REVIEW

N6-methyladenosine (m6A) RNA modification in fibrosis and collagen-related diseases

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Abstract

Fibrosis is an abnormal tissue healing process characterized by the excessive accumulation of ECM components, such as *COL I* and *COL III*, in response to tissue injury or chronic inflammation. Recent advances in epitranscriptomics have underscored the importance of m6A modification in fibrosis. m6A, the most prevalent modification in eukaryotic RNA, is catalyzed by methyltransferases (e.g., *METTL3*), removed by demethylases (e.g., *FTO*), and recognized by reader proteins (e.g., *YTHDF1/2*). These modifications are crucial in regulating collagen metabolism and associated diseases. Understanding the role of m6A modification in fibrosis and other collagen-related conditions holds promise for developing targeted therapies. This review highlights the latest progress in this area.

Keywords N6-methyladenosine, Collagen, Fibroblast, α-Smooth muscle actin

Introduction

Collagen is a crucial protein in the extracellular matrix (ECM) [1], providing essential structural support to various tissues and organs [2, 3]. Its metabolism involves a delicate balance between synthesis, assembly, and degradation. Dysregulation of collagen metabolism can lead to fibrosis, characterized by an excessive buildup of collagen and other matrix components in tissues. Fibrosis occurs as a response to tissue injury or chronic inflammation and can affect different organs in the body [4, 5].

In fibrosis, abnormal collagen synthesis and deposition play a central role. Activated fibroblasts and other cells increase collagen production, driven by signaling pathways like *TGF-β* [6] and *CTGF* [7]. Additionally, impaired collagen degradation contributes to fibrosis, resulting from an imbalanced ratio of matrix metalloproteinases (*MMPs*) and tissue inhibitors of metalloproteinases (*TIMPs*) [8].

Epitranscriptomics is an emerging and crucial field in recent years, encompassing over 170 distinct post-transcriptional RNA modifications or editing events, which play important roles in the regulation of fibroblasts and fibrosis [9, 10], such as the liver [11], lungs [12], kidneys, and heart [13]. Among these modifications, N6-adenosine methylation, known as m6A modification, stands out as the most prevalent modification in eukaryotic RNA and was first reported in 1974 [14]. The m6A modification is catalyzed by the methyltransferase complex (comprising *METTL3*, *METTL14*, and *WTAP* as co-factors), removed by demethylases (such as *FTO* and *ALKBH5*), and recognized by reader proteins (e.g., *YTHDF1/2/3*, *YTHDC1/2*, *IGF2BP1/2/3*), dynamically regulating gene expression at the post-transcriptional level and contributing to the development of various diseases [15]. Recent

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research has shed light on the roles of m6A regulatory factors in fibrosis and collagen-related diseases.

Understanding the role of m6A modification in fibrosis and other collagen-related conditions holds significant promise for the development of targeted therapies. This review highlights the latest advancements and progress in this area.

Collagen metabolism and fibrosis

The extracellular matrix is a vital three-dimensional macromolecular network consisting of collagen proteins, proteoglycans/glycosaminoglycans, elastin proteins, fibronectin, laminin, and other glycoproteins [16]. It plays a crucial role in tissue remodeling and the regulation of cell behavior. Collagen, a protein with a triple-helix structure [17], is the predominant constituent of the ECM, making up approximately 30% of the total protein content in the human body [1]. Its main functions include providing elasticity, stability, and support to tissues [2]. There are 28 different types of collagen identified so far, with *COL I, COL III*, and *COL V* mainly produced by fibroblasts, while *COL IV* is primarily expressed by epithelial cells and endothelial cells. In some cases, cancer cells and tumor-associated macrophages can also produce collagen [18].

Fibrosis is an abnormal tissue healing process characterized by excessive accumulation of ECM components such as *COL I* and *COL III* in response to tissue injury or chronic inflammation. It can affect various organs, such as the liver, lungs, kidneys, and heart. Fibrosis disrupts tissue architecture and function, leading to organ dysfunction and organ failure. Tissue healing involves three stages: inflammation, proliferation, and remodeling [19]. Fibroblasts play a significant role in this process, transforming into myofibroblasts with contractile force during the proliferation stage and driving wound contraction during the remodeling stage [20, 21]. The proper transformation of fibroblasts to myofibroblasts and their subsequent apoptosis are crucial for appropriate tissue healing. However, under pathological conditions, this normal wound healing process is disrupted, resulting in persistent myofibroblast presence and ECM remodeling [22].

In the context of fibrosis, abnormal collagen synthesis and deposition play a central role. Fibrotic tissues exhibit increased collagen production by activated fibroblasts and other cell types. This enhanced collagen synthesis is triggered by various signaling pathways, such as *TGF-β* [6] and *CTGF* [7]. These pathways promote the expression of collagen genes and drive fibroblast-to-myofibroblast transition, characterized by increased contractility and collagen production.

Furthermore, the degradation of collagen is finely regulated through a delicate balance between *MMPs* and *TIMPs* [23]. *MMPs* play a primary role in the breakdown of collagen [24], and their activity is controlled by *TIMPs* to prevent excessive degradation of the connective tissue. *TIMPs* counteract the effects of MMPs by forming complexes with them, impeding their interaction with substrates, and thus, slowing down the process of collagen degradation [25]. In fibrosis, this balance between *MMPs* and *TIMPs* is disrupted, resulting in reduced collagen breakdown and increased accumulation [8].

The regulation of collagen metabolism and fibrosis is a complex and dynamic process involving various factors. m6A modification may play a role in regulating collagen metabolism at multiple stages. Gaining insights into the molecular mechanisms of both collagen metabolism and m6A modification offers promising potential for developing targeted therapies for fibrosis and collagen-related diseases.

m6A regulatory proteins

"writers" of m6A methyltransferase

The m6A methyltransferase complex comprises *METTL3, METTL14,* and the co-factor *WTAP* [26]. *METTL3*, recognized as the catalytic core of the methyltransferase in 1997 [27], is the pioneering "writer" responsible for transferring the methyl group from S-adenosylmethionine (SAM) to the adenosine residues of RNA. *METTL14* serves as an RNA-binding platform, facilitating RNA substrate binding and enhancing the complex's integrity [28, 29]. In human cells, *METTL3* and *METTL14* form a 1:1 stoichiometric complex [30], which localizes in the cytoplasm and then translocates to the nucleus through a nuclear localization signal within *METTL3*, where it associates with *WTAP* [31]. Although *WTAP* lacks methyltransferase activity, it interacts with the *METTL3-14* complex and plays a regulatory role in recruiting the m6A methyltransferase complex to mRNA targets [32].

"erasers" of m6A demethylase

The "erasers" of m6A demethylase function akin to an eraser, removing m6A modifications from RNA. The first reported m6A demethylase in eukaryotic cells is the Fat mass and obesity-associated protein (*FTO*) [33]. The second identified m6A demethylase is *ALKBH5*, which has been shown to regulate mRNA output and RNA metabolism by reducing m6A levels in nuclear speckles [34].

"readers" of m6A modifications

"Readers" constitute a group of proteins that can recognize m6A modifications and regulate gene expression

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by influencing various biological processes, such as mRNA stability, splicing, structure, output, and translation efficiency [35]. Cytoplasmic m6A readers include *YTHDF1/2/3*, *YTHDC2*, and *IGF2BP1/2/3*. *YTHDF1* enhances the translation of m6A methylated mRNA; while, *YTHDF2* accelerates the degradation of m6A methylated mRNA. *YTHDF3* collaborates with *YTHDF1* and YTHDF2 to promote the metabolism of m6A methylated mRNA in the cytoplasm [36]. *YTHDC2*, located in nuclear speckles, preferentially binds to transcripts containing m6A modifications, leading to decreased mRNA abundance and increased translation efficiency through interactions with translation initiation and decay mechanisms [37]. Human insulin-like growth factor 2 mRNA-binding proteins (*IGF2BPs*) enhance mRNA stability by binding to target transcripts [38]. Nuclear m6A readers include *YTHDC1*, which interacts with splicing factors and nuclear export adapter protein *SRSF3* to facilitate the transport of m6A-modified mRNA from the nucleus to the cytoplasm [39].

m6A modification in fibrotic diseases
Pulmonary fibrosis
Research related to pulmonary fibrosis is shown in Table 1. m6A levels increase in the lung tissues of patients with IPF and in mice with bleomycin (BLM)-induced fibrosis. This increase is attributed to elevated *METTL3* expression. Silencing *METTL3* reduces m6A levels and inhibits *αSMA* and *COL I* expression in TGF-β1-induced WI-38 cells. m6A modification, mediated by *YTHDF1*, regulates the fibroblast-to-myofibroblast transition (FMT) by modulating *KCNH6* mRNA translation [41].

Another study, through immunohistochemical analysis, observed a decrease in *METTL3* expression in both pulmonary fibrosis patients and in a BLM-induced pulmonary fibrosis model in mice [45].

PM 2.5
PM2.5 exposure increases *METTL3* expression, leading to heightened m6A modification of *CDH1* mRNA. Moreover, enhanced recognition of *CDH1* mRNA m6A modification by *YTHDF2* inhibits its transcription and promotes its degradation, ultimately accelerating the progression of epithelial–mesenchymal transition (EMT) and pulmonary fibrosis after PM2.5 exposure [42].

Another study suggests that the upregulation of *METTL3* plays a protective role in PM2.5 exposure. PM2.5 exposure-induced *METTL3* expression promotes *YTHDF1/IGF2BP1*-mediated recognition of m6A sites on *Nrf2* mRNA, leading to enhanced *Nrf2* translation

Table 1 Pulmonary fibrosis

Diseases and cell types	Regulatory factors	Mechanisms	Functions	References
Silica-induced mice	*METTL3*↑, *ALKBH5*, *FTO*, *YTHDF1*, *YTHDF3*↓	–	–	[40]
Patients with IPF BLM-induced mice TGF-β1-induced WI-38	*METTL3*↑	*YTHDF1/KCNH6*	Regulating the fibroblast-to-myofibroblast transition	[41]
PM2.5-exposed mice BEAS-2B	*METTL3*↑, *YTHDF2*↑	*miR-494-3p/YTHDF2/CDH1*	Accelerating the progression of epithelial–mesenchymal transition and pulmonary fibrosis	[42]
Silicosis patients SiO₂-induced mice HPF-a, MRC-5	*METTL3*↑	*hsa_circ_0000672*, *hsa_circ_0005654*, *eIF4A3*	*METTL3* facilitates lung fibroblast activation, migration, and activity, contributing to SiO2-induced pulmonary fibrosis through circRNA m6A modification	[43]
PM2.5-exposed mice 16HBE	*METTL3*↑	*YTHDF*1, *IGF2BP1/Nrf2*	Activating the *Nrf2* antioxidant signaling pathway. Knockdown of *METTL3* increases *αSMA* expression after PM2.5 exposure	[44]
Patients with pulmonary fibrosis BLM-induced mice	*METTL3*↓	–	–	[45]
PM2.5-exposed mice BEAS-2B	*ALKBH5*↓	*Atg13/ULK* complex	The lack of *ALKBH5* exacerbates PM2.5 exposure-induced autophagy, inflammation, and fibrosis	[46]
SiO₂-induced mice TGF-β1-induced lung fibroblast	*ALKBH5*↑	*miR-320a-3p/FOXM1*	Promoting silica-induced pulmonary fibrosis	[47]
CB-induced rats 16HBE	*pri-miRNA-126* m6A↓	*miRNA-126/DGCR8/PI3K/AKT/mTOR*	Upregulating levels of pulmonary fibrosis markers, including *αSMA*, *fibronectin*, *COL I*, and *hydroxyproline*	[48]

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Table 2 Cardiac fibrosis

Tissues and cell types	Regulatory factors	Mechanisms	Functions	References
Myocardial infarction mice TGF-β1-induced CF	METTL3↑	–	Promoting proliferation and FMT and collagens accumulation	[49]
Atrial fibrillation patients Mice TGF-β1-induced CF	METTL3↑	YTHDF2/AR	Promoting glycolysis and cardiac fibroblast proliferation	[50]
Atrial fibrillation patients TAC/ISO-induced mice TGF-β1-induced CF	METTL3↑	IGFBP3	Silencing METTL3 can inhibit the activation of CFs and the degree of cardiac fibrosis	[51]
Atrial fibrillation patients ISO-induced mice TGF-β1-induced CF 3T3	METTL3↑	YTHDF2/GAS5/mitochondrial fission	Knockdown of METTL3/YTHDF2 improves ISO-induced cardiac fibrosis	[52]
Myocardial infarction mice HL1, AC16	METTL3	TNC	Overexpression of METTL3 exacerbates post-myocardial infarction cardiac dysfunction and cardiac fibrosis	[53]
Myocardial infarction mice TGF-β1-induced CF	MetBil↑	METTL3 binding lncRNA	Enhancing collagen deposition and CFs proliferation	[54]
Heart failure patients Myocardial infarction pigs Myocardial infarction mice Rat primary CF	FTO↓	–	Overexpression of FTO can reduce fibrosis and enhance angiogenesis	[55]
Diabetic cardiomyopathy mice	FTO↓	–	Overexpression of FTO in DCM model mice improved cardiac function by reducing myocardial fibrosis and myocyte hypertrophy	[56]
Myocardial infarction mice CF	FTO	Ang II/circCELF1/FTO/DKK2	FTO overexpression attenuates the upregulation of αSMA, COL I, and COL III induced by Ang II, inhibiting the progression of myocardial fibrosis	[57]
Heart failure with preserved ejection fraction mice	m6A level↑, FTO↓, METTL3↑	–	Overexpression of FTO cancels out the benefits of exercise in HFpEF + EXT mice by promoting myocyte apoptosis, myocardial fibrosis and myocyte hypertrophy	[58]
YTHDF2 KO mice, NRVM, ACM	YTHDF2	–	Knockdown of YTHDF2 results in cardiomyocyte growth and remodeling	[59]
Diabetic cardiomyopathy mice High glucose-induced CF	Airn → IMP2↑	Airn/IMP2/p53	CF cell cycle arrest and reduced cardiac fibrosis	[60]
Human PASMCs Mice	YTHDF1	Foxm1	Silencing of YTHDF1 alleviates pulmonary vascular changes and fibrosis	[61]

and activation of the Nrf2 antioxidant signaling pathway. Knockdown of *METTL3* increases *αSMA* expression after PM2.5 exposure [44].

Simultaneously, PM2.5 exposure downregulates *ALKBH5* expression, which promotes m6A modification of *Atg13* mRNA in BEAS-2B cells. This results in the upregulation of the *ULK* complex mediated by *Atg13*, promoting epithelial cell autophagy and inflammation under PM2.5 treatment. Consequently, the *NF-κB/NLRP3* signaling pathway is activated, driving pulmonary fibrosis [46].

Silicosis

m6A-seq and RNA-seq analyses on silica-induced silicosis mice showed increased m6A levels and *METTL3* expression; while, *ALKBH5*, *FTO*, *YTHDF1*, and *YTHDF3* expression decreased. Furthermore, 307 genes showed high methylation; while, 52 genes exhibited hypomethylation, mainly enriched in pathways related to "phagosome," "antigen processing and presentation," and "apoptosis" [40].

In silicosis patients, SiO2-treated fibroblasts, and mice, *METTL3* expression was found to increase. SiO2

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Table 3 Hepatic fibrosis

Tissues and cell types	Regulatory factors	Mechanisms	Functions	References
CCL4-induced mice	–	–	During hepatic fibrosis, m6A methylation differences are primarily enriched in processes related to oxidative stress and cytochrome metabolism	[62]
CCL4-induced rats THP-1/LX-2/293 T Primary Kupffer cells and HSCs	METTL3↑	NEAT1/Sp1/TGF-β1/Smad	METTL3 targets and enhances NEAT1 expression in macrophages, thereby promoting the proliferation and migration of HSCs and inducing the expression of fibrotic proteins	[63]
CCL4-induced mice KC, BMM IFN-γ/LPS-induced macrophages HEK293T, RAW264.7	METTL3↑	MALAT1/PTBP1/USP8/TAK1	Stimulating pyroptosis and inflammation of macrophages exacerbates liver fibrosis	[64]
METTL3 cKO mice CCL4-induced mice HSC	METTL3	Lats2/Hippo/YAP	METTL3 knockout suppresses HSC activation and alleviates liver fibrosis	[65]
CdCl2-induced mice HSC	METTL3↓	–	METTL3 overexpression in hepatocytes attenuates CdCl2-induced steatosis and liver fibrosis in mice, and ameliorates the CdCl2-induced cytotoxicity and activation of primary HSCs	[66]
CORT-induced chickens 293 T	METTL3↑	HSPs	Long-term exposure to CORT induces hepatic inflammation and fibrosis in chickens, while also leading to increased levels of various HSP mRNA and m6A methylation	[67]
NASH rats METTL14 cKO mice LPS-induced KC	METTL3↑, METTL14↑	LPS/NF-κB p65/METTL3/14/TGF-β1	Enhancing cap-independent translation of TGF-β1 exacerbates TGF-β1-mediated stellate cell activation, promoting the transition from NASH to liver fibrosis	[68]
CCL4-induced mice Primary HSCs HSC-T6	METTL3	ASIC1α/METTL3/DGCR8/miR-350/SPRY2/PI3K/KT and ERK pathways	Silencing of METTL3 reduces the expression of αSMA and COL1	[69]
Patients with hepatoblastoma/cholestasis/biliary atresia LX-2, primary HSC	METTL3, METTL14, WTAP↑, ALKBH5↓	THY1	Overexpression of METTL3 and METTL14 promotes the expression of COL IA1, MMP2	[70]
CHB patients HSC	METTL16↑	HLA-DPB1	Silencing METTL16 downregulates the m6A modification level of HLA-DPB1 mRNA, and is involved in the progression of fibrosis in chronic hepatitis B	[71]
Patients with liver cirrhosis complicated with HCC treated with sorafenib monotherapy Primary HSCs CCL4-induced mice	HSC ferroptosis → METTL4↑, FTO↓	YTHDF1/BECN1	HSC-specific inhibition of m6A modification could impair erastin-induced HSC ferroptosis in murine liver fibrosis	[72]
CCL4-induced mice Primary HSCs	m6A↓, WTAP↓, ALKBH5↓, YTHDF1↓	–	Differentially expressed m6A genes are found to be closely correlated with processes such as the endoplasmic reticulum stress response, PPAR signaling pathway, and TGF-β signaling pathway Decreased expression of WTAP was shown to promote HSC activation	[73]

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Table 3 (continued)

Tissues and cell types	Regulatory factors	Mechanisms	Functions	References
CCL4-induced rats TGF-β1-induced HSC	*WTAP*↑, *AcSDKP*→*WTAP*↓	*AcSDKP/WTAP/Ptch1*	*AcSDKP* inhibits CCl4-induced rat HSC apoptosis through the Hedgehog pathway	[74]
CCL4 and olive oil (1:9) -induced mice Primary HSCs, HSC-LX2	DHA induces iron-ferropto-sis → m6A level↑, *FTO*↓, *YTHDF1*↑	*DHA/FTO/YTHDF1/BECN1*	Overexpression of *FTO* reduces DHA-induced ferroptosis, and knocking down *YTHDF1* can prevent DHA-induced HSC ferroptosis and exacerbate liver fibrosis in mice	[75]
Patients with liver cirrhosis CCL4-induced mice HSC-T6, hepatocyte	*ALKBH5*↓	*YTHDF1/Drp1*	*ALKBH5* suppresses mitochondrial fission and HSC proliferation and migration by reducing Drp1 methylation in an m6A-*YTHDF1*-dependent manner	[76]
Patients with liver cirrhosis CCL4-induced mice TGF-β1-induced HSC	*ALKBH5*↓	*PTCH1*	Overexpression of *ALKBH5* reduces HSCs proliferation and migration	[77]
Patients received radiotherapy for intrahepatic tumor RILF mice HCC mice LX2, THP-1, HSC	Radiation → *ALKBH5*↑	*YTHDF2/TIRAP/NF-κB* pathway	*ALKBH5* mediates monocyte recruitment and M2 polarization, promoting radiation-induced liver fibrosis and reducing hepatocellular carcinoma radiosensitivity	[78]
CCL4-induced mice JS1	*YTHDF1*	Increase the stability of COL I A1 mRNA	Vitamin A-coupled *YTHDF1* siRNA alleviates CCl4-induced liver fibrosis in mice through HSC-specific inhibition of collagen production	[79]
Patients with liver cirrhosis CCL4-induced mice BDL-induced mice LX-2, Primary HSCs	*YTHDF3*↓	*PRDX3/ROS/TGF-β1/Smad2/3*	*YTHDF3* specifically regulates *PRDX3* translation and expression, inhibiting HSC activation, and ameliorating liver fibrosis	[80]
CCL4-induced mice Primary mouse HSCs, hepatocytes, and KCs	*YTHDC1*↑, *ZC3H13*↑, *FTO*↓	*NR1D1/DRP1^S616/cGAS*	Lowering m6A levels can reduce the expression of α*SMA* and *COL I*. DHA promotes the proteasomal degradation of *YTHDC1*, thereby restoring *NR1D1* expression and alleviating liver fibrosis	[81]

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Table 4 Renal fibrosis

Tissues and cell types	Regulatory factors	Mechanisms	Functions	References
UUO mice	m6A level↓, METTL3↓, METTL14↓, FTO↑	–	Differentially methylated genes are mainly associated with the *TGFβ* signaling pathway (downregulated genes) and the *axon* signaling pathway (upregulated genes)	[82]
UUO mice HK2	METTL3↑	HNRNPA2B1/miR-21-5p/SPRY1/ERK/NF-kB	Driving inflammation and the development of obstructive renal fibrosis	[83]
UUO mice V40 MES13	METTL3	AI662270/METTL3/CTGF	Activating interstitial fibroblasts and driving renal fibrosis	[84]
Patients with obstructive nephropathy UUO mice TGF-β1-induced HK2	METTL3↑, METTL14↑, WTAP↑	MALAT1/miR-145/FAK	Inhibiting METTL3 can attenuate TGF-β1-induced EMT and decrease αSMA expression	[85]
Patients with diabetic nephropathy UN/HFD/STZ-induced mice HG-induced SV40-MES-13	High glucose → METTL3↓	YTHDF1/NDS2	Overexpression of METTL3 alleviates renal impairment and renal fibrosis in DN	[86]
Diabetic kidney disease STZ-induced mice HG-induced HK2	METTL14	TUG1/MAPK1	Knockdown of METTL14 or overexpression of TUG1 protects diabetic kidney disease (DKD) mice from renal lesions and renal fibrosis induced by STZ	[87]
Renal tubular-specific Atg7-deficient and SQSTM1-deficient mice canagliflozin-induced mice, UUO mice TGF-β1-induced HK2	canagliflozin → FTO↓	SQSTM1/autophagy/STAT6	FTO overexpression weakens the impact of canagliflozin on autophagy induction and eliminates the protective effect of canagliflozin against renal fibrosis	[88]
Patients with tubulointerstitium fibrosis Renal tubular-specific Kcnk5 knockout mice Fto knockdown mice UUO/UIR mice HK2	FTO↑	Kcnk5/TASK-2	Blocking FTO can weaken cell cycle arrest and renal fibrosis	[89]
UUO mice TGF-β1-induced HK-2, TGF-β1-induced HKC-8	FTO↑	GAS5	Knocking down FTO inhibits the TGF-β1 and UUO-induced EMT and inflammatory response, leading to a decrease in αSMA and COL1 expression	[90]
UUO mice, URI mice TGF-β1-induced HK2	ALKBH5↓	genistein/ALKBH5/Snail	ALKBH5 knockdown enhanced the mesenchymal phenotype marker αSMA and snail expression	[91]
Alkbh5fl/flKspCre mice IRI mice mRTECs	ALKBH5	IGF2BP2/CCL28/Treg/inflammatory cell axis	Inhibiting ALKBH5 can prevent ischemia–reperfusion-induced AKI and fibrosis	[92]
CKD patients UUO mice SV40-MES-13	YTHDF1↑	YAP	Knocking down YTHDF1 alleviates the progression of renal fibrosis	[93]

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induced m6A modification of *hsa_circ_0000672* and *hsa_circ_0005654* in lung fibroblasts through *METTL3*, and this process involved cooperation with *eIF4A3*. Consequently, lung fibroblast proliferation, migration, and activation were induced, ultimately leading to pulmonary fibrosis [43]

Additionally, upregulation of *ALKBH5* in mice exposed to silica and *TGF-β1*-activated lung fibroblasts inhibited fibroblast activation. Mechanistically, *ALKBH5* demethylated *pri-miR-320a-3p*, blocking its maturation process and preventing its regulation of fibrosis through *FOXM1* mRNA 3'-UTR targeting. Furthermore, *ALKBH5* could directly regulate *FOXM1* in an m6A-dependent manner, promoting silica-induced pulmonary fibrosis [47].

Carbon black

In another study, the fibrosis-promoting factor, carbon black (CB), reduced the m6A modification of *pri-miRNA-126* and its binding with the RNA-binding protein *DiGeorge syndrome critical region gene 8* (*DGCR8*). This led to a decrease in mature miRNA-126 and activation of the *PI3K/AKT/mTOR* pathway, driving an increase in levels of pulmonary fibrosis markers, including *αSMA*, *fibronectin*, *COL I*, and *hydroxyproline*. [48]

Cardiac fibrosis

"writers" in cardiac fibrosis

Research related to cardiac fibrosis is shown in Table 2. In numerous studies, *METTL3* has been consistently shown to play a promoting role in cardiac fibrosis. Upregulation of *METTL3* was observed in human atrial fibrillation cardiac tissue [50–52], heart tissues of myocardial infarction mouse models [49, 51, 52], and TGFβ1-induced cardiac fibroblasts [49–52].

From a mechanistic perspective, silencing *METTL3* alleviated TGF-β1-induced cell proliferation, FMT, and collagen production in CFs, and reduced the m6A modification levels of fibrosis-related genes [49]. Additionally, *METTL3* downregulates AR expression through an m6A-*YTHDF2* dependent mechanism, promoting glycolysis and cardiac fibroblast proliferation, which ultimately leads to cardiac fibrosis [50]. Furthermore, silencing *METTL3* has been observed to downregulate the expression of *IGFBP3*, inhibiting the activation of CFs and reducing the degree of cardiac fibrosis [51]. Moreover, *METTL3* increases m6A methylation of *GAS5*, leading to *YTHDF2* binding to *GAS5* and inhibiting its expression, which further promotes CF proliferation, migration, and mitochondrial fission [52]. In addition to its fibrotic effects, *METTL3* is also involved in cardiac fibrosis and myocardial cell apoptosis by increasing the m6A level of *TNC* mRNA [53].

Furthermore, in the heart tissues of the myocardial infarction mouse model and *TGF-β1*-induced CFs, the expression of *MetBil* (METTL3 binding lncRNA) is significantly increased. *MetBil* overexpression enhances collagen deposition and CFs proliferation [54].

"erasers" in cardiac fibrosis

FTO plays a protective role against myocardial fibrosis. In heart failure mammalian hearts and hypoxic cardiomyocytes, *FTO* expression is reduced, leading to increased RNA m6A levels and impaired myocardial contractile function. Increased *FTO* expression in heart failure mice selectively demethylates contractile transcripts in the heart, preventing their degradation, thus mitigating the ischemia-induced increase in m6A and the decline in cardiac contractile function. This, in turn, reduces fibrosis and enhances angiogenesis [55]. In the diabetic cardiomyopathy mouse model, there is an increase in m6A levels and a downregulation of *FTO*. *FTO* overexpression can improve cardiac function in diabetic cardiomyopathy mice by reducing myocardial fibrosis and cardiomyocyte hypertrophy [56]. *circCELF1* upregulates the expression of *FTO*, reducing m6A modification on *DKK2* mRNA, inhibiting the binding of *miR-636* to *DKK2*, and promoting *DKK2* expression, thereby inhibiting the progression of myocardial fibrosis [57].

However, in another study, *FTO* played a contrasting role: HFpEF+Exercise training (EXT) mice showed higher m6A levels and downregulated *FTO* levels. *FTO* overexpression promoted myocardial cell apoptosis, myocardial fibrosis, and cardiomyocyte hypertrophy, thereby counteracting the benefits of exercise in HFpEF+EXT mice [58].

"readers" in cardiac fibrosis

YTHDF2 deficiency results in declined cardiac function in elderly mice, exacerbating the cardiac dysfunction and increasing fibrosis induced by the pressure overload from TAC surgery [59].

lncRNA *Airn* binds to *IMP2*, protecting it from degradation. The retained *IMP2* recognizes m6A modifications on *p53* mRNA, leading to increased stability and protein expression. This reduces *α-SMA* and *COL I* expression in high glucose-induced CFs, thereby reducing cardiac fibrosis in diabetic mice. Silencing *METTL3* decreases m6A modification on *p53*, resulting in reduced stability and downregulation of *p53* mRNA in CFs [60].

Pulmonary arterial hypertension

YTHDF1 interacts with *Foxm1* mRNA and upregulates *Foxm1* protein levels by enhancing translation efficiency through an m6A-dependent mechanism. This promotes the proliferation of hypoxic pulmonary arterial smooth

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muscle cells (PASMC) and the expression of proliferation markers. Silencing *YTHDF1* alleviates pulmonary vascular changes and fibrosis [61].

Hepatic fibrosis

Research related to hepatic fibrosis is shown in Table 3. In the study of hepatic fibrosis progression and reversal, dynamic analysis of m6A methylation profiles revealed that during hepatic fibrosis, m6A methylation differences are primarily enriched in processes related to oxidative stress and cytochrome metabolism, while in hepatic fibrosis reversal, they are mainly associated with immune response and apoptosis [62].

"writers" in hepatic fibrosis

Regarding the role of *METTL3* in hepatic fibrosis, it is upregulated in lipopolysaccharide (LPS)-activated THP-1 macrophages and plays a role in promoting the expression of fibrotic proteins, such as *COL I*, *α-SMA*, and *fibronectin*, through the *Sp1/TGF-β1/Smad* signaling pathway [63]. Additionally, *METTL3* is upregulated in the CCl4-induced mouse liver fibrosis model and IFN-γ/LPS-activated M1 macrophages, where it promotes macrophage pyroptosis and inflammation via the *PTBP1/USP8/TAK1* axis by increasing *MALAT1* levels through m6A modification, thereby exacerbating liver fibrosis [64]. Silencing *METTL3* in HSCs leads to inhibited HSC activation and reduced liver fibrosis. Mechanistically, silencing *METTL3* increases the stability and protein expression of *Lats2* mRNA, which leads to increased *YAP* phosphorylation, inhibiting *YAP* nuclear translocation and ultimately resulting in decreased expression of pro-fibrotic genes [65].

In CdCl2-exposed mouse liver tissue, *METTL3* expression decreases over time and correlates with the severity of liver injury. Liver-specific overexpression of *METTL3* in mice attenuates CdCl2-induced hepatic steatosis and fibrosis; while, METTL3 overexpression improves CdCl2-induced cytotoxicity and activation of HSCs [66]. Long-term exposure to chronic corticosterone (CORT) induces hepatic inflammation and fibrosis in chickens and increases the levels of various *heat shock proteins* (*HSPs*) mRNA and m6A methylation [67].

In non-alcoholic steatohepatitis (NASH) rats and LPS-treated Kupffer cells (KCs), *METTL3/METTL14* is upregulated; while, *FTO* is downregulated. After LPS stimulation, *NF-κB p65* directly activates *METTL3* and *METTL14*, promoting cap-independent translation of *TGF-β1* through m6A modification in the 5′UTR region. This upregulates *TGF-β1* and exacerbates *TGF-β1*-mediated stellate cell activation, promoting the transition from NASH to liver fibrosis [68]. *Acid-sensitive ion channel 1a* (*ASIC1a*) regulates the processing of *miR-350*

through *METTL3*-dependent m6A modification. Mature *miR-350* targets *SPRY2* and further promotes liver fibrosis through the *PI3K/KT* and *ERK* pathways [69].

In patients with biliary atresia, there is an increase in m6A levels, and the expression of *METTL3*, *METTL14*, and *WTAP* is upregulated; while, *ALKBH5* is downregulated. The overexpression of *METTL3* and *METTL14* promotes the expression of *COL1A1*, *MMP2*, and *THY1*. *THY1* may play a role in cholestatic fibrosis by interacting with the *ITGAX/ITGB2* complex in bone marrow cells [70].

METTL16 is upregulated in the liver tissues of chronic hepatitis B (CHB) with severe fibrosis. Silencing *METTL16* in HSCs downregulates the m6A modification level of *HLA-DPB1* mRNA, and it is involved in the progression of fibrosis in CHB [71].

In Sorafenib, erastin, and RSL3-induced ferroptosis of HSCs, *METTL4* expression is upregulated, and *FTO* is downregulated. *YTHDF1* recognizes m6A binding sites and stabilizes *BECN1* mRNA, triggering autophagy activation. Inhibition of m6A modification impairs erastin-induced ferroptosis in CCl4-induced liver fibrosis in mice and reverses the beneficial effect of erastin on liver fibrosis improvement [72].

The differentially expressed m6A genes in liver fibrosis mice are closely associated with processes such as the endoplasmic reticulum stress response, *PPAR* signaling pathway, and *TGF-β* signaling pathway. In liver fibrosis mice, the expression of *WTAP*, *ALKBH5*, and *YTHDF1* is reduced. Decreased expression of *WTAP* leads to an increase in *αSMA* and *COL I* expression, promoting HSC activation and inducing the occurrence of liver fibrosis [73]. However, in another study, *WTAP* is highly expressed in liver fibrosis and it targets the 3′-UTR of *Ptch1* mRNA to increase its stability. *N-acetyl-seryl-aspartyl-lysyl-proline* (*AcSDKP*) reduces the expression of *WTAP* and decreases the stability of *Ptch1* mRNA, thereby exerting an anti-fibrotic effect [74].

"erasers" in hepatic fibrosis

FTO downregulation and consequent upregulation of m6A modification are essential for DHA-induced autophagy activation and HSC ferroptosis. *YTHDF1* upregulation and *FTO* downregulation are involved in DHA-induced HSC ferroptosis by increasing the stability of *BECN1* mRNA. Knocking down *YTHDF1* can prevent this process, ultimately reducing the therapeutic effect of DHA on liver fibrosis [75].

In human fibrotic liver tissues and CCl4-induced mouse liver fibrosis, elevated m6A levels and decreased *ALKBH5* expression are observed. *ALKBH5* functions in a *YTHDF1*-dependent manner to inhibit mitochondrial fission, HSC proliferation, and migration by reducing

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Drp1 m6A modification. This regulatory process leads to a reduction in *αSMA* and *COL I* expression, contributing to improved liver fibrosis [76]. *ALKBH5* is downregulated in both human and mouse liver fibrotic tissues. Its overexpression leads to reduced *αSMA* and *COL I* expression, decreased collagen protein accumulation, and interstitial fibrosis. *ALKBH5*'s beneficial effects on liver fibrosis are achieved through m6A-dependent *PTCH1* activation, inhibiting HSC activation [77].

ALKBH5 is upregulated in radiation-induced HSCs. It mediates m6A demethylation of *toll-interleukin 1 receptor domain-containing adaptor protein* (*TIRAP*) mRNA and regulates *TIRAP* expression in a *YTHDF2*-dependent manner, promoting HSC activation through the *TIRAP/NF-κB* pathway. *ALKBH5* also regulates CCL5 secretion, facilitating monocyte recruitment and M2 polarization, further enhancing *ALKBH5* expression and *TIRAP/NF-κB* pathway activation. Irradiated HSCs educate monocytes, leading to HSC activation and reduced HCC radiosensitivity through CCL20 secretion. Blocking the *ALKBH5-CCR6* axis can alleviate radiation-induced liver fibrosis (RILF) and improve HCC radio sensitivity [78].

"readers" in hepatic fibrosis
A study suggests that DNA methylation (5mC) is essential for the initiation stage of HSC activation (myofibroblast transdifferentiation); while, m6A is crucial for the perpetuation stage of HSC activation (excessive ECM production). *YTHDF1* enhances *COL* I A1 protein production by stabilizing its mRNA. Silencing *YTHDF1* can alleviate CCl4-induced mouse liver fibrosis by inhibiting collagen synthesis [79].

YTHDF3 induces *PRDX3* translation in an m6A-dependent manner, leading to the upregulation of *PRDX3* expression. Through the mitochondrial reactive oxygen species (ROS)/*TGF-β1/Smad2/3* pathway, it inhibits HSC activation, exerting a protective effect against liver fibrosis [80].

CCl4-induced liver fibrosis and primary HSCs exhibit elevated levels of methylation, increased expression of *ZC3H13*, and decreased expression of *FTO*. Lowering m6A levels can reduce the protein levels of *αSMA* and *COL I*, thus improving liver fibrosis. *YTHDC1* is upregulated in CCl4-induced liver fibrosis and primary HSCs, promoting the degradation of *nuclear receptor subfamily 1 group d member 1* (*NR1D1*) mRNA. The absence of *NR1D1* inhibits phosphorylation of *DRP1S616*, leading to weakened mitochondrial fission function, increased mtDNA release, activation of the *cGAS* pathway, and promotion of liver fibrosis progression. DHA alleviates liver fibrosis by promoting the proteasomal degradation of *YTHDC1* in activated HSCs, restoring *NR1D1* expression [81].

Renal fibrosis
"writers" in renal fibrosis
Research related to renal fibrosis is shown in Table 4. In renal fibrosis, the UUO mouse model shows decreased m6A levels and reduced *METTL3/METTL14* expression; while, *FTO* is upregulated. Differentially methylated genes are mainly associated with the *TGFβ* signaling pathway (downregulated genes) and the *axon* signaling pathway (upregulated genes) [82]. However, another study using the UUO model found that *METTL3* upregulation increased *pri-miR-21* m6A modification, promoting *miRNA-21-5p* maturation. This triggered the *SPRY1/ERK/NF-κB* pathway, driving inflammation and the development of obstructive renal fibrosis. And *HNRNPA2B1* may be involved in recognizing m6A modifications in *pri-miR-21* and facilitating the maturation of *miR-21-5p* [83].

Long noncoding RNA *AI662270* promotes the transcriptional stage of *CTGF* expression by recruiting *METTL3* to the *CTGF* promoter and depositing m6A modifications on nascent mRNA. This activation of *CTGF* drives the activation of interstitial fibroblasts and promotes renal fibrosis [84]. TGF-β1 treatment upregulates *METTL3*, *METTL14*, and *WTAP* in HK2 cells. Inhibiting *METTL3* reduces *MALAT1* expression and contributes to DHA's anti-fibrotic effect against TGF-β1-induced renal fibrosis through the *MALAT1/miR-145/FAK* axis [85]. High glucose treatment in mouse mesangial cells (SV40-MES-13) results in decreased m6A levels and downregulation of *METTL3* expression. Overexpression of *METTL3* enhances the stability of *Nuclear receptor-binding SET domain protein 2* (*NSD2*) mRNA through *YTHDF1*, promoting its expression. Consequently, this alleviates kidney impairment and renal fibrosis in diabetic nephropathy [86].

METTL14 reduces the stability of *TUG1* mRNA by increasing its m6A modification, thereby inhibiting *TUG1* expression. *TUG1*, in turn, interacts with *LIN28B*, leading to the inactivation of the *MAPK1/ERK* signaling pathway. Knockdown of *METTL14* or overexpression of *TUG1* protects diabetic kidney disease (DKD) mice from renal damage and renal fibrosis induced by streptozotocin (STZ) [87].

"erasers" in renal fibrosis
Canagliflozin increases m6A levels in HK2 cells while reducing *FTO* expression. *FTO* overexpression weakens the effect of canagliflozin on autophagy induction, leading to decreased stability of *SQSTM1* mRNA. Deletion of *SQSTM1* abolishes the protective effect of canagliflozin against renal fibrosis. Therefore, canagliflozin combats renal lipotoxicity and interstitial fibrosis through

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the m6A-modified *SQSTM1*/autophagy/*STAT6* axis [88]. In UUO kidneys, the expression of *FTO*, *METTL3*, and *METTL14* increases, while *ALKBH5* expression decreases. In kidneys subjected to unilateral ischemia–reperfusion (UIR) and TGF-β1-treated HK-2 cells, *FTO* expression is elevated. In vivo and in vitro blocking of *FTO* can reduce the upregulation of *Kcnk5*, encoding *TWIK-related acid-sensitive K+ channel-2* (*TASK-2*), cell cycle arrest, and renal fibrosis. *TASK-2* is upregulated through *FTO*-mediated *Kcnk5* demethylation and is activated by intracellular alkalization, leading to reduced intracellular K+ concentration, G2/M cell cycle arrest, and exacerbation of renal fibrosis [89]. *FTO* expression increases in TGF-β1-treated HK-2 and HKC-8 cells, as well as in UUO mouse kidney tissues. *FTO* suppresses the expression of lncRNA *GAS5* by reducing its m6A modification. Knockdown of *FTO* inhibits TGF-β1 and UUO-induced EMT and inflammatory response, resulting in reduced expression of αSMA and *COL I* [90].

In the UUO model, the total m6A level increases; while, *ALKBH5* expression decreases. Knocking down *ALKBH5* suppresses E-cadherin expression and promotes *αSMA* and *Snail* levels. Genistein improves renal fibrosis by restoring *ALKBH5* expression and regulating EMT [91]. Another study found that inhibiting *ALKBH5* increases the m6A modification of CCL28 mRNA, leading to enhanced stability of CCL28 through recognition by IGF2BP2. This upregulates CCL28 levels, recruiting Tregs (regulatory T cells), which protect the kidneys from inflammation and immune cell infiltration. As a result, inhibiting *ALKBH5* has a protective effect against ischemia–reperfusion-induced acute kidney injury (AKI) and fibrosis [92].

"readers" in renal fibrosis
YTHDF1 is highly expressed in human fibrotic kidneys and upregulated in fibrotic mouse kidneys induced by UUO, high-dose folic acid administration, or the unilateral ischemia–reperfusion injury (IRI). Knocking down *YTHDF1* in cultured cells induced by TGF-β treatment and UUO mouse models alleviates the progression of renal fibrosis. This effect is likely mediated by *YTHDF1*'s regulation of Yes-associated protein (*YAP*) [93].

Retinal
During the process of laser-induced choroidal neovascularization and subretinal fibrosis in mice, *METTL3* is upregulated in retinal pigment epithelial (RPE) cells. *METTL3* enhances the stability of *HMGA2* mRNA through m6A modification, leading to an increase in *HMGA2* protein expression. This activation of *HMGA2* induces the transcription factor *SNAIL*, promoting EMT.

However, silencing *METTL3* effectively reduces subretinal fibrosis in the retina [94].

In patients with proliferative vitreoretinopathy (PVR), the expression of *METTL3* is reduced in retinal pigment epithelial cells. The expression of *METTL3* is downregulated in ARPE-19 cells after EMT. Overexpression of *METTL3* inhibits cell proliferation and weakens the ability of TGF*β1* to induce EMT by modulating the *Wnt/β-catenin* pathway. Intravitreal injection of cells overexpressing *METTL3* delays the occurrence of PVR [95].

High glucose upregulates the m6A modification level of *PARP1* mRNA in human retinal microvascular endothelial cells (hRMECs) and downregulates *YTHDF2*. Overexpression of *YTHDF2* reduces the expression of *Poly (ADP-ribose) polymerase 1* (*PARP1*) in hRMECs in an m6A-dependent manner, enhances hRMEC viability, and prevents glucose-induced inflammation, fibrosis, and angiogenesis [96].

Oral
In Oral submucous fibrosis (OSF) tissues, there is an increase in m6A modification levels. Arecoline promotes the expression of *METTL3* and *METTL14* through *TGFβ* signaling. Silencing *METTL14* reverses the effects of arecoline on Hacat cell proliferation and apoptosis by inhibiting *MYC* m6A modification and reducing *TIMP1* expression [97].

m6A modification in non-fibrotic collagen-related diseases
Osteoarthrosis
m6A modification promotes intervertebral disc degeneration [98] and osteoarthritis [99, 100], and enhances chondrocyte differentiation [101] and osteoblast differentiation [102].

In degenerative human endplate cartilage tissue, m6A levels are increased. Mechanical tension stimulation increases *METTL3*-mediated m6A levels in human endplate chondrocytes. *METTL3* mediates m6A modification of *SOX9* mRNA and disrupts the stability of *SOX9* mRNA, leading to the inhibition of downstream *COL II α1* expression. Suppression of *METTL3* expression in endplate cartilage can alleviate mechanical imbalance-induced intervertebral disc degeneration [98].

In ATDC5 chondroprogenitor cells treated with IL-1β, m6A levels and *METTL3* expression increase. Silencing *METTL3* reduces IL-1β-induced cell apoptosis, levels of inflammatory cytokines, and *NF-κB* signaling in chondrocytes. METTL3 silencing promotes extracellular matrix degradation by reducing *MMP13* and *COL X* expression, and increasing aggrecan and *COL II* expression [99]. Similarly, IL-1β stimulation in C28/

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I2 chondrocyte cell line results in increased m6A levels and *METTL3* expression, along with decreased ALKBH5 expression. Overexpression of *ALKBH5* downregulates IL-1β-induced *MMP13* and *COL X* expression, while upregulating *COL II* and *aggrecan* expression [100].

METTL3, *METTL14*, and m6A modification levels are increased in synovium-derived mesenchymal stem cells (SMSCs) during chondrogenic differentiation. Knockdown of *METTL3* inhibits chondrogenic differentiation, downregulates *SOX9*, *ACAN*, and *COL II α1*, and increases *MMP3*, *MMP13*, and *GATA3* expression [101]. *METTL3*-mediated m6A methylation of LncRNA *MIR99AHG* increases the expression of *Osterix*, *COL I α1*, *bone sialoprotein*, and *RUNX2* by targeting *miR-4660*, enhancing the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) [102].

Skin
In the mouse model of bleomycin-induced scleroderma, the differentially m6A-hypermethylated mRNAs were most significantly associated with growth hormone synthesis, secretion, and action, insulin secretion, and amphetamine addiction. On the other hand, the differentially m6A-hypomethylated mRNAs were most significantly associated with rheumatoid arthritis, Toll-like receptor signaling pathway, and amoebiasis [103]. In keloid tissue, m6A modification was decreased, and the expression of m6A demethylase *FTO* was increased. *FTO* overexpression in skin fibroblasts stimulated fibroblast migration and increased the expression of *COL I α1* and *α-SMA*. *FTO* upregulates *COL I α1* expression by regulating its m6A modification and stabilizing mRNA, thus promoting keloid formation. [104]. m6A sequencing and RNA sequencing revealed that differentially methylated m6A-related genes were associated with fibrosis-related pathways in hyperplastic scars compared to normal skin. Highly methylated genes were mainly related to the *P13K-Akt* signaling pathway, focal adhesion, and ECM-receptor interaction. On the other hand, lowly methylated genes were mainly associated with the *MAPK* signaling pathway and the *NF-κB* signaling pathway [105].

Cancer
The role of m6A varies in different types of tumors. In U87 and U251 cells, *METTL3* reduces the methylation level of *COL IV α1*, upregulates its expression, and stimulates the malignant development of glioblastoma [106]. In lung cancer, cancer-associated fibroblasts (CAFs) derived from lung squamous cell carcinoma (LUSC) upregulate the m6A modification of *COL X α1* by increasing *METTL3* expression, stabilizing *COL X α1* expression, promoting LUSC cell proliferation, and inhibiting apoptosis-induced oxidative stress [107]. Silencing *METTL3* can upregulate the expression of *COL III α1* chain by increasing m6A levels, ultimately promoting the metastasis of triple-negative breast cancer tumor cells [108]. lncRNA *NIFK-AS1* is highly expressed in HCC tissues and cells, and this upregulation is dependent on METTL3-mediated m6A methylation. *NIFK-AS1* affects HCC progression through the *NIFK-AS1/miR-637/AKT1* axis, regulating *MMP7* and *MMP9* expression. Knockdown of *NIFK-AS1* inhibits HCC cell proliferation, colony formation, migration, and invasion [109]. In prostate cancer tissues, however, METTL3 is highly expressed and can regulate the expression of *integrin β1* (*ITGB1*) through m6A modification, thereby affecting the binding of *ITGB1* to *COL I* and promoting prostate cancer bone metastasis。 [110]

Cerebrovascular
Downregulation of m6A reader *protein proline-rich coiled-coil 2B* (*PRRC2B*) mediates selective splicing of *COL XIIα1* chain in an m6A-dependent manner and regulates the decay of *MMP14* and *ADAM metallopeptidase domain 19* (*ADAM19*) mRNA in an m6A-independent manner, promoting hypoxia-induced endothelial cell migration. Conditional knockout of *PRRC2B* in endothelial cells enhances hypoxia-induced vascular remodeling and cerebral blood flow redistribution, thereby alleviating hypoxia-induced cognitive decline [111].

Conclusion and perspectives
In recent years, RNA epigenetics, particularly m6A modification, has emerged as a prominent research area. Among more than 100 different RNA modifications, m6A stands out as the most abundant in eukaryotic cells. This dynamic and reversible modification is meticulously controlled by "writers" and "erasers," while "readers" play a crucial role in its recognition and functionality. The significance of m6A modification in regulating collagen metabolism across various diseases cannot be overstated. This comprehensive review aims to provide an overview of the functions and mechanisms of m6A modification in organ fibrotic diseases and non-fibrotic collagen-related conditions. While the majority of research has focused on the core methyltransferase *METTL3*, there have been some investigations into other methyltransferases and demethylases, albeit with fewer studies dedicated to m6A readers.

In summary, the field of m6A regulation in collagen metabolism holds tremendous potential for further exploration. Recent advances have been made in elucidating the role of m6A in collagen regulation; however, many aspects of m6A modulators in collagen-related diseases remain unexplored, necessitating further inquiry.

Future research should prioritize the following areas: 1. Investigating the roles of other m6A methyltransferases and demethylases in collagen metabolism and their impact on collagen-related diseases. 2. Exploring the functions of various m6A readers and their contributions to collagen regulation. 3. Unraveling the intricate molecular mechanisms by which m6A modification regulates collagen synthesis, deposition, and degradation. 4. Developing potential therapeutic interventions targeting m6A modification for treating collagen-related diseases.

In conclusion, ongoing investigations into m6A modification in collagen metabolism offer promising directions for future research. Sustained efforts in this area will undoubtedly deepen our understanding of the regulatory mechanisms of m6A in collagen-related diseases and open up new possibilities for therapeutic applications.

Abbreviations

m6A	N6-methyladenosine
ECM	Extracellular matrix
TGF-β	Transforming growth factor beta
αSMA	α-Smooth muscle actin
CTGF	Connective tissue growth factor
MMPs	Matrix metalloproteinases
TIMPs	Tissue inhibitors of metalloproteinases
METTL	Methyltransferase like
WTAP	Wilms' tumor 1-associated protein
FTO	Fat mass and obesity-associated protein
ALKBH5	AlkB homolog 5
YTHDF1/2/3	YTH domain-containing family protein
YTHDC1/2	YTH domain-containing protein
IGF2BPs	Human insulin-like growth factor 2 mRNA-binding proteins
COL	Collagen
SAM	S-adenosylmethionine
SRSF3	Serine/arginine-rich splicing factor 3
IPF	Idiopathic pulmonary fibrosis
BLM	Bleomycin
FMT	Fibroblast-to-myofibroblast transition
KCNH6	Potassium channel, voltage gated Kcnh6
CDH1	Cadherin 1
EMT	Epithelial–mesenchymal transition
Nrf2	Nuclear factor erythroid 2-related factor 2
Atg13	Autophagy-related 13
ULK	Unc-51 like autophagy activating kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3	NOD-like receptor protein 3
eIF4A3	Eukaryotic translation initiation factor 4A3
FOXM1	Forkhead box M1
CB	Carbon black
DGCR8	DiGeorge syndrome critical region gene 8
CF	Cardiac fibrosis
TAC	Tacrolimus
ISO	Isoproterenol
GAS5	Growth arrest-specific 5
TNC	Tenascin C
CELF1	CUGBP Elav-like family member 1
DKK2	Dickkopf WNT signaling pathway inhibitor 2
HFpEF	Heart failure with preserved ejection fraction
EXT	Exercise training
IMP2	Insulin-like growth factor 2 mRNA-binding protein 2
PASMC	Pulmonary arterial smooth muscle cells
LPS	Lipopolysaccharide
Sp1	Specificity protein 1
Smad	Sma and Mad related proteins
PTBP1	Polypyrimidine tract-binding protein 1
USP8	Ubiquitin-specific protease 8
TAK1	TGF-β activated kinase 1
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
HSC	Hepatic stellate cells
Lats2	Large tumor suppressor kinase 2
YAP	Yes-associated protein
CORT	Chronic corticosterone
HSPs	Heat shock proteins
NASH	Non-alcoholic steatohepatitis
KCs	Kupffer cells
ASIC1a	Acid-sensitive ion channel 1a
SPRY2	Sprouty RTK signaling antagonist 2
PI3K/KT	Phosphoinositide 3-kinase/protein kinase B
ERK	Extracellular signal-regulated kinase
THY1	Thy-1 cell surface antigen
ITGAX	Integrin αX
ITGB2	Integrin β2
CHB	Chronic hepatitis B
HLA-DPB1	Major histocompatibility complex, class II, DP beta 1
BECN1	Beclin 1
PPAR	Peroxisome proliferator-activated receptor
AcSDKP	*N*-acetyl-seryl-aspartyl-lysyl-proline
PTCH1	Patched 1
TIRAP	Toll-interleukin 1 receptor domain-containing adaptor protein
RILF	Radiation-induced liver fibrosis
PRDX3	Peroxiredoxin 3
ROS	Reactive oxygen species
ZC3H13	Zinc finger CCCH-type containing 13
NR1D1	Nuclear receptor subfamily 1 group D member 1
DRP1S616	Dynamin-related protein 1 serine 616
cGAS	Cyclic GMP-AMP synthase
UUO	Unilateral ureteral obstruction
SPRY1	Sprouty RTK signaling antagonist 1
ERK	Extracellular signal-regulated kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
HNRNPA2B1	Heterogeneous nuclear ribonucleoprotein A2/B1
NSD2	Nuclear receptor-binding SET domain protein 2
TUG1	Taurine upregulated gene 1
MAPK1	Mitogen-activated protein kinase 1
DKD	Diabetic kidney disease
STZ	Streptozotocin
SQSTM1	Sequestosome 1
UIR	Unilateral ischemia–reperfusion
TASK-2	TWIK-related acid-sensitive K+ channel-2
AKI	Acute kidney injury
IRI	Ischemia–reperfusion injury
YAP	Yes-associated protein
RPE	Retinal pigment epithelial
HMGA2	High mobility group AT-Hook 2
PVR	Proliferative vitreoretinopathy
PARP1	Poly(ADP-ribose) polymerase 1
hRMECs	Human retinal microvascular endothelial cells
OSF	Oral submucous fibrosis
MYC	MYC proto-oncogene, BHLH transcription factor
SOX9	SRY-box transcription factor 9
SMSC	Synovium-derived mesenchymal stem cells
GATA3	GATA binding protein 3
RUNX2	Runt-related transcription factor 2
BMSCs	Bone marrow mesenchymal stem cells
CAFs	Cancer-associated fibroblasts
LUSC	Lung squamous cell carcinoma
ITGB1	Integrin β1
PRRC2B	Proline-rich coiled-coil 2B
ADAM19	ADAM metallopeptidase domain 19

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Availability of data and materials
No datasets were generated or analyzed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
No ethical approval is required.

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