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Review Article

Epigenetic regulatory mechanisms and translational applications in idiopathic pulmonary fibrosis

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a chronic, relentlessly progressive interstitial lung disease with limited treatment options and poor survival. Existing antifibrotic agents slow functional decline but do not halt or reverse established fibrosis, highlighting the need for IPF specific mechanistic understanding and new therapeutic targets. This review summarizes epigenetic regulatory mechanisms that are implicated in IPF, including DNA methylation, histone modifications, non-coding RNAs, and RNA modifications. These mechanisms can be viewed as interacting networks that reprogramme gene expression in alveolar epithelial cells, macrophages and fibroblasts, leading to impaired epithelial repair, profibrotic immune activation and maintenance of a chronically activated myofibroblast state. The contribution of cell type specific epigenetic signatures to chronic inflammation, disordered tissue remodelling and progressive extracellular matrix accumulation in IPF is underscored. Recent work that translates epigenetic insights into applications for IPF is also reviewed, with a focus on epigenetic marks and regulators as biomarkers for diagnosis, prognosis and treatment response, and as targets for small molecule drugs, nucleic acid based therapies and epigenome editing strategies. Overall the evidence assembled here provides a framework that focuses on IPF epigenetic regulation and can inform experimental design and support the development of more precise therapeutic approaches for patients with IPF.

Keywords: IPF, epigenetics, mechanisms, therapy

Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe progressive interstitial lung disease characterized by repeated injury and ineffective repair of the alveolar epithelium, abnormal accumulation of fibroblasts and myofibroblasts, and excessive extracellular matrix (ECM) deposition, which together drive honeycomb remodelling of the lung parenchyma and eventually result in respiratory failure [1]. Although the etiology of IPF has not been fully elucidated, important clues have emerged from clinical studies. Extensive evidence indicates that a range of environmental and occupational exposures, including cigarette smoke, air pollution, sulfur dioxide, wood dust and metal particles, can damage the alveolar epithelial-mesenchymal barrier, disturb lung tissue homeostasis and activate chronic inflammatory and oxidative stress pathways, thereby promoting pulmonary inflammation and fibrogenesis in genetically susceptible individuals [2-5]. Pirfenidone and nintedanib are approved to attenuate the loss of lung function, yet they are unable to reverse established fibrosis [6]. As a result, current therapeutic strategies offer limited benefit for long term survival and fail to address the pronounced heterogeneity of IPF, which underlines the need for further progress in both basic research and clinical practice.

Accumulating evidence suggests that epigenetic dysregulation plays a major part in the initiation and progression of IPF. In individuals with genetic susceptibility, environmental insults appear to act through DNA methylation and histone and RNA modifications to reprogram gene expression in pulmonary epithelial cells, fibroblasts and immune cells, disrupt the normal balance of injury and repair and promote fibrotic remodelling. Genome-wide stud-

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ies of IPF lung tissue have identified extensive changes in DNA methylation that correlate with altered transcription of genes involved in extracellular matrix turnover, TGF-β signalling and cell cycle control. Notably, methylation at the c8orf4 locus has been linked to reduced COX-2 expression, while epigenetic silencing of SOD2 has been associated with enhanced oxidative stress [7-9]. In addition, methylation programs differ between epithelial and myeloid compartments; loss of Dnmt3b in myeloid lineages exacerbates fibrotic lesions and promotes a profibrotic macrophage phenotype [10-12]. In the context of histone modification, inhibition of HDAC6 or HDAC8 reduces the expression of fibrotic markers, whereas reduced H4K16 acetylation in lung tissue is associated with a profibrotic transcriptional program. EZH2 and G9a repress CXCL10, whereas KMT2A enhances fibroblast-related transcription via PU.1 [13-16]. Immune metabolism is closely linked to epigenetic enzyme activity, with mitochondrial fission and reactive oxygen species accumulation being promoted by lactate signaling, macrophage polarization being shaped by the NAMPT/NAD^+ axis, and antifibrotic effects being associated with activation of Nrf2 [17-20]. Together, these findings outline a mechanistic framework that can guide future studies and refine therapeutic strategies in IPF [6, 21-23].

Although epigenetic control of cellular phenotype in IPF is well documented, it remains unclear how the different layers of epigenetic regulation act together to shape disease specific cellular states. This review assembles current knowledge on DNA methylation, histone modifications, non-coding RNAs and RNA modifications, and this body of work is used to propose an integrated model of epigenetic control of cell function. In this model, distinct epigenetic processes are shown to converge on transcriptional reprogramming in alveolar epithelial cells, macrophages and fibroblasts, which is thought to sustain progression of fibrotic pathology. By providing a more coherent and comprehensive overview of epigenetic regulation in IPF, this review aims to connect mechanistic insight with clinical relevance and to suggest new directions for future research on IPF epigenetic mechanisms and their translational potential.

Epigenetic regulatory mechanisms

In recent years, the significance of epigenetic mechanisms in the pathogenesis of IPF has become increasingly evident [24]. Epigenetic dysregulation contributes to IPF by converging on three interlinked cellular programs: impaired alveolar epithelial repair, profibrotic immune polarization, and persistent fibroblast/myofibroblast activation with excessive ECM deposition. DNA methylation, histone modifications, ncRNAs and RNA modifications form an interacting network that reshapes transcriptional programs across epithelial, immune and stromal compartments (**Figure 1**; **Table 1**). In the following sections, we focus on regulator-specific evidence and highlight the most consistently supported mechanisms.

DNA methylation modifications

DNA methylation (5-mC), written by DNMTs and erased by TET enzymes, regulates cell type specific transcriptional programs in IPF. Here, we highlight the most consistently supported methylation regulators/loci and their mechanistic links to oxidative stress control, macrophage polarization and fibroblast phenotypes, without reiterating general IPF pathobiology described above [25].

DNMTs and TET demethylases play key regulatory roles in the onset and progression of IPF. Studies have shown that the loss of DNMT3A induces hypermethylation of the SOD2 promoter in lung fibroblasts, leading to downregulation of SOD2 expression [26]. Conversely, loss of DNMT3B in myeloid cells promotes DNA hypomethylation at the Arg1 promoter and favours macrophage polarization toward a profibrotic phenotype [11]. In parallel, in vitro and in vivo experiments show that miR-30a targets TET1, suppresses hydroxymethylation of the Drp1 promoter in type II alveolar epithelial cells (AEC2s), and thereby reduces Drp1 expression [27]. However, another study reported that TET2 deficiency in AEC2s did not affect IPF progression through an epigenetic mechanism [10].

However, evidence for TET family enzymes in fibrotic progression is not fully consistent. While the miR-30a/TET1-Drp1 axis supports a hydroxymethylation-linked mechanism in AEC2

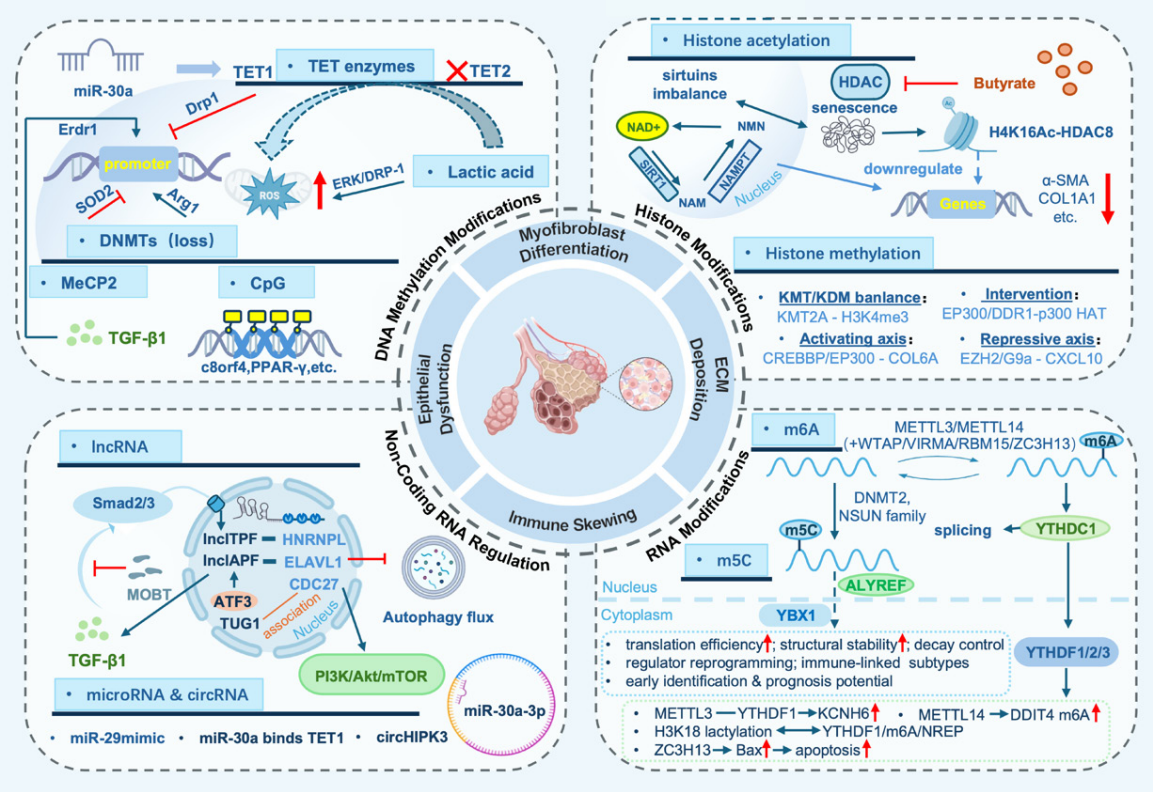

Figure 1. Overview of epigenetic regulatory mechanisms.

Table 1. Summary of epigenetic regulatory mechanisms in IPF

Category	Key molecules/ enzymes	Major cell types	Core pathways/mechanisms
DNA methylation	DNMT1/3A/3B, TET1/2/3, MeCP2, MBD2	Fibroblasts, AEC2s, Macrophages	Promoter methylation leads to SOD2 decrease, Drp1 decrease; TGF-β-Smad3-MBD2 loop; Arg1 hypomethylation leads to M2 polarization
Histone modification	HATs (p300/CBP), HDACs, SIRT1/8	Fibroblasts	H4K16Ac increases leads to pro-fibrotic genes decrease; SIRT1-NAD^+-AMPK axis; HDAC inhibition leads to α-SMA/COL1A1 decreases
NcRNA regulation	miR-29; miR-30a; circHIPK3; lncITPF; LINC00941; TUG1	Fibroblasts; AEC2s	miR-29 decreases COL1A1 and COL3A1; miR-30a reduces TET1 and Drp1 expression; circHIPK3 competes with miR-30a leading to FOXK2-mediated glycolysis enhancement; lncITPF-hnRNP-L increases α-SMA and ECM; LINC00941-HuR decreases autophagy and promotes myofibroblast transition; TUG1 activates PI3K/Akt/mTOR signaling
RNA modification	METTL3/14; WTAP; YTHDF1/2/3; NSUN2/3/5; DNMT2	Fibroblasts; Mesenchymal cells; Immune cells	METTL3-YTHDF1 enhances KCNH6 translation and fibroblast activation; METTL14 stabilizes DDIT4 and promotes aging-related fibrosis; m^5C regulators reshape immune infiltration patterns and serve as diagnostic and prognostic signatures

injury models, TET2 deletion in AEC2s did not alter bleomycin-induced fibrosis in another study [28, 29]. These findings likely reflect differences in experimental systems, the cell populations interrogated, and the timing of perturbation relative to injury and repair phases, and they underscore the need for validation in human AEC2 subsets and in chronic, spatially heterogeneous disease settings [17, 18]. Inhibition of lactate production or its downstream pathways can partially restore these abnormalities [30, 31]. Meanwhile, activation of the Nrf2 antioxidant pathway and mitochondrial protective mechanisms can indirectly preserve

the redox environment required for TET enzymatic activity [19, 32, 33], thereby influencing the progression of IPF.

In addition, methyl-CpG binding proteins such as MeCP2 and MBD2 participate in the regulation of DNA methylation in IPF. TGF-β1 can activate a TβRI-Smad3-MBD2 positive feedback loop to induce hypermethylation of the Erdr1-promoter CpG islands, leading to transcriptional repression of Erdr1 [34]. Silencing of MeCP2 has been shown to suppress TGF-β1-induced α-SMA expression in fibroblasts [35, 36], and also inhibit M2 macrophage polarization by downregulating interferon regulatory factor 4 (IRF4) [36].

At the level of CpG site regulation, transcriptional regulator C8orf4 hypermethylation mediates the downregulation of COX-2 in lung fibroblasts [9]. Conversely, inhibition of DNA methylation can induce demethylation of the PPAR-γ promoter, thereby enhancing PPAR-γ expression [37]. A recent retrospective study further revealed that exposure to PM2.5 was significantly associated with the methylation status of CRTAP (an extracellular matrix remodeling enzyme) and TLN2 (a fibroblast migration-related gene), which were directly correlated with clinical prognosis in IPF patients [38].

Histone modifications

Histone acetylation and methylation regulate chromatin accessibility and transcription through reversible enzymatic writing/erasing of specific histone marks. In IPF, dysregulated activity of these enzymes reshapes profibrotic transcriptional programs. This section focuses on acetylation and methylation, because they have the most developed evidence base in IPF [14].

Histone acetylation: Histone acetylation is a crucial post-translational modification of histones, primarily occurring at the ε-amino groups of specific lysine residues on histone tails (particularly those of H3 and H4). The dynamic balance of this modification is maintained by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Multiple studies have consistently reported that chromatin remodeling associated with cellular senescence in IPF is closely linked to the dysregulated activity and expression of the sirtuin (SIRT) family of deacetylases. Evidence also indicates that HDAC dependent chromatin regulation is altered in IPF. Pharmacologic inhibition of HDAC8 attenuates experimental pulmonary fibrosis, supporting HDAC8 as a tractable target. Separately, increasing H4K16 acetylation is associated with lower expression of profibrotic genes and improved fibrosis phenotypes. These findings suggest that changes in selected histone marks and loci do not necessarily reflect global acetylation states [13, 15, 39-41].

Studies have shown that specific deletion of SIRT1 in fibroblasts directly impairs their anti-apoptotic capacity [42]. Small-molecule blockade of the SIRT1-associated deacetylation axis not only induces fibroblast apoptosis but also mitigates fibrotic progression [43]. NAD^+ serves as an essential cofactor for SIRT1, and its intracellular concentration is a major determinant of SIRT1 deacetylase activity [44]. In fibroblasts, increased NAMPT expression has been demonstrated to raise NAD^+ availability, strengthen SIRT1-mediated deacetylation, and promote AMPK phosphorylation, ultimately correlating with lower transcription of fibrosis related genes and reduced collagen accumulation [20].

Histone methylation: Histone methylation also contributes to transcriptional control in IPF. In fibroblasts, EZH2 and G9a act together to deposit the repressive marks H3K27me3 and H3K9me2 at the CXCL10 regulatory region, thereby increasing local repressive methylation and suppressing CXCL10 transcription [45]. By contrast, KMT2A, through the KMT2A-WDR5-mediated H3K4me3 activation pathway, induces an increase in H3K4me3 levels at the PU.1 promoter region in fibroblasts, further promoting the expression of PU.1 and subsequent upregulation of pro-fibrotic genes [16]. Moreover, the CREBBP/EP300 acetyltransferase complex exerts its effects through activating the enhancer H3K27ac pathway, inducing an increase in global histone acetylation levels in fibroblasts, which in turn promotes the upregulation of collagen VI (COL6A) expression and aggravates fibrotic progression [46]. In addition, combined inhibition of EP300 and DDR1 can by suppressing p300 HAT activity and blocking DDR1 signaling in fibroblasts, reduce ECM expression, decrease α-SMA levels, and alleviate the fibrosis burden both in vitro and in vivo [47].

HDAC, HAT, KMT and KDM focused interventions show antifibrotic activity in several models, but many studies use broad inhibitors with pleiotropic effects, and the direction and specificity of responses vary across experimental settings. The acute bleomycin model also fails to capture key features of progressive, heterogeneous human IPF, which limits conclusions about long term efficacy. It is still unclear which cell compartments offer the best therapeutic window for targets such as EZH2, G9a, KMT2A and EP300 or CBP. It is also unclear which pharmacodynamic biomarkers best reflect on target chromatin engagement in vivo. Addressing these gaps will strengthen translational interpretation.

Non-coding RNA regulation

Non-coding RNAs (ncRNAs) modulate fibrotic gene programs in IPF, with effects that vary across cell types and disease contexts. Several miRNAs/lncRNAs/circRNAs have reproducible effects on ECM gene expression, fibroblast activation and epithelial/immune signaling, and we summarize the most representative axes below [48].

microRNAs and circRNAs: Lung-targeted miR-29 mimics have been reported to downregulate pro-fibrotic genes (e.g., COL1A1 and COL3A1) in pulmonary fibroblasts by regulating their target mRNAs [49]. For miR-30a, targeting TET1, reduces the hydroxymethylation level of the Drp-1 promoter in fibrosis-related cells, resulting in the downregulated expression of both TET1 and Drp-1 [27]. On the other hand, circHIPK3 acts as a competing endogenous RNA (ceRNA) for miR-30a-3p: it competitively binds to miR-30a-3p in fibroblasts, reducing the latter's binding to FOXK2 mRNA, which in turn upregulates FOXK2. This further enhances the expression of glycolysis-related genes and increases the glycolytic activity of fibroblasts; in mouse models, inhibition of circHIPK3 leads to decreased fibrosis markers [50].

Long non-coding RNAs: In IPF, multiple lncRNA-mediated signaling pathways have been implicated in ECM metabolism and myofibroblast differentiation. LncITPF not only correlates with its host gene ITGBL1 but also forms a functional complex with the RNA-binding protein hnRNP-L. In human lung fibroblasts, upregulation of lncITPF significantly promotes the expression of myofibroblast differentiation markers (e.g., α-SMA and COL1A1) and other ECM-related genes, whereas disruption of the lncITPF-hnRNP-L complex reverses such overexpression [51]. In a bleomycin-induced mouse model of fibrosis, the small-molecule compound MOBT-targeting the lncITPF-hnRNP-L complex-markedly reduces lung hydroxyproline content, collagen deposition, and histological fibrosis scores, highlighting the in vivo therapeutic tractability of this complex [52]. Collectively, these studies define the core role of lncITPF in regulating fibrosis-related genes and ECM deposition.

Another key lncRNA, LINC00941 (also known as lncIAPF), is tightly associated with autophagy regulation and myofibroblast differentiation. The transcription factor ATF3 directly activates LINC00941 transcription; in human lung fibroblasts, LINC00941 binds to ELAVL1 (HuR) to suppress autophagic flux and upregulate α-SMA and ECM-related genes. Under transforming growth factor-β (TGF-β) stimulation, this cascade promotes fibroblast-to-myofibroblast transition, an effect further confirmed by in vivo experiments showing that silencing LINC00941 substantially alleviates fibrotic pathology [53].

Additionally, upregulation of lncRNA TUG1 correlates with CDC27 expression and activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway. In cellular and animal fibrotic models, elevated TUG1 expression enhances collagen production and exacerbates histological fibrosis, suggesting that certain lncRNAs may modulate fibrosis phenotypes by regulating cell cycle and growth signaling cascades [54].

Many ncRNA studies describe differential expression in IPF, but results vary with sampling region, disease stage, and analytical methods. Some ncRNAs may be biomarkers rather than causal drivers. Mechanistic work often relies on overexpression or knockdown in vitro, where off target effects and nonphysiologic RNA levels can affect interpretation. For translation, major uncertainties include delivery to the relevant cell populations, durability of effect, innate immune activation, and safety with repeated dosing. Clinical relevance will be stronger when ncRNAs are supported by convergent human evidence, validated in vivo, and paired with clear pharmacodynamic readouts.

RNA modifications

RNA modifications regulate gene expression after transcription and may contribute to fibrotic remodeling. In IPF, studies have most consistently implicated m^6A and m^5C, and we therefore emphasize these modifications in this section [55-57].

m^6A modification: The most well-characterized modification, N^6-methyladenosine (m^6A), is catalyzed by the "writer" complex (with METTL3/METTL14 as the core) to covalently add a methyl group to the nitrogen-6 position of adenosine (A) in RNA molecules. The functional implementation of m^6A modification relies on its recognition by specific "reader" proteins (e.g., YTHDF1/2/3, YTHDC1), thereby precisely regulating the entire lifecycle of the target mRNA, including pre-mRNA splicing, nuclear export of mature mRNA, translation efficiency, as well as mRNA stability and degradation. Its regulatory network is closely associated with the fibrotic progression, immune microenvironment, and epithelial-mesenchymal transition (EMT) in IPF. The METTL3-YTHDF1 axis enhances m^6A-dependent translation of KCNH6 mRNA, inducing epigenetic phenotypic changes in fibroblasts, which leads to upregulated expression of α-SMA and COL1, accelerated fibroblast-to-myofibroblast transition (FMT), and subsequent exacerbation of pulmonary fibrotic phenotypes [58]. H3K18 lactylation acts through the YTHDF1/m^6A/NREP pathway to induce epigenetic phenotypic changes in lung tissue/mesenchymal cells (involving m^6A reader-mediated lactylation-RNA modification coupling), resulting in the upregulation of pro-fibrotic transcriptional programs and disease progression [59]. As one of the m^6A "writers", ZC3H13 regulates Bax expression to induce epigenetic phenotypic changes in lung tissue/fibroblasts, triggering the upregulation of pro-apoptotic programs and thereby alleviating pulmonary fibrosis [60]. METTL14-mediated m^6A modification of DDIT4 enhances DDIT4 mRNA stability, leading to epigenetic phenotypic alterations in aging-related mesenchymal cells, upregulated DDIT4 expression, and promotion of fibrotic progression in an age related manner [61].

Multi-cohort bioinformatics and model studies have shown that the m^6A regulatory network modulates immune cell infiltration and subset characteristics, inducing epigenetic phenotypic changes in macrophages, though further in vitro and in vivo experimental validation is required [62]. Meanwhile, the m^6A reader YTHDC1 regulates DNA damage responses and delays tissue aging in an m^6A-independent manner, suggesting its regulatory role in the fibrotic microenvironment [63].

m^5C modification: 5-methylcytosine (m^5C) is an RNA modification installed by methyltransferases such as DNMT2 and NSUN family proteins. It has been linked to RNA export, translation, stability, and turnover. This modification regulates nuclear export of RNA, enhances its translation efficiency, maintains its structural stability, and modulates its degradation [64]. Multi-omics analyses report altered expression of multiple m^5C regulators in IPF and cryptogenic organizing pneumonia compared with controls. These regulators can stratify samples into subtypes with distinct immune infiltration patterns, suggesting an association between m^5C related programs and the immune microenvironment. A signature score based on these patterns can distinguish IPF from cryptogenic organizing pneumonia and has been proposed for early identification and prognostic assessment [65].

Evidence for RNA modifications in IPF is still emerging when compared with DNA methylation and histone modifications, and most studies focus on m^6A. Many reports infer regulator function from expression changes or computational signatures. Site resolved mapping and direct links to phenotype remain limited. In addition, some regulators can influence gene expression through mechanisms that do not require the modification itself, which complicates target selection and biomarker interpretation. Future work should combine site level profiling with cell resolved functional experiments. It should also separate acute injury responses from progressive human IPF.

Translational applications and therapeutic strategies

Currently available drugs for IPF provide only partial benefit, and more effective therapies that modify disease biology are in urgent need [23, 66]. We provide an overview of key signaling targets in **Table 2**, and subsequently discuss epigenetic based therapeutic approaches and delivery strategies (**Figure 2**) [19, 20, 22, 23, 33, 41, 66-71].

Table 2. Signaling pathways and therapeutic targets in IPF

Category	Target/Intervention	Mechanism of Action
Cytokine-Receptor Signaling & JAK/STAT Pathway	Ruxolitinib	Alleviates pulmonary fibrosis and downregulate macrophage polarization-related transcripts in bleomycin-induced mouse models of lung fibrosis [67]
	Tacrolimus	Mitigates fibrosis and downregulates M2 macrophage markers by inhibiting the JAK2/STAT3 pathway [70]
Chemokine Receptors	CCR2-targeted nucleic acid drugs	Reduce macrophage-associated inflammation and collagen deposition [33]
	CCR2/CCR5	Druggable targets for regulating monocyte/macrophage recruitment [22, 23, 66]
Upstream Cytokine-Receptor Pathway	IL20RB	Upregulation associated with enhanced function of bone marrow-derived pro-fibrotic macrophages and increased fibrosis [69]
Immune Receptors	TREM2	Downregulation inhibits M2 macrophage polarization and mitigates pulmonary fibrosis in mice [70]
Metabolic Pathways	NAMPT	Upregulation enhances M2 polarization and aggravates fibrosis, indicating regulatory potential of NAD^+ biosynthesis pathway [71]
Redox & Inflammasome	Elamipretide (SS-31)	Suppresses Nrf2-dependent NLRP3 inflammasome activation in macrophages, alleviating pulmonary fibrosis [19]
	Amifostine	Improves mitochondrial function, enhances antioxidant capacity, remodels NAD^+/SIRT1/AMPK signaling axis, and reduce pulmonary fibrosis in animal models [20]
Metabolic-Epigenetic Crosstalk	Butyrate (short-chain fatty acid)	As an endogenous HDAC inhibitor, suppresses TGF-β1-induced myofibroblast differentiation, and regulates energy metabolism reprogramming [41]

DNA methylation regulation

Accumulating data show that changes in DNA methylation are closely associated with transcriptional regulation of genes that drive fibrotic responses. Aberrant DNA methylation profiles reshape the expression of fibrosis related genes in pulmonary cells, thereby promoting both disease initiation and progression in pulmonary fibrosis. In IPF, alveolar macrophages are found to have pronounced DNA methylation abnormalities at genes that regulate lipid and glucose metabolism, including LPCAT1 and PFKFB3, which indicates that macrophage specific methylation programmes contribute to disease pathogenesis and may be amenable to therapeutic intervention [12]. In preclinical models of pulmonary fibrosis, the DNA demethylating agent 5-azacytidine (5-aza) has been reported to restore PPARγ expression, reduce collagen deposition and epithelial to mesenchymal transition, and produce a consistent antifibrotic response [37]. Demethylating agents such as 5 azacytidine have genome wide effects and can cause dose limiting systemic toxicity, which makes systemic treatment difficult in IPF. Lung directed delivery may help address this limitation, and more selective strategies, including targeted epigenome editing, may also be needed.

Histone modification regulation

Research on histone acetylation and deacetylation clarifies critical pathogenic pathways in pulmonary fibrosis and points to potential therapeutic targets, and inhibition of HDAC8 in mouse models of bleomycin induced pulmonary fibrosis is consistently reported to attenuate lung fibrosis [13]. In fibroblasts derived from patients with IPF, the pan-HDAC inhibitor panobinostat markedly downregulates the transcriptional and protein expression of multiple ECM genes, exhibiting stronger inhibitory effects than pirfenidone which is a clinically approved drug. However, its translational feasibility and safety remain to be validated [14, 72]. Studies on HDAC6 have shown that selective HDAC6 inhibitors exert both anti-fibrotic and anti-inflammatory effects in vitro and in vivo [14, 73]. Research targeting acetylation sites indicates that increasing H4K16 acetylation levels reduces pro-fibrotic gene expression and mitigates fibrotic severity in aged

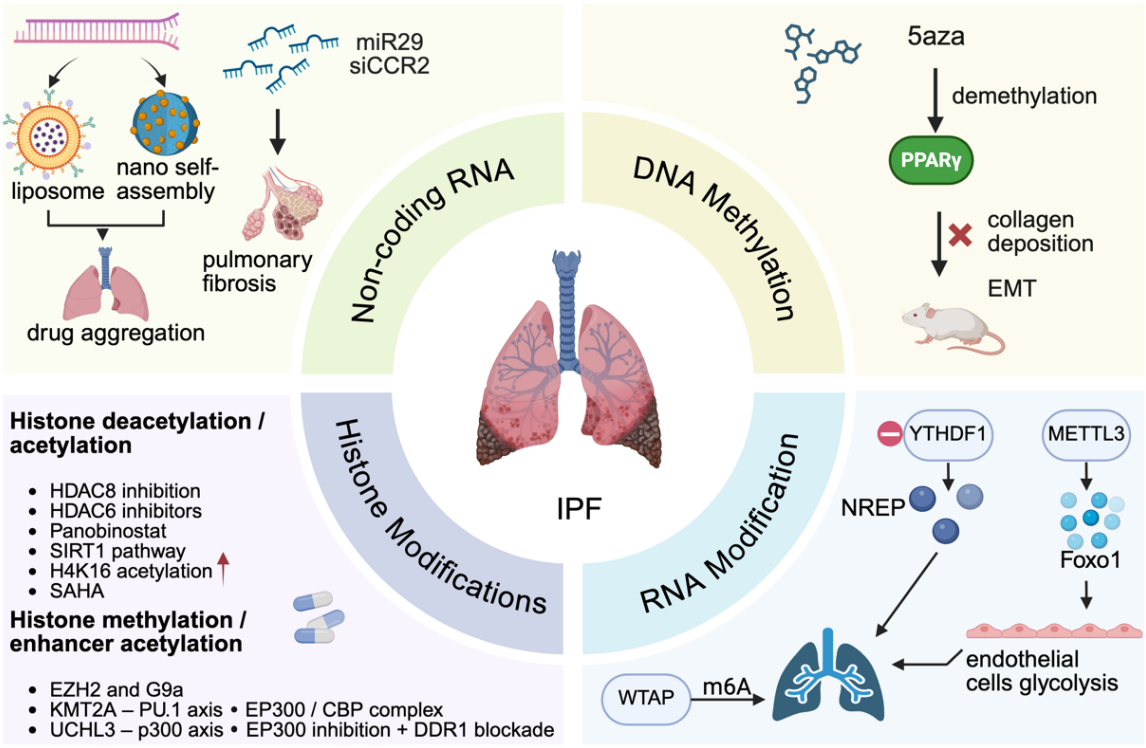

Figure 2. Epigenetic and signaling based therapeutic strategies in IPF.

mouse models of pulmonary fibrosis [15]. Additionally, the SIRT1 pathway regulates fibroblast survival: in vitro, compounds targeting SIRT1-Ku70 deacetylation promote apoptosis of IPF-derived fibroblasts and suppress experimental pulmonary fibrosis [43]; genetic studies have demonstrated that fibroblast-specific deletion of Sirt1 is significantly associated with fibrosis resolution [42]. At the transcriptional regulatory level, the HDAC inhibitor SAHA prevents TGF-β1-induced downregulation of COX-2 in human pulmonary fibroblasts, suggesting that deacetylation pathways are involved in the signaling regulation of inflammatory and anti-fibrotic mediators [74]. Overall, HDAC and HDAC-like pathways have demonstrated anti-fibrotic effects across cellular and animal models; however, the selectivity of different inhibitors, in vivo delivery methods, and long-term safety remain core directions for subsequent translational research [14, 72].

Histone methylation and enhancer acetylation-related targets also provide actionable clues for pulmonary fibrosis intervention. Regarding repressive methylation, the histone methyltransferases EZH2 and G9a synergistically downregulate the expression of the chemokine CXCL10, supporting their involvement in the epigenetic repression of immune-related genes [45]. In pulmonary fibroblasts, the activating methyltransferase KMT2A promotes pro-fibrotic gene transcription by regulating the transcription factor PU.1, and inhibition of this pathway alleviates pulmonary fibrosis [16]. At the enhancer level, the EP300/CBP complex has been confirmed to regulate the expression of ECM genes such as collagen VI, and is closely associated with the fibrotic phenotype [46]. In alveolar type II epithelial cells, the deubiquitinase UCHL3 stabilizes p300 (encoded by EP300), enhances its mediated enhancer acetylation activity, and upregulates the transcription of chemotactic and inflammatory genes [75]. Consistent with this mechanism, strategies combining inhibition of EP300 activity with DDR1 blockade have been shown to reduce ECM expression and collagen deposition both in vitro and in vivo [47].

Non-coding RNA regulation

Nucleic acid based strategies for IPF are increasingly supported by preclinical data, with

particular emphasis on lung directed delivery platforms. Small interfering RNAs formulated in liposomal or nanoassembled systems achieve preferential accumulation in the lung and enable modulation of macrophage activation states and extracellular matrix turnover. Sart1 specific siRNA encapsulated in liposomes reduces fibrotic burden and adjusts macrophage polarization markers in experimental models [76]. MeCP2 siRNA, when delivered by macrophage targeted systems, diminishes collagen deposition and improves histological fibrosis scores in vivo [36]. Interventions aimed at macrophage fibroblast crosstalk show similar promise: Bcar3 siRNA nanoassemblies suppress fibrosis related markers [77], and plekhf1 targeted siRNA in liposomal formulations ameliorates histopathological changes of pulmonary fibrosis after local pulmonary administration [78]. For immune chemotaxis, tetrahedral DNA nanostructures carrying siCCR2 inhibit proinflammatory macrophage phenotypes and attenuate pulmonary fibrosis [33]. Moreover, lung specific administration of miR-29 mimics reduces ECM gene expression and improves fibrotic histology, illustrating the translational potential of microRNA based pulmonary therapies [49].

RNA modification regulation

Although RNA modifying drugs for IPF are not yet approved, regulation of RNA modification, particularly m^{6}A methylation, plays a critical role in disease pathogenesis. Preclinical studies that manipulate m^{6}A regulators such as METTL3, YTHDF1 and WTAP often report antifibrotic effects. METTL3 is reported to control m^{6}A modification of Foxo1 mRNA and to support endothelial glycolytic function, whereas loss of METTL3 favours the emergence of Pfkfb3 positive, RhoJ positive endothelial subsets with profibrotic properties, pointing to a therapeutically relevant link between METTL3 and Foxo1 [79]. In mouse models of arsenic related IPF, silencing of YTHDF1 reduces NREP protein abundance, limits activation of the TGF β1 pathway, decreases collagen accumulation in the lung and improves respiratory function, which supports YTHDF1 as a candidate target for intervention [59]. Transcriptomic analyses of IPF lung tissue further identify 26 m^{6}A regulators with altered expression, including WTAP. On this basis, an IPF prediction model that incorporates WTAP is established, and structure informed virtual screening conducted in parallel identifies five WTAP binding small molecules that provide an initial pool of candidates for drug development [80].

Conclusion

Epigenetic dysregulation provides a unifying framework for IPF. It helps explain how genetic susceptibility and environmental exposures translate into persistent epithelial injury, maladaptive immune activation, and a stable profibrotic fibroblast state. Epigenetic mechanisms can convert injury signals into durable transcriptional change. For example, TGF β1 induces UHRF1, which methylates the Beclin 1 promoter, suppresses autophagy, and promotes fibroblast to myofibroblast transition. METTL3 mediated m^{6}A modification can also promote myofibroblast differentiation of mesenchymal stem cells through the miRNA 21/PTEN pathway. Together, these observations illustrate how epigenetic regulation can sustain fibrotic remodeling [81].

Epigenetic regulators and signatures are also being explored for diagnosis, risk stratification, and target discovery. Models based on differentially expressed m^{6}A regulators highlight WTAP as a candidate biomarker. Structure informed screening has further identified WTAP binding small molecules as starting points for drug development [80]. Early evidence also suggests that epigenetic interventions may enhance the effects of approved antifibrotic drugs, which supports combination strategies guided by mechanism [6].

Despite these advances, several limitations still constrain interpretation and translation. Many datasets lack spatial and temporal resolution, which restricts causal inference, and concordance across species is often weak. Immunometabolic findings, such as those involving lactate metabolism and mitochondrial fission, can also vary across studies [82]. Much of the current literature relies on whole lung tissue, simplified in vitro systems, and rodent models. This makes it difficult to define cell type specific and spatially localized epigenetic programs. Reproducibility of methylation and transcription correlations across cohorts is also affected by differences in inclusion criteria, clinical features, and assay platforms.

These issues complicate translation into reliable biomarkers or therapeutic targets [7, 8, 83]. Several pathways remain incompletely resolved, including the epithelial miR 30a, TET1, Drp1 axis and the effects of myeloid Dnmt3b deletion across species [10-12, 27]. Methylation readers such as MBD2 and MeCP2 also lack comprehensive binding maps and downstream programs in relevant cell states. Time dependent effects of mechanical stress and inflammatory signals on chromatin organization remain poorly defined without longitudinal single cell and spatial datasets [84-86].

Building on the evidence summarized above, future therapeutic development in IPF can follow a practical sequence, moving from target nomination to intervention design and then to rigorous validation of clinical benefit. At the level of epigenetic modulation, selective inhibition of HDAC6 and HDAC8 and modulation of the SIRT1 axis have demonstrated antifibrotic activity in experimental systems, but target specificity, therapeutic window, and compatibility with approved antifibrotic agents require confirmation in human derived samples [13-15, 43]. For histone methylation and enhancer regulation, the EZH2 and G9a, KMT2A and PU.1, and EP300 and UCHL3 pathways are supported by mechanistic and transcriptional data, and priority should be given to defining pharmacodynamic biomarkers and a clear risk benefit profile in patient derived material and early phase studies [16, 45-47]. In parallel, metabolism related networks and signaling focused targets may be evaluated in combination strategies to optimize dose selection and test additive or synergistic effects [17, 18, 20, 30, 71]. For small molecules and delivery platforms, lung directed delivery of miR-29 mimics, inhaled nano or microcapsules, and DNA nanostructure based siRNA carriers has shown early feasibility. Phase I studies should include pharmacokinetic assessment, long term safety follow up, and pharmacodynamic measures that reflect target engagement and mechanism [33, 49, 87]. Overall, this review delineates candidate therapeutic strategies and targetable pathways that warrant systematic investigation and provides a conceptual basis for advancing precision therapy in IPF.

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Disclosure of conflict of interest

None.

Abbreviations

IPF, Idiopathic pulmonary fibrosis; ECM, extracellular matrix; ROS, reactive oxygen species; 5-mC, 5-methylcytosine; DNMTs, DNA methyltransferases; AEC2s, type II alveolar epithelial cells; AT2, alveolar type II; IRF4, interferon regulatory factor 4; HATs, histone acetyltransferases; HDACs, histone deacetylases; SIRT, sirtuin; ncRNAs, non-coding RNAs; miRNAs, micro RNAs; lncRNAs, non-coding RNAs; circRNAs, circular RNAs; ceRNA, competing endogenous RNA; EMT, epithelial-mesenchymal transition; FMT, fibroblast-to-myofibroblast transition; COP, cryptogenic organizing pneumonia; NAMPT, nicotinamide phosphoribosyltransferase; 5-aza, 5-azacytidine; siRNAs, small interfering RNAs; As-IPF, arsenic-induced IPF; FVC, forced vital capacity.

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