Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
B S, R R, Musthafa MKM. **Epigenetic crosstalk between miR-144 and DNMT3A in the pathogenesis of chronic obstructive pulmonary disease: a narrative review**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.3844

Submitted: 5-12-2025
Accepted: 21-07-2026

Epigenetic crosstalk between miR-144 and DNMT3A in the pathogenesis of chronic obstructive pulmonary disease: a narrative review

Samjhana B,[1] Reeta R,[1] Muhamed Kamaludeen Muhamed Musthafa[2]

[1]Department of Biochemistry, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be University) Puducherry; [2]Department of Respiratory Medicine, Mahatma Gandhi Medical College & Research Institute, Sri Balaji Vidyapeeth (Deemed to be University) Puducherry, India

Correspondence: Reeta R, Department of Biochemistry, Mahatma Gandhi Medical College & Research Institute, SBV, Puducherry, India. E-mail: reetar@mgmcri.ac.in

Contributions: Reeta R: conceptualization, supervision. Samjhana B: literature search, literature synthesis, writing (original draft and review and editing. – Dr. Reeta R; Muhamed Kamaludeen Muhamed Musthafa: , clinical interpretation. All the authors have contributed significantly, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflict of interest.

Ethics approval and consent to participate: ethics approval was not required because this study is a narrative review based exclusively on previously published literature and did not involve human participants or animal experiments performed by the authors.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Acknowledgments: the authors would like to acknowledge the contributions of individuals and teams who supported the development of this review but do not meet the criteria for authorship. We thank the faculty of the Department of Biochemistry, MGMCRI, for their scholarly input and constructive discussions during the preparation of this manuscript. We also appreciate the assistance of the library staff at Sri Balaji Vidyapeeth for facilitating access to scientific databases and full-text articles. Administrative support provided by the Research Office of SBV during the manuscript preparation and submission process is gratefully acknowledged.

Declaration of generative artificial intelligence and artificial intelligence-assisted technologies in the writing process: no AI genarated content is used.

Abstract

This review consolidates and evaluates current evidence on the epigenetic interaction between microRNA-144 [miR-144] and DNA methyltransferase 3A (DNMT3A) and its collective role in the pathogenesis of chronic obstructive pulmonary disease (COPD). The available literature was narratively synthesized to provide a comprehensive overview of the current evidence regarding the mechanistic, epigenetic, and clinical implications of miR-144 and DNMT3A in COPD. Across the included studies, miR-144 was consistently reported to be upregulated in smokers and individuals with COPD, with parallel findings demonstrating a reduction in DNMT3A expression and associated hypomethylation of key inflammatory gene promoters. Functional assays and mechanistic analyses further substantiated that miR-144 directly targets and suppresses DNMT3A, leading to impaired methyltransferase activity, dysregulated DNA methylation patterns, heightened oxidative stress, and enhanced secretion of pro-inflammatory cytokines. These molecular alterations collectively contribute to a self-sustaining cycle of chronic inflammation, epithelial injury, and airway remodeling, which are potential features of COPD progression. The literature that is now available indicates that DNMT3A-mediated epigenetic regulation and miR-144 dysregulation both contribute to important molecular processes implicated in the pathophysiology of COPD, such as oxidative stress, inflammation, and aberrant gene regulation. There is currently little direct mechanistic evidence connecting the miR-144–DNMT3A axis in COPD, despite the literature supporting the individual roles of these molecules. Therefore, rather than being a completely developed pathway, this regulatory interaction should be viewed as an evolving mechanistic framework. To fully understand its diagnostic, prognostic, and therapeutic potential in COPD, more experimental research, extensive clinical validation, and phenotype-specific studies are needed.

Key words: COPD, miR-144, DNMT3A, epigenetics, DNA methylation, inflammation, oxidative stress.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous respiratory disorder characterised by irreversible airflow limitation and chronic inflammation. Although cigarette smoke exposure is the dominant risk factor, only a fraction of smokers develops COPD, suggesting that additional mechanisms—particularly epigenetic regulation—determine individual susceptibility [1]. DNA methylation and micro-RNA (miRNA)–mediated post-transcriptional regulation have recently emerged as key determinants of pulmonary inflammation and oxidative imbalance [2]. Among these, micro-RNA-144 (miR-144) has attracted attention for its ability to modulate antioxidant pathways and DNA methyltransferase 3A (DNMT3A), a major enzyme governing de novo methylation. This review synthesises current evidence on the miR-144–DNMT3A axis in COPD pathogenesis.

COPD remains a leading cause of morbidity and mortality, accounting for more than 3 million deaths annually worldwide [3]. The disease arises from a complex interplay between genetic predisposition, environmental insults, and epigenetic reprogramming [4]. Cigarette smoke contains > 4 chemicals that generate reactive oxygen species (ROS), causing direct DNA damage and persistent activation of pro-inflammatory signalling pathways [5]. However, the severity and progression of COPD vary greatly among individuals with similar exposure, implicating inherited or acquired molecular regulators in disease heterogeneity [6].

Epigenetic modifications—including DNA methylation, histone acetylation, and non-coding RNA regulation—link environmental stimuli to gene expression changes without altering DNA sequence [7]. Epigenetic alterations, particularly changes in DNA methylation, influence the expression of inflammatory mediators and matrix metalloproteinases in COPD, thereby contributing to chronic inflammation and progressive lung remodeling [8] . Concomitantly, aberrant miRNA expression profiles have been detected in sputum, serum, and lung tissue [9].

Among these miRNAs, miR-144 has gained prominence for its dual ability to suppress antioxidant responses via *Nrf2* inhibition [10] and to influence epigenetic regulation through targeting of EZH2 [11]. DNMT3A is a de novo DNA methyltransferase that establishes CpG methylation patterns essential for epigenetic regulation. In COPD, dysregulation of DNA methylation has been associated with hypomethylation of inflammatory loci and aberrant activation of pro-inflammatory pathways, highlighting the contribution of DNMT3A-mediated epigenetic changes to disease pathogenesis [11,12]. The interaction between miR-144-3p and EZH2 may represent

an epigenetic regulatory mechanism in COPD. Cigarette smoke exposure is associated with increased miR-144-3p expression, while miR-144-3p directly targets EZH2, a histone methyltransferase, potentially contributing to persistent inflammatory responses [11]. Despite several independent reports, a consolidated review describing this nexus across molecular, cellular, and clinical dimensions has been lacking.

This narrative review therefore examines:

- Patterns of miR-144 dysregulation in COPD;
- The mechanistic link between miR-144 and DNMT3A;
- Consequences of altered methylation on inflammatory and oxidative pathways; and
- Potential translational implications for biomarker development and targeted epigenetic therapy.

Materials and Methods

Literature sources and scope

This narrative review was developed through a structured survey of the literature using PubMed, Scopus, Web of Science, and Google Scholar. Publications available in English between January 2010 and March 2025 were considered. The review focused on studies describing miR-144 dysregulation, DNMT3A-mediated epigenetic regulation, oxidative stress, inflammatory signalling, biomarker potential, and therapeutic implications in COPD.

Selection and synthesis of evidence

Relevant experimental and clinical studies involving human subjects, animal models, and in vitro systems were evaluated based on their relevance to the objectives of this review. The available evidence was narratively synthesized to summarize current understanding of the molecular, epigenetic, and clinical interactions between miR-144 and DNMT3A in COPD. Because of substantial heterogeneity in study design, biological specimens, experimental models, and analytical methodologies, a qualitative narrative synthesis was performed rather than a quantitative meta-analysis.

Molecular mechanisms linking miR-144 and DNMT3A in COPD

Expression profile of miR-144 in COPD

Studies have reported altered miR-144 expression in COPD, with several reporting increased miR-144-3p levels compared with healthy controls; however, differences in study populations, biological specimens, disease severity, and experimental methodologies may contribute to variability in reported expression patterns [11,13] .

Up-regulation occurs in plasma, sputum, bronchial epithelial cells, and alveolar macrophages. miR-144 dysregulation has been demonstrated in COPD relavent experimental models [14], and miR-144 is among the miRNAs associated with human pathologies in blood-based profiling studies [15]; circulating miRNAs overall show diagnostic potential in COPD meta-analysis [10]. Cigarette smoke exposure alters miRNA expression in human bronchial epithelial models [16], promoting oxidative stress and apoptotic signalling [17]. Mechanistically, miR-144-3p has been implicated in COPD-associated inflammatory pathways, including regulation of the TLR2/MMP9 axis in pulmonary monocytes [18].

miR-144 resides on chromosome 17q11.2 within the miR-144/451a cluster, whose functional interplay with Nrf-2 is established in vivo [19]. Oxidative stress suppresses Nrf2 but activates Bach1, a relationship reviewed in the context of oxidative stress signalling [20]. The significance of DNMT3A in the pathophysiology of COPD is further highlighted by recent mechanistic studies. According to Huang et al., Th17/Treg immunological imbalance and chronic airway inflammation in COPD are caused by altered DNMT3A expression and nuclear translocation, which control dendritic-cell activity via the ELAVL1–DNMT3A–DACH1/c-Jun pathway. These results link DNMT3A to immunological dysregulation linked to the advancement of illness, extending its function beyond DNA methylation alone [21].

DNMT3A down-regulation and global hypomethylation

DNMT3A catalyses transfer of methyl groups to cytosine residues within CpG dinucleotides, establishing de novo methylation patterns essential for chromatin stability [22]. Altered expression of DNA methyltransferases has been reported in cigarette smoke exposure and COPD, with downregulation of DNMT3A and DNMT3B observed in experimental lung models [23] . Genome-wide methylation analyses have identified numerous CpG sites associated with COPD and with reduced lung function, including hypomethylation of *SERPINA1*, supporting a broader

role for aberrant DNA methylation in COPD pathogenesis [24]. Immunohistochemical analyses of bronchial biopsies revealed diminished nuclear DNMT3A staining in airway epithelium [25]. Mechanistically, oxidative stress and pro-inflammatory cytokines inhibit DNMT3A expression via ROS-mediated activation of p38 MAPK and NF-κB signalling [4]. Moreover, miR-144 directly targets DNMT3A 3′UTR, as validated by luciferase-reporter assays in macrophages and epithelial cells [26].

miR-144–DNMT3A axis and epigenetic feedback loop

Integration of molecular evidence supports a reciprocal regulatory circuit:

- Cigarette smoke and ROS activate transcription factors (Bach1, NF-Kb) → induce miR-144.
- miR-144 binds DNMT3A mRNA → suppresses methyltransferase expression.
- Decreased DNMT3A → hypomethylation of inflammatory promoters (*IL-6*, *IL-8*, *TNF-α*).
- Enhanced cytokine transcription and oxidative stress → further miR-144 induction.

This self-amplifying epigenetic circuit sustains inflammation even in the absence of ongoing smoke exposure [27]. In vitro studies have demonstrated that miR-144 inhibition restores transforming growth factor-beta (TGF-β) and polymeric immunoglobulin receptor (pIgR) expression in cigarette-smoke-extract-exposed bronchial epithelial cells, supporting a functional role for miR-144 in airway immune regulation [14]. Figure 1. Schematic representation of the hypothesized miR-144–DNMT3A epigenetic axis in COPD based on currently available experimental evidence.

Crosstalk between oxidative stress and inflammation

The oxidative–inflammatory axis is central to COPD pathology. Recent evidence by Ji et al. demonstrated that cumulative PM2.5 exposure is associated with widespread DNA methylation changes in COPD, further supporting the role of environmental exposures in driving epigenetic changes, oxidative stress, and persistent airway inflammation [28]. In healthy cells, *Nrf2* orchestrates antioxidant defense by inducing *HO-1*, *SOD*, and *GPx*. However, miR-144 up-regulation in COPD suppresses *Nrf2* translation, thereby dismantling the antioxidant shield [29]. The concurrent down-regulation of DNMT3A aggravates oxidative stress indirectly by allowing hypomethylation of pro-oxidant genes and by repressing genes that promote DNA repair [30].

This dual impairment fosters a cycle wherein oxidative stress induces miR-144 expression, and elevated miR-144 further weakens antioxidant capacity. ROS accumulation then amplifies inflammatory cytokine release *(IL-6, TNF-α, IL-8)* and activates the inflammasome, perpetuating epithelial injury and remodelling [31]. Animal models have demonstrated that inhibition of miR-144 restores *Nrf2* and DNMT3A levels, normalises methylation, and decreases macrophage infiltration [32].

Clinical correlations and biomarker implications

Circulating miRNAs are remarkably stable, protected within exosomes or protein complexes, making them attractive biomarker candidates [15]. Elevated serum miR-144 has been consistently reported in COPD patients relative to smokers without airflow limitation [18]. Levels correlate inversely with FEV_1/FVC and directly with CRP and serum IL-6 [33]. Cigarette smoke exposure has been shown to increase DNMT3A mRNA and protein expression in dendritic cells, implicating DNMT3A in cigarette smoke-induced Th17/Treg imbalance in COPD [21].

Circulating and extracellular-vesicle-associated miRNAs have emerged as potential non-invasive biomarkers for COPD diagnosis and disease stratification, although their diagnostic performance varies across cohorts and biological specimens [34]. Longitudinal evidence regarding miR-144 in COPD remains limited, highting the need for prospective studies to determine its potential value in monitoring disease progression and treatment response [35].

Despite these encouraging findings, the clinical application of DNMT3A and miR-144 as biomarkers remain limited. The reproducibility and generalizability of the results are limited because the majority of studies that are currently available are based on comparatively small cohorts with significant methodological heterogeneity in biological material, detection methodologies, and normalization strategies [10]. Additionally, the routine clinical application of these biomarkers in COPD management is currently hindered by the lack of prospective multicenter validation studies and standardized analytical protocols [10]. Therefore, even though miR-144 and DNMT3A show promise as diagnostic and prognostic biomarkers, more extensive longitudinal research is needed before they can be integrated into routine clinical practice for early diagnosis, risk stratification, or disease monitoring [36].

Representative studies investigating miR-144, DNMT3A, and related molecular pathways in COPD and relevant experimental models are summarized in Table 1.

Therapeutic prospects

Epigenetic therapy in COPD is still nascent. Targeting miR-144 with antisense oligonucleotides or miRNA sponges represents a plausible strategy. Modulation of miR-144 has been shown to influence Nrf2- mediated antioxidant responses, suggesting a potential therapeutic space for limiting oxidative stress [37]. Delivery systems such as lipid nanoparticles and inhalable exosome mimetics have achieved efficient pulmonary uptake in experimental models. Conversely, strategies aimed at enhancing DNMT3A- mediated methylation or reducing TET- mediated DNA dememthylation may represent potential approaches to restore methylation equilibrium [38,39]. Caution is warranted, however, since global modulation of methylation may yield off-target effects. A more refined approach could involve CRISPR-based epigenetic editing to re-methylate specific promoters dysregulated by the miR-144–DNMT3A axis [40]. Integration of these methods with anti-oxidant therapies might achieve synergistic suppression of inflammatory cascades.

Discussion

All of the information that is currently available points to the separate roles that DNMT3A-mediated epigenetic regulation and miR-144 dysregulation play in the pathophysiology of COPD. These molecules' altered expression has been linked to oxidative stress, inflammation, aberrant DNA methylation, and airway remodeling, all of which may contribute to the advancement of the disease. Nevertheless, there is still little direct mechanistic proof that miR-144 and DNMT3A particularly interact to regulate COPD. Much of the available evidence comes from separate research on these compounds or from relevant experimental illness models. Therefore, rather than being a completely developed molecular pathway, the suggested miR-144–DNMT3A axis should be viewed as an emergent mechanistic framework that incorporates the existing data. To confirm this regulatory connection and understand its biological and clinical importance, more mechanistic studies in COPD-specific experimental models and well-characterized clinical cohorts are imperative.

Comparative insights with other miRNAs and epigenetic marks

While numerous miRNAs—such as miR-21, miR-146a, and miR-223—modulate inflammatory signalling, these appear to simultaneously govern both DNA methylation and antioxidant responses [41]. miR-144 therefore occupies a unique dual-regulatory niche [29]. Similarly,

DNMT3A reduction in COPD mirrors genome-wide methylation drift observed with ageing ("inflammageing") [42]. The convergence of oxidative stress, senescence, and epigenetic erosion may underlie the accelerated biological ageing typical of COPD lungs [43] .

Histone modifications further interact with DNA methylation. Reduced DNMT3A often coincides with diminished histone-H3-lysine-9 methylation and increased acetylation at inflammatory gene promoters [44]. Such crosstalk accentuates chromatin relaxation and transcriptional activation. Thus, the miR-144–DNMT3A axis likely functions within a broader epigenetic network rather than as an isolated pathway.

Limitations of current evidence

Even though there is increasing evidence that miR-144 has a role in COPD, there is a lot of variation in the research that has been done. Although the majority of studies have found elevated miR-144 expression in COPD, differences among biological specimens [serum, plasma, sputum, peripheral blood mononuclear cells, bronchial epithelial cells, or lung tissue], demographics of patients, smoking history, disease severity, acute exacerbation status, sample size, and analytical techniques can all contribute to variations in expression profiles. Direct comparisons between research are made more difficult by this biological and methodological variability, which can also lead to discrepancies in published results. Additionally, not all published studies consistently demonstrate direct regulation of DNMT3A or dysregulation of miR-144 in COPD, indicating that the observed heterogeneity may represent both methodological variations between studies and biological heterogeneity within patient populations.

These variations highlight the necessity for standardized study designs and independent validation in larger, well-characterized COPD populations and should be taken into account when evaluating the available data [36]. Furthermore, significant confounding variables like smoking intensity, corticosteroid medication, and comorbidities like diabetes are frequently not well controlled, and sample sizes are typically small [45]. Few studies have used luciferase reporter assays, mutational analysis, or rescue experiments in COPD-relevant experimental settings to directly validate miR-144-mediated control of DNMT3A. Numerous differentially expressed and methylated genes linked to oxidative stress and inflammatory pathways in COPD have been found using recent integrative analyses that combine DNA methylation with gene expression profiling [4]. These results suggest that epigenetic instability in COPD goes beyond specific markers like

DNMT3A and miR-144, supporting the concept of a complex regulatory network that warrants further mechanistic investigation [4].

Temporal dynamics also remain unexplored: whether miR-144 elevation precedes DNMT3A loss or occurs as a secondary consequence of inflammation is unclear. Multi-omic approaches integrating transcriptomic, methylomic, and proteomic data are urgently needed to map causality [46]. Additionally, although recent single-cell and spatial studies have begun to delineate the contributions of epithelial, fibroblasts, and immune cell populations in COPD, their relative roles and intercellular interactions across disease sage remain incompletely understood [47].

Based on the evidence that is now available, a conceptual model can be put out in which oxidative stress and cigarette smoke cause miR-144 overexpression, which in turn suppresses DNMT3A expression. Decreased DNMT3A activity leads to aberrant DNA methylation, which causes extracellular matrix changes, increased airway damage, chronic activation of inflammatory pathways, and compromised antioxidant defense through Nrf2 dysregulation. This approach incorporates existing molecular, epigenetic, and functional evidence and offers a foundation for further experimental research, despite the fact that direct mechanistic validation of this regulatory axis remains limited [8,11,33].

Future directions

The major knowledge gaps identified from the current literature and the corresponding future research priorities are summarized in Table 2.

- Phenotype-specific research: Future research should assess the miR-144–DNMT3A regulatory axis in various COPD phenotypes, such as smoking-related versus biomass smoke-related COPD, emphysema-predominant COPD, chronic bronchitis-predominant COPD, stable COPD, acute exacerbation COPD (AECOPD), and frequent exacerbators. Although there is currently little evidence to establish these distinctions, such stratification may improve biomarker-guided precision medicine approaches and clarify phenotype-specific genetic signatures.
- Integrated clinical - Molecular cohorts: Parallel measurement of DNMT3A, miR-144, and sentinel gene methylation (IL-6, NFE2L2) throughout GOLD phases.
- Cell-specific analyses: To identify the cellular sources of miR-144 dysregulation, single-cell RNA sequencing and spatial methylome profiling are used.

- Functional validation: miR-144/DNMT3A overexpression or knockout using CRISPR-Cas in organoid and animal models.
- Therapeutic investigation: Studies combining antioxidant supplements and miR-144 inhibition.

Such multi-level analyses will clarify whether the miR-144–DNMT3A circuit represents a driver of disease or merely a biomarker of chronic exposure.

Conclusions

The cumulative evidence positions the miR-144–DNMT3A axis as an emerging mechanistic framework connecting oxidative stress, DNA methylation, and chronic inflammation in COPD. Up-regulated miR-144 represses DNMT3A, leading to demethylation of inflammatory promoters and sustained cytokine expression, while concurrently inhibiting *Nrf2*-dependent antioxidant pathways. This self-reinforcing feedback perpetuates tissue injury and functional decline.

Future translational studies integrating longitudinal sampling, precise methylome mapping, and therapeutic miRNA modulation are warranted to verify causality and clinical utility. Understanding this axis may pave the way for novel diagnostic and therapeutic strategies aimed at restoring epigenetic homeostasis in COPD.

References

1. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009;136:215-33.
2. Eisner MD, Anthonisen N, Coultas D, et al. An Official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693-718.
3. Ezzie ME, Crawford M, Cho JH, et al. Gene expression networks in COPD: microRNA and mRNA regulation. Thorax 2012;67:122-31.
4. Vucic EA, Chari R, Thu KL, et al. DNA methylation is globally disrupted and associated with expression changes in chronic obstructive pulmonary disease small airways. Am J Respir Cell Mol Biol 2014;50:912-2.
5. Sundar IK, Li D, Rahman I. Small RNA-sequence analysis of plasma-derived extracellular vesicle miRNAs in smokers and patients with chronic obstructive pulmonary disease as circulating biomarkers. J Extracell Vesicles 2019;8:1684816.

6. He LX, Tang ZH, Huang QS, Li WH. DNA methylation: a potential biomarker of chronic obstructive pulmonary disease. Front Cell Dev Biol 2020;8:585.
7. Zhang L, Valizadeh H, Alipourfard I, et al. Epigenetic modifications and therapy in chronic obstructive pulmonary disease (COPD): an update review. COPD 2020;17:333-42.
8. Eriksson Ström J, Kebede Merid S, Linder R, et al. Airway MMP-12 and DNA methylation in COPD: an integrative approach. Respir Res 2025;26:10.
9. Eriksson Ström J, Kebede Merid S, Pourazar J, et al. Chronic obstructive pulmonary disease is associated with epigenome-wide differential methylation in BAL lung cells. Am J Respir Cell Mol Biol 2022;66:638-47.
10. Li X, Fu G, Zhang C, et al. Blood miRNAs as potential diagnostic biomarkers for chronic obstructive pulmonary disease: a meta-analysis. Int J Chron Obstruct Pulmon Dis 2024;19:981-93.
11. Song B, Chen Y. Long non-coding RNA SNHG4 aggravates cigarette smoke-induced COPD by regulating miR-144-3p/EZH2 axis. BMC Pulm Med 2023;23:513.
12. Huo X, Jin S, Wang Y, Ma L. DNA methylation in chronic obstructive pulmonary disease. Epigenomics 2021;13:1145-55.
13. Liu P, Zhang M, Gao H, et al. Regulation of whole-transcriptome sequencing expression in COPD after personalized precise exercise training: a pilot study. Respir Res 2023;24:156.
14. Liu H, Zhao Y, Cao J, et al. The role of MicroRNA-144 in regulating airway immune dysfunction in COPD through the transforming growth factor-beta/polymeric immunoglobulin receptor pathway: an in vitro study. Chronic Obstr Pulm Dis 2025;12:285-93.
15. Keller A, Leidinger P, Vogel B, et al. miRNAs can be generally associated with human pathologies as exemplified for miR-144*. BMC Med 2014;12:224.
16. Mathis C, Poussin C, Weisensee D, et al. Human bronchial epithelial cells exposed in vitro to cigarette smoke at the air-liquid interface resemble bronchial epithelium from human smokers. Am J Physiol-Lung Cell Mol Physiol 2013;304:L489-503.
17. Zeng H, Li T, He X, et al. Oxidative stress mediates the apoptosis and epigenetic modification of the Bcl-2 promoter via DNMT1 in a cigarette smoke-induced emphysema model. Respir Res 2020;21:229.

18. Li Y, Lu X, Li W, et al. The circRERE/miR-144-3p/TLR2/MMP9 signaling axis in COPD pulmonary monocytes promotes the EMT of pulmonary epithelial cells. Biochem Biophys Res Commun 2022;625:1-8.
19. Yang L, He S, Ling L, et al. Crosstalk between miR-144/451 and Nrf2 during recovery from acute hemolytic anemia. Genes 2023;14:1011.
20. Kurinna S, Werner S. NRF2 and microRNAs: new but awaited relations. Biochem Soc Trans 2015;43:595-601.
21. Huang D, Zhou B, Luo Z, et al. Cigarette smoke extract promotes DNA methyltransferase 3A expression in dendritic cells, inducing Th-17/Treg imbalance via the C-JUN /allograft inflammatory factor 1 axis. Kaohsiung J Med Sci 2021;37:594-603.
22. Machin M, Amaral AFS, Wielscher M, et al. Systematic review of lung function and COPD with peripheral blood DNA methylation in population based studies. BMC Pulm Med 2017;17:54.
23. Sundar IK, Rahman I. Gene expression profiling of epigenetic chromatin modification enzymes and histone marks by cigarette smoke: implications for COPD and lung cancer. Am J Physiol-Lung Cell Mol Physiol 2016;311:L1245-58.
24. Qiu W, Baccarelli A, Carey VJ, et al. Variable DNA methylation is associated with chronic obstructive pulmonary disease and lung function. Am J Respir Crit Care Med 2012;185:373-81.
25. Sundar IK, Yin Q, Baier BS, et al. DNA methylation profiling in peripheral lung tissues of smokers and patients with COPD. Clin Epigenetics 2017;9:38.
26. Nasirzadeh M, Pouramir M, Gholizadeh-Ghaleh Aziz S, Alipour S. Upregulation of microRNA-144 suppresses Nrf2 antioxidant signaling pathway in patients with severe COVID-19. Iran J Allergy Asthma Immunol 2025;24:31-40.
27. Huang X, Zhu Z, Guo X, Kong X. The roles of microRNAs in the pathogenesis of chronic obstructive pulmonary disease. Int Immunopharmacol 2019;67:335-47.
28. Ji HW, Kang J, Kim HC, et al. The association between cumulative exposure to PM2.5 and DNA methylation measured using methyl-capture sequencing among COPD patients. Respir Res 2024;25:335.
29. Zhang J, Pan W, Zhang Y, et al. Comprehensive overview of Nrf2-related epigenetic regulations involved in ischemia-reperfusion injury. Theranostics 2022;12:6626-45.

30. Lujambio A, Calin GA, Villanueva A, et al. A microRNA DNA methylation signature for human cancer metastasis. Proc Natl Acad Sci 2008;105:13556-61.
31. Lopez-Serra P, Esteller M. DNA methylation-associated silencing of tumor-suppressor microRNAs in cancer. Oncogene 2012;31:1609-22.
32. Qiu J, Liu X, Yang G, et al. MiR-29b level-mediated regulation of Klotho methylation via DNMT3A targeting in chronic obstructive pulmonary disease. Cells Dev 2023;174:203827.
33. Kukoyi AT, Fan X, Staitieh BS, et al. MiR-144 mediates Nrf2 inhibition and alveolar epithelial dysfunction in HIV-1 transgenic rats. Am J Physiol-Cell Physiol 2019;317:C390-7.
34. Lv J, Xiong X. Extracellular vesicle microRNA: a promising biomarker and therapeutic target for respiratory diseases. Int J Mol Sci 2024;25:9147.
35. Zhang F, Cui Y, Zhang T, Yin W. Epigenetic regulation of macrophage activation in chronic obstructive pulmonary disease. Front Immunol 2024;15:1445372.
36. Hollander Z, DeMarco ML, Sadatsafavi M, et al. Biomarker development in COPD: moving from p values to products to impact patient care. Chest 2017;151:455-67.
37. Zhang C, Shu L, Kong ANT. MicroRNAs: new players in cancer prevention targeting Nrf2, oxidative stress and inflammatory pathways. Curr Pharmacol Rep 2015;1:21-30.
38. Ren W, Gao L, Song J. Structural basis of DNMT1 and DNMT3A-mediated DNA methylation. Genes 2018;9:620.
39. Rasmussen KD, Helin K. Role of TET enzymes in DNA methylation, development, and cancer. Genes Dev 2016;30:733-50.
40. Liu XS, Wu H, Ji X, et al. Editing DNA methylation in the mammalian genome. Cell 2016;167:233-47.e17.
41. Ibáñez-Cabellos JS, Pallardó FV, García-Giménez JL, Seco-Cervera M. Oxidative stress and epigenetics: miRNA involvement in rare autoimmune diseases. Antioxidants 2023;12:800.
42. Breen M, Nwanaji-Enwerem JC, Karrasch S, et al. Accelerated epigenetic aging as a risk factor for chronic obstructive pulmonary disease and decreased lung function in two prospective cohort studies. Aging 2020;12:16539-54.
43. Ragusa R, Bufano P, Tognetti A, et al. Recent evidences of epigenetic alterations in chronic obstructive pulmonary disease (COPD): a systematic review. Int J Mol Sci 2025;26:2571.
44. Bayarsaihan D. Epigenetic mechanisms in inflammation. J Dent Res 2011;90:9-17.

45. Gaddam M, Gullapalli D, Adrish M. From bench to bedside: the next frontier for biomarkers in COPD precision medicine. Biomark Med 2026;20:145-8.
46. Gillenwater LA, Helmi S, Stene E, et al. Multi-omics subtyping pipeline for chronic obstructive pulmonary disease. PLoS One 2021;16:e0255337.
47. Zhang Y, Wei H, Nouws J, et al. Aberrant cellular communities underlying disease heterogeneity in chronic obstructive pulmonary disease. Nat Genet 2026;58:376-91.

Table 1 Representative studies describing the role of miR-144 and DNMT3A in the pathogenesis of COPD.

Author / Year	Study Focus	Sample / Model	Key Findings	Relevance
Ezzie et al., 2012	miRNA and mRNA dysregulation in COPD	Human lung tissue (smokers with and without COPD)	Widespread differential expression of miRNAs and mRNAs in COPD lung tissue, enriching pathways relevant to COPD pathogenesis.	Established broad miRNA dysregulation as a feature of COPD lung tissue.
Song & Chen, 2023	miR-144-3p/EZH2 axis	Serum of COPD patients; cigarette-smoke-extract-exposed Beas-2B cells	miR-144-3p was up-regulated in COPD and in smoke-exposed cells, and directly targeted EZH2 as part of the SNHG4/miR-144-3p/EZH2 regulatory axis.	Direct experimental evidence linking miR-144 to an epigenetic regulator in COPD.
Li Y et al., 2022	circRERE/miR-144-3p/TLR2/MMP9 axis	COPD pulmonary monocytes (smoke-induced mouse model)	miR-144-3p suppressed TLR2 in monocytes; the circRERE/miR-144-3p/TLR2/MMP9 axis promoted epithelial-mesenchymal transition of pulmonary epithelial cells.	Links miR-144 to airway remodeling pathways in COPD.
Liu H et al., 2025	miR-144 and airway immune dysfunction	Human bronchial epithelial cells exposed to cigarette smoke extract (in vitro)	Cigarette smoke extract up-regulated miR-144, which suppressed pIgR via the TGF-β pathway; miR-144 inhibition restored pIgR expression.	Supports a functional role for miR-144 in COPD-related airway immune dysfunction.
Huang D et al., 2021	DNMT3A dysregulation	Dendritic cells exposed to cigarette smoke extract; co-cultured CD4+ T cells	Cigarette smoke extract increased DNMT3A expression, driving Th17/Treg imbalance via the c-Jun/AIF1 axis.	Links DNMT3A dysregulation to immune imbalance in a smoke-exposure model relevant to COPD.
Eriksson Ström et al., 2022	Epigenome-wide DNA methylation	Bronchoalveolar lavage (BAL) cells from COPD and control subjects	COPD was associated with epigenome-wide differential DNA methylation in BAL cells, with many differentially methylated positions linked to gene expression.	Demonstrates broad epigenetic (methylation alterations in the COPD airway.
Eriksson Ström et al., 2025	DNA methylation and MMP-12	Bronchoalveolar lavage [BAL] fluid and cells	COPD was associated with higher BAL MMP-12, and MMP-12 levels were linked to DNA methylation at multiple loci.	Demonstrates a contribution of epigenetic regulation to airway inflammation and remodeling.
Li X et al., 2024	Circulating miRNAs as biomarkers	Peripheral blood [meta-analysis of 18 studies]	Blood miRNAs showed good diagnostic accuracy for COPD, including during acute exacerbations.	Supports the potential of circulating miRNAs, including miR-144, as non-invasive COPD biomarkers.

Table 2 . Current knowledge gaps and future research priorities for elucidating the role of the miR-144–DNMT3A axis in COPD

Gap Identified	Current Evidence	Priority	Future Direction
Limited direct mechanistic evidence linking the miR-144–DNMT3A axis in COPD	Most studies investigate either miR-144 or DNMT3A independently, with only a few examining their direct interaction in COPD.	**High**	Conduct integrated studies simultaneously evaluating miR-144 expression, DNMT3A activity, DNA methylation, oxidative stress, and inflammatory mediators in the same patient cohorts.
Limited availability of human lung tissue studies	Much of the evidence is derived from peripheral blood, PBMCs, bronchial epithelial cell lines, or animal models.	**High**	Validate findings using lung tissue, bronchoalveolar lavage [BAL] samples, and multicenter clinical cohorts.
Insufficient functional validation of SNP–miRNA interactions	Predicted miR-144 binding-site polymorphisms have largely been identified through bioinformatic analyses with limited experimental confirmation.	**Medium**	Perform luciferase reporter assays, allele-specific expression studies, and CRISPR-based functional validation.
Small and heterogeneous study populations	Most published studies involve relatively small cohorts with variation in smoking history, disease severity, and analytical methodologies.	**High**	Conduct large multicenter studies with standardized protocols and phenotype-stratified patient recruitment.

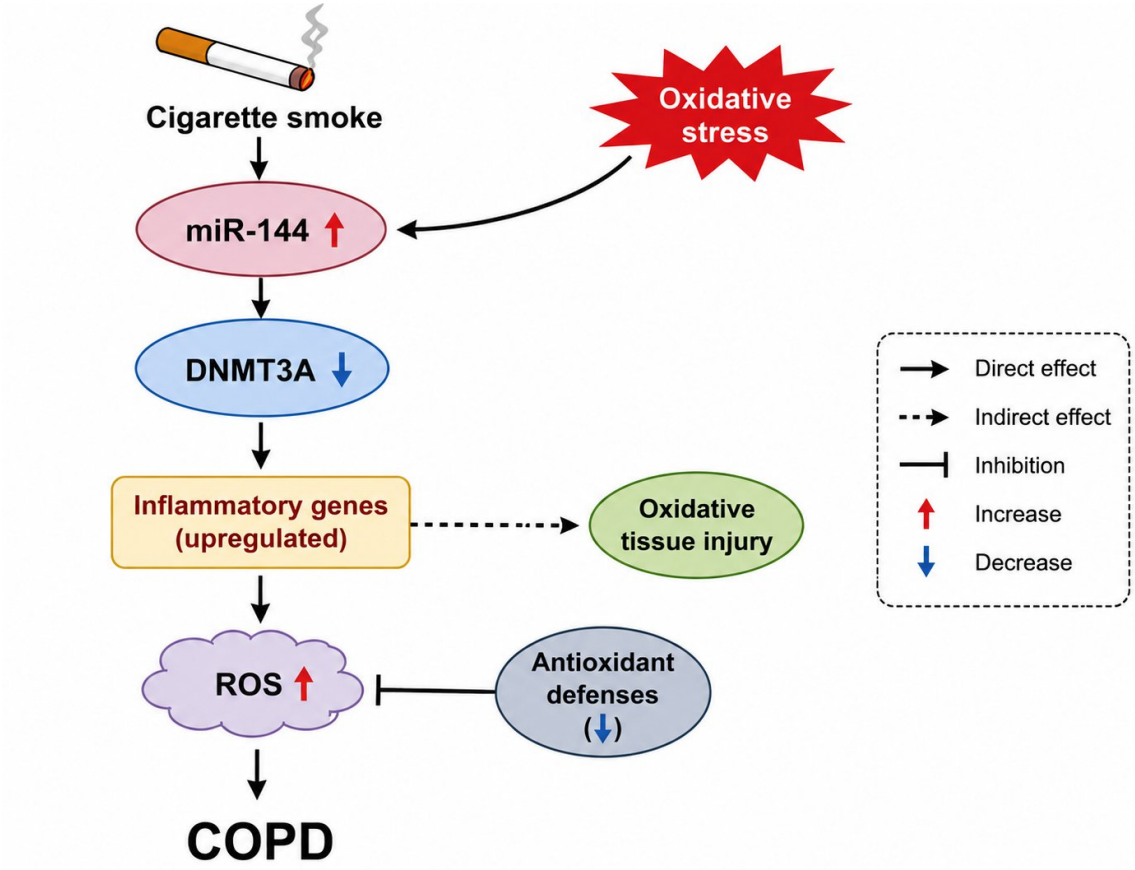

Figure 1. Schematic representation of the hypothesized miR-144–DNMT3A epigenetic axis in COPD based on currently available experimental evidence. Cigarette smoke exposure and oxidative stress are proposed to induce miR-144 overexpression, resulting in suppression of DNMT3A expression and subsequent upregulation of inflammatory genes. Enhanced inflammatory signalling contributes to increased reactive oxygen species (ROS) generation and may indirectly promote oxidative tissue injury, thereby facilitating COPD progression. Oxidative stress may further enhance miR-144 expression, suggesting a potential positive feedback mechanism that perpetuates inflammation and oxidative injury. miR-144, microRNA-144; DNMT3A, DNA methyltransferase 3A; ROS, reactive oxygen species.