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Review Article

Research progress on the characteristics and functions of m6A modification in lung cancer tumor stem cells

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Abstract: Lung cancer is one of the most common causes of cancer-related deaths, and drug-resistant lung cancer stem cells (LCSCs) play a significant role in its progression. N6-methyladenosine (m6A) is the most common modification on mRNA. It has been identified as an important epigenetic regulator of LCSC fate. This review focuses on the m6A regulatory machinery in regulating the basic biological functions of LCSCs, involving self-renewal, tumorigenesis, and its metastasis. In addition, this review specifically highlights how m6A modification is dysregulated in LCSCs' resistance to chemotherapy, targeted therapy, and immunotherapy. Moreover, new therapies, like small-molecule inhibitors aimed at enzymes such as METTL3 and FTO that play important roles in m6A are introduced in this review, which could aid in eradicating LCSCs and overcoming treatment failure. m6A pathway is a promising target for discovering new therapies to combat the recurrence of lung cancer.

Keywords: Lung cancer, cancer stem cells (CSCs), N6-methyladenosine (m6A), epigenetics, therapeutic resistance, METTL3, tumor microenvironment (TME)

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide [1-4]. It is projected to be responsible for nearly 1.8 million deaths across all age groups in 2024 and over 2.2 million new cases annually [5]. Although targeted therapies and immune checkpoint inhibitors (ICI) have greatly improved clinical outcomes for many patients in recent years, their long-term efficacy remains limited [6, 7]. Major obstacles in delivering effective treatment include intratumoral heterogeneity and high rate of metastatic dissemination (responsible for nearly 90% of lung cancer-related death) [8-11], eventually contributing to therapeutic resistance. These intermingled factors drive disease progression and treatment refractoriness, resulting in dismal 5-year survival rates and emphasizing the urgent need to elucidate the mechanisms underpinning tumor persistence and therapeutic resistance [12, 13].

The theory of cancer stem cell (CSC) has been proposed to explain mechanisms responsible for tumor relapse and resistance to therapy. The model hypothesizes that heterogeneous tumors harbor a unique sub-population of cells with self-renewal and multi-lineage differentiation abilities [14, 15]. These cells can self-renew to produce non-stem tumor cells and thereby act as critical drivers of tumor initiation, progression, and metastasis. In lung cancer, this sub-population is referred to as lung cancer stem cells (LCSCs). Studies have indicated that LCSCs are a major cause of treatment failure and cancer relapse [16]. They display intrinsic insensitivity to conventional chemotherapy and targeted agents, such as EGFR-TKIs, through diverse mechanisms, including epithelial-mesenchymal transition (EMT), enhanced cell plasticity, and activation of certain signaling pathways [17, 18]. Therefore, targeting and elimination of LCSCs is considered essential for overcoming therapy resistance and preventing disease relapse.

In recent years, increasing attention has been paid to the epigenetic mechanisms that govern LCSC fate decisions. Among various epigenetic modification, N6-methyladenosine (m6A) has

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garnered particular attention, as it represents the most common internal modification on mammalian mRNA [19-22]. Importantly, m6A marks are not static, and their deposition is a dynamic and irreversible process, which is regulated by a coordinated network of three classes of proteins [23]. This network consists of methyltransferases (Writers) (e.g., METTL3/METTL14, which install the methyl group), demethylases (Erasers) (e.g., FTO and ALKBH5 which catalyze the modification), and m6A-binding protein (Readers) (e.g., YTHDF protein family that specifically binds to the m6A mark and initiates the subsequent function) [24-26]. The interplay among methylation, demethylation, and m6A recognition precisely modulates post-transcriptional gene expression, thereby profoundly influencing cellular fate.

Given the association between chemoresistance of lung cancer and LCSCs, as well as the regulatory capacity of m6A modification to regulate gene expression, exploration of their relationship is necessary. Thus, in this review, we summarize recent progress in lung cancer research. First, the main biological features of LCSCs and their clinical implications are outlined. Then, how m6A modification, as an important type of epigenetic machinery, regulates LCSC self-renewal, differentiation, tumorigenesis, and drug resistance are discussed. Finally, promising therapeutic approaches targeting the m6A regulatory pathway are proposed, which may offer a theoretical insights and guide the development of novel therapies capable of efficiently eradicating LCSCs and overcoming treatment resistance in lung cancer.

Biological characteristics and challenges of LCSCs

Molecular identity and stemness maintenance mechanisms of LCSCs

Molecular identification of LCSCs is essential for understanding their biological properties. Assays such as tumor sphere formation *in vitro*, serial transplantation into immunodeficient mice to form tumors, have been considered the gold standard for LCSC identification [27]. At the molecule level, several markers have been identified for isolating and enriching LCSCs, making them potential therapeutic targets [28, 29]. These markers mainly include cell surface proteins, such as CD44 and CD133, and intracellular protein with high aldehyde dehydrogenase-1 (ALDH1) activity. In addition, other core pluripotency transcription factors such as OCT4, SOX2 and NANOG have also been found to be expressed in lung adenocarcinoma, suggesting the existence of CSC subpopulations within this cancer type [30, 31]. However, it is important to note that these marker are highly heterogenous, with significant variation across histological subtypes of lung cancer, making the identification challenging. The maintenance of LCSC stemness relies fundamentally on the abnormal activation of a set of well-conserved, core signal pathways. Similar with the mechanisms employed by normal tissue stem cells, LCSCs hijack pathways, such as Wnt/β-catenin, Notch, and Hedgehog, to sustain self-renewal and proliferation [32]. Dysregulation of these pathways not only supports the stem-like status of LCSCs but also correlates with their resistance to chemotherapy and targeted therapies. For example, preclinical models targeting key molecules in the β-catenin or Hedgehog pathways have demonstrated favorable anti-LCSC effects [33]. In addition to these classic developmental routes, intercellular communication through small extracellular vesicles (sEVs) have been recognized as an additional route for stemness propagation and maintenance [34, 35]. Therefore, LCSC identity is shaped by a complex network of surface markers and core signaling pathways. A deep understanding of these maintenance mechanisms is essential in developing targeted therapies aimed at eliminating LCSC.

Roles of LCSCs in tumor progression and therapeutic resistance

LCSCs play critical roles in tumors progression beyond autonomous proliferation, including a complex two-way interaction between LCSCs and tumors microenvironment (TME) [36]. LCSCs actively secrete immunosuppressive factors that recruit and modulate the function of regulatory immune cell, thereby establishing a local environment that resists anti-tumor immune responses and induces immune escape [37, 38]. On the contrary, components of the TME, such as cancer-associated fibroblasts (CAFs), hypoxia, and specific extracellular matrix (ECM) proteins, also provide support for LCSC survival and stemness maintenance. This creates a loop that drives tumor growth, invasion, and metastasis [39, 40]. The mutual interaction between LCSCs and the TME compli-

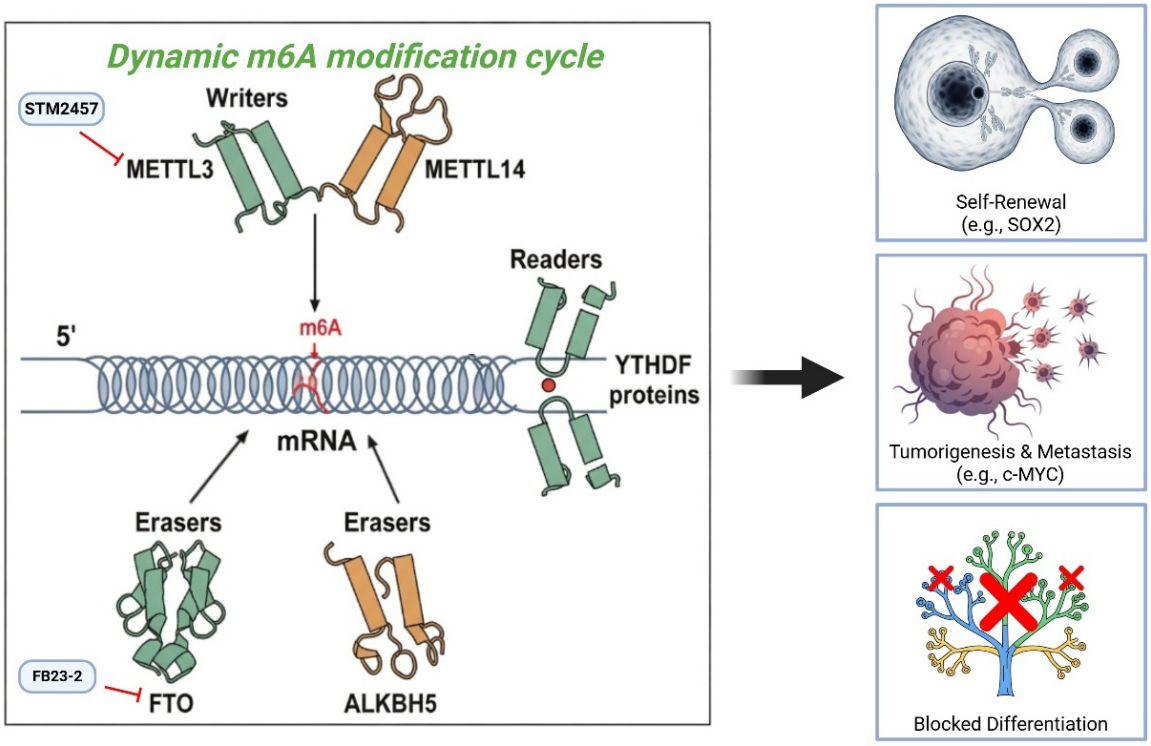

Figure 1. The regulatory mechanism of m6A modification and its impact on the core biological properties of LCSCs. The dynamic and reversible cycle of m6A modification is orchestrated by three key protein classes. "Writers" (e.g., the METTL3-METTL14 complex) catalyze the addition of a methyl group to adenosine residues on mRNA, while "Erasers" (e.g., FTO and ALKBH5) remove this modification. "Readers" (e.g., YTHDF proteins) recognize and bind to the m6A mark, subsequently mediating downstream effects on mRNA metabolism. In LCSCs, the dysregulation of this cycle leads to the modulation of key oncogenic and stemness-related genes, resulting in malignant phenotypes. This dysregulation ultimately manifests as core LCSC malignant phenotypes, including the enhancement of self-renewal (e.g., via SOX2), the promotion of tumorigenesis and metastasis (e.g., via c-MYC), and the maintenance of an undifferentiated state through blocked differentiation. Small-molecule inhibitors targeting key regulators, such as STM2457 (inhibiting METTL3) and FB23-2 (inhibiting FTO), are indicated in red to highlight potential therapeutic intervention sites.

cates the treatment of lung cancer. All of these leads to one the most critical clinical challenges - therapeutic resistance. Abundant evidence shows that LCSCs are central to the failure of chemotherapy, targeted therapy, and immune therapy [41, 42]. Their intrinsic properties, such as enhanced DNA damage repair, efficient drug efflux pumps, a stable cellular division state, and resistance to apoptosis, enable them to withstand conventional chemotherapies. Additionally, LCSCs evade immune surveillance by overexpressing immune checkpoint molecules such as PD-L1 and establishing an immunosuppressive microenvironment, therefore leading to immune therapy failure [43, 44]. Accordingly, novel strategies aiming at reducing resistance and preventing tumor regrowth must be based on a thorough understanding of the complex interactions between LCSCs and their defensive microenvironment.

m6A modification regulates core biological functions of LCSCs

Emerging studies on m6A RNA modification provide a new epigenetic framework to explain the biological characteristics of LCSCs. As a dynamic post-transcriptional regulatory hub, m6A modification is based on a sophisticated regulatory system composed of three different types of protein. This system contains methyltransferases (known as "Writers", which add the modification), demethylases (known as "Erasers", which remove it), and m6A-binding proteins (referred to as "Readers", which recognize the m6A mark and meditate downstream function). Through such regulatory mechanism, m6A modification profoundly influences and regulates various core biological functions of LCSCs on the molecular level [45-47] (**Figure 1**). However, the functional outcomes of m6A

modification can exhibit significant heterogeneity across different lung cancer subtypes. For instance, while METTL3 is consistently reported as a potent oncogene in lung adenocarcinoma (LUAD) by promoting cell proliferation and stemness [48], its role in lung squamous cell carcinoma (LUSC) remains less clear, with some studies suggesting a context-dependent or even tumor-suppressive function [49, 50]. This highlights the need to consider histological context when developing m6A-targeted therapies. Additionally, contradictory findings exist, particularly regarding the m6A eraser ALKBH5. In non-small cell lung cancer (NSCLC), ALKBH5 predominantly acts as a tumor suppressor, with its overexpression restoring chemosensitivity by destabilizing oncogenic targets like CEMIP mRNA [51]. In contrast, recent studies in glioblastoma have identified ALKBH5 as an oncogene that promotes tumor progression by destabilizing the tumor suppressor FOXO1 [52].

Regulating self-renewal and stemness maintenance

Self-renewal in LCSCs is orchestrated by a intrinsic m6A regulatory network, forming a comprehensive "Regulator → Target → Pathway → Phenotype" axis. This intricate control is exerted through at least two interconnected mechanisms that converge to sustain the self-renewing population. The first and most direct mechanism involves m6A modification of transcripts encoding core stemness transcription factors. For instance, MeRIP-seq and functional studies have validated that SOX2 mRNA, a key regulator of stemness, is a direct target of METTL3-mediated methylation. This modification, when recognized by the reader protein YTHDF1, significantly enhances the translation efficiency of SOX2 mRNA, leading to increased protein levels that are critical for maintaining LCSC stemness [53, 54]. In parallel, a second mechanism involves the indirect modulation of critical signaling pathways. In lung adenocarcinoma, m6A has been shown to activate the Wnt pathway not by directly targeting β-catenin but through an indirect route involving the stabilization of an upstream lncRNA that sponges a suppressive microRNA [55]. Similarly, the PI3-K/AKT survival pathway is also fine-tuned by m6A, often through regulation of upstream components [56]. Crucially, these direct and indirect pathways likely operate synergistically, with a single writer like METTL3 potentially creating a powerful feed-forward loop by concurrently enhancing core factors like SOX2 while also activating signaling cascades like Wnt. This multi-layered regulation robustly perpetuates the LCSC phenotype, making interference with this network a highly attractive therapeutic strategy.

Regulating differentiation and plasticity

m6A modification plays an important role in maintaining the identity of LCSCs, precisely controlling their differentiation and plasticity. On one hand, m6A can prevent LCSC differentiation to non-stem cell states by inducing mRNA degradation (e.g., lineage genes) or translational repression of specific mRNAs, thereby "locking" LCSCs in a stem-like state. On the other hand, M6A modification is an important mechanism in the process of EMT (a necessary phenomenon that enables cancer cells to acquire high plasticity and metastatic capacity) [57, 58]. In a TGF-β-induced EMT model of lung cancer cells, METTL3 acts as an m6A writer required for phenotypic switching by regulating transcription factors (e.g., JUNB gene expression). Additionally, m6A-regulated cellular plasticity not only drives the LCSC invasion and migration but also augments adaptability to dynamic TME, therefore contributing to distant metastasis and acquisition of drug resistance [59].

Driving tumorigenesis and metastasis

m6A modification directly endows LCSCs with powerful tumorigenic and metastatic capabilities by regulating key oncogenes and signaling pathways. A large amount of evidence indicates that the m6A writer enzyme METTL3 is highly expressed in NSCLC and significantly promotes tumor growth and metastasis. One of the core mechanisms is the regulation of m6A modification on the key oncogene c-MYC [60]. Initial *in vitro* studies using NSCLC cell lines revealed that METTL3 directly catalyzed the m6A methylation of c-MYC mRNA. This modification, recognized by the 'reader' protein YTHDF1, significantly enhances mRNA stability and translation efficiency [61]. Crucially, these findings were subsequently validated in *in vivo* mo-

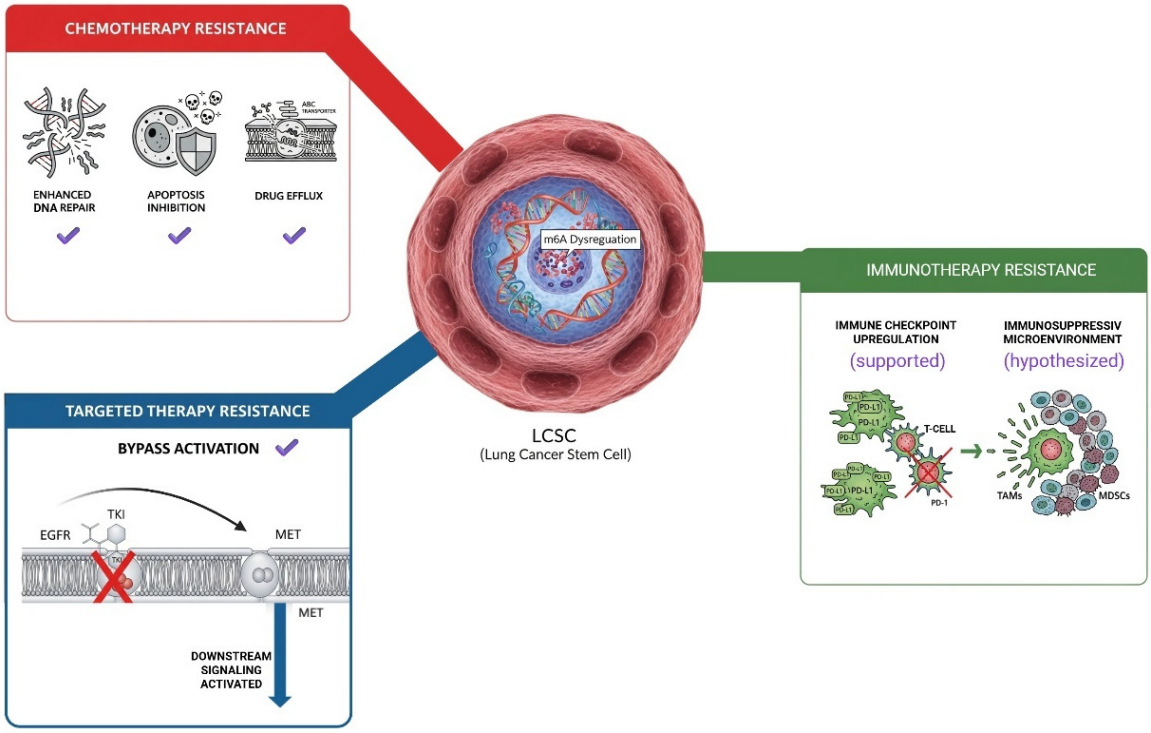

Figure 2. m6A-mediated mechanisms of therapeutic resistance in LCSCs. The m6A imbalance in LCSCs leads to resistance to chemotherapy, targeted therapy, and immunotherapy: Chemotherapy resistance is driven by three mechanisms that have been well-supported by experimental evidence: enhanced DNA repair (e.g., through ATM regulation), inhibition of apoptosis (e.g., through Bcl-2 upregulation), and drug efflux mediated by ABC transporters; for targeted therapy against EGFR tyrosine kinase inhibitors (TKIs), resistance is mainly achieved through MET bypass activation, which has been clinically documented, and studies have further linked m6A to the MET signaling; immunotherapy resistance can be broadly categorized into two aspects: upregulation of immune checkpoints (such as PD-L1 expression), which is partially supported by emerging evidence showing m6A-dependent stabilization of immune escape gene mRNA, and formation of an immunosuppressive microenvironment (involving the recruitment of TAMs and MDSCs), which remains at the hypothesis stage as there is currently a lack of direct mechanistic links between m6A and these cell populations, and further verification is needed. The figure uses the labels "supported" and "hypothesized" to visually distinguish the varying levels of evidence support.

dels, where conditional knockout of METTL3 in mouse lung tumors led to a marked reduction in c-MYC protein levels and suppressed tumor growth, confirming the clinical relevance of this axis [62].

m6A modification mediates therapeutic resistance in LCSCs

Disruption of m6A modification serves as a critical driver of a variety of therapeutic resistances in LCSCs. The m6A machinery alters the post-transcriptional expression of critical genes, endowing LCSCs with the potential to survive chemotherapy, evade targeted therapies, and escape immune surveillance, eventually resulting in relapse and tumor progression (**Figure 2**).

Chemoresistance

m6A modification is a core epigenetic mechanism by which LCSCs acquire chemoresistance, influencing multiple aspects of cellular resistance. First, m6A modification improves DNA damage repair ability of LCSCs, so as to resist DNA damage caused by chemotherapy (cisplatin). Second, the m6A regulation network stabilizes the mRNA of Bcl-2, disrupting the equilibrium between pro-apoptotic and anti-apoptotic signaling molecules, so as to protect LCSCs from chemotherapy-induced cell death [63, 64]. Third, m6A regulates the expression of ABC transporter family, which operate as efficient drug efflux pumps, expelling chemotherapeutic drugs out of the intracellular space of LCSCs. This reduces intracellular drug levels,

consequently rendering the cells resistant to therapy. In this way, m6A modification confers LCSCs with the potent multidimensional chemoresistance phenotype by simultaneously enhancing DNA repair, anti-apoptosis signaling, and drug efflux [65, 66].

Targeted therapy resistance

m6A modification is also critical in mediating LCSCs resistance to targeted therapies, especially EGFR tyrosine kinase inhibitors (EGFR-TKIs). One of the basic mechanisms through which m6A facilitates resistance is to activate alternative signaling channels that bypass the blocked target. Studies have shown that m6A methyltransferases, such as METTL3 and KIAA1429, enhance the stability or translation of MET receptor tyrosine kinase mRNA by m6A-dependent way, thereby amplifying and activating this MET signaling pathway, a typical mechanism of acquired resistance to EGFR-TKI [46]. In addition, m6A modification regulates other drug-resistant genes. For example, METTL3, an m6A WRITER, is over-expressed in the cells resistant to Osimertinib and promotes cell survival and growth by stabilizing the RNA of cell-motility-related genes (e.g., CDC25A, AURKB). Similarly, m6A readers like IGF2BP3 contribute to gefitinib resistance by stabilizing the mRNAs of alternative kinases (e.g., ERBB2) to activate downstream STAT3/Akt signaling [67-69]. These m6A-modified molecular functions endow LCSCs with enhanced adaptability to targeted treatment pressure, enabling them to withstand long-term tumor relapse. In addition, recent scRNA-seq studies have demonstrated that non-genetic mechanisms, including metabolic reprogramming, also contribute to acquired resistance to EGFR-TKIs [70]. A study conducted in 2025 using single-cell analysis observed that the resistant cell subpopulations exhibited a unique metabolic signature, including disrupted fatty acid metabolism, OXPHOS, and cholesterol metabolism, which support their capacity to resist therapeutic pressure [71]. This adaptive metabolic state, potentially modulated by m6A regulators, exemplifies the transcriptomic plasticity underlying therapeutic resistance.

Immunotherapy resistance

m6A modification plays a significant role in triggering immunotherapy resistance of LCSCs from multiple aspects. One key mechanism is to change the tumor immune microenvironment, shifting it toward an immune-suppressive state. Studies have shown that m6A modification in LCSCs regulates the secretion of certain cytokines and chemokines, thereby recruiting and activating immune suppressive cell types, such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSC). This immunosuppressive activity inhibits T-cell function and dampens the anti-tumor immune response. Furthermore, m6A modification also regulates the expression of immune checkpoint molecules, both directly and indirectly. For example, m6A modification of LCSCs can enhance PD-L1 expression, enabling these cells to evade detection and destruction by T cells, undermining the efficacy of immune checkpoint inhibitor [69]. Additionally, according to the expression profile of m6A regulators, an “m6A score” can be constructed to predict patients respond to PD-1 inhibitors. Patients with lower scores usually have higher CD8 + T cell infiltration and better treatment results, underscoring the importance of m6A modification in regulating tumor immunity [72, 73]. Recent single-cell RNA sequencing studies show that m6A dysregulation establishes an immune-evasive, stem-like niche by simultaneously enhancing cancer cell stemness and promoting the M2-like immunosuppressive phenotype in TAMs [74].

Therapeutic strategies targeting the m6A pathway

As summarized in **Table 1**, several key m6A regulators are dysregulated and play critical roles in lung cancer, making them compelling therapeutic targets. The following sections discuss specific strategies for targeting these components.

Targeting m6A writer

Since m6A writers play a key role in sustaining LCSC stemness and mediating drug resistance, inhibiting their activity using small-molecule inhibitors represents a promising therapeutic strategy. Of these, METTL3, the catalytic core protein of the m6A methyltransferase complex, is the most extensively studied target and has demonstrated potent anti-tumor activity in preclinical studies [60]. Small-molecule inhibitors targeting METTL3, such as STM2457, have

Table 1. Summary of m6A regulators as therapeutic targets in lung cancer

Regulator	Type	Expression Pattern in lung cancer	Prognostic Significance (High Expression)	Status of Targeted Inhibitors	References
METTL3	Writer	Upregulated	Poor	Preclinical (e.g., STM2457)	[75]
METTL14	Writer	Often Upregulated	Poor	Early discovery	[76]
WTAP	Writer	Upregulated	Poor	Early discovery	[77]
FTO	Eraser	Upregulated	Poor	Preclinical (e.g., FB23-2)	[78]
ALKBH5	Eraser	Often Upregulated	Poor	Early discovery	[79]
YTHDF1	Reader	Upregulated	Poor	Early discovery	[80]
YTHDF2	Reader	Upregulated (context-dependent)	Poor	Early discovery	[81]
YTHDC1	Reader	Downregulated	Good	Early discovery	[82]
IGF2BP1/2/3	Reader	Upregulated	Poor	Early discovery	[83-85]

shown effective anti-tumor efficacy in preclinical studies [68]. Notably, METTL3 inhibition not only directly attenuates LCSC stemness but also overcomes their resistance to chemotherapy (e.g., cisplatin) and targeted therapy (e.g., osimertinib), representing a novel opportunity to overcome treatment resistance in lung cancer [86]. Recent studies reinforce the therapeutic rationale for targeting METTL3 to overcome resistance. For instance, METTL3 has been shown to drive resistance to oxaliplatin by stabilizing CPSF6 mRNA in an m6A-dependent manner, leading to a metabolic shift towards glycolysis and reduced apoptosis [87]. Through this mechanism, METTL3 inhibitors emerge as a promising approach to disrupt pro-survival metabolism and drug resistance in lung cancer.

Targeting m6A eraser

Compared with the inhibition of m6A writers to down-regulate the m6A level, targeting m6A eraser represents an alternative strategy, as it could exert anti-tumor effects by selectively increasing m6A modification on specific transcripts rather than broadly suppressing m6A. Of the two main m6A demethylases, FTO has drawn more attention in drug discovery due to its oncogenic role in multiple cancers, including certain types of lung cancer [26, 88]. Elevated FTO expression is typically associated with enhanced tumor proliferation, stemness retention, and treatment resistance. Hence, selective inhibition of FTO is expected to overcome off-target effects. Small molecules FTO inhibitors, such as meclofenamic acid (MA) and its derivative FB23-2, have demonstrated strong anti-tumor activity in preclinical models [89, 90]. Mechanistically, inhibition of FTO can increase m6A levels on transcripts of key oncogenic and pro-survival genes, consequently promoting the degradation of these mRNAs through m6A "reader" proteins (e.g., YTHDF2) and thus inhibit tumor cells proliferation and trigger cell apoptosis [91]. Although studies on FTO in LCSCs remain at an early stage, accumulating evidence indicates that FTO plays a critical role in determining both tumor cell metabolic remodeling and stemness-associated signaling pathways. Therefore, targeting FTO may represent a potential innovative strategy to eradicate LCSCs by disrupting energy metabolism, impairing self-renewal capacity, and attenuating drug resistance [92].

Crucially, the distinct functions of different erasers, such as the FTO versus ALKBH5, are likely stem from their differential substrate specificity. While FTO might preferentially demethylate transcripts involved in glycolysis and survival pathways to promote resistance [93], ALKBH5 appears to target tumor suppressor mRNAs [94]. These differences help explain their opposing roles in cancer and highlight that therapeutic outcomes is determined by the specific downstream mRNA targets regulated by each eraser.

Combined treatment strategy

Considering the pivotal regulatory function of m6A in LCSC-associated drug resistance, monotherapy targeting m6A may be suboptimal to achieve effective tumors eradication. Instead, combination therapeutic strategies appear more promising for clinical application. The underlying rationale is that the pre- or co-

administration of m6A inhibitors can efficiently "prime" resistant LCSCs, thus restoring their sensitivity to conventional therapies [95]. For instance, METTL3 inhibitors combined with conventional chemotherapeutic agents (e.g., cisplatin) have demonstrated synergistic antitumor effects, potentially through suppression of m6A-regulated DNA damage repair (DDR) and drug efflux pumps [96, 97]. Likewise, in the context of targeted therapy, combining m6A inhibitors with EGFR-TKIs or VEGF pathway inhibitors may help overcome or reverse acquired resistance by suppressing activation of bypass signaling pathways. Notably, combinations of m6A inhibitors with immune checkpoint inhibitors (ICIs) are particularly promising. Targeting m6A pathway may remodel the tumor TME by reducing immunosuppressive cell infiltration and enhancing tumor antigen presentation, thereby converting immune-suppressed tumors into immunologically active cancers and greatly enhancing ICI efficacy [98-100]. By eliminating the tumor mass through conventional therapy and combining it with m6A inhibitors to target the remaining lung cancer stem cell populations, this may represent a novel and synergistic strategy for combating lung cancer.

Clinical challenges, limitations, and future perspectives of m6A-targeted therapies

While targeting the m6A pathway in LCSCs represents a promising frontier, its clinical translation faces significant challenges and fundamental knowledge gaps. First, from a drug development standpoint, m6A inhibitors remain in their infancy, with major challenges in pharmacokinetics and safety. For example, first-generation inhibitors often exhibit poor oral bioavailability or short half-lives, and systemic suppression of a fundamental epigenetic process raises concerns about off-target toxicity in healthy, rapidly dividing tissues, such as hematopoietic stem cells, highlighting an urgent need for highly selective drugs and tumor-targeted delivery systems [101]. Second, a key question is the clinical positioning of these novel agents. Rather than replacing standard-of-care therapies, m6A inhibitors are more likely to be used in combination with first-line therapies, such as EGFR-TKIs, to prevent or delay resistance by targeting residual LCSCs [102], or as second-line options to re-sensitize tumors that have developed acquired resistance through m6A-driven mechanisms [103]. Third, current research relies heavily on simplified cell line models, necessitating a transition towards preclinical systems, such as patient-derived organoids (PDOs) and genetically engineered mouse models (GEMMs) to accurately recapitulate the complex interplay with the tumor microenvironment [104]. Finally, several fundamental questions remain unresolved, including the precise downstream mechanisms of m6A 'readers' and the context-dependent, sometimes contradictory roles of regulators like ALKBH5 [105, 106]. These complexities caution against a universal m6A-targeted therapeutic strategy. Therefore, future research should focus on integrating advanced preclinical models, elucidating context-specific regulatory mechanisms, enhancing therapeutic specificity, and leveraging multi-omics to construct predictive frameworks that enable personalized therapies based on m6A modulation.

Conclusion

LCSCs represent a major obstacle to curative therapy for lung cancer, serving as the primary drivers of tumor recurrence, metastasis, and drug resistance. This review summarizes how m6A RNA modification functions as a central epigenetic regulator of LCSC biology. Dysregulation of the m6A pathway is implicated in nearly every aspect of the LCSC malignant phenotype, encompassing the maintenance of stemness and plasticity, the promotion of tumorigenesis and metastasis, and critically, the orchestration of multi-faceted resistance to chemotherapy, targeted therapy, and immunotherapy. Therefore, therapeutic strategies targeting the m6A regulatory axis, particularly those aimed at key writers (e.g., METTL3) and erasers (e.g., FTO), represent a highly promising and innovative frontier. These approaches may enable the selective elimination of LCSCs and overcome therapeutic resistance, offering novel clinical opportunities for combination strategies or later-line interventions aimed at achieving durable, long-term benefits for lung cancer patients.

Disclosure of conflict of interest

None.

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