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Review

The Dual Role of Autophagy in Lung Cancer: From Molecular Mechanisms to Metabolic Regulation and Targeted Therapy Strategies

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Abstract

Lung cancer remains the leading cause of cancer-related mortality worldwide, with five-year survival rates below 20%, underscoring the importance of understanding key biological processes like autophagy in this disease. Autophagy, a lysosome-mediated degradation and recycling pathway, exerts context-dependent effects in lung cancer, functioning as both a tumor suppressor and a facilitator of tumor progression. On one hand, basal autophagy maintains cellular homeostasis and genomic integrity, thereby curbing malignant transformation. On the other hand, established lung cancer cells exploit autophagy to survive under metabolic stress, hypoxia, and therapeutic pressure (for example, during chemotherapy or targeted therapy), facilitating tumor growth, metastasis, and therapy resistance. This review synthesizes current insights into the molecular mechanisms of autophagy in lung cancer, detailing how core regulatory pathways—including the phosphoinositide 3 kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling axis, the liver kinase B1-AMP-activated protein kinase (LKB1–AMPK) energy-sensing pathway, and key autophagy-related genes such as *Beclin 1* and autophagy related gene (ATG) proteins—intertwine with oncogenic signaling networks and cell death regulators (e.g., p53, Bcl-2). It also highlights the metabolic dimension of autophagy, illustrating how nutrient recycling and maintenance of mitochondrial function via autophagy enhance the metabolic plasticity and survival of lung tumors under stress. In addition, we critically appraise clinical attempts to modulate autophagy (e.g., with chloroquine/hydroxychloroquine (CQ/HCQ) or mTOR inhibitors), outlining reasons for mixed outcomes and proposing practical solutions for future trials. Finally, potential targeted therapeutic strategies are discussed, including approaches to inhibit cytoprotective autophagy and strategies to induce autophagy-dependent cell death using novel small-molecule activators. Collectively, the evidence supports a model in which precise, context-aware modulation of autophagy—guided by pharmacodynamic (PD) biomarkers and molecular stratification—will be key to improving outcomes in lung cancer.

Keywords: autophagy; lung neoplasms; metabolic networks and pathways; molecular targeted therapy; molecular mechanisms of action

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases. Despite significant advances in targeted therapies and immunotherapies, drug resistance and tumor relapse continue to pose major clinical challenges. Autophagy, a critical cellular homeostatic mechanism for responding to environmental stress, plays a complex and pivotal role in the initiation, progression, and treatment of lung cancer. Autophagy exhibits a "double-edged sword" behavior in tumors: on one hand, it maintains tumor cell homeostasis and promotes survival; on the other, excessive autophagy can lead to "autophagy-dependent cell death". Recent studies have revealed that oncogenic driver mutations (such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements) can rewire autophagy networks, and the autophagy status of cancer cells in turn influences their therapeutic sensitivity. Consequently, precise modulation of autophagy has emerged as a promising new strategy in lung cancer therapy. This review provides a comprehensive overview of the latest research on autophagy in lung cancer, focusing on its molecular regulatory networks, role in metabolic reprogramming, and interactions with targeted therapies. We discuss the dual (tumor-suppressive and tumor-promoting) roles of autophagy at different stages of lung cancer, delve into the interplay between autophagy and metabolic abnormalities (such as lipid and purine metabolism), explore novel therapeutic strategies targeting key autophagy nodes (e.g., the homeobox containing 1 (HMBOX1)–HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1 (HACE1)–autophagy related 5 (ATG5) axis, progestin and AdipoQ receptor family member 3 (PAQR3), small nucleolar RNA C/D box 88C (SNORD88C)), and evaluate the prospects of combining autophagy modulators with conventional chemotherapy, radiotherapy, and immunotherapy. This review aims to provide a systematic perspective on the multifaceted biological functions of autophagy in lung cancer and to offer a theoretical basis for developing innovative autophagy-based therapeutic strategies.

2. Molecular Mechanisms of Autophagy and Its Dual Role in Lung Cancer

2.1 Core Molecular Mechanism of Autophagy

Autophagy is orchestrated by a series of autophagy-related genes (ATGs) that encode protein complexes acting in concert. The autophagy process can be divided into several key stages: (i) induction or initiation; (ii) cargo selection; (iii) phagophore nucleation; (iv) phagophore membrane elongation and expansion; (v) retrieval and fusion with lysosomes; and (vi) degradation of intravesicular contents. Blocking autophagy at different stages may result in distinct biological effects and outcomes [1]. Adenosine triphosphate (ATP)/adenosine monophosphate (AMP) imbalance is one important trigger of autophagy [2]. The Unc-51-like kinase 1 (ULK1) complex is essential for autophagy initiation. ULK1 activity is finely regulated by upstream signals such as AMP-activated protein kinase (AMPK) [3] and by inhibitory signaling through the mechanistic target of rapamycin complex 1 (mTORC1) [4]. Downstream of the ULK1 complex, the coiled-coil myosin-like BCL2-interacting protein (*Beclin 1*) complex generates phosphatidylinositol-3-phosphate (PI3P), which facilitates the recruitment of other ATG proteins [5]. The nucleation stage of autophagosome formation involves interactions among *Beclin 1*-PI3KC3 (class III PI3K complex), Rubicon, Ambra1, and other factors [6]. Subsequent membrane elongation and closure depend on two ubiquitin-like conjugation systems: the ATG12–ATG5 conjugation system and the ATG8 conjugation system. The latter mediates the lipidation of ATG8 family members, including microtubule-associated protein 1 light chain 3 (LC3) [7]. LC3 serves as a structural component on the membranes of phagophores and autophagosomes [8], and it exists in three isoforms (LC3A, LC3B, and LC3C). Because LC3 is typically incorporated into both the inner and outer membranes of autophagosomes [9], it is widely used as a marker for monitoring autophagy [10].

2.2 Autophagy in Lung Cancer: Core Mechanisms

In NSCLC, dysregulation of mTORC1—a master nutrient and growth regulator—features prominently and intersects with ULK1-driven initiation to shape autophagic flux in a mutation- and context-dependent manner (Fig. 1). Studies have shown that inhibitor of apoptosis-stimulating protein of p53 (iASPP) is overexpressed in human NSCLC, and knockout of iASPP can block autophagosome formation via inhibition of the mTORC1-p70 ribosomal S6 kinase (p70S6K) signaling pathway, thereby impairing autophagy. Conversely, iASPP overexpression induces autophagic flux and promotes NSCLC cell growth and tumorigenesis. Circular RNAs (circRNAs) with 5-methylcytosine (m5C) modifications have been reported to suppress autophagy through the stratifin (SFN)/mTOR/ULK1 pathway, ultimately promoting lung cancer progression [11]. A newly identified regulatory pathway, the argonaute-4 (AGO4)–tripartite motif-containing protein 21 (TRIM21)–78-kDa glucose-regulated protein (GRP78) axis, induces apoptosis and inhibits autophagy by activating the mTOR signaling pathway, representing a potential therapeutic target for treating p53-deficient tumors [12]. Ubiquitin-conjugating enzyme E2T (UBE2T) has been shown to upregulate autophagy in NSCLC cells via activation of the p53/AMPK/mTOR signaling pathway [13]. Fas apoptosis inhibitory molecule 1 (FAIM1) can promote the binding of ULK1 to mTOR, which in turn suppresses autophagy induction [14].

Alterations in *Beclin 1*, a core autophagy gene, are associated with lung cancer prognosis. Low expression of *Beclin 1* has been linked to poor outcomes through diverse mechanisms. Ubiquitin-specific proteases (USPs) can promote NSCLC progression by deubiquitinating and stabilizing oncogenic target proteins [15]. For example, kirsten rat sarcoma viral oncogene homolog (KRAS) signaling increases reactive oxygen species (ROS) production, leading to the dimerization and stabilization of USP5. Activated USP5 deubiquitinates and stabilizes *Beclin 1*, which enhances autophagy and concurrently promotes the degradation of tumor suppressor p53. Inhibition of USP5 or *Beclin 1* suppresses autophagy and effectively blocks KRAS-driven NSCLC growth [16]. Similarly, disruption of Toll-like receptor 4 (TLR4)-induced TRAF6–*Beclin 1* signaling can suppress autophagy, resulting in reduced cancer cell migration and invasion [17]. USP15 is significantly downregulated in primary NSCLC (especially lung adenocarcinoma), and its expression is inversely correlated with disease progression. Mechanistically, USP15 positively regulates autophagy induction through the TRAF6–*Beclin 1* signaling axis, thereby acting as a negative regulator of lung cancer progression [18]. Aberrant RNA splicing has also been implicated in autophagy regulation in lung cancer. Splicing factor serine/arginine-rich splicing factor 6 (SRSF6) is frequently amplified in lung cancer and modulates the splicing of transcripts involved in cancer progression [19]. Likewise, depletion of another splicing factor, SRSF1, has been found to activate autophagy. Mechanistically, SRSF1 promotes the splicing of Bcl-x to produce the long isoform Bcl-xL, which can bind *Beclin 1* and inhibit autophagy; reduction of SRSF1 leads to increased production of the short isoform Bcl-xS, relieving this inhibition and thereby inducing autophagy. Tripartite motif-containing protein 59 (TRIM59) has been identified as a potential oncogene in NSCLC [20]. TRIM59 expression is negatively correlated with *Beclin 1* levels, and TRIM59 knockdown significantly elevates basal autophagy in NSCLC cells. TRIM59 appears to regulate autophagy by downregulating the NF-κB pathway, thereby reducing BECN1 (*Beclin 1* gene) transcription. An E3 ubiquitin ligase known as glycogenin-interacting protein 1 (GXRNIP1 also referred to as GNIP1) is overexpressed in lung tumor

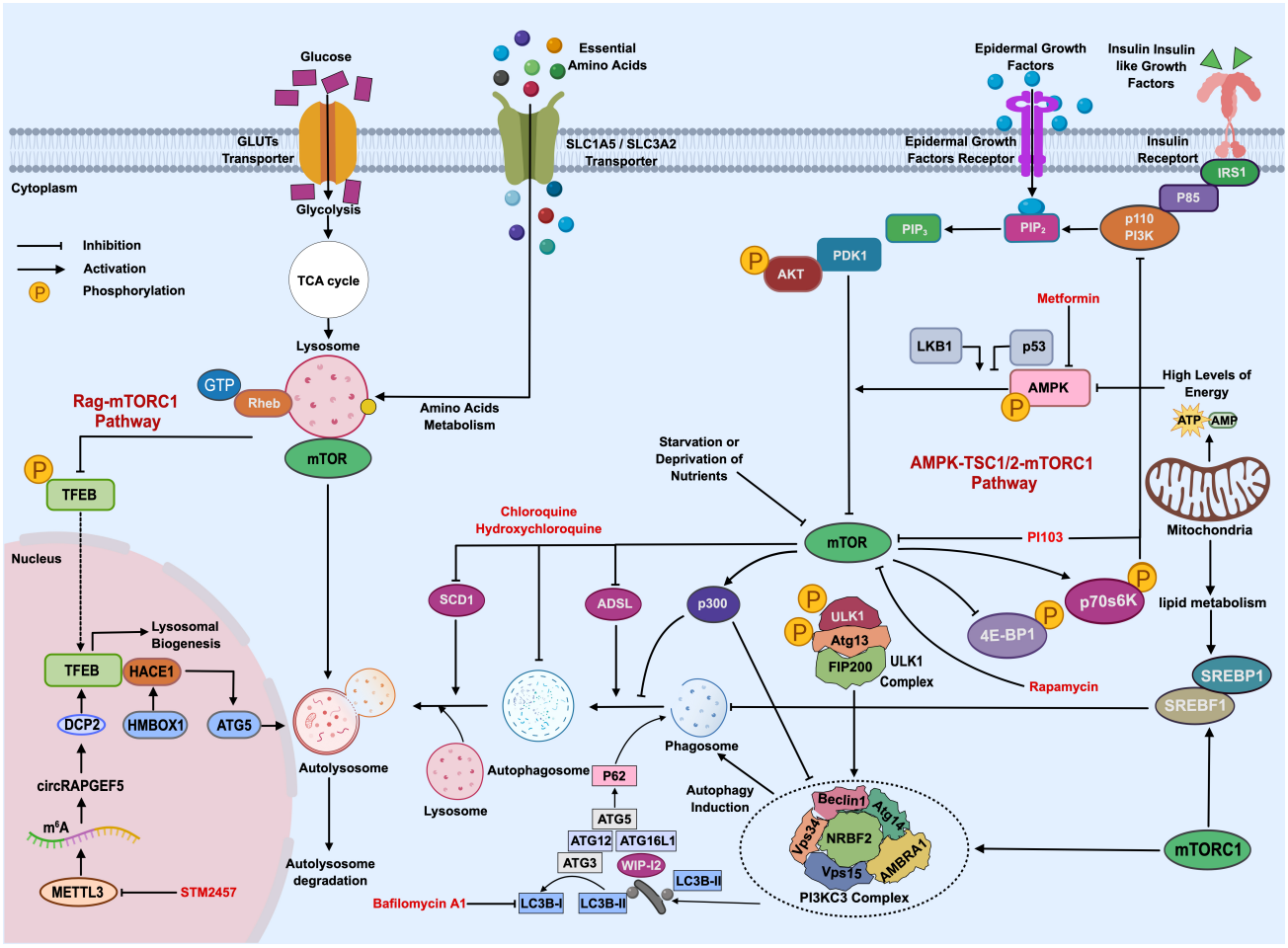

Fig. 1. Integrated signaling and metabolic regulation of autophagy in lung cancer. The figure illustrates key molecular pathways that regulate autophagy in lung cancer cells, emphasizing the central role of mTORC1 as an integration hub for nutrient, growth factor, and metabolic signals. 4E-BP1, Eukaryotic translation initiation factor 4E-binding protein 1; ADSL, Adenylosuccinate lyase; AKT, Protein kinase B; AMBRA1, Activating molecule in *Beclin-1*-regulated autophagy 1; AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, Adenosine triphosphate; ATG3, Autophagy related 3; ATG5, Autophagy related 5; ATG12, Autophagy related 12; ATG16L1, Autophagy related 16 like 1; Atg13, Autophagy related 13; circRAPGEF5, Circular RNA derived from *RAPGEF5*; DCP2, mRNA-decapping enzyme 2; FIP200, FAK family-interacting protein of 200 kDa (RB1CC1); GLUTs, Glucose transporters (GLUT/SLC2A family); GTP, Guanosine triphosphate; HACE1, HECT and ankyrin repeat containing E3 ubiquitin protein ligase 1; HMBOX1, Homeobox containing 1; IRS1, Insulin receptor substrate 1; LKB1, Liver kinase B1 (STK11); LC3B-I, Microtubule-associated protein 1 light chain 3 beta, non-lipidated form; LC3B-II, Microtubule-associated protein 1 light chain 3 beta, lipidated form; m6A, N6-methyladenosine; METTL3, Methyltransferase-like 3; mTOR, Mechanistic target of rapamycin; mTORC1, Mechanistic target of rapamycin complex 1; NRBF2, Nuclear receptor binding factor 2; p53, Tumor protein p53; p62, Sequestosome-1 (SQSTM1); p70S6K, 70-kDa ribosomal protein S6 kinase; p300, Histone acetyltransferase p300 (EP300); PDK1, 3-Phosphoinositide-dependent protein kinase-1; PI3K, Phosphoinositide 3-kinase; PI3KC3, Class III phosphatidylinositol 3-kinase complex (PIK3C3/Vps34 complex); PI103, PI-103 (PI3K/mTOR inhibitor); PIP2, Phosphatidylinositol (4,5)-bisphosphate; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; Rag, Rag GTPases (RRAGA/B and RRAGC/D); Rheb, Ras homolog enriched in brain (small GTPase); SCD1, Stearoyl-CoA desaturase 1; SLC1A5, Solute carrier family 1 member 5 (ASCT2); SLC3A2, Solute carrier family 3 member 2; SREBF1, Sterol regulatory element-binding transcription factor 1 (gene encoding SREBP1); SREBP1, Sterol regulatory element-binding protein 1; TCA, Tricarboxylic acid cycle; TFEB, Transcription factor EB; TSC1/2, Tuberous sclerosis complex 1/2; ULK1, Unc-51-like autophagy activating kinase 1; Vps15, Phosphoinositide 3-kinase regulatory subunit type 4 (PIK3R4); Vps34, Class III phosphatidylinositol 3-kinase (PIK3C3); WIPI2, WD repeat domain phosphoinositide-interacting protein 2.The dashed arrow represents transmembrane regulation, and the solid arrow represents direct regulation.

tissues, and higher GNIP1 levels are associated with poor prognosis in NSCLC patients. In NSCLC cells, GNIP1 facilitates the recruitment of *Beclin 1* and LC3B to form autophagosomes, promoting cancer cell proliferation and migration [21–23].

SOX2, a transcription factor, is highly expressed in lung cancer cells and exhibits oncogenic properties, contributing to tumorigenesis and therapy resistance [24]. There is evidence of crosstalk between autophagy and SOX2 signaling. Specifically, downregulation of LC3A (one of the LC3 isoforms) can inhibit lung cancer cell growth; the interaction between LC3A-mediated autophagy and SOX2 proliferative signaling suggests that autophagy may enhance SOX2-driven proliferation in lung cancer cells [25].

2.3 Dual Roles of Core Autophagy Mechanisms in Lung Cancer

Autophagy exerts both tumor-suppressive and tumor-promoting effects in lung cancer, depending on the stage of cancer development. In the early stages of lung tumorigenesis, autophagy predominantly acts as a tumor suppressor through several mechanisms: maintaining genomic stability by removing damaged organelles and proteins, promoting programmed cell death (including autophagy-dependent cell death and apoptosis) in aberrant cells, and participating in immune surveillance to eliminate nascent tumor cells. Thus, during early cancer development, inhibition of autophagy may unintentionally accelerate tumor growth. By contrast, at later stages of cancer, tumor cells often hijack autophagy to support survival, thereby overriding its tumor-suppressive effects. This stage-dependent switch means that blocking core autophagy regulators could have opposite effects at different times: potentially promoting tumorigenesis if applied too early, but impairing tumor cell viability in established cancers.

Early in tumorigenesis, autophagy mainly preserves genome and organelle integrity; once malignancy is established, the same machinery becomes a survival toolkit under hypoxia and therapy stress. The complex effect of autophagy on tumor dynamics is exemplified by studies on ATG7, a key autophagy gene. Deletion of Atg7 in mouse models initially accelerated lung tumor development, but at later stages it inhibited further tumor progression [26]. One proposed mechanism for this phenomenon is that Atg7-deficient tumor cells are unable to efficiently remove dysfunctional mitochondria, leading to excessive ROS accumulation. Elevated ROS can promote tumor initiation by increasing DNA damage and mutations, but persistent oxidative stress and damage in established tumors may eventually limit growth or viability of cancer cells [27]. The tumor suppressor p53 has also been shown to regulate autophagy in multiple ways. Notably, p53's effect on autophagy depends on its subcellular localization. Nuclear p53 can activate autophagy by transcriptionally upregulating autophagy-related genes (such as the Sestrin family), and cellular stress that stabilizes p53 often leads to the activation of genes that promote autophagy [28]. In contrast, cytoplasmic p53 can inhibit autophagy, in part through its effects on AMPK and mTOR signaling [29]. In lung cancer stem cells, autophagy has been reported to enhance stemness by degrading ubiquitinated p53, thereby alleviating the autophagy-inhibitory effect of cytosolic p53 [30]. Sestrin2, a conserved oxidative stress sensor and metabolic regulator downstream of p53, can strongly suppress oncogenic pathways by downregulating mTORC1 and hypoxia-inducible factor 1α (HIF-1α), linking p53 activity to metabolic control of tumor growth [31,32].

Autophagy also plays a role in anti-tumor immune responses. It can promote the presentation of tumor antigens and thus enhance both innate and adaptive immune surveillance of cancer cells. Immune checkpoint inhibitors have become a first-line immunotherapy for programmed cell death ligand 1 (PD-L1)-positive non-squamous NSCLC patients, highlighting the importance of immune evasion mechanisms in lung cancer therapy [33,34]. Intriguingly, autophagy has been found to regulate the expression and turnover of immune checkpoints such as PD-1 and its ligand PD-L1 [35]. The selective autophagy adaptor protein p62/SQSTM1 serves as an immunomodulator; p62-mediated selective autophagy can potentiate innate immune responses by modulating signaling pathways. In NSCLC, p62 accumulation has been shown to regulate PD-L1 levels by binding directly to PD-L1 and targeting it for lysosomal degradation, thereby potentially enhancing the anti-tumor immune response [36]. Natural killer (NK) cells are critical effectors in tumor immunosurveillance [37]. It has been demonstrated that chemokines like CXCL10 play a vital role in directing NK cell homing and infiltration into solid tumors and in enhancing their cytotoxic efficacy [38]. This suggests that inducing tumor cells to secrete chemoattractants such as CXCL10 and CCL5 via autophagy-related pathways could be an effective strategy to recruit NK cells and boost anti-tumor immunity.

As lung cancer progresses to advanced stages, the functional role of autophagy often shifts from tumor suppression to tumor promotion. Within the nutrient- and oxygen-deprived tumor microenvironment, autophagy becomes a survival mechanism, providing energy and metabolic substrates through the lysosomal degradation of cellular components. Loss-of-function mutations in tumor suppressors that normally restrain autophagy can thus confer a growth advantage to tumors. For instance, inactivating mutations of TP53 are among the most common genetic alterations in NSCLC [39]. TP53 loss leads to the indirect activation of multiple compensatory pathways that support tumor progression, many of which involve upregulation of autophagy. One such pathway is the liver kinase B1-AMP-activated protein kinase (LKB1–AMPK) signaling cascade, which, when activated, promotes tumor growth by enhanc-

ing autophagy-dependent metabolism [40]. Notably, approximately 50% of KRAS-mutant NSCLCs occur in the context of concurrent LKB1 loss-of-function mutations (the so-called "KL" genotype) [41]. LKB1 loss has been shown to induce the transcription of NEDD9, a scaffolding protein implicated in metastasis and autophagy regulation [42]. Recent findings indicate that in NSCLC cells deficient in LKB1 and NEDD9, there is a post-transcriptional induction of autophagy through the LKB1–AMPK signaling axis, which supports the survival of these aggressive cancer cells under metabolic stress [43].

The ubiquitin-conjugating enzyme E2C (UBE2C) is another factor linking autophagy to lung cancer progression. High UBE2C expression is associated with poor overall survival in lung cancer patients [44]. In cellular models, UBE2C overexpression leads to suppression of autophagy and is correlated with enhanced cell proliferation, survival, and malignant phenotype in lung cancer cells [45]. Mechanistically, UBE2C has been shown to target the mTOR pathway regulator DEP domain containing 6 (DEPTOR) for ubiquitination and degradation, in cooperation with the E-cadherin (CDH1) complex [46,47]. UBE2C forms a complex with CDH1 to promote DEPTOR ubiquitination; accordingly, knockdown of UBE2C causes accumulation of DEPTOR (stabilizing mTOR inhibition) and growth arrest, which can be largely reversed by co-knockdown of DEPTOR. Nuclear factor erythroid 2–related factor 2 (NRF2), a key transcription factor that upregulates a broad spectrum of antioxidant genes, is essential for KRAS-driven lung tumorigenesis, in part by mitigating oxidative stress. However, NRF2 hyperactivation can also lead to increased autophagy and has been linked to both autophagic and apoptotic cell death in NSCLC models [48].

Autophagy contributes to therapeutic resistance in lung cancer through multiple mechanisms. Hypoxic regions of the tumor stabilize HIF-1α, which in turn activates gene expression programs that drive cancer cell proliferation, migration, chemoresistance, and immune evasion [49]. For example, the long non-coding RNA plasmacytoma variant translocation 1 (PVT1) is highly expressed in lung tumors and cell lines, particularly under hypoxic conditions. PVT1 has been implicated in hypoxia-induced chemoresistance; HIF-1α directly upregulates PVT1, which then promotes autophagy via the PVT1/miR-551b/FGFR1 axis, leading to increased cell viability and reduced apoptosis in the presence of chemotherapy [50]. Another study found that HIF-1α interacts with eukaryotic initiation factor 5A2 (eIF5A2), resulting in its overexpression during hypoxia-induced autophagy and contributing to cisplatin resistance. Silencing eIF5A2 by RNA interference attenuated hypoxia-induced autophagy and resensitized NSCLC cells to cisplatin under hypoxic conditions [51]. Additionally, HIF-1α can cooperate with histone deacetylase 4 (HDAC4) to dysregulate the balance between apoptosis and autophagy through intersecting p53 and RAS signaling pathways, thereby actively driving cisplatin resistance [52].

A deep understanding of the stage-specific roles of autophagy in lung cancer is crucial for developing precise autophagy-targeted therapeutic strategies. In the following sections, we will explore the intricate interplay between autophagy and metabolic reprogramming in lung cancer, an area that has seen a series of groundbreaking advances in recent years.

3. Autophagy–Metabolic Crosstalk in Lung Cancer

There is a bidirectional regulatory relationship between autophagy and the metabolic abnormalities characteristic of lung cancer. This interplay is particularly pronounced in NSCLC and encompasses multiple metabolic axes, including lipid, purine, and glucose metabolism. Autophagy and metabolic reprogramming work together to enable tumor cells to thrive under unfavorable conditions, for example, by increasing glucose and glutamine uptake and upregulating *de novo* fatty acid synthesis to support rapid proliferation and metastasis [53]. Understanding this dynamic crosstalk provides new insights into lung cancer progression and therapeutic resistance.

3.1 Glucose and Bioenergetic Stress

Lung cancer cells exhibit profound metabolic reprogramming to meet the energy and biosynthetic demands of unchecked growth. Under conditions of nutrient starvation or hypoxia, glycolysis is often upregulated (the "Warburg effect"), and autophagy has been shown to support tumor cell survival and proliferation by sustaining aerobic glycolysis and fueling the tricarboxylic acid (TCA) cycle with recycled substrates [54]. For example, studies have demonstrated that autophagy promotes tumorigenesis in pancreatic cancer cells by maintaining glycolytic flux and cellular energy levels, while also preventing apoptosis through ROS-mediated activation of AMPK [55]. Conversely, in the tumor microenvironment, an abundance of glucose can inhibit autophagy: high glucose levels were found to upregulate SREBF1/SREBP1 (sterol regulatory element-binding protein 1), which in turn impairs autophagy and attenuates apoptosis in cancer cells. Furthermore, oxidative stress in tumor cells (excess ROS production) can induce metabolic reprogramming in cancer-associated fibroblasts (CAFs), increasing autophagy in the stromal cells and leading to the production of "fuel" molecules such as lactate, ketone bodies, fatty acids, and glutamine. These metabolites are released by CAFs and taken up by cancer cells to support tumor growth and metastasis under metabolic stress conditions [56].

To sustain the high metabolic demands, cancer cells utilize diverse nutrient sources to fuel the mitochondrial TCA cycle. Lipids represent one major alternative fuel. Through fatty acid β-oxidation (FAO), lipids can generate

significant amounts of ATP, and they also provide building blocks for membrane synthesis and serve as signaling molecules [57]. Altered lipid metabolism is a hallmark of NSCLC, and autophagy plays a central role in lipid homeostasis. Autophagy regulates lipid stores through a selective form of autophagy known as lipophagy, where lipid droplets are broken down to release free fatty acids that can be utilized for energy production or membrane remodeling [58]. In parallel, tumor cells often exhibit increased *de novo* lipogenesis and accumulation of lipid droplets. Notably, recent research highlights the involvement of small nucleolar RNAs (snoRNAs) in linking lipid metabolism with autophagy regulation in lung cancer. A panel of plasma snoRNAs has been proposed as potential NSCLC diagnostic biomarkers [59]. In particular, SNORD88C was identified as a snoRNA that drives lipid metabolic reprogramming and autophagy inhibition in NSCLC. SNORD88C, through 2′-O-methylation of 28S rRNA at a specific site, enhances the translation of stearoyl-CoA desaturase 1 (SCD1), an enzyme that synthesizes monounsaturated fatty acids (MUFA) [60]. As a result, elevated SCD1 levels suppress autophagy and promote lung tumor growth and metastasis. Mechanistically, SNORD88C forms a small nucleolar ribonucleoprotein (snoRNP) complex with the fibrillarin protein, which mediates 2′-O-methylation at nucleotide C3680 of 28S rRNA, thereby promoting ribosome biogenesis and preferential translation of SCD1 mRNA [61]. SCD1, the rate-limiting enzyme for MUFA synthesis, inhibits autophagy via two distinct mechanisms: (1) the MUFAs (e.g., oleic acid) produced by SCD1 reduce lipid peroxidation levels, which indirectly dampens autophagy; and (2) SCD1 activity leads to activation of the mTOR/ULK1 pathway, directly blocking autophagy initiation [62]. This discovery reveals a novel snoRNA-driven epitranscriptomic mechanism connecting lipid metabolism and autophagy, and it suggests SNORD88C as a potential plasma biomarker for NSCLC. Conversely, autophagy can feed back into lipid metabolism by degrading lipid droplets (lipophagy), thereby releasing fatty acids for β-oxidation or for reuse in membrane synthesis.

Another recent study highlighted the tumor-suppressive role of PAQR3 (progestin and AdipoQ receptor family member 3) in NSCLC and its connection to autophagy. PAQR3 is frequently downregulated in NSCLC cells, and restoration of PAQR3 expression significantly inhibits tumor cell proliferation [63]. Mechanistically, PAQR3 re-expression was found to markedly enhance erlotinib-induced autophagy, thereby suppressing tumor growth [64]. Strikingly, when autophagy was pharmacologically inhibited, the anti-proliferative effect of PAQR3 was completely abrogated, indicating that autophagy is a critical mediator of PAQR3's tumor suppressive function. This finding provides a fresh perspective on the anti-tumor mechanism of EGFR tyrosine kinase inhibitors (TKIs) like erlotinib, suggesting that they may exert some of their effects by perturbing tumor lipid homeostasis via a PAQR3-dependent autophagy pathway [65].

Autophagy also interfaces with ferroptosis, an iron-dependent form of programmed cell death characterized by the accumulation of lethal lipid peroxides. When lipid peroxides reach excessive levels, ferroptosis can be triggered; tumor cells often evade this form of death by suppressing processes like ferritinophagy (autophagic degradation of ferritin) that would otherwise increase free iron and promote lipid peroxidation. Indeed, evidence indicates that the autophagy machinery is critically involved in promoting ferroptosis. For instance, autophagy (particularly ferritinophagy) can facilitate erastin-induced ferroptosis by degrading ferritin and elevating intracellular iron levels, thereby enhancing lipid peroxidation [66]. Recent studies have identified factors that link mitochondrial metabolism, autophagy, and ferroptosis sensitivity in lung cancer. COX7A1, a subunit of cytochrome c oxidase in the mitochondrial electron transport chain, was found to increase NSCLC cell sensitivity to cystine deprivation–induced ferroptosis by enhancing the TCA cycle and complex IV activity, thereby altering mitochondrial metabolism and ROS production. Moreover, NSCLC cells rely on Atg7 to sustain mitochondrial fatty acid oxidation and maintain lipid homeostasis; loss of Atg7 leads to disrupted lipid metabolism and increased vulnerability to metabolic stress.

In summary, cancer cells adapt to metabolic stress not only by reprogramming metabolic pathways to support biosynthesis and maintain redox balance, but also by upregulating nutrient scavenging pathways, with autophagy being a prime example. Autophagy's degradative function captures and degrades intracellular macromolecules (proteins, lipid droplets, organelles) and recycles them into metabolic substrates, which becomes vital when extracellular nutrients are limited [67]. For example, NSCLC cells harboring co-mutations in KRAS and LKB1 (KL subtype) exhibit an epithelial-to-mesenchymal transition (EMT)-like phenotype and notably high autophagy-lysosomal activity [68]. In these KL mutant cancers, enhanced autophagy provides intracellular citrate and acetyl-CoA, which fuel epigenetic changes; specifically, autophagy-derived acetyl-CoA was shown to promote CBP-mediated acetylation of the EMT transcription factor Snail, thereby facilitating cancer cell invasion and metastasis [69]. Selective autophagy of mitochondria (mitophagy) is particularly important for mitochondrial quality control and metabolic adaptation [70]. In small cell lung cancer (SCLC), elevated autophagy (especially mitophagy) has been linked to chemotherapy resistance; SCLC cell lines that are chemoresistant show significantly higher autophagic activity than their chemosensitive counterparts [71]. One study found that METTL3 (an m6A RNA methyltransferase) is upregulated in chemoresistant SCLC cells and promotes mitophagy, contributing to chemotherapy resistance. Inhibition of METTL3 or mitophagy partially reversed this resistance, indicating

a potential therapeutic approach [72]. Indeed, mitophagy has been directly implicated in treatment resistance: excessive removal of damaged mitochondria can allow cancer cells to evade apoptosis induced by therapies. For example, brain-expressed X-linked 2 (BEX2) protein has been shown to protect cells from apoptosis by enhancing autophagic flux [73]. Likewise, S100A4 (fibroblast-specific protein 1) has been reported to promote lung cancer cell proliferation by activating Wnt/β-catenin signaling and concurrently inhibiting starvation-induced autophagy, thereby tipping the balance towards survival and growth [74]. Autophagy-deficient tumor cells often experience endoplasmic reticulum (ER) stress due to the accumulation of misfolded proteins and damaged organelles that would normally be degraded. TRAF3IP3 is one example of a protein that connects these processes: it can trigger ER stress via the PERK/ATF4/CHOP pathway, which in lung adenocarcinoma cells leads to the induction of a protective autophagy response (ER stress-induced autophagy) to cope with the unfolded protein burden [75]. In addition, a c-Myc/miR-150/EPG5 axis has been described in NSCLC whereby autophagy deficiency (caused by miR-150-mediated inhibition of the autophagy tethering factor EPG5) induces chronic ER stress, elevates ROS levels, and activates the DNA damage response, ultimately promoting cancer cell proliferation and tumor growth [76,77]. Notably, tumor–stromal interactions can influence autophagy as well. It has been shown that lung cancer cells can co-opt normal fibroblasts into cancer-associated fibroblasts (CAFs) through factors delivered by extracellular vesicles (EVs); one study identified EV-packaged miR-1290 as a key player that transforms normal fibroblasts into CAFs [78,79]. Moreover, these CAFs can transfer mitochondrial DNA to cancer cells via tunneling nanotubes, a process that involves autophagy-related mechanisms (termed "trogocytosis" or organelle transfer). By acquiring intact mitochondrial DNA from CAFs, cancer cells can restore mitochondrial function, better resist oxidative stress, and gain enhanced metastatic capacity. This underlines the multifaceted role of autophagy not only within cancer cells but also in modulating the tumor microenvironment to favor cancer progression.

3.2 Metabolic Enzyme-Mediated Epigenetic Regulation

Lipid metabolic reprogramming is a prominent feature of cancer cells and has profound effects on autophagy, thereby influencing malignant progression in NSCLC. This interaction operates at multiple levels:

Autophagy regulates lipid stores through lipophagy, wherein lipid droplets are degraded to release free fatty acids that feed β-oxidation and membrane biogenesis [80]. Lung tumors frequently exhibit increased *de novo* lipogenesis and lipid droplet accumulation, creating a dynamic balance between lipid storage and autophagic clearance that shapes membrane composition and signaling [81]. A notable epitranscriptomic axis links rRNA modification to lipogenesis and autophagy control: SNORD88C forms a snoRNP with fibrillarin to 2′-O-methylate 28S rRNA, selectively enhancing SCD1 translation [61]; the resulting MUFA output reduces lipid peroxidation and activates the mTOR/ULK1 brake, thereby suppressing autophagy and promoting metastasis. This finding suggests that epitranscriptomic control can steer membrane composition and autophagic set-points in NSCLC and nominates SNORD88C–SCD1 as a tractable node. Membrane sterol homeostasis also couples to autophagy: p-toluenesulfonamide (PTS) decreases membrane cholesterol, elevates LC3-II and reduces p62, and this autophagy induction is reversed by exogenous cholesterol—implicating an actionable cholesterol–autophagy axis. In parallel, PAQR3 restoration potentiates erlotinib-induced autophagy and growth suppression, whereas pharmacologic autophagy inhibition abolishes PAQR3's benefit, highlighting an autophagy-dependent tumor-suppressive route [62]. As a master nutrient sensor, mTOR integrates growth and lipid cues to modulate autophagy and cooperates with PPARγ and transcription factor EB (TFEB) to coordinate lysosome–lipid gene programs [82]. Therapeutically, co-modulating cholesterol handling (e.g., ACAT1/HMGCR) or desaturation (SCD1) alongside autophagy may rebalance membrane fluidity/vesicular trafficking and sensitize tumors to EGFR-TKIs or chemotherapy.

3.3 Purine Metabolism and Cautionary Extrapolation of the ADSL–Beclin 1 Axis

Mechanistic plausibility in NSCLC stems from the high purine demand and rewired central carbon metabolism of KRAS-driven—particularly KL (KRAS with LKB1 loss)—tumors, where increased ADSL flux could elevate intratumoral fumarate [83]. While this provides a biologically coherent premise, we deliberately frame ADSL–fumarate–*Beclin 1* as a falsifiable hypothesis until lung-specific data demonstrate (i) coordinated increases in ADSL activity, fumarate/2-succinocysteine (2-SC) burden, and *Beclin 1* dimethylation, and (ii) autophagy-flux enhancement that is not fully explained by parallel stress pathways [84].

To enable falsification rather than assumption, we outline an integrated experimental roadmap: (1) multimodal readouts in NSCLC models and specimens (targeted metabolomics for fumarate; 2-SC immunodetection; *Beclin 1* dimethylation by IP-MS or site-directed antibodies; autophagy flux via LC3-II/p62 dynamics under short lysosomal blockade and mCherry-GFP-LC3 reporting); (2) genetic and pharmacologic perturbations (CRISPR ADSL knockout/overexpression; catalytic-site mutants; rescue with cell-permeant fumarate versus non-equivalent dicarboxylate controls; *Beclin 1* methylation-deficient mutants to test pathway specificity); (3) isotope tracing with [U-^{13}C]-aspartate/glutamine to confirm fumarate routing into

the TCA cycle and its temporal coupling to flux changes; and (4) validation in KL-biased PDX/GEMM and prospective clinical cohorts with paired on-treatment biopsies. Because KEAP1/NRF2 alterations and hypoxia can confound fumarate-responsive stress programs, analyses should be stratified by KEAP1/NRF2 status and hypoxia scores to isolate pathway-specific effects [69,85].

Beyond ADSL, purine–autophagy crosstalk in lung cancer converges on energy and epigenetic routes already supported by our review: XDH-driven nucleotide catabolism sustains amino-acid supply and activates unfolded protein response (UPR)-linked autophagy under starvation to support LUAD survival [86]; Fat mass and obesity-associated protein (FTO)-mediated m6A demethylation upregulates PELI3, enhancing autophagy and gefitinib resistance [87]; NNT tunes autophagy through the NAD+/SIRT1 axis, shaping cisplatin sensitivity [88]; and Hsp70 can suppress AMPK and autophagy, whereas Hsp70 inhibition plus chemotherapy elicits robust (pro-death) autophagy and augments cisplatin cytotoxicity [89]. In parallel, CDK4/6 inhibitors induce autophagy and drive AMBRA1-dependent lysosomal degradation of CDK6, underscoring actionable cell-cycle–autophagy coupling and motivating dual-pathway designs that integrate purine-autophagy nodes with cycle control [90].

In sum, these observations should be regarded as graded-evidence mechanistic inferences. Only after lung-specific validation—demonstrating causal links among ADSL flux, fumarate/2-SC accumulation, *Beclin 1* dimethylation, and autophagy-dependent phenotypes—should therapeutic generalization be entertained. Until then, we advocate biomarker-embedded, genotype-stratified studies to determine whether the ADSL–*Beclin 1* axis represents a true autophagy dependency in NSCLC or a context-limited phenomenon.

3.4 Autophagy–Ferroptosis Coupling

By governing ferritinophagy (NCOA4-mediated ferritin turnover) and lipid peroxidation thresholds, autophagy can either gate or accelerate ferroptosis. Autophagic degradation of ferritin increases labile iron and amplifies lipid ROS, converting sublethal stress into ferroptotic death under defined metabolic states [91]. COX7A1-driven reinforcement of the TCA cycle and complex IV activity sensitizes NSCLC to cystine-deprivation ferroptosis, while Atg7 is required to sustain mitochondrial fatty-acid oxidation and lipid homeostasis; Atg7 loss disrupts lipid handling and increases ferroptosis vulnerability [92]. In addition to ferritinophagy, cargo selectivity determines directionality: (i) lipophagy mobilizes fatty acids and can enrich PUFA substrates in membranes via ACSL4/LPCAT3, thereby heightening peroxidation propensity, whereas SCD1-derived MUFAs dilute PUFA sites and dampen ferroptosis; (ii) mitophagy removes ROS-generating mitochondria and thus typically buffers lipid peroxidation [93]. Consequently, enhancing ferritinophagy or lipophagy while transiently restraining mitophagy can flip net autophagy from a survival gate to a pro-ferroptotic accelerator. Consistent with our lipid-focused sections, the SNORD88C–SCD1 axis provides an epitranscriptomic lever over membrane composition: elevated SCD1 skews MUFA/PUFA balance and suppresses both autophagy and lipid peroxidation, predicting reduced ferroptosis sensitivity in SNORD88C-high tumors [61].

A falsifiable workflow can anchor this model in lung cancer: (1) quantify labile iron (e.g., calcein quenching) and lipid ROS (C11-BODIPY) alongside NCOA4–FTH1 colocalization and autophagy flux (LC3-II/p62 under short lysosomal blockade; mCherry-GFP-LC3) in NSCLC lines, organoids, and biopsies [94]; (2) establish causality using NCOA4 loss/gain and FTH1/FTL stabilization, with ferroptosis rescue by ferrostatin-1/liproxstatin-1; (3) modulate lipid circuitry (ACSL4/LPCAT3 versus SCD1 inhibition or MUFA supplementation) to prove substrate dependency [95]; (4) manipulate mitophagy (e.g., USP30 inhibition or Atg7 perturbation) while monitoring mitoROS (MitoSOX), membrane potential, and oxygen consumption; and (5) validate in KL-biased PDX/GEMMs with paired on-treatment sampling. Stratification by KEAP1/NRF2 status and hypoxia scores is advisable to control confounding antioxidant programs.

Therapeutically, combining ferroptosis induction with selective autophagy modulation (enhancing ferritinophagy or preventing compensatory mitophagy) offers a route to flip autophagy from a survival shield to a lethal catalyst. Practically, pulse-timed regimens—initiating lipid peroxidation (e.g., system Xc^- or GPX4 blockade) followed by short-window ferritinophagy enhancement and/or mitophagy restraint—may maximize tumor-selective killing while preserving immune and normal-tissue autophagy. Biomarkers such as labile iron load, NCOA4 puncta density, lipid-ROS kinetics, and flux readouts should be embedded as PD endpoints to de-risk translation.

3.5 Biomarker Claims: Grading the Evidence and Validation Hurdles

While candidates such as SNORD88C, circRAPGEF5, and retinoblastoma binding protein 4 (RBBP4) show promise, their clinical utility remains unproven. To avoid overstatement, we explicitly distinguish the evidentiary ladder: analytical validity, clinical validity, clinical utility. Robust validation requires prespecified cut-offs, multi-center prospective cohorts, and head-to-head comparison against established benchmarks (e.g., PD-L1, ctDNA-MRD), ideally with decision-curve or net-benefit analyses to demonstrate added value. Pre-analytic variables (specimen type, ischemic time), intra-tumoral heterogeneity, and longitudinal dynamics must be controlled if these markers are to guide autophagy-targeted

therapy or trial enrollment. Accordingly, we downgrade the language from "biomarker" to "candidate biomarker" where appropriate and outline study designs that can move these candidates along the validation pathway.

SNORD88C, which enhances SCD1 translation and suppresses autophagy/lipid peroxidation, should have analytical validity demonstrated by cross-platform quantification in tissue and biofluids (small-RNA sequencing, RT-qPCR, and ddPCR) with spike-in normalization, hemolysis controls (e.g., miR-451/miR-23a index), freeze–thaw stability, and inter-laboratory reproducibility [61]. Clinical validity requires multi-center cohorts relating SNORD88C levels to diagnosis (NSCLC vs benign), prognosis (OS/PFS), and therapy response, with head-to-head comparison against PD-L1/TMB/ctDNA-MRD and optimism-corrected AUC, calibration, and DeLong tests. Clinical utility should be tested in biomarker-stratified trials where SNORD88C-high tumors—hypothesized to be MUFA-skewed and autophagy-suppressed—are randomized to standard care ± SCD1 inhibition and/or autophagy-rebalancing strategies, with net benefit assessed by decision-curve analysis.

circRAPGEF5, which inhibits autophagosome–lysosome fusion via an m6A-dependent "mRNA trap" (IGF2BP2–NUP160), analytical validity demands RNase-R resistance, junction-spanning assays, orthogonal confirmation by Sanger sequencing, and MeRIP-qPCR/RIP to prove m6A/IGF2BP2 engagement; subcellular fractionation should confirm cytoplasmic enrichment relevant to autophagy trafficking [96]. Clinical validity involves correlating circRAPGEF5 with flux phenotypes (LC3-II/p62 under short CQ/bafilomycin pulse; mCherry-GFP-LC3 reporter where available), metastatic risk, and therapeutic outcomes. Clinical utility could be addressed in an adaptive-strategy design testing whether circRAPGEF5-high tumors benefit from agents that restore autophagic flux (e.g., lysosome re-acidification or SNARE/ESCRT facilitation) combined with EGFR-TKIs or chemotherapy, with pre-specified interaction testing.

RBBP4, a chromatin regulator whose loss induces autophagy-dependent cell death, analytical validity requires standardized immunohistochemistry with digital H-score, intra/inter-observer concordance, and concordant protein/RNA measurements; HDAC1/2 activity assays can provide mechanistic orthogonality. Clinical validity should evaluate associations between RBBP4 levels, autophagy markers (LC3-II/*Beclin-1*/p62), and outcomes in independent cohorts [97]. Clinical utility is best tested in a biomarker-stratified trial where RBBP4-low (autophagy-elevated) patients receive pulse-timed autophagy inhibition plus chemotherapy or targeted therapy, with predefined PD endpoints (tumor LC3-II/p62 dynamics) to confirm on-target modulation.

To ensure rigor across markers, we recommend: (i) pre-registered statistical analysis plans with pre-specified thresholds (avoiding data-driven cut-offs); (ii) internal cross-validation and external validation with calibration, net reclassification improvement (NRI) and integrated discrimination improvement (IDI); (iii) systematic control of pre-analytic variables (fixation/ischemic time, tube type, processing timelines, freeze–thaw cycles); (iv) embedding autophagy flux readouts (LC3-II/p62 under short lysosomal blockade; mCherry-GFP-LC3) as PD companions; and (v) genomic/metabolic stratification (e.g., KRAS/LKB1, KEAP1/NRF2, TP53, hypoxia scores) to mitigate confounding. Taken together, these steps operationalize the analytical→clinical validity→clinical utility ladder and provide a concrete path for SNORD88C, circRAPGEF5, and RBBP4 to transition from candidate markers to clinically actionable tools—if and only if they demonstrate incremental value over current standards in prospective, multi-center studies.

4. Autophagy as an Adaptive Response to Metabolic Stress

Lung cancer cells are frequently subjected to harsh microenvironmental conditions—such as hypoxia, nutrient deprivation, and therapeutic stress—which impose metabolic challenges. Autophagy serves as a key adaptive response in these settings by recycling intracellular components, maintaining energy and redox homeostasis, and mitigating damage, thereby enabling tumor cell survival and therapy resistance. Recent studies have illuminated how lung cancer cells dynamically modulate autophagy in conjunction with various metabolic pathways to cope with metabolic stress while preserving their malignant phenotype.

Under conditions of glucose or amino acid starvation, the cellular AMP/ATP ratio increases, leading to activation of the energy sensor AMPK. Once activated, AMPK directly phosphorylates ULK1, promoting autophagy initiation, and concurrently inhibits mTORC1, thus lifting mTORC1's suppressive effect on autophagy [98]. AMPK also regulates fatty acid oxidation and mitochondrial biogenesis, which can influence autophagic flux by providing alternative energy sources and affecting mitochondrial quality control [99]. Studies have shown that KRAS-mutant lung cancer cells, when faced with metabolic stress, become highly dependent on the AMPK-autophagy axis for survival; pharmacologically targeting this pathway can enhance the efficacy of chemotherapy in these cells [100]. This suggests a vulnerability that could be exploited by using AMPK activators or autophagy inducers in a controlled manner to push cancer cells beyond their adaptive capacity.

Lipid metabolic stress is another context in which autophagy plays a protective role. As mentioned earlier, lipophagy allows tumor cells to tap into lipid reserves during energy crises by breaking down lipid droplets into free fatty acids (FFAs) for β-oxidation or membrane re-

assembly [101]. In NSCLC, inhibition of key lipogenic enzymes like SCD1 triggers excessive lipophagy and subsequent lipid peroxidation (lipotoxicity), leading to cell death—an outcome that could be therapeutically beneficial [102]. Meanwhile, cancer cells that develop resistance to treatments such as EGFR-TKIs often exhibit alterations in cholesterol metabolism: for example, TKI-resistant NSCLC cells may upregulate the cholesterol esterification enzyme ACAT1 to maintain plasma membrane fluidity and structural integrity. This adaptation is coupled with a suppression of excessive autophagy, helping the resistant cells to survive under drug pressure [103]. Therefore, co-targeting cholesterol metabolism and autophagy could be a promising strategy to eliminate drug-resistant cells.

ROS accumulation in the tumor microenvironment causes oxidative stress, which can damage proteins, lipids, and DNA. Autophagy provides a means to alleviate oxidative damage by removing ROS-producing organelles (through mitophagy of damaged mitochondria) and degrading oxidized macromolecules, thereby preventing cell death under moderate stress [104]. However, if autophagy is overactivated, it can itself lead to cell death or undermine cell viability by excessive self-digestion. Lung cancer cells often modulate autophagy to achieve a balance—sufficient to handle oxidative stress but not so much as to trigger autophagy-dependent cell death. The Nrf2–Keap1 pathway is central to the antioxidant response and exemplifies this balance: Nrf2 activation leads to upregulation of numerous antioxidant genes and has been associated with increased autophagy to maintain redox homeostasis. Lung cancer cells with Nrf2 pathway activation are more adept at surviving oxidative stress, whereas Nrf2-deficient cells are significantly more sensitive to autophagy inhibition (since they rely heavily on autophagy for dealing with ROS) [105]. This knowledge points to potential synthetic lethal strategies, such as combining autophagy inhibitors with agents that inhibit Nrf2 in tumors addicted to antioxidant autophagy pathways.

The metabolic crosstalk between cancer cells and their microenvironment also involves autophagy. Cancer-associated fibroblasts (CAFs) and immune cells in the tumor milieu can secrete metabolites and cytokines that impact cancer cell autophagy. For instance, glutamine secreted by CAFs can activate mTORC1 in cancer cells, thereby suppressing autophagy and promoting anabolic growth, whereas hypoxia-induced HIF-1α can upregulate BNIP3 in cancer cells to trigger mitophagy, helping them adapt to oxygen deprivation [106]. Furthermore, many cytotoxic chemotherapeutics (e.g., cisplatin) induce a protective autophagy response in cancer cells as a survival mechanism. This has led to clinical trials combining chemotherapy with autophagy inhibitors (like HCQ) to improve treatment efficacy. Preclinical studies have demonstrated that using autophagy inhibitors in tandem with chemotherapy significantly enhances tumor cell apoptosis and can overcome chemoresistance in lung cancer models [107].

In summary, autophagy acts as an adaptive shield for lung cancer cells under metabolic stress, interfacing with energy management, lipid utilization, oxidative defense, and microenvironmental interactions. These insights highlight the potential of tailoring autophagy-targeted interventions to specific metabolic contexts of lung cancer. For example, in KRAS-driven tumors or those with high lipid turnover, carefully timed autophagy inhibition could push cancer cells over the edge of metabolic catastrophe, whereas in other contexts, transient autophagy induction might be harnessed to potentiate immunogenic cell death. Ultimately, developing selective autophagy-modulating strategies that account for a tumor's metabolic background may lead to more effective lung cancer treatments.

5. Autophagy Regulation in Lung Cancer: Targeted Therapy Strategies

As our understanding of autophagy's molecular underpinnings and context-dependent roles in lung cancer deepens, targeting autophagy has become an attractive strategy to improve therapeutic outcomes. In recent years, researchers have developed various approaches to modulate autophagy in the clinical context, including small-molecule compounds that directly target core autophagy machinery, nanotechnology-based drug delivery systems to enhance the precision of autophagy modulation, and combinations of autophagy regulators with standard treatments (chemotherapy, targeted therapy, immunotherapy). The goal of these strategies is to fine-tune autophagy activity—either inhibiting or activating it as needed—to overcome therapy resistance and improve patient survival. Below, we discuss the latest progress and innovative developments in this rapidly evolving field (Table 1, Ref. [108–128]).

5.1 Molecular Strategies Targeting Key Autophagy Nodes

RNA epigenetic modifications have recently emerged as a critical layer of autophagy regulation, with significant implications for translational research in lung cancer therapy. One of the most studied modifications is N6-methyladenosine (m6A) on mRNA, which can influence mRNA stability and translation. Studies have shown that m6A modifications modulate the expression of autophagy-related molecules, thereby affecting chemosensitivity and metastatic progression in lung cancer [129]. In NSCLC, METTL3 (an m6A methyltransferase) was found to drive abnormal autophagy, particularly mitophagy, through two mechanisms [108]: first, METTL3-mediated m6A led to the accelerated degradation of DCP2 mRNA, resulting in continuous activation of the PINK1-Parkin mitophagy pathway; second, METTL3 enhanced the nuclear translocation of the master autophagy/lysosome regulator TFEB, promoting the transcription of autophagy-lysosome

Table 1. Autophagy-modulating agents in lung cancer research: mechanisms, targets, and development stage.

Clinical application	Detected biomarkers/substances	Detection method	Special microfluidic techniques	Current research stage	References
Rapamycin	mTORC1	Activator	Inhibits mTORC1, relieves suppression of autophagy	Phase I/II clinical trials	[121]
Chloroquine/hydroxychloroquine	Lysosome/vacuolar pH	Inhibitor	Blocks autophagosome-lysosome fusion, raises lysosomal pH	Phase I/II clinical trials	[115,128]
Bafilomycin A1	V-ATPase	Inhibitor	Inhibits lysosomal acidification, blocks autophagosome-lysosome fusion	Preclinical	[113]
Metformin	AMPK	Activator	Activates AMPK, inhibits mTORC1, promotes autophagy	Phase I/II clinical trials	[125,126]
STM2457	METTL3 (m6A methyltransferase)	Inhibitor	Inhibits METTL3, reduces aberrant mitophagy, reverses drug resistance	Preclinical	[108]
Sertaconazole nanoparticles	CD44, ROS/autophagy	Activator	Induces ROS-dependent apoptosis and autophagy	Preclinical	[114,116]
Apatinib	VEGFR2, STAT3, PD-L1, c-Myc	Activator (pro-death)	Induces ROS, promotes autophagy-dependent cell death	Preclinical	[109]
Baicalin	Lysosomal MCOLN3	Inhibitor (late stage)	Raises lysosomal pH, blocks autophagic flux	Preclinical	[110]
Halofuginone	ROS, cell cycle	Activator	Induces ROS, triggers autophagy and apoptosis	Preclinical	[111]
Aloperine (ALO)	VPS4A/ESCRT machinery	Inhibitor (fusion)	Blocks autophagosome-lysosome fusion, accumulates autophagosomes	Preclinical	[112]
Betulinic acid (BA)	EGFR, PI3K/AKT/mTOR pathway	Activator (pro-death)	Inhibits EGFR and PI3K/AKT/mTOR, induces autophagy	Preclinical	[122]
Berberine	EGFR degradation	Activator	Promotes autophagic degradation of EGFR	Preclinical	[123]
Tubeimoside-1 (TBM-1)	mTOR, TFEB, PD-L1	Activator	Inhibits mTOR, promotes TFEB activation, lysosomal degradation of PD-L1	Preclinical	[124]
Huaier extract	NCOA4-mediated ferritinophagy	Activator (ferroptosis)	Activates ferritinophagy, promotes ferroptosis	Preclinical	[127]
TFPA	Autophagosome-lysosome fusion	Inhibitor	Blocks fusion, increases pro-apoptotic effects	Preclinical	[128]
Cycloastragenol	AMPK/ULK1	Activator (protective)	Activates AMPK, induces protective autophagy	Preclinical	[120]
AKBA	ATG5–LC3 conjugation	Inhibitor	Inhibits autophagosome formation, sensitizes to chemo	Preclinical	[117]
HyFS (Hyperoside derivative)	ABCG2 efflux transporter	Activator (selective)	Induces autophagic degradation of ABCG2	Preclinical	[118]
Paclitaxel-PEI-siMDR1 nanoparticles	MDR1, lysosome, autophagy	Inhibitor	Blocks autophagosome-lysosome fusion, silences MDR1	Preclinical	[119]

mTORC1, Mechanistic Target of Rapamycin Complex 1; AMPK, AMP-activated Protein Kinase; V-ATPase, Vacuolar ATPase; METTL3, Methyltransferase Like 3 (m6A methyltransferase); CD44, Cluster of Differentiation 44; VEGFR2, Vascular Endothelial Growth Factor Receptor 2; STAT3, Signal Transducer and Activator of Transcription 3; PD-L1, Programmed Cell Death Ligand 1; c-Myc, Cellular Myelocytomatosis Oncogene; MCOLN3, Mucolipin 3; ROS, Reactive Oxygen Species; ESCRT, Endosomal Sorting Complex Required for Transport; EGFR, Epidermal Growth Factor Receptor; PI3K, Phosphoinositide 3-kinase; AKT, Protein Kinase B; mTOR, Mechanistic Target of Rapamycin; ABCG2, ATP-binding Cassette Sub-family G Member 2; MDR1, Multidrug Resistance Protein 1; TFEB, Transcription Factor EB; NCOA4, Nuclear Receptor Coactivator 4.

genes. Together, these effects caused excessive mitophagy, which contributed to the development of cisplatin resistance. Encouragingly, a selective METTL3 inhibitor (STM2457) was able to restore cisplatin sensitivity in resistant cells and also reprogram the tumor microenvironment *in vivo* to enhance the efficacy of PD-1 checkpoint blockade. This indicates that targeting RNA methylation can have multifaceted therapeutic benefits, both direct (tumor-intrinsic) and indirect (immune-mediated).

On the flip side of autophagy regulation, recent research has uncovered an intricate co-regulation network involving RNA modifications and the ubiquitin-proteasome system. Homeobox containing 1 (HMBOX1) was shown to influence autophagy homeostasis via an m6A-dependent mechanism [130]. Specifically, METTL3-catalyzed m6A modification increased the stability of HMBOX1 mRNA, leading to upregulated HMBOX1 protein, which in turn enhanced the expression of the E3 ubiquitin ligase HACE1. HACE1 was found to mediate K63-linked ubiquitination of ATG5, tagging it for proteasomal degradation and thus acting as a brake on autophagy. The HMBOX1-HACE1-ATG5 axis appears to fine-tune autophagy levels, and it has implications for chemosensitivity—elevated HMBOX1/HACE1 activity correlates with reduced autophagy and potentially greater sensitivity to certain drugs like 5-fluorouracil (5-FU). These findings suggest that components of the RNA epitranscriptomic machinery can serve as biomarkers for optimizing chemotherapy, and that targeted disruption of specific RNA modification readers or writers could recalibrate autophagy in cancer cells.

Circular RNAs (circRNAs) add another layer to the regulatory landscape. One example is circRAPGEF5, which was found to inhibit autophagy through an m6A-dependent "mRNA trap" mechanism [28]. m6A-modified circRAPGEF5 can form a complex with the m6A reader IGF2BP2 and the mRNA of NUP160 (a nucleoporin), leading to stabilization of NUP160 mRNA. The increased NUP160 in turn interferes with autophagosome-lysosome fusion, effectively stalling autophagic flux. Functionally, this enhances metastatic potential in lung adenocarcinoma. This insight not only elucidates a novel mechanism underlying metastasis but also suggests that circRNAs themselves (or their m6A status) could be therapeutic targets or diagnostic markers. Collectively, these advancements highlight RNA epigenetic modification networks (including m6A writers like METTL3, erasers like FTO, and readers like IGF2BP2) as promising intervention points to reverse lung cancer drug resistance and inhibit metastasis by modulating autophagy.

5.2 Anti-angiogenic Drugs and Autophagy Modulation

Anti-angiogenic therapy has become a cornerstone of cancer treatment, and in lung cancer its role is expanding beyond simply starving tumors of blood supply. There is growing recognition that anti-angiogenic agents can also influence autophagy and tumor immunity. Apatinib is one such agent, a multi-tyrosine kinase inhibitor that primarily targets VEGFR2. In NSCLC, apatinib has been observed to exert multiple anti-tumor effects. It inhibits tumor angiogenesis by blocking the VEGFR2/STAT3 signaling pathway and simultaneously downregulates oncogenic and immunosuppressive proteins like PD-L1 and c-Myc, thereby enhancing anti-tumor immune responses. Crucially, apatinib can induce an accumulation of ROS within tumor cells, which has downstream effects on autophagy. Elevated ROS from apatinib treatment was shown to inhibit the Nrf2/p62 pathway, leading to the promotion of autophagy-dependent cell death (a form of autophagic apoptosis) [130]. In essence, apatinib creates a multi-pronged assault on the tumor: it prunes the vasculature, reactivates immune elements, and drives cancer cells toward autophagy-dependent death. Additionally, Apatinib, in combination with camrelizumab, enhances the efficacy of neoadjuvant immunotherapy for oral squamous cell carcinoma (OSCC) by improving major pathological response (MPR) rates, with higher MPR observed in patients with elevated PD-L1 expression and increased CD4+ T-cell infiltration [109]. This suggests potential utility of apatinib in overcoming resistance mechanisms and immune evasion in lung cancer.

Anti-angiogenic therapy also reshapes autophagy and tumor immunity via a limited set of recurring mechanisms. In brief: VEGFR2 blockade (e.g., apatinib) elevates ROS, suppresses Nrf2/p62 signaling, and drives ADCD while lowering PD-L1/c-Myc [131]; vascular normalization (e.g., Endostar with PD-1 blockade) improves T-cell infiltration and, through PI3K/Akt/mTOR tuning, increases tumor-cell autophagy to enhance ICI efficacy; lysosome-targeting natural products (e.g., baicalin) alkalinize lysosomes and block autophagy flux [110]; and ROS-dependent agents (e.g., halofuginone) co-induce autophagy and apoptosis. To reduce redundancy, repeated assay readouts (LC3-II/p62 dynamics, lysosomal pH changes) are omitted here while preserved in the cited studies [111].

5.3 Organelle-Specific Autophagy Modulation

Targeting autophagy at the level of specific organelles has emerged as a novel therapeutic strategy, as different organelle-specific autophagy processes (such as mitophagy, ER-phagy, ribophagy, and others) can be selectively manipulated to kill cancer cells. Several breakthroughs illustrate the potential of organelle-targeted autophagy modulation in lung cancer.

5.3.1 Golgi Apparatus (Golgiphagy)

Liang *et al.* [132] designed a platinum(II) complex named Pt3 with a unique ability to localize to the Golgi apparatus in cells. Pt3 induces Golgi stress, causing fragmentation of this organelle, which specifically triggers Golgi autophagy (termed "Golgiphagy"). Concurrently, Pt3 se-

lectively inhibits the fusion of autophagosomes with lysosomes, leading to an accumulation of autophagosomes—a state of autophagy flux blockade. This two-pronged autophagy modulation (activation of Golgiphagy and inhibition of autophagic completion) results in the collapse of Golgi function and protein trafficking homeostasis, ultimately activating caspase-3-dependent apoptotic cell death in lung cancer cells. Importantly, Pt3 exhibited minimal disruption of the Golgi in normal (non-transformed) cells, indicating a therapeutic window and specificity for cancer cells. This study provides a compelling example of how a drug can be engineered to target a specific organelle and modulate autophagy in a controlled fashion, opening avenues for organelle-centric autophagy therapies.

5.3.2 Mitochondria (Mitophagy) and Immune Evasion

Mitochondrial turnover via autophagy (mitophagy) is a critical process for cellular quality control. A novel connection between mitophagy and oncogenic signaling was uncovered involving the tumor suppressor ralA-binding protein 1 associated eps domain containing 2 (REPS2). REPS2 was found to facilitate the selective autophagic degradation of β-catenin via the p62/SQSTM1 receptor, thereby suppressing Wnt/β-catenin signaling in lung cancer cells [133]. This degradation of β-catenin not only reduced the stem cell-like properties of the cancer cells but, when combined with a pharmacological β-catenin inhibitor, led to pronounced immunogenic cell death (ICD). The dying cancer cells released danger signals that promoted dendritic cell maturation and increased infiltration of CD8+ T cells in tumor tissue, highlighting a cooperative effect between autophagy modulation and immune activation. Another fascinating discovery is that tumor cells can transfer mutated mitochondrial DNA to tumor-infiltrating T cells through physical mitochondria exchange, contributing to T cell dysfunction or exhaustion. Tumor cells were found to exploit the deubiquitinase USP30 to suppress mitophagy, thereby preserving dysfunctional mitochondria (with mutated mtDNA) that they can pass to T cells, impairing T cell function [134]. Inhibiting USP30 was shown in preclinical models to restore mitophagy in T cells, improve T cell metabolic fitness, and enhance the efficacy of PD-1 checkpoint blockade (the reference [37] suggests this concept is based on earlier foundational work). This implies that drugs targeting negative regulators of mitophagy (like USP30) might bolster anti-tumor immunity when used in combination with immunotherapies.

5.3.3 Autophagosome Maturation (Fusion Blockade)

Aloperine (ALO), a natural quinolizidine alkaloid, was identified as an inhibitor of autophagosome-lysosome fusion [112]. ALO specifically targets VPS4A, an ATPase involved in the endosomal sorting complexes required for transport (ESCRT) machinery that is crucial for the final step of autophagosome maturation. By binding to the ATPase domain of VPS4A, ALO prevents VPS4A from interacting with CHMP4B, a component of ESCRT-III needed for membrane fission during autophagosome-lysosome fusion. The result is an accumulation of autophagosomes (elevated LC3-II levels) and p62, along with increased ROS within the cancer cells, culminating in apoptosis. Interestingly, combining ALO with a bispecific antibody targeting PD-L1 and TGF-β yielded enhanced anti-tumor effects in a lung cancer model, suggesting that late-stage autophagy inhibition can favorably alter the immune microenvironment—possibly by making tumor cells more susceptible to immune cell killing or by altering cytokine secretion patterns.

5.3.4 Autophagy Initiation (Autophagosome Nucleation)

The splicing factor SRSF1 has been found to repress autophagy through dual mechanisms [135]. SRSF1 promotes the production of the anti-apoptotic protein Bcl-xL (by alternative splicing of Bcl-x pre-mRNA) and also directly binds to the class III PI3K complex component PIK3C3/Vps34, impeding its interaction with *Beclin 1*. Both actions of SRSF1 prevent effective autophagosome nucleation. Overexpression of SRSF1 has been linked to EGFR-TKI resistance in NSCLC, as it helps tumor cells evade autophagy-dependent cell death that would otherwise be induced by therapy. This finding points to the potential of targeting the RNA splicing machinery (or specific splice variants of autophagy regulators) as a way to restore autophagy-dependent tumor suppression in resistant cancers.

5.3.5 Autophagic Secretion (Secretory Autophagy)

A novel mode of autophagy's involvement in metastasis has been described involving the protein deacetylase SIRT2. Macrophages in the tumor microenvironment were shown to secrete SIRT2 in exosomes through an autophagy-dependent pathway, and this secreted SIRT2 promoted lung cancer metastasis [136]. Mechanistically, TRAF6 (an E3 ubiquitin ligase) mediates K63-linked ubiquitination of SIRT2, which appears to be a signal for its packaging into autophagosomes and subsequent secretion (a process sometimes referred to as secretory autophagy). The ubiquitination also enhanced SIRT2's enzymatic (deacetylase) activity. In recipient cancer cells, SIRT2 deacetylated targets that led to increased invasive behavior, including deacetylation of ITGB3 (β3 integrin), which was associated with enhanced metastatic potential. Inhibiting either TRAF6 or core autophagy (for example, via ATG7 knockdown) significantly reduced this pro-metastatic cross-talk. Clinically, high SIRT2 expression in tumors correlated with low acetyl-ITGB3 levels and worse patient outcomes, underscoring the relevance of this pathway. This study suggests that blocking specific autophagy-dependent secretory pathways could be a strategy to prevent metastasis.

In aggregate, these examples underscore that "autophagy" is not a monolithic process; its selectivity for certain organelles or cargo can be leveraged to target vulnerabilities of cancer cells. Organelle-specific autophagy modulators (like Pt3 for Golgiphagy or ALO for autophagosome maturation) offer precision tools to dismantle critical cellular machinery in cancer cells while sparing normal cells, potentially improving therapeutic indices. Future research is expected to delve into how these organelle-targeted processes intersect with each other—for instance, how Golgi stress and ER stress autophagy might crosstalk, or how inhibiting mitophagy might inadvertently affect peroxisome turnover—and to harness these interactions for therapeutic gain. Spatial and temporal control of such interventions will also be an important consideration to maximize tumor cell kill while minimizing unintended side effects.

5.4 Immune Modulation and Key Autophagy Nodes

Interactions between autophagy regulation and the immune system are increasingly recognized as crucial in determining the success of cancer immunotherapy. Several key autophagy nodes have been identified that modulate antitumor immunity, offering new opportunities to overcome immune resistance in lung cancer.

5.4.1 Autophagy and Immune Checkpoint Regulation

There is a tight link between autophagy and the turnover of immune checkpoint molecules such as PD-L1. Studies have shown that promoting the autophagic degradation of PD-L1 can reinvigorate immune responses. For example, andrographolide (AD), a diterpenoid lactone from *Andrographis paniculata*, was found to enhance antitumor immunity by facilitating PD-L1 degradation. AD inhibits STAT3 phosphorylation, which not only downregulates PD-L1 transcription but also triggers p62/SQSTM1-dependent selective autophagy that targets PD-L1 for lysosomal degradation [137]. Through this dual action, AD effectively reduced PD-L1 levels on tumor cells, thereby boosting the activity of CD8+ T cells against the tumor. Similarly, baicalein (a flavonoid distinct from baicalin) has been shown to induce an interaction between PD-L1 and LC3B, earmarking PD-L1 for autophagosomal degradation [138]. By accelerating PD-L1 clearance, baicalein sensitized tumor cells to T cell killing. These findings illuminate a promising strategy: using small molecules or dietary phytochemicals to modulate autophagy in order to degrade immunosuppressive proteins like PD-L1, thereby potentially overcoming resistance to PD-1/PD-L1 checkpoint inhibitors.

5.4.2 Autophagy and Antigen Presentation

Autophagy can sometimes impede antigen presentation by mediating the degradation of major histocompatibility complex class I (MHC-I) molecules, which tumor cells use to present antigens to cytotoxic T cells. An autophagy receptor called NDP52 was identified as a factor that recognizes MHC-I and targets it for autophagic degradation, thus contributing to immune evasion by reducing antigen presentation on the tumor cell surface [139]. Pharmacological blockade of autophagy can counteract this effect. For instance, fangchinoline, a bisbenzylisoquinoline alkaloid, was shown to inhibit autophagy and thereby prevent the degradation of MHC-I, resulting in increased cell-surface MHC-I levels on tumor cells. This led to improved recognition of the cancer cells by T cells and enhanced efficacy of PD-1 blockade therapy. Along similar lines, classical autophagy inhibitors like CQ and bafilomycin A1 have been observed to upregulate human leukocyte antigen (HLA) class I molecule expression on tumor cells by preventing their autophagic turnover [113]. Thus, a combination of autophagy inhibitors with immunotherapy could be used to strengthen tumor antigen presentation and T-cell mediated killing.

5.4.3 Autophagy and Cytokine Signaling

Autophagy intersects with various immune signaling pathways. An interesting example involves TRIM35, a tripartite motif protein that was shown to suppress autophagy and simultaneously augment interferon signaling in cancer cells [140]. TRIM35 mediates K63-linked ubiquitination of the lysine-specific demethylase LSD1, which inhibits LSD1's activity. Since LSD1 can repress certain genes, its inhibition by TRIM35 leads to upregulation of ER-Golgi intermediate compartment protein 1 (ERGIC1), a factor that was found to inhibit autophagy (likely by affecting membrane dynamics required for autophagosome formation). The suppression of autophagy by TRIM35 contributed to stabilization of the interferon gamma receptor 1 (IFNGR1) on the cell surface, thereby enhancing responsiveness to IFN-γ and bolstering the anti-tumor immune response. These data link an epigenetic regulator (LSD1), autophagy, and cytokine signaling in one network, suggesting that co-targeting LSD1 (to modulate autophagy and gene expression) along with immunotherapy might have synergistic effects in tumors that evade immune responses via autophagy-related mechanisms.

5.4.4 YY1 Transcription Factor and Therapy Resistance

Ying Yang 1 (YY1) is a transcription factor that has been implicated in both autophagy regulation and immune modulation. Notably, downregulation of YY1 was found to cause an autophagy block and concurrently modulate signaling pathways that affect drug sensitivity. YY1 loss-of-function led to an accumulation of autophagosomes (autophagy flux blockade) and also upregulated DUSP1, a phosphatase that inactivates the EGFR/MAPK pathway, thus restoring sensitivity to EGFR-TKIs like osimertinib in previously resistant cells [141,142]. This finding indicates that YY1 could be an important node in integrating autophagy status with oncogenic signaling, and its modula-

tion might simultaneously tackle targeted therapy resistance and influence immune pathways (since EGFR/MAPK signaling can affect immune cell recruitment and PD-L1 expression).

5.4.5 Epigenetic Control of Autophagy and Immunity

Epigenetic factors that govern the expression of autophagy genes can have downstream effects on immune responses. RBBP4 (Retinoblastoma binding protein 4) is an example of a chromatin regulator that was recently identified as a modulator of autophagy with potential immunological consequences. Knockout of RBBP4 in lung cancer cells led to increased levels of LC3-II and *Beclin 1* and decreased p62, indicating an induction of autophagy-dependent cell death [143]. Mechanistically, the loss of RBBP4 was linked to reduced activity of histone deacetylases HDAC1/2, resulting in a more open chromatin state and de-repression of autophagy-related gene transcription. This enhanced autophagy not only directly induced cancer cell death, but it could also alter the tumor microenvironment—for instance, cells undergoing autophagy-dependent cell death may release ATP and other "find me/eat me" signals that attract immune cells. Although not explicitly stated in this reference, one can extrapolate that targeting epigenetic repressors like RBBP4 or HDAC1/2 in combination with immunotherapies might be beneficial, as it can both trigger autophagic tumor cell death and potentially increase tumor immunogenicity.

Taken together, these studies underscore the potential of manipulating autophagy to modulate the immune microenvironment in lung cancer. By targeting specific autophagy regulators (e.g., using small molecules like andrographolide or baicalein, or inhibiting autophagy receptors like NDP52), we can enhance the visibility of tumor cells to the immune system and counteract mechanisms of immune resistance such as checkpoint molecule expression or antigen presentation deficits. Moving forward, it will be important to identify which subsets of lung cancer patients (e.g., by molecular profiling of autophagy and immune markers) are most likely to benefit from autophagy-immune combinatorial strategies, and to refine the timing and dosing so as to maximize anti-tumor immunity while minimizing potential immune-related adverse effects.

5.5 Nanotechnology-Based Autophagy-Targeted Delivery Systems

Nanomedicine has introduced new possibilities for delivering autophagy-targeting therapies with improved precision and efficacy. By using nanoparticles and other nanoscale delivery vehicles, we can overcome challenges such as poor solubility of drugs, off-target effects, and drug resistance mechanisms. Several innovative nano-delivery systems have been developed to specifically modulate autophagy in lung cancer.

5.5.1 CD44-Targeted Autophagy-Inducing Nanoparticles

One study developed a nanoparticle system using sertaconazole, an antifungal drug repurposed for anti-cancer effects, encapsulated in a CD44-targeted nanocarrier (designated HTS NPs) [114]. The surface of these nanoparticles is functionalized to bind CD44, a hyaluronan receptor often overexpressed on lung cancer cells, enhancing selective uptake by tumor cells. Once internalized, the nanoparticle releases sertaconazole, which induces ROS-dependent apoptosis and concurrently triggers autophagy-dependent cell death. The importance of autophagy in this system's cytotoxic effect was evidenced by the finding that CQ, an autophagy inhibitor, could completely reverse the nanoparticle's cancer cell killing. This not only confirms that the mechanism of tumor cell death involves autophagy but also highlights a potential combination approach (with CQ) if needed to modulate the effect. Such "autophagy-dependent" nanomedicines offer a means to deliver treatment in a targeted fashion while exploiting the cell's own catabolic pathways.

5.5.2 Reversing Chemoresistance With Smart Nanogels

Overcoming chemoresistance is a major focus of current lung cancer research. A pH-sensitive nanogel composed of poly (acrylamide-co-styrene/acrylate) [P(AAm/SA)] was engineered to co-deliver 5-fluorouracil (5-FU) and modulators of RNA methylation [144]. This nanogel was shown to enhance autophagy and resensitize lung cancer cells to 5-FU by modulating the ALKBH5/Beclin1/ULK1signaling axis. ALKBH5 is an m6A demethylase (removing m6A modifications on RNA) and can influence autophagy-related gene expression. The nanogel's controlled release of 5-FU in the acidic tumor microenvironment, combined with its effect on ALKBH5 and autophagy pathways, led to increased cancer cell death where free 5-FU alone was ineffective. The surface of the nanogel could be further modified to target tumor tissues, improving drug accumulation at the tumor site while sparing normal tissues. This showcases how nanocarriers can be used to simultaneously tackle epigenetic regulation and drug delivery.

5.5.3 Co-Delivery of Autophagy Inhibitors and Other Therapies

Researchers at Sun Yat-sen University designed a composite nanoparticle (referred to as SHC4H NPs) that co-delivers the autophagy inhibitor HCQ and a mitochondria-targeted photosensitizer for photodynamic therapy (PDT) [115]. The rationale is to employ a two-hit strategy: HCQ blocks mitophagy, preventing cancer cells from removing damaged mitochondria, while the photosensitizer (activated by light) induces oxidative damage primarily in mitochondria. In hypoxic lung cancer models, where conventional therapies often fail, this combination proved highly effective: the photodynamic treatment creates lethal oxidative

damage, and the blockage of mitophagy ensures that cells cannot easily recover by clearing the damaged mitochondria. Such nanoparticles typically have targeting ligands (for tumor or mitochondrial targeting) and release their cargo in a controlled manner upon stimulation (e.g., light for PDT, or low pH for HCQ release), maximizing the synergistic effect.

5.5.4 Inhalable Nanoparticle Formulations

Direct pulmonary delivery of therapeutics can maximize local drug concentration and minimize systemic toxicity for lung cancer treatment. An example is an inhalable co-crystal formulation of niclosamide and clarithromycin developed to improve drug solubility and delivery [145]. Niclosamide is an old anthelmintic drug that has anticancer properties (including autophagy modulation), and clarithromycin is an antibiotic known to have autophagy-inhibiting properties. By forming a co-crystal and then a spray-dried powder, the researchers achieved enhanced aerosol characteristics suitable for deep lung deposition. Building on this, a further innovation involved creating chitosan-coated polycaprolactone nano-assemblies containing niclosamide and autophagy-affecting drugs (like clarithromycin or others) [146]. The chitosan coating can provide mucoadhesion and prolong retention in the lung, while the polycaprolactone polymer controls the release of the drug. This NIC-CS-PCL-NA system not only potentiated anticancer effects via dual modulation of autophagy and apoptosis pathways, but it also significantly lowered systemic side effects due to its lung-targeted delivery. In essence, by using inhalable nanoparticles, one can deliver autophagy modulators directly to lung tumors in a high concentration, potentially overcoming drug delivery barriers and improving therapeutic index.

5.5.5 Natural Compound Nano-Formulations

Researchers have also explored encapsulating natural compounds with autophagy-modulating activity into nanoparticles to improve their bioavailability and tumor targeting. For instance, a nano-complex containing phytol (Phy) and α-bisabolol (Bis)—two plant-derived compounds—was shown to synergistically induce autophagy-related cell death in A549 lung cancer cells [116]. The nano-formulation increased the stability and cellular uptake of these hydrophobic compounds. Mechanistically, the Phy/Bis nano-complex upregulated pro-autophagic genes (like Beclin-1 and LC3B) and downregulated the autophagy substrate SQSTM1/p62, while also activating apoptosis pathways. This resulted in significant cytotoxicity toward lung cancer cells, demonstrating that nano-encapsulation can enhance the anti-tumor efficacy of natural autophagy regulators.

Overall, nanotechnology offers distinct advantages in autophagy-targeted therapy: it can improve the pharmacokinetic properties of drugs, ensure that drugs affecting autophagy pathways accumulate preferentially in tumor tissue, allow co-delivery of multiple agents for combination therapy, and provide stimuli-responsive release for spatial-temporal control of autophagy modulation. Future research should focus on translating these systems from bench to bedside, which will involve scaling up production, ensuring batch-to-batch consistency, conducting thorough toxicity and safety evaluations, and potentially customizing nanotherapies to individual patient tumor profiles (personalized nanomedicine). If successful, nanotechnology-based autophagy modulators could become a powerful component of the lung cancer therapeutic arsenal.

5.6 Clinical Trials of Autophagy Modulation: Mixed Outcomes and Practical Lessons

Despite compelling preclinical data, clinical trials with CQ/HCQ or mTOR inhibitors in lung cancer have yielded variable efficacy [115]. Convergent explanations include: (i) insufficient tumor exposure and incomplete flux inhibition at tolerated doses; (ii) lack of real-time PD readouts (LC3-II/p62 dynamics with lysosomal blockade, lysosomal pH imaging); (iii) suboptimal timing with chemotherapy/EGFR-TKIs (continuous blockade may dampen immunogenic stress signals); (iv) off-target toxicities constraining dose intensity; (v) failure to stratify by autophagy-addicted genotypes/phenotypes (e.g., KL subtype). Actionable trial design upgrades: embed PD/PK biomarkers, adopt pulse-timed schedules synchronized to cytotoxic peak stress, prioritize lung-targeted delivery (e.g., inhalable CQ analogs), and pre-select patients by autophagy/metabolic signatures to enrich for benefit.

Given the heterogeneous roles and context-dependence of autophagy in lung cancer, clinical use of autophagy modulators should be anchored in three pillars: (i) biomarker-defined patient selection, (ii) prospective safety monitoring tailored to mechanism, and (iii) PD proof of on-target autophagy modulation in tumor tissue. First, selection should enrich for putative "autophagy-addicted" contexts—e.g., KL genotype (KRAS with LKB1 loss), KEAP1/NRF2 alterations, high TFEB/lysosomal signatures, mitophagy-high phenotypes, or elevated basal flux (LC3-II/p62 dynamics under short CQ/bafilomycin pulses). Where feasible, ferritinophagy/mitophagy readouts (NCOA4–ferritin puncta; PINK1/Parkin recruitment; mt-Keima ratio) and lipid circuitry (SCD1/MUFA–PUFA balance) can refine eligibility.

Second, safety profiles are mechanism-specific and warrant proactive monitoring. Lysosomotropic agents (e.g., CQ/HCQ) carry risks of QT prolongation, retinopathy (cumulative dose), cytopenias, and GI intolerance; rapalogs/mTOR inhibitors may cause stomatitis, hyperglycemia/dyslipidemia, and non-infectious pneumonitis; broad or prolonged autophagy suppression can impair immune and muscle/organelle homeostasis. Practical mitigations include pulse-timed/sequence-based dosing (rather

than continuous exposure), ECG monitoring when combined with TKIs, baseline ophthalmologic assessment for long courses, metabolic panels (glucose/lipids), and parallel immune fitness checks (e.g., LC3/ATG signatures in T/NK subsets).

Third, trial designs should mandate in-tumor PD confirmation (e.g., TFEB nuclear translocation, LC3-II kinetics under short BafA1/CQ pulses, lysosomal pH imaging) as co-primary or key secondary endpoints, with pre-specified stop/go rules tied to flux correction. Biomarker-embedded, enrichment or adaptive randomization strategies are preferred, and tumor-preferential delivery (inhalable or nano-enabled formulations; organelle-targeted agents) can widen the therapeutic window.

Current and prior clinical attempts (e.g., CQ/HCQ combinations; rapalog-based strategies) have yielded mixed efficacy—likely reflecting incomplete intratumoral flux blockade at tolerated doses, suboptimal scheduling relative to therapy-induced stress, and lack of PD/selection. We therefore advocate biomarker-guided, pulse-timed regimens that synchronize autophagy modulation with chemotherapy, EGFR-TKIs, or immune checkpoint inhibitors, while embedding safety and PD gates to balance antitumor benefit against on-target liabilities.

5.7 Combining Autophagy Modulators With Conventional Therapies

The integration of autophagy-targeted strategies with standard lung cancer treatments has shown great promise in overcoming resistance and improving efficacy. Below we outline how autophagy modulation can be combined with chemotherapy, targeted therapy, immunotherapy, and other novel strategies, highlighting recent advances and future prospects:

5.7.1 Combined With Chemotherapy: Overcoming Drug Resistance

Chemotherapy resistance is a major hurdle in lung cancer treatment, and aberrant activation of autophagy in cancer cells is a known contributor to chemoresistance. Consequently, combining autophagy modulators with chemotherapeutic agents has been explored as a way to resensitize tumors to treatment. Several innovative approaches have yielded encouraging results.

5.7.1.1 Lysosomal Inhibition to Abrogate Cytoprotective Autophagy. CQ and its derivatives, which raise lysosomal pH and inhibit autophagic degradation, have been tested in combination with chemotherapy. Circu *et al*. [147] demonstrated that CQ induces lysosomal membrane permeabilization (LMP), effectively undermining the cytoprotective autophagy of cisplatin-resistant lung cancer cells. When used with cisplatin, CQ significantly increased apoptosis of resistant cells. This effect was enhanced when autophagy was independently disrupted (e.g., by ATG5 knockdown), which caused an accumulation of mitochondrial ROS, further driving cell death. These findings suggest that pharmacological lysosomal inhibitors can synergize with chemotherapy by preventing completion of the autophagy process that would otherwise dispose of damaged mitochondria and drugs.

5.7.1.2 Natural Compounds Targeting Autophagy Pathways. The naturally derived pentacyclic triterpenoid acetyl-keto-beta-boswellic acid (AKBA) has been found to increase chemo-sensitivity through a dual mechanism [117]. AKBA upregulates the cyclin-dependent kinase inhibitor $p21^{Waf1/Cip1}$, causing G_1 cell cycle arrest, and simultaneously downregulates autophagy by inhibiting the ATG5–LC3 conjugation system, thereby reducing autophagosome formation. In 3D lung cancer spheroid models, AKBA in combination with chemotherapy agents produced significantly greater growth suppression than chemotherapy alone. This demonstrates that targeting autophagy with less conventional compounds like boswellic acid derivatives could be a viable adjunct to mainstream chemotherapy.

5.7.1.3 Selective Degradation of Drug Efflux Pumps via Autophagy. Overexpression of drug efflux transporters (like ABC family proteins) is a common mechanism of multidrug resistance in lung cancer. An intriguing strategy is to harness autophagy to degrade these pumps. A recent study showed that a synthetic derivative of hyperoside, named HyFS, could induce selective autophagy of the ATP-binding cassette subfamily G member 2 (ABCG2) transporter in lung cancer cells [118]. By activating autophagy, HyFS promoted the lysosomal degradation of ABCG2, thereby reducing drug efflux and restoring the efficacy of chemotherapeutic substrates of ABCG2 (such as mitoxantrone). In xenograft models, the combination of HyFS and mitoxantrone synergistically inhibited tumor growth without significant additional toxicity. This illustrates a novel therapeutic concept: using autophagy as a tool to eliminate resistance-conferring proteins from cancer cells.

5.7.1.4 Nanotechnology for Dual Action (Autophagy Blockade and Chemosensitization). Building on the idea of co-delivery mentioned earlier, one study developed a polyethyleneimine (PEI)-based nanoparticle carrying paclitaxel (PTX) and siRNA against MDR1 (P-glycoprotein) [119]. This nano-complex had a two-fold effect: the PEI component itself prevented autophagosome-lysosome fusion (likely by proton sponge effect and lysosomal destabilization), and the siMDR1 silenced the gene encoding a key drug efflux pump. In a cisplatin-resistant lung cancer cell model, this combination nanoparticle drastically lowered the IC_{50} of paclitaxel (to ~12.5% of its value in resistant cells without the nanoparticle). This showcases

how combining genetic approaches (siRNA) with pharmacological ones in a nanocarrier can tackle multiple resistance pathways concurrently—here, autophagy-dependent survival and drug efflux.

5.7.1.5 Targeting Mitophagy to Counter Apoptosis Resistance. As mentioned, excessive mitophagy can allow cancer cells to evade apoptosis by promptly clearing damaged mitochondria that pro-apoptotic signals originate from. BEX2, which enhances mitophagy via crotonylation of autophagy proteins, is overexpressed in lung adenocarcinoma and is associated with poor prognosis in lymph node metastasis-free cancer. Therefore, combination treatment with pharmaceutical approaches targeting BEX2-induced mitophagy and anticancer drugs may represent a potential strategy for NSCLC therapy [148]. This underscores the potential of targeting specific regulators of mitophagy or their modifications (like crotonylation) to counteract chemoresistance.

5.7.1.6 Autophagy's Janus-face with Herbal Compounds. Certain herbal or dietary compounds can induce protective autophagy that dampens their own cytotoxic effects. Cycloastragenol, a telomerase-activating compound derived from Astragalus, was shown to activate the AMPK/ULK1 axis, thus inducing autophagy in lung cancer cells [120]. While cycloastragenol has pro-apoptotic effects, the parallel induction of autophagy can counteract cell death by serving as a survival pathway. Indeed, when combined with CQ (to inhibit autophagy), the tumor-suppressive effect of cycloastragenol was markedly amplified (tumor growth inhibition was 2.3 times higher than with cycloastragenol alone). This example illustrates a scenario where autophagy plays a protective role for the cancer cell, and its inhibition can unleash the full potential of an anti-cancer agent.

In conclusion, by co-opting autophagy inhibition or modulation in conjunction with chemotherapy, we can in many cases dismantle the resistance mechanisms of lung cancer cells. These strategies range from broad approaches (like CQ-mediated lysosomal inhibition) to highly specific ones (like autophagic degradation of a particular protein such as ABCG2). A critical consideration for future development is the timing of autophagy inhibitor administration relative to chemotherapy—too early or too strong an autophagy blockade might cause excessive normal tissue toxicity or sensitize normal cells to chemotherapy, whereas too late might allow cancer cells to already neutralize the drug. Therefore, optimized dosing schedules and possibly spatial targeting (using nanocarriers or local delivery) will be crucial to maximize tumor-specific effects. Clinical trials investigating agents like HCQ in combination with chemotherapies in lung cancer are ongoing and will shed further light on the practicality and benefits of these approaches.

5.7.2 Combined With Targeted Therapy: Reversing EGFR-TKI Resistance

Resistance to EGFR tyrosine kinase inhibitors (TKIs) is a significant problem in the treatment of EGFR-mutant NSCLC. Autophagy has been identified as a key adaptive mechanism that cancer cells employ to survive TKI treatment, making it a promising target to overcome resistance. Multiple studies have explored combining autophagy modulators with EGFR-TKIs to reverse resistance:

5.7.2.1 Disabling Protective Autophagy in TKI-Resistant Cells. It has been observed that when EGFR-TKI-resistant NSCLC cells are exposed to drugs like erlotinib, they often exhibit elevated autophagic activity as a survival response [149]. By preemptively inhibiting autophagy, one can remove this "shield" and push cells towards apoptosis. CQ (or its analogs) has been shown to be effective in this regard; it blocks autophagosome-lysosome fusion, thereby preventing the completion of autophagy and sensitizing resistant cells to erlotinib. Experiments demonstrated that CQ restored the ability of erlotinib to induce cell death in TKI-resistant cell lines by preventing the autophagic clearance of damaged organelles and proteins that would otherwise mitigate drug-induced stress.

5.7.2.2 Leveraging Autophagy Activators in Certain Contexts. While autophagy inhibition is beneficial in many resistant scenarios, there are contexts where promoting autophagy can be advantageous. For instance, as discussed, re-expression of PAQR3 in resistant cells enhanced erlotinib-induced autophagic flux, which led to more effective elimination of stress-damaged components and ultimately to increased cell death (in this context, autophagy was acting in a pro-death manner rather than a protective one) [62]. This suggests that in certain resistant tumors, autophagy might be impaired or insufficient, and boosting it (beyond a threshold) could trigger autophagy-dependent cell death. Therefore, understanding the baseline autophagy status of a resistant tumor is key to deciding whether to use an autophagy inducer or inhibitor in combination therapy.

5.7.2.3 mTOR Inhibition and Co-delivery Strategies. Combining EGFR-TKIs with mTOR inhibitors like rapamycin has shown a synergistic effect by hitting two survival pathways. Rapamycin will activate autophagy (by inhibiting mTOR, the autophagy suppressor) but also directly impede a key growth pathway, while EGFR-TKIs target the primary oncogenic driver. One innovative approach used an aptamer-functionalized nanoparticle (NP-Apt) to co-deliver gefitinib (an EGFR-TKI) and rapamycin specifically to tumor cells [121]. The aptamer provided specificity by binding to a cancer cell surface marker, improving drug accumulation in tumor tissue. This combined treatment established a positive feedback loop: EGFR inhibition led to

upregulation of LC3B (a hallmark of autophagy) and increased autophagosome formation, while mTOR inhibition ensured that this autophagy was not aborted prematurely. The heightened autophagy, interestingly, was of a cytotoxic nature in this setting, and it also resulted in the presentation of more EGFR on the cell surface (perhaps through altered trafficking), which paradoxically made the cancer cells more susceptible to gefitinib again, thus breaking the resistance. The net result was substantial cancer cell death and tumor regression in models of TKI resistance.

5.7.2.4 Targeting ER Stress and Other Pathways. Resistance to therapy often involves crosstalk between autophagy and other cellular stress pathways, like the unfolded protein response/ER stress. PAK4, a kinase implicated in cytoskeletal dynamics and survival signaling, was found to modulate ER stress responses and autophagy. Knocking down PAK4 in lung cancer cells increased their sensitivity to cisplatin by exacerbating ER stress and reducing protective autophagy, pointing to a potential target for combination with TKIs as well if PAK4 contributes to TKI resistance via similar mechanisms [150]. Indeed, some EGFR-TKI-resistant cells show activation of bypass pathways (like MET, AXL, etc.) that can induce ER stress or alter autophagy, so adding agents that target those (like a PAK4 inhibitor) could synergize with EGFR-TKIs.

5.7.2.5 Natural Compounds and Dual-Targeting Strategies. Natural products continue to be a source of compounds that can target multiple pathways. Betulinic acid (BA), for example, can simultaneously inhibit wild-type EGFR signaling and downregulate the PI3K-AKT-mTOR pathway, effectively inducing autophagy and apoptosis. When BA was combined with osimertinib (a third-generation EGFR-TKI) in models with primary resistance (*de novo* resistance) to osimertinib, it helped overcome this resistance by fostering autophagy-dependent cell death [122]. Similarly, berberine, an alkaloid, has been found to promote the autophagic degradation of EGFR itself (thus downregulating both wild-type and mutant EGFR levels). In EGFR-TKI-resistant cells, berberine plus icotinib (a first-generation TKI) yielded a 4–6 fold increase in sensitivity compared to icotinib alone, highlighting a potentially low-toxicity combination strategy for TKI resistance [123].

5.7.2.6 Targeting Autophagy–Ferroptosis Crosstalk in KRAS-Mutant Cancers. KRAS-mutant lung adenocarcinomas often do not respond to EGFR-TKIs, but they have their own targeted therapies under development. Autophagy can contribute to therapy resistance in these cancers too. Recent work pinpointed USP13 as a regulator of the NRF2-p62-KEAP1 pathway that simultaneously affects autophagy and ferroptosis in KRAS-driven tumors [151]. By stabilizing NRF2 (through p62 and KEAP1 interactions), USP13 helps tumor cells cope with oxidative stress and avoid ferroptosis, a type of cell death. Inhibiting USP13 could thus make KRAS-mutant tumors more susceptible to oxidative damage and ferroptotic death, while also removing a block on autophagy flux that might be contributing to an aggressive phenotype. Combining a USP13 inhibitor with conventional therapy might produce a "double hit"—promoting a destructive form of autophagy or cell death while interfering with a metabolic stress defense.

5.7.2.7 Cell Cycle and Autophagy Intersection. Aurora kinase A (AURKA) has been implicated in cancer cell cycle progression and has connections to autophagy regulation. Alisertib, an AURKA inhibitor, was shown to overcome acquired resistance to osimertinib by upregulating the pro-apoptotic protein BIM and suppressing a form of autophagy that was protecting the resistant cells [152]. The study implied that resistant cells, when treated with osimertinib, may rely on AURKA-mediated signals to avoid death (potentially through autophagy or other stress pathways), and blocking AURKA tipped the balance towards apoptosis. This suggests that combining cell cycle kinase inhibitors (like alisertib) with EGFR-TKIs may be a fruitful approach in resistant cases, especially if those cases display high autophagic activity and survival signaling.

In summary, tackling EGFR-TKI resistance with autophagy-focused combination strategies requires a nuanced approach, as autophagy can either help or hinder cell survival depending on context. Key to success will be biomarkers that tell us whether a particular resistant tumor is "autophagy-addicted" (hence vulnerable to autophagy inhibition) or "autophagy-impaired" (hence could be pushed into lethal autophagy). Ongoing clinical trials are evaluating combinations like osimertinib with HCQ, and preclinical research continues to propose new combinations (like EGFR-TKIs with METTL3 inhibitors, or with natural compounds like BA/berberine). As these strategies move forward, careful patient selection and real-time monitoring of autophagy markers during therapy might be necessary to ensure that the autophagy is being modulated in the intended direction.

5.7.3 Combined With Immunotherapy: Remodeling the Tumor Microenvironment

Immunotherapy, particularly immune checkpoint blockade (ICB), has revolutionized the treatment of advanced NSCLC. However, only a subset of patients achieve durable responses, often due to an immunosuppressive tumor microenvironment (TME) that fosters immune evasion. Modulating autophagy presents an opportunity to favorably alter the TME and improve the efficacy of immunotherapies. Some key insights and strategies include:

5.7.3.1 Normalization of Tumor Vasculature to Enhance Immune Infiltration. Combining angiogenesis inhibitors

with immunotherapy can improve T-cell delivery to the tumor. As mentioned, Endostar (endostatin) combined with anti-PD-1 therapy led to more normalized tumor vessels and greater CD8+ T cell infiltration in a lung cancer model [131]. This was accompanied by autophagy activation in tumor cells via the PI3K/AKT/mTOR pathway. The autophagy activation in tumor cells may increase the presentation of tumor antigens or the release of immune-stimulating factors (due to autophagy-related secretion or cell death), thereby enhancing the response to PD-1 blockade. This combination exemplifies a multi-target approach: starving the tumor, feeding the immune system, and modulating autophagy to make cancer cells more immunogenic.

5.7.3.2 Direct Autophagy–Immune Synergy. Tubeimoside-1 (TBM-1), a natural compound from Bolbostemma paniculatum, showed an interesting synergy with immunotherapy [124]. TBM-1 inhibited mTOR, thereby activating autophagy as well as promoting nuclear translocation of TFEB (which drives expression of lysosomal and autophagy genes). One consequence was that TBM-1 induced lysosomal degradation of PD-L1 in tumor cells, reducing their ability to inhibit T cells. In a murine model, TBM-1 combined with CTLA-4 blockade not only reduced PD-L1 levels but also decreased immunosuppressive cells (MDSCs and Tregs) in the TME, while increasing effector T cell infiltration. This highlights how an autophagy activator that also degrades PD-L1 can convert a "cold" tumor into a "hot" one more receptive to immunotherapy.

5.7.3.3 Mitophagy and Immune Resistance. As discussed earlier, excessive mitophagy via proteins like BEX2 can help tumor cells avoid apoptosis. It appears such mechanisms might also dampen the effectiveness of immune-mediated killing. If a tumor cell quickly removes damaged mitochondria and other cell stress signals through autophagy, it might not undergo immunogenic cell death (which is often required to fully activate T cells). High BEX2 expression in LUAD correlates with poor prognosis, and one could speculate that it also correlates with poor response to immunotherapy (as it keeps the cells from dying in a way that alerts the immune system) [148]. Therapeutically, inhibiting BEX2 or its pathway (e.g., NDP52-LC3 interactions) could make tumor cells more prone to die in an immunogenic manner when challenged by T cells or immunotherapy.

5.7.3.4 PAK4 and Immune Evasion. PAK4 was mentioned as influencing ER stress and autophagy in the context of chemotherapy. Interestingly, it also has a role in shaping the immune environment. Tumors with high PAK4 activity have been linked to exclusion of T cells and an increase in immunosuppressive factors, leading to resistance to PD-1 therapy. The PAK4 inhibitor KPT-9274 has been shown to increase tumor infiltration by T cells and potentiate PD-1 blockade effects in preclinical models [153]. Part of this effect might be due to alterations in autophagy or metabolism in the tumor cells or stroma (PAK4 can affect metabolic pathways and potentially autophagy). Thus, combining PAK4 inhibitors with ICB could be another strategy to turn immunologically cold tumors hot, possibly by relieving a brake on autophagy-related immunogenic processes or by inducing a form of cell stress that draws immune attention.

5.7.3.5 Ferroptosis-Related Autophagy and Immunotherapy. Ferroptosis is known to release distinct signals that can influence immune responses. A protein called TMEM164 was identified as a positive regulator of autophagy that specifically promotes ferroptosis in lung adenocarcinoma by facilitating autophagosome formation in an ATG5-dependent manner, leading to ferritin degradation and iron release [154]. Upregulation of TMEM164 led to more ferroptotic cell death and slowed tumor growth. Importantly, tumors with higher TMEM164 (hence higher ferroptosis and autophagy levels) responded better to anti-PD-1 therapy, possibly because ferroptosis can be inflammatory and immune-stimulating. This suggests that inducing ferroptosis through autophagy (e.g., via drugs that mimic TMEM164's effect or via NCOA4-mediated ferritinophagy as seen with Huaier in section 5.7.4) might improve checkpoint inhibitor outcomes. Therefore, combining ferroptosis inducers or autophagy modulators that cause ferroptosis with PD-1/PD-L1 inhibitors might be an effective strategy.

5.7.3.6 Targeting CAF Autophagy to Overcome Immune Suppression. The role of autophagy in stromal cells, particularly CAFs, also impacts immune response. As noted, p62 in CAFs can drive a pro-tumor, immunosuppressive microenvironment by activating Nrf2 and ATF6, leading to secretion of TGF-β and other factors that inhibit effector immune cells [155]. If we inhibit autophagy in CAFs or block the p62-Nrf2 pathway, we might reduce the release of those suppressive factors and thereby enhance T and NK cell penetration and activity. While directly targeting CAF autophagy is complex, therapies like AXL inhibitors or others that affect CAF biology could indirectly modulate autophagy in those cells. Alternatively, using autophagy inhibitors might need to be timed and delivered in a way that affects CAFs or myeloid cells more than T cells (to avoid impairing T cell function, as T cells also use autophagy for memory and survival).

5.7.3.7 ER Stress, Autophagy, and Immune Checkpoints. The connection between ER stress and autophagy means that ER stress regulators can affect immune signaling. PRKCSH, a gene involved in protein folding and ER stress, was found to modulate PD-L1 levels through the IRE1α branch of the UPR [156]. Loss of PRKCSH de-

creased PD-L1 and some other inhibitory molecules, while boosting immune cell cytotoxicity. Although not directly stated as an autophagy effect, severe ER stress often leads to autophagy. Thus, there might be a link where modulating ER stress (by targeting PRKCSH or IRE1α) could indirectly modulate autophagy and improve antigen presentation or other immune functions. Combining ER stress inducers or modulators with immunotherapy might be another frontier, ensuring that any induced autophagy in this process is the kind that helps alert the immune system.

In summary, the interplay of autophagy and immunity is offering a new suite of combination therapy opportunities: from using autophagy inducers to break down immunosuppressive checkpoints and barriers, to using autophagy inhibitors to promote antigen presentation and inflammatory cell death, to reprogramming the metabolism of cancer and stromal cells for a more immune-favorable environment. The major challenge will be the complexity of these interactions—what helps T cells might hurt them if done excessively (for example, T cells also need some autophagy for longevity), and vice versa. Therefore, combination regimens will likely require careful titration and possibly sequential scheduling (e.g., a short pulse of autophagy induction to clear PD-L1 followed by an autophagy inhibition phase to boost antigen presentation, all while administering a checkpoint inhibitor). Personalization based on tumor immune profiling will be key to determine which approach fits a given patient (for instance, a patient with high PD-L1 might benefit from autophagy inducers that degrade PD-L1, whereas a patient with poor antigen presentation might need autophagy inhibition). Nonetheless, these strategies hold promise for converting partial immunotherapy responders into full responders and turning "cold" tumors "hot".

5.7.4 Novel Combination Strategies: Metabolic and Apoptotic Modulation

Beyond traditional chemo- and immunotherapy, newer combination paradigms are being explored that involve modulating tumor metabolism and apoptosis alongside autophagy, effectively attacking cancer cells on multiple homeostatic fronts simultaneously. Key examples include:

5.7.4.1 Metformin and Metabolic Reprogramming. Metformin, a widely used anti-diabetic drug, has gained attention for its anticancer properties, especially in lung cancer, where it has been observed to reduce incidence and improve outcomes in diabetic patients. Mechanistically, metformin activates AMPK and inhibits mitochondrial complex I, which affects the energy status and mTOR signaling in cells. Recent studies demonstrated that metformin has multi-faceted anti-tumor effects in both NSCLC and SCLC [125,126]. For example, in NSCLC A549 cells, metformin was found to synergize with the HSP90 inhibitor gedunin to co-suppress the EGFR/PI3K/AKT pathway, and this was associated with altered autophagy levels leading to increased apoptosis [157,158]. In SCLC, metformin combined with cisplatin yielded superior outcomes by influencing the EGFR/AKT/AMPK/mTOR axis; essentially, metformin helped convert cisplatin-induced autophagy from cytoprotective to autophagy-dependent cell death, thereby enhancing cancer cell kill [159]. Remarkably, metformin also appeared to ameliorate some cisplatin side effects (like nephrotoxicity and myelosuppression), possibly by protecting normal tissues through its mild metabolic effects. In a cisplatin-resistant setting, metformin helped re-sensitize tumors to the drug, likely by altering the tumor metabolic microenvironment—reducing levels of tumor-derived lactate and insulin/IGF signals that can promote resistance, and by maintaining a pressure on the tumor's energy production that when combined with cisplatin becomes unsustainable for the cancer cells [160]. These findings support the idea that metabolic drugs like metformin can be repurposed to hit cancer metabolism and autophagy simultaneously, weakening the tumor's defenses and enhancing standard therapy efficacy.

5.7.4.2 Ferroptosis Induction via Autophagy Modulation. Huaier, a traditional Chinese medicinal mushroom (Trametes robiniophila), has shown promise as an anti-cancer agent. Its extract or active components have been reported to inhibit lung cancer progression by a dual mechanism relevant to ferroptosis [127]. Huaier was shown to simultaneously suppress the cystine/glutamate antiporter system Xc^- (thus lowering glutathione and inactivating GPX4, which normally prevents lipid peroxidation) and to activate NCOA4-mediated ferritinophagy, which releases free iron from ferritin. This combination leads to accumulation of lipid ROS and triggers ferroptosis in NSCLC cells. Essentially, Huaier takes off the brakes and presses the accelerator for ferroptosis—it disables an antioxidant system and promotes iron-catalyzed ROS generation via autophagy of ferritin. By doing so, it significantly inhibited lung tumor growth in models. This "two birds, one stone" approach is particularly elegant because ferroptosis is a form of cell death that cancer cells are often not primed to resist (unlike apoptosis), and it can be highly inflammatory (thus potentially drawing immune attention as well). Using compounds like Huaier in combination with other treatments could help in cases where cells have become apoptosis-resistant but might still be ferroptosis-sensitive. It's also a largely non-overlapping toxicity profile, since ferroptosis inducers like Huaier might not harm normal cells as much as chemo does, providing a therapeutic window.

5.7.4.3 Autophagy Inhibition to Enhance Apoptosis (TFPA example). A novel benzimidazole derivative, TFPA, has been identified as an autophagy inhibitor that specifically blocks autophagosome-lysosome fusion, akin to CQ but

possibly more specific or potent. When used with the topoisomerase inhibitor camptothecin (CPT), TFPA was able to significantly increase apoptosis in lung cancer cells by preventing the autophagic removal of CPT-induced damage [128]. The combination was tested in a zebrafish xenograft model (a rapid *in vivo* screening model) and demonstrated enhanced efficacy and safety. This underscores the potential of targeting the final stages of autophagy to ensure that pro-apoptotic signals (like DNA damage from CPT) are not mitigated by autophagy. It's a proof-of-concept that by judiciously inhibiting autophagy at the right time, one can tip the balance fully towards apoptosis. TFPA's specificity for the autophagosome-lysosome fusion step might give it an advantage in terms of reducing side effects compared to inhibiting autophagy initiation (which could have complex systemic effects, given autophagy's role in normal cell homeostasis).

Looking forward, these novel strategies—whether using metabolic drugs like metformin, ferroptosis inducers like Huaier, or apoptosis boosters like TFPA—expand the toolkit for oncologists. They reflect an understanding that cancer cells are robust precisely because they have redundant survival strategies: if not by glycolysis, then by oxidative phosphorylation; if not by blocking apoptosis, then by avoiding ferroptosis; if not by one pathway, then by another. Thus, combination strategies that strike multiple essential survival pathways concurrently stand the best chance at overcoming resistance.

6. Autophagy Regulation in Lung Cancer: Targeted Therapy Strategies

6.1 EMT and Metastasis

Autophagy supports EMT by supplying acetyl-CoA for chromatin remodeling (e.g., Snail acetylation) and by buffering redox stress during invasion; conversely, excessive selective autophagy of focal-adhesion/β-catenin components can restrain motility—implying a non-linear relationship that may be exploited to time autophagy modulation around metastatic bottlenecks [69]. Mechanistically, autophagy-derived acetyl-CoA sustains CBP/p300-dependent acetylation of EMT TFs (e.g., Snail), while mitophagy curbs mitoROS to permit survival during detachment and intravasation; in contrast, p62/SQSTM1-mediated targeting of β-catenin or adhesion scaffolds can limit protrusion dynamics and migration [161]. Operationally, we propose pulse-timed autophagy modulation at two bottlenecks—(i) early dissemination (to blunt survival during anoikis and circulation) and (ii) post-extravasation seeding (to prevent metabolic adaptation)—guided by PD readouts such as LC3-II/p62 dynamics under short CQ/BafA1 pulses, Snail acetylation status, and ^{13}C-tracing of autophagy-derived acetyl-CoA [162]. Lipid circuitry intersects this axis: SCD1/MUFA accumulation lowers lipid peroxidation and may reduce EMT-coupled autophagy stress, suggesting that SCD1 inhibition combined with autophagy re-balancing could constrain invasion in MUFA-skewed tumors.

6.2 SCLC-Specific Considerations

SCLC exhibits high basal autophagy/mitophagy linked to chemo-resistance. Targeting mitophagy regulators (e.g., METTL3-TFEB axes or BEX2-NDP52 interactions) can resensitize cells to platinum/etoposide in models, warranting SCLC-tailored trials with mitophagy-centric PD endpoints [108]. Given the neuroendocrine lineage and rapid cycling of SCLC, mitophagy sustains mitochondrial quality and ATP homeostasis during platinum-induced stress; enforcing mitophagy blockade unmasks ROS-driven death. Prospective SCLC studies should embed mitophagy PD (mt-Keima ratio, PINK1/Parkin recruitment, TFEB nuclear translocation) alongside clinical endpoints, and test pulse-timed mitophagy restraint (e.g., USP30 inhibition or late-stage fusion blockade) layered onto platinum/etoposide, with mandatory tumor or ctPD surrogates confirming on-target flux modulation. Because autophagy also shapes antigen processing, combinations with PD-1/PD-L1 blockade merit evaluation only when PD shows tumor-selective autophagy engagement, to avoid compromising T/NK cell fitness.

6.3 Tumor Microbiome and the Autophagy–Immunity Axis

Early evidence suggests that intratumoral and airway microbiota can tune epithelial and myeloid autophagy, thereby shaping antigen presentation and checkpoint responses. Defining causality—and whether selective autophagy modulation can "normalize" dysbiotic signals—represents a tractable, high-yield research direction. Microbial ligands (e.g., LPS, peptidoglycan) engage TLR/cGAS–STING pathways that intersect with autophagy/xenophagy [163], influencing PD-L1 turnover, MHC-I presentation, and cytokine milieus. We advocate paired airway/tumor microbiome profiling (16S/shotgun plus metabolomics) with epithelial/myeloid autophagy PD (LC3 puncta, p62 turnover, lysosomal pH) to map microbe–autophagy–immunity triads and identify actionable "dysbiosis-autophagy" phenotypes. Interventional concepts—such as short-course antibiotics avoidance, pre-/post-biotics, or bacterially derived autophagy modulators—should be tested cautiously in window-of-opportunity designs, with predefined safety gates and immune monitoring to preserve antitumor immunity.

7. Conclusions and Future Perspectives

Autophagy in lung cancer is neither uniformly protective nor uniformly lethal; it is conditional biology governed by genotype, stress context, and microenvironment. Past clinical efforts often failed not because the target was unimportant, but because modulation was untimed, unstratified, and unmeasured. Going forward, we advocate: (i) biomarker-guided patient selection (au-

tophagy/metabolic signatures); (ii) embedded PD assessment of flux in early-phase trials; (iii) spatiotemporally controlled delivery (including inhalable or tumor-targeted platforms); (iv) organelle-selective interventions (mitophagy/Golgiphagy) aligned to resistance mechanisms; and (v) rational combinations (with EGFR-TKIs, immunotherapy, anti-angiogenesis, ferroptosis inducers, or metabolic drugs) using pulse-timed schedules. Equally important, proposed biomarkers (e.g., SNORD88C, circRAPGEF5, RBBP4) must traverse the full validation pathway—analytic robustness, multicenter prospective clinical validity, and demonstrated clinical utility over standard-of-care metrics. If these principles are implemented, autophagy modulation can transition from broad, empiric add-on to a precise and testable pillar of lung cancer therapy. Clinically, successful autophagy modulation will likely require biomarker-defined selection, PD-confirmed target engagement, and safety-aware pulse-timed regimens that convert context-dependent autophagy from a survival mechanism into a therapeutic liability.

Abbreviations

AAA, abdominal aortic aneurysm; ACAT1, acyl-CoA:cholesterol acyltransferase 1; AD, andrographolide; ADSL, adenylosuccinate lyase; AKBA, acetyl-keto-beta-boswellic acid; ALO, aloperine; ALT, alanine transaminase; AMPK, AMP-activated protein kinase; AMBRA1, autophagy/beclin-1 regulator 1; ATF4, activating transcription factor 4; ATG, autophagy-related gene/protein; BA, betulinic acid; BECN1, *Beclin 1* gene; BEX2, brain-expressed X-linked 2; Bcl-xL, B-cell lymphoma-extra large; Bcl-xS, B-cell lymphoma-extra small; Bis, α-bisabolol; CAF, cancer-associated fibroblast; CBP, CREB-binding protein; CD133, cluster of differentiation 133; CD44, cluster of differentiation 44; CD8, cluster of differentiation 8; CDH1, E-cadherin; CQ, chloroquine; CPT, camptothecin; CRRT, continuous renal replacement therapy; CT, computed tomography; CXCL10, C-X-C motif chemokine ligand 10; DBIL, direct bilirubin; DUSP1, dual specificity phosphatase 1; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; eIF5A2, eukaryotic translation initiation factor 5A2; ER, endoplasmic reticulum; ERGIC1, endoplasmic reticulum-Golgi intermediate compartment protein 1; ESCRT, endosomal sorting complexes required for transport; FAIM1, Fas apoptosis inhibitory molecule 1; FFAs, free fatty acids; FTO, fat mass and obesity-associated protein; GPX4, glutathione peroxidase 4; GRP78, glucose-regulated protein 78; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor 1 alpha; HMBOX1, homeobox containing 1; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HTS NPs, hyaluronan-modified sertaconazole nanoparticles; ICD, immunogenic cell death; ICU, intensive care unit; IFNGR1, interferon gamma receptor 1; iASPP, inhibitor of apoptosis-stimulating protein of p53; IVC, inferior vena cava; LC3, microtubule-associated protein 1 light chain 3; LMP, lysosomal membrane permeabilization; LUAD, lung adenocarcinoma; m6A, N^6-methyladenosine; METTL3, methyltransferase-like 3; MCOLN3, mucolipin 3; MDSC, myeloid-derived suppressor cell; MHC-I, major histocompatibility complex class I; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; MUFA, monounsaturated fatty acid; NC, negative control; NCOA4, nuclear receptor coactivator 4; NDP52, nuclear dot protein 52 kDa; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIC-CS-PCL-NA, niclosamide–chitosan–polycaprolactone nano-assemblies; NK, natural killer; NNT, nicotinamide nucleotide transhydrogenase; NRF2, nuclear factor erythroid 2-related factor 2; NSCLC, non-small cell lung cancer; PAK4, p21-activated kinase 4; PAQR3, progestin and AdipoQ receptor family member 3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PEI, polyethyleneimine; PEL13, pellino E3 ubiquitin protein ligase 3; PINK1, PTEN-induced putative kinase 1; PVT1, plasmacytoma variant translocation 1; PTS, p-toluenesulfonamide; PTX, paclitaxel; ROS, reactive oxygen species; SCD1, stearoyl-CoA desaturase 1; SCLC, small cell lung cancer; SIRT2, sirtuin 2; SNORD88C, small nucleolar RNA, C/D box 88C; SQSTM1/p62, sequestosome 1; SREBF1/SREBP1, sterol regulatory element-binding protein 1; TFEB, transcription factor EB; TFPA, 2-(3-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazol-2-yl)acetonitrile; TCA, tricarboxylic acid; TBIL, total bilirubin; TBM-1, tubeimoside-1; TKI, tyrosine kinase inhibitor; TLR4, toll-like receptor 4; TMEM164, transmembrane protein 164; TRAF6, TNF receptor-associated factor 6; TRIM21, tripartite motif-containing 21; UBE2C, ubiquitin-conjugating enzyme E2C; UBE2T, ubiquitin-conjugating enzyme E2T; ULK1, Unc-51-like kinase 1; UPR, unfolded protein response; USP, ubiquitin-specific protease; VPS4A, vacuolar protein sorting-associated protein 4A; VEGFR2, vascular endothelial growth factor receptor 2; YY1, ying yang 1.

Author Contributions

CY conceived and executed the idea for this manuscript and finalized it. YM and JC wrote several sections of the manuscript and designed figures. JC designed Table 1. HC and CY substantially contributed to the conception and drafting of the review. All authors contributed to the final editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Klionsky DJ. The molecular machinery of autophagy: unanswered questions. Journal of Cell Science. 2005; 118: 7–18. https://doi.org/10.1242/jcs.01620.

[2] Sil P, Muse G, Martinez J. A ravenous defense: canonical and non-canonical autophagy in immunity. Current Opinion in Immunology. 2018; 50: 21–31. https://doi.org/10.1016/j.coi.2017.10.004.

[3] Singh SS, Vats S, Chia AYQ, Tan TZ, Deng S, Ong MS, *et al*. Dual role of autophagy in hallmarks of cancer. Oncogene. 2018; 37: 1142–1158. https://doi.org/10.1038/s41388-017-0046-6.

[4] Zhao YG, Codogno P, Zhang H. Machinery, regulation and pathophysiological implications of autophagosome maturation. Nature Reviews. Molecular Cell Biology. 2021; 22: 733–750. https://doi.org/10.1038/s41580-021-00392-4.

[5] Noda T, Matsunaga K, Taguchi-Atarashi N, Yoshimori T. Regulation of membrane biogenesis in autophagy via PI3P dynamics. Seminars in Cell & Developmental Biology. 2010; 21: 671–676. https://doi.org/10.1016/j.semcdb.2010.04.002.

[6] Shpilka T, Weidberg H, Pietrokovski S, Elazar Z. Atg8: an autophagy-related ubiquitin-like protein family. Genome Biology. 2011; 12: 226. https://doi.org/10.1186/gb-2011-12-7-226.

[7] Iriondo MN, Etxaniz A, Varela YR, Ballesteros U, Hervás JH, Montes LR, *et al*. LC3 subfamily in cardiolipin-mediated mitophagy: a comparison of the LC3A, LC3B and LC3C homologs. Autophagy. 2022; 18: 2985–3003. https://doi.org/10.1080/15548627.2022.2062111.

[8] Kabeya Y, Mizushima N, Ueno T, Yamamoto A, Kirisako T, Noda T, *et al*. LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing. The EMBO Journal. 2000; 19: 5720–5728. https://doi.org/10.1093/emboj/19.21.5720.

[9] Mizushima N, Murphy LO. Autophagy Assays for Biological Discovery and Therapeutic Development. Trends in Biochemical Sciences. 2020; 45: 1080–1093. https://doi.org/10.1016/j.tibs.2020.07.006.

[10] Xue Y, Han H, Wu L, Pan B, Dong B, Yin CC, *et al*. iASPP facilitates tumor growth by promoting mTOR-dependent autophagy in human non-small-cell lung cancer. Cell Death & Disease. 2017; 8: e3150. https://doi.org/10.1038/cddis.2017.515.

[11] Chen S, Cai D, Zhao Q, Wu J, Zhou X, Xu H, *et al*. NSUN2-mediated m5C modification of circFAM190B promotes lung cancer progression by inhibiting cellular autophagy. International Journal of Biological Macromolecules. 2025; 306: 141528. https://doi.org/10.1016/j.ijbiomac.2025.141528.

[12] Wang L, Li D, Su X, Zhao Y, Huang A, Li H, *et al*. AGO4 suppresses tumor growth by modulating autophagy and apoptosis via enhancing TRIM21-mediated ubiquitination of GRP78 in a p53-independent manner. Oncogene. 2023; 42: 62–77. https://doi.org/10.1038/s41388-022-02526-0.

[13] Zhu J, Ao H, Liu M, Cao K, Ma J. UBE2T promotes autophagy via the p53/AMPK/mTOR signaling pathway in lung adenocarcinoma. Journal of Translational Medicine. 2021; 19: 374. https://doi.org/10.1186/s12967-021-03056-1.

[14] Han T, Wang P, Wang Y, Xun W, Lei J, Wang T, *et al*. FAIM regulates autophagy through glutaminolysis in lung adenocarcinoma. Autophagy. 2022; 18: 1416–1432. https://doi.org/10.1080/15548627.2021.1987672.

[15] Zhang Z, Cui Z, Xie Z, Li C, Xu C, Guo X, *et al*. Deubiquitinase USP5 promotes non-small cell lung cancer cell proliferation by stabilizing cyclin D1. Translational Lung Cancer Research. 2021; 10: 3995–4011. https://doi.org/10.21037/tlcr-21-767.

[16] Li J, Wang Y, Luo Y, Liu Y, Yi Y, Li J, *et al*. USP5-Beclin 1 axis overrides p53-dependent senescence and drives Kras-induced tumorigenicity. Nature Communications. 2022; 13: 7799. https://doi.org/10.1038/s41467-022-35557-y.

[17] Min Y, Kim MJ, Lee S, Chun E, Lee KY. Inhibition of TRAF6 ubiquitin-ligase activity by PRDX1 leads to inhibition of NFKB activation and autophagy activation. Autophagy. 2018; 14: 1347–1358. https://doi.org/10.1080/15548627.2018.1474995.

[18] Kim MJ, Min Y, Jeong SK, Son J, Kim JY, Lee JS, *et al*. USP15 negatively regulates lung cancer progression through the TRAF6-BECN1 signaling axis for autophagy induction. Cell Death & Disease. 2022; 13: 348. https://doi.org/10.1038/s41419-022-04808-7.

[19] Cohen-Eliav M, Golan-Gerstl R, Siegfried Z, Andersen CL, Thorsen K, Ørntoft TF, *et al*. The splicing factor SRSF6 is amplified and is an oncoprotein in lung and colon cancers. The Journal of Pathology. 2013; 229: 630–639. https://doi.org/10.1002/path.4129.

[20] Lv Y, Zhang W, Zhao J, Sun B, Qi Y, Ji H, *et al*. SRSF1 inhibits autophagy through regulating Bcl-x splicing and interacting with PIK3C3 in lung cancer. Signal Transduction and Targeted Therapy. 2021; 6: 108. https://doi.org/10.1038/s41392-021-00495-6.

[21] Zhan W, Han T, Zhang C, Xie C, Gan M, Deng K, *et al*. TRIM59 Promotes the Proliferation and Migration of Non-Small Cell Lung Cancer Cells by Upregulating Cell Cycle Related Proteins. PloS One. 2015; 10: e0142596. https://doi.org/10.1371/journal.pone.0142596.

[22] Han T, Guo M, Gan M, Yu B, Tian X, Wang JB. TRIM59 regulates autophagy through modulating both the transcription and the ubiquitination of BECN1. Autophagy. 2018; 14: 2035–2048. https://doi.org/10.1080/15548627.2018.1491493.

[23] Zhou F, Liu Y, Ai W, Wang Y, Gan M, Jiang Q, *et al*. GNIP1 functions both as a scaffold protein and an E3 ubiquitin ligase to regulate autophagy in lung cancer. Cell Communication and Signaling: CCS. 2022; 20: 133. https://doi.org/10.1186/s12964-022-00936-x.

[24] Hussenet T, Dali S, Exinger J, Monga B, Jost B, Dembelé D, *et al*. SOX2 is an oncogene activated by recurrent 3q26.3 amplifications in human lung squamous cell carcinomas. PloS One. 2010; 5: e8960. https://doi.org/10.1371/journal.pone.0008960.

[25] Miao CC, Hwang W, Chu LY, Yang LH, Ha CT, Chen PY, *et al*. LC3A-mediated autophagy regulates lung cancer cell plasticity. Autophagy. 2022; 18: 921–934. https://doi.org/10.1080/15548627.2021.1964224.

[26] Strohecker AM, Guo JY, Karsli-Uzunbas G, Price SM, Chen GJ, Mathew R, *et al*. Autophagy sustains mitochondrial glutamine metabolism and growth of BrafV600E-driven lung tumors. Cancer Discovery. 2013; 3: 1272–1285. https://doi.org/10.1158/2159-8290.CD-13-0397.

[27] White E. Deconvoluting the context-dependent role for autophagy in cancer. Nature Reviews. Cancer. 2012; 12: 401–410. https://doi.org/10.1038/nrc3262.
[28] Budanov AV. Stress-responsive sestrins link p53 with redox regulation and mammalian target of rapamycin signaling. Antioxidants & Redox Signaling. 2011; 15: 1679–1690. https://doi.org/10.1089/ars.2010.3530.
[29] Crighton D, Wilkinson S, O'Prey J, Syed N, Smith P, Harrison PR, *et al*. DRAM, a p53-induced modulator of autophagy, is critical for apoptosis. Cell. 2006; 126: 121–134. https://doi.org/10.1016/j.cell.2006.05.034.
[30] Tasdemir E, Maiuri MC, Galluzzi L, Vitale I, Djavaheri-Mergny M, D'Amelio M, *et al*. Regulation of autophagy by cytoplasmic p53. Nature Cell Biology. 2008; 10: 676–687. https://doi.org/10.1038/ncb1730.
[31] Ishihara M, Urushido M, Hamada K, Matsumoto T, Shimamura Y, Ogata K, *et al*. Sestrin-2 and BNIP3 regulate autophagy and mitophagy in renal tubular cells in acute kidney injury. American Journal of Physiology-Renal Physiology. 2013; 305: F495–F509. https://doi.org/10.1152/ajprenal.00642.2012.
[32] Ala M. Sestrin2 in cancer: a foe or a friend? Biomarker Research. 2022; 10: 29. https://doi.org/10.1186/s40364-022-00380-6.
[33] Trefny MP, Kaiser M, Stanczak MA, Herzig P, Savic S, Wiese M, *et al*. PD-1$^+$ natural killer cells in human non-small cell lung cancer can be activated by PD-1/PD-L1 blockade. Cancer Immunology, Immunotherapy: CII. 2020; 69: 1505–1517. https://doi.org/10.1007/s00262-020-02558-z.
[34] Wang X, Wu WKK, Gao J, Li Z, Dong B, Lin X, *et al*. Autophagy inhibition enhances PD-L1 expression in gastric cancer. Journal of Experimental & Clinical Cancer Research: CR. 2019; 38: 140. https://doi.org/10.1186/s13046-019-1148-5.
[35] Zhang J, Lin X, Sun Y, Wei J, Wu J. Trim14 promotes osteoclastogenesis and noncanonical NF-κB activation by targeting p100/p52 in chronic periodontitis. Oral Diseases. 2022; 28: 1958–1967. https://doi.org/10.1111/odi.13888.
[36] Li H, Kuang X, Liang L, Ye Y, Zhang Y, Li J, *et al*. The Beneficial Role of Sunitinib in Tumor Immune Surveillance by Regulating Tumor PD-L1. Advanced Science. 2020; 8: 2001596. https://doi.org/10.1002/advs.202001596.
[37] Crinier A, Narni-Mancinelli E, Ugolini S, Vivier E. SnapShot: Natural Killer Cells. Cell. 2020; 180: 1280–1280.e1. https://doi.org/10.1016/j.cell.2020.02.029.
[38] Wennerberg E, Kremer V, Childs R, Lundqvist A. CXCL10-induced migration of adoptively transferred human natural killer cells toward solid tumors causes regression of tumor growth in vivo. Cancer Immunology, Immunotherapy: CII. 2015; 64: 225–235. https://doi.org/10.1007/s00262-014-1629-5.
[39] Karachaliou N, Mayo C, Costa C, Magrí I, Gimenez-Capitan A, Molina-Vila MA, *et al*. KRAS mutations in lung cancer. Clinical Lung Cancer. 2013; 14: 205–214. https://doi.org/10.1016/j.cllc.2012.09.007.
[40] Karsli-Uzunbas G, Guo JY, Price S, Teng X, Laddha SV, Khor S, *et al*. Autophagy is required for glucose homeostasis and lung tumor maintenance. Cancer Discovery. 2014; 4: 914–927. https://doi.org/10.1158/2159-8290.CD-14-0363.
[41] Mowers EE, Sharifi MN, Macleod KF. Autophagy in cancer metastasis. Oncogene. 2017; 36: 1619–1630. https://doi.org/10.1038/onc.2016.333.
[42] Sanchez-Cespedes M, Parrella P, Esteller M, Nomoto S, Trink B, Engles JM, *et al*. Inactivation of LKB1/STK11 is a common event in adenocarcinomas of the lung. Cancer Research. 2002; 62: 3659–3662.
[43] Ji H, Ramsey MR, Hayes DN, Fan C, McNamara K, Kozlowski P, *et al*. LKB1 modulates lung cancer differentiation and metastasis. Nature. 2007; 448: 807–810. https://doi.org/10.1038/nature06030.
[44] Deneka AY, Kopp MC, Nikonova AS, Gaponova AV, Kiseleva AA, Hensley HH, *et al*. *Nedd9* Restrains Autophagy to Limit Growth of Early Stage Non-Small Cell Lung Cancer. Cancer Research. 2021; 81: 3717–3726. https://doi.org/10.1158/0008-5472.CAN-20-3626.
[45] Zhao L, Jiang L, Wang L, He J, Yu H, Sun G, *et al*. UbcH10 expression provides a useful tool for the prognosis and treatment of non-small cell lung cancer. Journal of Cancer Research and Clinical Oncology. 2012; 138: 1951–1961. https://doi.org/10.1007/s00432-012-1275-2.
[46] Wang Y, Shi F, Tao R, Wu J, Gu J, Yang R, *et al*. The Relationship Between UBE2C and AGGF1 Overexpression and Tumor Angiogenesis in Non-Small Cell Lung Cancer. Cancer Management and Research. 2021; 13: 5919–5930. https://doi.org/10.2147/CMAR.S320393.
[47] Zhang S, You X, Zheng Y, Shen Y, Xiong X, Sun Y. The UBE2C/CDH1/DEPTOR axis is an oncogene and tumor suppressor cascade in lung cancer cells. The Journal of Clinical Investigation. 2023; 133: e162434. https://doi.org/10.1172/JCI162434.
[48] Biswas U, Roy R, Ghosh S, Chakrabarti G. The interplay between autophagy and apoptosis: its implication in lung cancer and therapeutics. Cancer Letters. 2024; 585: 216662. https://doi.org/10.1016/j.canlet.2024.216662.
[49] Jing X, Yang F, Shao C, Wei K, Xie M, Shen H, *et al*. Role of hypoxia in cancer therapy by regulating the tumor microenvironment. Molecular Cancer. 2019; 18: 157. https://doi.org/10.1186/s12943-019-1089-9.
[50] Wang X, Cheng Z, Dai L, Jiang T, Li P, Jia L, *et al*. LncRNA PVT1 Facilitates Proliferation, Migration and Invasion of NSCLC Cells via miR-551b/FGFR1 Axis. OncoTargets and Therapy. 2021; 14: 3555–3565. https://doi.org/10.2147/OTT.S273794.
[51] Xu G, Chen H, Wu S, Chen J, Zhang S, Shao G, *et al*. Eukaryotic initiation factor 5A2 mediates hypoxia-induced autophagy and cisplatin resistance. Cell Death & Disease. 2022; 13: 683. https://doi.org/10.1038/s41419-022-05033-y.
[52] Zhang X, Qi Z, Yin H, Yang G. Interaction between p53 and Ras signaling controls cisplatin resistance via HDAC4- and HIF-1α-mediated regulation of apoptosis and autophagy. Theranostics. 2019; 9: 1096–1114. https://doi.org/10.7150/thno.29673.
[53] Svensson RU, Parker SJ, Eichner LJ, Kolar MJ, Wallace M, Brun SN, *et al*. Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. Nature Medicine. 2016; 22: 1108–1119. https://doi.org/10.1038/nm.4181.
[54] Guo JY, Chen HY, Mathew R, Fan J, Strohecker AM, Karsli-Uzunbas G, *et al*. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. Genes & Development. 2011; 25: 460–470. https://doi.org/10.1101/gad.2016311.
[55] Ashrafizadeh M, Zhang W, Zou R, Sethi G, Klionsky DJ, Zhang X. A bioinformatics analysis, pre-clinical and clinical conception of autophagy in pancreatic cancer: Complexity and simplicity in crosstalk. Pharmacological Research. 2023; 194: 106822. https://doi.org/10.1016/j.phrs.2023.106822.
[56] Chen X, Song E. Turning foes to friends: targeting cancer-associated fibroblasts. Nature Reviews. Drug Discovery. 2019; 18: 99–115. https://doi.org/10.1038/s41573-018-0004-1.
[57] Beloribi-Djefaflia S, Vasseur S, Guillaumond F. Lipid metabolic reprogramming in cancer cells. Oncogenesis. 2016; 5: e189. https://doi.org/10.1038/oncsis.2015.49.
[58] Huang C, Freter C. Lipid metabolism, apoptosis and cancer therapy. International Journal of Molecular Sciences. 2015; 16: 924–949. https://doi.org/10.3390/ijms16010924.
[59] Bhatt V, Khayati K, Hu ZS, Lee A, Kamran W, Su X, *et al*. Au-

tophagy modulates lipid metabolism to maintain metabolic flexibility for *Lkb1*-deficient *Kras*-driven lung tumorigenesis. Genes & Development. 2019; 33: 150–165. https://doi.org/10.1101/gad.320481.118.

[60] Liao J, Yu L, Mei Y, Guarnera M, Shen J, Li R, *et al*. Small nucleolar RNA signatures as biomarkers for non-small-cell lung cancer. Molecular Cancer. 2010; 9: 198. https://doi.org/10.1186/1476-4598-9-198.

[61] Wang K, Wang S, Zhang Y, Xie L, Song X, Song X. SNORD88C guided 2'-O-methylation of 28S rRNA regulates SCD1 translation to inhibit autophagy and promote growth and metastasis in non-small cell lung cancer. Cell Death and Differentiation. 2023; 30: 341–355. https://doi.org/10.1038/s41418-022-01087-9.

[62] Cao Q, You X, Xu L, Wang L, Chen Y. PAQR3 suppresses the growth of non-small cell lung cancer cells via modulation of EGFR-mediated autophagy. Autophagy. 2020; 16: 1236–1247. https://doi.org/10.1080/15548627.2019.1659654.

[63] Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. Cell Research. 2021; 31: 107–125. https://doi.org/10.1038/s41422-020-00441-1.

[64] Xie Y, Zhou Y, Wang J, Du L, Ren Y, Liu F. Ferroptosis, autophagy, tumor and immunity. Heliyon. 2023; 9: e19799. https://doi.org/10.1016/j.heliyon.2023.e19799.

[65] Xu D, Wang Z, Zhang Y, Jiang W, Pan Y, Song BL, *et al*. PAQR3 modulates cholesterol homeostasis by anchoring Scap/SREBP complex to the Golgi apparatus. Nature Communications. 2015; 6: 8100. https://doi.org/10.1038/ncomms9100.

[66] Guo JY, White E. Autophagy is required for mitochondrial function, lipid metabolism, growth, and fate of KRAS(G12D)-driven lung tumors. Autophagy. 2013; 9: 1636–1638. https://doi.org/10.4161/auto.26123.

[67] Vander Heiden MG, DeBerardinis RJ. Understanding the Intersections between Metabolism and Cancer Biology. Cell. 2017; 168: 657–669. https://doi.org/10.1016/j.cell.2016.12.039.

[68] Kim HS, Mendiratta S, Kim J, Pecot CV, Larsen JE, Zubovych I, *et al*. Systematic identification of molecular subtype-selective vulnerabilities in non-small-cell lung cancer. Cell. 2013; 155: 552–566. https://doi.org/10.1016/j.cell.2013.09.041.

[69] Han JH, Kim YK, Kim H, Lee J, Oh MJ, Kim SB, *et al*. Snail acetylation by autophagy-derived acetyl-coenzyme A promotes invasion and metastasis of KRAS-LKB1 co-mutated lung cancer cells. Cancer Communications (London, England). 2022; 42: 716–749. https://doi.org/10.1002/cac2.12332.

[70] Chang JY, Yi HS, Kim HW, Shong M. Dysregulation of mitophagy in carcinogenesis and tumor progression. Biochimica et Biophysica Acta. Bioenergetics. 2017; 1858: 633–640. https://doi.org/10.1016/j.bbabio.2016.12.008.

[71] Wang Q, Zeng F, Sun Y, Qiu Q, Zhang J, Huang W, *et al*. Etk Interaction with PFKFB4 Modulates Chemoresistance of Small-cell Lung Cancer by Regulating Autophagy. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2018; 24: 950–962. https://doi.org/10.1158/1078-0432.CCR-17-1475.

[72] Sun Y, Shen W, Hu S, Lyu Q, Wang Q, Wei T, *et al*. METTL3 promotes chemoresistance in small cell lung cancer by inducing mitophagy. Journal of Experimental & Clinical Cancer Research: CR. 2023; 42: 65. https://doi.org/10.1186/s13046-023-02638-9.

[73] Zhou J, Li G, Zheng Y, Shen HM, Hu X, Ming QL, *et al*. A novel autophagy/mitophagy inhibitor liensinine sensitizes breast cancer cells to chemotherapy through DNM1L-mediated mitochondrial fission. Autophagy. 2015; 11: 1259–1279. https://doi.org/10.1080/15548627.2015.1056970.

[74] Liu L, Qi L, Knifley T, Piecoro DW, Rychahou P, Liu J, *et al*. S100A4 alters metabolism and promotes invasion of lung cancer cells by up-regulating mitochondrial complex I protein NDUFS2. The Journal of Biological Chemistry. 2019; 294: 7516–7527. https://doi.org/10.1074/jbc.RA118.004365.

[75] Zhao G, Qi J, Li F, Ma H, Wang R, Yu X, *et al*. TRAF3IP3 Induces ER Stress-Mediated Apoptosis with Protective Autophagy to Inhibit Lung Adenocarcinoma Proliferation. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2025; 12: e2411020. https://doi.org/10.1002/advs.202411020.

[76] Kongara S, Karantza V. The interplay between autophagy and ROS in tumorigenesis. Frontiers in Oncology. 2012; 2: 171. https://doi.org/10.3389/fonc.2012.00171.

[77] Wang B, Wang Y, Zhang J, Hu C, Jiang J, Li Y, *et al*. ROS-induced lipid peroxidation modulates cell death outcome: mechanisms behind apoptosis, autophagy, and ferroptosis. Arch Toxicol. 2023; 97: 1439–1451. https://doi.org/10.1007/s00204-023-03476-6.

[78] Li H, Liu J, Cao W, Xiao X, Liang L, Liu-Smith F, *et al*. C-myc/miR-150/EPG5 axis mediated dysfunction of autophagy promotes development of non-small cell lung cancer. Theranostics. 2019; 9: 5134–5148. https://doi.org/10.7150/thno.34887.

[79] Zhou Z, Qu C, Zhou P, Zhou Q, Li D, Wu X, *et al*. Extracellular vesicles activated cancer-associated fibroblasts promote lung cancer metastasis through mitophagy and mtDNA transfer. Journal of Experimental & Clinical Cancer Research: CR. 2024; 43: 158. https://doi.org/10.1186/s13046-024-03077-w.

[80] Zhou X, Zhu X, Li C, Li Y, Ye Z, Shapiro VS, *et al*. Stearoyl-CoA Desaturase-Mediated Monounsaturated Fatty Acid Availability Supports Humoral Immunity. Cell Reports. 2021; 34: 108601. https://doi.org/10.1016/j.celrep.2020.108601.

[81] Shi D, Fang G, Chen Q, Li J, Ruan X, Lian X. Six-hour time-restricted feeding inhibits lung cancer progression and reshapes circadian metabolism. BMC Medicine. 2023; 21: 417. https://doi.org/10.1186/s12916-023-03131-y.

[82] Tian X, Bai X, Han Y, Ye Y, Peng M, Cui H, *et al*. PPAR γ changing ALDH1A3 content to regulate lipid metabolism and inhibit lung cancer cell growth. Molecular Genetics and Genomics: MGG. 2025; 300: 41. https://doi.org/10.1007/s00438-025-02243-9.

[83] Tong X, Patel AS, Kim E, Li H, Chen Y, Li S, *et al*. Adeno-to-squamous transition drives resistance to KRAS inhibition in LKB1 mutant lung cancer. Cancer Cell. 2024; 42: 413–428.e7. https://doi.org/10.1016/j.ccell.2024.01.012.

[84] Wang L, Shi R, Wang S, Duan Y, Wang Z, Zheng P, *et al*. ADSL promotes autophagy and tumor growth through fumarate-mediated Beclin1 dimethylation. Nature Chemical Biology. 2025; 21: 894–905. https://doi.org/10.1038/s41589-024-01825-9.

[85] Adam J, Hatipoglu E, O'Flaherty L, Ternette N, Sahgal N, Lockstone H, et al. Renal cyst formation in Fh1-deficient mice is independent of the Hif/Phd pathway: roles for fumarate in KEAP1 succination and Nrf2 signaling. Cancer Cell. 2011; 20: 524–537. https://doi.org/10.1016/j.ccr.2011.09.006.

[86] Yang L, Li A, Yu W, Wang H, Zhang L, Wang D, *et al*. Blockade of purine metabolism reverses macrophage immunosuppression and enhances anti-tumor immunity in non-small cell lung cancer. Drug Resistance Updates: Reviews and Commentaries in Antimicrobial and Anticancer Chemotherapy. 2025; 78: 101175. https://doi.org/10.1016/j.drup.2024.101175.

[87] He YZ, Li XN, Li HT, Bai XH, Liu YC, Li FN, *et al*. FTO promotes gefitinib-resistance by enhancing PELI3 expression and autophagy in non-small cell lung cancer. Pulmonary Pharmacology & Therapeutics. 2024; 87: 102317. https://doi.org/10.1016/j.pupt.2024.102317.

[88] Xu C, Jiang S, Ma X, Jiang Z, Pan Y, Li X, *et al*. CRISPR-based DNA methylation editing of NNT rescues the cisplatin resistance of lung cancer cells by reducing autophagy. Archives of Toxicology. 2023; 97: 441–456. https://doi.org/10.1007/

s00204-022-03404-0.
[89] Alhasan B, Gladova YA, Sverchinsky DV, Aksenov ND, Margulis BA, Guzhova IV. Hsp70 Negatively Regulates Autophagy via Governing AMPK Activation, and Dual Hsp70-Autophagy Inhibition Induces Synergetic Cell Death in NSCLC Cells. International Journal of Molecular Sciences. 2024; 25: 9090. https://doi.org/10.3390/ijms25169090.
[90] Wen Y, Sun X, Zeng L, Liang S, Li D, Chen X, *et al*. CDK4/6 Inhibitors Impede Chemoresistance and Inhibit Tumor Growth of Small Cell Lung Cancer. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2024; 11: e2400666. https://doi.org/10.1002/advs.202400666.
[91] Yang S, Zhang T, Ge Y, Cheng Y, Yin L, Pu Y, *et al*. Ferritinophagy Mediated by Oxidative Stress-Driven Mitochondrial Damage Is Involved in the Polystyrene Nanoparticles-Induced Ferroptosis of Lung Injury. ACS Nano. 2023; 17: 24988–25004. https://doi.org/10.1021/acsnano.3c07255.
[92] Zhao L, Chen X, Feng Y, Wang G, Nawaz I, Hu L, *et al*. COX7A1 suppresses the viability of human non-small cell lung cancer cells via regulating autophagy. Cancer Medicine. 2019; 8: 7762–7773. https://doi.org/10.1002/cam4.2659.
[93] Terry AR, Nogueira V, Rho H, Ramakrishnan G, Li J, Kang S, *et al*. CD36 maintains lipid homeostasis via selective uptake of monounsaturated fatty acids during matrix detachment and tumor progression. Cell Metabolism. 2023; 35: 2060–2076.e9. https://doi.org/10.1016/j.cmet.2023.09.012.
[94] Luo C, Liang H, Ji M, Ye C, Lin Y, Guo Y, *et al*. Autophagy induced by mechanical stress sensitizes cells to ferroptosis by NCOA4-FTH1 axis. Autophagy. 2025; 21: 1263–1282. https://doi.org/10.1080/15548627.2025.2469129.
[95] Yuan Y, Xu J, Jiang Q, Yang C, Wang N, Liu X, *et al*. Ficolin 3 promotes ferroptosis in HCC by downregulating IR/SREBP axis-mediated MUFA synthesis. Journal of Experimental & Clinical Cancer Research: CR. 2024; 43: 133. https://doi.org/10.1186/s13046-024-03047-2.
[96] Zhou H, Huang X, Yang X, Jiang F, Shao F, Shi W, *et al*. CircRAPGEF5 Promotes the Proliferation and Metastasis of Lung Adenocarcinoma through the miR-1236-3p/ZEB1 Axis and Serves as a Potential Biomarker. International Journal of Biological Sciences. 2022; 18: 2116–2131. https://doi.org/10.7150/ijbs.66770.
[97] Zhan Y, Zhang Z, Yin A, Su X, Tang N, Chen Y, *et al*. RBBP4: A novel diagnostic and prognostic biomarker for non-small-cell lung cancer correlated with autophagic cell death. Cancer Medicine. 2024; 13: e70090. https://doi.org/10.1002/cam4.70090.
[98] Zachari M, Ganley IG. The mammalian ULK1 complex and autophagy initiation. Essays in Biochemistry. 2017; 61: 585–596. https://doi.org/10.1042/EBC20170021.
[99] Peng P, Chavel C, Liu W, Carlson LM, Cao S, Utley A, *et al*. Pro-survival signaling regulates lipophagy essential for multiple myeloma resistance to stress-induced death. Cell Reports. 2024; 43: 114445. https://doi.org/10.1016/j.celrep.2024.114445.
[100] Maertin S, Elperin JM, Lotshaw E, Sendler M, Speakman SD, Takakura K, *et al*. Roles of autophagy and metabolism in pancreatic cancer cell adaptation to environmental challenges. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2017; 313: G524–G536. https://doi.org/10.1152/ajpgi.00138.2017.
[101] Song X, Narzt MS, Nagelreiter IM, Hohensinner P, Terlecki-Zaniewicz L, Tschachler E, *et al*. Autophagy deficient keratinocytes display increased DNA damage, senescence and aberrant lipid composition after oxidative stress in vitro and in vivo. Redox Biology. 2017; 11: 219–230. https://doi.org/10.1016/j.redox.2016.12.015.
[102] Janikiewicz J, Hanzelka K, Dziewulska A, Kozinski K, Dobrzyn P, Bernas T, *et al*. Inhibition of SCD1 impairs palmitate-derived autophagy at the step of autophagosome-lysosome fusion in pancreatic β-cells. Journal of Lipid Research. 2015; 56: 1901–1911. https://doi.org/10.1194/jlr.M059980.
[103] Liu J, Fu J, Fu P, Liu M, Liu Z, Song B. Pitavastatin sensitizes the EGFR-TKI associated resistance in lung cancer by inhibiting YAP/AKT/BAD-BCL-2 pathway. Cancer Cell International. 2024; 24: 224. https://doi.org/10.1186/s12935-024-03416-z.
[104] Sharma A, Ahmad S, Ahmad T, Ali S, Syed MA. Mitochondrial dynamics and mitophagy in lung disorders. Life Sciences. 2021; 284: 119876. https://doi.org/10.1016/j.lfs.2021.119876.
[105] Wang R, Liang L, Matsumoto M, Iwata K, Umemura A, He F. Reactive Oxygen Species and NRF2 Signaling, Friends or Foes in Cancer? Biomolecules. 2023; 13: 353. https://doi.org/10.3390/biom13020353.
[106] Yang G, Xu M, Wu M, Zhang Y, Yang F. Worenine enhances the sensitivity of non-small cell lung cancer A549/DDP cells to cisplatin via HIF-1α/BNIP3-mediated mitophagy. General Physiology and Biophysics. 2025; 44: 317–326. https://doi.org/10.4149/gpb_2025012.
[107] Wu HM, Jiang ZF, Ding PS, Shao LJ, Liu RY. Hypoxia-induced autophagy mediates cisplatin resistance in lung cancer cells. Scientific Reports. 2015; 5: 12291. https://doi.org/10.1038/srep12291.
[108] Zhang H, Wu D, Wang Y, Guo K, Spencer CB, Ortoga L, *et al*. METTL3-mediated N6-methyladenosine exacerbates ferroptosis via m6A-IGF2BP2-dependent mitochondrial metabolic reprogramming in sepsis-induced acute lung injury. Clinical and Translational Medicine. 2023; 13: e1389. https://doi.org/10.1002/ctm2.1389.
[109] Ju WT, Xia RH, Zhu DW, Dou SJ, Zhu GP, Dong MJ, *et al*. A pilot study of neoadjuvant combination of anti-PD-1 camrelizumab and VEGFR2 inhibitor apatinib for locally advanced resectable oral squamous cell carcinoma. Nature Communications. 2022; 13: 5378. https://doi.org/10.1038/s41467-022-33080-8.
[110] Dong X, Liu X, Lin D, Zhang L, Wu Y, Chang Y, *et al*. Baicalin induces cell death of non-small cell lung cancer cells via MCOLN3-mediated lysosomal dysfunction and autophagy blockage. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2024; 133: 155872. https://doi.org/10.1016/j.phymed.2024.155872.
[111] Han Y, Liu S, Zhu J, Liu P, Meng Z, Li Y, *et al*. Experimental study on the inhibitory effect of Halofuginone on NSCLC. European Journal of Pharmacology. 2025; 988: 177221. https://doi.org/10.1016/j.ejphar.2024.177221.
[112] Guo W, Zhou H, Wang J, Lu J, Dong Y, Kang Z, *et al*. Aloperine Suppresses Cancer Progression by Interacting with VPS4A to Inhibit Autophagosome-lysosome Fusion in NSCLC. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2024; 11: e2308307. https://doi.org/10.1002/advs.202308307.
[113] Xanthopoulou E, Lamprou I, Mitrakas AG, Michos GD, Zois CE, Giatromanolaki A, *et al*. Autophagy Blockage Up-Regulates HLA-Class-I Molecule Expression in Lung Cancer and Enhances Anti-PD-L1 Immunotherapy Efficacy. Cancers. 2024; 16: 3272. https://doi.org/10.3390/cancers16193272.
[114] Liu R, Li Q, Qin S, Qiao L, Yang M, Liu S, *et al*. Sertaconazole-repurposed nanoplatform enhances lung cancer therapy via CD44-targeted drug delivery. Journal of Experimental & Clinical Cancer Research: CR. 2023; 42: 188. https://doi.org/10.1186/s13046-023-02766-2.
[115] Wang W, Yao SY, Luo J, Ding C, Huang Q, Yang Y, *et al*. Engineered hypoxia-responsive albumin nanoparticles mediating mitophagy regulation for cancer therapy. Nature Communications. 2025; 16: 596. https://doi.org/10.1038/s41467-025-55905-y.
[116] Kiruthiga C, Niharika K, Devi KP. Phytol and α-Bisabolol

Synergy Induces Autophagy and Apoptosis in A549 Cells and Additional Molecular Insights through Comprehensive Proteome Analysis *via* Nano LC-MS/MS. Anti-cancer Agents in Medicinal Chemistry. 2024; 24: 773–788. https://doi.org/10.2174/0118715206289038240214102951.

[117] Lv M, Zhuang X, Zhang Q, Cheng Y, Wu D, Wang X, *et al*. Acetyl-11-keto-β-boswellic acid enhances the cisplatin sensitivity of non-small cell lung cancer cells through cell cycle arrest, apoptosis induction, and autophagy suppression via p21-dependent signaling pathway. Cell Biology and Toxicology. 2021; 37: 209–228. https://doi.org/10.1007/s10565-020-09541-5.

[118] Wu RH, Xie WJ, Dai SZ, Chen MH, Tan GH, Huang FY. 3'-epi-12β-hydroxyfroside induces autophagic degradation of ABCG2 to overcome drug resistance in lung cancer cells. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2025; 187: 118085. https://doi.org/10.1016/j.biopha.2025.118085.

[119] Wang C, Li Z, Xu P, Xu L, Han S, Sun Y. Combination of polythyleneimine regulating autophagy prodrug and Mdr1 siRNA for tumor multidrug resistance. Journal of Nanobiotechnology. 2022; 20: 476. https://doi.org/10.1186/s12951-022-01689-y.

[120] Zhu LH, Liang YP, Yang L, Zhu F, Jia LJ, Li HG. Cycloastragenol induces apoptosis and protective autophagy through AMPK/ULK1/mTOR axis in human non-small cell lung cancer cell lines. Journal of Integrative Medicine. 2024; 22: 503–514. https://doi.org/10.1016/j.joim.2024.05.004.

[121] Liu Y, Dai X, Jiang S, Qahar M, Feng C, Guo D, *et al*. Targeted Co-Delivery of Gefitinib and Rapamycin by Aptamer-Modified Nanoparticles Overcomes EGFR-TKI Resistance in NSCLC via Promoting Autophagy. International Journal of Molecular Sciences. 2022; 23: 8025. https://doi.org/10.3390/ijms23148025.

[122] Wang H, Du X, Liu W, Zhang C, Li Y, Hou J, *et al*. Combination of betulinic acid and EGFR-TKIs exerts synergistic anti-tumor effects against wild-type EGFR NSCLC by inducing autophagy-related cell death via EGFR signaling pathway. Respiratory Research. 2024; 25: 215. https://doi.org/10.1186/s12931-024-02844-9.

[123] Hsu CY, Pallathadka H, Gupta J, Ma H, Al-Shukri HHK, Kareem AK, *et al*. Berberine and berberine nanoformulations in cancer therapy: Focusing on lung cancer. Phytotherapy Research: PTR. 2024; 38: 4336–4350. https://doi.org/10.1002/ptr.8255.

[124] Liu X, Yin M, Dong J, Mao G, Min W, Kuang Z, *et al*. Tubeimoside-1 induces TFEB-dependent lysosomal degradation of PD-L1 and promotes antitumor immunity by targeting mTOR. Acta Pharmaceutica Sinica. B. 2021; 11: 3134–3149. https://doi.org/10.1016/j.apsb.2021.03.039.

[125] Fatehi Hassanabad A, MacQueen KT. Molecular mechanisms underlining the role of metformin as a therapeutic agent in lung cancer. Cellular Oncology (Dordrecht, Netherlands). 2021; 44: 1–18. https://doi.org/10.1007/s13402-020-00570-0.

[126] Ponnusamy L, Natarajan SR, Thangaraj K, Manoharan R. Therapeutic aspects of AMPK in breast cancer: Progress, challenges, and future directions. Biochimica et Biophysica Acta. Reviews on Cancer. 2020; 1874: 188379. https://doi.org/10.1016/j.bbcan.2020.188379.

[127] Jin H, Liu C, Liu X, Wang H, Zhang Y, Liu Y, *et al*. Huaier suppresses cisplatin resistance in non-small cell lung cancer by inhibiting the JNK/JUN/IL-8 signaling pathway. Journal of Ethnopharmacology. 2024; 319: 117270. https://doi.org/10.1016/j.jep.2023.117270.

[128] Chou HL, Lin IL, Chen YT, Chang WT, Yu A, Chen WC, *et al*. Aniline TFPA enhances camptothecin-induced anti-NSCLC by modulating oxidative stress and impairing autophagy. Cancer Cell International. 2025; 25: 81. https://doi.org/10.1186/s12935-025-03657-6.

[129] Ling L, Hu T, Zhou C, Dai Y, Hu L, Chen Y, *et al*. M6A-Methylated circRAPGEF5 drives lung adenocarcinoma progression and metastasis via IGF2BP2/NUP160-mediated autophagy suppression. Molecular Cancer. 2025; 24: 192. https://doi.org/10.1186/s12943-025-02399-3.

[130] Gao Y, Fu S, Peng Y, Zhou Y, Zhu J, Zhang X, *et al*. HMBOX1 reverses autophagy mediated 5-fluorouracil resistance through promoting HACE1-induced ubiquitination and degradation of ATG5 in colorectal cancer. Autophagy. 2025; 21: 1556–1577. https://doi.org/10.1080/15548627.2025.2477443.

[131] Wu J, Zhao X, Sun Q, Jiang Y, Zhang W, Luo J, *et al*. Synergic effect of PD-1 blockade and endostar on the PI3K/AKT/mTOR-mediated autophagy and angiogenesis in Lewis lung carcinoma mouse model. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2020; 125: 109746. https://doi.org/10.1016/j.biopha.2019.109746.

[132] Liang BB, Liu Q, Liu B, Yao HG, He J, Tang CF, *et al*. A Golgi-Targeted Platinum Complex Plays a Dual Role in Autophagy Regulation for Highly Efficient Cancer Therapy. Angewandte Chemie (International Ed. in English). 2023; 62: e202312170. https://doi.org/10.1002/anie.202312170.

[133] Liu L, Chen S, Lei Y, Lin Z, Zhou R, Zeng G, *et al*. REPS2 attenuates cancer stemness through inhibiting Wnt signaling by autophagy mediated degradation of β-catenin. Oncogene. 2025; 44: 2942–2955. https://doi.org/10.1038/s41388-025-03469-y.

[134] Cai Q, Cai X, Shubhra QTH. Mitochondrial transfer drives immune evasion in tumor microenvironment. Trends in Cancer. 2025; 11: 424–426. https://doi.org/10.1016/j.trecan.2025.04.002.

[135] Qu Y, He Y, Wang Y, Han Z, Qin L. Targeted down-regulation of SRSF1 exerts anti-cancer activity in OSCC through impairing lysosomal function and autophagy. iScience. 2023; 26: 108330. https://doi.org/10.1016/j.isci.2023.108330.

[136] Wu M, Zhang JB, Xiong YW, Zhao YX, Zheng MG, Huang XL, *et al*. Promotion of Lung Cancer Metastasis by SIRT2-Mediated Extracellular Protein Deacetylation. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2023; 10: e2205462. https://doi.org/10.1002/advs.202205462.

[137] Wang XR, Jiang ZB, Xu C, Meng WY, Liu P, Zhang YZ, *et al*. Andrographolide suppresses non-small-cell lung cancer progression through induction of autophagy and antitumor immune response. Pharmacological Research. 2022; 179: 106198. https://doi.org/10.1016/j.phrs.2022.106198.

[138] Liu M, Li C, Qu J, Sun S, Zhao Z, Wang W, *et al*. Baicalein enhances immune response in TNBC by inhibiting leptin expression of adipocytes. Cancer Science. 2023; 114: 3834–3847. https://doi.org/10.1111/cas.15916.

[139] Song Y, Jiang YX, Guan JY, Jiang JB, Xu MS, Zhong XY, *et al*. Fangchinoline-mediated autophagy inhibition amplifies antigen presentation and PD-1 blockade efficacy in lung cancer. Acta Pharmacologica Sinica. 2025. https://doi.org/10.1038/s41401-025-01541-7. (online ahead of print)

[140] Tang F, Lu C, He X, Lin W, Xie B, Gao X, *et al*. E3 ligase Trim35 inhibits LSD1 demethylase activity through K63-linked ubiquitination and enhances anti-tumor immunity in NSCLC. Cell Reports. 2023; 42: 113477. https://doi.org/10.1016/j.celrep.2023.113477.

[141] Ning Y, Zheng H, Yang Y, Zang H, Wang W, Zhan Y, *et al*. YAP1 synergize with YY1 transcriptional co-repress DUSP1 to induce osimertinib resistant by activating the EGFR/MAPK pathway and abrogating autophagy in non-small cell lung cancer. International Journal of Biological Sciences. 2023; 19: 2458–2474. https://doi.org/10.7150/ijbs.79965.

[142] Tseng YH, Chou WR, Liu WL, Dung ZX, Lin CH, Hsieh CH, et al. Effects of methylation and transcription factor YY1 on ID2 expression in non-small cell lung carcinoma cells. Amer-

ican Journal of Cancer Research. 2024; 14: 2424–2438. https://doi.org/10.62347/KXKL1421.

[143] Ke X, Huang M, Zheng Y, Chen G. Polygenic insight identifies precision biomarkers decoding protein catabolism and autophagy pathways in obstructive sleep apnea. Scientific Reports. 2025; 15: 28347. https://doi.org/10.1038/s41598-025-13687-9.

[144] Kodous AS, Eldin ES, Mohamed HE, Ghobashy MM, El-Maghraby DF. Targeting cell signaling pathway ALKBH5/Beclin1/ULK1 in lung cancer by 5-flurouracil-loaded P (AAm/SA) nanogel in rats. Apoptosis: an International Journal on Programmed Cell Death. 2025; 30: 1628–1644. https://doi.org/10.1007/s10495-025-02102-3.

[145] Ray E, Jadhav K, Kadian M, Sharma G, Sharma K, Jhilta A, *et al*. Targeted delivery of the metastasis-specific tumour homing TMTP1 peptide to non-small-cell lung cancer (NSCLC) using inhalable hybrid nano-assemblies. Journal of Materials Chemistry. B. 2024; 12: 9740–9759. https://doi.org/10.1039/d4tb00694a.

[146] Ray E, Jadhav K, Kadian M, Sharma G, Sharma K, Jhilta A, *et al*. Inhalable chitosan-coated nano-assemblies potentiate niclosamide for targeted abrogation of non-small-cell lung cancer through dual modulation of autophagy and apoptosis. International Journal of Biological Macromolecules. 2024; 279: 135411. https://doi.org/10.1016/j.ijbiomac.2024.135411.

[147] Circu M, Cardelli J, Barr M P, O'byrne K, Mills G, El-Osta H. Modulating lysosomal function through lysosome membrane permeabilization or autophagy suppression restores sensitivity to cisplatin in refractory non-small-cell lung cancer cells. PLoS One. 2017; 12: e0184922. https://doi.org/10.1371/journal.pone.0184922.

[148] Mu N, Wang Y, Li X, Du Z, Wu Y, Su M, *et al*. Crotonylated BEX2 interacts with NDP52 and enhances mitophagy to modulate chemotherapeutic agent-induced apoptosis in non-small-cell lung cancer cells. Cell Death & Disease. 2023; 14: 645. https://doi.org/10.1038/s41419-023-06164-6.

[149] Liu Z, Gao W. Synergistic effects of Bcl-2 inhibitors with AZD9291 on overcoming the acquired resistance of AZD9291 in H1975 cells. Archives of Toxicology. 2020; 94: 3125–3136. https://doi.org/10.1007/s00204-020-02816-0.

[150] Liu S, Yang P, Wang L, Zou X, Zhang D, Chen W, *et al*. Targeting PAK4 reverses cisplatin resistance in NSCLC by modulating ER stress. Cell Death Discovery. 2024; 10: 36. https://doi.org/10.1038/s41420-024-01798-7.

[151] Chen L, Ning J, Linghu L, Tang J, Liu N, Long Y, *et al*. USP13 facilitates a ferroptosis-to-autophagy switch by activation of the NFE2L2/NRF2-SQSTM1/p62-KEAP1 axis dependent on the KRAS signaling pathway. Autophagy. 2025; 21: 565–582. https://doi.org/10.1080/15548627.2024.2410619.

[152] Zheng D, Li J, Yan H, Zhang G, Li W, Chu E, *et al*. Emerging roles of Aurora-A kinase in cancer therapy resistance. Acta Pharmaceutica Sinica. B. 2023; 13: 2826–2843. https://doi.org/10.1016/j.apsb.2023.03.013.

[153] Abril-Rodriguez G, Torrejon DY, Liu W, Zaretsky JM, Nowicki TS, Tsoi J, *et al*. PAK4 inhibition improves PD-1 blockade immunotherapy. Nature Cancer. 2020; 1: 46–58. https://doi.org/10.1038/s43018-019-0003-0.

[154] Su Y, Li L, Chen J, Gao C. TMEM164 promotes ferroptosis by selectively mediating ATG5-dependent autophagosome formation to inhibit the progression of LUAD. Autoimmunity. 2024; 57: 2410192. https://doi.org/10.1080/08916934.2024.2410192.

[155] Kang JI, Kim DH, Sung KW, Shim SM, Cha-Molstad H, Soung NK, *et al*. p62-Induced Cancer-Associated Fibroblast Activation via the Nrf2-ATF6 Pathway Promotes Lung Tumorigenesis. Cancers. 2021; 13: 864. https://doi.org/10.3390/cancers13040864.

[156] Cressey R, Han MTT, Khaodee W, Xiyuan G, Qing Y. Navigating PRKCSH's impact on cancer: from N-linked glycosylation to death pathway and anti-tumor immunity. Frontiers in Oncology. 2024; 14: 1378694. https://doi.org/10.3389/fonc.2024.1378694.

[157] Hasan A, Khamjan N, Lohani M, Mir SS. Targeted Inhibition of Hsp90 in Combination with Metformin Modulates Programmed Cell Death Pathways in A549 Lung Cancer Cells. Applied Biochemistry and Biotechnology. 2023; 195: 7338–7378. https://doi.org/10.1007/s12010-023-04424-x.

[158] Hasan A, Haque E, Hameed R, Maier PN, Irfan S, Kamil M, *et al*. Hsp90 inhibitor gedunin causes apoptosis in A549 lung cancer cells by disrupting Hsp90:Beclin-1:Bcl-2 interaction and downregulating autophagy. Life Sciences. 2020; 256: 118000. https://doi.org/10.1016/j.lfs.2020.118000.

[159] Xia H, Tai XJ, Cheng W, Wu Y, He D, Wang LF, *et al*. Metformin inhibits the growth of SCLC cells by inducing autophagy and apoptosis via the suppression of EGFR and AKT signalling. Scientific Reports. 2025; 15: 6081. https://doi.org/10.1038/s41598-025-87537-z.

[160] Di J, Bo W, Wang C, Liu C. Ailanthone Increases Cisplatin-induced Apoptosis and Autophagy in Cisplatin Resistance Non-small Cell Lung Cancer Cells through the PI3K/AKT/mTOR Pathway. Current Medicinal Chemistry. 2024. https://doi.org/10.2174/0109298673315460240816091032. (online ahead of print)

[161] Pierre L, Juszczak F, Delmotte V, Decarnoncle M, Ledoux B, Bultot L, *et al*. AMPK protects proximal tubular epithelial cells from lysosomal dysfunction and dedifferentiation induced by lipotoxicity. Autophagy. 2025; 21: 860–880. https://doi.org/10.1080/15548627.2024.2435238.

[162] Han JH, Kim YK, Kim H, Lee J, Oh MJ, Kim SB, et al. Snail acetylation by autophagy-derived acetyl-coenzyme A promotes invasion and metastasis of KRAS-LKB1 co-mutated lung cancer cells. Cancer Communications (London, England). 2022; 42: 716–749. https://doi.org/10.1002/cac2.12332.

[163] Yan X, Yao C, Fang C, Han M, Gong C, Hu D, *et al*. Rocaglamide promotes the infiltration and antitumor immunity of NK cells by activating cGAS-STING signaling in non-small cell lung cancer. International Journal of Biological Sciences. 2022; 18: 585–598. https://doi.org/10.7150/ijbs.65019.