lymphoma patients, the subunits and regulatory factors of the vesicular H^+-transporting ATPase undergo repeated mutations, resulting in impaired lysosomal acidification function. This lysosomal dysfunction triggers the compensatory activation of macroautophagy/autophagy, thereby creating conditions for the survival of tumor cells. Studies on pancreatic ductal adenocarcinoma have shown that the proximity of cells to the ECM regulates autophagy levels through the integrin α3-Hippo-Yes-associated protein 1 axis. Cells adjacent to the stroma exhibit high autophagy and chemotherapy resistance, while cells far from the stroma show high proliferative activity. This spatial heterogeneity in the autophagy process can be intervened and treated by regulating the matrix-mediated autophagy pathway. In cross-system model validation, the tumor chip platform effectively recapitulates the tumor microenvironment, providing a new platform for evaluating the efficacy, safety, and clinical relevance of nanomedicines, and addressing the limitations of traditional models [47]. These technology-driven studies not only deepen our understanding of the autophagy-lysosome function in tumor heterogeneity but also provide pathways for biomarker discovery and model validation.

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5. Conclusion

The role of autophagy-lysosomal dysfunction in tumors is not a single direction. In the early stage, it suppresses malignant transformation by maintaining genomic stability and limiting oxidative stress; after entering the advanced stage, the same pathway turns to enhance metabolic adaptability, promote treatment tolerance, assist immune escape, and promote tumor progression. This duality is not an isolated phenomenon. It is closely intertwined with metabolic reprogramming, ferroptosis inhibition, inflammasome activation, and the spatial and temporal heterogeneity of the tumor microenvironment. This dysfunction also interacts with other cellular stress networks to regulate programmed cell death and inflammasome activation, including pyroptosis and ferroptosis, thereby shaping the pathological microenvironment. Early non-specific interventions (such as chloroquine) face clinical difficulties due to high toxicity and limited efficacy, which has prompted the focus of research to shift to precise regulation. The progress of targeted degradation technology has expanded the treatment options: LYTACs can direct extracellular or membrane proteins to lysosomes for degradation [44]; the ubiquitin-proteasome system-based PROTAC technology has driven more than 30 candidate drugs into clinical trials to overcome drug resistance [43]. The nano-drug platform realizes the space-time controllable release of autophagy regulators by means of acid response or targeted carrier, which makes up for the deficiency of single therapy. The combined application of single-cell omics, spatial transcriptomics and live cell imaging revealed the spatiotemporal heterogeneity of autophagy-lysosomal function, identified autophagy-sensitive subsets, and provided a basis for patient stratification based on biomarkers. The combination of epigenetic drugs and autophagy modulators, combined with the synchronous regulation of transcription factors (such as TFEB) and post-translational regulatory networks, provides a new entry point for treatment. These advances mean that the treatment of targeted autophagy is moving from broad-spectrum inhibition to context-dependent and mechanism-driven intervention strategies.

References

[1] Guilbaud, E., Ryan, K. M., Green, D. R., & Galluzzi, L. (2026). Autophagy modulation in cancer. *Nature Reviews Drug Discovery, 25*, 701–722.
[2] Hickey, K. L., Swarup, S., Smith, I. R., Paoli, J. C., Whelan, E. M., Paulo, J. A., & Harper, J. W. (2023). Proteome census upon nutrient stress reveals Golgiphagy membrane receptors. *Nature, 623*(7985), 167–174.
[3] Wang, R., Fortier, T. M., Chai, F., Miao, G., Shen, J. L., Restrepo, L. J., DiGiacomo, J. J., Velentzas, P. D., & Baehrecke, E. H. (2023). PINK1, Keap1, and Rtnl1 regulate selective clearance of endoplasmic reticulum during development. *Cell, 186*(19), 4172–4188.
[4] Wang, J.-Y., Lu, Y.-Q., Tan, X.-R., et al. (2026). Fusobacterium nucleatum manipulates host autophagy to promote its intracellular survival and treatment resistance in nasopharyngeal carcinoma. *Molecular Cancer, 25*(1), 59.
[5] Clavel, M., Bianchi, A., Kobylinska, R., et al. (2026). Selective autophagy fine-tunes plant immunity to promote cell survival during viral infection. *Science, 392*(6801), eadu9554.
[6] Lascaux, P., Hoslett, G., Tribble, S., et al. (2024). TEX264 drives selective autophagy of DNA lesions to promote DNA repair and cell survival. *Cell, 187*(20), 5698–5718.
[7] Herhaus, L., Gestal-Mato, U., Eapen, V. V. et al. (2024). IRGQ-mediated autophagy in MHC class I quality control promotes tumor immune evasion. *Cell, 187*(25), 7285-7302.
[8] Frison, M., Lockey, B. S., Nie, Y. et al. (2025). Ubiquitin-mediated mitophagy regulates the inheritance of mitochondrial DNA mutations. *Science, 390*(6769), 156-163.
[9] Zhang, Y., Shen, X., Shen, Y. et al. (2025). Cytosolic acetyl-coenzyme A is a signalling metabolite to control mitophagy. *Nature, 649*(8098), 1022-1031.
[10] Prieto-Garcia, C., Matkovic, V., Mosler, T. et al. (2024). Pathogenic proteotoxicity of cryptic splicing is alleviated by ubiquitination and ER-phagy. *Science, 386*(6723), 768-776.
[11] Borlepawar, A., Neu, M., Ma, Z., Deshpande, A., Bühringer, H., Hajieva, P., Frey, N. & Rangrez, A. Y. (2026). Emerging perspectives in proteostasis: Bridging mechanisms and therapeutics for human diseases. *Signal*

DOI: 10.54254/2753-8818/2026.39056

Transduction and Targeted Therapy, 11, 224.
[12] Wang, M., Bieging-Rolett, K. T., Kaiser, A. M. et al. (2026). p53 drives lung cancer regression through a TSC2/TFEB-dependent senescence program. *Cancer Discovery, 16*(2), 391-411.
[13] Akter, S., Madhuvilakku, R., Kar, A. K., Nila, I. S., Liu, P., Inuzuka, H., Wei, W., & Hong, Y. (2026). Reactive oxygen species (ROS) in cancer: From mechanism to therapeutic implications. *Signal Transduction and Targeted Therapy, 11*(1), 111.
[14] Moon, H.-R., Cho, B. K., Kang, S. H., Ryu, J. H., & Kwon, I. C. (2025). Targeting and exploiting macropinocytosis in cancer therapy. *Journal of Controlled Release, 385*, 113962.
[15] Deng, Q., Ji, Y., Liu, J., & Wen, T. (2025). Lipid reprogramming and ferroptosis crosstalk in clear cell renal cell carcinoma: Metabolic vulnerabilities and therapeutic targeting. *Molecular Cancer, 24*, 236.
[16] Cheng, C., Hu, J., Mannan, R., et al. (2025). Targeting PIKfyve-driven lipid metabolism in pancreatic cancer. *Nature, 642*(8068), 776–784.
[17] Gremke, N., Besong, I., Stroh, A., et al. (2025). Targeting PI3K inhibitor resistance in breast cancer with metabolic drugs. *Signal Transduction and Targeted Therapy, 10*(1), 92.
[18] Guo, D., Meng, Y., Zhao, G., Wu, Q., & Lu, Z. (2025). Moonlighting functions of glucose metabolic enzymes and metabolites in cancer. *Nature Reviews Cancer, 25*(6), 426–446.
[19] Ling, L., Hu, T., Zhou, C. et al. (2025). M6A-methylated circRAPGEF5 drives lung adenocarcinoma progression and metastasis via IGF2BP2/NUP160-mediated autophagy suppression. *Molecular Cancer, 24*, 192.
[20] Li, S., Han, H., Yang, K., Li, X., Ma, L., Yang, Z., & Zhao, Y. X. (2025). Exosome-mediated metabolic reprogramming: Effects on thyroid cancer progression and tumor microenvironment remodeling. *Molecular Cancer, 24*, 247.
[21] Kuppala, V., Chintapudi, H., Kovuru, G., Nagaraju, G. P., & El-Rayes, B. F. (2026). Autophagy in cancer-associated fibroblasts: Its role in gastrointestinal cancers. *Molecular Cancer, 25*(1), 99.
[22] Assi, M., Wang, R., Kawaler, E. A. et al. (2026). Extracellular matrix sensing regulates intratumoral heterogeneity of autophagic flux. *Cell, 189*(6), 1731–1747.
[23] Zhao, Y., Shang, Y., Luan, T. et al. (2026). Endoplasmic reticulum stress in antitumor immunity and immunotherapy resistance: Mechanisms and therapeutic implications. *Molecular Cancer, 25*, 153.
[24] Ikeda, H., Kawase, K., Nishi, T. et al. (2025). Immune evasion through mitochondrial transfer in the tumour microenvironment. *Nature, 638*(8049), 225–236.
[25] Cheng, X., Peng, T., Chu, T., Yang, Y., Liu, J., Gao, Q., Cao, C., & Wei, J. (2025). Application of single-cell and spatial omics in deciphering cellular hallmarks of cancer drug response and resistance. *Journal of Hematology & Oncology, 18*(1), 70.
[26] Lei, G., Zhuang, L., & Gan, B. (2024). The roles of ferroptosis in cancer: Tumor suppression, tumor microenvironment, and therapeutic interventions. *Cancer Cell, 42*(4), 513-534.
[27] Wu, K., Vaughan, A. J., Bossowski, J. P., et al. (2025). Targeting FSP1 triggers ferroptosis in lung cancer. *Nature, 649*(8096), 487-495.
[28] Lin, H., Tison, K., Du, Y., et al. (2024). Itaconate transporter SLC13A3 impairs tumor immunity via endowing ferroptosis resistance. *Cancer Cell, 42*(12), 2032-2044.
[29] Fan, W., An, Q., Wang, X., et al. (2026). The Treg-cell death axis in lung cancer: Implications for immune evasion and novel therapeutic strategies. *Molecular Cancer, 25*(1), 187.
[30] Wang, Y., Hu, J., Wu, S., et al. (2023). Targeting epigenetic and posttranslational modifications regulating ferroptosis for the treatment of diseases. *Signal Transduction and Targeted Therapy, 8*, 449.
[31] Groborz, K. M., Truong, M. E., Stowe, I. et al. (2026). Gasdermin D-mediated delivery of caspase inhibitors to suppress pyroptosis. *Nature, 658*, 508–513.
[32] Zheng, Z., Wang, J. B., Sun, R. et al. (2025). Dual targeting PD-L1 and 4-1BB to overcome dendritic cell-mediated lenalidomide resistance in follicular lymphoma. *Signal Transduction and Targeted Therapy, 10*(1), 29.
[33] Li, J., Huang, C., Tang, P., Wu, R., Wu, Q., & Zhang, C. (2026). The distinct roles of ROS in tumor immunity: From mechanisms to immunotherapeutic applications. *Journal of Hematology & Oncology, 19*(1), 16.
[34] Ning, H., Jiang, Y., Li, B. et al. (2025). CircABCA1 promotes ccRCC by reprogramming cholesterol metabolism and facilitating M2 macrophage polarization through IGF2BP3-mediated stabilization of SCARB1 mRNA. *Molecular Cancer, 24*(1), 199.
[35] Zhao, J., Yang, L., Qin, Y. et al. (2026). Distinct molecular pathways regulated by activated AKT and YAP signaling during intrahepatic cholangiocarcinoma progression. *Journal of Hepatology, 85*(2), 301–313.
[36] DeMichele, A., Clark, A. S., Shea, E. et al. (2025). Targeting dormant tumor cells to prevent recurrent breast cancer: A randomized phase 2 trial. *Nature Medicine, 31*(10), 3464–3474.

DOI: 10.54254/2753-8818/2026.39056

[37] Huang, W. Q., You, W., Zhu, Y. Q. et al. (2025). Autophagosomes coated in situ with nanodots act as personalized cancer vaccines. *Nature Nanotechnology, 20*(3), 451-462.
[38] Gupta, A., Das, R., Reed, K. et al. (2026). Immune-remodeling mRNAs expressing IRF8 or NIK generate durable antitumor immunity in multiple cancer models. *Nature Biotechnology*.
[39] Dong, S., Tsai, S. N., Xu, Y. et al. (2025). A modular mRNA platform for programmable induction of tumour-specific immunogenic cell death. *Nature Nanotechnology, 20*(12), 1856-1870.
[40] Pan, X., Wang, Z., Tan, M., Fu, Z., Nie, G., & Wang, H. (2025). Nanoinducer-mediated mitochondria-selective degradation enhances T cell immunotherapy against multiple cancers. *Nature Nanotechnology, 20*(7), 947-958.
[41] Zhou, Q., Xiang, J., Qiu, N., Wang, Y., Piao, Y., Shao, S., Tang, J., Zhou, Z., & Shen, Y. (2023). Tumor abnormality-oriented nanomedicine design. *Chemical Reviews, 123*(18), 10920-10989.
[42] Gomerdinger, V. F., Nabar, N., & Hammond, P. T. (2025). Advancing engineering design strategies for targeted cancer nanomedicine. *Nature Reviews Cancer, 25*(9), 657-683.
[43] Huang, H., Deng, A., Pan, F. et al. (2026). PROTAC-mediated regulation of programmed cell death: From molecular mechanisms to therapeutic breakthroughs. *The Innovation, 7*(7), 101359.
[44] Mamun, M. A. A., Bakunts, A. G., & Chernorudskiy, A. L. (2025). Targeted degradation of extracellular proteins: State of the art and diversity of degrader designs. *Journal of Hematology & Oncology, 18*(1), 52.
[45] Chitra, U., Arnold, B. J., Sarkar, H., Sanno, K., Ma, C., Lopez-Darwin, S., & Raphael, B. J. (2025). Mapping the topography of spatial gene expression with interpretable deep learning. *Nature Methods, 22*(2), 298-309.
[46] Radtke, A. J., Postovalova, E., Varlamova, A. et al. (2024). Multi-omic profiling of follicular lymphoma reveals changes in tissue architecture and enhanced stromal remodeling in high-risk patients. *Cancer Cell, 42*(3), 444-463.
[47] Wu, C., Chen, J., Zhang, C. et al. (2026). Tumor organoids as a revolutionary platform for advancing cancer nanomedicine. *Molecular Cancer, 25*(1), 198.