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Context-Dependent Autophagy in Cancer: Deciphering Cytoprotective vs. Cytotoxic Roles and Therapeutic Modulation Strategies

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ABSTRACT:

Autophagy is a highly conserved cellular process activated when cells are exposed to stress. It is responsible for maintaining cellular homeostasis by degrading and recycling the exhausted cell components. However, autophagy is considered a cell survival mechanism; recent studies revealed its dual role in cancer. Autophagy can act as a cytoprotective in early tumor stages or cytotoxic in advanced malignancies. This review explores the underlying molecular mechanisms and key regulatory pathways of autophagy, such as mTOR, AMPK, and p53, and their roles in tumorigenesis. The contradictory nature of autophagy in cancer varies according to the cellular context and depends on genomic stability, metabolic adaptation, immune evasion, and therapy resistance. Additionally, this review discusses different therapeutic strategies targeting autophagy, including inhibitors such as hydroxychloroquine and inducers like rapamycin, which have shown promise in modulating autophagy for improved cancer treatment outcomes. The review also examines the role of autophagy in cancer stem cells, metastasis, and therapy resistance, providing insights into how autophagy modulation can enhance chemotherapy, radiotherapy, and immunotherapy. Given its context-dependent functions, a deeper understanding of autophagy's intricate regulation is crucial for developing precision medicine approaches to effectively integrate autophagy-targeting strategies in cancer treatment.

Keywords: *autophagy, cytoprotective, cytotoxic, cellular context, cancer .*

1. Introduction

Autophagy is a cellular process that is responsible for maintaining cellular homeostasis by degrading and recycling the intracellular components. It has been preserved throughout evolution [1]. The term autophagy is derived from two Greek words, "auto" (self) and "phage" (eating), which allows cells to remove damaged organelles, misfolded proteins, and infections to protect their cellular integrity and survival [2]. The process begins with the formation of the phagophore, which is a double membrane vesicle that engulfs the cytoplasmic debris until maturing into an autophagosome. Subsequently, the autophagosome fuses with hydrolytic lysosome enzymes that break down the engulfed content and release macromolecule building blocks to be reused by the cell. Control of autophagic activity in response to food availability and cellular stress comes from autophagy-related (ATG) genes and signaling pathways, including mTOR and AMP-activated protein kinase (AMPK) [3]. The beginning of the study of autophagy stretches back to the 1950s and 1960s when Christian de Duve discovered that intracellular breakdown is done by the lysosomes. Hereafter, the word "autophagy" was created in 1963, but its importance in cellular homeostasis was not completely understood until the 1990s when Yoshinori Ohsumi discovered ATG genes in yeast, which earned him the 2016 Nobel Prize in Physiology or Medicine [4]. Recently, autophagy has been associated with various physiological and pathological processes, including immunological modulation, neurodegeneration, and, most importantly, cancer. Recent findings

have increased our knowledge of autophagy's involvement in cellular metabolism, aging, and disease development, emphasizing its potential as a therapeutic target [1, 5]. Autophagy is well known for its controversial role in cancer, as it acts by dual function, and it may operate as a tumor suppressor or promoter depending on the cellular context. Autophagy protects normal cells by eliminating damaged organelles and reducing genetic instability, which inhibits tumorigenesis. However, in some tumors, cancer cells may adapt cytoprotective autophagy to evade apoptosis, increase cell survival under metabolic stress, and develop drug resistance [6]. The dual function of autophagy complicates therapy attempts as, depending on the kind and stage of cancer, both repression and activation have benefits. Designing effective cancer treatments depends on understanding the processes behind cytoprotective rather than cytotoxic autophagy [7]. Autophagy has a significant impact on cancer treatment and drug resistance. Many cancers use autophagy to adapt to harsh microenvironmental circumstances, including hypoxia and food deprivation, which help cell growth and survival. Moreover, autophagy helps chemoresistance by boosting cytotoxic agent breakdown and inhibiting drug-induced apoptosis [8]. This has led to using autophagy inhibitors in clinical trials, such as hydroxychloroquine, as adjuvant chemotherapy to enhance the effect of the treatment [9]. In contrast, in malignancies, when autophagy is reduced, reactivating autophagy may restore normal cellular functions and trigger tumor cell death [10]. Small-molecule autophagy activators, such as rapamycin and metformin, have been shown in certain studies to have anti-cancer characteristics by increasing autophagy-mediated cell death and decreasing resistance to treatment. Given the context-dependent nature of autophagy in cancer, targeting autophagic pathways offers a viable route for precision medicine techniques [7]. This review attempts to clarify the molecular mechanisms controlling autophagy by means of key regulatory pathways and signaling networks, differentiate between the conditions under which autophagy displays cytoprotective rather than cytotoxic activities in cancer, and investigate therapeutic strategies targeting autophagy, including both inhibitors and activators, to enhance the outcome of cancer treatment.

1. Types of Autophagy

Autophagy has three forms: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), all of which depend on lysosomal degradation [11]. Macroautophagy is the most studied form that involves the formation of autophagosomes to sequester damaged organelles, misfolded proteins, and pathogens. Then, the autophagosome is fused with the lysosome for content degradation. This form of autophagy is regulated by mTOR and AMPK signaling and is important for cancer suppression, neuroprotection, and immune function. Any dysregulation with macroautophagy is always associated with neurodegenerative diseases and cancer [1]. The microautophagy directly engulfs the small cytoplasmic portions with the aid of lysosomes without autophagosome formation. It is responsible for organelle turnover, lipid metabolism, and protein homeostasis, with roles in aging, metabolic disorders, and neurodegeneration [12]. On the other hand, chaperone-mediated autophagy is a specific mode of lipophagy that begins with the recognition of a conserved KFERQ peptide sequence in the target proteins, LD coat proteins, including PLIN2 and PLIN3, which are demonstrated to be substrates of this pathway. Specifically, cargos to be degraded are recognized by a chaperone, Hsc70. Hsc70 thereby links these cargo molecules to a lysosomal structural protein called LAMP2A. It is vital for protein quality control, oxidative stress response, and metabolic regulation, with implications in aging, cancer, and neurodegenerative diseases [13]. Although different, these autophagy mechanisms are constantly controlled depending on cellular demands and are linked, so their regulation has immense potential as a therapeutic approach for disorders like cancer and neurodegeneration. Therefore, their crosstalk is an important focus for further studies.

2. Molecular mechanism of autophagy

Autophagy's molecular mechanism is a process controlled by many proteins and signaling pathways that guarantee exact execution and control by means of several consecutive phases. The induction phase of autophagy is the one in which cellular stress or nutrient deprivation inhibits the mTOR complex 1 (mTORC1) [14]. The inhibition of mTOR activates Unc-51-like autophagy, which further activates the kinase 1 (ULK1) complex, which includes ULK1, ATG13, FIP200, and ATG101. After activation of the ULK1 complex, the nucleation phase is initiated, recruiting ATG proteins to form the pre-autophagosomal structure (PAS) [15]. Nucleation is facilitated by the class III PI3K complex, consisting of VPS34, Beclin-1, VPS15, and ATG14L. These complexes form phosphatidylinositol 3-phosphate (PI3P) at the PAS, which leads to

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the accumulation of ATG proteins necessary for the elongation of the autophagosome membrane [16]. Membrane elongation and expansion depend critically on the ATG12-ATG5-ATG16L1 complex and microtubule-associated protein one light chain 3 (LC3). LC3-II is formed by conjugating phosphatidylethanolamine with LC3-II, which hooks the autophagosomal membrane to permit cytoplasmic cargo to be engulfed [17]. Some adaptor proteins like p62/SQSTM1, NBR1, and optineurin will bind to ubiquitinated cargo and LC3 to guarantee the selective destruction of certain cellular components [18]. Linking ubiquitinated proteins to the autophagic machinery for destruction and acting in the nuclear factor-kappa B (NF-κB) pathway, P62 functions both in autophagy and signaling pathways [19].

Autophagosome closure involves additional ATG proteins and membrane fusion events, leading to a mature autophagosome formation. Then, the lysosomes are fused with the autophagosome; this fusion process is regulated by SNARE proteins such as syntaxin 17, vesicle-associated membrane protein 8, and synaptosomal-associated protein 29. Consequently, the autolysosome is formed after the fusion, where lysosomal hydrolases degrade the autophagic cargo [20]. Autophagy is regulated by miRNA-34 by targeting ATG, which induces the expression and function of proteins involved in autophagic pathways [21]. P2X7 receptor also stimulates autophagy by increasing calcium influx and thereby activating downstream signaling pathways [22]. Interacting with Beclin-1, Bcl-2 is an anti-apoptotic protein that reduces autophagy under normal settings. BH3-only proteins may replace Beclin-1 from Bcl-2 under stress, thereby enabling autophagy [23]. Additionally, autophagy is activated when the AMPK pathway inhibits mTORC1 and directly phosphorylates ULK1 [24]. The JNK pathway can also regulate autophagy by phosphorylating Bcl-2, disrupting its interaction with Beclin-1 [25].

Overall, autophagy regulation is a complex process involving interactions between molecules and interplay of many signaling pathways. Understanding these mechanisms, including the roles of miRNA-34, P2X7, p62, Bcl-2, AMPK, and JNK, is important to develop new therapeutic strategies to modulate autophagy in diseases such as cancer, where autophagy can play both protective and detrimental roles depending on the context.

3. *Functional Roles of Autophagy: Cellular Homeostasis, Organelle Turnover, and Response to Stress*

Autophagy maintains cellular homeostasis through the degradation and recycling of damaged organelles, misfolded proteins, and any toxic content. This process is crucial to preserve cellular integrity and prevent dysfunction, especially in metabolically active tissues like neurons, muscles, and the liver [26]. However, autophagy is responsible for removing aged proteins and defective cytoplasmic content; its malfunction leads to aging and cancer progression, making it a promising therapeutic target [6].

One of the major functions of autophagy is organelle turnover to ensure the removal of dysfunctional organelles such as mitochondria, peroxisomes, and the endoplasmic reticulum (ER) [1]. For example, mitophagy is the selective clearance of damaged mitochondria, which further prevents oxidative stress and inflammation and preserves redox homeostasis to maintain metabolic balance [27]. Similarly, reticulophagy is responsible for removing damaged ER segments and preventing ER stress, which is a key factor in Alzheimer's and Parkinson's [28].

Furthermore, autophagy acts as a first-line defense when the cell is exposed to nutrient deprivation, hypoxia, infection, and oxidative stress. Under these conditions, it provides an alternative energy source by repurposing the intracellular macromolecules for metabolism. It also gets rid of oxidized proteins and damaged mitochondria to prevent excessive ROS accumulation and reduce age-related disorders [29]. However, excessive autophagy for a prolonged duration of stress may result in autophagy-dependent cell death (ADCD) and is known as cytotoxic autophagy, which highlights its dual role in cell survival and disease [30].

The balance between cytoprotective and cytotoxic autophagy relies on cellular context, activation intensity, and environmental conditions [31]. Understanding its molecular mechanisms will allow for precise therapeutic modulation and offer potential treatments for neurodegeneration, cancer, metabolic disorders, and aging-related diseases.

4. Role of autophagy in tumorigenesis

4.1. Tumor-Suppressive Role of Autophagy in Early Tumorigenesis

In the early stages of tumorigenesis, autophagy acts as a tumor suppressor by maintaining cellular homeostasis and genomic integrity by removal of damaged organelles and misfolded proteins to prevent the release of ROS and genomic instability, which may lead to carcinogenesis [32]. Previous studies highlight the role of autophagy as a preventive factor of tumorigenesis by the elimination of precancerous cells and inhibiting oncogenic mutations. For example, in mouse models, deletion of ATGs, including ATG5, ATG7, and Beclin-1, has been found to speed carcinogenesis, especially in liver and breast cancer models [33], thereby highlighting the protective function of autophagy in early cancer suppression.

Moreover, as discussed, autophagy uses a selective mechanism called mitophagy to break down defective mitochondria, hence promoting metabolic balance. Early tumor formation is characterized by mitochondrial dysfunction as it causes metabolic reprogramming and increases oncogenic signaling. By preventing mitochondrial dysfunction, autophagy inhibits cancer progression [27]. Furthermore, autophagy is known to regulate oncogene-induced senescence (OIS), which is a tumor-suppressive mechanism that decreases the proliferation of cells carrying oncogenic mutations. This results in inhibiting the escape of precancerous cells for senescence and reducing malignant transformation [34].

Autophagy also has an immune function that is involved in tumor suppression through intracellular pathogen degradation and antigen presentation. Autophagy also enhances the ability of various immune cells, such as natural killer cells and cytotoxic T cells, to recognize and eliminate early tumor cells. The failure of autophagy-mediated immune surveillance allows pre-malignant cells to evade detection and progress to more aggressive tumor phenotypes [35]. This highlights the importance of autophagy in preventing tumor initiation by integrating metabolic regulation, immune response, and genomic stability.

4.2. Tumor-Promoting Role of Autophagy in Established Cancers

Autophagy, in some cases, shifts from a cytoprotective form into a cytotoxic one as the tumor progresses, which promotes the transformation of normal cells to cancerous ones and increases therapy resistance. When cancer cells are exposed to a hypoxic and nutrition–deprived environment, autophagy will degrade the cellular components to sustain the tumor growth and survival, as seen in pancreatic, lung, and colorectal cancers [36]. Furthermore, the poor prognosis of cancer and treatment resistance is proved by high autophagic flux.

Autophagy provides the cancer cell with an alternative energy source through the AMPK/mTOR pathway to ensure tumor cell progression and proliferation [37]. Autophagy also helps cancer cells to evade immune cells by degrading damage-associated molecular patterns (DAMPs) and inhibiting type I interferon signaling, subsequently preventing effective immune responses [38].

Furthermore, autophagy is widely known nowadays as a tumor protector because it increases chemotherapy resistance and protects tumor cells from radiation and targeted therapy through its cleaning machinery process. Previous studies in glioblastoma and breast cancer have shown that chemotherapy-induced autophagy prevents apoptosis and reduces treatment efficacy [39, 40]. Some autophagy inhibitors like chloroquine (CQ) and hydroxychloroquine (HCQ) are used to increase cancer sensitivity to therapy, though their effectiveness varies by tumor type and stage [41].

5. Molecular Pathways Involved in Cancer-Associated Autophagy: PI3K/AKT/mTOR, p53, and Hypoxia-Inducible Factors

Autophagy in cancer is regulated by various signaling pathways such as PI3K/AKT/mTOR, p53, and HIF-1α pathways that play a crucial role in tumor progression, cell survival, and drug resistance [7]. Recent studies demonstrated that these pathways are promising targets for cancer therapy.

The activation PI3K/AKT/mTOR pathway upon decreasing cell nutrients, inhibits autophagy by phosphorylating ULK1/2 and further prevents autophagosome formation [42]. This pathway is highly activated in breast [43], prostate [44], and lung cancers [45], which inhibits autophagy and supports tumor growth and therapy resistance.

However, mTOR inhibitors like rapamycin, everolimus induce autophagy, which can either increase cancer cells sensitivity to chemotherapy or enhance their survival by providing metabolic flexibility [46]. Combining mTOR inhibitors with

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autophagy inhibitors like CQ is now considered an inducer of cancer cell death [47].

P53 has dual roles in autophagy. Nuclear p53 acts as an autophagy inducer through activation of DRAM1 and SESN2, suppressing mTOR and preventing genomic instability, which will suppress tumor growth. Conversely, cytoplasmic p53 acts as an autophagy inhibitor and promotes tumor growth and survival, furthermore increasing therapy resistance as seen in glioblastoma and pancreatic cancers [48].

More than 50% of cancers develop p53 mutations that lead to dysregulation in autophagy and increasing tumor growth [49]. Therefore, therapies like PRIMA-1 and APR-246 aim to restore p53-dependent autophagy, promoting tumor cell death [50].

In solid tumor, hypoxia is known to stabilize HIF-1α, which will induce autophagy via BNIP3/BNIP3L and further inhibit mTOR and enable tumor adaptation. HIF-1α-driven autophagy enhances metabolic reprogramming (Warburg effect) and therapy resistance, as demonstrated in glioblastomas and pancreatic and liver cancers [51].

Digoxin, acriflavine, and PX-478 are HIF-1α inhibitors and are used to block hypoxia-induced autophagy and enhance chemotherapy and radiation sensitivity [52]. Combining HIF-1α and autophagy inhibitors represents a promising anti-cancer strategy.

6. *Autophagy and Cancer Metabolism: Adaptation to Metabolic Stress*

Autophagy is one of the cell machinery processes that help cancer cells to adapt to nutrient deprivation, hypoxia, oxidative stress, and chemotherapy by recycling the intracellular components to sustain metabolism. Through playing a dual role, autophagy supports tumor survival in stressed microenvironments while also acting as a potential mechanism of cell death in specific contexts [7].

Autophagy can recycle nutrients under high metabolic stress through the degradation of damaged organelles and lipid droplets to generate energy. One such mechanism is lipophagy, which releases free fatty acids and induces tumor growth in cancers like pancreatic ductal adenocarcinoma (PDAC) and glioblastoma. High autophagic flux in tumors also enhances amino acid homeostasis, which maintains tumor growth even under systemic nutrient depletion [53].

HIF-1α induces BNIP3/BNIP3L-mediated autophagy, known as mitophagy, in case of hypoxia, which prevents the release of ROS and shifts the cell metabolism towards anaerobic glycolysis (Warburg effect) [51]. This adaptation has been shown in lung, breast, and colorectal cancers, and this is believed to support tumor survival and therapy resistance [36].

Finally, autophagy has a significant role in helping chemotherapy-resistant tumors to survive the metabolic stress induced by therapy through maintaining glutamine metabolism and redox balance. It acquires glutaminolysis to sustain the TCA cycle and relieves oxidative damage by destroying dysfunctional mitochondria [54]. The observed active autophagic flux seen in multiple myeloma and ovarian cancer is always associated with drug resistance [55].

7. *Autophagy in Cancer Stem Cells (CSC) and Metastasis*

Autophagy is one of the cell signaling pathways that is essential for CSC survival, therapy resistance, and metastasis, which enables tumors to adapt to stress, escape immune cells, and sustain growth [56]. CSCs use autophagy to survive hypoxic and nutrient-poor environments, which further prevents apoptosis and maintains stemness factors such as SOX2, OCT4, and NANOG. This directs the cell to self-renewal and resistance to chemotherapy and radiotherapy [57]. Previous studies in glioblastoma, colorectal, and pancreatic cancers have shown that targeting ATG5, ATG7, and Beclin-1 could reduce CSC tumor-initiating capacity and enhance chemotherapy sensitivity [58].

Autophagy aids the metastatic cancer cells in surviving harsh oxidative and metabolic stress. Epithelial-to-mesenchymal transition (EMT) is one of the crucial processes for metastasis; it is widely known to be regulated by some transcription factors derived from autophagy, such as ZEB1, SNAIL, and TWIST [59]. Studies indicate that inhibiting autophagy suppresses EMT and reduces metastasis in lung and breast cancer [60].

Autophagy can also adapt to mitochondrial dysfunction by acquiring lipophagy that provides metastatic growth by converting the lipid content into free fatty acids to sustain oxidative phosphorylation in distant organs like the liver and lungs [53].

Furthermore, autophagy degrades MHC

proteins to help circulating tumor cells evade immune destruction, which results in preventing recognition by NK cells and cytotoxic T cells. It also promotes metastatic potential by allowing disseminated tumor cells (DTCs) to survive in a dormant state before transforming into secondary tumors [61]. Therefore, targeting autophagy in latent cells is considered a promising approach to prevent metastasis.

Recently, clinical trials are investigating the role of the combination of autophagy inhibitors such as CQ and HCQ with chemotherapy, radiotherapy, and immunotherapy to inhibit CSC survival and metastasis [62]. Some metabolic strategies using glutaminase and glycolysis inhibitors can target lipophagy and oxidative phosphorylation, which could deprive metastatic cells of essential nutrients [63]. Moreover, autophagy-targeting immunotherapies seek to boost antigen presentation to restore anti-tumor immune responses [61].

8. Determinants of Cytoprotective Versus Cytotoxic Autophagy

8.1. Determinants of Cytoprotective Versus Cytotoxic Autophagy: Intracellular Determinants

P53, Beclin-1, PI3K/AKT/mTOR, AMPK, and stress-responsive pathways are key regulators, which determine whether autophagy will induce tumor suppression or trigger tumor growth [64, 65]. More research is done to investigate those molecular determinants to help in developing promising therapies against autophagy.

8.1.1. p53 and Beclin-1: Key Regulators of Autophagy Fate

Wild-type p53 normally inhibits mTOR and activates DRAM1 and SESN1/2, which in turn enhances cytoprotective autophagy and promotes the degradation of dysfunctional organelles. Consequently, the cell preserves its genomic stability and prevents tumorigenesis. However, mutant p53 inhibits autophagy, promotes tumor survival, and increases drug resistance. At the same time, cytoplasmic p53 prevents the initiation of through interaction with ATG7 and Beclin-1, which further halts autophagosome formation [65]. On the other hand, tumors with p53 deficiency will exhibit a highly active autophagic flux that allows the cancer cells to escape immune cells and develop resistance to chemotherapy [66]. That is why targeting autophagy-mediated cell death in p53-mutant cancers is a promising therapeutic strategy.

Beclin-1 is a key component of the PI3KC3 complex, and it is important for autophagy to initiate and maintain the integrity of the phagophore membrane [67]. In some cancers, Beclin-1 is lost, such as breast, ovarian, and prostate cancers, which will impair autophagy and lead to genomic instability and tumor metastasis [68]. Bcl-2 and Bcl-XL usually inhibit Beclin-1 as they bind and inhibit it, further preventing excessive autophagy. Therefore, recent studies aim to disrupt Bcl-2/Beclin-1 interactions to enhance cytotoxic autophagy, making it a potential therapeutic target [69].

Autophagy-related biomarkers have significant potential in cancer diagnosis, prognosis, and treatment stratification. Among these, LC3-II, p62/SQSTM1, and Beclin-1 are widely studied for their roles in autophagy regulation and their expression patterns in various malignancies. Their levels can reflect autophagy activity and correlate with therapeutic response and clinical outcomes [70]. T**able 1** below summarizes the key autophagy biomarkers, their biological functions, associated tumor types, and their clinical significance in guiding biomarker-driven therapies.

Table 1: Autophagy Biomarkers in Cancer

Biomarker	Biological Function	Associated Cancers	Clinical Relevance
LC3-II	The marker of autophagosome formation reflects autophagy flux	Pancreatic, Breast, Colorectal	High levels indicate active autophagy, linked to poor prognosis in pancreatic cancer, a potential predictor of response to autophagy inhibitors. [71]
p62/SQSTM1	Selective autophagy substrate accumulates when autophagy is impaired	Hepatocellular, Colorectal, Lung	Elevated levels correlate with therapy resistance and reduced survival, potential prognostic and predictive biomarkers. [72]
Beclin-1	Initiates autophagosome formation; regulates autophagy initiation	Breast, Glioblastoma, Ovarian	Reduced expression in breast cancer associated with tumor progression; overexpression in glioblastoma linked to chemoresistance. [73]

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The clinical utility of autophagy biomarkers extends beyond their prognostic value, offering significant potential for guiding biomarker-driven cancer therapies. These biomarkers can facilitate patient stratification based on autophagy dependency, predict therapeutic response, and refine personalized treatment approaches. Their integration with genomic and transcriptomic profiling enables a precision oncology framework, supporting the development of tailored autophagy-targeted interventions [74]. The following **table 2** outlines key clinical applications of autophagy biomarkers and examples of their relevance in current therapeutic strategies.

Table 2: Clinical Applications of Autophagy Biomarkers in Biomarker-Driven Cancer Therapy

Clinical Application	Biomarker(s) Involved	Example/Context	Implications
Patient Stratification Based on Autophagy Dependency	LC3-II, p62/SQSTM1	High LC3-II or p62 levels may identify patients suitable for autophagy inhibition therapy.	Enhances treatment personalization; avoids ineffective therapies in autophagy-independent tumors [75]
Predicting Therapeutic Response to Autophagy Inhibitors	LC3-II, p62/SQSTM1	Trials using hydroxychloroquine + chemotherapy stratify patients by autophagy biomarker levels.	Improves therapeutic efficacy; reduces adverse effects from unnecessary drug exposure [76]
Integration with Omics Data for Precision Medicine	LC3-II, Beclin-1, p62 + Genomic Profiling	TCGA data integration correlates biomarker levels with tumor genotype and transcriptome	Enables development of personalized, genotype-specific autophagy-targeted therapies [77]

8.1.2. Signaling Pathways Controlling Cytoprotective vs. Cytotoxic Autophagy

The PI3K/AKT/mTOR pathway is known to inhibit ULK1/2, which inhibits autophagy and promotes cancer cell survival. Hyperactivation of PI3K/AKT in cancer cells shifts autophagy to a cytoprotective form, which helps tumors withstand harsh metabolic stress by recycling intracellular components. However, mTOR inhibitors such as rapamycin, everolimus, or temsirolimus induce cytotoxic autophagy and lead to apoptosis. Therefore, recent studies investigate the combination effect of mTOR inhibitors with autophagy modulators, which may enhance cancer therapy [44].

AMPK is another signaling pathway known as a metabolic stress sensor that activates autophagy by inhibiting mTOR and activating ULK1. Unlike PI3K/AKT, AMPK is considered a cytotoxic autophagic factor inducer, particularly in tumors that depend on glycolysis, as AMPK activation results in the induction of mitophagy, which further decreases ATP production and induces apoptosis in cancer cells [42]. One example of an AMPK activator is metformin, which is combined with autophagy inducers, and recently, this combination has shown a promising therapeutic option to induce autophagy-dependent cancer cell death, particularly in therapy-resistant tumors [78].

Under oxidative stress and DNA damage, JNK and MAPK pathways control autophagy. JNK activation phosphorylates Bcl-2, therefore disturbing its regulation of Beclin-1 and triggering autophagy-mediated cell death [79]. Furthermore, autophagy driven by ER stress via the PERK-eIF2α pathway may cause death in aggressive cancers. A proteasome inhibitor, bortezomib, causes ER stress and excessive autophagy, which results in cell death in many myelomas [80].

8.2. Determinants of Cytoprotective Versus Cytotoxic Autophagy: Extracellular Factors

Autophagy is highly affected by tumor microenvironment conditions such as availability of nutrients, hypoxic conditions, and immune signaling. Studies confirm that tumors acquire autophagy to adapt to high-stress conditions. However, excessive autophagy can shift into a cytotoxic form, which induces cancer cell death under certain conditions [81].

The TME is a composition of cancer cells, stromal fibroblasts, immune cells, and ECM components, which are the determinants of whether the cell will acquire cytoprotective or cytotoxic autophagy. In response to harsh TME conditions, autophagy helps cancer cells maintain cell integrity, genomic stability, metabolic balance, and resist therapy [82]. Cytokines and growth factors such as TGF-β, IL-6, TNF-α, and IL-1β are secreted by stromal cells and tumor-associated macrophages and will upregulate pro-survival autophagy under metabolic stress. However, tumors in the early stages will adapt

autophagy to remove the damaged organelles and maintain the metabolic balance to prevent genetic mutation function as tumor suppressors. In advanced cancer, tumors hijack autophagy for self-survival and therapy resistance; that's why it is considered an attractive therapeutic target [83].

As tumors proliferate, the level of glucose, amino acids, and lipids is decreased, which inhibits mTOR through AMPK activation that results in activation of autophagy and sustained energy homeostasis [84]. Lipophagy is an activated specialized form of autophagy that converts the lipid droplets to free fatty acids to fuel oxidative phosphorylation and support tumor survival and growth under metabolic stress. This is demonstrated in several types of cancer, such as pancreatic and colorectal cancers, which depend mainly on lipid metabolism. However, nutrient deprivation for prolonged durations may lead to excessive autophagy that results in ADCD, further degradation of mitochondria and ER, and the release of ROS and apoptosis [53].

A common characteristic of solid tumors is hypoxia that stabilizes HIF-1α and further activates ATGs (BNIP3, BNIP3L) to induce mitophagy, hence avoiding ROS buildup and facilitating tumor survival under low oxygen conditions. In some types of cancer, such as glioblastoma, hepatocellular carcinoma, and breast cancer, autophagy induced by hypoxia is considered a cytoprotective one and correlates with increased tumor aggression and therapy resistance [36]. However, therapies like radiation therapy can exacerbate hypoxia and shift autophagy to a cytotoxic one, which is favorable in cancer treatment. Targeting HIF-1α or decreasing autophagy induced by hypoxia could enhance radiation therapy efficacy in hypoxia-adaptive tumors [85].

8.3. Determinants of Cytoprotective vs. Cytotoxic Autophagy: Role of Cellular Context and Stressors

Autophagy in cancer is influenced by cellular context as well external stress factors such as chemotherapy, radiotherapy, and oxidative stress. Although tumors often use autophagy as a defense mechanism against therapy and metabolic changes, excessive autophagy activation may result in ADCD. This balance relies on stressor type, duration of autophagy, and tumor genetics [86].

8.3.1. Autophagy in Chemotherapy: Survival vs. Cell Death

Chemotherapy is known to damage DNA and increase the release of ROS, which leads to cell apoptosis. However, cancer cells induce autophagy as a protective mechanism to counteract these effects. Some chemotherapies, such as cisplatin, doxorubicin, and temozolomide, activate p53 and inhibit mTOR, which consequently activate cytoprotective autophagy and develop chemoresistance [87]. For example, ovarian cancer adapts autophagy to resist chemotherapy and promote tumor recurrence, which is demonstrated by increased autophagic flux biomarkers such as Beclin-1 [88]. Cytoprotective autophagy in leukemia, glioblastoma, and pancreatic cancer decreases ATP, which further increases ROS [89]. Recent studies support the use of autophagy inhibitors such as CQ and HCQ to suppress cytoprotective autophagy and improve the effect of chemotherapy [62].

8.3.2. Autophagy in Radiotherapy: A Double-Edged Sword

Radiotherapy is widely used nowadays in early-stage cancer due to its reduced side effects, and it kills tumor cells by inducing DNA damage and oxidative stress induction, but tumors subjected to radiotherapy activate autophagy as a survival mechanism [90]. In glioblastoma, prostate cancer, and hepatocellular carcinoma, the cancer cells induce mitophagy, which helps radio-resistance by removing damaged mitochondria and reducing ROS released from the tumor [91]. Additionally, radiation-induced autophagy promotes CSC survival, increasing therapy resistance. However, excessive autophagic flux can push cells into autophagy-mediated apoptosis [57]. Autophagy inducers (rapamycin, resveratrol) have shown potential in sensitizing tumors to radiation [92]. Recent clinical trials have used autophagy inhibitors as lysosomal inhibitors to prevent DNA repair induced by autophagy and, hence, enhance radiotherapy outcomes [93].

8.3.3. Oxidative Stress and Autophagy: A Critical Balance

ROS affects responsiveness to treatment and tumor development. Moderate ROS levels enable autophagy for survival, therefore enabling tumors to adapt to hypoxia and inflammation [89]. In colorectal and breast cancer, KEAP1-NRF2 is activated to maintain redox homeostasis by autophagy [94]. However, excessive ROS shifts autophagy to a cytotoxic one that is irresistible to antioxidant defenses and degrades mitochondria. Lung, ovarian, and pancreatic tumors, where oxidative stress-

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induced autophagy drives death, have also shown this impact [86]. Recently, some pro-oxidant therapies, such as arsenic trioxide and photodynamic therapy, utilize ROS overload to induce cytotoxic autophagy. The combination of an autophagy inducer and oxidative stress shows a profound effect as an anti-cancer strategy [95].

8.4. Biomarkers for Predicting Autophagic Response: Determinants of Cytoprotective Versus Cytotoxic Autophagy

Biomarkers play a vital role in predicting the fate of autophagy; therefore, it is crucial to identify them for targeted cancer therapy. These biomarkers include ATGs, transcription factors, metabolic markers, and lysosomal activity, which serve as key determinants of autophagic responses [6].

8.4.1. Autophagy-Related Gene (ATG) Expression as Biomarkers

ATGs such as ATG5 and ATG12 are considered autophagy key markers as they are known to regulate autophagosome formation and autophagic flux [96]. In breast and lung cancer, the presence of high levels of ATG12 is often associated with therapy resistance due to cytoprotective adaptations by these cancers [97]. Conversely, ATG5 induces cytotoxic autophagy and is considered a target to increase therapy response. LC3 is a protein that maintains the integrity of the autophagosome membrane, and it is widely used as an autophagic flux marker. Its accumulation is an indicator of enhanced autophagic activity, which is often associated with therapy resistance [98]. However, in the presence of lysosomal inhibitors such as CQ, the increased level of LC3-II may be an indicator of impaired degradation, which further leads to cytotoxic autophagy [99].

8.4.2. Beclin-1 and PI3K/AKT/mTOR Pathway Components

Another biomarker is Beclin-1, which is a key autophagy initiator. Recent studies in breast and ovarian cancers demonstrated a downregulation in Beclin-1 and promoted tumor progression [100]. However, in some cancers, such as glioblastoma and colorectal cancer, the increased level of Beclin-1 is associated with tumor suppression and is considered a biomarker for cytotoxic autophagy [101]. The PI3K/AKT/mTOR pathway is an important one that inhibits autophagy. The elevated levels of phosphorylated AKT (p-AKT) and activation of mTOR are always accompanied by decreased autophagy processes that indicate the tumors suppress autophagy for cytoprotective functions. Low mTOR activity, on the other hand, seen in metabolically stressed tumors, are indicators of enhanced autophagic flux, which depends on context and may either contribute to cancer cell survival or death [44].

8.4.3. Lysosomal Markers and Autophagic Degradation Biomarkers

LAMP1 (Lysosomal Associated Membrane Protein 1) is one of the lysosomal activity's key determinants of autophagic function and is used to assess autophagic degradation. A high level of LAMP1 is associated with an efficient lysosomal function that enhances tumor growth even under stress conditions [102]. However, HCQ, one of the lysosomal inhibitors, can block LAMP1-mediated autophagy, which shifts autophagy to a cytotoxic one [103].

p62 (SQSTM1) is another cargo protein that is decreased by enhanced autophagic processes while its level is increased upon autophagy impairment. The elevated expression level of p62 is an indicator of poor response to autophagy-targeting therapies, while reduced levels of p62 are linked to cancers, which adapt cytotoxic autophagy [104].

8.4.4. Metabolic and Redox Biomarkers for Autophagic Response

Autophagy is intricately linked to tumor metabolism. Glutamine metabolism under control by glutaminase (GLS1) predicts survival driven by autophagy in pancreatic cancer. While GLS1 inhibition with autophagy activation pushes cells toward autophagic death, high GLS1 expression shows autophagy promotes metabolism [105]. Oxidative stress markers such as ROS levels and Nrf2 activation are used as detriments of autophagic response. Increased activation of Nrf2 enhances cancer cells to acquire cytoprotective autophagy; conversely, excessive ROS accumulation promotes autophagy-mediated cell death. Reducing Nrf2 activation in tumors associated with high autophagic activity could shift autophagy toward cytotoxicity and enhance therapy [106].

8.4.5. Autophagy-related miRNAs and Predictive Genetic Markers

Different families of microRNAs (miRNAs) regulate autophagy. For example, the downregulation of miR-148a-3p could enhance autophagic flux and promote chemotherapy resistance in gastric cancer [107]. On the other

hand, some miRNAs, such as miR-101, suppress Beclin-1-mediated autophagy and push tumors toward cytotoxic autophagy [108].

Autophagic fate in ATG genes is influenced by genetic variants. In colorectal cancer, ATG16L1 mutations reduce autophagy, hence increasing sensitivity to treatments that induce autophagy. Also, mutations in ULK1 may disrupt autophagy initiation and potentially make tumors more sensitive to autophagy activators [109].

9. Therapeutic Implications: Autophagy Modulators in Cancer Therapy

Autophagy modulators could be autophagy inhibitors such as CQ and HCQ or autophagy inducers such as rapamycin and everolimus. Both autophagy inhibitors and inducers have gained attention as potential co-adjuvant therapies to traditional cancer therapies. The ability to either prevent or promote autophagy offers a special opportunity to sensitize tumors to chemotherapy, radiation, and immunotherapy, thereby improving the effectiveness of cancer treatment [110].

9.1. Autophagy Inhibitors in Cancer Therapy

CQ and HCQ are used as autophagy inhibitors that prevent lysosomal acidification, which disrupts the last step of autophagic degradation. It works by preventing the fusion of autophagosomes with lysosomes and the formation of autolysosomes, which further leads to this accumulation of defective proteins and organelles and finally shifts the cancer cells to apoptosis [103]. Recent studies in pancreatic cancer, glioblastoma, and non-small cell lung cancer (NSCLC) have demonstrated that when CQ and HCQ are used in combination with chemotherapy, the effect of the treatment increases compared to chemotherapy alone [111]. One such known combination is HCQ and gemcitabine, doxorubicin, and temozolomide, which is used in pancreatic cancer, and this combination has the effect of inhibiting tumor growth by inhibiting the cytoprotective autophagy [112]. Similarly, in GBM, the combination treatment of CQ and temozolomide has been reported to enhance the cytotoxic effects and prevent chemoresistance induced by autophagy [113]. Also, their ability to inhibit autophagy to overcome therapy-induced resistance is well-studied in CSCs. Recent research investigated the effect of CQ to reduce the stemness properties of CSCs, which prevents tumor relapse and metastasis [114]. Furthermore, clinical trials are actively examining CQ and HCQ as adjuvants in combination with chemotherapy and immunotherapy for therapy-resistant cancers. However, CQ and HCQ have some limitations, such as potential toxicity and off-target effects, especially for prolonged treatment duration, including retinopathy and cardiotoxicity [115]. Therefore, more studies are being conducted to develop next-generation autophagy inhibitors with greater specificity, such as Lys05 and dimeric CQ derivatives, which exhibit enhanced potency with reduced toxicity [116].

9.2. Autophagy Inducers in Cancer Therapy

Rapamycin is an mTOR inhibitor. It is one of the most widely studied autophagy inducers in cancer therapy. When mTOR is inhibited by rapamycin, autophagy is enhanced, which may lead to cancer suppression and increase the treatment response when used in combination with antitumor therapies [46]. Recent studies done on breast cancer, renal cell carcinoma, and glioblastoma have investigated the effect of other mTOR inhibitors, such as everolimus, temsirolimus, and sirolimus, to determine their anti-tumor effect [117]. Rapamycin is known to suppress tumor growth through the induction of cytotoxic autophagy, especially in cancer with hyperactive PI3K/AKT/mTOR signaling. Research shows that rapamycin restores autophagic flux in PTEN-deficient cancers, which show constitutive mTOR activity, therefore suppressing the tumors [118]. Triple-negative breast cancer (TNBC) has very clearly shown this impact where PI3K/mTOR pathway dysregulation is prevalent [119]. Another novel strategy is to combine autophagy inducers with apoptosis inducers to promote cancer cells to adapt to cytotoxic autophagy. For example, in leukemia and lymphoma, studies have demonstrated that rapamycin has a synergistic effect with Bcl-2 inhibitors, such as venetoclax, to enhance cell death autophagy. This strategy is justified by the fact that autophagy stimulation may provide metabolic stress, which drives cancer cells into irreversible cell death pathways [120].

However, using rapamycin and its analogs as autophagy inducers is their context-dependent effects is still a major challenge because in some cancers, such as glioblastoma, the prolonged use of rapamycin could induce adaptive resistance mechanisms, where tumors use autophagy to prevent themselves from dying [121].

9.3. Therapeutic Implications: Combination Therapies Targeting Autophagy

Recently, studies demonstrated that combination of different classes of autophagy modulator could enhance the therapeutic

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outcome, which has been reported in different types of cancer as shown in table 3.

Table 3: Combination Strategies Targeting Autophagy to Enhance Cancer Therapy

Combination Therapy	Strategy	Key Findings	Cancer Types
Autophagy Inhibition + Chemotherapy	Blocking autophagic degradation to enhance chemosensitivity	- CQ and HCQ block lysosomal degradation, sensitizing tumors to chemotherapy [122]. - HCQ + gemcitabine/nab-paclitaxel improves survival in pancreatic cancer [123]. - CQ + temozolomide enhances chemotherapy response in glioblastoma [124]. - CQ reduces CSC survival in breast and colorectal cancers, preventing relapse [114].	Breast cancer [114, 122], Pancreatic cancer [123], Glioblastoma [124], Colorectal cancer [114]
Autophagy Induction + Chemotherapy	Inducing autophagic apoptosis to increase DNA-damaging agent efficacy	- mTOR inhibitors (rapamycin, everolimus) shift cells into autophagic apoptosis [125]. - In PTEN-deficient prostate and breast cancers, rapamycin + etoposide/cisplatin enhances tumor suppression [126, 127].	PTEN-deficient prostate cancer [125, 126], Breast cancer [127]
Autophagy Inhibition + Immunotherapy	Inhibiting autophagy to improve immune checkpoint blockade (ICB) response	- CQ + anti-PD-1 therapy increases CD8+ T-cell infiltration in TNBC, improving immune response [128]. - CQ and HCQ stimulate cytotoxic T cells to recognize tumors in lung cancer and melanoma [41]. - Autophagy inhibition in Tregs and MDSCs reduces tumor immune suppression, enhancing PD-1 and CTLA-4 blockade responses [129].	TNBC [128], Melanoma [41, 129], Lung cancer [129]

10. Challenges and Future Directions in Autophagy-Targeting Cancer Therapy

Recently, autophagy has become an essential target in cancer therapy, which can help in tumor suppression and decreasing treatment resistance. Although there are many promising preclinical and clinical findings, several major challenges remain in translating autophagy-targeting strategies into effective personalized cancer treatments. The most common challenge is overcoming autophagy-induced resistance and developing individualized therapy tailored to the genetic profile of the specific tumor. Therefore, recent studies highlight the need for developing novel strategies to modulate autophagy while addressing therapy resistance and inter-patient variability [130].

10.1. Overcoming Resistance to Autophagy-Targeting Therapies

10.1.1. Adaptive Resistance to Autophagy Inhibition

Tumors always use the possibility of switching in the autophagy pathway to switch between cytoprotective and cytotoxic autophagy. This phenomenon has been investigated in tumors that are subjected to prolonged durations of autophagic inhibition, leading to exhibiting a compensatory metabolic reprogramming, which allows cancer cells to survive by stimulating other nutrient scavenging pathways such as macropinocytosis and mitochondrial biogenesis [1, 3, 6].

For example, in PDAC, where autophagy is a vital survival strategy, extended suppression with either HCQ or CQ has been demonstrated to induce metabolic changes that maintain tumor development despite autophagy inhibition [131]. Likewise, chronic autophagy suppression increases mitochondrial oxidative phosphorylation in GBM, therefore enabling tumor cells to survive in nutrient-deprived environments [121].

To overcome this adaptive resistance, some recent researchers investigated the dual-targeting strategies that combine autophagy inhibition with metabolic inhibitors, such as the combination of autophagy inhibitors like CQ or HCQ with glycolysis inhibitors (2-deoxyglucose). This combination has been shown to have a better effect against tumors more effectively than monotherapy [132]. Another combination that targets both autophagy and mitochondrial function, such as metformin + HCQ, has been proposed as a strategy to prevent metabolic compensation [133].

10.1.2. Overcoming Resistance to Autophagy Induction Therapies

While autophagy induction has been investigated as a means of inducing tumor cell death, certain cancer cells acquire resistance by altering important survival pathways. One of the main obstacles is that tumors with intact PI3K/AKT/

mTOR signaling generally restrict the efficacy of autophagy inducers such as rapamycin and everolimus by suppressing autophagy induction [43]. Recent research suggests that tumors that develop mTOR-resistant need additional combination approaches, such as combining autophagy inducers with proteasome inhibitors (rapamycin + bortezomib), which could switch the autophagy pathway to a cytotoxic one as seen in hematological malignancies [134]. Another strategy is combining autophagy inducers with checkpoint inhibitors that may enhance T-cell activation and tumor cell recognition [128]. Additionally, heterogeneity plays a key role in therapy resistance. For example, different subpopulations within a tumor may show various levels of autophagic activity. For instance, single-cell RNA sequencing studies have demonstrated that some cells within TNBC depend mainly on autophagy for survival and growth, while other cells demonstrate autophagy suppression [135]. This highlights the need for individualized treatment approaches that consider tumor heterogeneity when designing targeted therapies against autophagy.

10.2. Developing Patient-Specific Autophagy-Targeting Therapies

10.2.1. Biomarker-Driven Personalized Treatment Approaches

The development of biomarker-driven, patient-specific treatment plans is one of the main potential paths in autophagy-targeting therapy. Given the double function of autophagy in cancer, it is essential to predict whether a patient's tumor will react to autophagy suppression or autophagy stimulation. Insight into autophagic flow and tumor dependence on autophagy may come from biomarkers such as LC3-II/LC3-I ratios, p62/SQSTM1 levels, Beclin-1 expression, and lysosomal activity indicators. Since cancers with high LC3-II and low p62 expression are often autophagy-dependent, indicating that autophagy suppression might be a more effective treatment strategy [136]. Conversely, cancers with defective autophagy with low Beclin-1 expression may benefit from autophagy-inducing treatments such as caloric restriction mimics or mTOR inhibitors [137].

Future studies should concentrate on creating real-time imaging tools to evaluate tumor autophagy levels, therefore enabling tailored, real-time changes to treatment plans.

10.2.2. Integrating Artificial Intelligence (AI) and Precision Medicine in Autophagy Therapy

Recently, with the evolution of precision oncology, machine learning, and AI-driven approaches are being evaluated to predict autophagy dependence in tumors and optimize treatment regimens. AI-driven models can integrate multi-omics data such as genomics, proteomics, and metabolomics, which help in classifying tumors based on autophagy signatures, which further predict whether inhibition or induction of autophagy would have a better effect [138]. Hence, identifying novel drug combinations tailored to specific autophagic responses that reduce trial-and-error in clinical settings. For example, an AI-driven model published recently is used to analyze more than 10,000 tumor samples to predict which tumors are most likely to develop resistance to autophagy inhibitors [139]. This approach further guides clinical trial design and patient selection.

11. Future Directions: Expanding Autophagy-Targeting Approaches in Clinical Trials

Currently, several autophagy-targeting therapies are being evaluated in clinical trials; for instance, phase II trials use CQ and HCQ as adjuvant therapy in pancreatic cancer, glioblastoma, and NSCLC [115] and determine the effect of combinations of rapamycin with chemotherapy and immunotherapy in triple-negative breast cancer and melanoma [41, 128]. Several novel agents, such as HCQ derivatives (e.g., Lys05) and specific VPS34 inhibitors (e.g., SAR405), are under investigation in preclinical and early-phase clinical trials, aiming to selectively inhibit autophagy in tumor cells while minimizing systemic toxicity [140]. Many areas still need further research despite these developments. Optimizing The ideal timing and dose techniques for combining autophagy modulators with chemotherapy, radiation, or immunotherapy must be found via further study. Also, reducing off-target effects requires the development of new autophagy modulators with enhanced selectivity and less toxicity. Therapies should be targeted to tumor microenvironmental circumstances, as hypoxia, immune cell penetration, and metabolic stress affect autophagy. Finally, future clinical studies should stratify patients depending on autophagy-related indicators so that treatments are administered only in malignancies where autophagy targeting is probably advantageous.

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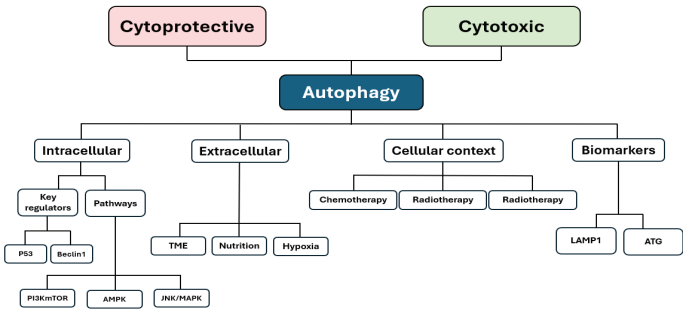

Graphical abstract

Data Availability

This study did not perform any data

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

1. Gómez-Virgilio L, Silva-Lucero MDC, Flores-Morelos DS, Gallardo-Nieto J, Lopez-Toledo G, Abarca-Fernandez AM, et al. Autophagy: A Key Regulator of Homeostasis and Disease: An Overview of Molecular Mechanisms and Modulators. Vol. 11, Cells. 2022.

2. Khandia R, Dadar M, Munjal A, Dhama K, Karthik K, Tiwari R, et al. A comprehensive review of autophagy and its various roles in infectious, non-infectious, and lifestyle diseases: Current knowledge and prospects for disease prevention, novel drug design, and therapy. Vol. 8, Cells. 2019.

3. Parzych KR, Klionsky DJ. An overview of autophagy: Morphology, mechanism, and regulation. Vol. 20, Antioxidants and Redox Signaling. 2014.

4. Harnett MM, Pineda MA, Latré de Laté P, Eason RJ, Besteiro S, Harnett W, et al. From Christian de Duve to Yoshinori Ohsumi: More to autophagy than just dining at home. Vol. 40, Biomedical Journal. 2017.

5. Ariosa AR, Lahiri V, Lei Y, Yang Y, Yin Z, Zhang Z, et al. A perspective on the role of autophagy in cancer. Biochim Biophys Acta Mol Basis Dis. 2021;1867(12).

6. Vitto VAM, Bianchin S, Zolondick AA, Pellielo G, Rimessi A, Chianese D, et al. Molecular Mechanisms of Autophagy in Cancer Development, Progression, and Therapy. Vol. 10, Biomedicines. 2022.

7. Yang ZJ, Chee CE, Huang S, Sinicrope FA. The role of autophagy in cancer: Therapeutic implications. Vol. 10, Molecular Cancer Therapeutics. 2011.

8. Rakesh R, PriyaDharshini LC, Sakthivel KM, Rasmi RR. Role and regulation of autophagy in cancer. Biochim Biophys Acta Mol Basis Dis. 2022;1868(7).

9. Cook KL, Wärri A, Soto-Pantoja DR, Clarke PAG, Cruz MI, Zwart A, et al. Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer. Clinical Cancer Research. 2014;20(12).

10. Degenhardt K, Mathew R, Beaudoin B, Bray K, Anderson D, Chen G, et al. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. Cancer Cell. 2006;10(1).

11. Kaushik S, Massey AC, Mizushima N, Cuervo AM. Constitutive activation of chaperone-mediated autophagy in cells with impaired macroautophagy. Mol Biol Cell. 2008;19(5).

12. Li WW, Li J, Bao JK. Microautophagy: Lesser-known self-eating. Vol. 69, Cellular and Molecular Life Sciences. 2012.

13. Alfaro IE, Albornoz A, Molina A, Moreno J, Cordero K, Criollo A, et al. Chaperone mediated autophagy in the crosstalk of neurodegenerative diseases and metabolic disorders. Vol. 10, Frontiers in Endocrinology. 2019.

14. Wang CW, Klionsky DJ. The Molecular Mechanism of Autophagy. Molecular Medicine. 2003 Mar 15;9(3–4):65–76.

15. Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation. Vol. 61, Essays in Biochemistry. 2017.

16. Thoresen SB, Pedersen NM, Liestøl K, Stenmark H. A phosphatidylinositol 3-kinase class III sub-complex containing VPS15, VPS34, Beclin 1, UVRAG and BIF-1 regulates cytokinesis and degradative endocytic traffic. Exp Cell Res. 2010;316(20).

17. Iriondo MN, Etxaniz A, Varela YR, Ballesteros U, Lázaro M, Valle M, et al. Effect of ATG12–ATG5-ATG16L1 autophagy E3-like complex on the ability of LC3/GABARAP proteins to induce vesicle tethering and fusion. Cellular and Molecular Life Sciences. 2023;80(2).

18. Gatica D, Lahiri V, Klionsky DJ. Cargo recognition and degradation by selective autophagy. Vol. 20, Nature Cell Biology. 2018.

19. Hennig P, Fenini G, Filippo M Di, Karakaya T, Beer HD. The pathways underlying the multiple roles of p62 in inflammation and cancer. Vol. 9, Biomedicines. 2021.

20. Nishimura T, Tooze SA. Emerging roles of ATG proteins and membrane lipids in autophagosome formation. Vol. 6, Cell Discovery. 2020.

21. Roy SG. Regulation of autophagy by miRNAs in human diseases. Vol. 64, Nucleus (India). 2021.

22. Orioli E, De Marchi E, Giuliani AL, Adinolfi E. P2X7 Receptor Orchestrates Multiple Signalling Pathways Triggering Inflammation, Autophagy and Metabolic/Trophic Responses. Curr Med Chem. 2017;24(21).

23. Levine B, Sinha S, Kroemer G. Bcl-2 family members: Dual regulators of apoptosis and autophagy. Vol. 4, Autophagy. 2008.

24. Afinanisa Q, Cho MK, Seong HA. AMPK localization: A key to differential energy regulation. Vol. 22, International Journal of Molecular Sciences. 2021.

25. Sabapathy K. Role of the JNK Pathway in human diseases. In: Progress in Molecular Biology and Translational Science. 2012.

26. Chun Y, Kim J. Autophagy: An essential degradation program for cellular homeostasis and life. Vol. 7, Cells. 2018.

27. Ma K, Chen G, Li W, Kepp O, Zhu Y, Chen Q. Mitophagy, Mitochondrial Homeostasis, and Cell Fate. Vol. 8, Frontiers in Cell and Developmental Biology. 2020.

28. Guan X, Iyaswamy A, Sreenivasmurthy SG, Su C, Zhu Z, Liu J, et al. Mechanistic Insights into Selective Autophagy Subtypes in Alzheimer's Disease. Vol. 23, International Journal of Molecular Sciences. 2022.

29. Filomeni G, De Zio D, Cecconi F. Oxidative stress and autophagy: The clash between damage and metabolic needs. Vol. 22, Cell Death and Differentiation. 2015.

30. Bialik S, Dasari SK, Kimchi A. Autophagy-dependent cell death - where, how and why a cell eats itself to death. Vol. 131, Journal of Cell Science. 2018.

31. Wilson EN, Bristol ML, Di X, Maltese WA, Koterba K, Beckman MJ, et al. A Switch Between Cytoprotective and Cytotoxic Autophagy in the Radiosensitization of Breast Tumor Cells by Chloroquine and Vitamin D. Horm Cancer. 2011;2(5).

32. Miller DR, Thorburn A. Autophagy and organelle homeostasis in cancer. Vol. 56, Developmental Cell. 2021.

33. Huang T, Song X, Yang Y, Wan X, Alvarez AA, Sastry N, et al. Autophagy and hallmarks of cancer. Crit Rev Oncog. 2018;23(5–6).

34. Schmitt CA, Wang B, Demaria M. Senescence and cancer — role and therapeutic opportunities. Vol. 19, Nature Reviews Clinical Oncology. 2022.

35. Gerada C, Ryan KM. Autophagy, the innate immune response and cancer. Vol. 14, Molecular Oncology. 2020.

36. Zaarour RF, Azakir B, Hajam EY, Nawafleh H, Zeinelabdin NA, Engelsen AST, et al. Role of hypoxia-mediated autophagy in tumor cell death and survival. Vol. 13, Cancers. 2021.

37. Zhang J, Xiang Q, Wu M, Lao YZ, Xian YF, Xu HX, et al. Autophagy Regulators in Cancer. Vol. 24, International Journal of Molecular Sciences. 2023.

38. Pan H, Chen L, Xu Y, Han W, Lou F, Fei W, et al. Autophagy-associated immune responses and cancer immunotherapy. Oncotarget. 2016;7(16).

39. Hwang YK, Lee DH, Lee EC, Oh JS. Importance of Autophagy Regulation in Glioblastoma with Temozolomide Resistance. Cells. 2024 Aug 11;13(16):1332.

40. Jain K, Paranandi KS, Sridharan S, Basu A. Autophagy in breast cancer and its implications for therapy. Vol. 3, American Journal of Cancer Research. 2013.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1251

41. Manic G, Obrist F, Kroemer G, Vitale I, Galluzzi L. Chloroquine and hydroxychloroquine for cancer therapy. Vol. 1, Molecular and Cellular Oncology. 2014.

42. Alers S, Löffler AS, Wesselborg S, Stork B. Role of AMPK-mTOR-Ulk1/2 in the Regulation of Autophagy: Cross Talk, Shortcuts, and Feedbacks. Mol Cell Biol. 2012;32(1).

43. Skolariki A, D'Costa J, Little M, Lord S. Role of PI3K/Akt/mTOR pathway in mediating endocrine resistance: concept to clinic. Vol. 3, Exploration of Targeted Anti-tumor Therapy. 2022.

44. Butler DE, Marlein C, Walker HF, Frame FM, Mann VM, Simms MS, et al. Inhibition of the PI3K/AKT/mTOR pathway activates autophagy and compensatory Ras/Raf/MEK/ERK signalling in prostate cancer. Oncotarget. 2017;8(34).

45. Sanaei MJ, Razi S, Pourbagheri-Sigaroodi A, Bashash D. The PI3K/Akt/mTOR pathway in lung cancer; oncogenic alterations, therapeutic opportunities, challenges, and a glance at the application of nanoparticles. Vol. 18, Translational Oncology. 2022.

46. Tian T, Li X, Zhang J. mTOR signaling in cancer and mtor inhibitors in solid tumor targeting therapy. Vol. 20, International Journal of Molecular Sciences. 2019.

47. Liu T, Zhang J, Li K, Deng L, Wang H. Combination of an Autophagy Inducer and an Autophagy Inhibitor: A Smarter Strategy Emerging in Cancer Therapy. Vol. 11, Frontiers in Pharmacology. 2020.

48. Tasdemir E, Maiuri MC, Morselli E, Criollo A, D'Amelio M, Djavaheri-Mergny M, et al. A dual role of p53 in the control of autophagy. Autophagy. 2008;4(6).

49. Shi Y, Norberg E, Vakifahmetoglu-Norberg H. Mutant p53 as a Regulator and Target of Autophagy. Vol. 10, Frontiers in Oncology. 2021.

50. Menichini P, Monti P, Speciale A, Cutrona G, Matis S, Fais F, et al. Antitumor Effects of PRIMA-1 and PRIMA-1Met (APR246) in Hematological Malignancies: Still a Mutant P53-Dependent Affair? Cells. 2021 Jan 7;10(1):98.

51. Pandey A, Yadav P, Shukla S. Unfolding the role of autophagy in the cancer metabolism. Biochem Biophys Rep. 2021;28.

52. Zhao T, Ren H, Jia L, Chen J, Xin W, Yan F, et al. Inhibition of HIF-1α by PX-478 enhances the anti-tumor effect of gemcitabine by inducing immunogenic cell death in pancreatic ductal adenocarcinoma. Oncotarget. 2015 Feb 10;6(4):2250–62.

53. Maan M, Peters JM, Dutta M, Patterson AD. Lipid metabolism and lipophagy in cancer. Biochem Biophys Res Commun. 2018;504(3).

54. Villar VH, Merhi F, Djavaheri-Mergny M, Durán R V. Glutaminolysis and autophagy in cancer. Vol. 11, Autophagy. 2015.

55. Chang H, Zou Z. Targeting autophagy to overcome drug resistance: further developments. Vol. 13, Journal of Hematology and Oncology. 2020.

56. Li D, Peng X, He G, Liu J, Li X, Lin W, et al. Crosstalk between autophagy and CSCs: molecular mechanisms and translational implications. Vol. 14, Cell Death and Disease. 2023.

57. Jahangiri L, Ishola T, Pucci P, Trigg RM, Pereira J, Williams JA, et al. The role of autophagy and lncrnas in the maintenance of cancer stem cells. Vol. 13, Cancers. 2021.

58. Nazio F, Bordi M, Cianfanelli V, Locatelli F, Cecconi F. Autophagy and cancer stem cells: molecular mechanisms and therapeutic applications. Vol. 26, Cell Death and Differentiation. 2019.

59. Strippoli R, Niayesh-Mehr R, Adelipour M, Khosravi A, Cordani M, Zarrabi A, et al. Contribution of Autophagy to Epithelial Mesenchymal Transition Induction during Cancer Progression. Vol. 16, Cancers. 2024.

60. Gundamaraju R, Lu W, Paul MK, Jha NK, Gupta PK, Ojha S, et al. Autophagy and EMT in cancer and metastasis: Who controls whom? Biochim Biophys Acta Mol Basis Dis. 2022;1868(9).

61. Leone K, Poggiana C, Zamarchi R. The interplay between circulating tumor cells and the immune system: From immune escape to cancer immunotherapy. Vol. 8, Diagnostics. 2018.

62. Agalakova NI. Chloroquine and Chemotherapeutic Compounds in

Experimental Cancer Treatment. Vol. 25, International Journal of Molecular Sciences. 2024.

63. Schiliro C, Firestein BL. Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation. Vol. 10, Cells. 2021.

64. Rascio F, Spadaccino F, Rocchetti MT, Castellano G, Stallone G, Netti GS, et al. The pathogenic role of PI3K/AKT pathway in cancer onset and drug resistance: an updated review. Vol. 13, Cancers. 2021.

65. Rahman MA, Park MN, Rahman MH, Rashid MM, Islam R, Uddin MJ, et al. p53 Modulation of Autophagy Signaling in Cancer Therapies: Perspectives Mechanism and Therapeutic Targets. Vol. 10, Frontiers in Cell and Developmental Biology. 2022.

66. Rosenfeldt MT, O'Prey J, Morton JP, Nixon C, Mackay G, Mrowinska A, et al. P53 status determines the role of autophagy in pancreatic tumour development. Nature. 2013;504(7479).

67. McKnight NC, Yue Z. Beclin 1, an Essential Component and Master Regulator of PI3K-III in Health and Disease. Curr Pathobiol Rep. 2013;1(4).

68. Hu YJ, Zhong JT, Gong L, Zhang SC, Zhou SH. Autophagy-related beclin 1 and head and neck cancers. Vol. 13, OncoTargets and Therapy. 2020.

69. Pattingre S, Tassa A, Qu X, Garuti R, Xiao HL, Mizushima N, et al. Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. Cell. 2005;122(6).

70. Zamani M, Sadeghi E, Mokarram P, Kadkhodaei B, Ghasemi H. Autophagy related proteins as potential biomarkers in predicting cancer prognosis after chemoradiotherapy: systematic review and meta-analysis. Int J Radiat Biol. 2025 Mar 4;101(3):232–9.

71. Tanida I, Ueno T, Kominami E. LC3 and Autophagy. In 2008. p. 77–88.

72. Kumar A V., Mills J, Lapierre LR. Selective Autophagy Receptor p62/SQSTM1, a Pivotal Player in Stress and Aging. Vol. 10, Frontiers in Cell and Developmental Biology. 2022.

73. Kang R, Zeh HJ, Lotze MT, Tang D. The Beclin 1 network regulates autophagy and apoptosis. Vol. 18, Cell Death and Differentiation. 2011.

74. Bortnik S, Gorski SM. Clinical applications of autophagy proteins in cancer: From potential targets to biomarkers. Vol. 18, International Journal of Molecular Sciences. 2017.

75. Jiang P, Mizushima N. LC3- and p62-based biochemical methods for the analysis of autophagy progression in mammalian cells. Methods. 2015;75.

76. Rajendran P, Renu K, Ali EM, Genena MAM, Veeraraghavan V, Sekar R, et al. Promising and challenging phytochemicals targeting LC3 mediated autophagy signaling in cancer therapy. Immun Inflamm Dis. 2024 Oct 22;12(10).

77. Park JM, Huang S, Wu TT, Foster NR, Sinicrope FA. Prognostic impact of Beclin 1, p62/sequestosome 1 and LC3 protein expression in colon carcinomas from patients receiving 5-fluorouracil as adjuvant chemotherapy. Cancer Biol Ther. 2013;14(2).

78. Li W, Saud SM, Young MR, Chen G, Hua B. Targeting AMPK for cancer prevention and treatment. Vol. 6, Oncotarget. 2015.

79. Wyrsch P, Blenn C, Bader J, Althaus FR. Cell Death and Autophagy under Oxidative Stress: Roles of Poly(ADP-Ribose) Polymerases and Ca 2+ . Mol Cell Biol. 2012;32(17).

80. Velasco G, Verfaillie T, Salazar M, Agostinis P. Linking ER stress to autophagy: Potential implications for cancer therapy. International Journal of Cell Biology. 2010.

81. Xia H, Green DR, Zou W. Autophagy in tumour immunity and therapy. Vol. 21, Nature Reviews Cancer. 2021.

82. Anderson NM, Simon MC. The tumor microenvironment. Vol. 30, Current Biology. 2020.

83. Toledo B, Zhu Chen L, Paniagua-Sancho M, Marchal JA, Perán M, Giovannetti E. Deciphering the performance of macrophages in tumour microenvironment: a call for precision immunotherapy. J Hematol Oncol. 2024 Jun 11;17(1):44.

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1251

84. Keerthana CK, Rayginia TP, Shifana SC, Anto NP, Kalimuthu K, Isakov N, et al. The role of AMPK in cancer metabolism and its impact on the immunomodulation of the tumor microenvironment. Vol. 14, Frontiers in Immunology. 2023.

85. Hill RM, Fok M, Grundy G, Parsons JL, Rocha S. The role of autophagy in hypoxia-induced radioresistance. Vol. 189, Radiotherapy and Oncology. 2023.

86. Taucher E, Mykoliuk I, Fediuk M, Smolle-Juettner FM. Autophagy, Oxidative Stress and Cancer Development. Vol. 14, Cancers. 2022.

87. Xu J, Patel NH, Gewirtz DA. Triangular relationship between p53, autophagy, and chemotherapy resistance. Int J Mol Sci. 2020;21(23).

88. Ahmadi-Dehlaghi F, Mohammadi P, Valipour E, Pournaghi P, Kiani S, Mansouri K. Autophagy: A challengeable paradox in cancer treatment. Vol. 12, Cancer Medicine. 2023.

89. Hasan A, Rizvi SF, Parveen S, Pathak N, Nazir A, Mir SS. Crosstalk Between ROS and Autophagy in Tumorigenesis: Understanding the Multifaceted Paradox. Vol. 12, Frontiers in Oncology. 2022.

90. Roy A, Bera S, Saso L, Dwarakanath BS. Role of autophagy in tumor response to radiation: Implications for improving radiotherapy. Vol. 12, Frontiers in Oncology. 2022.

91. Vara-Perez M, Felipe-Abrio B, Agostinis P. Mitophagy in cancer: A tale of adaptation. Vol. 8, Cells. 2019.

92. Tian Y, Song W, Li D, Cai L, Zhao Y. Resveratrol as a natural regulator of autophagy for prevention and treatment of cancer. Vol. 12, OncoTargets and Therapy. 2019.

93. Saleh T, As Sobeai HM, Alhoshani A, Alhazzani K, Almutairi MM, Alotaibi M. Effect of Autophagy Inhibitors on Radiosensitivity in DNA Repair-Proficient and -Deficient Glioma Cells. Medicina (Lithuania). 2022;58(7).

94. Shan C, Wang Y, Wang Y. The Crosstalk between Autophagy and Nrf2 Signaling in Cancer: from Biology to Clinical Applications. Int J Biol Sci. 2024 Nov 11;20(15):6181–206.

95. Fang S, Wan X, Zou X, Sun S, Hao X, Liang C, et al. Arsenic trioxide induces macrophage autophagy and atheroprotection by regulating ROS-dependent TFEB nuclear translocation and AKT/mTOR pathway. Cell Death Dis. 2021;12(1).

96. Mai S, Muster B, Bereiter-Hahn J, Jendrach M. Autophagy proteins LC3B, ATG5 and ATG12 participate in quality control after mitochondrial damage and influence lifespan. Autophagy. 2012 Jan 27;8(1):47–62.

97. Cook KL, Shajahan AN, Clarke R. Autophagy and endocrine resistance in breast cancer. Vol. 11, Expert Review of Anticancer Therapy. 2011.

98. Silva VR, Neves SP, Santos L de S, Dias RB, Bezerra DP. Challenges and therapeutic opportunities of autophagy in cancer therapy. Vol. 12, Cancers. 2020.

99. Tanida I, Ueno T, Kominami E. LC3 conjugation system in mammalian autophagy. Vol. 36, International Journal of Biochemistry and Cell Biology. 2004.

100. Cao Z, Tian K, Ran Y, Zhou H, Zhou L, Ding Y, et al. Beclin-1: a therapeutic target at the intersection of autophagy, immunotherapy, and cancer treatment. Front Immunol. 2024 Nov 22;15.

101. Wechman SL, Pradhan AK, DeSalle R, Das SK, Emdad L, Sarkar D, et al. New Insights Into Beclin-1: Evolution and Pan-Malignancy Inhibitor Activity. In: Advances in Cancer Research. 2018.

102. Cheng XT, Xie YX, Zhou B, Huang N, Farfel-Becker T, Sheng ZH. Revisiting LAMP1 as a marker for degradative autophagy-lysosomal organelles in the nervous system. Vol. 14, Autophagy. 2018.

103. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema KJ, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy. 2018;14(8).

104. Sahani MH, Itakura E, Mizushima N. Expression of the autophagy substrate SQSTM1/p62 is restored during prolonged starvation depending on transcriptional upregulation and autophagy-derived

amino acids. Autophagy. 2014;10(3).

105. Wang L, Bi RR, Li L, Zhou K, Liu HL. Functional characteristics of autophagy in pancreatic cancer induced by glutamate metabolism in pancreatic stellate cells. Journal of International Medical Research. 2019;48(4).

106. Ngo V, Duennwald ML. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. Vol. 11, Antioxidants. 2022.

107. Li B, Wang W, Li Z, Chen Z, Zhi X, Xu J, et al. MicroRNA-148a-3p enhances cisplatin cytotoxicity in gastric cancer through mitochondrial fission induction and cyto-protective autophagy suppression. Cancer Lett. 2017;410.

108. Wei J, Wang X, Yu D, Tu Y, Yu Y. MicroRNA-mediated autophagy and drug resistance in cancer: mechanisms and therapeutic strategies. Discover Oncology. 2024 Nov 16;15(1):662.

109. Levine B, Kroemer G. Biological Functions of Autophagy Genes: A Disease Perspective. Vol. 176, Cell. 2019.

110. Tavakol S, Ashrafizadeh M, Deng S, Azarian M, Abdoli A, Motavaf M, et al. Autophagy modulators: Mechanistic aspects and drug delivery systems. Vol. 9, Biomolecules. 2019.

111. Li Y, Cao F, Li M, Li P, Yu Y, Xiang L, et al. Hydroxychloroquine induced lung cancer suppression by enhancing chemo-sensitization and promoting the transition of M2-TAMs to M1-like macrophages. Journal of Experimental and Clinical Cancer Research. 2018;37(1).

112. Boone BA, Bahary N, Zureikat AH, Moser AJ, Normolle DP, Wu WC, et al. Safety and Biologic Response of Pre-operative Autophagy Inhibition in Combination with Gemcitabine in Patients with Pancreatic Adenocarcinoma. Ann Surg Oncol. 2015;22(13).

113. Elshazly AM, Gewirtz DA. Is Autophagy Inhibition in Combination with Temozolomide a Therapeutically Viable Strategy? Vol. 12, Cells. 2023.

114. Lo Iacono M, Gaggianesi M, Bianca P, Brancato OR, Muratore G, Modica C, et al. Destroying the Shield of Cancer Stem Cells: Natural Compounds as Promising Players in Cancer Therapy. Vol. 11, Journal of Clinical Medicine. 2022.

115. Verbaanderd C, Maes H, Schaaf MB, Sukhatme VP, Pantziarka P, Sukhatme V, et al. Repurposing drugs in oncology (ReDO) - Chloroquine and hydroxychloroquine as anti-cancer agents. Ecancermedicalscience. 2017;11.

116. Amaravadi RK, Winkler JD. Lys05: A new lysosomal autophagy inhibitor. Vol. 8, Autophagy. 2012.

117. Pal SK, Quinn DI. Differentiating mTOR inhibitors in renal cell carcinoma. Vol. 39, Cancer Treatment Reviews. 2013.

118. Dai ZJ, Gao J, Kang HF, Ma YG, Ma X Bin, Lu WF, et al. Targeted inhibition of mammalian target of rapamycin (mTOR) enhances radiosensitivity in pancreatic carcinoma cells. Drug Des Devel Ther. 2013;7.

119. Massihnia D, Galvano A, Fanale D, Perez A, Castiglia M, Incorvaia L, et al. Triple negative breast cancer: Shedding light onto the role of pi3k/akt/mtor pathway. Vol. 7, Oncotarget. 2016.

120. Satta T, Li L, Chalasani SL, Hu X, Nkwocha J, Sharma K, et al. Dual mTORC1/2 Inhibition Synergistically Enhances AML Cell Death in Combination with the BCL2 Antagonist Venetoclax. Clinical Cancer Research. 2023;29(7).

121. Escamilla-Ramírez A, Castillo-Rodríguez RA, Zavala-Vega S, Jimenez-Farfan D, Anaya-Rubio I, Briseño E, et al. Autophagy as a potential therapy for malignant glioma. Vol. 13, Pharmaceuticals. 2020.

122. Maycotte P, Aryal S, Cummings CT, Thorburn J, Morgan MJ, Thorburn A. Chloroquine sensitizes breast cancer cells to chemotherapy independent of autophagy. Autophagy. 2012;8(2).

123. Karasic TB, O'Hara MH, Loaiza-Bonilla A, Reiss KA, Teitelbaum UR, Borazanci E, et al. Effect of Gemcitabine and nab-Paclitaxel with or Without Hydroxychloroquine on Patients with Advanced Pancreatic Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019;5(7).

124. Golden EB, Cho HY, Jahanian A, Hofman FM, Louie SG, Schönthal AH, et al. Chloroquine enhances temozolomide cytotoxicity in

Advances in Medical, Pharmaceutical and Dental Research Journal (AMPDR)- ISSN 2812-4898
http://dx.doi.org/10.21622/AMPDR.2025.05.1.1251

malignant gliomas by blocking autophagy. Neurosurg Focus. 2014;37(6).

125. Cao C, Subhawong T, Albert JM, Kim KW, Geng L, Sekhar KR, et al. Inhibition of mammalian target of rapamycin or apoptotic pathway induces autophagy and radiosensitizes PTEN null prostate cancer cells. Cancer Res. 2006;66(20).

126. Imrali A, Mao X, Yeste-Velasco M, Shamash J, Lu Y. Rapamycin inhibits prostate cancer cell growth through cyclin D1 and enhances the cytotoxic efficacy of cisplatin. Am J Cancer Res. 2016;6(8).

127. Wong SW, Tiong KH, Kong WY, Yue YC, Chua CH, Lim JY, et al. Rapamycin synergizes cisplatin sensitivity in basal-like breast cancer cells through up-regulation of p73. Breast Cancer Res Treat. 2011;128(2).

128. Zhou M, Luo C, Zhou Z, Li L, Huang Y. Improving anti-PD-L1 therapy in triple negative breast cancer by polymer-enhanced immunogenic cell death and CXCR4 blockade. Journal of Controlled Release. 2021;334.

129. Alissafi T, Hatzioannou A, Mintzas K, Barouni RM, Banos A, Sormendi S, et al. Autophagy orchestrates the regulatory program of tumor-associated myeloid-derived suppressor cells. Journal of Clinical Investigation. 2018;128(9).

130. Gewirtz DA. The challenge of developing autophagy inhibition as a therapeutic strategy. Cancer Res. 2016;76(19).

131. Troumpoukis D, Papadimitropoulou A, Charalampous C, Kogionou P, Palamaris K, Sarantis P, et al. Targeting autophagy in pancreatic cancer: The cancer stem cell perspective. Vol. 12, Frontiers in Oncology. 2022.

132. Zhou N, Liu Q, Wang X, He L, Zhang T, Zhou H, et al. The combination of hydroxychloroquine and 2-deoxyglucose enhances apoptosis in breast cancer cells by blocking protective autophagy and sustaining endoplasmic reticulum stress. Cell Death Discov. 2022;8(1).

133. Zhao W, Chen C, Zhou J, Chen X, Cai K, Shen M, et al. Inhibition of Autophagy Promotes the Anti-Tumor Effect of Metformin in Oral Squamous Cell Carcinoma. Cancers (Basel). 2022;14(17).

134. Fang J, Rhyasen G, Bolanos L, Rasch C, Varney M, Wunderlich M, et al. Cytotoxic effects of bortezomib in myelodysplastic syndrome/acute myeloid leukemia depend on autophagy-mediated lysosomal degradation of TRAF6 and repression of PSMA 1. Blood. 2012;120(4).

135. Song H, Zhao Z, Ma L, Zhao W, Hu Y, Song Y. Novel exosomal circEGFR facilitates triple negative breast cancer autophagy via promoting TFEB nuclear trafficking and modulating miR-224-5p/ATG13/ULK1 feedback loop. Oncogene. 2024;43(11).

136. Schläfli AM, Adams O, Galván JA, Gugger M, Savic S, Bubendorf L, et al. Prognostic value of the autophagy markers LC3 and p62/SQSTM1 in early-stage non-small cell lung cancer. Oncotarget. 2016;7(26).

137. Fu W, Wu G. Targeting mTOR for Anti-Aging and Anti-Cancer Therapy. Vol. 28, Molecules. 2023.

138. Theodorakis N, Feretzakis G, Tzelves L, Paxinou E, Hitas C, Vamvakou G, et al. Integrating Machine Learning with Multi-Omics Technologies in Geroscience: Towards Personalized Medicine. J Pers Med. 2024 Aug 31;14(9):931.

139. Sun F, Zhang L, Tong Z. Application progress of artificial intelligence in tumor diagnosis and treatment. Front Artif Intell. 2025 Jan 7;7.

140. Chude CI, Amaravadi RK. Targeting autophagy in cancer: Update on clinical trials and novel inhibitors. Vol. 18, International Journal of Molecular Sciences. 2017.