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Autophagy in Cancer: Mechanisms, Dual Roles, and Therapeutic Targeting

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ABSTRACT

Autophagy is an evolutionarily conserved intracellular degradation mechanism essential for maintaining cellular homeostasis. It regulates the turnover of damaged organelles, misfolded proteins, and metabolic by-products through lysosomal degradation. In cancer biology, autophagy exhibits a context-dependent and paradoxical role. While it prevents malignant transformation by maintaining genomic stability and suppressing inflammation in early tumorigenesis, established tumors often exploit autophagy to sustain survival during metabolic stress, resist anticancer therapies, and support metastasis. This review provides a comprehensive analysis of the molecular mechanisms of autophagy, its dual role in cancer initiation and progression, and its significance in cancer cell metabolism, tumor microenvironment, and therapy resistance. Current therapeutic strategies targeting autophagy both inhibitors and activators are evaluated, including ongoing clinical trials. Finally, the article discusses emerging challenges and future perspectives in utilizing autophagy modulation for cancer therapy.

Introduction

Autophagy, a highly conserved cellular recycling process, enables cells to degrade and reuse damaged organelles and misfolded proteins through lysosomal machinery (Trivedi et al., 2020). This dynamic mechanism serves as a critical adaptive response to metabolic stress, nutrient deprivation, and environmental challenges, thereby maintaining cellular homeostasis and genomic integrity (Gómez-Virgilio et al., 2022). In the context of cancer, however, autophagy assumes a profoundly complex and dualistic nature, functioning as both a tumor-suppressive pathway and a tumor-promoting survival mechanism, which presents significant challenges and opportunities for therapeutic intervention (Mathur et al., 2024).

Initially, autophagy acts as a barrier against tumorigenesis by mitigating oxidative stress, preventing the accumulation of toxic cellular debris, and averting chronic tissue damage that can fuel malignant transformation (Rahman et al., 2023). The loss of autophagic function is frequently associated with increased genomic instability and tumor initiation. Paradoxically, established tumors often exploit upregulated autophagy to survive in the harsh, nutrient-poor and hypoxic microenvironment of solid tumors

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(Vitto et al., 2022). By recycling intracellular components, autophagy provides essential metabolic substrates that fuel mitochondrial metabolism and sustain cell survival, facilitating tumor progression, metastasis, and resistance to conventional therapies (Wang et al., 2023).

This Janus-faced role underscores the intricate regulatory networks governing autophagy, involving key sensors like mTOR and AMPK, and execution proteins such as those in the ATG family (Sendtner et al., 2025). Understanding these mechanisms is paramount for developing rational cancer treatments. Current therapeutic strategies aim to either inhibit autophagy to sensitize tumors to chemotherapy and radiation or induce it to exacerbate stress in vulnerable cancer cells. However, the context-dependent outcomes of such modulation demand precise, tumor-specific approaches. This review will comprehensively explore the molecular mechanisms of autophagy, dissect its context-dependent roles in oncogenesis and tumor progression, and critically evaluate the promising yet challenging landscape of autophagy-targeting therapies in oncology.

Molecular mechanisms of autophagy

Autophagy proceeds through several tightly regulated steps:

Initiation

Autophagy is primarily regulated by the balance between mTOR (mechanistic target of rapamycin) and AMPK (AMP-activated protein kinase).

mTOR Signaling

The mechanistic target of rapamycin complex 1 (mTORC1) serves as the primary nutrient-sensing hub and a central negative regulator of autophagy. Under nutrient-rich conditions, mTORC1 is active and phosphorylates key autophagy-initiating proteins, such as ULK1/2 and ATG13, thereby suppressing the formation of the autophagosome (Mandic et al., 2025). This inhibitory signal is potently reinforced by growth factor signaling through the PI3K/AKT pathway, which activates mTORC1. Consequently, the integration of growth factor and nutrient availability through mTORC1 ensures that autophagy is tightly repressed when cellular resources are abundant, aligning cellular catabolism with anabolic growth signals (Stefani et al., 2021).

AMPK Signaling

The AMP-activated protein kinase (AMPK) pathway functions as a central energy sensor that potently induces autophagy under conditions of metabolic stress. Activated by a high AMP/ATP ratio, AMPK promotes catabolism by phosphorylating and inhibiting mTORC1, thereby relieving its suppression of autophagy (Saikia and Joseph, 2021). Concurrently, AMPK directly phosphorylates and activates key components of the autophagic machinery, such as ULK1, at specific sites distinct from those targeted by mTORC1 (Iorio et al., 2021). This dual mechanism ensures the rapid and efficient initiation of the autophagic cascade, enabling cells to generate essential nutrients and restore energy homeostasis during periods of scarcity (He, 2022).

ULK1 complex

The ULK1/ATG13/FIP200/ATG101 complex represents the indispensable molecular switch that translates upstream inhibitory or activatory signals into the physical initiation of autophagy. Acting as the convergent node for mTORC1 and AMPK signaling, this complex is precisely regulated by phosphorylation (Mizushima, 2010). Under nutrient-rich conditions, active mTORC1 phosphorylates ULK1 to inhibit its kinase activity and disrupts its interaction with AMPK. Conversely, upon energy stress, AMPK directly phosphorylates and activates ULK1, prompting the complex to translocate to the site of phagophore assembly (Yao et al., 2024). Here, it phosphorylates downstream effectors, initiating the recruitment of ATG proteins and ATG9 vesicles to form the phagophore, the precursor to the autophagosome (Ahsan et al., 2024).

Nucleation

Following initiation, nucleation of the phagophore membrane is critically regulated by the Beclin-1 (BECN1) interactome. Beclin-1 forms the core of distinct complexes, most notably with the class III phosphatidylinositol 3-kinase (PI3K) VPS34, which generates phosphatidylinositol-3-phosphate (PI3P) at the nascent autophagosomal membrane (Cao et al., 2024). This lipid platform is essential for recruiting downstream PI3P-binding effectors, such as WIPI proteins, which facilitate membrane expansion (Nähse et al., 2024). Importantly, Beclin-1 functions as a haploinsufficient tumor suppressor, with its frequent monoallelic deletion in breast, ovarian, and prostate cancers highlighting the tumor-suppressive

role of proficient autophagy nucleation in preventing oncogenesis (Ayub et al., 2024).

Autophagosome formation

The subsequent elongation and closure of the phagophore are executed by two conserved ubiquitin-like conjugation systems. The ATG5-ATG12-ATG16L1 complex forms an E3-like enzyme essential for priming the second pathway, which involves the microtubule-associated protein 1 light chain 3 (LC3) (Ryu *et al.*, 2021). Cytosolic LC3-I is conjugated to phosphatidylethanolamine to form membrane-anchored LC3-II, a critical step that facilitates membrane expansion and cargo recruitment (Reggiori et al., 2021). LC3-II becomes incorporated into both the inner and outer autophagosomal membranes, serving as a definitive marker for autophagic structures (Zhang et al., 2025). Consequently, the detection of LC3-II by immunoblotting or microscopy remains a fundamental and widely used biomarker for monitoring autophagic flux in experimental and clinical contexts (Corkery et al., 2021).

Fusion and degradation

Following membrane closure, the mature autophagosome must fuse with a lysosome to form an autolysosome, a process mediated by specific SNARE complexes, such as STX17 and SNAP29. This fusion delivers the sequestered cargo into the acidic, hydrolase-rich lysosomal lumen for degradation. The resultant breakdown products including amino acids, free fatty acids, and sugars are subsequently transported back into the cytosol. This recycling provides essential building blocks and energy for biosynthesis and ATP production, thereby completing the catabolic cycle and sustaining cellular homeostasis during stress. This final degradative stage also reactivates mTORC1, signaling nutrient repletion and suppressing further autophagy (Liu et al., 2025).

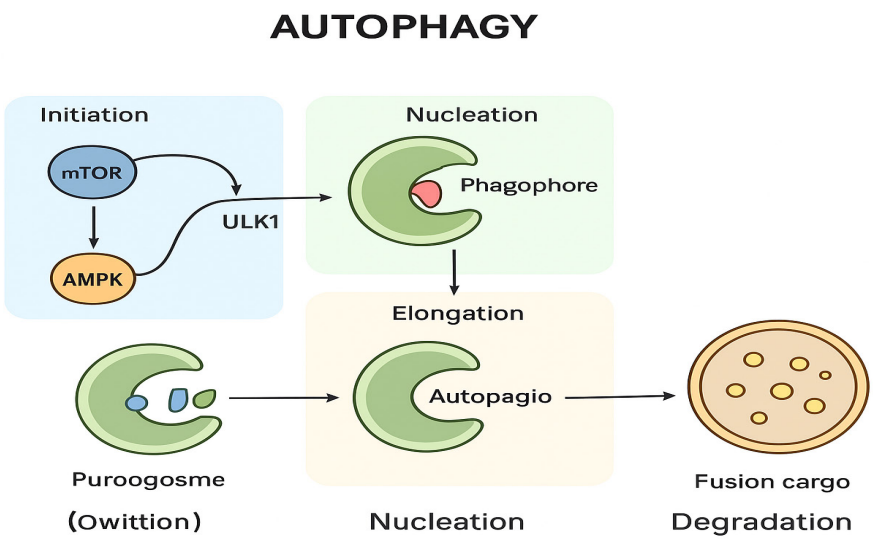

Figure 1: Overview of the autophagy pathway and key molecular regulators.

Dual Roles of Autophagy in Cancer

Autophagy acts as a "double-edged sword" in cancer.

Tumor-Suppressive Role (Early Cancer Stages)

Maintenance of genomic stability

By selectively degrading damaged organelles, particularly through mitophagy, autophagy plays a fundamental role in preserving genomic integrity. This clearance mechanism prevents the accumulation of dysfunctional mitochondria, which are a major source of harmful reactive oxygen species (ROS) (Yao et al., 2021). Elevated ROS levels cause oxidative stress, leading to DNA damage, mutations, and chromosomal instability. Therefore, by mitigating this oxidative burden, autophagy acts as a critical cellular housekeeper, safeguarding the genome and functioning as a potent, early tumor-suppressive barrier (Cabrera-Serrano et al., 2025).

Prevention of chronic inflammation

Autophagy suppresses tumorigenesis by preventing chronic inflammation, a well-established driver of cancer. The process sequesters and degrades damaged proteins and organelles that would otherwise act as danger-associated molecular patterns (DAMPs) (Zeng-Brouwers et al., 2020). By eliminating these intracellular triggers, autophagy inhibits the activation of cytosolic inflammasome complexes, such as NLRP3. This blockade prevents the subsequent release of pro-inflammatory cytokines like IL-1β and IL-18, thereby disrupting the tumor-promoting microenvironment fueled by persistent inflammatory signaling (Missiroli et al., 2021).

Regulation of oncogenes and tumor suppressors

Autophagy's tumor-suppressive function is further exemplified by its regulation through classic oncogenic pathways. The core autophagy protein Beclin-1 acts as a haploinsufficient tumor suppressor, with its frequent monoallelic deletion in human cancers directly linking defective autophagy to tumorigenesis (Maheshwari et al., 2025). Additionally, the master tumor suppressor p53 can transcriptionally upregulate pro-autophagic genes, inducing autophagy as a mechanism to eliminate damaged cells and prevent cancer initiation. Thus, autophagy operates as an integrated component of the cellular tumor-suppressor network (Rahman et al., 2022).

Clearance of misfolded or toxic proteins

The selective clearance of misfolded or aggregated proteins through autophagy, a process termed aggrephagy, is vital for preventing proteotoxic stress. The accumulation of such aberrant proteins can overwhelm the ubiquitin-proteasome system, leading to endoplasmic reticulum stress and activation of pro-survival or apoptotic pathways that may foster genomic instability (Gavilán et al., 2024). By efficiently degrading these toxic cytosolic components, autophagy maintains proteostasis, thereby protecting against cellular dysfunction that can precipitate malignant transformation and supporting its role as a tumor-suppressive mechanism (Verma, 2025).

Tumor-promoting role (Established Tumors)

Once a tumor forms, autophagy supports cancer cell survival:

Metabolic adaptation

In stark contrast to its suppressive functions, autophagy is co-opted by established tumors as a critical survival mechanism. Under the nutrient deprivation and hypoxia common in solid tumors, cancer cells upregulate autophagy to degrade intracellular components (Verma et al., 2024). This catabolic recycling liberates amino acids, free fatty acids, and other metabolic precursors, which are funneled into the TCA cycle to sustain mitochondrial ATP production. This metabolic plasticity allows tumors to withstand metabolic stress, promoting their progression and contributing to therapeutic resistance (MacLean et al., 2023).

Resistance to hypoxia

Within the hypoxic core of solid tumors, stabilized hypoxia-inducible factor 1-alpha (HIF-1α) transcriptionally upregulates key autophagy genes, such as BNIP3 and BNIP3L. This induction serves as a vital adaptive response, enabling cancer cells to mitigate metabolic and oxidative stress imposed by low oxygen tension (Jalouli, 2025). By promoting the autophagic turnover of damaged organelles and providing recycled macromolecules, HIF-1α-driven autophagy sustains cell survival, fosters tumor progression, and enhances resistance to therapies within these hostile micro environmental niches (Huang et al., 2025).

Chemotherapy and radiotherapy resistance

A major clinical challenge driven by autophagy is the development of resistance to conventional anti-cancer therapies. Both chemotherapy and radiotherapy induce significant cellular damage, and tumor cells frequently upregulate autophagy as a cytoprotective response (Silva et al., 2020). By efficiently clearing damaged proteins and organelles, particularly mitochondria, autophagy mitigates treatment-induced stress, prevents the initiation of apoptotic pathways, and promotes cell survival. This adaptive mechanism underpins the rationale for combining autophagy inhibitors, such as chloroquine, with standard therapies to sensitize resistant tumors (Usman et al., 2021).

Cancer stem cell (CSC) maintenance

Autophagy is instrumental in maintaining the cancer stem cell (CSC) population, a subset of cells responsible for tumor initiation, recurrence, and metastasis. By mitigating

metabolic and oxidative stress, autophagy supports the survival and self-renewal capacity of CSCs within hostile tumor microenvironments (Wang et al., 2022). This enhanced resilience not only preserves the tumorigenic core but also facilitates the dissemination and seeding of metastatic colonies. Consequently, targeting autophagic pathways presents a promising strategy to eradicate this therapy-resistant cell population and improve clinical outcomes (Jia et al., 2025).

Tumor dormancy and recurrence

Autophagy serves as a critical survival mechanism for disseminated tumor cells that enter a state of dormancy, often for years, before causing clinical recurrence. By enabling a state of low metabolic turnover and recycling intracellular components, autophagy allows these quiescent cells to withstand nutrient deprivation, hypoxia, and immune surveillance (Vera-Ramirez et al., 2018). This sustained viability protects dormant cells from apoptosis, providing them with the longevity required to eventually adapt, proliferate, and seed lethal metastatic outgrowths upon receiving permissive signals (Tan et al., 2025).

Autophagy in cancer metabolism

Autophagy supports metabolic pathways essential for rapid tumor growth:

Amino acid recycling

Autophagy is a vital source of intracellular amino acids, particularly under the metabolic stress of rapid tumor growth. By degrading proteins and organelles, it replenishes the cellular pool of free amino acids. These recycled building blocks are indispensable for de novo protein synthesis, fueling the production of enzymes, signaling molecules, and structural components required for unchecked proliferation. This process allows tumors to sustain anabolism even when external nutrients are limited, supporting their biosynthetic demands (Comito et al., 2020).

Lipid metabolism

Through a selective process termed lipophagy, autophagy degrades lipid droplets, releasing free fatty acids and glycerol into the cytosol. These fatty acids are then utilized in mitochondria via β-oxidation to generate acetyl-CoA, a crucial substrate for the tricarboxylic acid (TCA) cycle. This provides an alternative energy source for ATP production, maintaining cellular viability and bioenergetics in nutrient-poor tumor environments, thereby supporting overall tumor metabolism and growth (Filali-Mouncef et al., 2022).

Mitochondrial quality control (Mitophagy)

Mitophagy, the selective autophagic removal of damaged mitochondria, is essential for metabolic efficiency in cancer. It eliminates dysfunctional organelles that would otherwise produce excessive ROS and have low ATP yield. By maintaining a healthy mitochondrial network, mitophagy optimizes oxidative phosphorylation for energy production. Concurrently, it prevents the release of pro-apoptotic factors from damaged mitochondria, thereby reducing apoptosis and enhancing the survival of cancer cells under stress (Zhu et al., 2020).

Redox balance

Autophagy plays a dual role in managing cellular redox status. It clears damaged, ROS-generating mitochondria and protein aggregates, preventing lethal oxidative stress. Ho wever, it also maintains ROS at a moderate, pro-tumorigenic level by eliminating antioxidant regulators like p62. This careful modulation creates a redox environment that supports survival signals, drives proliferation, and promotes genomic instability, all of which are advantageous for tumor progression and adaptation (Nigam et al., 2025).

Autophagy in the tumor microenvironment (TME)

Autophagy affects not only cancer cells but also the surrounding microenvironment.

Immune evasion

Autophagy within cancer cells significantly modulates anti-tumor immunity, facilitating immune evasion. By degrading endogenous antigens, it can limit their presentation on major histocompatibility complex class I (MHC-I) molecules, reducing recognition by cytotoxic T cells. Conversely, autophagy is also involved in processing antigens for cross-presentation. This dual role creates a complex dynamic where the net effect often suppresses

effective immune surveillance, allowing tumors to escape detection and destruction by the host's immune system (Duan et al., 2021).

Interaction with CAFs

Cancer-associated fibroblasts (CAFs) exploit autophagy to enact a "reverse Warburg effect," a critical metabolic coupling in the TME. Here, CAFs undergo autophagy and glycolysis, producing energetic metabolites such as lactate and ketone bodies. These nutrients are then exported and taken up by adjacent cancer cells, who utilize them in their mitochondria for oxidative phosphorylation. This metabolic symbiosis fuels tumor growth, highlighting how autophagy in stromal cells directly supports cancer cell anabolism (Sari et al., 2024).

Angiogenesis

Autophagy regulates tumor angiogenesis, the formation of new blood vessels, primarily by modulating the secretion of vascular endothelial growth factor (VEGF). Under hypoxic stress, autophagy enables cancer and stromal cells to manage metabolic stress and ER stress, processes that influence VEGF transcription and release (Schaaf et al., 2019). By supporting endothelial cell survival and function, autophagy thereby promotes the development of the tumor vasculature, which is essential for delivering oxygen and nutrients to support expansion and metastasis (Hou et al., 2025).

Macrophages and immune cells

Autophagy in tumor-associated macrophages (TAMs) and other immune cells critically shapes their function. In TAMs, autophagy promotes polarization towards an M2 phenotype, which is immunosuppressive and pro-tumorigenic. These M2 macrophages support tissue remodeling, angiogenesis, and suppress cytotoxic T-cell activity. Thus, autophagy within the immune compartment helps establish an immunosuppressive microenvironment that fosters tumor progression and undermines the efficacy of immunotherapies (Ji et al., 2025).

Autophagy and Therapy Resistance

Autophagy is activated in response to nearly all cancer therapies.

Chemotherapy resistance

A major clinical obstacle is the induction of cytoprotective autophagy by numerous chemotherapeutic agents, including cisplatin, paclitaxel, and doxorubicin. These drugs cause cellular damage that paradoxically activates the autophagic pathway as a survival response (Zhang et al., 2025). By clearing damaged proteins and organelles, autophagy mitigates therapy-induced stress, suppresses apoptosis, and maintains cellular homeostasis. This mechanism underpins the rationale for combining autophagy inhibitors with traditional chemotherapy to overcome resistance and enhance tumor cell death in various cancers (Kostandy et al., 2025).

Radiotherapy resistance

Ionizing radiation generates significant oxidative damage, triggering autophagy as a compensatory mechanism in tumor cells. This response facilitates the removal of radiation-damaged mitochondria and protein aggregates, reducing lethal reactive oxygen species (ROS) accumulation and preventing the initiation of apoptotic pathways (Ahmed et al., 2025). Consequently, autophagy promotes the survival of a subset of cancer cells post-treatment, contributing to tumor regrowth and local recurrence. Targeting this adaptive survival pathway is a promising strategy to improve radiotherapeutic efficacy (Yin et al., 2025).

Targeted therapy resistance

Resistance to molecularly targeted agents, such as EGFR, BRAF, or MEK inhibitors, is frequently associated with adaptive autophagy upregulation. When oncogenic signaling pathways are blocked, tumors experience metabolic stress and often exploit autophagy to provide alternative energy and biosynthetic precursors. This metabolic rewiring allows cancer cells to maintain viability despite pathway inhibition. Therefore, co-targeting the specific oncogene and autophagic flux is being explored to delay or prevent the emergence of resistance (Cosci et al., 2025).

Immunotherapy resistance

Autophagy modulates tumor response to immunotherapies, including immune checkpoint inhibitors, through complex mechanisms. It can influence antigen presentation on MHC class I and II molecules, affecting immune recognition

(Gestal-Mato and Herhaus, 2024). Furthermore, autophagy in cancer cells can degrade key immunogenic components or promote the release of immunosuppressive signals, shaping a hostile tumor microenvironment that impairs T-cell infiltration and function. These roles position autophagy as a significant regulator of immunotherapy efficacy and a potential therapeutic target to enhance immune-mediated killing (Yang and Wang, 2025).

Therapeutic targeting of autophagy in cancer

Autophagy modulation is an emerging therapeutic strategy.

Autophagy Inhibitors

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

These lysosomotropic agents are the most clinically advanced autophagy inhibitors. They function by accumulating within lysosomes, neutralizing their acidic pH, and inhibiting the activity of hydrolytic enzymes. This prevents autolysosome formation and cargo degradation, effectively blocking the final, degradative stage of autophagy. Due to their established safety profiles, CQ and HCQ have been extensively evaluated in numerous clinical trials across various cancers, typically in combination with standard therapies, to overcome chemo resistance (Mahri et al., 2025).

Lysosomal inhibitors

Pharmacological agents such as Bafilomycin A1 and Concanamycin A represent a more specific class of autophagy inhibitors that directly target the vacuolar-type H+-ATPase (V-ATPase) on the lysosomal membrane. By preventing the acidification of the lysosome, they disrupt the activity of acid hydrolases required for degrading autophagic cargo. While these compounds are potent tools for preclinical research to study autophagic flux, their significant toxicity currently limits their utility as systemic anti-cancer therapeutics in patients (Song et al., 2025).

ULK1/PI3K inhibitors

A newer generation of small-molecule inhibitors aims to block autophagy upstream by targeting key initiating complexes. Compounds like SBI-0206965 inhibit the kinase activity of ULK1, preventing phagophore initiation. Similarly, specific inhibitors of the Class III PI3K VPS34 (e.g., SAR405, VPS34-IN1) disrupt the Beclin-1 complex and the production of phosphatidylinositol 3-phosphate, essential for nucleation. These targeted agents offer more precise modulation and are under active investigation in preclinical cancer models (Deng et al., 2025).

Autophagy Activators

Useful in early cancers or for promoting apoptosis.

Rapamycin (mTOR inhibitor)

The macrolide rapamycin and its analogues (rapalogs) are prototypical autophagy inducers that function by allosterically inhibiting mTORC1. By suppressing this central negative regulator, they relieve the inhibitory phosphorylation on ULK1 and promote autophagosome formation. In an oncological context, this induction can be beneficial in early tumorigenesis by enhancing the tumor-suppressive clearance of damaged organelles, or in specific cancers by promoting a form of autophagy that leads to autophagic cell death, thereby complementing apoptosis (Dossou and Basu, 2019).

Resveratrol and curcumin (natural regulators)

Natural polyphenols like resveratrol and curcumin are broad-spectrum regulators that can induce autophagy through multiple pathways. They often function by activating AMPK or sirtuin deacetylases (e.g., SIRT1), which in turn inhibit mTORC1 activity. These compounds can promote pro-death autophagy in certain cancer contexts, contributing to their observed chemopreventive and anti-tumor effects. However, their pleiotropic actions and complex pharmacokinetics present challenges for clinical development as specific autophagy-modulating therapies (Abaidullah et al., 2025).

AMPK activators

Direct pharmacological activation of AMPK is a strategic approach to induce autophagy. Metformin, a widely used anti-diabetic drug, activates AMPK indirectly by inhibiting mitochondrial complex I. This leads to mTORC1 inhibition and ULK1 activation, stimulating autophagic flux. This mechanism is thought to contribute

to metformin's potential anti-cancer effects. More specific AMPK activators are under investigation for their ability to leverage autophagy for tumor suppression, particularly in contexts where restoring cellular energy homeostasis is detrimental to cancer cell survival (Barbosa et al., 2025).

Combination Therapies

Autophagy inhibitors are often combined with:

Combination with Chemotherapy

The most established strategy combines autophagy inhibitors like hydroxychloroquine (HCQ) with cytotoxic chemotherapy. Many chemotherapeutics, including doxorubicin and gemcitabine, inadvertently induce cytoprotective autophagy in cancer cells as a survival response (Jalali et al., 2025). By co-administering an autophagy inhibitor, this adaptive mechanism is blocked, leading to the catastrophic accumulation of therapy-induced damage. This combination prevents tumor cells from weathering the therapeutic insult, thereby sensitizing them to death and overcoming a key mechanism of chemoresistance in clinical trials (Solomon et al., 2025).

Combination with radiotherapy

Autophagy is a recognized contributor to radioresistance, as it helps clear radiation-damaged organelles and proteins. Combining radiotherapy with autophagy inhibition aims to exacerbate the cytotoxic effects of ionizing radiation. By preventing the autophagic disposal of lethal debris, inhibitors increase oxidative stress and DNA damage persistence within irradiated cancer cells. This approach enhances radiosensitivity, promotes mitotic catastrophe, and is being explored to improve local tumor control and prevent recurrence in various solid malignancies (Ramamurthy et al., 2025).

Combination with immunotherapy

Emerging evidence suggests autophagy inhibition can augment certain immunotherapies. Autophagy in cancer cells can degrade immunogenic antigens and promote an immunosuppressive tumor microenvironment. Combining checkpoint inhibitors (e.g., anti-PD-1) with autophagy blockers like HCQ may enhance anti-tumor immunity by increasing antigen presentation, reducing the release of immunosuppressive signals, and potentially improving T-cell infiltration and function. This synergy aims to convert immunologically "cold" tumors into "hot" ones, thereby overcoming a major mode of immunotherapy resistance (Hassan et al., 2024).

Combination with targeted therapy

Targeted agents against drivers like EGFR or BRAF often induce autophagy as a feedback survival mechanism. Combining these drugs with autophagy inhibition prevents cancer cells from adapting to the metabolic stress caused by pathway blockade. This dual approach can lead to enhanced apoptosis and tumor regression, as seen in preclinical models of RAS- and BRAF-mutant cancers. Clinical trials are actively testing combinations such as HCQ with BRAF/MEK inhibitors to delay or prevent the inevitable emergence of resistance. These combinations enhance cancer cell death by preventing stress adaptation (Reinius and Smyth, 2021).

Clinical Trials Targeting Autophagy

Multiple Phase I/II trials are ongoing:

HCQ + Chemotherapy (Breast and Pancreatic Cancer)

Numerous Phase I/II trials have evaluated hydroxychloroquine (HCQ) combined with standard chemotherapy in aggressive cancers. In breast cancer, HCQ has been tested with regimens like paclitaxel or gemcitabine to block therapy-induced survival autophagy (Kim et al., 2021). Similarly, in pancreatic ductal adenocarcinoma, HCQ is combined with gemcitabine or FOLFIRINOX based on strong preclinical rationale. While some trials show signals of efficacy and established safe dosing, overall results have been mixed, highlighting challenges in patient selection and optimal biomarker-driven strategies (Gao et al., 2024).

CQ + Temozolomide (Brain Tumors)

Given the role of autophagy in glioma survival, clinical studies have combined chloroquine (CQ) with the alkylating agent temozolomide. This approach aims to inhibit the cytoprotective autophagy triggered by temozolomide-induced DNA damage, thereby sensitizing glioblastoma cells (Durga and Pusapati, 2024). Early-phase trials have explored this combination's safety and preliminary efficacy. A key pharmacological challenge is

ensuring sufficient blood-brain barrier penetration for CQ to achieve effective lysosomal inhibition within the tumor microenvironment (Gaiaschi et al., 2024).

ULK1 Inhibitors with Kinase Inhibitors

Next-generation clinical strategies are investigating more specific upstream autophagy inhibitors. This includes combining novel ULK1 kinase inhibitors (e.g., DCC-3116) with targeted agents like RAS or RAF pathway inhibitors. The rationale is to co-target an oncogenic driver and the adaptive autophagy it induces upon inhibition, a key resistance mechanism. These precision-based combinations are entering early-phase trials, aiming to deliver more effective and selective autophagy blockade with potentially improved therapeutic indices compared to lysosomotropic agents (Miyashita et al., 2024).

Challenges

Lack of Biomarkers

A fundamental challenge in clinically targeting autophagy is the current absence of validated, dynamic biomarkers to guide patient selection and monitor therapeutic efficacy. While markers like LC3-II and p62 are used preclinically, their quantification in human biopsies is complicated by tumor heterogeneity, static sampling, and variable autophagic flux. Without reliable methods to identify "autophagy-dependent" tumors or to confirm in vivo target engagement by inhibitors, clinical trials risk failing due to the inclusion of unresponsive patient populations, obscuring potential therapeutic benefits (Shakerdi et al., 2025).

Incomplete Autophagy Inhibition *In-Vivo*

Achieving complete and sustained autophagy inhibition within tumors remains technically difficult. Widely used agents like hydroxychloroquine (HCQ) may not sufficiently neutralize lysosomal pH in all cellular compartments, especially within dense tumor regions, allowing residual degradative activity. Furthermore, the compensatory upregulation of alternative degradation pathways or feedback loops can enable tumor cell survival. This partial inhibition often results in suboptimal therapeutic effect, highlighting the need for more potent and bioavailable next-generation inhibitors (Halcrow et al., 2021).

Toxicity due to autophagy's physiological functions

Systemic autophagy inhibition poses significant toxicity risks because the process is essential for normal tissue homeostasis. Critical organs like the liver, nervous system, and immune system rely on basal autophagy for protein quality control, energy balance, and infection resistance. Chronic, broad inhibition can therefore lead to adverse effects such as neurotoxicity, immunosuppression, and metabolic dysfunction. This narrow therapeutic window necessitates the development of tumor-selective delivery systems or agents that specifically target cancer-associated autophagic dependencies (Al-Karmalawy et al., 2025).

Future perspective

Specific targeting of selective autophagy

Future therapeutic strategies are shifting from broad autophagy inhibition towards targeting specific selective autophagy pathways. Inhibiting mitophagy, ribophagy, or ER-phagy could allow precise disruption of the specific organelle quality control mechanisms a particular tumor relies on, while sparing global cellular homeostasis (Men et al., 2025). This approach promises greater efficacy and reduced toxicity, as exemplified by the development of mitophagy-specific inhibitors that could target cancers dependent on mitochondrial turnover for survival (Dueren et al., 2025).

Autophagy biomarkers for patient selection

A major hurdle in clinical translation is the lack of robust biomarkers to identify patients most likely to benefit from autophagy modulation. Future efforts will focus on validating dynamic biomarkers of autophagic flux, such as LC3-II/p62 ratios in tumor biopsies, gene expression signatures of ATG proteins, and novel non-invasive imaging probes (Shifa et al., 2025). These tools are essential for stratifying patients into trials and monitoring real-time therapeutic response, enabling a more precise and effective application of autophagy-targeting drugs (Wei et al., 2025).

Personalized medicine

The future of autophagy-targeting therapy lies in personalized approaches that identify "autophagy-addicted" tumors. This involves using functional genomic screens and metabolic profiling to classify cancers based on their specific dependency on autophagy for survival, stress adaptation, or metastasis (Mohanty et al., 2024). By matching these dependencies with corresponding autophagy inhibitors or inducers, treatments can be tailored to exploit a tumor's unique vulnerability, moving beyond a one-size-fits-all strategy to significantly improve therapeutic outcomes (Pandey et al., 2024).

Nanotechnology-based delivery

Nanotechnology offers a promising solution to overcome the pharmacokinetic limitations and systemic toxicity of current autophagy modulators. Engineered nanoparticles can be designed to deliver autophagy-inducing or -inhibiting cargo specifically to tumor cells or the tumor microenvironment. This allows for higher local drug concentrations, protects drugs from degradation, enables controlled release, and minimizes off-target effects, thereby enhancing therapeutic efficacy and improving the safety profile of autophagy-based combination regimens (Tripathi et al., 2024).

Combination with immunotherapies

Combining autophagy modulation with immunotherapy represents a highly promising frontier. Future research will elucidate the precise mechanisms by autophagy influences antigen presentation, immune cell infiltration, and T-cell exhaustion. Strategic inhibition or induction of autophagy could then be used to convert immunologically "cold" tumors into "hot" ones, enhance the durability of T-cell responses, and overcome primary and acquired resistance to checkpoint inhibitors, opening a new synergistic avenue for cancer treatment (Ma et al., 2025).

Conclusion

In conclusion, autophagy exemplifies a context-dependent double-edged sword in cancer, transitioning from a tumor-suppressive to a tumor-promoting mechanism. Its therapeutic targeting remains challenging due to broad toxicity and the lack of predictive biomarkers. Future success depends on moving beyond indiscriminate inhibition. Strategies must precisely identify autophagy-dependent tumors, selectively disrupt specific pathways like mitophagy, and integrate modulation into personalized combination therapies. Ultimately, a nuanced, biomarker-driven approach is essential to exploit autophagy as a conditional therapeutic vulnerability rather than a universal target in oncology.

Conflicts of interest and financial disclosures

The authors state that there are no conflicts of interest to disclose.

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