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Adverse outcome pathway of ambient fine particulate matter-induced respiratory toxicity: role of non-coding RNAs

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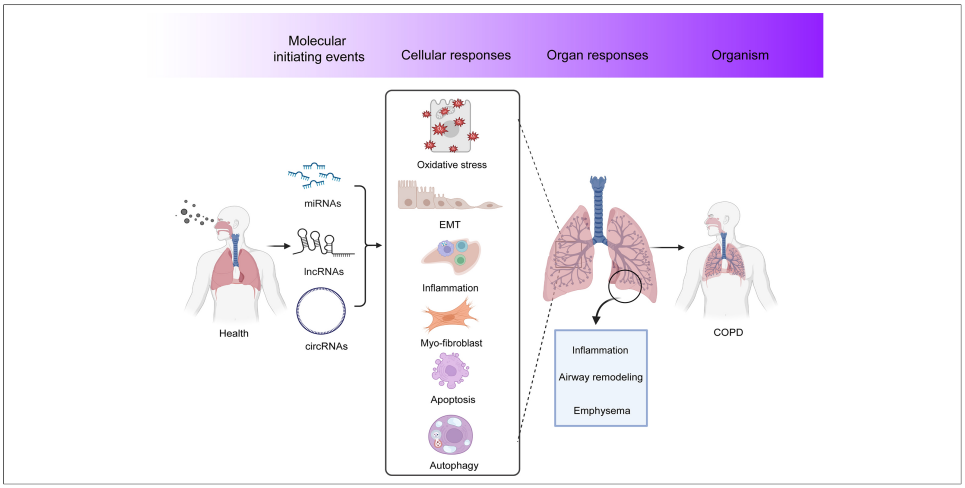

Abstract

Fine particulate matter ($PM_{2.5}$) exposure has been recognized as one of the risk factors for chronic obstructive pulmonary disease (COPD). With increased $PM_{2.5}$-related research, the mechanism of $PM_{2.5}$-induced toxicity suggests the role of non-coding RNA (ncRNA) in this process; however, a comprehensive framework to link $PM_{2.5}$ exposure with COPD remains vacant. The adverse outcome pathway (AOP) framework integrates research from different models to achieve a systematic assessment of $PM_{2.5}$ toxicity in the respiratory system. This review focused on $PM_{2.5}$-related pathology of COPD at molecular, cellular, organic, individual and population levels using the AOP framework. Combined with our previous studies, the AOP-Wiki website, and other available evidence, we established an AOP framework in which the molecular initiating event is the alteration of ncRNA expression profiles. Subsequently, oxidative stress and activation of the inflammatory pathway induced pulmonary inflammation, epithelial-mesenchymal transition, fibroblast proliferation, and myofibroblast differentiation, leading to airway remodeling, pulmonary

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epithelial cell apoptosis, and emphysema caused by autophagy. These were identified as key events. They collectively contribute to the pathogenesis of COPD by altering the structure and function of the airways and lung tissue, thus exacerbating respiratory symptoms and disease progression. This framework will provide a reference to identify biomarkers of $PM_{2.5}$ exposure-triggered respiratory diseases.

INTRODUCTION

Fine particulate matter ($PM_{2.5}$) remains a major air pollutant and has been identified as the second most significant risk factor for chronic obstructive pulmonary disease (COPD) prevalence in China[1-3]. Epidemiological evidence indicates that $PM_{2.5}$ exposure is correlated with COPD morbidity[4], and even short-term exposure can increase hospitalizations and mortality related to the disease[5]. Despite progress in elucidating the underlying mechanisms, a comprehensive framework linking $PM_{2.5}$ exposure to COPD pathology - including lung inflammation, emphysema, and small airway remodeling - remains incomplete. Key challenges include the complexity and diversity of molecular and cellular responses to $PM_{2.5}$, which involve multiple pathways and targets, as well as the difficulty in integrating epidemiological, *in vitro*, and *in vivo* data to connect molecular initiation events with adverse outcomes (AOs). Additionally, the lack of integration between epidemiological, *in vitro*, and *in vivo* studies has made it difficult to establish a clear link between molecular initiation events and AOs. This integration is challenging due to: (i) the variability in homology of non-coding RNA (ncRNA) sequences across organisms (e.g., human, rodent, and nematode), making their expression levels difficult to verify at both the human and other model organism levels; (ii) the complexity of $PM_{2.5}$ components across seasons and regions, which exerts varying effects on ncRNA profiles and leads to a wide array of molecular and cellular responses; (iii) the lack of standardization in ncRNA sequence platforms and analysis processes, making some results incomparable across studies.

To address these gaps, the adverse outcome pathway (AOP) framework offers a conceptual tool for organizing and evaluating the evidence linking environmental exposures to adverse health outcomes. First formally proposed in 2010[6], an AOP describes a structured sequence of events beginning with a molecular initiating event (MIE) and progressing through key biological processes to an AO at the individual or population level[7]. Since its introduction, the AOP approach has simplified chemical toxicity assessment, with over 500 AOPs now documented in the AOP-Wiki (https://www.aopwiki.org/). It has been successfully applied in chemical risk assessment - for instance, Da Silva *et al.* used an AOP to demonstrate how inhaled substances affect lung function via surfactant inhibition[8]. However, an AOP specific to $PM_{2.5}$-induced COPD has not yet been established.

Many existing AOPs employ MIEs such as reactive oxygen species (ROS) generation[9] or receptor activation/inhibition[10,11]. However, these early events are often difficult to access or quantify, delaying the detection of AOs following pollutant exposure. In this context, ncRNAs - including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs)[12] - offer distinct advantages as early biomarkers. Compared to proteins or mRNAs, ncRNAs have several benefits: they are upstream regulators of mRNAs and proteins, meaning they respond earlier in the biological process; they are highly stable in biofluids, tissue-specific, and rapidly responsive to environmental stressors. Additionally, ncRNAs can be quantified using standard techniques such as reverse transcription-quantitative polymerase chain reaction (RT-qPCR), making them ideal for non-invasive monitoring and early risk assessment[13,14]. These properties position ncRNAs as excellent candidates for early risk detection and non-invasive monitoring.

Therefore, we hypothesize that the alteration of ncRNA expression profiles serves as the crucial MIEs in $PM_{2.5}$ exposure-induced respiratory toxicity. This review aims to establish a comprehensive AOP framework

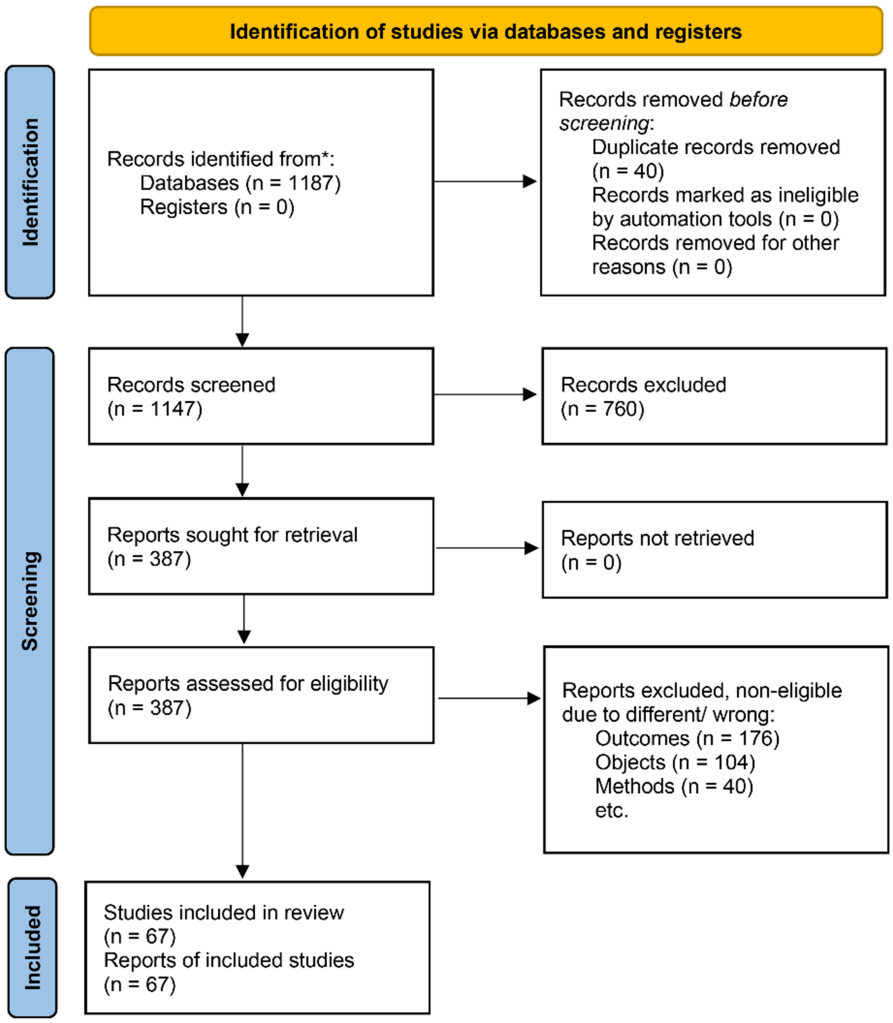

Figure 1. Systematic literature selection process for the review.

that systematically links $PM_{2.5}$ exposure to COPD pathogenesis through ncRNA-mediated key events (KEs), integrating existing literature and our previous studies to identify potential biomarkers and mechanistic insights.

METHODS

Literature review and study selection

A systematic literature search was conducted using PubMed, Web of Science, and Scopus databases up to 2023. The search strategy combined keywords related to ("$PM_{2.5}$" OR "particulate matter") AND ("ncRNA" OR "miRNA" OR "lncRNA" OR "circRNA") AND ("COPD" OR "pulmonary inflammation" OR "airway remodeling" OR "emphysema"). The retrieved articles were screened by title, abstract, and full text for relevance. The literature selection process is detailed in Figure 1.

AOP development and key event relationship evaluation

The AOP framework was constructed based on the OECD guidelines and integrated evidence from *in vitro*, *in vivo*, and epidemiological studies. KEs were identified from the literature, and key event relationships (KERs) were evaluated based on the Bradford-Hill considerations (biological plausibility, essentiality, and empirical evidence) as outlined in Table 1. The definitions of key terms and abbreviations used in AOP were shown in Supplementary Table 1.

Table 1. Summary and evaluation of KERs from the AOP

Upstream event	Relationship type	Downstream event	Weight of evidence		
			Biological plausibility	Essentiality	Empirical evidence
ncRNA expression profiles alterations	Adjacent	Oxidative stress	Strong	Moderate	Strong
ncRNA expression profiles alterations	Adjacent	Activation of the inflammatory pathway	Strong	Moderate	Strong
ncRNA expression profiles alterations	Adjacent	Epithelial mesenchymal transformation	Strong	Moderate	Strong
ncRNA expression profiles alterations	Adjacent	Fibroblast proliferation and myofibroblast differentiation	Strong	Moderate	Strong
ncRNA expression profiles alterations	Adjacent	Cellular apoptosis	Strong	Moderate	Strong
ncRNA expression profiles alterations	Adjacent	Cellular autophagy	Strong	Moderate	Strong
Oxidative stress	Adjacent	Pulmonary inflammation	Strong	Strong	Strong
Activation of the inflammatory pathway	Adjacent	Pulmonary inflammation	Strong	Strong	Strong
Epithelial mesenchymal transformation	Adjacent	Airway remodeling	Strong	Strong	Strong
Fibroblast proliferation and myofibroblast differentiation	Adjacent	Airway remodeling	Strong	Strong	Strong
Cellular apoptosis	Adjacent	Emphysema	Strong	moderate	Strong
Cellular autophagy	Adjacent	Emphysema	Strong	moderate	Strong
Pulmonary inflammation	Adjacent	COPD	Strong	Strong	Strong
Airway remodeling	Adjacent	COPD	Strong	Strong	Strong
Pulmonary dysfunction	Adjacent	COPD	Strong	Strong	Strong

KERs: Key event relationships; AOP: adverse outcome pathway; ncRNA: non-coding RNA; COPD: chronic obstructive pulmonary disease.

MIE TRIGGERED BY $PM_{2.5}$ EXPOSURE: THE ALTERATION IN ncRNA EXPRESSION PROFILES (KE2007)

With the development of sequencing and bioinformatics technologies, the biological functions of ncRNAs have been gradually elucidated. To date, miRNAs have been proposed to bind the 3'-untranslated region (3'UTR) of messenger RNAs (mRNAs)[15]; lncRNAs and circRNAs act as miRNA sponges to regulate target gene expression[16]. Additionally, lncRNAs and circRNAs can act as competing endogenous RNAs (ceRNAs) and establish protein-protein interaction networks[17]. ncRNAs are also involved in the epigenetic modification process, such as histone modification[18], and DNA or RNA methylation[19]. These ncRNAs play a crucial role in regulating mammalian gene expression, influencing development, and tissue homeostasis, and contributing to various human diseases[20].

The significance of ncRNAs in the development of COPD upon $PM_{2.5}$ exposure derives from their role as key regulators of epigenetic reprogramming. Environmental stress, such as $PM_{2.5}$ exposure, exerts effects on organisms usually through a rapid epigenetic regulation. Numerous studies confirmed that $PM_{2.5}$ exposure rapidly altered ncRNA expression by modifications at ncRNA gene loci[21,22]. This $PM_{2.5}$-driven dysregulation of ncRNAs, including miRNAs, lncRNAs, and circRNAs, in turn orchestrates changes in the downstream target gene networks. The hallmarks of COPD - persistent inflammation, oxidative stress, and tissue remodeling - are driven by the altered expression of target genes. Thus, the alteration of ncRNA expression represents the critical molecular at early stage of $PM_{2.5}$ exposure, bridging the gap between $PM_{2.5}$ exposure and pulmonary pathology, emphasizing their roles as MIEs.

Increasing evidence suggests that ncRNA expression profiles are altered following exposure to environmental stresses, such as air pollutants[23]. These abnormally expressed ncRNAs disrupt homeostasis and participate in pathophysiological processes. Our previous research found that ncRNA expression profiles are altered and act as upstream drivers in $PM_{2.5}$ exposure-induced injuries[24-27].

Despite the growing evidence, a systematic and causal framework linking specific $PM_{2.5}$-induced ncRNA alterations to the downstream pathogenesis of COPD is still lacking. This review aims to address this critical gap by constructing an evidence-driven AOP, in which ncRNA dysregulation acts as the MIE.

THE CELLULAR LEVEL: EFFECTS OF $PM_{2.5}$ EXPOSURE ON BRONCHIAL EPITHELIAL CELLS AND FIBROBLASTS

Key event (KE1392): oxidative stress

Intracellular metabolic processes and certain exogenous chemicals stimulate the production of ROS, which can be cleared by antioxidant enzymes[28]. When the balance between oxidation and antioxidation is disrupted, excessive ROS accumulates, leading to oxidative stress and further accelerating ROS accumulation[29]. Molecular pathways that are closely associated with $PM_{2.5}$ exposure-induced oxidative stress include the nuclear factor erythroid 2-related factor 2 (Nrf2) - antioxidant response element (ARE) pathway[30-32], nuclear factor κB (NF-κB) pathway[33-35], and p38 mitogen-activated protein kinase (MAPK) pathway[29,36].

Oxidative stress following miRNA alteration

miRNAs play a crucial role in maintaining cellular redox homeostasis, which can lead to oxidative damage and the development of diseases[37]. A randomized crossover study has found that miR-144 participated in PM-induced oxidative stress[38].

Multiple animal and cellular studies have further clarified the mechanisms by which oxidative stress is linked to changes in miRNA profiles. At the cellular levels, Eaves *et al.* found that 33 out of 59 miRNAs differentially expressed in $PM_{2.5}$-treated human bronchial epithelial BEAS-2B cells were associated with nuclear factor erythroid 2-related factor 2 (NRF2)-mediated oxidative stress pathways[39]. $PM_{2.5}$ exposure was also shown to upregulate miRNAs such as miR-222, miR-210, miR-101, miR-34a, and miR-93, leading to ROS generation in pulmonary cells, while miR-486 downregulation caused oxidative stress in A549 cells[31,40]. Additionally, miR-217-5p reduces $PM_{2.5}$-induced inflammation and oxidative stress in macrophages, reducing lung injury caused by $PM_{2.5}$ exposure[41]. $PM_{2.5}$-induced miR-760 upregulation reduced Heme Oxygenase-1 (HMOX1) expression, increasing ROS generation in human bronchial epithelial (HBE) cells[42]. Crucially, experimental overexpression of miR-760 was shown to attenuate ROS generation, providing direct functional evidence of its causal role. At the animal level, Zhao *et al.* reported increased oxidative stress in rat lung tissues after two months of $PM_{2.5}$ exposure, suggesting miRNA upregulation and 8-oxoguanine DNA glycosylase 1 (OGG1) expression as potential mechanisms for $PM_{2.5}$-induced lung injury[22].

Oxidative stress following lncRNA alteration

Reduced expression of long noncoding-interleukin-7 receptor (lnc-IL7R) in $PM_{2.5}$-treated cells led to increased oxidative stress, which in turn induced the expression of p16INK4a and p21CIP1/WAF1[43]. This study demonstrated a causal link through knockdown experiments, where reducing lnc-IL7R expression exacerbated oxidative stress markers. Additionally, the upregulation of lncRNA loc146880 further aggravated oxidative stress in A549 cells[44]. In mouse alveolar epithelial cells, lncRNA Nqo1 antisense transcript 1 (Nqo1-AS1) was linked to cigarette smoke-induced oxidative stress by stabilizing Nqo1 mRNA[45]. Furthermore, lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) acts as a sponge

for miR-145, activating Nrf2 protein and contributing to oxidative stress. In contrast, lncRNA Forkhead box D3 antisense RNA1 (FOXD3-AS1) exacerbates oxidative stress in lung epithelial cells by interacting with miRNA-150[46].

Oxidative stress following circRNA alteration

Several studies have shown that upregulation of circRNA expression, either independently or in combination with miRNA alterations, can mediate oxidative stress in cells and contribute to lung inflammation. For example, circ_0008553, hsa_circ_0006872, and circRNA oxysterol binding protein-like 2 (Circ-OSBPL2) mediated oxidative stress in human HBE cells following $PM_{2.5}$ or smoke exposure[47-49]. CircRNA RNA binding motif single stranded interacting protein 1 (Circ-RBMS1) plays a crucial role in $PM_{2.5}$-induced oxidative stress by targeting miR-197-3p and silencing circ-RBMS1 worsened oxidative stress by lowering superoxide dismutase (SOD) levels and increasing malondialdehyde (MDA) levels in HBE cells[50]. This interaction was validated functionally, as silencing circ-RBMS1 worsened oxidative stress, an effect that could be rescued by a miR-197-3p inhibitor.

In summary, $PM_{2.5}$-induced alterations in ncRNAs disrupt redox homeostasis by altering key gene expression on antioxidant signaling pathways, most notably the Nrf2-ARE axis. The experimental evidence from gain- and loss-of-function studies strongly supports a causal role for specific miRNAs, lncRNAs, and circRNAs in regulating oxidative stress.

Key event (KE2009): activation of inflammatory pathway

Numerous studies have shown that $PM_{2.5}$ exposure is positively correlated with the activation of inflammatory pathways. The endpoints of activated inflammatory pathways were excessive expression of inflammatory cytokines[26,51]. With the in-depth study, ncRNAs have been proven to facilitate or inhibit some inflammatory pathway activation following $PM_{2.5}$ exposure, such as the NF-κB pathway.

Inflammatory pathway activation related to miRNAs

Solid epidemiological evidence supports that miRNA alterations contribute to lung inflammation[26,51]. For example, a randomized crossover study suggested that five miRNAs were down-regulated in young healthy adults, which modulated inflammatory cytokine expression[52]. On the contrary, studies found increased expression levels of let-7a, miR-146a-5p, and miR-155-5p in children[53], and miR-223-3p, miR-199a/b in older individuals[54], which were associated with an inflammatory response.

In laboratory studies, miR-466i-5p, miR-203-5p, and miR-7a-5p were correlated with inflammatory pathways in $PM_{2.5}$-exposed mice using mRNA and miRNA sequencing analysis[55]. Additionally, miR-29b-3p was highly expressed in $PM_{2.5}$-exposed HBE cells, promoting pro-inflammatory cytokine secretion by inhibiting the AMPK pathway[56]. Furthermore, exposure to secondary organic aerosol (SOA), a key component of $PM_{2.5}$, altered the expression of 31 miRNAs in BEAS-2B cells, with some involved in inflammation pathogenesis[39].

Our studies identified several miRNAs associated with inflammatory pathway activation and explored potential mechanisms at both animal and cellular levels[26,27]. We found that in $PM_{2.5}$-induced lung inflammation, miR-297 inhibited NF-κB activating protein (NKAP) expression in a dose-dependent manner, promoting Notch pathway activation and the secretion of interleukin-1β (IL-1β) and tumor necrosis factor (TNF)[26,27]. Overexpression of miR-382-5p in mice significantly inhibited C-X-C motif chemokine ligand 12 (CXCL12) and matrix metallopeptidase 9 (MMP9) expression induced by $PM_{2.5}$, alleviating inflammatory symptoms in lung tissue[27]. In summary, both epidemiological and animal evidence indicate that $PM_{2.5}$ exposure leads to dysregulation of miRNAs linked to lung inflammation.

Inflammatory pathway activation related to lncRNAs

Traffic-related $PM_{2.5}$ exposure enhanced the expression of lncRNA RP11-86H7.1, NF-κB pathway activation, and the secretion of inflammatory factors (e.g., IL-6 and TNF-α) as a ceRNA of miR-9-5p in HBE cells[57]. lncRNA uc001.dgp.1 played a role in $PM_{2.5}$-induced inflammatory responses in BEAS-2B cells[58].

In animal models, $PM_{2.5}$ intra-tracheal instillation resulted in 885 differentially expressed lncRNAs in murine lung tissues, with three lncRNAs associated with NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome upregulation and inflammation development[59]. High-throughput sequencing suggested that $PM_{2.5}$ increased the expression of lncRNA AABR07005593.1, which regulated IL-6 secretion to promote pulmonary inflammation in rats[60].

Inflammatory pathway activation related to circRNAs

Several studies have observed that altered circRNA expression levels, in combination with miRNAs or lncRNAs, may trigger the secretion of immune factors and contribute to pulmonary inflammation pathogenesis. Decreased levels of circRNA CBT15_circR_1011 and mm9_circ_005915 were found in $PM_{2.5}$ intra-tracheal instillation mouse models, which regulated inflammatory factor expression and participated in pulmonary inflammation[59].

Using human HBE cells, circ-RBMS1/miR-197-3p/F-box protein 11 (FBXO11) axis mediated IL-1β and TNF-α secretion, promoting $PM_{2.5}$-triggered inflammation[50]; circ_406961 interacts with ILF2 protein, modulating signal transducer and activator of transcription 3 (STAT3)/JNK pathway activation and participating in PM-induced inflammation[61]; long-term $PM_{2.5}$ exposure induced circRNA104250 and lncRNA uc001.dgp.1, which acted as ceRNA for miR-3607-5p and regulated NF-κB pathway activation via the miR-3607-5p-IL1R1 axis[58]; circ-OSBPL2 facilitated IL-1β, IL-8, and TNF-α expression via miR-193a-5p/bromodomain protein 4 (BRD4) signaling, contributing to smoke-induced inflammation[48].

In summary, ncRNAs participated in inflammatory pathway activation, leading to the secretion of inflammatory cytokines. These cytokines can recruit macrophages and other immune cells, triggering a local inflammatory response that ultimately contributes to the development of pulmonary inflammation.

Key event (KE1650): epithelial-mesenchymal transformation

Epithelial-mesenchymal transformation (EMT) is a transformation process of epithelial to mesenchymal cells[62] and plays an essential role in ontogeny, tissue healing, organ fibrosis, and carcinogenesis[63]. In recent years, studies suggested that EMT plays an important role in the increased incidence of respiratory diseases[64,65]. ncRNAs have been proven to participate in EMT by regulating associated gene expressions[66,67].

miRNA expressions and EMT

Most laboratory studies revealed that $PM_{2.5}$ exposure decreased several miRNA expression levels and promoted EMT development. Vimentin expression was upregulated in human lung cancer cells treated with $PM_{2.5}$, regulated by miR-125a-3p, which plays a crucial role in the EMT process[68]. Chronic $PM_{2.5}$ exposure decreased miR-139-5p expression, regulated Notch1 pathway activation, and contributed to EMT in HBE cells[69]. miR-122 regulated Notch pathway activation, promoting EMT development in A549 cells[70]. Decreased miR-26a expression promoted EMT and enhanced the invasion capacity of $PM_{2.5}$-exposed A549 cells via the Lin-28 Homolog B (LIN28B)/IL-6/STAT3 axis[71].

lncRNA expressions and EMT

A study using $PM_{2.5}$-exposed HBE cells confirmed increased lncRNA MALAT1 expression, promoting the EMT process through the ceRNA mechanism[72]. Besides ceRNAs, studies also showed that lncRNAs directly increased EMT-associated gene expressions. For instance, lncRNA loc146880 participated in $PM_{2.5}$-induced EMT by up-regulating e-cadherin and vimentin expression in A549 cells[44]. lncRNA loc107985872 was induced in $PM_{2.5}$ organic extract-treated A549 cells, increasing e-cadherin, n-cadherin, and vimentin expression via the Notch1 pathway, promoting tumor progression[66]. lncRNA Gm16410 plays a crucial role in the EMT process of pulmonary microvascular endothelial cells via the TGF-β1/SMAD family member 3 (Smad3)/Phospho SMAD family member 3 (p-Smad3) pathway[73]. Our research revealed that upregulation of lncRNA SRY-box transcription factor 2 overlapping transcript (SOX2-OT) significantly increased EGFR mRNA and protein levels, further promoting EMT after long-term $PM_{2.5}$ exposure[24].

circRNA expression and EMT

To date, no circRNAs have been reported to mediate the $PM_{2.5}$-induced EMT process. However, circRNAs do play a role in the EMT of pulmonary cells following exposure to environmental particles/aerosols. For example, elevated levels of e-cadherin, n-cadherin, and vimentin were positively associated with circ0061052 expression in cigarette smoke extract (CSE)-treated HBE cells. circ0061052 also plays a role in cigarette smoke-induced EMT and airway remodeling in COPD by regulating miR-515-5p through a forkhead box C1 (FoxC1)/Snail regulatory axis[74]. Hsa_circ_0058493 was highly expressed in silicosis patients, validated in medical research council cell strain-5 (MRC-5) cell models, involved in EMT, and influenced fibrotic molecule expression[75].

Taken together, ncRNAs were involved in EMT pathway activation and facilitated the expression of EMT-related proteins (e-cadherin, n-cadherin, and vimentin). Airway epithelial cells gradually transform into interstitial cells, causing excess mucus production and basement membrane thickening, finally leading to airway remodeling.

Key event (KE1500): fibroblast proliferation and myofibroblast differentiation

Research has confirmed that long-term $PM_{2.5}$ exposure triggered fibroblast proliferation and myofibroblast differentiation, which eventually aggravated pulmonary fibrosis and airway remodeling[76]. In this section, we only discuss relevant miRNAs and lncRNAs because there are no reports about circRNAs.

Fibroblast proliferation, myofibroblast differentiation and miRNAs

Studies on miRNA expressions and pulmonary fibrosis found that the upregulation of miRNAs, such as miR-503[77], miR-29b[78], miRNA-34c-5p[79], and miR-125a-5p[80] in silica-induced mouse models significantly decreased α-smooth muscle actin (α-SMA), collagen 1, collagen 3, and extracellular matrix synthesis, reducing fibroblast migration and alleviating pulmonary fibrosis. For $PM_{2.5}$ exposure, direct evidence of miRNA-associated fibrosis is limited; only miRNA-126[81] expression in circulation has been reported to be significantly inhibited following $PM_{2.5}$ exposure. These findings emphasize the role of miRNAs in regulating $PM_{2.5}$-induced pulmonary fibrosis.

Fibroblast proliferation, myofibroblast differentiation and lncRNAs

Similar to miRNAs, evidence of lncRNA-mediated pulmonary fibrosis has been collected from silicosis studies. lncRNA plasmacytomvariant translocation 1 (PVT1) was induced in $PM_{2.5}$-exposed pulmonary cells and is recognized for promoting fibroblast proliferation and migration by acting as a ceRNA for miR-497-5p in mice lung tissue[82]. lncRNA small nucleolar RNA host gene 1 (SNHG1) was highly expressed in pulmonary fibrosis mouse models triggered by silica, where it combined with miR-326 to regulate the

fibroblast-to-myofibroblast transition[83]. In addition, long intergenic non-protein coding RNA 941 (LINC00941)/inhibit autophagy in pulmonary fibrogenesis (lncIAPF) accelerates pulmonary fibrosis by promoting fibroblast-to-myofibroblast differentiation and myofibroblast proliferation and migration[84].

While the relationship between ncRNAs and $PM_{2.5}$-induced fibroblast proliferation and myofibroblast differentiation requires further exploration, silica, a major toxic component of $PM_{2.5}$[85], strongly suggests that aberrant ncRNA expression can promote abnormal collagen fiber deposition and smooth muscle hypertrophy, fundamental pathological features of pulmonary fibrosis.

Key event (KE1262): cellular apoptosis

Available evidence suggested that $PM_{2.5}$ inhalation caused cellular apoptosis[86], and an epigenetic study has shown that ncRNAs play a role in the pathogenesis of apoptosis caused by $PM_{2.5}$ exposure.

Cellular apoptosis and miRNAs

Several *in vitro* and *in vivo* studies have shown that $PM_{2.5}$ exposure downregulates miRNAs such as miR-486 and miR-194-3p[87], increasing apoptosis in A549 cells, bronchial epithelium cells[40], BEAS-2B cells[88], and HBE cells[42]. $PM_{2.5}$ exposure also decreases let-7a expression, exacerbating cell apoptosis via the let-7a/Arginase 2 (ARG2) axis in BEAS-2B cells[88]. Heme-oxygenase 1 has been shown to protect cells from $PM_{2.5}$-induced toxicity, with hsa-miR-760 upregulating Heme-oxygenase 1 and reducing apoptosis in HBE cells[42].

Our previous study demonstrated that $PM_{2.5}$ treatment causes apoptosis through mitochondrial dysfunction in A549 cells, and miRNA microarray analysis revealed downregulation of miR-1228-5p, correlated with $PM_{2.5}$-induced apoptosis[89]. We also found that miR-802 and miR-382-5p are associated with $PM_{2.5}$-triggered cell apoptosis[27,90].

Cellular apoptosis and lncRNAs or circRNAs

Altered expression of lncRNA maternally expressed 3 (MEG3) in $PM_{2.5}$-exposed pulmonary cells has been extensively reported. For instance, traffic-related $PM_{2.5}$ treatment induced lncRNA MEG3, which inhibits apoptosis significantly through interaction with miR-149-3p via the NF-κB pathway[91]. lncRNA Sox2-OT was associated with $PM_{2.5}$-induced mitochondria damage and apoptosis in A549 cells[92]. Additionally, lncRNA LINC00341 and lung cancer associated transcript 1 (LUCAT1) were upregulated in $PM_{2.5}$-treated bronchial cells, promoting apoptosis[93,94]. Our study found that the expression level of lncRNA taurine up-regulated 1 (TUG1) was increased after PM exposure as ceRNA of miR-222-3p, mediated apoptosis, and ultimately caused airway hyper-reactivity[24].

One circRNA, circ_0038467, has been identified to promote cellular apoptosis in lung cells following $PM_{2.5}$ exposure and acts as a sponge for miR-138-1-3p[95]. Apoptosis in $PM_{2.5}$-exposed pulmonary cells is frequently linked to ncRNA dysregulation. miRNAs (e.g., miR-486), lncRNAs (e.g., MEG3), and circRNAs regulate apoptosis-related genes (e.g., caspase-3) directly or via ceRNA networks.

Key event (KE1945): cellular autophagy

Autophagy is a process by which cells degrade and recycle damaged or excess materials through lysosomes to maintain homeostasis in mammal cells. Our study reported that $PM_{2.5}$ exposure dysregulated the process of autophagy and eventually contributed to the pathogenesis of COPD[96]. Autophagy-related genes, hypoxia-inducible factor 1 subunit alpha (*HIF1A*), cyclin-dependent kinase inhibitor 1A (*CDKN1A*), Bcl-2 associated athanogene 3 (*BAG3*), rythroblastic oncogene B (*ERBB2*), and autophagy related protein 16 like 1

(*ATG16L1*) may contribute to COPD pathogenesis and aid in developing targeted treatments[97-99]. Studies found that ncRNAs are correlated with the autophagy process in lung cells[100] and mouse models[101]. In this section, we only discuss relevant miRNAs and lncRNAs because circRNAs have not been reported yet.

Autophagy and miRNAs

Sufficient evidence from animal experiments to population studies has demonstrated that miRNA expression is widely involved in cellular autophagy processes. Quezada-Maldonado *et al.* observed 45 down-regulated miRNAs that influenced cell autophagy and cell cycle in lung epithelial cells exposed to $PM_{2.5}$[102]. MiR-146a-5p was upregulated after $PM_{2.5}$ exposure, modulating the expression of target genes interleukin-1 receptor-associated kinase 1 (*IRAK1*) and TNF receptor-associated factor 6 (*TRAF6*), ultimately affecting cellular autophagy[103]. Our previous study also identified increased miR-4516 expression in A549 cells treated with $PM_{2.5}$, which regulated the autophagy process[104]. In animal models, miR-338-3p acts as an autophagy inhibitor in rats of allergic rhinitis exacerbated by $PM_{2.5}$ by directly targeting ubiquitin conjugating enzyme E2 Q1 (UBE2Q1) and affecting the protein kinase B/mammalian target of rapamycin (AKT/mTOR) pathway[105].

Autophagy and lncRNAs

Many studies focused on the mechanism underlying lncRNA-regulated autophagy in pulmonary cells upon $PM_{2.5}$ exposure. lncRNA loc146880 increased autophagy in $PM_{2.5}$-exposed A549 cells by promoting ROS generation[44]. LINC00987 and MIR155HG acted as ceRNA for Let-7b-5p and miR-218-5p, respectively, to modulate the autophagy process in lungs with COPD-like lesions[106,107]. lncRNA MEG3 participated in HBE cell autophagy by directly down-regulating the expression of autophagy-related biomarkers[108].

Overall, ncRNAs are involved in regulating cellular autophagy via multiple autophagy pathways, where autophagy biomarkers are evaluated, further activating lysosomal activity, and inducing HBE cell autophagy. These studies also provided new therapeutic targets for COPD patients.

THE ORGAN/TISSUE LEVELS: $PM_{2.5}$ AND PULMONARY INJURIES

Key event (KE 2010): $PM_{2.5}$ and pulmonary inflammation

Pulmonary inflammation is the body's defensive response to inhaled exogenous stimulation[109]. In this process, airway epithelial cells secrete inflammatory cytokines, which recruit inflammatory cells and induce mucus secretion[110]. Persistent acute inflammation can develop into chronic inflammation, exacerbating pulmonary inflammation, a major characteristic of COPD[111]. The recruitment level of inflammatory cells can be evaluated by inflammatory cell counts in bronchoalveolar lavage fluid (BALF). Increased numbers of inflammatory cells, including leukocytes, neutrophils, lymphocytes, and secreted cytokines, were observed in BALF from mice exposed to $PM_{2.5}$[112,113], indicating adverse pulmonary effects of $PM_{2.5}$ exposure.

Alterations of miRNA expression and pulmonary inflammation

In-depth studies have explored the roles of miRNA expression and potential molecular mechanisms in the pathogenic process of pulmonary inflammation and immune response regulation. Prominent pulmonary inflammation was observed in mice exposed to $PM_{2.5}$, with miRNA-seq analysis revealing that differentially expressed miRNAs were associated with B cell receptor signaling, promoting the development of pulmonary inflammation[55]. miRNAs also facilitate immune cell infiltration in the lungs; for instance, miRNA-149-5p is linked to macrophage, neutrophil, and lymphocyte infiltration in $PM_{2.5}$-exposed mice[114]. Neutrophil infiltration has been associated with increased let-7 or decreased miR-6747-5p expression in lungs exposed to $PM_{2.5}$[115,116]. We also observed inflammatory infiltration around $PM_{2.5}$ deposition, obvious pulmonary hemorrhage, and significantly increased pathological score in murine lungs; however, overexpression of

miR-382-5p inhibited CXCL12 and alleviated these inflammatory symptoms[27].

Alterations of lncRNA expression and pulmonary inflammation

Many studies have linked induced cytokine levels, especially IL-6, IL-8, and TNF-α, and IL-1β in $PM_{2.5}$-exposed pulmonary cells, to altered lncRNA expression. For example, increased expression of lncRNA RP11-86H7.1 in HBE cells[117], lncRNA AABR07005593.1 in rat lungs[60], and decreased lncRNA Gm16410 were associated with immune cell infiltration and increased cytokine secretion. lncRNA TUG1 was highly expressed in $PM_{2.5}$-treated fibroblasts, enhancing the expression of IL-6 and TGF-β1, thereby exacerbating pulmonary inflammation[118]; meanwhile, in $PM_{2.5}$-exposed murine lungs, lncRNA TUG1 aggravated inflammation infiltration as a sponge for miRNA-181b[119].

Alterations of circRNA expression and pulmonary inflammation

Several studies have found that circBbs9 in mouse lung tissue can activate the NLRP3 inflammasome after exposure to $PM_{2.5}$[59,120]. $PM_{2.5}$ treatment enhanced lymphocyte adhesion, with circRNA 406961 linked to the activation of STAT3/JNK pathways, regulating inflammatory responses[61]. Besides, thioredoxin reductase 1 (TXNRD1) and circRNA 104250 promoted the expression of proinflammatory cytokines, IL-6 and IL-8, in human HBE cells, contributing to PM-induced inflammation[58,121].

Overall, airway inflammation is a key characteristic of COPD, often accompanied by the infiltration of neutrophils, macrophages, B lymphocytes, and T lymphocytes, which are recruited by inflammatory cytokines regulated by ncRNAs.

Key event (KE2013): $PM_{2.5}$ and airway remodeling

With the worsening of chronic airway inflammation, basement membrane thickening, glandular hypertrophy, smooth muscle hypertrophy, and other pathological changes in the airway epithelium are defined as airway remodeling[122]. In recent years, the pathogenesis of airway remodeling has been gradually clarified, with ncRNAs playing an indispensable role in this process, such as miR-192-5p[123]. Additionally, exogenous chemicals also induced airway remodeling via altered levels of ncRNA expression.

Alterations of miRNA expression and airway remodeling

A population study showed that biomass combustion-produced PM upregulated miR-34a levels in the serum of COPD patients, which were involved in airway remodeling[124]. Animal experiments revealed that $PM_{2.5}$ exposure could aggravate collagen deposition and inflammation in asthma mice and promote airway remodeling in mouse models by downregulating miR-224, miR-155, or miR-21 levels[125-127].

Alterations of lncRNA expression and airway remodeling

As mentioned above, lncRNA TUG1 has been associated with massive biological processes and cellular phenotypes in response to $PM_{2.5}$ exposure. As for airway remodeling, lncRNA TUG1 knockdown alleviated airway remodeling in CSE-exposed mice by inhibiting collagen deposition[118]. Similarly, lncRNA TUG1 participated in the underlying mechanism of airway remodeling as a target for miRNA-181b in asthmatic mice[119]. Our previous study also found that $PM_{2.5}$ exposure induced the upregulation of lncRNA TUG1 *in vivo* and *in vitro*, which led to airway hyperactivity by the TUG1/mir-222-3p/CELF1/p53 network[25]. Therefore, the upregulation of lncRNA TUG1 contributes to pathological processes in airway remodeling.

Alterations of circRNA expression and airway remodeling

Till now, direct evidence showing that circRNA plays a role in $PM_{2.5}$ exposure resulting in airway remodeling

remains insufficient. Studies on environmental stressors such as cigarette smoke have linked circ0061052, circRNA casein kinase 1 epsilon (circ_CSNK1E), Circ-Osbpl2, circRNA ankyrin repeat domain (ANKRD) 11 (circANKRD11), and Circ-RBMS1 to airway remodeling; however, the expression of these circRNAs in pulmonary cells or lung tissues following $PM_{2.5}$ exposure requires further validation[48,50,74,128,129].

Key event (KE2011): $PM_{2.5}$ and emphysema

Emphysema is characterized by lung parenchymal damage and airflow limitation, which can be diagnosed through computed tomography (CT) imaging and pulmonary function (PF) tests. In a cohort study conducted in the USA, long-term $PM_{2.5}$ exposure was correlated with increased morbidity of emphysema[130]. Here, we discuss the mechanism underlying ncRNAs in the process of emphysema induced by $PM_{2.5}$ exposure.

Alterations of miRNA expression and emphysema

At individual level, Cong *et al.* reported that miR-644 levels in peripheral blood were associated with personal $PM_{2.5}$ exposure levels, during which the PF was decreased[131]. A pilot study of young healthy adults exposed to $PM_{2.5}$ indicated that decreased circulating miR-194-3p levels were statistically correlated with reduced PF, suggesting a role of miR-194-3p in $PM_{2.5}$ exposure-associated COPD[40]. In a $PM_{2.5}$-exposed cellular model, decreased miR-194-3p was shown to enhance death associated protein kinase 1 (DAPK1) expression and caspase 3 activities, promoting pulmonary cell apoptosis[87]. An animal study found that miR-146a expression levels influenced lung function indexes in mice, with micro-CT images showing lung tissue shrinkage and increased density after $PM_{2.5}$ exposure[132].

Alterations of lncRNA expression and emphysema

Population-level studies have shown that $PM_{2.5}$ exposure is associated with decreased levels of lnc-IL7R and the aggravation of emphysema in COPD patients[133]. In addition, lncRNA plasmacytoma variant translocation 1 (PVT1) and nuclear enriched abundant transcript 1 (NEAT1) are novel biomarkers to evaluate emphysema exacerbation risk in COPD patients[134,135]. Low expression levels of lnc-IL7R during $PM_{2.5}$ exposure led to the aggravation of emphysema in COPD patients[133]. These studies all suggest potential roles in regulating emphysema. Beyond population studies, lncRNA major histocompatibility complex molecules (MHC)-R was upregulated in lung tissue from $PM_{2.5}$-exposed mice, showing damage to lung parenchyma, distal alveolar enlargement, and pulmonary dysfunction[136].

Alterations of circRNA expression and emphysema

No studies have yet focused on circRNA, $PM_{2.5}$, and emphysema. However, it is well-known that increased apoptosis in airway cells is a major cause of emphysema; theoretically, the miRNAs, lncRNAs, and circRNAs associated with apoptosis, as mentioned above, could potentially contribute to emphysema development during $PM_{2.5}$ exposure.

To summarize, $PM_{2.5}$-induced cellular changes gradually accumulate until they surpass the host's compensatory mechanisms, leading to tissue/organ-level damage (pulmonary inflammation, airway remodeling, and emphysema), which are hallmarks of COPD. Given the role of ncRNAs in pulmonary changes, we believe that ncRNAs are key regulators of $PM_{2.5}$-induced pulmonary injuries.

Adverse outcome (AO2008): COPD

COPD is a chronic bronchitis or emphysema characterized by airflow obstruction[137]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2022 pointed out that COPD is one of the top three causes of death in the world today. Ninety percent of the deaths occur in low- and middle-income countries, which

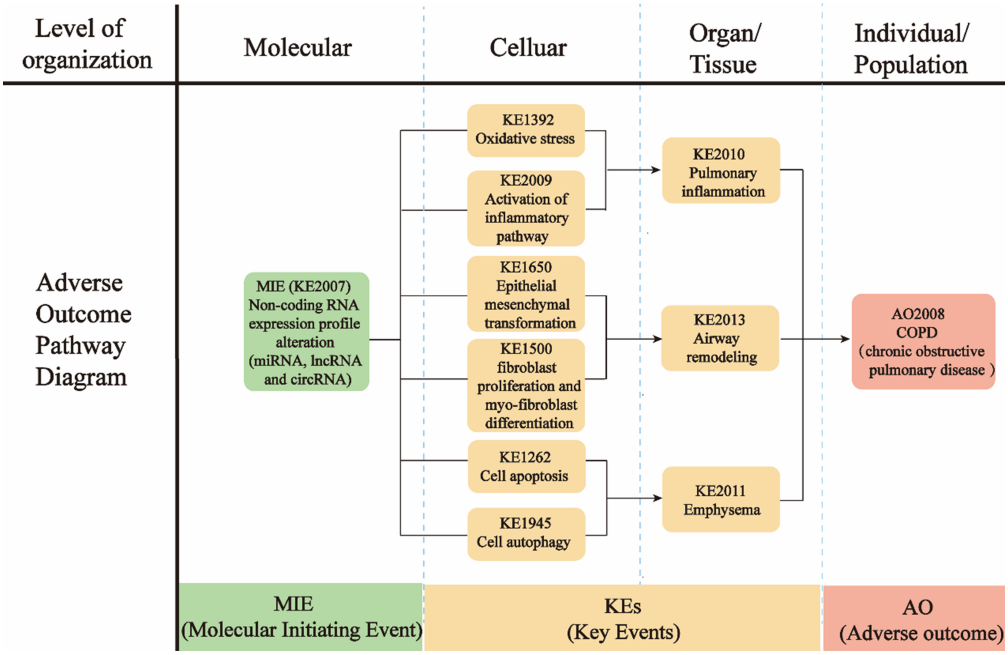

Figure 2. AOP diagram related to $PM_{2.5}$ exposure-triggered respiratory toxicity. AOP: Adverse outcome pathway; $PM_{2.5}$: fine particulate matter; miRNA: microRNA; lncRNA: long non-coding RNA; circRNA: circular RNA; COPD: chronic obstructive pulmonary disease.

has become the main economic burden of chronic diseases in the future[138]. A national cross-sectional study reported that exposure to an annual mean $PM_{2.5}$ of 50 μg/m³ or higher ranked as the second risk factor for COPD prevalence in China[1]. Prevention and early detection of COPD should be a public health priority in China to reduce COPD-related morbidity and mortality, which relies heavily on understanding underlying mechanisms and discovering novel biomarkers. Specific ncRNA expressions have been reported in response to $PM_{2.5}$-induced lung diseases, with their circulating levels often reflecting changes in their pulmonary counterparts. Therefore, ncRNAs are sensitive, predictive, accessible, and quantifiable indicators of disease. This summary highlights potential ncRNAs linking $PM_{2.5}$ exposure to COPD hallmarks, aiding in the understanding of the AOP of $PM_{2.5}$-induced COPD with alterations in ncRNAs such as MIE.

As shown in Figure 2, the AOP framework describes the development of COPD triggered by $PM_{2.5}$ exposure. Alterations in ncRNA expressions are identified as the MIE, which triggers downstream signal pathway activation at cellular levels and pathological changes at the organ/tissue level, eventually resulting in the development of COPD at the individual /population level. The summary of MIE, KEs, and AO is listed in Table 2. The KERs, evaluated based on Bradford-Hill's weight of evidence considerations, are shown in Table 1[139]. Tables 3-5 show the roles of ncRNAs in regulating KEs of $PM_{2.5}$-induced respiratory toxicity and how $PM_{2.5}$-altered ncRNAs target specific pathways or genes to contribute to the development of COPD. The detailed information of supportive evidence of KERs was summarized in Supplementary Tables 2-5. Each event will be elaborated in detail in the subsequent sections.

miRNA expression in the pathogenesis of COPD

Though many miRNAs have been associated with $PM_{2.5}$ exposure-induced COPD or the pathological alterations of COPD, it is notable that increased expression of miRNA let-7a, miR-199a-5p, miR-21, or decreased expression of miR-224 and miR-194-3p are consistently associated with COPD in cellular, animal models, or individuals exposed to $PM_{2.5}$, which have been validated in multi-studies.

Table 2. Summary of the AOP

Sequence	Type	Event ID	Title	Short name
1	MIE	2007	ncRNA expression profiles alterations	ncRNA expression alteration
2	KE	1392	Oxidative stress	Oxidative stress
3	KE	2009	Activation of inflammatory pathway	Inflammation
4	KE	1650	Epithelial mesenchymal transformation	EMT
5	KE	2012	Fibroblast proliferation and myofibroblast differentiation	Fibrosis
6	KE	1262	Cellular apoptosis	Apoptosis
7	KE	1945	Cellular autophagy	Autophagy
8	KE	2010	Pulmonary inflammation	Pulmonary inflammation
9	KE	2013	Airway remodeling	Airway remodeling
10	KE	2011	Emphysema	Emphysema
11	AO	2008	COPD	COPD

AOP: Adverse outcome pathway; MIE: molecular initiating event, ncRNA: non-coding RNA; KE: key event; EMT: epithelial-mesenchymal transformation; AO: adverse outcome; COPD: chronic obstructive pulmonary disease.

lncRNA and circRNA expression alteration in the pathogenesis of COPD

As for lncRNA, increased expression of SOX2-OT, TUG1, PVT1, NEAT1, MALAT1, and MEG3 has been consistently associated with COPD in cellular, animal models, and individuals following $PM_{2.5}$ exposure. However, all these lncRNAs are intensively investigated in many biological processes, such as cancers. While several studies have explored the role of circRNAs in response to $PM_{2.5}$-induced COPD, the evidence is insufficient to identify specific molecules as biomarkers. Up to now, many studies have already constructed disease prediction or prognosis models by using ncRNA clusters. For example, such models have been developed for diseases such as lung adenocarcinoma[178], cardiovascular disease[179], and ovarian cancer[180]. We thus proposed that a cluster of ncRNAs, but not single ncRNAs, should be combined to predict the development of COPD upon $PM_{2.5}$ exposure.

Patients with different COPD grades may exhibit distinct ncRNA expression profiles and downstream KEs, which can influence treatment strategies. For example, mild COPD (GOLD stages 1 and 2) may show early alterations in ncRNA expression that contribute to oxidative stress and inflammation, while moderate to severe COPD (GOLD stages 3 and 4) may involve more extensive changes, such as EMT, fibroblast proliferation, and myofibroblast differentiation, leading to airway remodeling and emphysema. By integrating COPD grading into our AOP framework, we aim to provide a more comprehensive view of the disease's impact on patient care and public health strategies. This will help in the identification of stage-specific biomarkers and therapeutic targets, thereby improving the prevention and management of COPD, especially in areas with high $PM_{2.5}$ exposure.

Suggested as functional and applicable biomarkers, a single ncRNA or a cluster of ncRNAs could be used to predict the development or aggravation of COPD. For example, the accuracy of hsa_circ_0005045 is around 70% to predict the aggravation of COPD upon $PM_{2.5}$ exposure, combined with other characteristics (group of COPD, smoking, and age)[181]. For further clinical application, more studies should focus on the application of ncRNA panels to predict $PM_{2.5}$ exposure-related COPD at the individual level. When combined with clinical parameters, their predictive accuracy is expected to be higher than that of the existing biomarkers. This validation is the essential next step towards translating mechanistic work into a clinically applicable strategy for prediction and personalized management of $PM_{2.5}$-induced COPD.

Table 3. Overview of miRNAs involved in respiratory toxicity: expression profiles, target pathways, and associated respiratory toxicity types

Name	Cellular KE	Tissue KE	Expression	Target pathway/gene	Respiratory toxicity	Ref.
miR-140-5p	Activation of inflammatory pathway	Airway remodeling	Downregulated	TLR4/NF-κB signaling pathway	Airway inflammation	[140]
miR-644	Cellular apoptosis	Airway remodeling	Upregulated	GAPDH, β-actin	Pulmonary inflammation	[131]
miR-135b	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	Adamts9, Bmper, Klf4, Cxcl12, and Rrbp1	Pulmonary inflammation	[141]
miR-217-5p	Fibroblast proliferation and myofibroblast differentiation	Airway remodeling	Upregulated	miR-217-5p/PTEN axis	Airway inflammation	[142]
miR-181a-2-3p	Cellular apoptosis	Pulmonary inflammation	Downregulated	MEG3	Pulmonary inflammation	[143]
miR-195	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	PHLPP2, Akt signaling	Pulmonary inflammation	[144]
miR-338-5p	Fibroblast proliferation and myofibroblast differentiation	Airway remodeling	Downregulated	HIF-1α/Fhl-1 pathway	Pulmonary inflammation	[145]
miR-21	Activation of inflammatory pathway	Airway remodeling	Upregulated	SATB1/S100A9/NF-κB axis STAT3	Airway inflammation	[146,147] [148]
miR-222-3p	Cellular apoptosis	Airway remodeling	Downregulated	TUG1/miR-222-3p/CELF1/p53 network	Airway inflammation	[25]
miR-155	Oxidative stress	Pulmonary inflammation	Upregulated	miR-155/FOXO3a signaling pathway	Pulmonary inflammation	[127]
miR-29a-3p	Cellular autophagy	Pulmonary inflammation	Downregulated	Akt3/mTOR pathway	Pulmonary inflammation	[149]
miR-1228-5p	Cellular apoptosis	Pulmonary inflammation	Downregulated	NOL3	Pulmonary inflammation	[89]
miR-6747e5p	Activation of inflammatory pathway	Airway remodeling	Downregulated	NF-κB2	Airway inflammation	[116]
miR-146a	Activation of inflammatory pathway	Airway remodeling	Upregulated	NF-κB signaling pathway	Airway inflammation	[147,150]
let-7c	Activation of inflammatory pathway	Airway remodeling	Downregulated	IL-6/STAT3 pathway	Pulmonary inflammation	[151]
miR-1246	Cellular apoptosis	Airway remodeling	Upregulated	NFAT1c	Airway inflammation	[152]
miR-34c-5p	Cellular apoptosis	Airway remodeling	Downregulated	Fra-1	Airway inflammation	[79]
miR-146a-5p	Cellular autophagy	Pulmonary inflammation	Upregulated	IL-8, IRAK1 and TRAF6	Pulmonary inflammation	[103]
miR-6515-5p	Activation of inflammatory pathway	Airway remodeling	Downregulated	MAPK/ERK signaling pathway, CSF3	Pulmonary inflammation	[153]
miR-21-5p	Fibroblast proliferation and myofibroblast differentiation	Airway remodeling	Upregulated	Smad7	Pulmonary inflammation	[154]
miR-212-5p	Cellular apoptosis	Airway remodeling	Upregulated	ARAF, MEK/ERK signaling pathway	Airway inflammation	[155]
miR-93	Cellular apoptosis	emphysema	Upregulated	DUSP2	Pulmonary inflammation	[156]

miR-218	Activation of inflammatory pathway	Pulmonary inflammation	Downregulated	TNFR1	Airway inflammation	[157]
miR-297	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	NKAP	Pulmonary inflammation	[26]
miR-382-5p	Activation of inflammatory pathway	Airway remodeling	Downregulated	CXCL12	Pulmonary inflammation	[27]
miR-96	Activation of inflammatory pathway	Pulmonary inflammation	Downregulated	FOXO3a	Pulmonary inflammation	[158]
miR-194-3p	Cellular apoptosis	Airway remodeling	Downregulated	DAPK1	Pulmonary inflammation	[40,87]
miR-150-5p	Oxidative stress	Pulmonary inflammation	Downregulated	IRE1α	Pulmonary inflammation	[159]
miR-22	Activation of inflammatory pathway	Emphysema	Upregulated	miR-22-HDAC4-DLCO axis	Pulmonary inflammation	[160]
miR-223	Activation of inflammatory pathway	Airway remodeling	Upregulated		Airway inflammation	[161]
miR-143	Activation of inflammatory pathway	Airway remodeling	Downregulated		Airway inflammation	[161]
miR-145	Activation of inflammatory pathway	Airway remodeling	Downregulated		Airway inflammation	[161]
miR-199a	Activation of inflammatory pathway	Airway remodeling	Downregulated		Airway inflammation	[161]
miR-27a	Activation of inflammatory pathway	Airway remodeling	Upregulated		Airway inflammation	[162]
let-7e	Activation of inflammatory pathway	Airway remodeling	Downregulated		Airway inflammation	[162]
let-7g	Activation of inflammatory pathway	Airway remodeling	Downregulated		Airway inflammation	[162]
miR-139	Oxidative stress	Airway remodeling	Upregulated		Airway inflammation	[163]
miR-340	Oxidative stress	Airway remodeling	Upregulated		Airway inflammation	[163]
miR-513a-5p	Activation of inflammatory pathway		Upregulated		Airway inflammation	[164]
miR-494	Activation of inflammatory pathway		Upregulated		Airway inflammation	[164]
miR-923	Activation of inflammatory pathway		Upregulated		Airway inflammation	[164]
miR-96	Activation of inflammatory pathway		Downregulated		Airway inflammation	[164]
miR-223-5p			Upregulated			[40]
miR-495-3p			Upregulated			[40]

miRNAs: MicroRNAs; KE: key event.

Table 4. Overview of circRNAs involved in respiratory toxicity: expression profiles, target pathways, and associated respiratory toxicity types

Name	Cellular KE	Tissue KE	Expression	Target pathway/gene	Respiratory toxicity	Ref.
circ_406961	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	STAT3/JNK pathway	Pulmonary inflammation	[61]
circ_0008672	Activation of inflammatory pathway	Pulmonary inflammation	Downregulated	circ_0008672/miR-1265/MAPK1 axis	Pulmonary inflammation	[165]
circ_0002854	Cellular apoptosis	Airway remodeling	Upregulated	MAPK signaling pathway	Airway inflammation	[166]
circ_0000157	Oxidative stress	Airway remodeling	Upregulated	miR-149-5p/BRD4 pathway	Airway inflammation	[167]
circ_0006872	Cellular apoptosis	Pulmonary inflammation	Upregulated	miR-145-5p/NF-κB pathway	Pulmonary inflammation	[49]
circ_0026344	Cellular autophagy and apoptosis	Emphysema	Downregulated	miR-21, PTEN/ERK axis	Pulmonary inflammation	[57]
circ_002906		Airway remodeling	Upregulated	SEPT10	Airway inflammation	[168]
circ_kif26b	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	miR-346-3p/p21	Pulmonary inflammation	[169]
circ_104250	Activation of inflammatory pathway	Airway remodeling	Upregulated	miR-3607-5p	Airway inflammation	[58]
circ_0008553	Oxidative stress	Airway remodeling	Upregulated		Airway inflammation	[47]
circ_1011			Downregulated		Pulmonary inflammation	[59]
circ_005915			Downregulated		Pulmonary inflammation	[59]
	Cellular apoptosis			miR-103a-3p/BCL2L13 axis		[170]
circBBS9	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	circBbs9-miR-30e-5p-Adar axis	Pulmonary inflammation	[120]
circRBMS1	Cellular apoptosis	Airway remodeling	Upregulated	miR-197-3p/FBXO11 axis	Airway inflammation	[50]
circOSBPL2	Cellular apoptosis, inflammation, and oxidative stress	Airway remodeling	Upregulated	miR-193a-5p/BRD4 axis	Airway inflammation	[48]
circHACE1	Cellular apoptosis, inflammation, and oxidative stress	Airway remodeling	Upregulated	miR-485-3p	Airway inflammation	[171]
circFOXO3	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	miR-214-3p	Pulmonary inflammation	[172]

circRNAs: Circular RNAs; KE: key event.

STRENGTHS AND LIMITATIONS

This study presents a comprehensive AOP framework that integrates current knowledge on $PM_{2.5}$-induced COPD, with a unique focus on ncRNAs as the central MIE. A key strength is the integration of multi-level evidence from cellular, animal, and individual studies, evaluated using structured Bradford-Hill criteria. However, several limitations should be considered. Firstly, the majority of mechanistic evidence derives from *in vitro* or *in vivo* models, and the extrapolation to human pathophysiology may be limited by interspecies

Table 5. Overview of lncRNAs involved in respiratory toxicity: expression profiles, target pathways, and associated respiratory toxicity types

Name	Cellular KE	Tissue KE	Expression	Target pathway/gene	Respiratory toxicity	Ref.
lncRNA MIR155HG	Activation of inflammatory pathway	Airway remodeling	Upregulated	miR-128-5p/BRD4 axis	Airway inflammation	[107,173]
lncRNA MEG3	Cellular autophagy and apoptosis	Airway remodeling	Upregulated	p53	Airway inflammation	[108]
	Cellular apoptosis and inflammation			miR-218		[174]
lncRNA AABR07005593.1	Activation of inflammatory pathway	Airway remodeling	Upregulated	MCCC1	Airway inflammation	[60]
lncRNA MALAT1	Activation of inflammatory pathway	Airway remodeling	Upregulated	miR-204/ZEB1 pathway	Airway inflammation	[72]
lncRNA NEAT1	Activation of inflammatory pathway	Pulmonary inflammation	Upregulated	miR-193a	Pulmonary inflammation	[134]
lncRNA SNHG4	Cellular apoptosis and inflammation	Airway remodeling	Downregulated	miR-144-3p/EZH2 axis	Airway inflammation	[175]
lncRNA LOC101927514	Activation of inflammatory pathway	Airway remodeling	Upregulated	STAT3	Airway inflammation	[176]
lncRNA Gm16410	Activation of inflammatory pathway	Pulmonary inflammation	Downregulated	PI3K/AKT signaling pathway	Pulmonary inflammation	[73]
lncRNA RP11-86H7.1	Activation of inflammatory pathway	Airway remodeling	Upregulated	NFκB1	Airway inflammation	[57]
lncRNA uc001.dgp.1	Activation of inflammatory pathway	Airway remodeling	Upregulated	miR-3607-5p	Airway inflammation	[58]
lncRNA MHC-R	Cellular apoptosis	Pulmonary inflammation	Upregulated		Pulmonary inflammation	[136]
n405968	Activation of inflammatory pathway	Airway remodeling	Upregulated		Airway inflammation	[177]

lncRNAs: Long non-coding RNA; KE: key event.

differences. Secondly, $PM_{2.5}$ composition is highly variable geographically; ncRNA responses may differ depending on the toxic components, of which our framework does not fully discuss. Thirdly, while we propose numerous ncRNA-disease links, many are based on correlation rather than direct causal evidence from gain- or loss-of-function models. Future research should prioritize validating these pathways in human-relevant cohort studies.

CONCLUSION

In conclusion, this review establishes an AOP framework for $PM_{2.5}$-induced respiratory toxicity, positioning the alteration of ncRNA expression profiles as the MIE. By integrating evidence from molecular, cellular, tissue, and population levels, we delineate a cascade of KEs - from cellular levels to tissue levels. This framework not only provides a mechanistic understanding of $PM_{2.5}$ pathogenesis but also highlights a panel of ncRNAs as promising biomarkers for risk prediction. Future efforts to validate this AOP, through human studies and multi-ncRNA biomarker panels, will be crucial for translating these findings into public health strategies aimed at mitigating the burden of air pollution-related COPD.

DECLARATIONS

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Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Supplementary Materials

Supplementary Materials

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