m^6A methylation regulatory network in pulmonary fibrosis: Molecular mechanisms from RNA stability to cellular phenotype transition (Review)

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Abstract. Pulmonary fibrosis (PF) is a progressive and often irreversible interstitial lung disease characterized by aberrant wound healing, excessive extracellular matrix deposition and distortion of lung architecture. N6-methyladenosine (m^6A), the most abundant internal modification in eukaryotic mRNA, dynamically regulates RNA metabolism through m^6A writers, erasers and readers. Evidence indicates that m^6A dysregulation contributes to PF by modulating fibroblast activation, epithelial injury and senescence, epithelial-mesenchymal plasticity, macrophage-associated inflammation, oxidative stress responses and extracellular matrix remodeling. In the present review, the expression characteristics and functional alterations of m^6A machinery in fibrotic lung tissue, the role of m^6A-mediated epitranscriptomic remodeling in pulmonary cell fate determination and the potential translational value of m^6A regulators as biomarkers and therapeutic targets are summarized. In addition, particular focus is placed on cell-type-specific and context-dependent mechanisms, including the distinct roles of METTL3, METTL14, FTO, ALKBH5 and YTHDF proteins in different fibrotic settings. The present review highlights that m^6A modification is not a uniform pro-fibrotic or anti-fibrotic switch, but rather a dynamic regulatory network that links RNA metabolism to PF progression and therapeutic opportunities.

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Abbreviations: ALKBH5, alkB homolog 5; circRNA, circular RNA; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FTO, fat mass and obesity-associated protein; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; IPF, idiopathic pulmonary fibrosis; lncRNA, long non-coding RNA; m^6A, N6-methyladenosine; METTL3/14, methyltransferase-like 3/14; miRNA, microRNA; PF, pulmonary fibrosis; PF-ILD, progressive fibrosing interstitial lung disease; ROS, reactive oxygen species; YTHDF1/2/3, YTH N6-methyladenosine RNA binding protein 1/2/3; YTHDC1, YTH domain-containing protein 1

Key words: m^6A modification, pulmonary fibrosis, RNA methylation, epitranscriptomic, fibroblast activation

Contents

1. Introduction

N6-methyladenosine (m^6A) is the most abundant internal modification in eukaryotic mRNA, with over 440,000 high-confidence m^6A sites identified across human and animal transcriptomes (1). m^6A is dynamically regulated by 'writers' such as methyltransferase-like (METTL)3 and METTL14, 'erasers' such as fat mass and obesity-associated protein (FTO) and alkB homolog 5 (ALKBH5) and 'readers' such as YTH domain proteins, and is enriched near stop codons and in 3' untranslated regions (2,3). Functionally, m^6A modification influences multiple aspects of RNA metabolism, including alternative splicing, nuclear export, mRNA stability and decay and translation efficiency (4). For example, m^6A-marked transcripts are often recognized by N6-methyladenosine RNA binding protein (YTHDF)2, which accelerates their degradation, whereas m^6A can also promote translation by recruiting YTHDF1 or eukaryotic translation initiation factor 4 γ 2 (5). In circular (circ)RNAs, m^6A controls both their biogenesis and translation potential through regulators such as METTL3 and YTH domain-containing protein 1 (YTHDC1) (5). Quantitative studies have shown that m^6A is present on 0.1-0.4% of adenosines in mRNA, and transcriptome-wide mapping has revealed that m^6A sites are notably conserved among vertebrates (6). The reversibility and metabolic sensitivity of m^6A allow cells to rapidly adjust gene expression in response to environmental stress, nutrient status and disease-associated stimuli (7). Thus, m^6A acts as a flexible post-transcriptional regulatory layer rather than a static RNA mark.

Pulmonary fibrosis (PF), particularly idiopathic PF (IPF), imposes a substantial global disease burden, with incidence rates in Europe and North America estimated at 3-9 cases per 100,000 per year and rising over time (8). Patients experience marked symptom burden, impaired health-related quality of life and a median survival of only 2.7-3.0 years after diagnosis (9). The economic impact is also notable, with annual per capita healthcare costs for patients with IPF in North America reaching ~$20,000, which is 2.5-3.5 times higher than average national healthcare expenditures (10). Beyond direct medical costs, progressive fibrosing interstitial lung diseases also lead to indirect costs such as job loss, psychological stress and caregiver burden (11). Although antifibrotic drugs such as pirfenidone and nintedanib can slow disease progression, they do not cure PF, reverse established scarring or sufficiently improve symptoms and quality of life (12). Clinical research is further challenged by disease heterogeneity, incomplete understanding of fibrotic mechanisms, lack of sensitive biomarkers and difficulty in demonstrating additional therapeutic benefits in the era of approved antifibrotic therapies (13). Notably, research priorities identified by patients, caregivers and clinicians include reversing lung scarring, improving lung function, relieving symptoms, preventing disease progression and enabling earlier diagnosis (14). Therefore, mechanistic research in PF should be connected to patient-centered goals, including early diagnosis, prognostic stratification, symptom-relevant outcomes and development of disease-modifying therapies.

Emerging studies have revealed a close association between m^{6}A RNA methylation and PF. The expression patterns of key m^{6}A regulators are model- and context-dependent: METTL3 is upregulated in fibrotic lung tissue, whereas METTL14 is downregulated in aging-related IPF; FTO is suppressed in silica-induced PF, and ALKBH5 is downregulated or destabilized in PM2.5-, silica- and 1-nitropyrene-associated models (15-25). These alterations may contribute to PF through cell-type- and stimulus-specific mechanisms. For example, METTL3-dependent m^{6}A modification promotes lung fibroblast-to-myofibroblast transition by modulating potassium voltage-gated channel subfamily H member 6 *(KCNH6)* mRNA translation (18), whereas METTL14-mediated regulation of DNA damage inducible transcript 4 *(DDIT4)* mRNA stability has been implicated in aging-related IPF (16). ALKBH5 dysregulation contributes to environmental exposure-related PF through mechanisms involving autophagy dysfunction, inflammatory responses and epithelial senescence (17,19-22). FTO suppression is associated with increased m^{6}A RNA methylation and silica-induced pulmonary inflammation and fibrosis (23). m^{6}A modification also regulates non-coding RNAs such as circRNAs and micro (mi)RNAs, thereby influencing fibrotic signaling pathways (24,25). However, the available evidence also shows that m^{6}A regulators may exert different effects depending on cell type, environmental stimulus, disease stage and target transcript. Therefore, m^{6}A should not be described as a simple universal driver of PF.

Several issues in the current literature require careful clarification. First, although oxidative stress can regulate m^{6}A machinery, the relationship between reactive oxygen species (ROS) and m^{6}A should not be generalized as a universal feedback loop without cell-specific evidence. Second, regulators such as METTL14 and ALKBH5 have context-dependent roles and may not be uniformly pro-fibrotic or anti-fibrotic. Third, the translational relevance of m^{6}A regulators needs to be discussed in relation to patient-centered needs, including early diagnosis, prognosis, treatment response and therapeutic safety. Finally, existing reviews have discussed m^{6}A in fibrosis or non-coding RNA regulation; therefore, the novelty of the present review should be defined more cautiously as a PF-focused synthesis emphasizing cell-type specificity, validated mechanisms and translational implications rather than as the first systematic classification of this field (26-29).

To minimize overinterpretation, representative m^{6}A-related mechanisms were appraised using an author-defined framework that considered four dimensions: i) The source of evidence, including human specimens, animal models and/or cultured cells; ii) causal perturbation of the m^{6}A regulator or target transcript; iii) direct validation of the regulator-m^{6}A-target RNA-phenotype axis; and iv) replication across experimental settings. Evidence was classified as strong when human evidence was supported by both *in vivo* and *in vitro* causal validation, moderate when evidence from at least two experimental settings and partial mechanistic validation was available, limited when findings were derived from a single model or were predominantly associative, and indirect when the proposed mechanism was extrapolated mainly from non-PF systems. Cell type, fibrotic stimulus and disease setting were recorded separately as model-context variables (Table I). This framework was developed for the present review and was not adapted from a previously published evidence-grading system.

2. m^{6}A modification system in PF

m^{6}A belongs to a dynamic regulatory system that can be subdivided into writers, erasers and readers, which are notable mediators of PF pathogenesis (30). Previous studies have demonstrated that m^{6}A contributes to PF development by modulating mRNA stability and degradation, translational regulation, fibroblast activation, epithelial-mesenchymal transition, macrophage-associated inflammation, oxidative stress responses and aging-related epithelial senescence (31,32). In this framework, the role of each m^{6}A regulator is interpreted according to experimental context, cell type and target transcript, rather than being classified simply as pro-fibrotic or anti-fibrotic. The principal components of the m^{6}A regulatory system and their proposed roles in PF are summarized in Fig. 1.

Expression characteristics of the m^{6}A modification system in lung tissue. METTL3 is a core component of the m^{6}A methyltransferase complex and serves as the main catalytic subunit responsible for transferring a methyl group to the N6 position of adenosine residues in RNA, thereby regulating RNA stability, splicing, translation and degradation (33). Structurally, METTL3 contains a methyltransferase domain that binds the methyl donor S-adenosylmethionine and directly catalyzes m^{6}A modification (30). Although it contains a methyltransferase-like domain, METTL14 primarily functions as an RNA-binding platform that enhances substrate recognition and complex stability (31). METTL14 forms a stable heterodimer with METTL3, and this complex is

Table I. Evidence-based classification of representative m^{6}A-related mechanisms in PF.

Mechanism	Main evidence in the present manuscript	Evidence strength	Revised interpretation
METTL3-YTHDF1-KCNH6 axis in fibroblast-to-myofibroblast transition	Human PF tissue, *in vivo* PF models and *in vitro* causal experiments (18)	Strong	A well-supported PF-specific mechanism of fibroblast-to-myofibroblast transition.
METTL3-YTHDF2-TSC1 axis in EMT-associated epithelial remodeling	PF-related animal and cellular experiments with mechanistic validation (36)	Moderate	Supports a pro-fibrotic role for METTL3 in epithelial remodeling.
METTL14–DDIT4 axis in aging-related IPF	Human IPF samples, transcriptome-wide analyses and experimental validation in animal and senescent-cell models (16)	Strong	A well-supported aging-related mechanism that should not be generalized to all PF contexts.
ALKBH5–FBXW7 axis in 1-nitropyrene-induced epithelial senescence	*In vivo* and *in vitro* toxicant-induced PF models with causal mechanistic validation (17)	Moderate	Supports a protective role for epithelial ALKBH5 in this exposure-specific model.
FTO suppression in silica-induced PF	Silicosis models, single-cell transcriptomic data and global m^{6}A measurements without validated transcript-specific causal targets (23)	Limited	Associated with inflammatory and fibrotic remodeling, but causality requires further validation.
m^{6}A-dependent regulation of macrophage polarization	Predominantly inflammatory, metabolic and cancer models outside PF (66,68-73)	Indirect	Mechanistic background requiring direct PF-specific validation.
m^{6}A-mediated ECM remodeling	Predominantly multi-organ fibrosis and non-PF studies (28,80-83)	Indirect	Biologically plausible, but PF-specific transcript targets remain insufficiently validated.
Pharmacological inhibition of METTL3 by STM2457 in experimental PF	A single preclinical mouse study reporting pharmacological intervention in experimental IPF (88)	Limited	Provides preliminary pharmacological proof of concept requiring independent validation.
Other m^{6}A-targeted compounds and delivery systems	Predominantly cancer and neurological models, with little or no direct validation in PF (84-87,89-95)	Indirect	Should be regarded as non-PF preclinical tools rather than established PF therapies.

m^{6}A, N6-methyladenosine; PF, pulmonary fibrosis; EMT, epithelial-mesenchymal transition; ALKBH5, alkB homolog 5; METTL, methyltransferase; DDIT4, DNA damage inducible transcript 4; ECM, extracellular matrix; FTO, fat mass and obesity-associated protein; KCNH6, potassium voltage-gated channel subfamily H member 6; FBXW7, F-box/WD repeat-containing protein 7; FMT, fibroblast-to-myofibroblast transition.

essential for efficient and specific m^{6}A modification in eukaryotic RNAs (32). Previous studies also suggest that METTL14 may have additional roles in chromatin regulation and gene expression independent of its RNA methyltransferase activity (34,35). METTL14 expression is notably decreased in lung tissue from patients with IPF compared with normal lung tissue (16). High-throughput sequencing and experimental validation indicate that METTL14 downregulation reduces m^{6}A methylation of *DDIT4* mRNA, increases *DDIT4* mRNA stability and protein expression and promotes alveolar epithelial cell senescence and fibrosis progression (16). This finding provides a mechanistic link between m^{6}A remodeling and aging-related epithelial vulnerability in IPF; however, METTL14 should not be described as universally pro-fibrotic. In this model, reduced METTL14 expression promotes senescence by stabilizing DDIT4, whereas the role of METTL14 may differ in other cell types, disease stages or injury contexts.

METTL3 is notably upregulated in fibrotic lung tissue compared with normal lung tissue (36). In mouse models and *in vitro* experiments, increased METTL3 expression leads to elevated m^{6}A methylation of (TSC complex subunit 1) *TSC1* mRNA. Through YTHDF2-mediated degradation of *TSC1* mRNA, METTL3 reduces TSC1 protein levels and activates the AKT/mTOR pathway, thereby driving epithelial-mesenchymal transition (EMT) and fibrosis progression (36). Knockdown of METTL3 markedly impedes EMT, indicating its role in promoting fibrosis (36). In addition, METTL3-mediated m^{6}A modification also promotes lung fibroblast-to-myofibroblast transition through *KCNH6* mRNA translational regulation in a YTHDF1-dependent manner (18). Together, these data support a relatively consistent pro-fibrotic role for METTL3 in fibroblast activation and epithelial remodeling, although its therapeutic targeting still requires cell-specific safety evaluation.

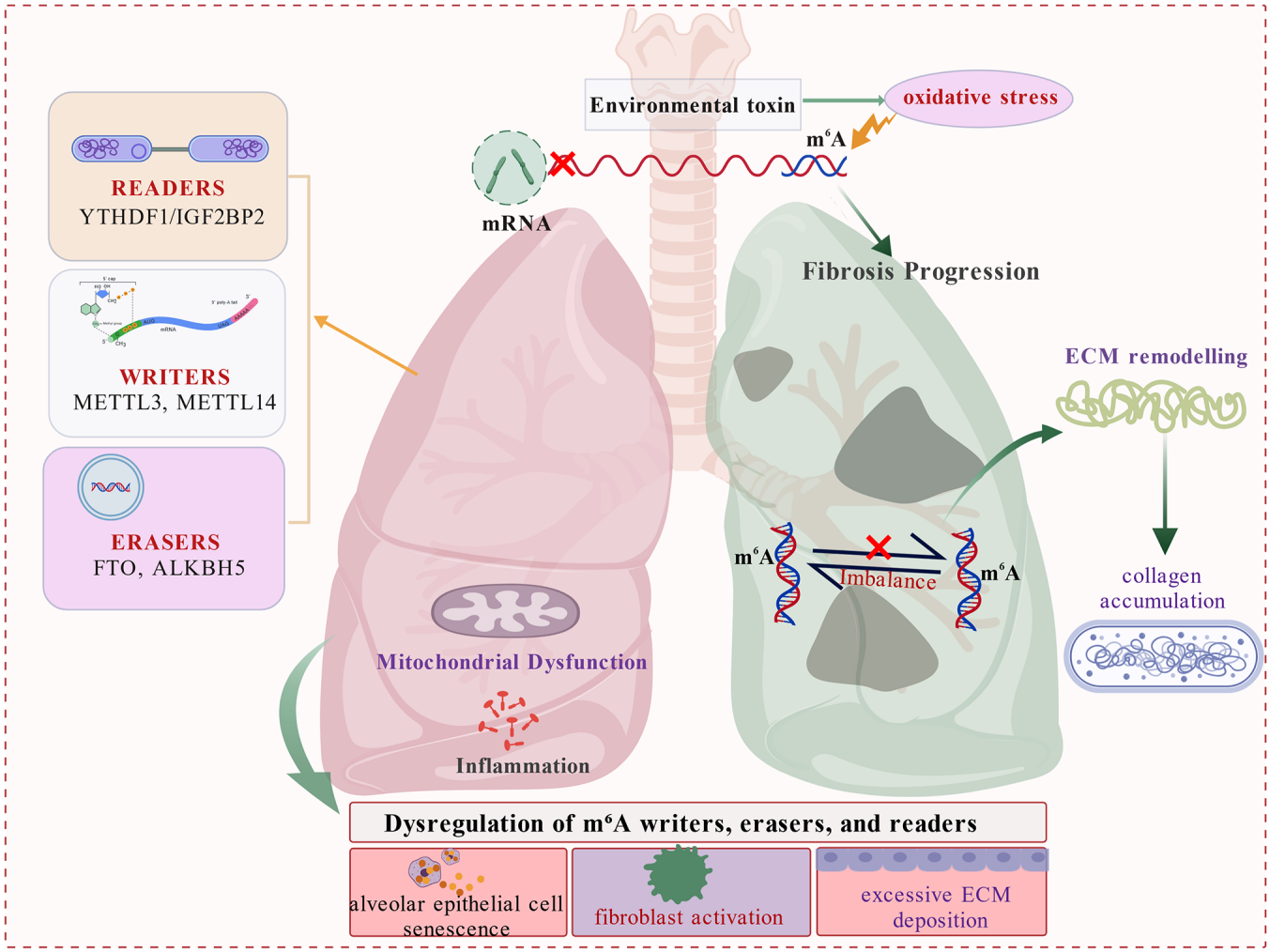

Figure 1. Overview of the m^{6}A regulatory system in pulmonary fibrosis. The m^{6}A machinery comprises writers, including METTL3 and METTL14; erasers, including FTO and ALKBH5; and readers, including YTHDF1/2/3 and IGF2BP1/2/3. In PF-related models, dysregulation of these regulators is associated with alveolar epithelial injury and senescence, fibroblast activation, inflammatory remodeling and excessive ECM deposition. Environmental toxicants and aging-related stressors may alter m^{6}A regulation in a cell- and stimulus-dependent manner. The figure was created using BioGDP (Biological Graphics Design Platform, version 2.0) (106). ALKBH5, alkB homolog 5; ECM, extracellular matrix; FTO, fat mass and obesity-associated protein; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; METTL, methyltransferase-like; m^{6}A, N6-methyladenosine; PF, pulmonary fibrosis; YTHDF, YTH N6-methyladenosine RNA-binding protein.

FTO and ALKBH5 are the two major RNA demethylases that remove m^{6}A modifications from RNA and dynamically regulate gene expression. FTO catalyzes oxidative demethylation of m^{6}A, primarily producing N6-hydroxymethyladenosine as an intermediate, whereas ALKBH5 directly converts m^{6}A to adenosine with rapid formaldehyde release, reflecting distinct biochemical mechanisms and cellular functions (37,38). Both enzymes influence RNA splicing, export, stability and translation and participate in biological processes such as differentiation, stress responses and tumor progression (39,40). ALKBH5 plays a tissue- and cell-type-specific regulatory role in PF. In PM2.5- and silica-induced PF models, ALKBH5 expression is downregulated in lung epithelial cells and macrophages, leading to increased m^{6}A modification of target mRNAs such as autophagy related 13 and SLAM family member 7 (*SLAMF7*), thereby promoting autophagy dysfunction, inflammation and extracellular matrix (ECM) deposition (19,20). Proteasome-dependent degradation of ALKBH5 aggravates PF by enhancing autophagy-related dysfunction and activating YAP1 signaling in epithelial cells (21). In alveolar epithelial cells exposed to 1-nitropyrene, ALKBH5 undergoes SUMOylation, a reversible post-translational modification in which a small ubiquitin-like modifier protein is covalently attached to lysine residues on a substrate protein. In this model, ALKBH5 SUMOylation promotes its proteasomal degradation, thereby increasing m^{6}A modification of *FBXW7* mRNA, enhancing FBXW7 expression and promoting TRF2 degradation, telomere damage, cellular senescence and fibrosis (17). Moreover, ALKBH5 in macrophages regulates m^{6}A modification of SLAMF7 and affects autophagy and inflammatory responses during silica-induced lung injury (22). These findings support a context-dependent role of ALKBH5. In toxicant-induced epithelial injury, ALKBH5 loss promotes senescence and fibrosis, suggesting a protective role of ALKBH5 in epithelial cells. However, ALKBH5-related pathways may differ in macrophages, fibroblasts and other environmental exposure models. Therefore, ALKBH5 should be described as a context-dependent regulator rather than a uniformly anti-fibrotic or pro-fibrotic factor.

FTO is notably downregulated in lung tissues during PF, specifically in a mouse model of silicosis (23). This suppression leads to increased global m^{6}A RNA methylation in fibrotic lungs. Single-cell sequencing further revealed that FTO expression is reduced in epithelial cells, endothelial cells, fibroblasts and monocytes, all of which are involved in fibrosis (23). By contrast, ALKBH5 and other m^{6}A regulators such as METTL3 and METTL14 did not show notable changes between normal and fibrotic lung tissues in that specific dataset (23). These findings suggest that FTO may act as a cell-type-sensitive regulator in silica-induced pulmonary inflammation and fibrosis. Nevertheless, whether FTO downregulation is an initiating event, a secondary response to injury or an amplifier of fibrotic inflammation remains to be clarified by cell-specific gain- and loss-of-function studies. YTHDF1, YTHDF2, YTHDF3 and insulin-like growth factor 2 mRNA-binding protein (IGF2BP)1-3 are key m^{6}A reader proteins that recognize m^{6}A modifications and regulate mRNA fate. YTHDF1 primarily promotes the translation of selected m^{6}A-modified transcripts, whereas YTHDF2 generally facilitates their degradation. YTHDF3 has been reported to act as a co-reader that enhances YTHDF1-associated translation of certain m^{6}A-marked transcripts and facilitates YTHDF2-associated decay of others. Therefore, the function of YTHDF3 depends on the bound transcript and cellular context rather than representing a uniform translational or degradative effect (41-43). By contrast, IGF2BP1-3 recognize m^{6}A-containing transcripts through their K homology domains and recruit RNA-stabilizing proteins, thereby protecting the bound RNAs from degradation, prolonging their half-lives and, in some contexts, increasing protein translation (44,45). These proteins participate in cell proliferation, differentiation, stress responses and disease progression. During PF progression, the expression of m^{6}A readers such as YTHDF1, YTHDF3 and IGF2BP2 undergoes dynamic changes. In arsenite-related IPF, YTHDF1 recognizes m^{6}A-modified neuronal regeneration-related protein (*NREP*) mRNA and enhances *NREP* translation, increasing TGF-β1 secretion from alveolar epithelial cells and promoting fibroblast-to-myofibroblast transition. The resulting myofibroblasts release extracellular lactate; therefore, lactate is a metabolic product of activated myofibroblasts rather than a direct product of NREP. After uptake into alveolar epithelial cells through monocarboxylate transporter 1, lactate increases H3K18 lactylation, which promotes YTHDF1 transcription and reinforces the YTHDF1/m^{6}A/NREP/TGF-β1 fibrotic circuit (25). This mechanism illustrates crosstalk between metabolic remodeling, histone lactylation and m^{6}A-mediated translational control. However, the term 'positive feedback loop' should be used only for this experimentally supported axis and should not be generalized to all oxidative stress-m^{6}A interactions. In hypoxia/reoxygenation injury models, YTHDF3 and IGF2BP2 knockdown protects bronchial epithelial cells by reducing apoptosis and inflammation and inhibiting p38 MAPK, AKT, ERK1/2 and NF-κB pathways (46). Direct evidence for dynamic changes in YTHDF2 and IGF2BP1/3 in PF remains limited, and these readers should be presented as potential rather than fully validated PF regulators. m^{6}A modification regulates the degradation of fibrosis-related mRNAs through writers, erasers and readers. Deadenylation is the progressive shortening of the 3' poly(A) tail of an mRNA, which reduces transcript stability and commonly precedes decapping and exonucleolytic degradation. YTHDF2 binds m^{6}A-modified transcripts and recruits the CCR4/NOT deadenylase complex to initiate poly(A)-tail shortening and RNA decay. Alternatively, YTHDF2 can engage the HRSP12-RNase P/MRP endoribonuclease complex to promote endonucleolytic cleavage (47,48). Although these are general m^{6}A-dependent RNA-decay mechanisms, they are directly relevant to PF, as METTL3-dependent methylation enables YTHDF2-mediated degradation of TSC1 mRNA. The resulting reduction in TSC1 protein activates AKT/mTOR signaling and promotes alveolar epithelial remodeling and fibrotic progression (36).

Beyond mRNAs, m^{6}A also regulates non-coding RNAs, including miRNAs, long non-coding RNAs and circRNAs, which modulate fibrosis-related genes and signaling pathways (26). Dynamic changes in m^{6}A modification affect the stability of fibrotic mRNAs involved in TGF-β signaling, collagen production, fibroblast activation, apoptosis and inflammation (27,49). However, because much of the evidence for m^{6}A-mediated ECM regulation comes from multiple-organ fibrosis rather than PF-specific systems, PF-specific transcript targets should be distinguished from extrapolated mechanisms (28). The reported expression or functional alterations of major m^{6}A writers, erasers and readers in PF-related mechanisms are summarized in Table II.

m^{6}A-mediated epitranscriptomic remodeling and cell fate determination. Fibroblast-to-myofibroblast transition is a central event in the development and progression of PF. Myofibroblasts arise from activated fibroblasts and are major effector cells responsible for excessive ECM production, tissue contraction and structural remodeling in the fibrotic lung (50). This transition is driven by TGF-β/Smad signaling, mechanical cues from stiffened ECM and mechanosensitive ion channels such as TRPV4 and BK channels (51). The process is marked by increased α-SMA expression, cytoskeletal reorganization and enhanced collagen synthesis (52). Inhibiting fibroblast-to-myofibroblast transition reduces collagen deposition and improves lung function in animal models, supporting its potential as a therapeutic target (53). m^{6}A RNA modification plays a notable role in the translational regulation underlying fibroblast activation. Elevated m^{6}A levels mediated by methyltransferases such as METTL3 enhance translation of specific mRNAs required for fibroblast-to-myofibroblast transition. For example, m^{6}A modification promotes *KCNH6* mRNA translation in a YTHDF1-dependent manner, facilitating fibroblast activation and fibrotic progression (18). Silencing METTL3 reduces m^{6}A levels and inhibits this transition *in vitro* and *in vivo* (18). This pathway represents one of the stronger causal examples linking m^{6}A modification to PF because it is supported by patient tissue, animal models and cellular experiments. In addition, m^{6}A reader proteins such as IGF2BP1 and YTHDF1 can bind to m^{6}A-modified mRNAs and enhance stability or translation in related biological contexts (54,55). In a non-PF myogenic model, IGF2BP1 bound m^{6}A-modified FGFR1 mRNA, increased its stability and translation, and activated downstream ERK signaling, thereby promoting myogenic differentiation (55). This finding illustrates how an m^{6}A reader can stabilize a receptor transcript; however, it

Table II. Summary of m^{6}A regulator alterations in pulmonary fibrosis-related mechanisms.

Regulator	Category	Expression or functional change	Main cell type/model	Target/pathway	Biological effect	(Refs.)
METTL3	Writer	Upregulated in fibrotic contexts	Fibroblasts; epithelial cells; IPF/PF models	KCNH6/YTHDF1; TSC1/YTHDF2;	Promotes FMT and EMT-like remodeling AKT/mTOR	(18,36)
METTL14	Writer	Downregulated in aging-related IPF	Alveolar epithelial cells	DDIT4 mRNA stability	Promotes epithelial senescence when reduced	(16)
FTO	Eraser	Downregulated in silica-induced PF	Epithelial cells, endothelial cells, fibroblasts, monocytes	Global m^{6}A increase; inflammatory remodeling	Associated with inflammation and fibrosis	(23)
ALKBH5	Eraser	Downregulated or degraded depending on exposure	Epithelial cells, macrophages	FBXW7; Atg13; Slamf7	Regulates senescence, autophagy and inflammation	(17,19-21)
YTHDF1	Reader	Increased in arsenite-related IPF	Alveolar epithelial cells; fibroblast crosstalk	NREP/TGF-β1; KCNH6 translation	Promotes FMT and fibrotic signaling	(18,25)
YTHDF2	Reader	Functionally involved in mRNA decay	Epithelial remodeling models	TSC1 mRNA degradation	Activates AKT/mTOR pathway through TSC1 reduction	(36,47,48)
YTHDF3	Reader	Functionally implicated in a hypoxia/reoxygenation injury model	Bronchial epithelial cells	p38 MAPK, AKT, ERK1/2, NF-κB	Regulates apoptosis and inflammation	(46)
IGF2BP2	Reader	Differentially expressed in lung injury model	Bronchial epithelial cells	Inflammatory and survival	Regulates injury responses pathways	(46)
circRNA-associated m^{6}A	Non-coding RNA regulation	Altered in silica-induced PF	Fibroblasts	circRNA methylation/ eIF4A3-related	Promotes fibroblast activation and migration regulation	(24)

m^{6}A, N6-methyladenosine; PF, pulmonary fibrosis; IPF, idiopathic PF; EMT, epithelial-mesenchymal transition; DDIT4, DNA damage inducible transcript 4; KCNH6, potassium voltage-gated channel subfamily H member 6; FBXW7, F-box/WD repeat-containing protein 7; FMT, fibroblast-to-myofibroblast transition; circRNA, circular RNA; eIF4A3, eukaryotic initiation factor 4A-3; NREP, neuronal regeneration related protein; Atg13, autophagy related 13.

is included only as supportive mechanistic background and should not be interpreted as direct evidence for fibroblast activation in PF.

EMT is a process in which epithelial cells lose polarity and cell-cell adhesion and acquire mesenchymal characteristics, thereby contributing to epithelial dysfunction, migratory capacity and ECM-associated signaling (56,57), and EMT has been implicated in PF. In IPF, EMT-like changes and abnormal epithelial-fibroblast crosstalk can activate local fibroblasts, increase collagen deposition and impair lung function (58,59). However, whether complete EMT directly contributes substantially to the myofibroblast pool *in vivo* remains debated. Therefore, the present review uses 'epithelial plasticity' and 'EMT-like remodeling' where appropriate, rather than overstating full EMT as a dominant source of myofibroblasts. During EMT, m^{6}A RNA methylation undergoes dynamic changes. METTL3 expression and global m^{6}A levels are often upregulated during TGF-β-induced EMT in lung and other epithelial cells (60,61). Increased m^{6}A promotes translation or stability of EMT-related transcription factors such as Snail, JUN, JUNB and zinc finger MYM-type containing 1 (ZMYM1), thereby enhancing mesenchymal marker expression and repressing epithelial markers such as E-cadherin (62,63). Mechanistically, m^{6}A modifications on specific mRNAs facilitate recognition by readers such as YTHDF1 and human antigen R, which promote translation or stability of EMT drivers (64). In a breast cancer model, METTL3-dependent m^{6}A modification increased MALAT1 stability. MALAT1 subsequently acted as a competing endogenous RNA for miR-26b, thereby relieving miR-26b-mediated repression of HMGA2. The resulting increase in HMGA2 was accompanied by decreased CDH1/E-cadherin expression and increased CDH2/N-cadherin and VIM/vimentin expression, thereby promoting EMT, migration and invasion (65). As this evidence was obtained outside PF, it is presented as a mechanistic example rather than PF-specific proof.

Macrophage activation states contribute to the temporal evolution of PF, although they are more appropriately viewed as a continuum than as a strict M1/M2 dichotomy (66,67). Pro-inflammatory macrophage programs may aggravate epithelial injury during the early stages of disease, whereas persistent M2-like or pro-fibrotic macrophages release TGF-β1 and other pro-fibrotic mediators, thereby promoting epithelial plasticity, fibroblast activation, myofibroblast differentiation and ECM deposition. m^{6}A modification may regulate these macrophage states by altering the stability, translation and decay of transcripts involved in inflammatory and metabolic programs. METTL3 is upregulated during M1-like polarization and modifies transcripts such as STAT1 and HDGF, thereby promoting inflammatory responses (68,69). Conversely, ALKBH5-mediated demethylation of CPT1A mRNA enhances fatty-acid metabolism and supports M2-like polarization in a colorectal cancer model (70). As most of these mechanisms were identified outside PF, they should be interpreted as mechanistic background requiring direct validation in lung macrophage-specific PF models. Multi-omics studies reveal dynamic m^{6}A and 5-hydroxymethylcytosine changes during macrophage differentiation and polarization (71,72). For example, in rheumatoid arthritis macrophages, circ_0066715 acts as a competing endogenous RNA for miR-486-5p, thereby relieving miR-486-5p-mediated repression of ETS1 and altering macrophage-polarization programs (73). This axis is cited as an inflammatory-disease example and has not yet been validated in PF. However, most macrophage-polarization mechanisms cited here are not PF-specific. Therefore, these mechanisms are interpreted as mechanistic background, and PF-specific macrophage m^{6}A regulation still requires direct validation using lung macrophage-specific models, single-cell analysis and lineage-resolved functional studies. Collectively, these findings indicate that m^{6}A-dependent regulation may influence pulmonary cell fate through fibroblast activation, epithelial plasticity and macrophage-associated responses, although the strength and PF specificity of the evidence differ among these cellular processes, as summarized in Fig. 2.

Aberrant m^{6}A modification in PF pathogenesis. Oxidative stress is a major contributor to PF pathogenesis because it promotes epithelial injury, mitochondrial dysfunction, DNA damage, inflammatory signaling, cellular senescence and fibrotic remodeling (12,17,23). Oxidative stress and m^{6}A modification may interact through specific regulatory axes, but current evidence does not justify a universal ROS-m^{6}A feedback model across all PF contexts. Exposure to 1-nitropyrene leads to excessive mitochondrial ROS production in alveolar epithelial cells, which triggers SUMOylation and proteasomal degradation of ALKBH5 (17). Consequently, loss of ALKBH5 increases m^{6}A modification of *FBXW7* mRNA, enhances FBXW7 expression and promotes telomeric repeat binding factor 2 (TRF2) degradation, telomere damage and cellular senescence, thereby accelerating PF (17). Antioxidant treatment can reverse some of these effects, highlighting the notable effect of oxidative stress-induced m^{6}A dysregulation in this specific model (17). Similarly, in silica-induced PF, oxidative stress suppresses FTO and increases global m^{6}A abundance across epithelial cells, endothelial cells, fibroblasts and monocytes (23). However, the cited study did not identify or functionally validate individual FTO-dependent methylated transcripts. Therefore, this finding should be interpreted as a cell-type-resolved global methylation change rather than evidence for specific methylated genes.

Aging is a marked risk factor for PF, particularly IPF, which predominantly affects older adults (74,75). Aging-related mechanisms include genomic instability, telomere shortening, epigenetic alterations, mitochondrial dysfunction, cellular senescence, impaired tissue repair and chronic inflammation (76-79). In IPF, methylated RNA immunoprecipitation-sequencing and RNA-sequencing analyses have revealed widespread remodeling of m^{6}A methylation patterns, with thousands of m^{6}A peaks altered compared with healthy controls (16). METTL14 is notably downregulated in IPF, leading to reduced m^{6}A modification of *DDIT4* mRNA, increased DDIT4 stability and higher DDIT4 protein expression, which promotes alveolar epithelial cell senescence (16). These findings were validated in animal and senescent cell models (16). These findings indicate that METTL14-DDIT4 represents a notable m^{6}A-dependent aging-senescence axis in IPF, but aging-related PF remains multifactorial and cannot be attributed to m^{6}A dysregulation alone.

m^{6}A methylation also participates in ECM remodeling. Disruption of m^{6}A regulation can alter the expression and

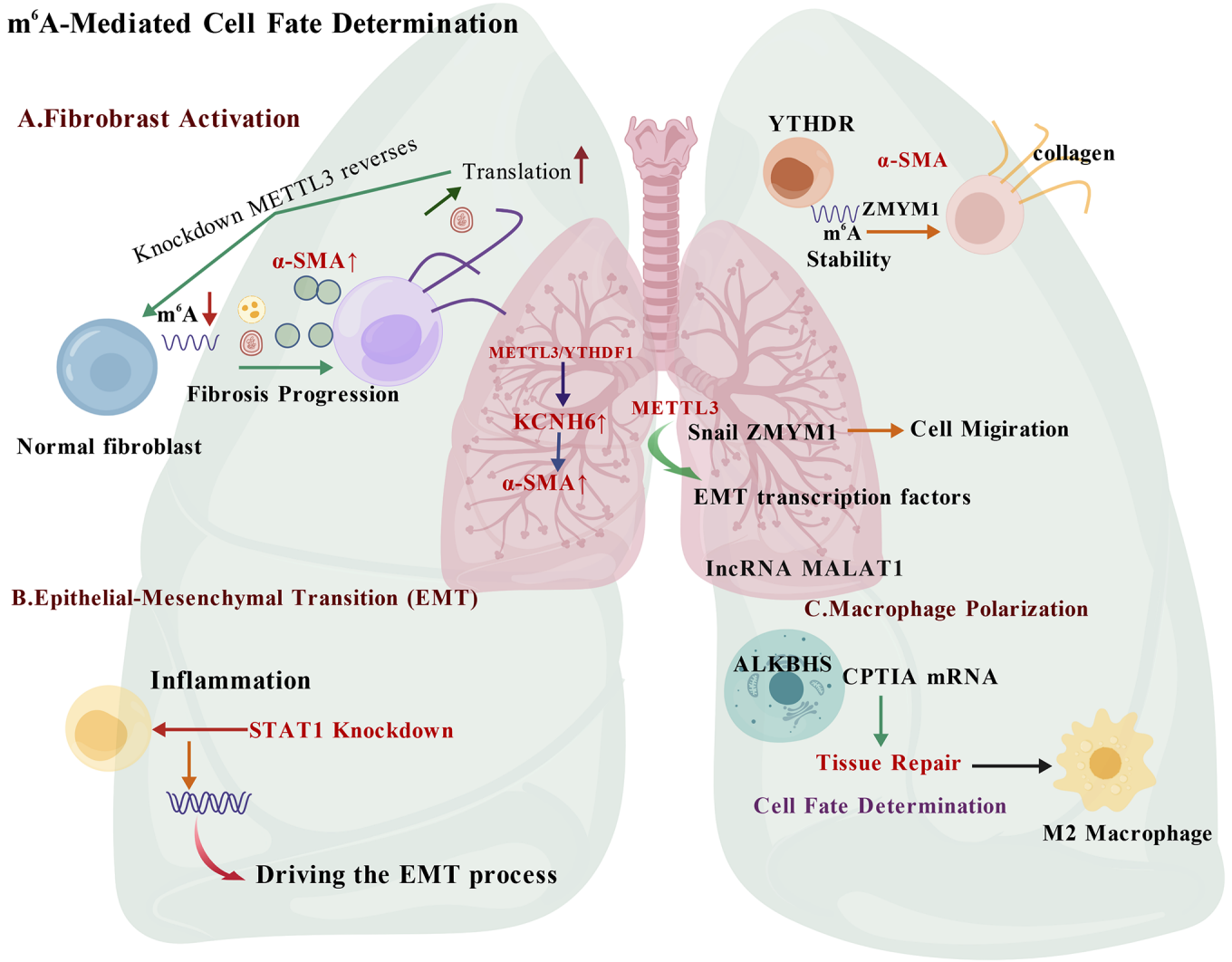

Figure 2. m^{6}A-mediated cell fate determination in pulmonary fibrosis. (A) Fibroblast activation. METTL3-mediated m^{6}A modification of KCNH6 mRNA is recognized by YTHDF1, which enhances KCNH6 translation and promotes fibroblast-to-myofibroblast transition. METTL3 silencing suppresses this response in PF models. (B) EMT-associated epithelial plasticity. In lung and other epithelial models, METTL3-dependent m^{6}A regulation increases the expression or stability of EMT-associated factors, including SNAI1, JUN, JUNB and ZMYM1, as well as the lncRNA MALAT1. These alterations reduce epithelial-marker expression, increase mesenchymal-marker expression and enhance cell migration. Mechanisms derived from non-PF systems are presented as supportive mechanistic background. (C) Macrophage polarization. METTL3-dependent m^{6}A modification of STAT1 supports pro-inflammatory macrophage activation, whereas ALKBH5-mediated demethylation of CPT1A supports fatty-acid metabolism and M2-like polarization in a non-PF cancer model. Direct PF-specific validation of these macrophage mechanisms remains limited. The figure was created using BioGDP (Biological Graphics Design Platform, version 2.0) (106). ALKBH5, alkB homolog 5; CPT1A, carnitine palmitoyltransferase 1A; EMT, epithelial-mesenchymal transition; KCNH6, potassium voltage-gated channel subfamily H member 6; lncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; METTL3, methyltransferase-like 3; m^{6}A, N6-methyladenosine; PF, pulmonary fibrosis; STAT1, signal transducer and activator of transcription 1; YTHDF1, YTH N6-methyladenosine RNA-binding protein 1; ZMYM1, zinc finger MYM-type containing 1.

deposition of ECM components such as collagen, elastin and fibrosis-associated genes in multiple organs (28,80). For example, METTL3-mediated m^{6}A regulation contributes to cardiac fibroblast activation and ECM deposition after myocardial infarction (81). In hypertrophic-scar fibroblasts, ALKBH5 directly regulates the m^{6}A status of COL1A1, COL3A1 and ELN transcripts. Loss of ALKBH5 increases their m^{6}A modification and expression, leading to excessive collagen I, collagen III and elastin deposition, whereas ALKBH5 overexpression reduces pathological ECM accumulation (82). As this evidence is derived from cutaneous fibrosis, its applicability to PF remains to be established. FTO also regulates ECM-related genes such as ADAM metallopeptidase with thrombospondin type 1, collagen type XII alpha 1 chain and thrombospondin-2 in pancreatic cancer cell migration and invasion (83). Although these studies support the broader concept that m^{6}A can regulate ECM homeostasis, direct PF-specific evidence for individual ECM transcripts remains limited. Collectively, current evidence links m^{6}A dysregulation to toxicant-induced oxidative injury, aging-related epithelial senescence and abnormal ECM remodeling in PF; however, these mechanisms remain stimulus-, cell-type- and model-dependent, as summarized in Fig. 3.

Therapeutic strategies targeting m^{6}A modification. The development of small-molecule m^{6}A modulators has progressed in several disease fields. FTO inhibitors, including Compound 2 and Compound 3, have been evaluated in

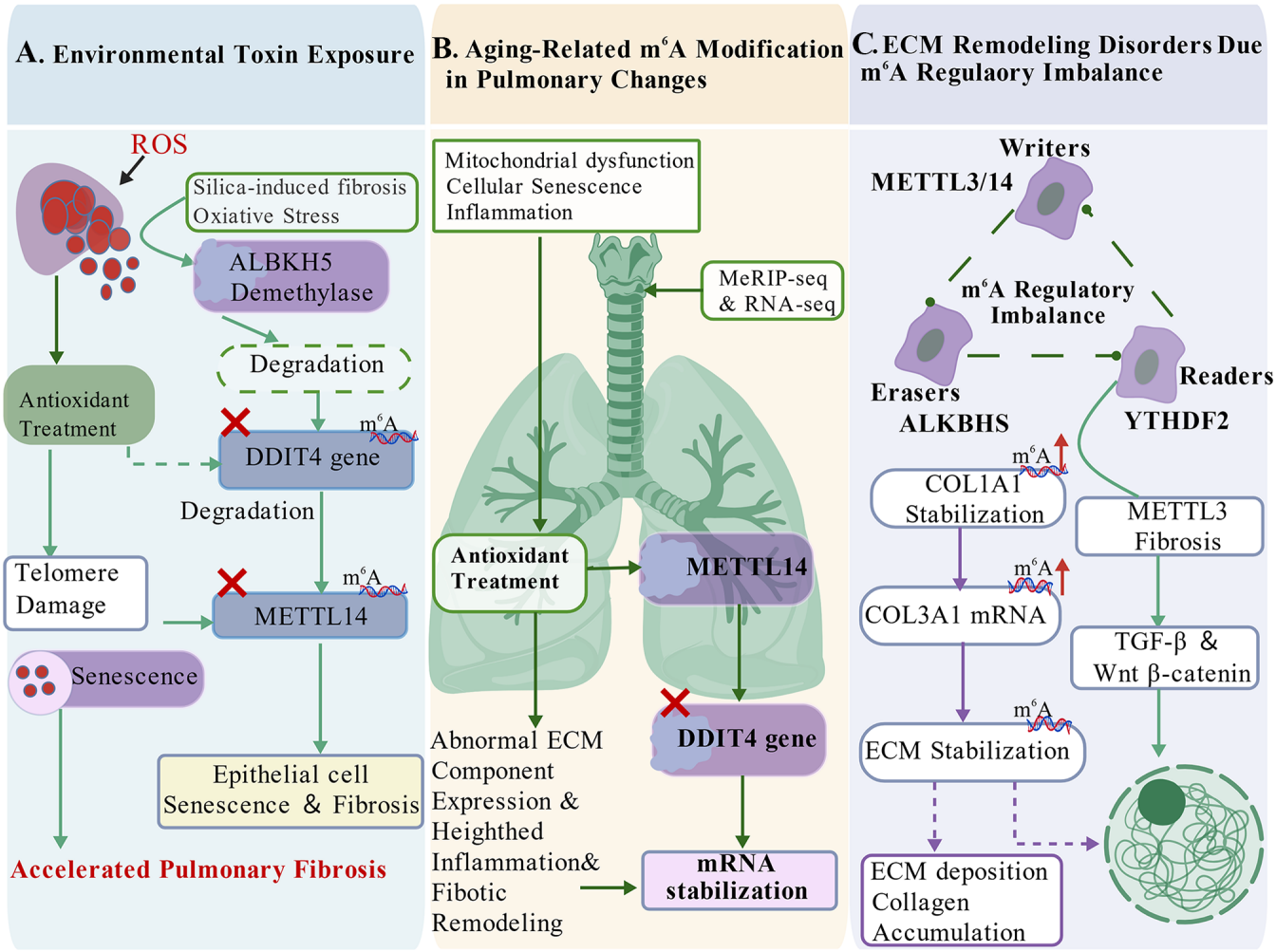

Figure 3. Oxidative stress, aging and ECM remodeling in m^{6}A-associated pulmonary fibrosis. (A) Environmental toxin exposure. In a 1-nitropyrene-associated model, mitochondrial ROS promotes ALKBH5 SUMOylation and proteasomal degradation, thereby increasing m^{6}A modification of FBXW7 mRNA and promoting TRF2 loss, telomere damage and alveolar epithelial cell senescence. In silica-induced PF, FTO suppression is associated with increased global m^{6}A abundance and inflammatory and fibrotic remodeling. (B) Aging-related m^{6}A remodeling. Integrated MeRIP-seq and RNA-seq analyses were used to identify transcripts showing concurrent alterations in m^{6}A enrichment and gene expression in IPF. This approach identified the METTL14-DDIT4 axis, in which reduced METTL14 expression decreases m^{6}A modification of DDIT4 mRNA, increases DDIT4 stability and promotes alveolar epithelial cell senescence. (C) ECM remodeling. Dysregulated m^{6}A machinery may alter ECM-related transcripts and pro-fibrotic signaling pathways, resulting in abnormal collagen and elastin deposition. Because much of the transcript-specific evidence is derived from non-PF fibrotic systems, these mechanisms are presented as supportive background rather than as validated PF-specific pathways. The figure was created using BioGDP (Biological Graphics Design Platform, version 2.0) (106). ALKBH5, alkB homolog 5; DDIT4, DNA damage-inducible transcript 4; ECM, extracellular matrix; FBXW7, F-box and WD repeat domain-containing 7; FTO, fat mass and obesity-associated protein; IPF, idiopathic pulmonary fibrosis; MeRIP-seq, methylated RNA immunoprecipitation sequencing; METTL14, methyltransferase-like 14; m^{6}A, N6-methyladenosine; PF, pulmonary fibrosis; RNA-seq, RNA sequencing; ROS, reactive oxygen species; TRF2, telomeric repeat-binding factor 2.

neurological models (84), whereas the YTH-family inhibitor N-7 broadly interferes with m^{6}A recognition by YTH-domain proteins (85). In cancer models, the METTL3 inhibitor STM2457 and FTO inhibitors, including FB23, FB23-2, CS1 and CS2, have shown antitumor activity (86). Quercetin and rutin have also been reported to influence m^{6}A-related pathways, although their pleiotropic effects preclude their classification as selective m^{6}A modulators (87). Among these compounds, STM2457 has been evaluated directly in an experimental IPF model in C57BL/6 mice. Intraperitoneal administration of STM2457 reduced fibroblast activation, collagen deposition and pathological and functional lung abnormalities, reportedly through inhibition of the METTL3/CTGF signaling axis (88). By contrast, Compound 2, Compound 3, N-7, FB23, FB23-2, CS1 and CS2 have not been tested in PF models. Accordingly, these agents should be presented as non-PF tool compounds, whereas STM2457 represents preliminary preclinical evidence rather than an established anti-fibrotic therapy. Therefore, they are presented as tool compounds or preclinical candidates rather than established anti-fibrotic therapies. Gene editing technologies, especially CRISPR/dCas13 or dCasRx fused with m^{6}A methyltransferases or demethylases, have enabled transcript-specific regulation of m^{6}A modification (89-91). These tools allow targeted installation or removal of m^{6}A marks on selected transcripts and may help determine the causal roles of specific m^{6}A sites. For PF research, such technologies could be used to validate disease-relevant targets such as KCNH6, DDIT4, FBXW7, NREP and ECM-associated transcripts. However, clinical application

remains limited by delivery efficiency, off-target effects, immunogenicity, long-term safety and the complexity of fibrotic lung tissue. Tissue-specific delivery systems have also advanced through nanocarriers, biomembrane modification and molecular targeting strategies. Examples include PLGA nanoparticles loaded with METTL3 inhibitors, engineered small extracellular vesicles delivering YTHDF1 small interfering (si)RNA, mesenchymal stem cell-derived exosomes co-delivering YTHDF1 siRNA and chemotherapeutic agents and exosome-liposome hybrid nanoparticles delivering ALKBH5 mRNA in tumor models (92-95). These systems demonstrate the feasibility of cell- or tissue-targeted m^{6}A modulation, but most data are derived from cancer models. For PF, future studies should focus on lung-targeted delivery, epithelial- or fibroblast-specific uptake, inhalable formulations and safety in chronically injured lung tissue. From a patient-centered perspective, m^{6}A-targeted therapy should be evaluated according to clinically meaningful outcomes, including slowing lung function decline, reducing symptom burden, preventing acute exacerbation, improving exercise capacity and enhancing quality of life. Preclinical target validation in PF also includes METTL3 silencing in KCNH6-dependent fibroblast activation (18), modulation of the METTL14/DDIT4 axis in aging-related epithelial senescence (16), and manipulation of the ALKBH5/FBXW7 and YTHDF1/NREP axes in toxicant-induced PF (17,25). These studies establish mechanistic target validity, whereas STM2457 currently provides direct small-molecule evidence among the compounds discussed in the present review.

Research prospects and emerging technologies. Studies have revealed that m^{6}A modification may interact with other epigenetic and post-translational mechanisms in PF. For example, m^{6}A interacts with histone lactylation, particularly H3K18 lactylation, in alveolar epithelial cells. Extracellular lactate from myofibroblasts increases H3K18 lactylation, which promotes YTHDF1 transcription, enhances NREP translation and increases TGF-β1 secretion, thereby facilitating fibroblast-to-myofibroblast transition (25). m^{6}A modification is also linked to protein SUMOylation and ubiquitination; SUMOylation of ALKBH5 leads to its degradation, increases m^{6}A modification of *FBXW7* mRNA and promotes TRF2 degradation, alveolar epithelial senescence and fibrosis (17). m^{6}A also acts in concert with circRNA methylation in silica-induced PF. Specifically, METTL3-dependent m^{6}A modification of hsa_circ_0000672 and hsa_circ_0005654 promotes pulmonary fibroblast activation and migration. Both circRNAs converge on eIF4A3, producing a synergistic pro-fibrotic effect (24). These examples suggest that m^{6}A should be understood as part of a multilayer regulatory network involving RNA methylation, histone modification, non-coding RNA regulation and post-translational modification. Single-cell m^{6}A profiling technologies provide new opportunities for understanding PF heterogeneity. Techniques such as single cell DART-sequencing and single nucleus-m^{6}A-CUT&Tag enable mapping of m^{6}A RNA modifications at single-cell or single-nucleus resolution (96,97). These technologies may help identify cell-type-specific m^{6}A landscapes in alveolar epithelial cells, fibroblast subpopulations, macrophages, endothelial cells and immune-cell subsets. In IPF, single-cell transcriptomic analysis has already revealed disease-associated epithelial, stromal and immune-cell states (98). Future integration of single-cell transcriptomics, spatial transcriptomics and m^{6}A profiling may clarify whether m^{6}A dysregulation occurs early in disease initiation, during fibrotic progression or as a secondary response to tissue remodeling. From a translational medicine perspective, m^{6}A-related biomarkers have been investigated in several cancers. Examples include m^{6}A-related lncRNA signatures associated with prognosis and immune-response patterns in lung adenocarcinoma, as well as m^{6}A-based signatures linked to drug resistance, cancer stemness and immunotherapy response in other malignancies (99-103). In PF, m^{6}A regulators may help classify patients according to dominant pathological processes, such as epithelial senescence (16), fibroblast activation (104), inflammatory remodeling (105) or environmental exposure-associated injury (23). However, direct evidence for m^{6}A-related prognostic biomarkers in PF remains limited. Large independent cohorts, standardized detection methods and comparison with established indicators such as HRCT features, pulmonary function decline, MMP7, KL-6 and surfactant proteins are required before clinical translation.

Unique contributions and framework of the present review. Previous reviews have discussed m^{6}A in non-coding RNAs, fibrotic diseases and collagen-related disorders (26-29). The contribution of the present review is more precise, as it provides a PF-focused synthesis of m^{6}A regulatory mechanisms, emphasizing pulmonary cell-type specificity, validated transcript targets, context-dependent regulator function, multilayer epigenetic crosstalk and patient-centered translational implications. The translational research perspective, the review integrates evidence showing how m^{6}A regulators participate in fibroblast activation, epithelial plasticity, macrophage-associated inflammation, oxidative stress, aging-related epithelial senescence and ECM remodeling. These mechanisms involve writers such as METTL3 and METTL14, erasers such as FTO and ALKBH5 and readers such as YTHDF1, YTHDF3 and IGF2BP2 across epithelial cells, fibroblasts and macrophages (16-25,36). In addition, for the patient-centered care perspective, the present review connects m^{6}A biology with patient-prioritized needs, including early diagnosis, risk stratification, prevention of progression and development of therapies that may eventually affect lung scarring, lung function and quality of life (14). The discussion of biomarkers therefore avoids overclaiming clinical readiness and emphasizes the need for validation in large patient cohorts. From the perspective of novel advances in interstitial lung disease, the present review highlights multilayer crosstalk between m^{6}A and H3K18 lactylation, SUMOylation, ubiquitination and circRNA methylation (17,24,25). These mechanisms are not presented as universal pathways, but as specific examples showing how m^{6}A machinery can be integrated into broader epigenetic and post-translational regulatory networks in PF. Overall, the present review does not claim that m^{6}A is the sole or dominant driver of PF. Instead, it positions m^{6}A as a dynamic regulatory hub that connects RNA metabolism with pulmonary cell fate, fibrotic signaling and potential translational strategies.

3. Conclusion

m^6A RNA methylation has emerged as a notable epitranscriptomic mechanism in PF. It regulates disease-associated processes including fibroblast activation, epithelial plasticity, epithelial senescence, macrophage-associated inflammation, oxidative stress responses and ECM remodeling. The present review emphasizes that m^6A regulation in PF is context-dependent. For example, METTL3 generally shows pro-fibrotic activity in fibroblast activation and epithelial remodeling, whereas METTL14, FTO and ALKBH5 may exert distinct effects depending on disease stage, cell type, environmental exposure and target transcript. Therefore, m^6A should not be interpreted as a single directional driver of fibrosis. Current evidence supports several mechanistically informative axes, including METTL3/YTHDF1/KCNH6-mediated fibroblast-to-myofibroblast transition, METTL3/YTHDF2/TSC1-mediated epithelial remodeling, METTL14/DDIT4-mediated aging-related epithelial senescence, ALKBH5/FBXW7-mediated toxicant-induced epithelial senescence and H3K18 lactylation/YTHDF1/NREP-mediated fibrotic signaling. However, numerous proposed mechanisms, especially those related to macrophage polarization, ECM remodeling and therapeutic targeting, still require PF-specific validation. Future studies should move beyond expression profiling and focus on cell-type-specific, transcript-specific and temporally resolved m^6A mechanisms. Single-cell m^6A profiling, spatial transcriptomics, RNA epitranscriptomic editing, disease-relevant animal models and clinically annotated patient cohorts will be essential for determining whether m^6A regulators can serve as reliable biomarkers or therapeutic targets. A more precise understanding of the m^6A regulatory network may ultimately support earlier diagnosis, improved risk stratification and development of safer patient-centered therapeutic strategies for PF.

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Availability of data and materials

Not applicable.

Authors' contributions

LLM, DKZ and GQZ contributed to the conception and design of the review. Material preparation was performed by XFL, DKZ and LLM. The first draft of the manuscript was written by XFL. DKZ, LLM and GQZ critically revised the manuscript. All authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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