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REVIEW

A Comprehensive Review of Advances in Molecular Mechanisms and Targeted Therapies for the Specific Type of Cystic Lung Cancer

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Background and Objective: Cystic lung cancer (CLC) presents diagnostic and treatment challenges due to its complex imaging features and unclear molecular mechanisms. Although surgery and standard chemotherapy are frequently used, there is limited information on targeted therapy and other precision treatments. It is crucial to comprehensively understand the molecular mechanisms and explore precision treatments based on targeted therapy.

Methods: Topic keywords including "CLC", "cystic lung cancer", "cavitary lung cancer", "Lung cancer associated with cystic airspaces", and "lung cancer" with ("sac cavity" OR "cystic degeneration" OR "thin-walled cavity" OR "adenocystic carcinoma" OR "cystic airspaces" OR "pulmonary cysts" OR "adenoid cystic carcinoma") searched in the relevant databases, such as PubMed, Google Scholar, and CNKI (China National Knowledge Infrastructure). Then, we reviewed and analyzed the molecular mechanism and its precision therapeutics of CLC.

Key Content and Findings: Various subtypes of CLC can be identified through histopathological examination, such as cystic adenocarcinoma, and squamous cell carcinoma. However, we still have much to learn about the molecular mechanisms behind CLC. Gene mutation, the abnormal tumor microenvironment, and immune dysfunction are the main mechanisms, along with potential factors like epigenetic modifications and gene susceptibility related to COPD. Recent advancements in treatment include targeted therapies, such as targeted inhibitors for EGFR, ALK, ROS1, BRAF, and MET. Surgical treatment, standardized chemotherapy, immunotherapy, and combination therapy remain important. Future research should focus on genomic and molecular profiling, and the development of precision medicine based on insights into the heterogeneity of CLC. Additionally, investigating resistance mechanisms and developing predictive biomarkers are important for future CLC research.

Conclusion: The key molecular mechanisms of CLC involve gene mutations and TME immune dysfunction. CLC still requires standard comprehensive treatment based on lung cancer staging, and targeted therapy has shown significant advantages and development prospects.

Keywords: pathogenesis, molecular mechanism, targeted therapy, therapeutics, cystic lung cancer

Introduction

Cystic lung cancer (CLC) is a clinically important type of lung cancer, although it is a rare type. However, similar to the incidence of lung cancer, it is also increasing year by year, and the number of cases has significantly increased. Due to its complex imaging manifestations, and unique clinical, imaging, histopathological, and molecular characteristics, it is easy to be misdiagnosed and mistreated.[1] Moreover, the mechanism of the formation of CLC remains unclear. An in-depth analysis of the definition and classification of CLC, potential genetic and molecular mechanisms, immunology, and standardized therapy progress is conducive to deepening the understanding of its pathogenesis and improving the relevant treatment measures and patient prognosis. At present, the early diagnosis and treatment of lung cancer still face great challenges. With the development and popularization of CT and other high-resolution imaging techniques, more and more lung diseases have been detected early, mainly including pulmonary alveolar shadows and pulmonary nodules, and

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some of them have been diagnosed as early lung cancer. Although it appears on imaging as a pulmonary vesicular shadow, it is easily mistaken for a pulmonary bulla. This particular bulla may be CLC; CLC can be formed by the deterioration of pulmonary alveolar shadow and other pulmonary cystic lesions.[2,3] In their past research history, he also has a variety of names, including CLC, luminal lung cancer, cavitary lung cancer, vesicular lung cancer, cancer with air lucency, and so on.

CLC is a rare disease with low incidence and atypical imaging findings. Due to the lack of specificity in clinical manifestations, some patients may have respiratory symptoms such as cough and sputum, chest pain, hemoptysis, etc. Patients are also accidentally found by physical examination, so misdiagnosis and missed diagnoses often occur. Currently, the definition of CLC is mainly based on the imaging characteristics of electronic computed tomography (CT), that is, the CT imaging is normal. Round, thin-walled structures were found in the lung tissue, and the following two conditions were excluded: the presence of the actual nodule followed by the presence of a cavity inside the nodule; Or inability to distinguish cystic cavities from surrounding emphysema, bronchiectasis, and interstitial lung disease. Based on current understanding, CLC should be defined as a subtype of lung cancer characterized by the presence of cystic or cavitary lesions within lung tissue.[1] These cystic spaces can contain necrotic material, fluid, or air and are lined with malignant epithelial cells. CLC can be associated with various histological subtypes of lung tissue, including cystic adenocarcinoma, cystic squamous cell carcinoma, and pulmonary adenoid cystic carcinoma (PACC).

In this review, we reviewed the classification and pathogenesis of CLC, analyzed the molecular mechanism of CLC mainly caused by gene mutation and immune dysfunction; and comprehensively summarized the therapeutics of CLC, including surgical treatment, chemotherapy, targeted therapy, immunotherapy, and combination immunotherapy, and radiation therapy. We present the following article by the Narrative Review reporting checklist.

Methods

Topic keywords including “cystic lung cancer”, “cavitary lung cancer”, “Lung cancer associated with cystic airspaces”, and “lung cancer” with (“sac cavity” OR “cystic degeneration” OR “thin-walled cavity” OR “adenocystic carcinoma” OR “cystic airspaces” OR “pulmonary cysts” OR “adenoid cystic carcinoma”) searched in the relevant databases, such as PubMed, CNKI (China National Knowledge Infrastructure), and Google Scholar (Table 1 and Table 2). The literature retrieved above on the topic also served as a substrate for compiling “pathogenesis”, “molecular mechanism”, “gene mutation”, “targeted therapy”, and “therapeutics”. The relevant search strategies and Methodology are shown in Table 1 and Table 2.

Table 1 Methodology Applied for the Development of This Narrative Review

Items	Specification
Date of search	April 5, 2024
Databases and other sources searched	PubMed, Google Scholar, and CNKI
Search terms used	Searching terms were described in the main text. A complete search term is listed in Table 2
Timeframe	No time restriction
Inclusion and exclusion criteria	Language: English
Selection process	The selection has been conducted by Beinuo Wang. The authors individually discussed all the discrepancies, and Prof. Hu Liao served as the scientific reviewer

Table 2 Search Strategy

PubMed, Google Scholar and CNKI	
1.	Cystic lung cancer
2.	Cavitary lung cancer
3.	Lung cancer associated with cystic airspaces
4.	(lung cancer) and (“sac cavity” OR “cystic degeneration” OR “thin-walled cavity” OR “adenocystic carcinoma” OR “cystic airspaces” OR “pulmonary cysts” OR “adenoid cystic carcinoma”)

Histopathological Mechanisms of CLC

Past studies have reported that CLC encompasses several histopathological subtypes, each characterized by distinct architectural patterns, cytological features, and molecular profiles.[2,4–10] These subtypes play a crucial role in determining prognosis, guiding treatment decisions, and assessing therapeutic responses in CLC.

(1) Cystic adenocarcinoma and cystic squamous cell carcinoma: Cystic adenocarcinoma represents a common subtype of CLC characterized by the presence of cystic or glandular structures within the tumor mass.[2,4,11] Histologically, cystic adenocarcinomas may demonstrate lepidic growth patterns, papillary structures, or mucinous differentiation. This subtype often exhibits histological diversity, including acinar, papillary, micropapillary, solid, or lepidic growth patterns. The presence of mucin-producing cells and epithelial differentiation is based on their histological heterogeneity. Immunohistochemical analysis may reveal the expression of markers such as thyroid transcription factor-1 (TTF-1) and napsin A, supporting the diagnosis of adenocarcinoma.

Cystic squamous cell carcinoma represents another histopathological subtype of CLC, characterized by the keratinizing squamous epithelium within cystic or cavitary lesions.[12–15] Histologically, cystic squamous cell carcinomas may exhibit keratinization, intercellular bridges, and dysplastic squamous epithelium within the cystic spaces. The subtyping of squamous cell carcinoma is crucial for determining appropriate treatment strategies and assessing prognosis. Immunohistochemical staining for markers such as p40 and p63 can aid in confirming the squamous differentiation.

(2) Other cystic non-small cell lung cancer types: Cystic large cell carcinoma, lymphoepithelioma-like carcinoma of the lung, cystic adenosquamous carcinoma.[10,16–18] Cystic large cell carcinoma is synonymous with cystic large cell undifferentiated and large cell anaplastic carcinoma. Previously, large cell carcinoma included variants such as basaloid carcinoma, large cell neuroendocrine carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype.

(3) Cystic bronchioloalveolar carcinoma (CBAC): CBAC represents a distinct subtype of cystic lung adenocarcinoma, characterized by lepidic growth along the alveolar septa. Histologically, cystic BACs may present with mucinous or non-mucinous features within the cystic spaces.[19,20] BAC is a special type of lung adenocarcinoma, which contains a malignant tumor originating in the basal cells of the bronchioles or type II alveolar cells. Relatively rare, accounting for 2% to 3% of lung cancer; When the differentiation was poor, the cells were cuboidal, the nuclei were uneven in size, and protruded into the alveolar cavity. The malignant degree was similar to that of adenocarcinoma.

(4) Cystic small cell carcinoma: It means cystic small cell lung cancer (SCLC), which is an aggressive, poorly differentiated, and high-grade neuroendocrine carcinoma.[16] SCLC is the most neuroendocrine lung tumor, and it also commonly presents in advanced-stage diseases. It is always diagnosed by small biopsies or cytology specimens.[21]

(5) Pulmonary adenoid cystic carcinoma (PACC): It means primary adenoid cystic lung cancer (PACLC), which was previously known as “columnar tumor”, usually comes from submucosal glands of the trachea and bronchus. PACC is clinically rare and constitutes one of the major types of salivary gland carcinoma affecting the lung.[22–25] Importantly, it is difficult to distinguish early PACC from common respiratory diseases such as chronic obstructive pulmonary disease or asthma, due to its irregular clinical characteristics.

Molecular Mechanism of CLC

Although the concept of CLC was proposed earlier, it was a major concern in clinical research, especially imaging research, and there were few basic studies involving molecular mechanisms such as gene mutations related to CLC. Indeed, some encouraging studies report that mutations such as EGFR in CLC should be key mechanisms in its pathogenesis. On the other hand, there are potential pathogenesis of CLC, including certain genetic susceptibility, DNA damage and repair, and chronic inflammatory mediators. These are due to the common genetic predisposition of chronic obstructive pulmonary disease (COPD), emphysema bullae, and lung cancer; The interaction between genetic variation and environmental exposure is deeply reflected in epigenetics. In addition, the relationship between chronic inflammation and lung cancer is clear; Chronic stimulation of inflammatory mediators associated with COPD emphysema and lung cancer may induce CLC.

Gene Mutation of CLC

Here is a more detailed overview of the research progress related to the genes involved in CLC, including genetic alterations and oncogenic drivers:

(1) EGFR mutations: Epidermal growth factor receptor (EGFR) mutations are among the most well-studied genetic alterations in CLC.[26–30] EGFR activating mutations, such as exon 19 deletions and L858R point mutations, confer constitutive activation of the EGFR signaling pathway, driving oncogenesis and tumor progression. These mutations occur in about 10–20% of CLC cases and are more common in non-smokers or patients with a limited smoking history. EGFR inhibitors, such as gefitinib and erlotinib, have shown significant clinical benefits in patients with CLC harboring EGFR mutations.

(2) ALK fusion and rearrangements: Anaplastic lymphoma kinase (ALK) rearrangements are another pivotal genetic alteration observed in CLC, leading to the fusion of the ALK gene with various partner genes.[31,32] ALK fusions and rearrangements drive constitutive ALK signaling, promoting tumorigenesis and tumor growth, although in a small subset of these cancer patients. CLC patients harboring ALK rearrangements benefit from targeted therapy with ALK inhibitors, such as crizotinib, alectinib, and brigatinib, which have demonstrated substantial efficacy and durable responses in this molecular subset.

(3) KRAS mutations: Kirsten Rat Sarcoma viral oncogene homolog (KRAS) mutations are frequently observed in various cancers, including CLC.[33,34] However, the prevalence of KRAS mutations is relatively low in CLC compared to other types of lung cancers. Targeted therapies directly inhibiting KRAS mutations have not been successful thus far, KRAS-mutant CLC represents a molecularly distinct subset possibly associated with intrinsic resistance to EGFR TKIs and ALK inhibitors, posing therapeutic challenges. Research efforts are focused on developing alternative targeted strategies, such as downstream pathway inhibitors and synthetic lethality approaches, to overcome the oncogenic effects of KRAS mutations in CLC.

(4) HER2, ROS1 fusion and BRAF mutation: Similar to ALK fusions, HER2, ROS1 gene fusions have been identified in CLC.[35–38] ROS1 fusions lead to the constitutive activation of the ROS1 kinase and promote tumor growth. BRAF mutations, predominantly BRAF V600E, are detected in a small subset of CLC cases. Vemurafenib and dabrafenib, BRAF inhibitors, have exhibited encouraging responses in lung cancer patients with BRAF mutations.

(5) Other possible mutations and genetic alterations: Tumor protein p53 (TP53) mutation is frequently observed in CLC, exerting tumor-suppressive and regulatory roles in cell cycle control, DNA repair, and immune responses.[39,40] Understanding the functional consequences of these mutations is crucial for elucidating their impact on tumor biology and therapeutic responses. Other genetic mutations have been identified in CLC, including RET fusion, and NTRK fusions.[41,42] Clinical trials and studies are ongoing to evaluate targeted therapies and inhibitors for these genetic alterations. In addition to the aforementioned genetic alterations, CLC harbors additional mutations affecting genes involved in cellular growth, DNA repair, and cell cycle regulation, such as MYB and others.[43–45] These alterations collectively will contribute to the molecular heterogeneity and adaptive capabilities of CLC, influencing disease behavior, treatment responses, and clinical outcomes.

In brief, significant progress has been made in understanding the genetic landscape of CLC. The identification of specific genetic alterations has enabled the development of targeted therapies and personalized treatment strategies for patients with CLC.

Immunological Mechanisms

Immunology and immune response are always included in lung cancer. CLC displayed high levels of immunosuppressor infiltration (M2 macrophages, CAFs, and MDSCs) and distinct cell death and metabolic patterns.[46] The immunosuppressive tumor microenvironment (TME) plays a critical role in the pathogenesis of cancers, encompassing a complex interplay of inflammatory, immune, and stromal components that interact with the tumor cells to modulate their behavior and therapeutic responses.[47–49] Understanding the dynamic interactions within the TME is crucial for unraveling the pathophysiology of CLC and developing effective therapeutic strategies for this disease. Furthermore, dysregulated expression of immune checkpoint molecules, such as PD-1, and PD-L1, modulates immune evasion mechanisms in NSCLC and CLC.[50] The main molecular mechanisms of CLC are summarized in Figure 1. Tumor cells and immune cells

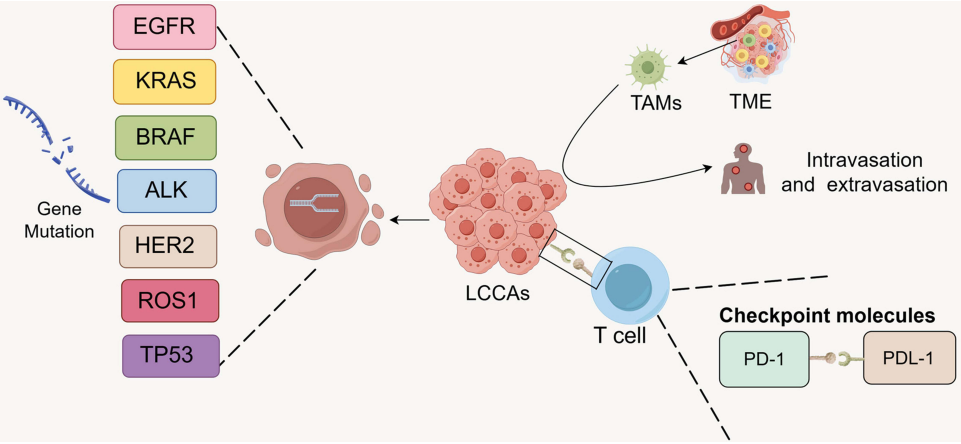

Figure 1 The main molecular mechanisms of CLC are summarized (By Figdraw).

within the tumor microenvironment exploit these checkpoint pathways to evade immune surveillance and suppress anti-tumor immunity, contributing to disease progression.

Epigenetic Alterations and Related DNA Damage and Repair in COPD and CLC

CLC is believed to result from a complex interplay of genetic and epigenetic alterations, including dysregulation of DNA damage and repair mechanisms. The pathogenesis of CLC should involve the accumulation of genetic mutations and epigenetic modifications that drive tumorigenesis.[51–53] Here, we will delve into the potential role of DNA damage and repair pathways in the development of COPD, involved in CLC.

(1) DNA damage and repair: DNA damage can arise from various sources, including environmental exposures, such as cigarette smoke, industrial pollutants, and radiation, as well as endogenous factors, like reactive oxygen species and errors in DNA replication. The accumulation of DNA damage, if left unrepaired, can lead to the formation of mutations and genomic instability, contributing to the initiation and progression of CLC.[54,55] The critical DNA repair pathways involved in maintaining genomic integrity include base excision repair (BER): Responsible for repairing damaged DNA bases resulting from oxidative stress and other small DNA lesions. Nucleotide excision repair (NER): Recognizes and removes bulky DNA lesions induced by environmental carcinogens. Mismatch Repair (MMR): Corrects errors that occur during DNA replication, thereby preventing the accumulation of mutations. Double-strand break repair: Involves homologous recombination (HR) and non-homologous end joining (NHEJ) pathways, essential for repairing double-strand breaks, the most lethal form of DNA damage.

(2) Specific epigenetic alterations in lung cancer, including DNA methylation, histone modifications, and non-coding RNA-mediated regulation, play a critical role in gene expression and chromatin remodeling. Perturbations in epigenetic regulation can impact critical cellular processes, including DNA repair, cell cycle control, and tumor suppressor gene expression, which may be helpful to the development of CLC.[56–61]

There are three key patterns of specific epigenetic changes. DNA methylation: Aberrant DNA methylation patterns, such as hypermethylation of tumor suppressor gene promoters and global hypomethylation, have been associated with NSCLS and CLC. These alterations can influence DNA repair gene expression and genomic stability. Histone modifications: Dysregulation of histone acetylation, methylation, and other modifications can affect chromatin structure and gene transcription, influencing DNA repair capacity and tumor suppressor gene function. Non-coding RNAs: MicroRNAs and long non-coding RNAs have been implicated in the repair of gene expression and development of CLC.

The intricate relationship between DNA damage and repair pathways, and epigenetic alterations underscores the multifaceted nature of CLC pathogenesis. Understanding these molecular mechanisms is crucial for identifying potential therapeutic targets, developing biomarkers for prognosis and treatment response, and advancing precision medicine approaches for patients with CLC. Ongoing research into the interplay of DNA damage and repair with epigenetic

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dysregulation will pave the way for innovative strategies to address the complexities of CLC and improve patient outcomes.

(3) Interaction of Epigenetics and COPD in CLC: COPD, characterized by persistent airflow limitation and chronic inflammation in the airways, is a known risk factor for developing CLC. The underlying mechanisms linking COPD to CLC involve chronic airway inflammation, oxidative stress, and lung tissue remodeling. Persistent inflammation and oxidative damage in COPD patients can lead to DNA damage, cellular senescence, and the accumulation of genetic and epigenetic alterations in the lung tissue, contributing to the development of CLC. Additionally, impaired lung function compromised mucociliary clearance, and alteration in the lung microbiota associated with COPD may create a microenvironment conducive to initiation and progression of CLC. There is growing evidence that epigenetic alterations and COPD interact in the pathogenesis of CLC. Epigenetic modifications, including DNA methylation and histone alterations, have been implicated in the molecular pathways linking COPD to lung cancer. For example, specific DNA methylation changes in COPD-related genes and lung cancer-associated genes have been identified, suggesting a potential mechanistic link between epigenetic dysregulation in COPD patients and the development of CLC. Furthermore, epigenetic alterations may mediate the effects of environmental risk factors, such as cigarette smoke exposure, on the pathogenesis of CLC in individuals with COPD. Genetic studies have confirmed that methylation patterns of CCDC37 (coiled helical structure protein 37) and MAP1B (microtubule-binding protein 1B) are associated with susceptibility to COPD and lung cancer.

Gene Susceptibility

The pathogenesis of CLC in the context of COPD involves a complex interplay between genetic susceptibility, environmental exposures, and molecular mechanisms underlying both conditions. In this comprehensive discussion, we will delve into the intricate relationship between COPD-related genetic susceptibility and the pathogenesis of CLC.[62–65]

The genetic underpinnings of COPD involve a complex interplay of multiple genetic factors contributing to disease susceptibility, severity, and progression. Notably, genetic variations in genes related to pulmonary function, inflammation, oxidative stress, and tissue repair have been implicated in the pathogenesis of COPD,[66,67] which includes alpha-1 antitrypsin deficiency and mutations in the SERPINA1 gene and Lung function regulatory genes, such as CHRNA3/5, HHIP, and FAM13A; Inflammatory genes; Oxidative Stress and Antioxidant Genes, such as NQO1, GSTM1, and SOD3. In the context of COPD, genetic susceptibility factors contribute to the increased risk of developing CLC and modulate the molecular pathways underlying tumorigenesis.

The following genetic aspects play crucial roles in the pathogenesis of CLC in the context of COPD. (1) DNA Repair and Genomic Stability: Genetic variations in genes involved in DNA repair mechanisms, such as BRCA1/2, ATM, and other DNA repair pathways, are implicated in both COPD and CLC. Deficient DNA repair capacity due to genetic susceptibility factors can lead to the accumulation of DNA damage, mutational burden, and genomic instability, promoting CLC development in individuals with COPD. (2) Inflammatory and Immune Response Genes: Genetic polymorphisms in genes controlling inflammatory and immune responses, including cytokines, chemokines, and immune cell function-related genes, can modulate the inflammatory microenvironment in the lungs of COPD patients. These genetic variations contribute to chronic inflammation, immune dysregulation, and modulation of the tumor immune microenvironment, influencing CLC initiation and progression. (3) Oxidative Stress and Tissue Damage Response Genes: Genetic susceptibility factors related to oxidative stress, antioxidant defense, and tissue repair mechanisms are relevant to COPD and CLC. Variations in genes involved in cellular responses to oxidative damage, such as NRF2-regulated antioxidant pathways, impact the susceptibility of bronchial epithelial cells to malignant transformation in the setting of COPD-associated oxidative stress.

Furthermore, the interplay between genetic susceptibility and environmental exposures, particularly cigarette smoke, occupational hazards, and air pollution, amplifies the risk of CLC in individuals with COPD. The cumulative effects of genetic vulnerabilities and environmental insults contribute to the intricate pathogenesis of CLC in the context of COPD, emphasizing the multifactorial nature of the disease.

Treatment Strategy for CLC

Targeted Therapies

Targeted therapies have emerged as a crucial treatment modality for CLC, offering the promise of more precise and effective interventions that directly target specific molecular alterations driving tumor growth and survival. These therapies exploit the unique genetic and molecular characteristics of cancer cells, allowing for personalized treatment approaches that aim to improve outcomes and minimize treatment-related toxicity.

(1) Epidermal growth factor receptor (EGFR) inhibitors are the most and earliest targeted drugs reported.[68,69] EGFR mutations represent one of the most prevalent oncogenic drivers in CLC, particularly in non-small cell lung cancer (NSCLC). Patients with EGFR-mutant CLC may benefit from targeted therapies such as EGFR tyrosine kinase inhibitors (TKIs), which specifically inhibit the activity of the mutated EGFR protein.[29]

First-generation EGFR TKIs, such as erlotinib and gefitinib, were among the initial targeted therapies developed for EGFR-mutant NSCLC. These agents demonstrated significant clinical benefits, including improved progression-free survival and quality of life, leading to their widespread adoption in the management of EGFR-mutant CLC.

Subsequent generations of EGFR TKIs, including afatinib, dacomitinib, and osimertinib, have shown further improved efficacy and broader activity against EGFR-activating mutations and resistant mutations, such as the T790M mutation. Osimertinib, in particular, has demonstrated impressive clinical efficacy in patients with advanced EGFR-mutant NSCLC, including those with CNS metastases, and is currently recommended as a standard of care for this patient population.

(2) Anaplastic Lymphoma Kinase (ALK) Inhibitors: Rearrangements of the ALK gene represents another important oncogenic driver in lung cancer, including CLC, accounting for a subset of NSCLC cases. ALK inhibitors, such as crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib, have revolutionized the treatment landscape for ALK-positive NSCLC by some reports,[70–72] demonstrating superior efficacy compared to traditional chemotherapy and significantly improving progression-free survival and overall survival.

(3) ROS1 Inhibitors: ROS1 gene rearrangements, although less common than EGFR and ALK alterations, have been identified in a subset of CLC cases.[73–75] Crizotinib was the first targeted therapy to receive approval for ROS1-positive NSCLC based on robust clinical data demonstrating substantial antitumor activity and durable responses in this patient population.

(4) BRAF and MET Inhibitors: Targeted therapies directed against other molecular alterations, such as BRAF mutations and MET exon 14 skipping mutations, have also shown promise in the treatment of CLC.[76–78] For example, the BRAF inhibitor dabrafenib, in combination with or without the MEK inhibitor trametinib, has demonstrated efficacy in BRAF V600E-mutant NSCLC. Similarly, MET inhibitors, including crizotinib and capmatinib, have shown encouraging results in MET-altered NSCLC, particularly in patients with MET exon 14 skipping mutations.

Currently, there are four types of inhibitors for the targeted therapy of CLC, and their relevant drugs are summarized in Table 3. Some of these drugs have been used in CLC and some have been used in other NSCLCs and are expected to be used in CLC in the future. Meanwhile, the targets of these targeted drugs and their related clinical trial information are also listed in the table Indeed, targeted therapies have revolutionized the treatment paradigm for CLC, offering personalized and effective interventions that directly target specific molecular alterations driving tumor growth. The expanding arsenal of targeted agents, in combination with immunotherapies and novel precision medicine strategies, holds great promise for improving patient outcomes and addressing the challenges of treatment resistance in CLC. Current research, molecular profiling, and clinical trials are shaping the future of targeted therapy in CLC, aiming to provide more effective and personalized treatments for patients.

Surgery

Surgery remains a cornerstone of treatment for resectable CLC reported by some researchers, achieving complete tumor removal and curative intent.[87,88] The resectable of the tumor is determined based on various factors, including the size, location, and extent of the CLC. Surgical intervention aims to eradicate the tumor and preserve lung function, providing patients with the best chance for long-term survival. It is important to note that while surgery is an effective treatment option for resectable CLC, it is crucial to consider individual patient factors, including overall health, the stage of the

Table 3 Target Therapy Strategies for CLC Based on Current Drugs

Therapeutic Drug	Therapy Type	Target	PFS (month)	OS (month)	Ref
Icotinib	TKI	Anti-EGFR	19.0	179.0	[79]
Erlotinib	TKI	Anti-EGFR	8.0	33.0	[80]
Gefitinib	TKI	Anti-EGFR	6.0	19.0	[81]
Gefitinib	TKI	Anti-EGFR	19.0	NM	[27]
Afatinib	TKI	Anti-EGFR	NM	NM	[29]
Axitinib	Targeted therapy	Anti-VEFGRs/PDGFRs	5.7	NM	[43]
Imatinib	Targeted therapy	Anti-KIT	12.0	NM	[82]
Pyrotinib	Targeted therapy	Anti-ERBB	6.0	168.0	[83]
Anlotinib	Targeted therapy	Anti-VEGFRs/FGFRs/PDGFRs/KIT	NM	NM	[84]
Sorafenib	Targeted therapy	Anti-VEGFR2/PDGFRs/KIT/Flt-3/RET	6.0	NM	[42]
Crenigacestat	Targeted therapy	Anti-Notch	5.3	NM	[44]
Trastuzumab	Targeted therapy	Anti-HER2	4.2	NM	[85]
Dovitinib	Targeted therapy	Anti- FGFR	8.2	20.6	[85]
Sunitinib	Targeted therapy	Anti-VEFGRs/PDGFRs/RET	7.2	18.7	[86]

Abbreviations: OS, overall survival; NM, not mentioned; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; ALK, anaplastic lymphoma kinase; VEFGRs, vascular endothelial growth factor receptors; PDGFRs, platelet derived growth factor receptors.

disease, and the potential benefits and risks of surgery. A multidisciplinary approach involving thoracic surgeons, medical oncologists, radiation oncologists, and pulmonologists is essential to develop comprehensive treatment plans tailored to the specific needs of each patient with CLC. In short, surgery plays a critical role in the resectable CLC, aiming to achieve complete tumor removal and curative intent.

Immunotherapeutics

Immunotherapy has emerged as a promising therapeutic approach in the management of cancers, particularly in the setting of advanced or metastatic disease.[89,90] Immunotherapies by harnessing the body's immune system to recognize and eliminate cancer cells, leading to durable responses and improved survival in a subset of patients. Key elements of immunotherapy in CLC include immune checkpoint inhibitors, adoptive cell therapies, and other immune-modulating agents.[91,92] Recent research has suggested that CLC patients with high PD-L1 expression may benefit from the combination of immune checkpoint inhibitors with chemotherapy or targeted therapies, while those with low or negative PD-L1 expression may require alternative combination approaches or treatment strategies. Additionally, ongoing efforts are focused on exploring novel biomarkers and molecular signatures that may predict response to specific combination therapies, allowing for the personalized tailoring of treatment regimens in CLC.

Other Treatment Regimens

Chemotherapy is a systemic treatment that uses drugs to destroy cancer cells throughout the body.

In CLC, chemotherapy may be used as a primary treatment for unresectable tumors or in combination with other modalities to enhance treatment outcomes.[93] Platinum-based chemotherapy regimens, one type of drug such as cisplatin or carboplatin, are commonly employed in the management of CLC. Additionally, chemotherapy regimens are often integrated into multimodal treatment approaches, such as neoadjuvant or adjuvant therapy alongside surgical resection, or in combination with targeted therapies and immunotherapies.[94]

Radiation therapy serves as a valuable palliative intervention to alleviate symptoms, such as pain, dyspnea, hemoptysis, and cough, and to manage local complications, including tumor-related airway obstruction and superior vena cava syndrome. Radiation therapy plays a significant role in the multimodal management of CLC, offering curative and palliative benefits in various clinical scenarios. As an essential component of local-regional treatment, radiation therapy is employed with curative intent as definitive therapy for locally advanced disease or as adjuvant therapy following surgical resection.[95,96] For patients with unresectable tumors, radiation therapy can be utilized as primary treatment, aiming to achieve tumor control and alleviate symptoms.

Prospects and Future Research Directions

Liquid biopsy, next-generation sequencing (NGS), and other molecular profiling techniques are increasingly utilized to identify actionable genetic alterations and track changes in the tumor's molecular landscape, allowing for the early detection of resistance mechanisms and the adaptation of treatment strategies.[97]

In terms of diagnosis, firstly, the development of advanced imaging technologies and diagnostic tools such as radiomics, molecular imaging, and liquid biopsy analysis will improve the accurate diagnosis and classification of CLC. Secondly, the development of emerging biomarkers and advances in molecular analysis techniques, including NGS and liquid biopsy, will continue to expand our understanding of the CLC molecular pattern. Future research is expected to

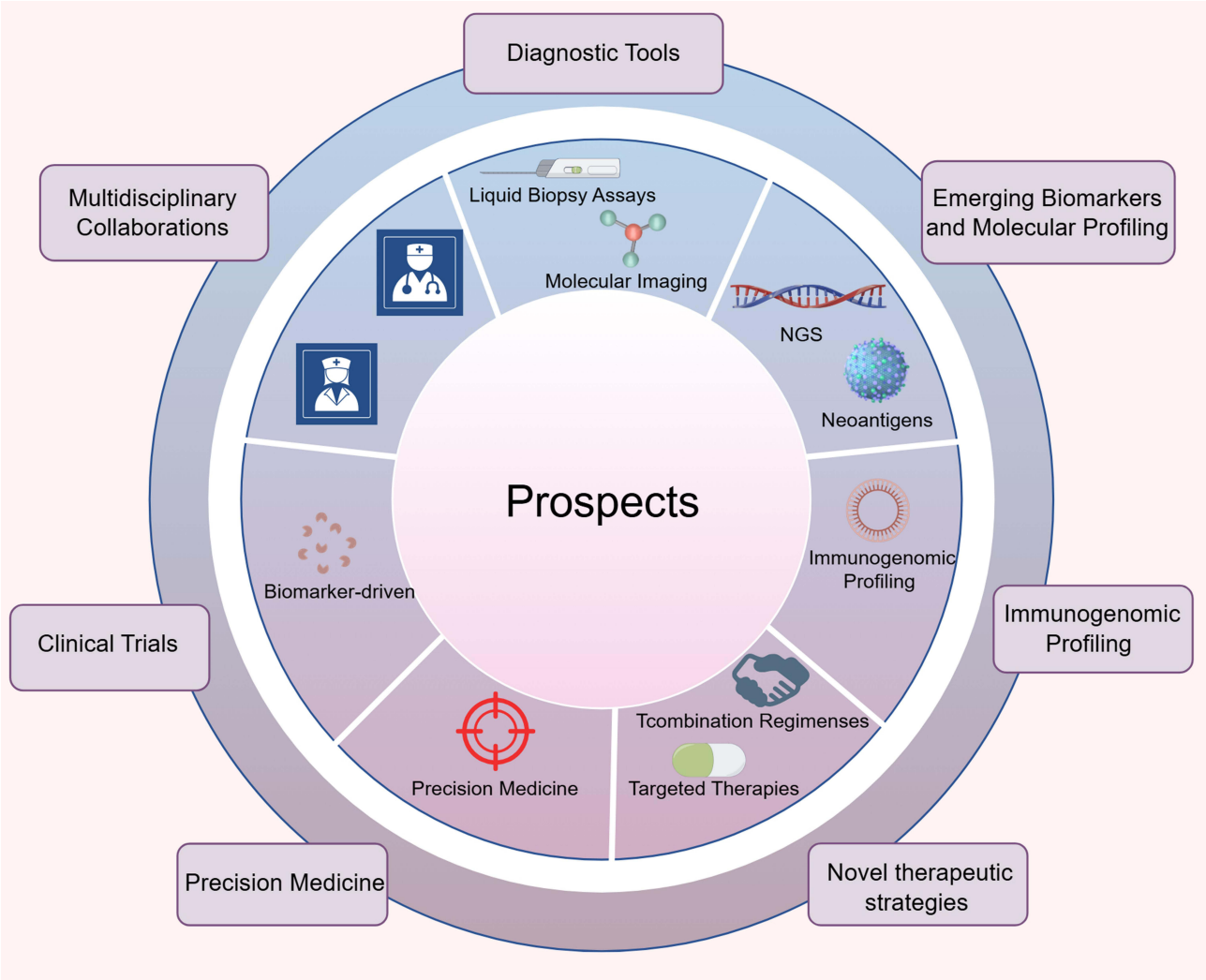

Figure 2 Schematic illustration of Prospects and future research directions of CLC (By Figdraw).

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focus on identifying new biomarkers and molecular features, such as tumor mutation burden (TMB), neoantigens, and specific genetic changes, to improve patient diagnosis and stratification. Then, immunogenomic analysis can be further utilized to combine genetic changes with the tumor immune microenvironment. This emerging research field has the potential to reveal the interaction between tumor genetics and immune response in CLC. Thus revealing mechanisms including immune cell infiltration, immune checkpoint expression, and immune evasion.

In terms of treatment, the emergence of precision medicine is expected to change the treatment mode of CLC. Future research should focus on integrating comprehensive molecular and genomic analyses to characterize genetic changes, mutation landscapes, and specific molecular pathways in CLCs. This approach will promote the development of tailored and targeted therapies, as well as the identification of predictive biomarkers to guide treatment decisions. The development of new treatment strategies, including targeted therapy and immunotherapy, is the focus of future research on CLC. In addition, the rational design of combination methods, integration of targeted therapy, immunotherapy, and emerging treatment methods, as well as exploration of the synergistic effects of targeted drugs combined with immunotherapy, chemotherapy, adoptive cell therapy, and other immune regulation methods, are expected to pave the way for optimizing and personalized treatment plans.

In the clinical management of CLC patients, it is recommended to collaborate among oncologists, pulmonologists, radiologists, pathologists, and researchers to address the complexity of CLC. A multidisciplinary approach can integrate different professional knowledge to achieve comprehensive patient care, research coordination, and translate scientific discoveries into clinical practice. In addition, the design of innovative clinical trials, including basket trials, umbrella trials, and adaptive trial designs, will help evaluate the potential of multiple treatment options for different patient populations with CLC and promote the translation of new treatment strategies in clinical practice.

A summary of the above seven strategies is shown in Figure 2. Comprehensive application of the measures may bring new hopes and breakthroughs for the mechanism, diagnosis, and treatment of CLC in the future.

Conclusion

In summary, as a rare subset of pulmonary malignancies characterized by cystic structures, CLC are increasingly under investigation to understand their unique molecular mechanisms and improve therapeutic options. Recent research has emphasized the importance of gene mutations such as EGFR, ALK, ROS1, and KRAS genes, which play critical roles in tumorigenesis. These mutations lead to aberrant signaling pathways that promote cell proliferation and survival, contributing to cancer development and progression. Immune dysfunction is also a hallmark of CLC, with tumor cells frequently exhibiting immune escape mechanisms. The tumor microenvironment of CLC can suppress immune responses via the expression of immune checkpoint proteins, such as PD-L1, which interacts with PD-1 on T cells to reduce their activity. This immune evasion usually significantly impedes their ability to mount an effective anti-tumor response.

Targeted therapy has shown promise, particularly with TKIs that can interfere with specific pathways activated by gene mutations. For example, TKIs targeting EGFR have shown validity in shrinking cystic tumors with such mutations. Additionally, the emergence of next-generation sequencing allows for more personalized approaches based on the unique molecular profile of the patient's tumor. Immunotherapy, including checkpoint inhibitors like anti-PD-1 and anti-PD-L1, has revolutionized the treatment landscape, offering a potential for durable responses in some patients. However, these therapies' effectiveness is often restricted to a subset of patients, which need for biomarkers to predict response. At the same time, should the current limitations in the literature be addressed, targeted therapy and immunotherapy could be effectively tailored for patients who have truly progressed from cystic lesions to CLC. This would enable earlier diagnosis and treatment, making interventions far more impactful. However, realizing this potential will require additional foundational and clinical research in the future, which may include animal studies.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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