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EDITED BY

Qingqing Wei,
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REVIEWED BY

Domitilla Mandatori,
G. d'Annunzio University of Chieti and
Pescara, Italy
Tapan A. Patel,
University of Nebraska Medical Center,
United States

*CORRESPONDENCE

Bolívar Samir,
✉ samirbolivar@mail.uniatlantico.edu.co

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Epigenetic modifications in cardiac fibrosis: recent evidence of new pharmacological targets

Marian Pérez¹, Mónica Gómez², Jairo Castellar-López³,
Patricio Araos⁴, Evelyn Mendoza-Torres² and Samir Bolívar^{1*}

¹Molecular Pharmacology Laboratory, Pharmacy and Pharmacology Research Group, Universidad del Atlántico, Barranquilla, Colombia, ²Faculty of Health, Exact and Natural Sciences, Universidad Libre de Colombia, Seccional Barranquilla, Barranquilla, Colombia, ³Faculty of Health Sciences, Universidad de la Guajira, Riohacha, Colombia, ⁴Institute of Biomedical Sciences, Universidad Autonoma de Chile, Santiago de Chile, Chile

Cardiac fibrosis (CF) is characterized by the excessive deposition of collagen types I (COI I) and III (COI III), primarily mediated by cardiac fibroblasts (CFB). Recent advances in epigenetic research have enhanced our understanding of the molecular mechanisms underlying CF and have facilitated the identification of novel therapeutic strategies targeting key proteins and signaling pathways involved in its progression. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs (ncRNAs), are structural and chemical alterations that regulate gene expression and cellular responses without changing the DNA sequence. Investigating the role of epigenetic enzymes in CF may reveal promising pharmacological targets. This review summarizes current evidence on epigenetic modifications implicated in CF and discusses their potential as therapeutic targets for modulating this pathological process.

KEYWORDS

cardiac fibrosis, cardiac fibroblasts, epigenetic modifications, cardiovascular epigenetics, non-coding RNA, DNA methylation

1 Introduction

Epigenetics refers to heritable changes in gene expression that are not caused by alterations in the DNA sequence but rather by chemical modifications at the DNA level, such as DNA methylation and histone modifications. These modifications influence DNA accessibility and chromatin structure, thereby regulating gene expression, cell differentiation, X-chromosome inactivation, and genomic stability (Loscalzo and Handy, 2014; Cao et al., 2014; Ling and Rönn, 2019). Chromatin is composed of DNA and histones, which undergo various modifications, including phosphorylation, methylation, acetylation, propionylation, and acylation. Additionally, DNA and RNA can be chemically modified through methylation to regulate gene expression (Sun et al., 2022).

Epitranscriptomic regulation refers to post-transcriptional chemical modifications in coding and ncRNAs that modulate their function and contribute to cellular homeostasis (Orsolic et al., 2023). RNA in all living organisms can undergo over 100 distinct post-transcriptional modifications, among which N⁶-methyladenosine (m⁶A) is the most abundant internal modification in eukaryotic mRNA. This modification influences mRNA metabolism and translation, directing transcripts toward different cellular fates by promoting their processing, stability, or degradation (Zhao et al., 2017).

Post-translational modifications (PTMs) occur on specific amino acid residues within the regulatory domains of target proteins, influencing their stability and function. These regulatory regions, known as degrons, are modulated by PTMs that act as molecular signals, either accelerating protein degradation (PTM-activated degrons) or inhibiting degradation to stabilize proteins (PTM-inactivated degrons) (Lee et al., 2023). Among the most extensively studied PTMs are histone modifications. Given that chromatin serves as the template for all DNA-mediated processes, histone modifications play a crucial role in regulating chromatin structure and function. For example, a combination of H4K8 acetylation, H3K14 acetylation, and H3S10 phosphorylation is associated with transcriptional activation, whereas H3K9 trimethylation and the absence of H3 and H4 acetylation correlate with transcriptional repression (Peterson and Laniel, 2004).

The reversible nature of these chemical modifications makes epigenetic regulators, proteins responsible for “writing,” “erasing,” and “reading” the epigenetic code, attractive therapeutic targets (Esteller, 2017). This potential has been increasingly explored in the context of cardiovascular diseases, including CF, a condition characterized by excessive extracellular matrix (ECM) deposition in the myocardium following cardiac injury (Xu et al., 2022). The development and progression of CF involve complex molecular and cellular mechanisms, in which epigenetic regulation plays a fundamental role in both physiological and pathological cardiac remodeling (Aguado-Alvaro et al., 2024; Liu et al., 2023).

In CF, epigenetic dysregulation contributes to maladaptive remodeling by promoting excessive ECM accumulation and CFBs activation. Alterations in DNA methylation and histone acetylation have been implicated in these processes. Notably, histone deacetylase (HDAC) inhibitors have demonstrated anti-fibrotic effects by reducing inflammation and cardiac hypertrophy, thereby attenuating fibrosis-associated remodeling (Loscalzo and Handy, 2014). Additionally, the transition of CFBs into myoFIBs, a hallmark of fibrosis, has been linked to changes in DNA methylation. Given the central role of histone deacetylation in maladaptive remodeling, HDAC inhibitors are being explored as potential therapeutic agents (Loscalzo and Handy, 2014; Cao et al., 2014).

Recent evidence indicates that epigenetic modifications affecting both DNA and RNA are critically involved in CF progression by regulating profibrotic biomarkers and modulating CFBs behavior, activation, and differentiation (see Table 1) (Li et al., 2021; Mathiyalagan et al., 2019; Dong et al., 2023). Understanding these mechanisms may open new avenues for therapeutic interventions targeting epigenetic regulators to mitigate fibrosis-related cardiac dysfunction.

2 Cardiac fibrosis: classification and cellular mechanisms

CF can be classified into focal scar fibrosis and diffuse fibrosis, depending on its etiology and distribution. Focal scar fibrosis, also known as reparative fibrosis, replaces dead cardiomyocytes following myocardial infarction or other ischemic events. In contrast, diffuse fibrosis, or reactive fibrosis, occurs in the interstitial and perivascular spaces without significant cardiomyocyte loss and

is more commonly associated with heart failure (Xu et al., 2022; Heymans et al., 2015). The primary distinction between these two forms of fibrosis lies in their origin. In clinical practice, CF often presents as a combination of both: following myocardial infarction, reparative fibrosis develops within the necrotic zone, while reactive fibrosis occurs in the surrounding border zone, driven by an inflammatory response triggered by cell necrosis. This process significantly impacts cardiac function. While replacement fibrosis is generally considered irreversible and essential for maintaining structural integrity, reactive fibrosis is regarded as maladaptive and contributes to pathological remodeling (Delacroix and Hulot, 2022).

2.1 The role of cardiac fibroblasts in fibrosis progression

CFBs are the primary cellular mediators of the fibrotic process. CFBs, in general, generate and maintain structurally diverse ECM-rich connective tissues that provide mechanical resilience, facilitate elastic recovery, and support organ function. In addition to ECM synthesis, CFBs contribute to tissue homeostasis by influencing the microarchitecture, biomechanics, and biochemical composition of the ECM. They also regulate cellular communication through the secretion of soluble mediators, including cytokines, growth factors, and metabolites. Following myocardial injury, CFBs become activated and differentiate into myoFIBs, a highly proliferative and secretory phenotype characterized by excessive ECM deposition. This transition plays a central role in fibrotic remodeling and contributes to the pathological stiffening of the myocardium (Liu et al., 2021; Plikus et al., 2021; Tallquist, 2020) (see Figure 1).

2.2 Molecular signaling and therapeutic targets

In CFBs, transforming growth factor beta (TGF- β) acts as a central effector in the fibrotic response, as it strongly induces collagen synthesis and promotes the differentiation of CFBs into myoFIBs. In addition, TGF- β facilitates the acquisition of a cellular phenotype oriented toward ECM preservation, characterized by increased expression of antiproteases and the secretion of enzymes involved in collagen cross-linking (Frangogiannis, 2020).

Moreover, CFBs express a wide array of receptors that regulate their activation, proliferation, and ECM production. Among these, β_2 -adrenergic receptors (β_2 AR) modulate fibroblast function through the activation of protein kinase A (PKA) and the exchange protein directly activated by cAMP (EPAC), which differentially influence the behavior of both CFBs and myoFIBs. Additionally, angiotensin II (Ang II) receptors particularly the AT₁R subtype stimulate collagen synthesis and fibroblast proliferation; however, their overexpression may lead to apoptosis. CFBs also express bradykinin B₁ and B₂ receptors, whose activation triggers signaling pathways that inhibit collagen synthesis and secretion through nitric oxide- and prostacyclin I₂ (PGI₂)-dependent mechanisms. Beyond their structural role, CFBs actively participate in the inflammatory response during cardiac repair. They express several immune-associated receptors, including Toll-like receptor 4 (TLR4), NLRP3, and the interferon receptor (IFNAR), all of which have attracted

TABLE 1 Synthesis of experimental studies exploring the role of epigenetically active proteins in CF.

Epigenetic modifications				
Protein	Epigenetic - function	Experimental model of cardiac fibrosis	Findings	References
METTL3	m6A	Murine model of myocardial infarction	Increased expression of COL I and III, α -SMA, and enhanced proliferation and differentiation of CFBs	Li et al. (2021)
METTL3	m6A	Murine model of CF	METTL3 methylates GAS5, promoting its degradation and activating mitochondrial fission via Drp1, ultimately leading to the proliferation and migration of CFBs	Tu et al. (2023)
METTL3	m6A	Murine model of myocardial infarction	METTL3 methylates Drp1, activates mitochondrial fission, and promotes CF.	Huang et al. (2023)
METTL3	m6A	METTL3 floxed murine model/Cardiomyocyte-specific Mettl3 knockout murine model	Inhibition of METTL3 can alleviate myocardial fibrosis and inflammation, and prevent cardiomyocyte death under reperfusion injury conditions by disrupting DNA-PKcs/Fis1-dependent mitochondrial fission	Ma et al. (2024)
METTL3	m6A	Murine model of myocardial infarction	METTL3 increased the m ⁶ A levels of TNC mRNA and enhanced its stability, thereby contributing to the regulation of myocardial dysfunction	Cheng et al. (2023)
METTL3	m6A	Murine model of CF	Silencing METTL3 downregulates IGFBP3 expression and inhibits cardiac fibroblast (CFB) activation and the progression of CF.	Ding et al. (2023a)
METTL3	m6A	Murine model of myocardial infarction	MetBil interacts with METTL3 and regulates the expression of methylated fibrosis-associated genes	Zhuang et al. (2023)
METTL3	m6A	Murine model of cardiac remodeling	Deficiencies in METTL3 and METTL14 significantly attenuated Ang II-induced myocardial inflammation and fibrosis by reducing m ⁶ A modifications on MyD88 and TGF- β 1 mRNAs. This reduction inhibited NF- κ B pathway activation and decreased the expression of CXCR2 and TGF- β 1	Li et al. (2024a)
FTO	m6A	Male and female murine (C57BL/6) and rats (Sprague-Dawley rats)	Selective demethylation of cardiac contractile transcripts, including SERCA2a, MYH6, MYH7, and RyR2	Mathiyalagan et al. (2019)
FTO	m6A	Neonatal rat CFBs	LE prevents the downregulation of FTO and reduces cardiac fibroblast proliferation, migration, and collagen synthesis	Meng et al. (2024)
FTO	m6A	Myocardial infarction Sprague-Dawley rats	HIF-1 α binds to the promoter region of FTO and suppresses its expression. Functionally, FTO inhibits collagen synthesis	Wang et al. (2024)

(Continued on the following page)

TABLE 1 (Continued) Synthesis of experimental studies exploring the role of epigenetically active proteins in CF.

Epigenetic modifications				
Protein	Epigenetic - function	Experimental model of cardiac fibrosis	Findings	References
WTAP	m6A	Murine model of diabetic CF.	Androgen receptor (AR) directly interacts with the mitochondrial lipid oxidation enzyme Decr1. Overexpression of AR suppresses Decr1-mediated mitochondrial lipid oxidation, thereby inhibiting CFBs proliferation and migration	Song et al. (2023)
<i>Alkbh5</i>	m6A	Leptin receptor-deficient mice cardiac fibroblast-specific <i>Notch 1</i> conditional knockout mice Cre mice	ALKBH5- and YTHDF2-mediated degradation of Notch1 promotes mitochondrial fission in diabetic cardiac fibrosis	Liu et al. (2024)
Dot1L	Histone modification	Adult Sprague–Dawley rats and neonatal rat	The interaction between Dot1L and FOX3 promotes the activation of CFBs	Xu et al. (2022)
PRMT5	Histone modification	Murine model of CF.	Activation and differentiation of cardiac fibroblasts (CFBs) are mediated through the PRMT5/Smad3 interaction	Dong et al., 2023
PRMT5/MLL1	Histone modification	Murine models with transverse aortic constriction (TAC)	PRMT5-induced arginine methylation and MLL1-mediated lysine methylation initiate α -SMA gene transcription, thereby promoting myoFIBs differentiation	Katanasaka et al. (2024)
p300	Histone modification	Murine model of CF	p300 interacts with SMAD2, as inhibition of p300 activity prevents TGF- β 1-induced SMAD2 phosphorylation and nuclear translocation	Lim et al. (2021)
p300	Histone modification	Murine model of hypertension	MyoFIBs differentiation	Rai et al. (2019)
KDM5B	Histone modification	Murine models with transverse aortic constriction (TAC)	KDM5B promotes the binding of CFs to ATF3, an antifibrotic regulator, thereby inhibiting its expression	Wang et al. (2022)
KDM5B	Histone modification	Murine models with transverse aortic constriction (TAC)	KDM5B-mediated activation of cardiac fibroblasts (CFBs) is associated with the activation of the Wnt/ β -catenin signaling pathway	Tang et al. (2022)
HDAC8	Histone modification	Experimental murine model of heart failure	Increased MMP12	Zhou et al. (2024)
BRD4	Histone modification	Murine model of pathological cardiac remodeling	BRD4 is functionally associated with the TGF- β 1/Smad2/3 signaling pathway	He et al. (2022)
BRD4	Histone modification	Neonatal Sprague-Dawley rats	BRD4 downregulation is associated with the inhibition of Ang II-induced transdifferentiation of CFBs	Han et al. (2023)
DNMT1	DNA methylation	Murine model of CF	Inhibition of DNMT1 leads to the overexpression of miR-152-3p, which suppresses the proliferation of CFBs	Xu et al. (2021)
DNMT3A	DNA methylation	Murine model of CF	Hypermethylation of the sFRP3 promoter is associated with CFBs activation and CF.	Jiang et al. (2024)

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TABLE 1 (Continued) Synthesis of experimental studies exploring the role of epigenetically active proteins in CF.

Epigenetic modifications				
Protein	Epigenetic - function	Experimental model of cardiac fibrosis	Findings	References
miR-223	miRNA	Experimental murine model of heart failure	miR-223 enhances proliferation, migration, and differentiation of CFBs, thereby promoting CF, partially through the regulation of RASA1	Liu et al. (2018)
miRNA-99b-3p	miRNA	Murine model of CF	miRNA-99b-3p interacts with GSK3β, leading to Smad3 activation and promoting CF.	Yu et al. (2021)
miRNA-331	miRNA	Murine model of CF	Interaction with the TGF-β/Smad3 pathway inhibits profibrotic gene expression in MyoFIBs	Yousefi et al. (2021)
LncRNA GAS5	LncRNA	Murine model of CF	Interaction with the NLRP3 inflammasome reduces the expression of caspase-1 and IL-1β, thereby alleviating CF.	Zhang et al. (2024)
CircNSD1	circRNA	Murine model of myocardial infarction	CFBs proliferation is promoted through activation of the Wnt/β-catenin signaling pathway	Ji et al. (2024)

This section describes the proteins analyzed and their epigenetic functions (such as histone modifications, DNA methylation, and non-coding RNAs), along with the experimental models of fibrosis used, and the observed effects on CFBs activation, ECM remodeling, and the progression of the fibrotic phenotype.

increasing interest as potential therapeutic targets for modulating fibrotic responses in CF ([Díaz-Araya et al., 2015](#)).

levels and a methyltransferase for specific small nuclear RNAs (snRNAs), expanding the functional scope of the m⁶A machinery ([Sun et al., 2019](#)).

3 m⁶A modification in mRNA

m⁶A is the most prevalent internal modification in eukaryotic messenger RNA and plays a pivotal role in regulating RNA transcription, splicing, stability, degradation, and translation ([Ye et al., 2023](#)). This dynamic and reversible modification is mediated by three groups of proteins commonly referred to as “writers,” “readers,” and “erasers,” which together orchestrate the m⁶A epitranscriptomic landscape ([Oerum et al., 2021](#)).

3.1 Writers: Installation of m⁶A marks

The core methyltransferase complex responsible for m⁶A deposition comprises methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), and Wilms tumor 1-associated protein (WTAP). METTL3 serves as the catalytic subunit, transferring a methyl group from S-adenosylmethionine (SAM) to specific adenosine residues within the RNA sequence. METTL14 acts as an RNA-binding scaffold, enhancing substrate recognition and stabilizing the METTL3-METTL14 complex. WTAP, although catalytically inactive, functions as a regulatory component that guides the complex to specific RNA targets and may also interact with other RNA species and associated regulatory proteins ([Tan et al., 2024](#)).

A homolog of METTL3, methyltransferase-like 16 (METTL16), has been identified as a regulator of intracellular SAM

3.2 Readers: interpreting the m⁶A signal

Reader proteins selectively bind to m⁶A-modified transcripts, mediating downstream processes such as translation enhancement, transcript degradation, and subcellular localization. The YTH domain family proteins—including YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2—are the best-characterized m⁶A readers. In addition, members of the heterogeneous nuclear ribonucleoprotein (HNRNP) family, such as HNRNPA2/B1, HNRNPC, and HNRNPG, can recognize m⁶A-modified RNAs and influence splicing or RNA structure.

Furthermore, insulin-like growth factor 2 mRNA-binding proteins (IGF2BP1/2/3) have been shown to bind m⁶A-containing mRNAs and promote their stability and translation in an m⁶A-dependent manner ([Gao et al., 2024](#)).

3.3 Erasers: removal of m⁶A marks

The reversibility of m⁶A modification is controlled by demethylases, also known as “erasers.” The fat mass and obesity-associated protein (FTO) demethylates m⁶A by oxidizing it to N6-hydroxymethyladenosine and N6-formyladenosine, which are subsequently hydrolyzed to adenine. ALKBH5 (AlkB homolog 5) is another demethylase that removes m⁶A in a similar manner,

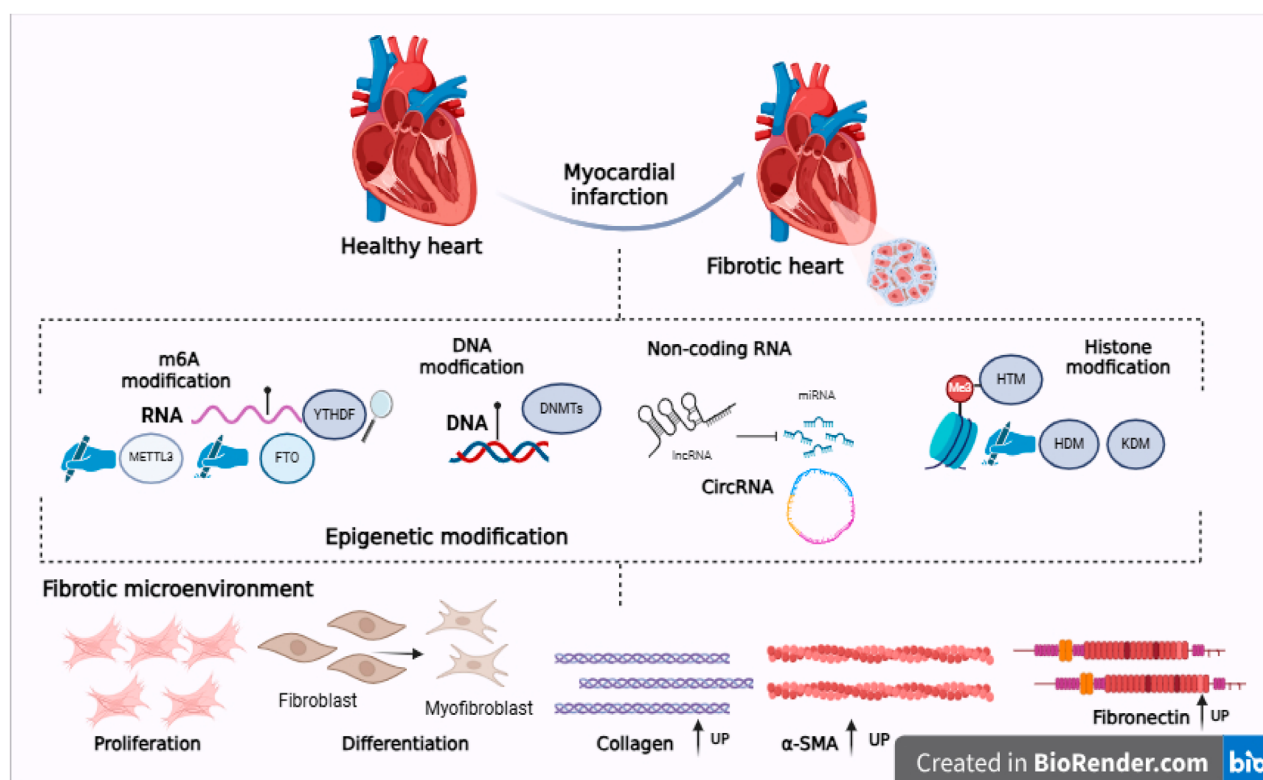


FIGURE 1

In response to cardiac injury, CFBs become activated, proliferate, and differentiate into cardiac myofibroblasts (myoFIBs). This phenotypic transition is associated with the upregulation of fibrotic markers, including COI I, COI III, alpha-smooth muscle actin (α -SMA), and fibronectin. Accumulating evidence indicates that various epigenetic modifications play a key role in regulating the activation, proliferation, and fibrogenic behavior of CFBs, as well as the expression of proteins that characterize the fibrotic cardiac phenotype.

thereby fine-tuning the transcriptome in response to physiological or pathological stimuli (Hu et al., 2025).

3.4 Additional regulators of the m⁶A machinery

Other accessory proteins contribute to the regulation and specificity of the m⁶A methylation machinery. RNA-binding motif protein 15 and 15B (RBM15/RBM15B) are involved in recruiting the methyltransferase complex to target RNAs. Zinc finger CCCH domain-containing protein 13 (ZC3H13) facilitates RNA interaction with the complex, while VIRMA (VIR-like m⁶A methyltransferase-associated) protein enhances complex stability and localization at specific transcript regions (Gao et al., 2024; Hu et al., 2025).

4 Role of M6A IN CF

4.1 METTL3 and CF

Recent studies have increasingly highlighted the role of m⁶A RNA modification in heart failure, particularly its association with METTL3. One of the earliest reports demonstrated elevated

METTL3 levels in fibrotic cardiac tissue from mice following myocardial infarction, as well as in cultured CFBs stimulated with TGF- β 1. METTL3 overexpression promoted CFBs proliferation, differentiation into myoFIBs, and collagen deposition, whereas its silencing had the opposite effect. The proposed mechanism involves activation of the classical TGF- β 1/SMAD2/3 signaling pathway, as METTL3 upregulates SMAD2/SMAD3 expression (Li et al., 2021).

In addition to its role in fibrotic signaling, METTL3 has been implicated in metabolic reprogramming, particularly through glycolysis modulation. METTL3 methylates androgen receptor (AR) mRNA, promoting its degradation via a YTHDF2-dependent mechanism. This downregulation of AR enhances hypoxia-inducible factor 1- α (HIF-1 α) signaling, a key glycolytic pathway, thereby stimulating CFBs proliferation (Zhou et al., 2022).

Furthermore, METTL3 regulates mitochondrial fission, a process closely linked to CF. Elevated METTL3 expression promotes mitochondrial fragmentation, increasing CFBs proliferation and migration. Conversely, METTL3 downregulation attenuates these effects. Mechanistically, METTL3 mediates m⁶A methylation of the long non-coding RNA (lncRNA) GAS5, which interacts with dynamin-related protein 1 (Drp1), a key regulator of mitochondrial fission. Overexpression of GAS5 suppresses Drp1 activity, mitigating fibrosis progression (Tu et al., 2023).

A recent study introduced a novel therapeutic approach using a timed-release microneedle system containing S-adenosylhomocysteine (SAH), an inhibitor of the METTL3-METTL14 complex. In experimental models of TGF- β 1-induced and hypoxia-ischemic cardiac injury, inhibition of METTL3-METTL14 reduced mitochondrial fragmentation and myoFIBs transdifferentiation. This treatment significantly improved cardiac function and decreased fibrosis markers (collagen I, collagen III, and α -SMA) in rat models. Mechanistically, the inhibitor suppressed Drp1 expression and phosphorylation, preserving mitochondrial integrity and reducing cardiomyocyte loss post-ischemic injury (Huang et al., 2023).

Additional research has linked METTL3 to ischemia/reperfusion (I/R)-induced CF through mitochondrial fission. In METTL3 knockout mice, reduced cardiac remodeling and fibrosis were observed compared to wild-type controls. METTL3 expression correlated positively with caspase-3 activity, implicating it in cardiomyocyte apoptosis. The study proposed that METTL3 regulates mitochondrial fission via DNA-dependent protein kinase catalytic subunit (DNA-PKcs), which phosphorylates mitochondrial fission protein 1 (Fis1) (Ma et al., 2024).

Other studies have explored METTL3's regulation of ECM components. Tenascin-C (TNC), a glycoprotein involved in cardiomyocyte proliferation and apoptosis, is stabilized by METTL3-mediated m6A methylation, exacerbating myocardial dysfunction (Cheng et al., 2023). Similarly, METTL3 influences CFBs activity by modulating insulin-like growth factor-binding protein 3 (IGFBP3), which is positively associated with CF. METTL3 silencing reduces IGFBP3 expression, attenuating pathological remodeling (Ding et al., 2023a).

Recent findings have also identified the LncRNA, MetBil as a regulator of METTL3 stability. Elevated MetBil levels correlate with increased expression of fibrosis markers (COI I and COI III) and CFBs proliferation. Mechanistically, MetBil inhibits METTL3 ubiquitination, stabilizing its protein levels and enhancing its activity (Zhuang et al., 2023).

Finally, METTL3 inhibition using STM2457, delivered via erythrocyte-derived microvesicles, has shown promise in models of cardiac device-associated fibrosis. In patients with ventricular septal defects who developed conduction blocks after occluder implantation, METTL3 and METTL14 were upregulated in peripheral blood mononuclear cells. The inhibition of METTL3/14 decreased m6A methylation of myeloid differentiation primary response protein 88 (MyD88) and TGF- β 1 mRNAs, thereby suppressing the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathway and downregulating CXC motif chemokine receptor 2 (CXCR2) and TGF- β 1 expression. Consequently, monocyte infiltration, inflammation, and CF were significantly reduced (Li J. et al., 2024).

4.2 FTO and m6A modification in CF

FTO plays a key role in CF through its m6A demethylase activity. Following cardiac injury, FTO expression is significantly downregulated, contributing to adverse cardiac remodeling. FTO's cardioprotective effects have been attributed to its selective demethylation of transcripts encoding cardiac contractile

proteins, including sarcoplasmic/endoplasmic reticulum Ca²⁺ ATPase 2a (SERCA2a), myosin heavy chains (MYH6/7), and ryanodine receptor 2 (RyR2). This demethylation enhances mRNA stability and protein expression, thereby supporting contractile function (Mathiyalagan et al., 2019).

The antifibrotic role of FTO has also been demonstrated *in vitro* using leonurine (LE), a natural cardioprotective compound. LE inhibited Ang II-induced CFBs proliferation, migration, and collagen synthesis. Ang II suppresses FTO expression, whereas LE restores it. Silencing FTO reversed the effects of LE, promoting fibrosis by increasing collagen I, collagen III, and α -SMA expression. These findings suggest that FTO-mediated m6A demethylation is essential for LE's antifibrotic action (Meng et al., 2024).

Additionally, FTO has been shown to suppress collagen synthesis after myocardial infarction. One study identified IGF2BP3 as a stabilizer of profibrotic mRNAs, including glutamyl-prolyl-tRNA synthetase (EPRS). FTO's demethylase activity antagonizes this process by destabilizing these mRNAs, reducing fibrosis progression (Wang et al., 2024).

4.3 Other components of the m6A machinery in cardiac fibrosis

Recent studies have identified WTAP as a novel regulator of CF. WTAP promotes mitochondrial lipid oxidation, facilitating CFBs activation and differentiation into myoFIBs. This effect appears to be mediated by WTAP's m6A-dependent downregulation of AR mRNA (Song et al., 2023).

Additionally, Notch homolog 1 (Notch1) has been implicated in fibrosis regulation. Reduced Notch1 expression correlates with increased m6A methylation and mitochondrial fission. Specific deletion of Notch1 in CFBs exacerbates CF in diabetic mouse models. ALKBH5, an m6A demethylase, mediates Notch1 mRNA demethylation at its 3'untranslated region (3'UTR), influencing mRNA stability and fibrotic remodeling (Liu et al., 2024).

The role of m6A RNA modification extends beyond CF, having been implicated in cancer progression (Luo et al., 2018; Wang et al., 2020; Zhu et al., 2024) and fibrotic diseases (Xiao et al., 2024; Tsai et al., 2024). Growing evidence suggests that m6A methylation is a key regulator of CF, particularly through METTL3 and FTO. The opposing roles of these enzymes highlight their potential as therapeutic targets. Further research into the molecular consequences of METTL3 and FTO modulation will be critical for developing epigenetic therapies to mitigate CF and adverse remodeling.

5 Histone modification

In multicellular eukaryotic organisms, all cells generally contain the same genome, which is packaged within the nucleus into a highly complex and dynamic superstructure known as chromatin. The fundamental unit of chromatin is the nucleosome, composed of DNA wrapped around an octamer of core histones—H2A, H2B, H3, and H4, forming approximately two superhelical turns. This structure is further stabilized by the linker histone H1, which facilitates chromatin compaction. Extending from the nucleosome

core, histone tails are highly conserved peptide sequences subject to numerous PTMs that play pivotal roles in regulating chromatin structure and function (Fellows and Varga-Weisz, 2020).

Chromatin exists in a highly dynamic state, transitioning between transcriptionally active and repressive conformations. Histone PTMs serve as key determinants of these chromatin states and influence essential biological processes, including transcription, DNA replication, repair, and remodeling (Izzo and Schneider, 2010). Among the most extensively studied PTMs are acetylation, phosphorylation, and methylation of specific histone residues (Rothbart and Strahl, 2014).

Histone acetylation typically occurs at the ϵ -amino groups of lysine residues in the N-terminal tails of histones H3 and H4 and is generally associated with transcriptional activation by promoting chromatin relaxation. In contrast, histone lysine methylation is a more intricate regulatory mechanism, with its functional outcome depending on the specific lysine residue modified and the degree of methylation. For instance, trimethylation of histone H3 at lysine 4 (H3K4me3) is linked to transcriptional activation, whereas trimethylation at lysine 9 (H3K9me3) or lysine 27 (H3K27me3) is typically associated with transcriptional repression and heterochromatin formation (Fellows and Varga-Weisz, 2020).

Histone methylation plays a critical role in cardiac remodeling and is among the most predominant PTMs in this context. This modification is catalyzed by histone methyltransferases (HMTs), which transfer methyl groups from the donor coenzyme SAM to specific lysine or arginine residues on histone tails, thereby modulating chromatin structure and gene expression (Miller and Grant, 2013). HMTs are categorized into three major families: SET domain-containing enzymes (responsible for the majority of lysine methylation, also known as KMTs), DOT1-like histone lysine methyltransferases (DOT1L), which specifically methylate H3K79, and PRMTs, which catalyze arginine methylation. Conversely, histone demethylases (HDMs) counteract these modifications by removing methyl groups, thereby maintaining a dynamic regulatory balance. HDMs are classified into two major groups: amine oxidases and Jumonji C (JmjC) domain-containing dioxygenases, the latter being iron- and α -ketoglutarate-dependent (Black et al., 2012; Gong and Miller, 2019).

Methylated histones function as docking sites for various reader proteins containing methyl-binding domains that interpret these modifications. These reader domains include ankyrin, BAH, DCD, MBT, TTD, and zf-CW, among others (Musselman et al., 2012) (See Table 2).

Histone acetylation is catalyzed by HATs, which transfer an acetyl group from acetyl-coenzyme A to the ϵ -amino group of lysine residues on histone tails. This modification neutralizes the positive charge of lysine, weakening histone, DNA interactions and promoting a more relaxed chromatin structure that facilitates transcription. HATs are classified into several families, including GCN5, p300/CBP, and the MYST family, which includes MOZ, Ybf2/Sas3, Sas2, and Tip60 (Yao et al., 2024; Miziak et al., 2024; Guo et al., 2018).

Histone acetylation is reversible and tightly regulated by HDACs. These enzymes are categorized based on their catalytic mechanisms into two main groups: canonical zinc-dependent

HDACs and SIRT6s, which are NAD⁺-dependent deacetylases (Park and Kim, 2020; Poziello et al., 2021).

Acetylated histones are recognized by specific reader domains that interpret these marks and mediate downstream biological effects. BRD is the most well-characterized reader domain, while other recognition motifs include DPF and PH (Musselman et al., 2012) (See Table 3).

5.1 Role of histone modification in cardiac fibrosis

5.1.1 Writers: histone modifications and cardiac fibrosis

Several studies have demonstrated the involvement of histone-modifying enzymes, or writers, in the regulation of CF. One such enzyme is DOT1L. Its expression has been directly correlated with elevated levels of profibrotic markers in CFBs. Notably, DOT1L regulates the transcription of forkhead box O3 (FOXO3), a transcription factor implicated in CFBs activation. Inhibition of DOT1L significantly reduces FOXO3 transcription, leading to a marked decrease in fibrogenic gene expression (Xu et al., 2022).

Another key writer implicated in CF is protein arginine methyltransferase 5 (PRMT5). Overexpression of PRMT5 in CFBs induces their activation and differentiation into myoFIBs, whereas its inhibition exerts the opposite effect. This process is mechanistically linked to the TGF- β 1/Smad3 signaling pathway (Dong et al., 2023). *In vivo*, PRMT5 deficiency results in reduced CF, as evidenced by decreased expression of fibrotic markers such as α -SMA. In CFBs, PRMT5 inhibition downregulates Col1A1 and Acta2, and its interaction with Smad3 is essential for the recruitment of fibrogenic gene promoters (Katanasaka et al., 2024).

Further mechanistic insights reveal that the lysine methyltransferase complex WDR5/MLL1 (WD repeat-containing protein 5 and Mixed-Lineage Leukemia 1) recruited to PRMT5-dependent arginine methylation sites. This complex mediates H3K4me3, a modification associated with gene activation. Both PRMT5-induced arginine methylation and MLL1-induced lysine methylation cooperatively promote the transcription of α -SMA and myoFIBs differentiation. Disruption of WDR5/MLL1 leads to significant downregulation of Col1a1, Acta2, and α -SMA protein expression in CFBs (Katanasaka et al., 2024). Additionally, MLL1 has been implicated in cardiovascular inflammation by promoting the transcription of chemokines CCL3 and CCL4 through H3K4me3 modification, thereby contributing to the inflammatory response in atherosclerosis associated with diabetes (Chen et al., 2024).

The HAT p300 also plays a key role in CF. Silencing of p300 in TGF- β 1-treated cellular models reduces the expression of collagen I and α -SMA while attenuating fibroblast activation. Moreover, p300 is involved in the acetylation and activation of Smad2, as its inhibition prevents Smad2 phosphorylation and nuclear localization (Lim et al., 2021). In a hypertensive mouse model, myocardial tissue exhibited increased differentiation of myoFIBs and H3K9 acetylation, correlating with elevated α -SMA expression. Pharmacological inhibition of p300 significantly reduced interstitial and perivascular collagen deposition in the myocardium (Rai et al., 2019).

TABLE 2 Histone-methylation enzymes.

Methylation									
Writers	KMTs	KMT1A KMT1B KMT1C KMT1D KMT1E KMT1F	KMT2A KMT2B KMT2C KMT2D KMT2E KMT2F KMT2G KMT2H	KMT3A KMT3B KMT3C KMT3D KMT3E KMT3F KMT3G	KMT4	KMT5A KMT5B KMT5C	KMT6	KMT7	KMT8A KMT8B KMT8C KMT8D KMT8E KMT8F
	PRMTs	PRMT1 PRMT2 PRMT3 PRMT4 PRMT5 PRMT6 PRMT7 PRMT8 PRMT9							
Eraser	KDMs	KDM1A KDM1B	KDM2A KDM2B	KDM3A KDM3B KDM3C	KDM4A KDM4B KDM4C KDM4D	KDM5A KDM5B KDM5C KDM5D	KDM6A KDM6B	KDM7A KDM7B KDM7C	KDM8
Readers	BAH Ankyrin DCD MBT TTD zf-CW								

Mammalian histone methyltransferases (including KMT and PRMT) and demethylases (KDM) are classified according to their ability to transfer or reverse one, two, or three methyl groups. Abbreviations: KMT: histone lysine methyltransferases; PRMT: protein arginine methyltransferases; KDM: histone demethylases; BAH: bromo-adjacent homology; DCD: chromobarrel, chromodomain, double chromodomain; MBT: malignant brain tumor; TTD: Tudor tandem domain; zf-CW: zinc finger CW.

5.1.2 Erasers: histone modifications and cardiac fibrosis

Histone demethylases and deacetylases, collectively known as erasers, are critical regulators of epigenetic mechanisms associated with CF. Lysine demethylase 5B (KDM5B) has been identified as a key player in CF, as its expression increases under pathological stress conditions. Inhibition of KDM5B significantly reduces CF, as evidenced by decreased mRNA levels of fibrotic markers including Col1A1, Col3A1, fibronectin 1 (FN1), cell communication network factor 2 (CCN2), TGF-β, and Acta2 (Wang et al., 2022). Mechanistically, KDM5B exerts its profibrotic effects by binding to the promoter of activating transcription factor 3 (ATF3), a known antifibrotic regulator, suppressing its expression through H3K4me2/3 demethylation, thereby enhancing TGF-β signaling and profibrotic gene overexpression.

The role of KDM5B in cardiac remodeling has been further elucidated using TK-129, a potent pyrazole-based KDM5B inhibitor. TK-129 attenuates Ang II-induced CFBs activation *in vitro* and mitigates isoprenaline-induced myocardial remodeling and fibrosis *in vivo*. KDM5B upregulation has been associated with activation of the Wnt/β-catenin signaling pathway, suggesting an epigenetic link between KDM5B and this profibrotic signaling cascade (Tang et al., 2022).

In terms of histone deacetylation, HDAC8 has emerged as a key regulator in CF. The novel hydroxamic acid-based HDAC inhibitor YAK577 has been shown to attenuate left

ventricular systolic dysfunction and CF in an isoproterenol (ISO)-induced heart failure model, partly by downregulating metalloproteinase 12 (MMP12). Both HDAC8 and CF-related genes (Col1A1, FN1) are upregulated in ISO-induced heart failure and TGF-β1-treated CFBs, whereas YAK577 treatment reverses these changes (Zhou et al., 2024). Furthermore, HDAC8 overexpression elevates MMP12 mRNA levels, while HDAC8 knockdown decreases its expression. Mechanistically, HDAC8 interacts with signal transducer and activator of transcription 3 (STAT3), facilitating its binding to the MMP12 promoter and potentially enhancing transcriptional activity.

5.1.3 Readers: bromodomain-containing proteins and cardiac fibrosis

Epigenetic “reader” proteins recognize specific histone PTMs and play essential roles in the regulation of gene expression during CF. Among these, bromodomain-containing protein 4 (BRD4) has emerged as a critical regulator due to its ability to bind specifically to acetylated lysine residues on histone tails.

BRD4 has been identified as a promising therapeutic target in cardiac remodeling and heart failure. Inhibition of BRD4 using small-molecule inhibitors, such as JQ1, has been shown to reduce CF *in vivo* and prevent CFBs activation *in vitro* (He et al., 2022). These antifibrotic effects are mechanistically linked to modulation of the TGF-β1/Smad2/3 signaling pathway, which plays a central role in fibrotic gene expression. Additionally, BRD4 activity is modulated by

TABLE 3 Histone-acetylation enzymes.

Acetylation		
Writers	GNAT	HAT1 HAT4 GNC5
	p300/CBP	
	MYST	Tip60 MOZ MORF HBO1 MOF
Eraser	HDAC	
	Class I	HDAC1 HDAC2 HDAC3 HDAC8
	Class IIa	HDAC4 HDAC5 HDAC7 HDAC9
	Class IIb	HDAC6 HDAC10
	Class III	SIRT2 SIRT3 SIRT4 SIRT5 SIRT6 SIRT7
	Class IV	HDAC11
Readers	DPF PH BRD	

While the histone acetyltransferases are classified according to substrate recognition and cellular localization, histone deacetylases are classified into two groups according to the catalytic mechanisms (HDAC and SIRT). Likewise, the HDAC family has also been divided into four classes according to structural and functional characteristics. Abbreviations: HAT: Histone acetyltransferase; GNC5: GCN5-related N-acetyltransferases; p300/CBP: 300 kDa protein and CREB-binding protein. HDAC: histone deacetylases; SIRT: Sirtuins; BRD: bromodomains; DPF: double plant homeodomain finger; PH: double pleckstrin homology domain.

the p38 mitogen-activated protein kinase (MAPK) pathway, further supporting its role in fibrotic remodeling (Stratton et al., 2019).

BRD4 inhibition has also been shown to counteract Ang II-induced myoFIBs differentiation, a process partly mediated by activation of the Keap1/Nrf2/HO-1 antioxidant pathway, highlighting a potential role in oxidative stress modulation (Han et al., 2023). Moreover, BRD4 has been implicated in atrial CF, where its silencing prevents ECM synthesis and CFBs activation (Song et al., 2024).

A recent innovative approach has introduced biomimetic nanoparticle-based drug delivery systems to enhance the specificity and efficacy of BRD4 inhibition in CF. One such system employs nanoparticles coated with platelet and erythrocyte membranes to facilitate targeted delivery of JQ1. The platelet membrane

confers specificity for myoFIBs and cardiac collagen, while the erythrocyte membrane prolongs nanoparticle circulation time. This strategy has shown promising antifibrotic outcomes by effectively reducing CFBs activation and collagen secretion in myocardial tissue (Li Y. et al., 2024).

Histones are fundamental structural components of chromatin, and their functions are intricately regulated by a diverse array of PTMs. These modifications govern chromatin accessibility and transcriptional activity, ultimately shaping cellular responses such as CFBs activation and differentiation into myoFIBs. A comprehensive understanding of how chromatin-modifying enzymes including KMTs, PRMTs, KDMs, HATs, HDACs and their corresponding reader proteins orchestrate the transcriptional landscape in CF may provide valuable insights for the development of epigenetically targeted antifibrotic therapies.

6 DNA methylation

DNA methylation is a key epigenetic modification associated with gene silencing (Ping et al., 2014; Wu et al., 2014). This process regulates gene expression by recruiting transcriptional repressors and inhibiting transcription factor binding to DNA. During embryonic development, DNA methylation patterns are dynamically established and modified through *de novo* methylation and demethylation (Moore et al., 2013). DNA methylation primarily occurs at cytosines within CpG dinucleotides (Ikeda, 2023) and is catalyzed by DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B (Edwards et al., 2017). These modifications are recognized by protein families such as methyl-CpG-binding domain proteins and zinc finger proteins (e.g., Kaiso, ZBTB4, ZBTB38), which repress transcription by binding to methylated CpGs (Hendrich and Bird, 1998; Filion et al., 2006). Additionally, plant homeodomain (PHD) and Really Interesting New Gene (RING) finger domain-containing proteins help maintain DNA methylation by interacting with DNMT1, ensuring methylation pattern propagation during DNA replication (Deogharia and Gurha, 2024).

6.1 DNA methyltransferases (DNMT) as mediators of cardiac fibrosis

DNMTs play a crucial role in CF by regulating genes involved in cell differentiation and ECM production. α -SMA, a marker of CFBs-to-myofibers differentiation (Phan, 2002; Zhang et al., 2015), is modulated through promoter demethylation, which is facilitated by downregulation of DNMT1 (He et al., 2019).

Extracellular superoxide dismutase (EC-SOD) also influences DNA methylation under hypoxic stress by inhibiting DNMT1 and DNMT3B-mediated methylation of tumor suppressor genes such as RASSF1A, thereby reducing fibrotic markers (Rajgarhia et al., 2021).

DNMT1 overexpression suppresses the microRNA (miRNA) miR-152-3p, leading to activation of the Wnt/ β -catenin signaling pathway. Conversely, DNMT1 inhibition restores miR-152-3p levels and reduces CFBs proliferation (Xu et al., 2021). In diabetic cardiomyopathy, DNMT1-mediated methylation of the suppressor of cytokine signaling 3 (SOCS3) promoter suppresses its expression,

promoting STAT3 activation and fibrotic remodeling. Inhibition of DNMT1 reverses this effect (Tao et al., 2021).

Moreover, *in silico* analysis of heart failure patients with clonal hematopoiesis of indeterminate potential (CHIP) mutations in DNMT3A revealed enhanced monocyte-CFBs interactions, which were confirmed *in vivo* and associated with fibrotic remodeling (Shumliakivska et al., 2024).

DNMT3A also promotes CF via hypermethylation of the secreted frizzled-related protein 3 (sFRP3) promoter, leading to its repression. This downregulation impairs Drp1-regulated mitochondrial fission and promotes CFBs proliferation. DNMT3A knockdown restores sFRP3 expression, normalizes mitochondrial dynamics, and attenuates fibrosis (Jiang et al., 2024).

Collectively, DNMTs contribute significantly to CF through regulation of gene expression networks controlling CFBs differentiation, proliferation, and ECM deposition. Nevertheless, their precise and context-dependent roles require further investigation to inform the development of targeted epigenetic therapies.

7 Noncoding rna and cardiac fibrosis

Non-coding RNAs, including miRNAs, lncRNAs, and circular RNAs (circRNAs), regulate gene expression through diverse mechanisms such as miRNA sponging, direct interaction with messenger RNAs (mRNAs), protein scaffold formation, and even encoding regulatory peptides (Olson et al., 2024).

7.1 MicroRNAs (miRNAs) in cardiac fibrosis

MiRNAs are key post-transcriptional regulators that play a crucial role in CF by modulating gene expression related to CFBs activation, differentiation, and ECM production. For instance, microRNA-223 (miR-223) has been implicated in CF following myocardial infarction. Its overexpression enhances CFBs proliferation, migration, and fibrotic protein expression, whereas its inhibition yields opposite effects. Mechanistically, miR-223 targets and suppresses the RAS protein activator p21, leading to the activation of the RAS signaling pathway (Liu et al., 2018).

Similarly, miR-10a has been associated with prolonged atrial fibrillation and upregulation of profibrotic genes. Its silencing mitigates these pathological effects (Li et al., 2019). Another miRNA, miR-99b-3p, promotes CF by increasing the expression of FN1, COI I, vimentin, and α -SMA, and by stimulating CFBs proliferation and migration. This action is mediated via inhibition of glycogen synthase kinase-3 beta (GSK3 β), leading to Smad3 activation (Yu et al., 2021). Conversely, miR-331 exerts antifibrotic effects by suppressing profibrotic genes through the TGF- β /Smad3 pathway. Its overexpression reduces the expression of Smad3 and Col1A1, both *in vitro* and *in vivo* fibrosis models (Yousefi et al., 2021).

miR-29a-3p has been identified as a modulator of CF. Knockdown of miR-29a-3p increases the expression of TGF- β , COI I and COI III in CFBs, reversing the antifibrotic effects of LE. LE and miR-29a-3p act synergistically to reduce CF (Wang et al., 2021). The tumor suppressor p53 has also been implicated in this mechanism. p53 directly binds to the promoter

region of miR-29a-3p, upregulating its expression. LE promotes the expression of both p53 and miR-29a-3p, thereby inhibiting CFBs overactivation (Xi et al., 2023).

In addition, Xu et al. (2023) demonstrated that DNMT3A-mediated methylation of miR-145 inhibits autophagy, promoting CFBs proliferation and CF. miR-129-5p also contributes to fibrosis regulation by inhibiting CFBs-to-myofibroblasts transition through the suppression of asporin and the transcription factor SOX9 (Medzikovic et al., 2023).

7.2 lncRNAs and circRNAs in cardiac fibrosis

lncRNAs and circRNAs are emerging as pivotal regulators in CF through their involvement in transcriptional and post-transcriptional gene regulation. Silencing of lncRNA NEAT1 has been shown to promote CF. This effect is mediated by DNMT3A-induced methylation of NEAT1, which activates the NLRP3 inflammasome pathway and triggers pyroptosis in CFBs, contributing to fibrotic progression (Ding et al., 2023b). Conversely, overexpression of lncRNA GAS5 exerts antifibrotic effects by negatively regulating NLRP3. This is achieved through reduced expression of caspase-1 and interleukin-1 β (IL-1 β). Moreover, GAS5 downregulates miR-217 and upregulates SIRT1 expression, collectively alleviating CF (Zhang et al., 2024).

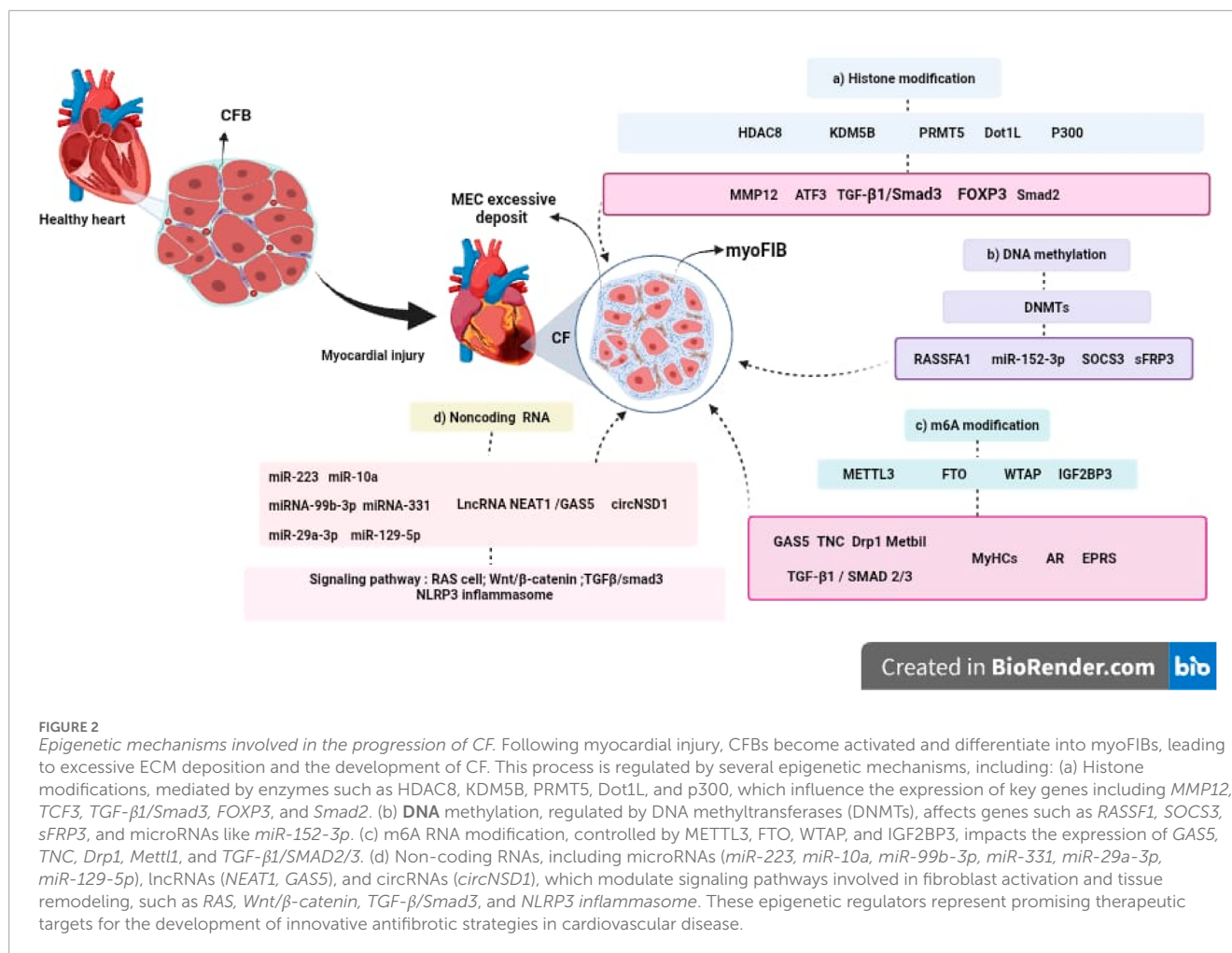
With respect to circRNAs, the circNSD1/miR-429-3p axis plays a significant role in the modulation of CF. circNSD1 acts as a sponge for miR-429-3p, thereby increasing the expression of sulfatase 1 (SULF1) and activating the Wnt/ β -catenin signaling pathway. This cascade enhances the fibrotic response in CFBs, as evidenced by increased expression of fibrotic proteins in response to circNSD1 overexpression (Ji et al., 2024).

8 Drugs targeting epigenetic modifications in cardiac fibrosis

Although no active clinical trials or approved drugs currently target epigenetic mechanisms specifically for the treatment of CF, preclinical studies have identified several epigenetic enzymes as potential therapeutic targets. Among these, the HAT p300 has received considerable attention due to its role in promoting the transcription of profibrotic genes via histone acetylation.

Curcumin, a natural compound with epigenetic properties, has been investigated as a selective inhibitor of p300. Its administration suppresses cardiomyocyte hypertrophy and fibrosis, accompanied by a reduction in brain natriuretic peptide (BNP) expression without affecting blood pressure. This effect appears to result from inhibition of p300 acetyltransferase activity, limiting the transcription of genes associated with oxidative stress and inflammation in the myocardium (Funamoto et al., 2022). Complementary studies have shown that curcumin also reduces perivascular fibrosis and downregulates pro-hypertrophic gene expression in hypertensive models, further supporting its potential as an epigenetic modulator with antifibrotic effects (Sunagawa et al., 2021).

Beyond histone modifications, RNA epigenetic regulation has also emerged as a relevant mechanism in CF, particularly through



m6A methylation. In this context, metformin, widely used as a first-line therapy for type 2 diabetes mellitus, has demonstrated inhibitory effects on METTL3, a key methyltransferase responsible for m6A deposition. Although its role in CF remains under investigation, recent studies have shown that metformin downregulates METTL3 expression, potentially influencing mRNA stability and translation of transcripts involved in fibrotic pathways (Chen et al., 2023).

These epigenetic effects have been confirmed in both *in vitro* and *in vivo* models, where metformin mitigated fibrotic and inflammatory myocardial remodeling post-myocardial infarction (Loi et al., 2021), and attenuated diabetes-induced CF (Li et al., 2023). These findings support the potential of metformin as a candidate for drug repurposing in the epigenetic treatment of CF.

8.1 Clinical implications

This review highlights the critical role of epigenetic modifications in cardiac remodeling, emphasizing the function of “writers,” “erasers,” and “readers” in the regulation of CF. The evidence presented provides new insights into the therapeutic potential of targeting these epigenetic regulators.

The studies discussed herein demonstrate that epigenetic modifications significantly influence the cellular behavior of CFBs,

positioning epigenetic interventions as promising strategies for the treatment of CF. The modulation of DNA methylation, histone modifications, and ncRNAs has shown potential in preclinical models to reverse fibrotic responses, offering novel therapeutic avenues for cardiac disease management.

Epigenetic therapies, including inhibitors of DNMTs and BRD4, as well as modulators of ncRNAs, are being explored as potential antifibrotic strategies. Some of these approaches, such as DNMT inhibitors (e.g., decitabine, 5-azacytidine) and BET protein inhibitors (e.g., JQ1, CPI-0610), have demonstrated efficacy in modulating fibrotic pathways in preclinical models, suggesting their potential translation into clinical applications.

Additionally, epigenetic biomarkers could serve as diagnostic and prognostic tools for CF. The identification of methylation patterns, histone modifications, and specific ncRNAs associated with fibrosis progression may enable earlier detection and risk stratification of patients. These biomarkers could also help monitor treatment response in future epigenetic-based therapies.

Despite these promising findings, several challenges remain before epigenetic therapies can be fully integrated into clinical practice. Given that epigenetic modifications regulate multiple cellular processes, ensuring treatment specificity and minimizing off-target effects will be critical. Future research should focus on optimizing targeted delivery systems, such as nanoparticle-based

therapies, to enhance the selectivity of epigenetic drugs and reduce potential side effects.

By elucidating the molecular mechanisms underlying CF, this review identifies novel epigenetic targets that could be leveraged to modulate fibrosis progression, paving the way for innovative therapeutic approaches in cardiovascular disease. Further clinical and translational research is required to refine these strategies and determine their feasibility for human application.

9 Conclusion

Cardiac fibrosis (CF) is a prevalent pathophysiological process characterized by excessive ECM deposition, primarily driven by the activation and abnormal proliferation of cardiac fibroblasts (CFBs) into myofibroblasts (myoFIBs). These cells play a central role in ECM production and fibrotic remodeling, ultimately contributing to cardiac dysfunction (Garvin and Hale, 2022; Kong et al., 2014; Krenning et al., 2010).

Epigenetic modifications, including DNA methylation, histone modifications, and ncRNAs, have emerged as key regulators of CF. The evidence reviewed suggests that epigenetic enzymes, referred to as “writers,” “readers,” and “erasers,” modulate fibrotic responses by influencing gene expression patterns, CFBs activation, and ECM synthesis. In particular, the m6A RNA modification machinery, DNMTs, and histone-modifying enzymes have been implicated in fibrosis progression, often through interactions with major signaling pathways such as Wnt/ β -catenin and TGF- β /Smad (see Figure 2).

Despite recent advances, the precise role of specific epigenetic regulators in CF remains to be fully elucidated. While preclinical studies support the therapeutic potential of targeting DNMTs, BRD4, and ncRNAs, further research is needed to optimize selectivity, safety, and delivery strategies for epigenetic-based therapies.

9.1 Future prospects

To advance the clinical translation of epigenetic therapies, future research should focus on:

- Deciphering the interplay between different epigenetic mechanisms in CF pathophysiology, particularly in the regulation of CFBs-to-myofIBs differentiation.
- Exploring the therapeutic potential of epigenetic inhibitors, such as DNMT and BRD4 inhibitors, and evaluating their effects in large-animal models and clinical trials.
- Developing targeted delivery systems, such as nanoparticle-based epigenetic therapies, to enhance specificity and minimize off-target effects.
- Identifying and validating epigenetic biomarkers for CF, which could aid in early diagnosis, prognosis, and monitoring of therapeutic responses.
- Investigating antifibrotic factors that inhibit CFBs-to-myofIBs transition, as these may offer complementary or synergistic effects with epigenetic interventions.

Understanding the intricate regulatory networks of epigenetic modifications in CF will pave the way for novel therapeutic strategies in cardiovascular disease, ultimately improving patient outcomes and addressing the unmet clinical need for effective antifibrotic therapies.

Author contributions

PM: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review and editing. C-LJ: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review and editing. GM: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review and editing. AP: Writing – review and editing, Supervision, Conceptualization, Formal Analysis, Investigation, Validation. M-TE: Conceptualization, Formal Analysis, Supervision, Writing – original draft, Writing – review and editing. BS: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review and editing.

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Conflict of interest

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

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Glossary

CF	Cardiac fibrosis
ECM	extracellular matrix
myoFIB	myofibroblasts
m6A	N6-methyladenosine
METTL3	methyltransferase 3
METTL14	methyltransferase 14
WTAP	Wilms tumor-associated protein 1
SAM	S-adenosylmethionine
IGF2BP	insulin-like growth factor 2 mRNA binding proteins
FTO	alpha-ketoglutarate-dependent dioxygenase
TGF-β1	transforming growth factor beta 1
AR	Androgen receptor
Drp1	dynammin-related protein 1
LE	leonurine
KMTs	histone methyltransferases acting on lysines
PRMT	arginine N-methyltransferase
KDMs	Lysine demethylases
HDACs	histone deacetylases
GNATs	GCN5-related N-acetyltransferases
p300	300 kDa protein
CBP	CREB-binding protein
SIRT6	sirtuins
BAH	bromo-adjacent homology
DCD	chromobarrel, chromodomain, double chromodomain
MBT	malignant brain tumor
TTD	Tudor tandem domain
Zf-CW	zinc finger CW
DOT1	DOT1-like histone lysine methyltransferase
Col1a1	alpha 1 chain
H3K4	trimethylates histone H3
MMP12	metalloproteinase 12
DNMTs	DNA methyltransferases
SOCS3	Cytokine signaling 3
sFRP3	frizzled-related protein 3
ncRNA	non-coding RNA