

Autophagy and Glycometabolic Reprogramming in the Malignant Progression of Lung Cancer: A Review

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Abstract

Lung cancer is one of the leading causes of cancer-related deaths worldwide. However, there are currently limited treatment options that are widely available to patients with advanced lung cancer, and further research is required to inhibit or reverse disease progression more effectively. In lung and other solid tumor cancers, autophagy and glycometabolic reprogramming are critical regulators of malignant development, including proliferation, drug resistance, invasion, and metastasis. To provide a theoretical basis for therapeutic strategies targeting autophagy and glycometabolic reprogramming to prevent lung cancer, we review how autophagy and glycometabolism are regulated in the malignant development of lung cancer based on research progress in other solid tumors.

Keywords

Lung cancer, autophagy, glycolysis, metabolic reprogramming, glycometabolic reprogramming

Introduction

Lung cancer is a type of short primary bronchial lung cancer that originates in the bronchial mucosal epithelium. Based on its pathomorphological characteristics, lung cancer is categorized into nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for over 85% of cases.¹ Lung cancer is the leading cause of cancer-related deaths globally, and its morbidity and mortality rates are increasing²; however patient survival rates have increased considerably because of treatment techniques including surgery, chemotherapy, targeted therapy, and immunotherapy.³ However, the majority of patients with lung cancer are at a locally advanced or advanced stage at the time of diagnosis, inhibiting the surgical options at the time of initial diagnosis. Chemotherapy medicines lack specificity and have significant toxic side effects.⁴ Therefore, exploring the mechanisms of lung cancer progression can help prolong or lessen disease metastasis and recurrence and improve patient quality of life and overall survival (OS).

Autophagy and glycometabolic reprogramming have become increasingly crucial during lung cancer development. As a type of solid tumor, lung cancer cells are located in a tumor microenvironment (TME) composed of cancer tissue, normal tissue, intercellular substances, and microvasculature, which are typically in a state of inflammation, hypoxia, or starvation.

With additional stimulation, such as radiotherapy, changes in the internal environment can lead to increased metabolic pressure in cancer cells, which can help cancer cells avoid autophagy.⁵ As a result, the morphology, metabolic status, and biological behavior of cancer cells are altered, with some cancer cells undergoing tumor progression such as enhanced tumor proliferation, increased tumor invasion, increased metastatic capacity, and increased tumor immune evasion.⁶ Reprogramming of glucose metabolism, which is a distinctive change in cancer cells and may also be caused by TME

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stimulation can alter cellular glycometabolism and decrease oxygen consumption in the presence of nutrient deficiency, which promotes cancer progression.⁷ Autophagy and glycometabolic reprogramming play significant roles in the malignant progression of lung cancer; however, they have primarily been studied as independent factors. In other solid tumors such as liver and breast cancers, autophagy and glycometabolic reprogramming may interact during tumor progression, but little is known about this in lung cancer. Therefore, this paper reviews recent research progress on autophagy and glycometabolic reprogramming in lung cancer and summarizes their relationship between and their effects on tumors in an attempt to elucidate how these mechanisms affect the development and progression of lung cancer from a new perspective and the potential research directions for the treatment of lung cancer.

Advances in the Glycometabolic Reprogramming in Lung Cancer

Tumor metabolic reprogramming is a series of metabolic changes, including the Warburg effect, which is the main biochemical characteristic caused by structural and functional changes in some genes in tumor cells that include enhanced glycolysis, increased glucose uptake and consumption, enhanced lipid and protein synthesis, and increased amino acid uptake and catabolism, such as that of glutamine.^{8–10} These metabolic changes are conducive to malignant tumor proliferation and adaptation to unfavorable environments, as well as modifications to the modes and pathways of glycometabolism that are critical for survival.⁸ Glucose is the primary energy source for sustaining cell growth. Under normal conditions, glucose is taken up by cells to produce adenosine triphosphate (ATP) for energy in the mitochondria through aerobic metabolism. However, solid tumor cells not only exhibit characteristics of rapid proliferation, but also frequently exist in the TME, which can cause hypoxia and starvation. Therefore, solid tumor cells metabolize glucose quickly through aerobic glycolysis to generate energy and raw materials.⁸ Aerobic glycolysis, also known as the Warburg effect, refers to the rapid production of ATP by cancer cells through high rates of glycolysis even in a well-oxygenated state that is not coupled to mitochondrial oxidative metabolism.⁹ Subsequently, pyruvate production is mostly catalyzed by lactate dehydrogenase (LDH) and converted to lactic acid in the cytoplasmic matrix.⁹ The Warburg effect has been observed in cancer cells even though they have intact mitochondria, which contrary to Warburg's initial hypothesis that claimed aerobic glycolysis is caused by damaged mitochondria and that glycometabolic reprogramming is closely related to alterations in mitochondrial DNA, oncogenes, and tumor suppressors.¹⁰ Therefore, glycometabolic reprogramming in tumor cells may be involved in tumorigenesis and cancer progression. Recent studies have identified abnormal glycometabolic reprogramming in lung cancer cells, and alterations in their metabolic patterns may play a key role in lung cancer progression¹¹ (Figure 1).

Correlation Between Glycometabolic Reprogramming and Lung Cancer Malignancy

Recent studies have demonstrated that aerobic glycolysis is involved in tumor differentiation, genesis, and progression in a variety of solid tumors and is closely related to prognosis.^{12–14} Cancer cell lines with higher malignancy also show a stronger glycolytic shift. Despite being cultured in vitro in a well-oxygenated environment, noninvasive breast cancer cell lines consume less glucose than invasive strains, indicating that the metabolic change in glycolysis may be higher in more malignant tumor cells.¹⁵

Correlation Between Glycometabolic Reprogramming and Lung Cancer Metastasis

A similar increase in glycolysis is observed in lung cancer cells, possibly due to the reprogramming of energy metabolism, which attenuates oxidative phosphorylation and enhances glycolysis.¹⁶ Furthermore, in patients with NSCLC with distant metastases, baseline serum LDH levels are associated with a distant metastatic burden, and patients with elevated LDH have a worse prognosis.¹⁷ Serum LDH levels can be used to predict the efficacy of treatment in patients with advanced NSCLC receiving antivasular therapy with the targeted drug bevacizumab. Patients with lower serum LDH levels after treatment had better outcomes and were more likely to achieve complete or partial disease remission.¹⁸ A similar phenomenon was reported with the use of current immunotherapy, where NSCLC patients with elevated serum LDH levels at baseline had shorter progression-free survival (PFS) and OS than those with normal LDH levels after treatment with the PD-1 inhibitor, nabumab.¹⁹ However, further research is needed to understand how these changes occur and how aerobic glycolysis affects lung cancer cell invasion and metastasis.

Glycometabolic Reprogramming and Drug Resistance in Lung Cancer

Glycometabolic reprogramming is associated with drug resistance in lung cancer.²⁰ Abnormally elevated glycolysis in lung cancer cells is linked to the overexpression of glycolysis-related genes and aberrant production or function of essential glycolytic enzymes, which may promote drug resistance in cancer cells. Hexokinase (HK) is a crucial enzyme in glycolysis that catalyzes the first step of glycometabolism by producing glucose-6-phosphate from glucose. Numerous studies have shown that HK is overexpressed in lung cancer cells and a significant factor in their resistance to chemotherapeutic drugs such as cisplatin.^{21,22} This has a negative impact on the prognosis of patients with tumors and shortens their OS. Additionally, HK2 is overexpressed in patients with osimertinib-resistant NSCLC and is regulated in osimertinib-resistant NSCLC cells by targeting miR-498 via circular RNA, thereby affecting cell proliferation, apoptosis, and glycolysis.²³ The small molecule

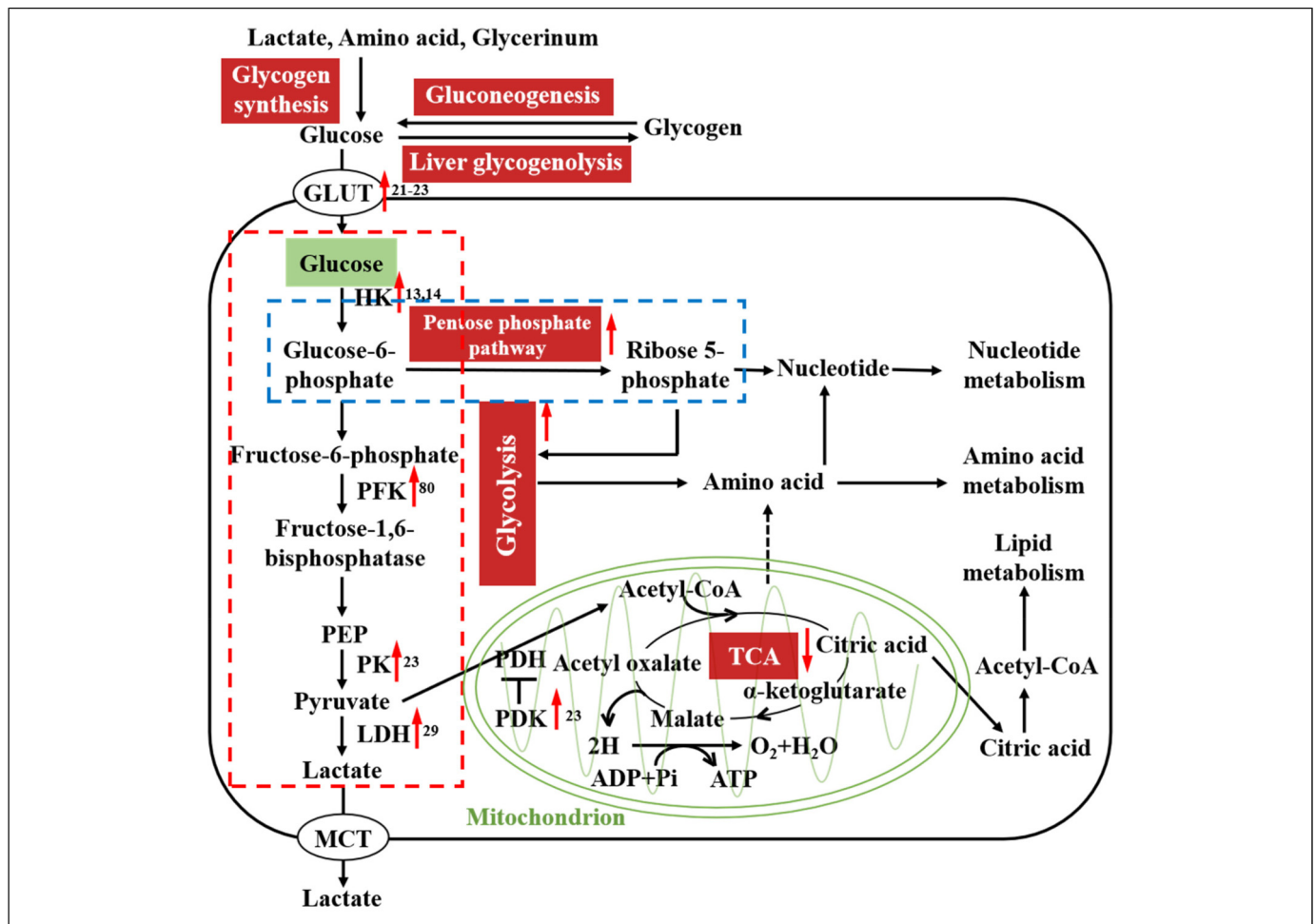


Figure 1. Glycometabolic reprogramming in cancer cells. Abbreviations: GLUT, glucose transporters; HK, hexokinase; PEP, phosphoenolpyruvic acid; PK, pyruvate kinase; LDH, lactate dehydrogenase; TCA, tricarboxylic acid cycle; PFK, phosphofructokinase; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase; MCT, monocarboxylate transporter. ↑: content increased; ↓: content decreased.

inhibitor, 2-deoxy-D-glucose (2-deoxyD-glucose, 2-DG), targets HK and significantly inhibits cellular glycolysis, thus activating the BIM/BCL-2 signaling pathway to induce apoptosis and reverse osimertinib resistance in lung cancer cells.²⁴

Glucose transporters (GLUT) facilitate glucose and extracellular glucose transport across the cell membrane, which is essential for cell growth and proliferation. WZB117 is an irreversible GLUT1 inhibitor that reduced the levels of GLUT1 protein, intracellular ATP, and glycolytic enzymes in A549 lung cancer cells.²⁵ The addition of exogenous ATP decreased the inhibitory effect of WZB117, suggesting that GLUT1 inhibition prevents tumor growth by blocking ATP synthesis.²⁵ Furthermore, in an A549 tumor-bearing mouse model, WZB117 slowed tumor growth by more than 70%,²⁵ while subsequent studies showed that GLUT3 had a higher affinity for glucose than GLUT1, GLUT2, or GLUT4, and a higher transport capacity than GLUT1 or GLUT4.²⁶ In addition, among the members of the GLUT family, GLUT3 had the highest turnover rate.²⁷ In EGFR-TKI-resistant NSCLC cells, Caveolin-1 (Cav1) mediates glucose uptake via GLUT3, and interaction between Cav1 and GLUT 3 was only observed in TKI-resistant cells,

indicating that Cav1-GLUT3-mediated glucose uptake was critical for cellular energy homeostasis in TKI-resistant tumor cells.²⁸ Other studies found that gefitinib downregulated GLUT expression in EGFR-sensitive mutant NSCLC cells, whereas both GLUT receptor expression and glucose uptake were elevated in gefitinib-resistant NSCLC cells.^{29,30} Therefore, targeting GLUT-mediated glucose transport and metabolism may be a strategy for reversing drug resistance in lung cancer cells.

Pyruvate kinase (PK) is the rate-limiting enzyme in glycolysis that catalyzes the conversion of phosphoenolpyruvic acid and ADP to pyruvate and ATP. Pyruvate kinase M (PKM) encodes 2 isoforms: PKM1 and PKM2, with PKM2 predominantly expressed in tumor cells. It has been demonstrated that suppressing PKM2 activity decreases glucose uptake and lactate generation, and enhances the sensitivity of NSCLC mice to the chemotherapeutic drug cisplatin.³¹

The pyruvate dehydrogenase kinase (PDK) family regulates pyruvate dehydrogenase (PDH) activity, which promotes aerobic glycolysis by transferring pyruvate from the mitochondria to the cytosol. In lung adenocarcinoma, upregulation of *PDK2* and *PDK4* is directly related to the development of

chemoresistance and in clinical samples, this upregulation is associated with a worse prognosis in patients with lung adenocarcinoma.^{32,33} Moreover, *PDK1* expression is higher in tumors than in normal tissue, and inhibition of *PDK1* efficiently prevents NSCLC cells from developing resistance to EGFR-TKIs.^{34,35}

LDH is particularly useful to research because it is situated at the “pyruvate bifurcation point” in the glycolytic pathway and participates in the final step of glycolysis, catalyzing lactate from pyruvate. Of the 2 major isozymes of LDH, LDH-A is overexpressed in hypoxic tumor environments, whereas LDH-B is predominantly expressed in normal cells. The upregulation of LDH-A ensures efficient aerobic glycolysis in tumor cells, but this enzyme is not required by healthy cells under normal conditions³⁶ and is, therefore, a potential target for overcoming drug resistance in tumors. The inhibition of LDH-A can lead to a decrease in ATP and a burst of reactive oxygen species (ROS) in cancer cells, resulting in apoptosis and G2/M blockade in H1395 cells.³⁷

Increasing evidence suggests that glycometabolic reprogramming contributes to the emergence of drug resistance in lung cancer; however, the underlying mechanisms remain unclear. Glycometabolic reprogramming may be influenced by elevated glucose intake, metabolic abnormalities, or other aspects of tumor cell metabolism, such as lipid metabolism and amino acid synthesis. In both lung and other cancers, the inhibition of glycometabolic reprogramming can effectively reverse drug resistance and enhance the tumor-killing ability of drugs.^{36,37} Current studies show that lung cancer cells regulate programmed apoptosis by altering the expression levels of essential glycolytic enzymes and mitochondrial metabolism that leads to drug resistance, making it a mainstream direction of research.^{32–35,37} However, the causes of key enzyme expression or post-transcriptional modifications, whether through the addition or subtraction of transcription factors, modifying enzymes, or changes in the DNA itself, are also worth further investigation.

In summary, although the impact of the Warburg effect on cancer was proposed almost a century ago and research on it has not stopped, the mechanisms underlying the decline or inhibition of mitochondrial function and glycometabolic reprogramming are not fully understood. The application of glucose analog tracer technology, such as 18F-fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT), further demonstrates that both primary and metastatic lesions have higher glucose uptake rates in patients who have more malignant tumors when compared with those with a lower tumor load.³⁸ The higher the level of aerobic glycolysis in lung cancer cells, especially in those with higher malignancy, suggests that it could affect the progression of lung cancer with respect to invasion, proliferation, and drug resistance, suggesting that it is crucial to understand how glycometabolic reprogramming functions in cancer pathologies. Investigating the upstream mechanisms of glycometabolic reprogramming and blocking could help prevent lung cancer or other solid tumors from progressing and offer new therapeutic options.

Research Progress of Autophagy in Lung Cancer

Autophagy and Cancer

Autophagy is a conserved physiological catabolic process that evolved in eukaryotic cells. Autophagy plays a crucial role in maintaining cellular homeostasis, which is a physiological phenomenon universal in eukaryotes.³⁹ Cellular autophagy can be divided into macroautophagy, microautophagy, and molecular chaperone-mediated autophagy depending on how substances are transported to lysosomes. Macroautophagy is a relatively important research hotspot and this review discusses macroautophagy as the main form of autophagy.

Studies have shown that autophagy plays a dual role in cancer, either by promoting or suppressing tumors, and that the precise function of autophagy in cancer progression depends on the tumor type, stage, and the TME.^{40,41} In the precancerous state, autophagy clears damaged proteins and organelles from cells. The inhibition of autophagy results in elevated levels of ROS, increased genomic instability, and the accumulation of p62 (also known as sequestome 1, SQSTM1), which induces endoplasmic reticulum stress that results in DNA damage and contributes to tumorigenesis.⁴² In this context, autophagy usually acts as a tumor suppressor. In contrast, cancer cells in advanced metastatic tumors support their survival by obtaining nutrients and energy via autophagy during metabolic and oxidative stress.^{43,44} Therefore, autophagy serves as a pro-cancer factor at advanced cancer stages and can supply energy for resistance to chemotherapeutic drugs by eliminating damaged proteins and organelles.⁴⁵ The induction of autophagy can significantly improve the resistance of cancer cells to cisplatin in human-acquired cisplatin-resistant esophageal cancer cells, and reduced autophagy, can significantly inhibit tumor growth.⁴⁶ Since autophagy is a biological process, an increasing number of studies have confirmed that it may facilitate advanced lung cancer progression and cause critical alterations in lung cancer invasion and the emergence of drug resistance.

Autophagy and Drug Resistance in Lung Cancer

Autophagy can act as a protective mechanism for cancer cells, inducing acquired drug resistance in response to anti-tumor drugs by upregulating autophagy to resist drug-induced apoptosis and evade their killing effects. Autophagy may also be involved in the emergence of platinum, EGFR-TKI, and immune checkpoint inhibitors resistance.^{47–48}

The clinical resistance to platinum-based systemic chemotherapy over time is a serious challenge for cancer therapies and it is now believed that platinum resistance is associated with autophagy. Circu et al⁴⁸ found that the autophagy inhibitor chloroquine induced lysosomal membrane permeabilization in A549cisR cisplatin-resistant cells and enhanced the toxic effects of cisplatin through a histone-mediated partial caspase-independent mechanism. *ATG* (autophagy-related

gene) 5 silencing markedly increases cisplatin cytotoxicity, suggesting it is effective at activating lysosomal membrane permeabilization and suppressing autophagy as treatment for acquired cisplatin resistance in NSCLC.⁴⁸

EGFR-TKIs are currently an important treatment for NSCLC; however, as treatment progresses, drug resistance occurs in most patients.⁴⁹ An important part of drug resistance establishment is that EGFR-TKIs induce protective autophagy involving PI3K-AKT-mTORC1, P53-AMPK-mTORC1-ULK1, EGFR-Rubicon-Beclin 1, and RAS/RAF/MEK/ERK1/2 pathways.⁵⁰ Autophagy is upregulated in NSCLC cells treated with erlotinib and the use of the autophagy inhibitor chloroquine in combination with erlotinib increased its sensitivity.⁵¹ Thus, the combination of EGFR-TKIs and autophagy inhibitors may be a novel clinical strategy for enhancing the efficacy of EGFR-targeted NSCLC treatments.

There has been considerable interest in cancer immunotherapy, which has yielded encouraging results in many cancer patients. Currently, pembrolizumab is recommended as the first-line treatment for NSCLC, whereas nivolumab and atezolizumab are used as second-line treatments.⁵² In cancer cells, the PD-1 receptor and its ligand, PD-L1, may participate in autophagy. Clark et al⁵³ demonstrated that endogenous PD-L1 in tumor cells upregulates mTOR in mouse melanoma and human ovarian cancers. Wang et al⁵⁴ found that autophagy regulates PD-L1 protein expression in gastric cancer cells through the p62-NF- κ B signaling pathway. Thus, we speculate that the combination of autophagy inhibition and PD-L1

antibody treatment may enhance the sensitivity of tumor cells to the PD-L1 antibody, especially for tumors with high levels of autophagy. This strategy could also be used in the treatment of lung cancer, although further basic and clinical studies are required to support this hypothesis.

ATG and Lung Cancer Malignancy Progression

The ATG family encodes several proteins involved in many cellular processes, including autophagy initiation, onset, and termination, suggesting that changes in ATGs may play a significant role in the progression of lung cancer. Wen et al⁵⁵ genotyped 9 potential functional single nucleotide polymorphisms (SNPs) in 4 ATGs (*ATG2B*, *ATG10*, *ATG12*, and *ATG16L2*) by studying 393 patients with North American NSCLC treated with radiation therapy. They discovered that patients with the *ATG16L2* rs10898880 CC variant genotype exhibited superior local relapse-free survival, PFS, and OS, suggesting that this polymorphism is involved in anti-tumor therapy. Additionally, Li et al⁵⁶ analyzed DNA from blood samples obtained from 323 patients with NSCLC and discovered that 3 SNPs (*ATG16L1*: rs2241880, *ATG10*: rs10036653, and *ATG12*: rs26532) were associated with brain metastasis in these patients. Similarly, *ATG16L1* (T300A) was found to be linked to a lower risk of metastasis in patients with colorectal cancer.⁵⁷ These studies suggest that autophagy influences the occurrence, progression, and prognosis of lung cancer.

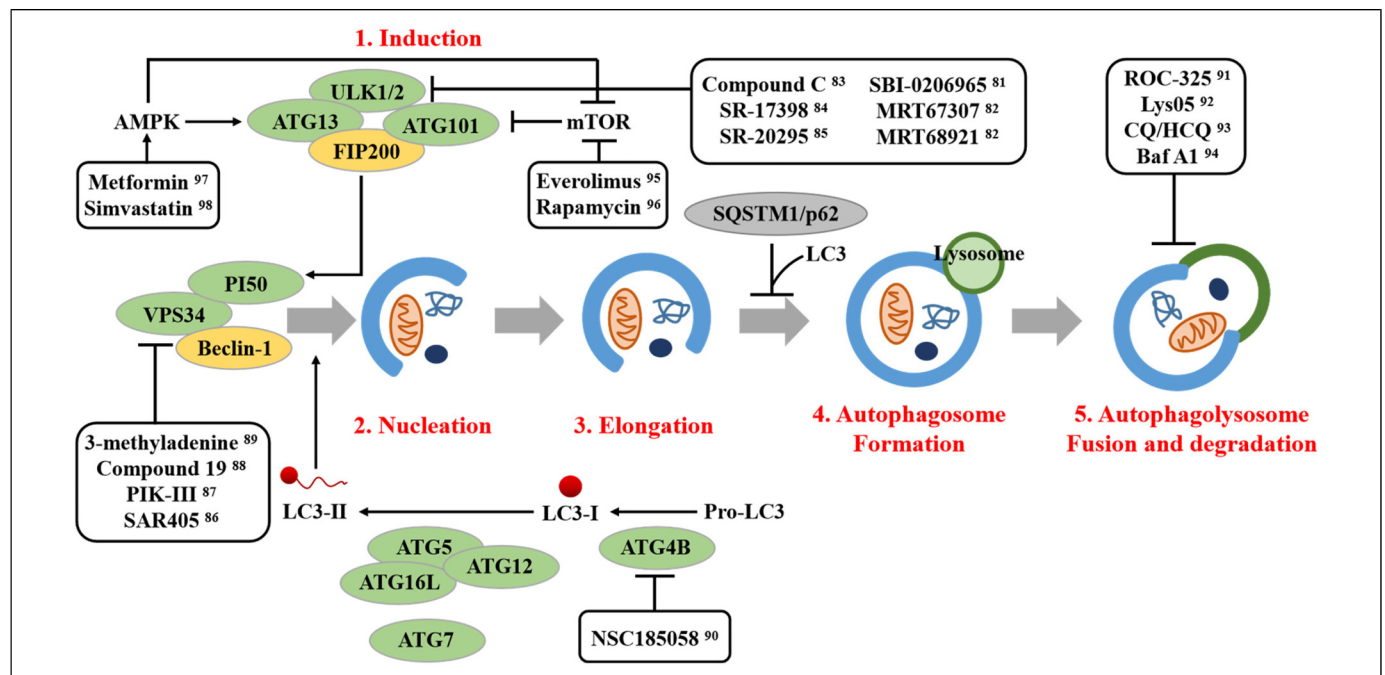


Figure 2. Autophagy processes and the targets of related drugs. Abbreviations: AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; mTOR, mammalian target of rapamycin; ULK, UNC-51-like kinase; ATG, autophagy associated gene; FIP, focal adhesion kinase family interacting protein; VPS, vacuolar protein sorting; LC3, light chain 3; SQSTM1, sequestosome 1; CQ, chloroquine; HCQ, hydroxychloroquine; Baf A1, bafilomycin A1. →: promotion; ⊥: inhibition.

In conclusion, autophagy may act as a cellular response mechanism in the progression of lung cancer, particularly in the development of drug resistance and metastasis, through various signaling pathways involved in the regulation of the cell cycle or metabolic modulation (Figure 2).

The Role of Autophagy in Regulating Glycolysis in Cancer Progression

Autophagy-Mediated Regulation of Metabolic Reprogramming in Cancer Progression

Abnormal proliferative capacity, lack of TME nutrients, and a poor TME seem to be contradictory during cancer progression, but all conditions can co-exist. A potential explanation for this is the increased metabolite reuse, degradation of non-growth-related substances or damaged organelles, and alteration of the metabolic patterns and structures of cells to maximize the supply of substances synthesized for cancer cell growth and progression.⁵⁸ Theoretically, metabolic reprogramming and

autophagy can interact to provide the majority of the nutrients needed by the cell; autophagy is crucial for the metabolic reprogramming of cancer cells and is associated with the core of the tricarboxylic acid cycle. Numerous studies have investigated the metabolic reprogramming of cancer cells, including glycometabolism, lipid metabolism, and amino acid metabolism, which have a strong correlation between these processes and cancer progression, in all of which autophagy plays a key part.^{59–61} Strohecker et al⁶² reported that knocking down *ATG7* affected the oxygen consumption rate and growth of lung cancer cells by blocking autophagy. In contrast, the addition of exogenous glutamine to the knockdown cells restored their proliferative capacity, suggesting that lung cancer cells affect the reprogramming of glutamine metabolism through autophagy, which in turn affects the progressive growth of cancer cells. Ma et al⁶³ found that the abnormally high expression of HAGLROS in bile duct cancer cells was significantly correlated with cancer growth and malignant progression. Similarly, lncRNA HAGLROS knock-down inhibited the mTOR pathway to promote autophagy and improved lipid metabolic reprogramming in cancer cells,

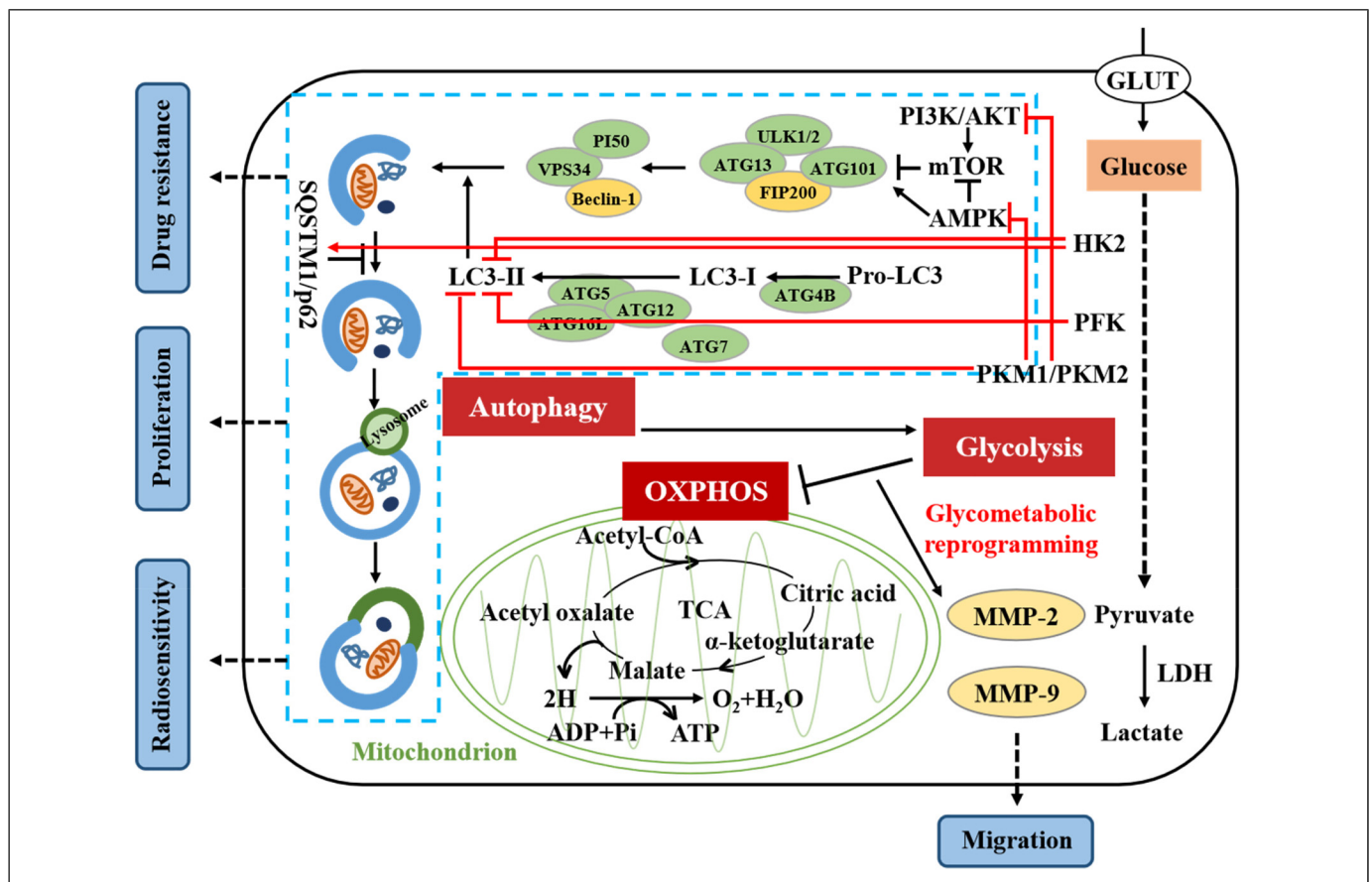


Figure 3. Autophagy regulates glycometabolic reprogramming in cancers. Abbreviations: MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; GLUT, glucose transporters; HK2, hexokinase 2; PKM1, pyruvate kinase M 1; PKM2, pyruvate kinase M 2; LDH, lactate dehydrogenase; TCA, tricarboxylic acid cycle; PFK, phosphofructokinase; OXPHOS, oxidative phosphorylation; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; mTOR, mammalian target of rapamycin; ULK, UNC-51-like kinase; ATG, autophagy associated gene; FIP, focal adhesion kinase family interacting protein; VPS, vacuolar protein sorting; LC3, light chain 3; SQSTM1, sequestosome 1. →: promotion; ⊥: inhibition.

blocking the malignant progression of cancer cells.⁶³ Thus, autophagy may function as an upstream switch in regulating the metabolic reprogramming of cancer cells, which in turn alters their biological behavior.

Autophagy Regulates Glycometabolic Reprogramming in Lung and Other Cancers

One of the characteristics of cancer cells is a shift from oxidative phosphorylation to glycolysis. The effects of autophagy and its influence on the malignant progression of cancer cells have been extensively studied. When cells are in a nutrient-rich environment, the mammalian target of rapamycin complex 1 (mTORC1) promotes cell growth and suppresses autophagy by inhibiting ULK1; whereas, when cells are undersupplied, AMPK is activated and regulates autophagy by inhibiting mTORC1 and activating ULK1, suggesting that cellular glycometabolism and autophagy are functionally associated with one another.⁶⁴ Moreover, HK2-mediated glycolysis may limit lung cancer cell growth in the lung cancer cell lines, KP2 and H23, by causing cell cycle arrest and triggering autophagy and apoptosis pathways.⁶⁵ Another study showed that PFKFB4 and endothelial tyrosine kinases interact to promote SCLC chemoresistance by regulating autophagy.⁶⁶ In addition, *PKM2* silencing improved radiosensitivity in lung cancer cell lines by promoting ionizing radiation-induced autophagy *in vitro* and *in vivo*.⁶⁷ When *PKM1* or *PKM2* are knocked down in H1299 cells, AMPK signaling is activated, which induces mitochondrial biosynthesis and autophagy to maintain energy homeostasis.⁶⁸ Wang et al⁶⁹ found that cadmium-induced glycolysis was autophagy-dependent and that the autophagy-glycolysis axis plays an important role in the proliferation of A549 cells treated with cadmium. Hasenbilige et al⁷⁰ showed that GLUT1, HKII, LDHA, and *PKM2* were significantly inhibited in HMGA2-overexpressed A549 cells treated with the autophagy inhibitor, 3-MA, indicating that autophagy is involved in HMGA2-mediated glycolysis in A549 cells, which is essential for cadmium-induced migration. In addition, Let-7-mediated and mTOR-dependent autophagy were reported to participate in glucose metabolism.⁷¹

Autophagy-regulated glycometabolic reprogramming has been reported in bladder, liver, breast, gastric, acute myeloid leukemia, myeloma, and ovarian cancers^{72,73} but is less studied in lung cancer. Li et al⁷⁴ found that long noncoding RNA *UCA1* activates HK2, a key glycolytic enzyme, which triggers the Warburg effect in bladder cancer cells. The specific mechanism includes lncRNA *UCA1* activation of STAT3 and inhibition of miRNA-143 through mTOR. In addition, the regulation of HK2 activity in hepatocellular carcinoma acts as a switch for autophagy to regulate glycolysis. Lys63 is catalyzed by the ubiquitin ligase TRAF6 to ubiquitinate HK2 in hepatocellular carcinoma cells, while autophagy relies on SQSTM1/p62 receptors to recognize and selectively degrade the ubiquitinated HK2 and aerobic glycolysis and hepatocellular carcinoma cell proliferation.⁵⁹ Qin et al⁷⁵ reported that the inhibition of

autophagy promoted metastasis and glycolysis in gastric cancer cells via the ROS-NF- κ B-HIF-1 α pathway. Moreover, quercetin inhibited autophagy in MCF-7 and MDA-MB-231 breast cancer cells through suppression of the Akt-mTOR pathway-mediated autophagy, preventing cellular glycolysis and cell migration.⁷⁶ In addition, knockdown of lncRNA HOTAIRM1 in AML effectively prevented the activity of P-type phosphofructokinase (PFKP) through the Wnt/ β -catenin pathway, inhibiting glycolysis and reversing cytarabine resistance in cancer cells.^{77,78} Conversely, silencing PFKP effectively inhibited the increase in aerobic glycolysis and epithelial-mesenchymal transformation in cancer cells caused by starvation-induced upregulation of autophagy.^{77,78} These findings suggest that the aberrant activation of autophagy may be a consequence of increased autophagy in cancer cells and that abnormal autophagy activation may control glycometabolic reprogramming in both positive and negative directions, acting as both an oncogenic and pro-cancer agent. The intricate regulatory connection between the 2 changes in autophagic activities may be closely related to different upstream mechanisms, and the different outcomes induced by the different activation pathways are very significant to understanding and treating cancer progression (Figure 3).

Solid tumors are located in the TME, where tumor cells with restricted normal metabolism rely on autophagy to survive and their metabolism is reprogrammed for rapid cell growth and proliferation.⁵ Although numerous studies have been conducted on the role of various signaling pathways to bridge the gap between autophagy and glycometabolic reprogramming in cancer cells, we now understand that changes in autophagy and metabolic reprogramming in cancer cells are inextricably linked to cancer progression, invasive metastasis, drug resistance, and immune evasion. These mechanisms contribute to the mutual regulation of ATGs and key glycolytic enzymes, indicating that the complex initiation and regulatory networks involved are worth exploring. Currently, there is no research on the relationship between autophagy and glycometabolic reprogramming in lung cancer; however, more thorough investigations may provide new insights and lay the foundation for investigating the mechanisms underlying lung cancer development and potential therapeutic approaches to halt its progression.

Concluding Remarks

Targeted treatment modalities have emerged with the rapid development of science and technology, especially in their application to in-depth understanding of the pathogenic mechanisms of lung cancer. The optimized diagnosis and treatment of operable lung cancer, new targeted therapy, and immunotherapy strategies for patients with lung cancer have achieved good efficacy, especially the monoclonal antibody therapy that blocks the immune checkpoints PD-1 and PD-L1. However, patients with lung cancer still face problems such as drug resistance, metastasis, and recurrence.⁷⁹ Malignant progression of cancer is closely correlated with the abnormal upregulation of autophagy and glycometabolic reprogramming in lung cancer

cells. The effects of autophagy on glycolysis and the transcription or expression levels of key enzymes are also potentially important in influencing cancer development and progression. The combined inhibition of both strategies may be a new, safer, and more effective treatment option for patients with lung cancer. Therefore, their effects on lung cancer progression warrant further investigation.

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