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Review Article

Metabolomic Characteristics and Clinical Implications in Pathological Subtypes of Lung Cancer

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Abstract

Lung cancer remains the leading cause of cancer-related mortality worldwide, with marked phenotypic differences observed among its major histological subtypes, adenocarcinoma (ADC), squamous cell carcinoma (SCC), and small cell lung cancer (SCLC), in both clinical presentation and therapeutic response. In recent years, metabolomics has emerged as a powerful tool for studying cancer metabolic reprogramming, providing new insights into the metabolic distinctions among lung cancer subtypes. This review summarizes recent research advances in the metabolomics of ADC, SCC, and SCLC. Studies have revealed that ADC and SCC display distinct metabolic profiles in lipid metabolism, amino acid metabolism, and cell membrane synthesis, while SCLC demonstrates a unique metabolic pattern. Through metabolomic technologies, particularly mass spectrometry and liquid chromatography, it is possible to effectively differentiate lung cancer subtypes and identify potential biomarkers for early diagnosis and personalized treatment. This review also explores the clinical potential of metabolomics in lung cancer, emphasizing its critical role in early diagnosis and subtype stratification. These methodological advances establish a robust foundation for precision oncology paradigms in thoracic malignancies.

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with its high mortality rate closely linked to delayed diagnosis.[1] The association between late-stage diagnosis and poor prognosis has been well documented in epidemiological studies. Analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (2010–2019 cohort) reveals significant gender disparities in diagnostic staging: 24.9% of female patients presented with localized disease at diagnosis compared to 20.1% of males. Conversely, distant metastases were observed in 46.5% of female cases versus 50.9% of male cases.[2] Lung cancer is significantly heterogeneous and is primarily classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC constituting approximately 85% of pulmonary malignancies.[2] These subtypes exhibit considerable heterogeneity in histological features, clinical manifestations, and therapeutic responsiveness, necessitating precise differentiation for optimal diagnostic accuracy, prognostic evaluation, and treatment stratification. Tumor subtypes are typically assessed morphologically using optical microscopy. *EGFR* mutations are common in adenocarcinoma (ADC), while *TP53* mutations frequently occur in squamous cell carcinoma (SCC). Traditional diagnosis relies on imaging techniques such as computed tomography (CT), X-ray, and positron emission tomography (PET)/CT, alongside histopathological evaluation. However, the high false-positive rate of low-dose CT screening, ranging from 7.9% to 49.3%, highlights the need for more precise auxiliary diagnostic tools.[3] Moreover, conventional histopathological evaluation may not consistently achieve diagnostic precision, with interobserver concordance rates for NSCLC subtyping reported between 67.1% and 89.6%.[4] Although immunohistochemical markers demonstrate good performance, the lengthy testing duration and high tissue consumption required for individual marker testing are significant drawbacks. In clinical practice, especially for small nodules obtained via fine-needle aspiration, the sample size is often limited.

Metabolomics, a core discipline within systems biology, is emerging as a critical methodology for elucidating tumor heterogeneity through systematic analysis of small-molecule metabolite flux. It offers advantages such as high sensitivity, non-invasive sample acquisition (e.g., blood, saliva), and diverse technological platforms including mass spectrometry and nuclear magnetic reso-

Keywords: Metabolomics; Adenocarcinoma; ADC; Squamous cell carcinoma; SCC; Non-small cell lung cancer; NSCLC; Small cell lung cancer; SCLC.

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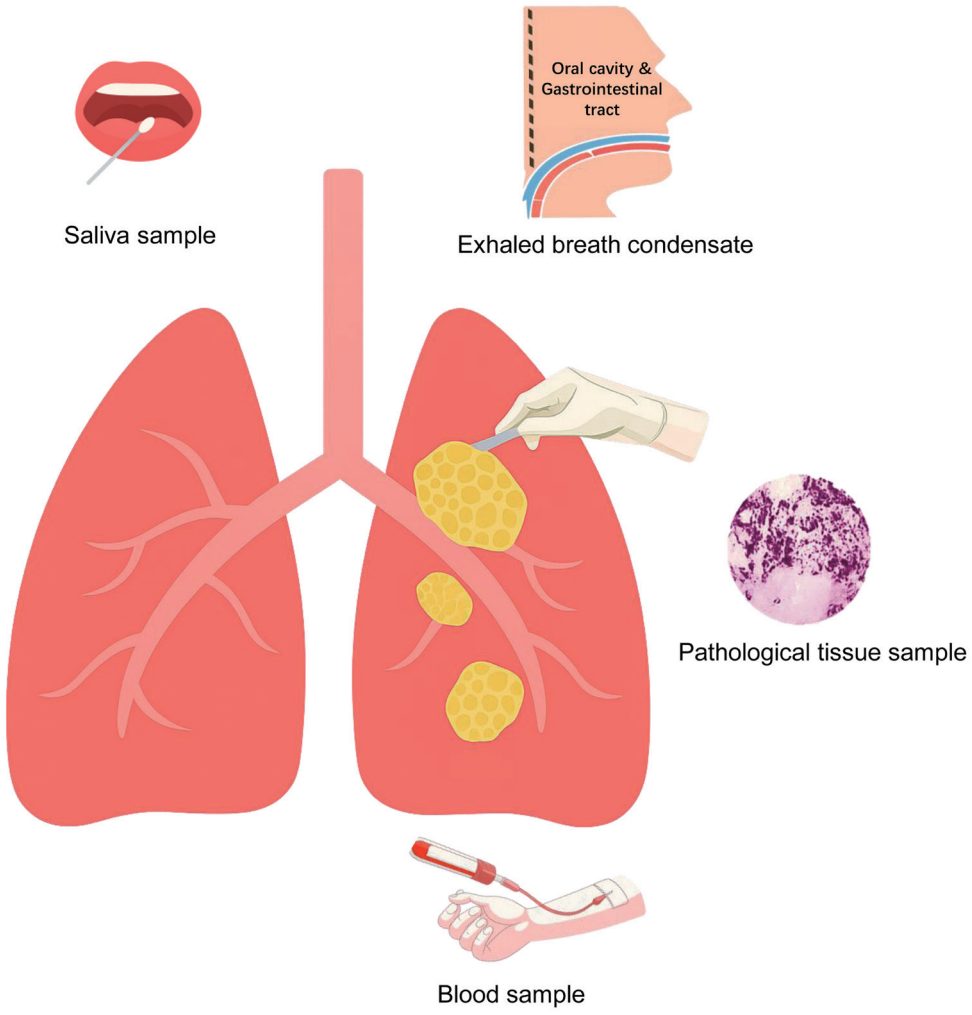

Fig. 1. The anatomical origins and collection sites of the biological samples in this study, such as saliva, blood, exhaled breath condensate, and tissue samples.

nance. Recent studies have revealed significant metabolic differences among lung cancer subtypes,[5] which not only facilitate subtype differentiation but also enable the construction of diagnostic models based on metabolic markers, providing new directions for early screening and personalized treatment.

Therefore, this paper systematically reviews recent progress in metabolomics, focusing on the metabolic characteristics of NSCLC and SCLC and the development and application of metabolomics in lung cancer. First, the development and application of metabolomics in lung cancer are summarized. Next, we analyze the metabolic differences among various lung cancer types. Finally, we evaluate the translational potential and clinical implications of metabolomics in three clinical domains: early detection, molecular subtyping frameworks, and personalized treatment strategies, through a critical analysis of contemporary studies.

The development of metabolomics in lung cancer

Metabolomics has evolved into a pivotal research tool for studying tumor metabolic reprogramming, with potential applications in early diagnosis, prognosis prediction, and personalized treatment of lung cancer. Metabolomic analyses can be performed using biological samples, such as blood, urine, and biopsy tissues, obtained through non-invasive or minimally invasive methods (Fig. 1).[6] The systematic characterization of biofluid metabolomes (e.g., saliva, plasma, and urine) facilitates the identification of metabolic signatures correlated with dietary exposures, microbiome dynamics, and environmental carcinogens, thereby elucidating multifactorial mechanisms of oncogenesis. Compared to tissue samples, biofluids can be collected non-invasively or with minimal invasiveness, making them suitable for monitoring treatment response and cancer progression. Metabolic reprogramming is a hallmark of cancer cells, as tumor cells alter their metabolic pathways to meet the demands of rapid proliferation. By systematically interrogating intra- and extracellular metabolite fluxes, metabolomics platforms enable the discovery of novel oncobiomarkers with clinical utility in diagnostic and therapeutic decision-making. Low-dose CT is widely used for early lung cancer screening, but its high false-positive rate leads to unnecessary medical resource consumption and patient anxiety. Thus, identifying sensitive and specific biomarkers is essential to complement imaging techniques.[7] Several studies have demonstrated the promising potential of metabolomics in this

Table 1. Metabolomics techniques and their advantages and disadvantages

Technique	Advantages	Limitations	Reference
Nuclear magnetic resonance (NMR)	1. Non-destructive analysis, allowing sample reuse; 2. Minimal sample preparation; 3. Supports *in vivo* detection	1. Lower sensitivity and limited dynamic range compared to MS; 2. Poor resolution for low-abundance metabolites	13
Gas chromatography-MS (GC-MS)	1. High sensitivity, resolution, and reproducibility; 2. Mature technology with comprehensive databases; 3. Ideal for volatile compounds	1. Requires derivatization for non-volatile/thermally unstable compounds; 2. Complex sample pretreatment	14
Liquid chromatography-MS (LC-MS)	1. Suitable for non-volatile and polar compounds; 2. Strong separation capability for complex mixtures; 3. Flexible chromatographic conditions	1. Limited database compatibility; 2. Complex data interpretation	14
Capillary electrophoresis-MS (CE-MS)	1. Excellent for polar/charged compounds; 2. Minimal pretreatment and low solvent consumption; 3. Rapid separation	1. Lower stability and sensitivity; 2. Restricted applicability	15
Imaging mass spectrometry (IMS)	Providing spatial metabolite distribution in tissues (spatial metabolomics)	Relatively new technology, and the standardization and popularity to be improved	16
Single-cell metabolomics	Enabling high-resolution analysis of metabolites at the single-cell level by microfluidics	Technically challenging with high instrumentation/operational costs	17
Metabolic flux analysis (Fluxomics)	Dynamic tracking of metabolic pathway changes by isotopic labeling	Requiring complex experimental design and multi-omics integration	18
Ultra-high performance LC-MS (UHPLC-MS)	1. Enhanced separation efficiency and speed; 2. Ideal for high-throughput studies	Demanding high-pressure-resistant columns and instruments	19
Ion mobility spectrometry-MS (IMS-MS)	1. Additional separation dimension for improved identification; 2. Suitable for complex biological samples	High cost and need for advanced data analysis algorithms	20

context.[8,9] Schult *et al*.[8] collected serum samples from 79 NSCLC patients and 79 healthy controls, using high-resolution magic angle spinning magnetic resonance spectroscopy to measure metabolite differences between the groups. The results showed that changes in organic acids, amino acids, carnitines, phosphosugars, vitamins, coenzymes, nucleosides, nucleobases, and their derivatives could establish an early diagnostic model for lung cancer. Additionally, this model could predict the 5-year survival rate of lung cancer patients. Zheng *et al*.[9] employed gas chromatography-mass spectrometry (GC-MS) to analyze plasma samples from lung cancer patients and healthy individuals. Their study revealed the diagnostic value of several differential metabolites, such as oleic acid, 2-hydroxybutyrate, cholesterol, and inositol, in accurately diagnosing lung cancer. Other studies have utilized saliva and bronchoalveolar lavage fluid for metabolomic analysis. In a 2022 study, Takamori *et al*.[10] collected saliva samples from 41 lung cancer patients and 21 patients with benign lung lesions. Using capillary electrophoresis-mass spectrometry, they detected and analyzed salivary metabolites, identifying 10 significantly different metabolites between the two groups. The concentration of tryptophan in saliva from the lung cancer group was significantly lower than that in the benign lesion group. Concentrations of choline, thymine, cytosine, phenylalanine, leucine, isoleucine, lysine, and tyrosine were higher in the lung cancer group, although these differences were not statistically significant. A diagnostic model combining diethanolamine, cytosine, lysine, and tyrosine showed good discriminatory ability in differentiating benign lung lesions from lung cancer. Callejón-Leblic *et al*.[11] collected bronchoalveolar lavage fluid from lung cancer patients and analyzed the samples using GC-MS to identify differential metabolites. Their results indicated that glycerol and phosphate could be used not only for lung cancer diagnosis but also for prognosis. In recent years, researchers have explored exhaled breath condensate (EBC), a biological fluid obtained non-invasively by collecting and cooling exhaled air.[12] Typically, EBC is collected using a device equipped with a condenser and saliva collector, capturing both volatile and non-volatile metabolites. Its composition is believed to reflect that of the airway lining fluid.[13] In a 2025 study, Wang *et al*.[12] used a non-targeted metabolomics approach based on ultra-performance liquid chromatography–high-resolution mass spectrometry to identify differential metabolites in EBC between NSCLC patients and controls. Upregulated metabolites in NSCLC EBC included amino acids and their derivatives, dipeptides, and fatty acids. Downregulated metabolites included 3,4-methylenesebacic acid, 2-isopropylmalic acid / 3-isopropylmalic acid / 2,3-dimethyl-3-hydroxyglutaric acid, and trimethylamine-N-oxide.

Technical methods in metabolomics

Metabolomics employs advanced analytical techniques to identify and quantify small molecules (metabolites) in biological samples, providing a snapshot of metabolic activity under physiological and pathological conditions (Table 1).[13–20] The two most commonly used platforms in metabolomics are nuclear magnetic resonance (NMR) and mass spectrometry (MS), each with unique advantages for lung cancer research. NMR is a crucial technique in metabolomics, offering advantages such as non-destructive detection, simple sample preparation, and the ability to detect metabolites *in*

vivo. However, NMR has limitations, including lower sensitivity compared to MS, a limited dynamic range, and reduced efficiency in detecting low-abundance metabolites. Despite these drawbacks, NMR remains irreplaceable in metabolite structure identification and quantitative analysis, especially in scenarios requiring non-destructive detection and *in vivo* analysis.[14] MS is one of the most widely used techniques in metabolomics research and is often combined with separation methods to enhance analytical capabilities. Common combinations include GC-MS, liquid chromatography-mass spectrometry (LC-MS), and capillary electrophoresis-mass spectrometry. GC-MS offers several advantages[15]: it is suitable for stable and easily vaporized samples, such as the separation of homologs and isomers; it has high sensitivity, efficient separation, high resolution, and good reproducibility; and the technology is mature, with relatively comprehensive public databases. However, its limitations include the need for derivatization to analyze non-volatile and thermally unstable compounds, which increases experimental complexity. LC-MS is suitable for non-volatile and polar compounds,[15] with a broad detection range. The preceding liquid chromatography effectively separates complex mixtures, making LC-MS ideal for detecting potential biomarkers in biological samples. It also allows flexible selection of chromatographic columns and separation conditions based on experimental needs. However, its limitations include weaker compatibility with public databases and more complex data interpretation. Capillary electrophoresis-mass spectrometry is well suited for separating polar and charged compounds.[15] It requires minimal sample pretreatment, consumes little organic solvent, and is cost-effective, with fast separation enabled by fused silica capillaries. However, its limitations include lower stability and sensitivity, which restrict its application in certain studies. New Technologies: 1. Imaging Mass Spectrometry[16]: Used for spatial metabolomics research, providing information on the distribution of metabolites within tissues. 2. Single-Cell Metabolomics[17]: Combines microfluidic technology and mass spectrometry to achieve high-precision analysis of metabolites in individual cells. 3. Metabolic Flux Analysis (Fluxomics)[18]: Studies dynamic changes in metabolic pathways using isotope labeling and mass spectrometry. 4. Ultra-high-performance liquid chromatography-mass spectrometry[19]: Builds on LC-MS by using ultra-high-performance liquid chromatography to improve separation efficiency. It offers higher separation efficiency, faster analysis speed, and is suitable for high-throughput metabolomics research. 5. Ion Mobility Mass Spectrometry[20]: Introduces ion mobility separation into mass spectrometry, adding an additional dimension of separation. It enhances separation capability and metabolite identification accuracy for complex samples and is used for high-precision analysis of metabolites in complex biological samples. By integrating these technologies, metabolomics has revealed critical metabolic alterations across lung cancer subtypes, such as increased glycolysis and disrupted lipid metabolism. These findings provide a deeper understanding of the biological mechanisms underlying lung cancer.

Metabolomic characteristics of NSCLC and SCLC

Metabolomic differences between subtypes of NSCLC and SCLC

SCLC accounts for approximately 15% of all lung cancers and is characterized by rapid growth, early distant metastasis, and frequent high resistance to treatment.[21] Although research on metabolic reprogramming in SCLC remains limited, recent studies have uncovered unique metabolic features with crucial implications for early diagnosis and personalized treatment. In a 2024 multicenter study, Shang *et al*.[21] conducted metabolomic and lipidomic analyses on serum samples from 461 subjects using liquid chromatography-tandem mass spectrometry. They identified a biomarker panel consisting of eight metabolites that effectively distinguished SCLC patients from NSCLC patients and healthy controls. The panel included 1-myristoyl-sn-glycero-3-phosphocholine, 16β-hydroxyestradiol, 3-phosphoserine, DL-lactate, cholesterol sulfate, D-lysine, dioctyl phthalate, and Leu-Phe. The significantly elevated levels of these metabolites suggest substantial differences in lipid metabolism, amino acid metabolism, and other pathways between SCLC, NSCLC, and healthy individuals. Notably, these metabolic changes demonstrated subtype-specific stability, confirming unique metabolic reprogramming patterns in SCLC.

The emerging understanding of SCLC metabolic reprogramming provides novel therapeutic targets to address clinical challenges such as aggressive invasion and rapid chemoresistance. Future research should focus on integrating multi-omics approaches (combining metabolomics with epigenomic profiling and tumor microenvironment analysis), potentially shifting SCLC treatment from conventional chemotherapy to molecular subtype-guided precision therapies. Concurrently, developing metabolic signature-based early detection systems and dynamic treatment response predictors could substantially improve clinical outcomes for this highly malignant disease.

Metabolomic characteristics of NSCLC

Current diagnostic methodologies for lung cancer primarily utilize two specimen types: histopathological specimens and peripheral blood plasma, the latter of which can more accurately reflect the metabolomic characteristics of cancer cells. Pioneering work by Rocha *et al*.[22] employed tissue samples from 56 primary lung cancer patients, 19 ADC, 19 SCC, and 18 cases of rare histological variants, and analyzed them using NMR spectroscopy. The study revealed that phospholipid-related metabolites (phosphatidylcholine (PC), glycerophosphocholine, and polyethylene) showed significant correlations in ADC compared to SCC ($|r| > 0.7$, $P < 0.004$, Bonferroni correction), while SCC exhibited stronger correlations with lactate, glucose, glutamate, alanine, glutathione, and creatine. Changes in glucose and lactate levels were more pronounced in SCC tumors, showing a negative correlation, whereas these correlations were attenuated in ADC. Enhanced fluorodeoxyglucose avidity on PET imaging and significant glucose transporter 1 overexpression characterized SCC specimens, supporting high glycolytic rates. Regarding amino acid metabolism, glutamate and alanine were significantly increased and positively correlated in SCC tumors. Creatine levels were elevated in both tumor types but more so in SCC than in ADC (126.4% vs. 28.2%, respectively). Spatial metabolomic profiling through matrix-assisted laser desorption/ionization-mass spectrometry imaging of 35 NSCLC tissue samples, reflecting clinical prevalence (69% ADC vs. 31% SCC), found taurine abundant in adenocarcinoma tumor regions, while glutamine was more abundant in SCC.[23] Taurine, a sulfur-containing amino acid, may be related to cell membrane stability and antioxidant responses, while glutamine is closely associated with amino acid metabolism in cancer cells. In 2022, Zang *et al*.[24] used ultra-high-performance liquid chromatography-high-resolution mass spectrometry to analyze 227 tissue samples from 79 NSCLC patients, confirming metabolomic differences between ADC and SCC. Valine, sphingosine, glutamate γ-methyl ester, and lysophosphatidylcholine (16:0) were characteristic of ADC, while SCC

Table 2. Differential metabolites in tissue and plasma samples of squamous cell carcinoma and adenocarcinoma

Metabolite	Tissue/Blood	Higher in ADC	Higher in SCC	Reference
PC, GPC, PE	Tissue	+	–	2014 Study (NMR technology)[22]
Lactate	Tissue	–	+	2014 Study (NMR technology)[22]
Glucose	Tissue	–	+	2014 Study (NMR technology)[22]
Glutamate	Tissue	–	+	2014 Study (NMR technology)[22]
Alanine	Tissue	–	+	2014 Study (NMR technology)[22]
GSH (Glutathione)	Tissue	–	+	2014 Study (NMR technology)[22]
Creatine	Tissue	+	+++	2014 Study (NMR technology)[22]
Taurine	Tissue	+	–	2021 Study (MALDI-MSI)[23]
Glutamine	Tissue	–	+	2021 Study (MALDI-MSI)[23]
Valine	Tissue	+	+	2022 Study (UPLC-HRMS)[24]
Sphingosine	Tissue	+	+	2022 Study (UPLC-HRMS)[24]
Glutamate γ-methyl ester	Tissue	+	–	2022 Study (UPLC-HRMS)[24]
Lysophosphatidylcholine (LPC)	Tissue	LPC(16:0)(+)	LPC(18:1) (+)	2022 Study (UPLC-HRMS)[24]
Leucine derivatives	Tissue	–	+	2022 Study (UPLC-HRMS)[24]
Fatty acids	Plasma	–	+(early stage)	2021 Study (LC-MS)[26]
Carnitine	Plasma	–	+(early stage)	2021 Study (LC-MS)[26]
Glycerophospholipids	Plasma	–	+(early stage)	2021 Study (LC-MS)[26]
Amines	Plasma	–	+(early stage)	2021 Study (LC-MS)[26]
Amino acids	Plasma	–	+(early stage)	2021 Study (LC-MS)[26]
Fatty acid amides	Plasma	–	+(late stage)	2021 Study (LC-MS)[26]
Lysophosphatidic acids (LPAs)	Plasma	–	+(late stage)	2024 Study (LC-MS)[4]
Oxidized phosphatidylcholines (oxPCs)	Plasma	+(late stage)	–	2024 Study (LC-MS)[4]

ADC, adenocarcinoma; EGFR, epidermal growth factor receptor; GLUT1, glucose transporter 1; GPC, glycerophosphocholine; LC-MS, liquid chromatography-mass spectrometry; MALDI-MSI, matrix-assisted laser desorption/ionization-mass spectrometry imaging; NMR, nuclear magnetic resonance; PC, phosphatidylcholine; PE, phosphatidylethanolamine; SCC, squamous cell carcinoma; tRNA, transfer RNA; UPLC-HRMS, ultra performance liquid chromatography-high resolution mass spectrometry; VEGF, vascular endothelial growth factor.

was characterized by valine, sphingosine, lysophosphatidylcholine (18:1), and leucine derivatives. These distinct metabolic signatures enable histopathological discrimination between adenocarcinoma and SCC. Complementing tissue analysis, peripheral blood plasma has emerged as a viable biological matrix for lung cancer metabolomics research. Several recent studies have explored metabolic differences between ADC and SCC through plasma metabolite analysis. In 2021, Cao *et al*.[25] used LC-ESI-QTrap-MS/MS to analyze 128 plasma samples from NSCLC patients and established a logistic regression model integrating four differential metabolites. This model successfully distinguished ADC from SCC, with a sensitivity of 92.0% and specificity of 92.9%, indicating the high potential of plasma metabolites in identifying lung cancer subtypes. Also in 2021, Kowalczyk *et al*.[26] conducted a study involving 99 NSCLC tissue samples and plasma samples from 72 NSCLC and 20 chronic obstructive pulmonary disease patients, analyzed using LC-MS. In early-stage SCC vs. ADC tissue comparisons, creatine, creatinine, xanthine, and dihydrothymine were upregulated in SCC, while fatty acids, carnitine, glycerophospholipids, lysoglycerophospholipids, amines, amino acids, and amides were upregulated in ADC. Plasma analysis from NSCLC patients revealed that only two metabolites (PC 15:0/22:6 and 18:1/22:6) showed significant differences between early-stage SCC and ADC. In late-stage plasma samples, metabolites distinguishing NSCLC subtypes were primarily fatty acids, carnitine, and fatty acid amides. In 2024, Michal and Joanna's team analyzed 101 plasma samples from NSCLC patients (41 ADC and 60 SCC) using LC-MS.[4] They observed elevated levels of lysophosphatidic acids (LPAs) in SCC patients and oxidized phosphatidylcholines (oxPCs) in ADC subjects. oxPCs act as ligands for vascular endothelial growth factor (VEGF) receptors, promoting tumor angiogenesis via strong mitogenic effects on vascular endothelial cells. VEGF receptors are known molecular targets for NSCLC treatment. Furthermore, hypoxia upregulates VEGF-A protein levels in lung cancer cell lines, and VEGF-A correlates significantly with tumor size, lymph node metastasis, and poorer overall survival in ADC patients.[27] LPAs are derived from lysophosphatidylcholine through the action of extracellular autotaxin (ATX), which is present in body fluids such as plasma and malignant effusions. To date, seven LPA receptors have been identified. LPAs activate cell proliferation, differentiation, and migration, playing important roles in wound healing. Elevated ATX expression leads to increased LPA levels, which are associated with tumor severity. The ATX-LPA axis contributes to inflammation and lung cancer progression by increasing pro-inflammatory cytokines.[28] Therefore, LPAs and oxPCs serve as potential diagnostic biomarkers for ADC and SCC (Table 2).[4,22–24,26]

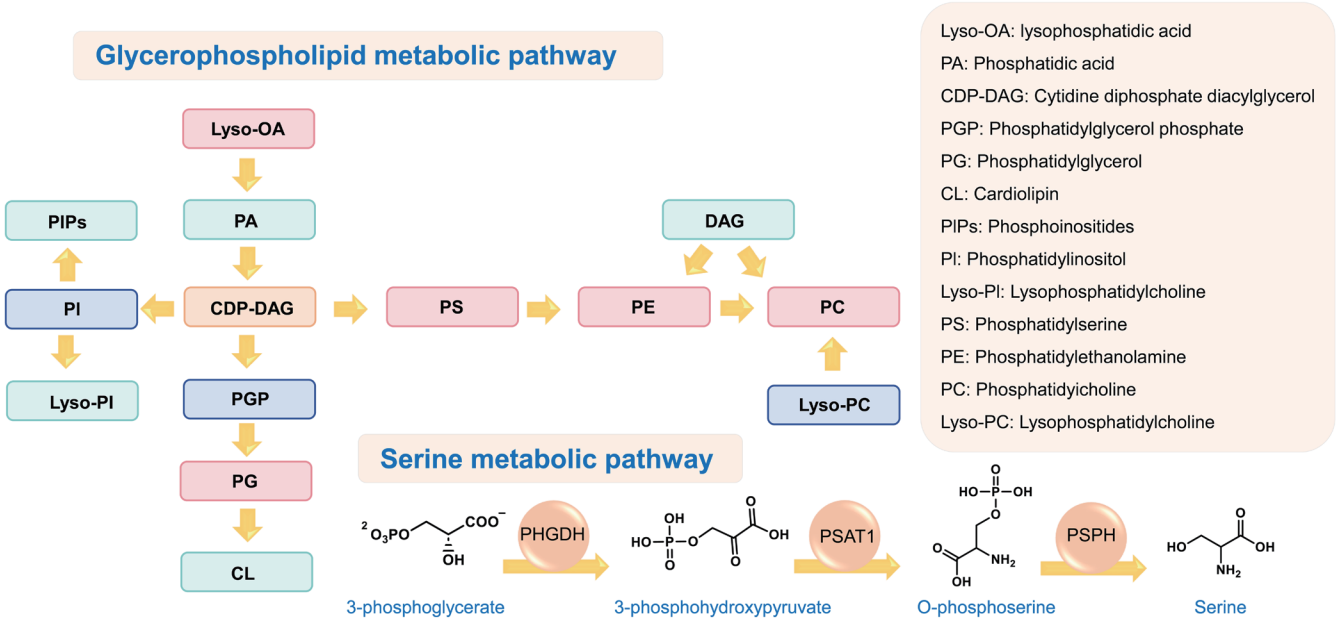

Fig. 2. The metabolic pathway of glycerophospholipids and the synthesis pathway of tryptophan, detailing the generation of lysophosphatidic acid (LPA) mediated by phospholipase, and membrane phospholipid synthesis through the CDP-choline pathway. CDP, cytidine diphosphate; DAG, diacylglycerol; PHGDH, phosphoglycerate dehydrogenase; PI, phosphatidylinositol; PSAT1, phosphoserine aminotransferase 1; PSPH, phosphoserine phosphatase.

Clinical implications

Metabolomics is gradually being applied in clinical practice, especially in areas such as early screening, treatment monitoring, and personalized therapy. In diagnosis, an increasing number of cancer cell–related metabolic gene targets have been discovered, providing new directions for the early detection of lung cancer. The research mentioned above, such as the significant correlation between phospholipid metabolites in ADC and the relationship between SCC and glycolysis, has provided additional avenues for early lung cancer diagnosis. Regarding the metabolomics of plasma from lung cancer patients, current logistic regression models can distinguish subtypes with high sensitivity and specificity using markers such as phosphatidylcholine and oxidized phosphatidylcholine. However, diagnostic models based on plasma samples still require the inclusion of more metabolites to provide sufficient data support. The treatment of lung cancer heavily depends on determining the pathological nature of the tumor. Metabolomics can predict the likely subtype before tissue specimens are obtained, thereby assisting clinical decision-making. A study by Nie *et al*.[29] found through metabolomics analysis that metabolic disorders progressively intensified from precancerous lesions (atypical adenomatous hyperplasia/adenocarcinoma in situ) to invasive adenocarcinoma. This progression manifested as dysregulation in pathways such as nicotinic acid, glutathione, and purine metabolism, with specific metabolites showing dynamic changes alongside disease progression. These metabolic characteristics may serve as early diagnostic markers or therapeutic targets but require validation in larger cohorts. Qin *et al*.[30] classified early-stage lung cancer patients based on serum metabolites and revealed that different clusters of lymph node metastasis risks were significantly correlated with indicators such as elevated liver enzymes, uric acid, triglycerides, SCC antigen, and globulin levels. This offers a predictive tool for lymph node metastasis in lung cancer patients.

Metabolomics can also support treatment decision-making for lung cancer. ADC and SCC exhibit distinct metabolic pathways that may be closely related to tumor biological behavior and clinical prognosis. A key metabolic pathway in ADC is glycerophospholipid metabolism, which primarily supports cell membrane formation (Fig. 2).[31] Glycerophospholipids are essential for forming lipid bilayers in all cells. Because cancer cells require increased glycerophospholipid synthesis to meet membrane generation demands, this pathway is particularly crucial. Another significant pathway in adenocarcinoma is serine metabolism. Phosphoglycerate dehydrogenase (PHGDH) is a key enzyme in the de novo biosynthesis of serine. Upregulation of PHGDH promotes serine synthesis, supporting nucleotide and protein synthesis (Fig. 2).[31] High PHGDH expression predicts poor prognosis in NSCLC, especially in lung adenocarcinoma (Fig. 3).[32] NCT-503, a PHGDH inhibitor, has been shown to reduce glucose-derived serine production and nucleotide synthesis by decreasing the one-carbon units from glucose-derived and exogenous serine.[33] In contrast to ADC's metabolic dependencies, SCC exhibits distinct activation of the pantothenate/coenzyme A (CoA) biosynthesis pathways. Pantothenate, or vitamin B5, is a precursor for CoA synthesis.[31] CoA is vital for cell growth as it participates in numerous metabolic pathways, including phospholipid synthesis and fatty acid synthesis, and fatty acid degradation. The pantothenate and CoA biosynthesis pathway is essential for cancer cells to generate the energy required for survival.[14] Other important pathways include methionine and cysteine metabolism, which involve sulfur-containing amino acids critical for producing essential protein structures and metabolites. Cancer cell proliferation requires proteins containing disulfide bonds, for which methionine serves as a key precursor. Glutamine metabolism is also notable, as cancer cells rely on glutamine as a carbon and nitrogen source. Glutamine is converted to glutamate by glutaminase, which then enters the tricarboxylic acid cycle or supports nucleotide synthesis. In SCLC, a crucial metabolic pathway is aminoacyl-transfer RNA biosynthesis, which facilitates the translation of the mRNA genetic code into amino acid chains for

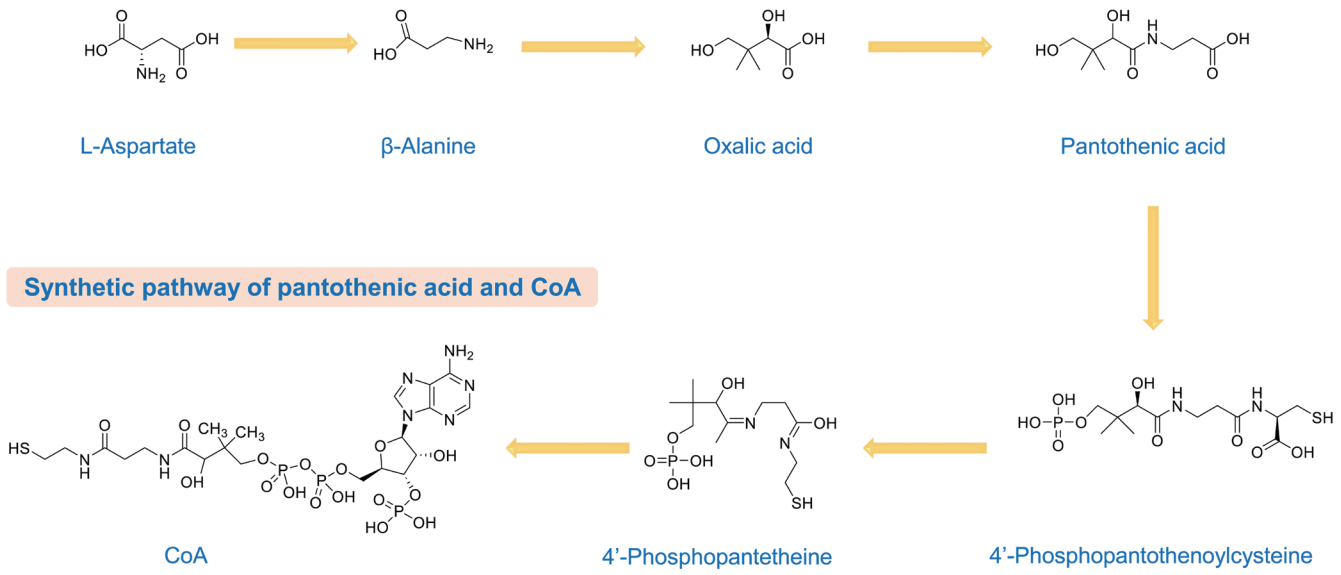

Fig. 3. The enzymatic synthesis process from pantothenic acid to functional coenzyme A (CoA).

protein production.[31] This pathway helps cancer cells produce the proteins essential for their survival.

Aloxatin is a vascular endothelial growth factor receptor tyrosine kinase inhibitor recommended for the treatment of advanced lung cancer patients who have previously received at least two systemic chemotherapies.[34] A study by Pan *et al*.[35] elucidated the molecular mechanisms of Aloxatin's action and identified potential biomarkers and pathways related to its therapeutic effects. This included 13 endogenous differential metabolites and five potential metabolic pathways. Osimertinib is a third-generation epidermal growth factor receptor tyrosine kinase inhibitor primarily used to treat NSCLC patients with *EGFR* mutations.[36] Ma *et al*.[37] applied cell metabolomics to demonstrate that amino acid metabolism regulation, hypoxia-inducible factor 1 (HIF-1), and phosphatidylinositol-3-kinase (*PI3K*)-protein kinase B (*Akt*) signaling pathways are strongly correlated with osimertinib resistance. Resistance to osimertinib is associated with upregulation of the HIF-1 and PI3K-Akt signaling pathways, as well as oxidative phosphorylation, alongside downregulation of glycolysis and arginine metabolism. These studies not only provide methods for monitoring resistance during lung cancer treatment but also suggest potential target molecules and directions for further drug development. Surgery is an important treatment modality for early-stage lung cancer, and it can alter the metabolite profiles of patients. One study observed that levels of sphingolipids (such as ceramide and sphingomyelin) in lung cancer patients were elevated both before and after surgery compared to controls.[38] Plasma metabolomics analysis may therefore offer additional approaches for postoperative monitoring in early-stage lung cancer patients. Typically, postoperative paraffin pathology is required to confirm R0 resection in lung cancer surgery, while intraoperative frozen pathology often has considerable uncertainty. A 2019 study divided 31 NSCLC patients into a preoperative intravenous injection group receiving [U-13C]-glucose and a non-injection group.[39] Isolated sections from resected tumors and adjacent normal lung tissue were used for metabolic tracing, combined with NMR, GC-MS, and fluoro-D-glucose-PET analyses. The study found that SCC exhibited different glucose and glutamine catabolic metabolic activities compared to ADC and non-cancerous lung tissue sections. This research provides insights for more precise resection of lesion tissues during surgery. With the advancement of metabolomics technology and model establishment, it is expected to greatly improve the accuracy of intraoperative rapid frozen section analysis.

Future directions and limitations

In the future, metabolomics holds great potential for application in lung cancer research. With the continuous advancement of technology, especially the optimization of high-throughput analysis methods such as mass spectrometry and liquid chromatography, metabolomics will provide deeper insights into the metabolic differences among various lung cancer subtypes. This will offer more precise support for early diagnosis, subtype classification, and personalized treatment. In the field of precise diagnosis and early screening, metabolite markers will be screened through large-scale cohort validation to identify high-specificity biomarkers (such as phosphatidylcholine, oxidized phosphatidylcholine, etc.), and non-invasive detection tools based on blood or breath will be developed for early lung cancer screening and stratification of high-risk populations. For subtype classification assistance, multimodal models (metabolomics + imagingomics + genomics), combined with AI algorithms, will be established to achieve precise subtype classification and guide the selection of preoperative treatment strategies. Combined drug strategies (e.g., targeting metabolic pathways + traditional chemotherapy/tailored tyrosine kinase inhibitor) will be developed by revealing metabolic reprogramming related to drug resistance (such as the dysregulation of the HIF-1/PI3K-Akt pathway in osimertinib resistance). We can also establish a recurrence warning model and optimize postoperative follow-up plans by using changes in postoperative metabolites (such as plasma sphingolipids, including neuroceramide and sphingomyelin) for lung cancer patients requiring surgery. Spatial metabolomics, an important research direction for the future, can, when combined with mass spectrometry imaging technology,[40] locate the spatial distribution of metabolites in tumor tissues, thereby guiding the design of surgical resection boundaries or radiotherapy target areas.

However, there are still many challenges that need to be addressed in the clinical application and translation of metabolomics. These include sample processing issues, where metabolites can be easily affected by collection and storage conditions. A unified pre-treatment process (such as rapid freezing and standardized extraction methods) needs to be established. Additionally, there is a significant variation in detection sensitivity among different mass spectrometry/NMR platforms, necessitating cross-platform data calibration and the construction of a shared database.

In terms of clinical translation, existing studies are mostly based on small, single-center samples, and multi-center, large-sample validation is needed to assess the universality of biomarkers. Mechanism studies are also lacking, as most metabolic markers are only correlated with diseases, without understanding the underlying mechanisms (such as whether elevated liver enzymes directly drive metastasis). Furthermore, metabolites can interfere with the accuracy of test results, and some markers (such as lactate) may also increase in non-cancerous conditions such as inflammation or infection. This highlights the need for integrating multi-omics data to improve specificity.

Metabolomics provides a new perspective for the precise diagnosis and treatment of lung cancer. In the future, its transformation from a "research tool" to a "clinical weapon" will require technical standardization, multi-omics integration, and large-sample validation. Additionally, targeting metabolic pathways and developing strategies to reverse drug resistance are expected to reshape the treatment landscape of lung cancer. However, overcoming current technical bottlenecks and insufficient mechanistic research will be essential for the comprehensive implementation of individualized medical care.

Admittedly, this review provides only a general overview of the current mainstream studies. There is no universally accepted standard for evaluating study quality, and we did not conduct an in-depth analysis of how heterogeneity in sample types, sample sizes, or experimental techniques across studies may influence the generalizability of their conclusions. Consequently, potential biases associated with small-sample studies were not systematically assessed, and the reported performance of diagnostic models should be interpreted with appropriate caution to avoid overly optimistic evaluations.

Conclusions

This review systematically integrates recent advances in metabolomics within lung cancer research, highlighting its potential to establish a novel paradigm for the precise diagnosis and treatment of lung cancer by elucidating the mechanisms of tumor metabolic reprogramming. Studies have shown that different subtypes of lung cancer exhibit distinct metabolic profiles. These findings not only deepen the understanding of tumor heterogeneity but also drive innovation in non-invasive diagnostic techniques. Metabolic models based on plasma, saliva, and EBCs are increasingly integrated with traditional imaging screening, which can effectively reduce the high false-positive rate of low-dose CT and the uncertainty of pathological diagnoses of small specimens. In clinical practice, metabolomics is reshaping lung cancer management through three key pathways: early screening, therapeutic decision-making, and prognostic management. Moving forward, addressing current bottlenecks, such as technical standardization, multi-center validation, and the limited depth of mechanistic research, will be critical for promoting the clinical translation and further development of metabolomics in lung cancer.

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Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

Data collection (XY), writing of the manuscript (CWX), discussion of the results, and revision of the manuscript (CWX, XY, LHS). All authors have read and approved the final manuscript.

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