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Molecular mechanisms of airborne particulate matter-induced carcinogenesis: A systematic review of experimental evidence

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ABSTRACT

Airborne particulate matter, especially PM2.5 and ultrafine particles, has been classified as a carcinogen; however, experimental evidence elucidating the molecular mechanisms underlying cancer risk remains limited. This review synthesizes experimental evidence on the molecular mechanisms by which airborne PM induces carcinogenesis, emphasizing pathways involved in cancer initiation, progression, and metastasis. A systematic review was conducted in accordance with PRISMA guidelines. Literature searches were performed across six databases (Scopus, PubMed, ScienceDirect, Wiley, SpringerLink, and Taylor & Francis) for English-language studies published between January 2015 and December 2025. Eligible studies included in vitro, in vivo, and ex vivo experimental investigations using human-relevant models that examined molecular responses to PM exposure. Risk of bias was assessed using the Office of Health Assessment and Translation (OHAT) tool. Of 5,962 records screened, 29 studies met the inclusion criteria; most examined PM2.5 exposure in lung cancer models, with A549 cells being the most frequently used model. Across studies, six interconnected carcinogenic mechanisms were consistently identified: oxidative stress and chronic inflammation driven by reactive oxygen species; genotoxicity accompanied by impaired DNA repair; epigenetic dysregulation involving DNA methylation, histone modifications, and non-coding RNAs; activation of epithelial–mesenchymal transition and metastasis; evasion of apoptosis with metabolic reprogramming; and deregulated cell proliferation and growth suppression. Experimental evidence indicates that PM-induced carcinogenesis extends beyond direct DNA damage to include persistent epigenetic alterations, metabolic adaptation, and activation of oncogenic signaling networks. These findings underscore potential molecular biomarkers and therapeutic targets for early detection and prevention of air pollution–related cancers.

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Introduction

Particulate matter (PM), particularly $PM_{2.5}$ and ultrafine particles ($PM_{0.1}$), is a major air pollutant with significant adverse effects on human health, particularly the respiratory system. $PM_{2.5}$, with an aerodynamic diameter of <2.5 µm, can penetrate deeply into the alveoli, whereas $PM_{0.1}$ (<0.1 µm) can cross biological barriers and translocate into the systemic circulation, thereby inducing multisystemic effects (1-3). Particle size is considered a primary determinant of biological toxicity because it influences particle deposition, tissue penetration, and chemical reactivity. PM is highly heterogeneous in composition and contains a wide range of toxic compounds, including heavy metals such as chromium, cadmium, arsenic, mercury, nickel, and lead, as well as polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs). Several studies have demonstrated that heavy metal and PAH concentrations in PM2.5 increase during winter, which is associated with an increased toxic and genotoxic potential of PM (4-6). PAHs, particularly benzo[a]pyrene, are potent carcinogens because they can induce DNA damage and promote DNA adduct formation (7).

Mechanistically, PM generates reactive oxygen species (ROS), leading to oxidative stress, inflammation, and damage to cellular macromolecules (1, 6). $PM_{0.1}$ possess a relatively larger surface area, resulting in greater chemical reactivity than larger particles and making them more effective in inducing oxidative stress and inflammatory responses (7). Furthermore, their small size enables these particles to evade physiological defense mechanisms, such as mucociliary clearance, thereby increasing particle retention within pulmonary tissues. PM toxicity is also influenced by the bioaccessibility of its chemical constituents in lung fluids, particularly metals such as zinc, arsenic, and chromium, which are highly soluble and thus enhance biological toxicity (2). Seasonal variations further intensify these effects because winter $PM_{2.5}$ generally contains higher levels of PAHs and pro-oxidant minerals that promote

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ROS generation and inflammation (5). In addition, PM exposure can also disrupt the integrity of the pulmonary epithelial barrier, facilitating deeper particle penetration and exacerbating respiratory dysfunction (8).

Current scientific evidence indicates that PM contributes to carcinogenesis through multiple interconnected molecular mechanisms, particularly oxidative stress, chronic inflammation, mitochondrial dysfunction, DNA damage, and epigenetic dysregulation. PM2.5 and ultrafine particles not only carry carcinogenic agents but also create an oxidative microenvironment that increases ROS accumulation, promoting genetic mutations and epigenetic alterations (1, 9, 10). Mitochondrial dysfunction represents another central mechanism, as PM exposure can disrupt the electron transport chain, induce metabolic imbalance, and activate both pro-apoptotic and pro-survival cellular pathways that support malignant transformation (11, 12). In addition, PM activates several inflammatory and cellular signaling pathways, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and the aryl hydrocarbon receptor (AhR), which enhance proinflammatory cytokine production and sustain chronic inflammatory responses (3, 13). Activation of the NLRP3 inflammasome further amplifies inflammatory responses and contributes to tumorigenesis (12). At the same time, disruption of antioxidant pathways mediated by nuclear factor erythroid 2-related factor 2 (Nrf2) reduces the cell's capacity to neutralize ROS, increasing susceptibility to oxidative damage (14). PM also interferes with genetic and epigenetic regulation by altering the expression of long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), contributing to cell cycle arrest, genomic instability, and cancer progression (12, 15).

Although the International Agency for Research on Cancer (IARC) has classified PM as a human carcinogen, most systematic reviews have focused primarily on epidemiological studies and *in vivo* animal models. However, these approaches have not comprehensively integrated mechanistic evidence from *in vitro* studies using human cells, particularly regarding the involvement of specific pathways, such as AhR, lncRNAs, and miRNAs, in PM-induced carcinogenesis (16). Beyond oxidative stress and genotoxicity, the relationship between PM exposure and other oncogenic signaling pathways, such as the EGFR/PI3K/AKT/mTOR pathway, which is associated with lung cancer proliferation through glutamine metabolism, remains poorly synthesized (9, 17). Recent evidence suggests that PM not only contributes to cancer initiation but also promotes tumor progression through angiogenesis, proliferation, and metastasis. PM exposure enhances vascular endothelial growth factor A (VEGFA) expression and MAPK pathway activation, both of which promote tumor angiogenesis (18). PM also promotes lung cancer proliferation through amphiregulin-mediated activation of the EGFR/PI3K/AKT/mTOR pathway and the regulation of glutamine metabolism (17). Moreover, PM enhances metastasis by inducing the expression of heparin-binding EGF-like growth factor (HBEGF) in macrophages, thereby triggering epithelial–mesenchymal transition (EMT) in cancer cells (3). Furthermore, interactions between PM and endocrine-disrupting chemicals, particularly through AhR activation by PAHs, may further enhance the carcinogenic potential of airborne particles (19, 20).

In the context of emerging environmental pollutants, microplastics and nanoplastics have been increasingly recognized as potential carcinogens. These particles can cross biological barriers, accumulate in tissues, and induce oxidative stress and inflammation, contributing to a tumor-promoting microenvironment (21, 22). Meanwhile, miRNA dysregulation resulting from air pollutant exposure further complicates the molecular processes underlying cancer progression because miRNAs play critical roles in modulating oxidative stress, inflammatory responses, and EMT pathways (23). Elucidating the molecular mechanisms underlying PM-induced carcinogenesis has important clinical implications for biomarker discovery and targeted therapy development. Several potential biomarkers, including 15-LOX1, lncRNA NORAD, miR-125b-5p, and miR-100-5p, have been associated with lung cancer in individuals exposed to PM, particularly among non-smokers (24, 25). Furthermore, PM2.5-induced metabolic reprogramming, including enhanced glycolysis and altered DLAT-related gene expression, offers promising opportunities to develop molecularly targeted therapies that improve clinical outcomes and reduce lung cancer incidence (25). Therefore, a comprehensive synthesis of *in vitro* experimental evidence is urgently needed to deepen our understanding of the molecular mechanisms underlying PM-induced carcinogenesis. Such understanding is essential for identifying biological targets involved in cancer initiation, progression, and metastasis, while also supporting the development of early-detection biomarkers, chemopreventive strategies, and precision therapeutic approaches.

Methods

Literature search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26). Data were collected from November 2025 to February 2026. Studies investigating the relationship between airborne PM and carcinogenesis were retrieved from six electronic databases: Scopus, Wiley, SpringerLink, Taylor & Francis, ScienceDirect, and PubMed using predefined search keywords. We selected these databases for their broad indexing coverage of peer-reviewed biomedical, toxicological, and oncological literature. The search strategy combined terms related to particulate air pollution and carcinogenesis, as detailed in Table 1. Two reviewers independently conducted the literature search, limited to English-language articles published between January 2015 and December 2025.

Eligibility criteria and screening method

Articles retrieved from the electronic database searches were imported into Mendeley, and duplicate records were removed. Two independent reviewers screened the titles and abstracts of all identified studies based on predefined inclusion and exclusion criteria. Articles deemed potentially eligible were subsequently assessed through a full-text review to confirm eligibility. Any disagreements between reviewers were resolved through discussion or, when necessary, by consultation with a third reviewer. The research question and eligibility criteria were developed using the PI(E)COS framework (Population, Intervention/Exposure, Comparison, Outcome, and Study Design).

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Table 1. Databases, number of retrieved articles, and search terms

Database	Number of Articles	Search Terms
Scopus	589	TITLE-ABS-KEY (("airborne particulate matter" OR "particulate matter" OR PM2.5 OR PM10 OR "ultrafine particles") AND (carcinogenesis OR carcinogenicity OR cancer OR tumor OR neoplastic) AND (cellular OR molecular OR mechanistic)) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (OA, "all"))
Wiley	1.188	("airborne particulate matter" OR "particulate matter" OR PM2.5) AND (carcinogenesis OR cancer) AND (molecular OR mechanistic)
SpringerLink	2,398	("airborne particulate matter" OR PM2.5 OR PM10) AND (carcinogenesis OR cancer OR neoplastic) AND (molecular OR cellular)
Taylor & Francis	155	("airborne particulate matter" OR "particulate matter") AND (carcinogenesis OR carcinogenicity OR cancer) AND (molecular)
ScienceDirect	1.015	("airborne particulate matter" OR "ultrafine particles") AND then (carcinogenesis OR carcinogenicity OR cancer) AND (molecular OR mechanism)
Pubmed	617	("Particulate Matter"[MeSH] OR "Air Pollution"[MeSH] OR "airborne particulate matter" OR PM2.5 OR PM10 OR "ultrafine particles") AND ("Carcinogenesis"[MeSH] OR "Neoplasms"[MeSH] OR carcinogenesis OR carcinogenicity OR cancer) AND ("*In vitro* Techniques"[MeSH] OR "Cells, Cultured"[MeSH] OR molecular OR mechanistic)

The inclusion criteria included peer-reviewed English-language studies investigating the effects of airborne PM on carcinogenesis, involving cancer cells or patients with any cancer type, and employing experimental approaches, including *in vitro*, *in vivo*, and *ex vivo* studies using human samples. The exclusion criteria included studies unrelated to the review topic, experimental studies conducted exclusively in animals, and non-experimental studies. Review articles, meta-analyses, editorials, letters to the editor, case reports, conference abstracts, theses, dissertations, books, and book chapters were also excluded. Additionally, studies focusing solely on cancer outcomes, such as cancer mortality, were excluded (Table 2). Animal studies were excluded from this review to maintain the analytical focus on human-relevant experimental models, as these models more accurately reflect human physiological conditions and the pathophysiological mechanisms underlying carcinogenesis.

Data extraction

We extracted data from all full-text articles included in this review. Extracted information included the first author's name, publication year, study design, setting, sample size, intervention, molecular targets, population characteristics, the air pollutant investigated, exposure assessment methods, exposure dose/concentration, exposure duration, and principal findings and outcomes. Two reviewers independently extracted data from all selected studies using a standardized data extraction form. Any discrepancies were resolved through consensus discussion and, when necessary, through consultation with a third reviewer. The extracted data were summarized in Supplementary Table 1 and Table 3. We did not perform a meta-analysis because of substantial heterogeneity in outcome measures, differences in PM doses across studies, and variations in the experimental cell lines used. The preparation of Figures 2 and 3 included the use of artificial intelligence (AI) to generate the initial schematic illustrations. The authors then carefully reviewed, verified, and manually revised all illustrations to ensure scientific accuracy and consistency with the study content. This approach aligns with findings from previous studies showing that AI can facilitate the efficient creation of scientific illustrations while emphasizing the need for author-led validation and revision to ensure the accuracy and reliability of the information presented (27-30).

Risk of bias assessment

This study employed the Risk of Bias (ROB) assessment tool developed by the National Institute of Environmental

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Table 2. PI(E)COS criteria for study inclusion and exclusion

Parameter	Inclusion Criteria	Exclusion Criteria
Participants	Human cells/molecular and tissue samples and/or humans associated with particulate matter exposure	*In vitro*, *in vivo*, or *ex vivo* animal studies, epidemiological studies, clinical studies, or *ex vivo* models without a clear molecular approach
Intervention/ Exposure	Exposure to airborne PM, including but not limited to $PM_{2.5}$, PM_{10}, ultrafine particles (UFPs), diesel exhaust particles, or ambient particulates from environmental/industrial sources	Exposure to non-particulate air pollutants (e.g., O_3, NO_2, SO_2 without PM), non-airborne particles (e.g., engineered nanoparticles without environmental relevance), or mixed exposures where PM-specific effects could not be isolated
Comparison	PM-exposed groups, sham/control vehicle groups, or comparisons across PM exposure levels/doses/durations to evaluate molecular changes associated with carcinogenesis	Studies without a clear comparison group, without control conditions, or lacking comparisons enabling evaluation of PM-specific molecular carcinogenic effects
Outcomes	Molecular/cellular evidence related to carcinogenesis, including DNA damage, oxidative stress, inflammation, gene mutations, altered gene/protein expression, cell cycle disruption, apoptosis, cellular transformation, or epigenetic alterations	Studies reporting only general cytotoxicity without molecular analysis, or non-carcinogenic outcomes irrelevant to this review
Study Design	Original experimental *in vitro*, *in vivo*, and *ex vivo* human studies published in English-language scientific journals	Animal-only experimental studies and non-experimental studies, including reviews, meta-analyses, editorials, letters, case reports, conference abstracts, theses, dissertations, books, or book chapters

Table 3. Summary of the included studies

No	Type of particulate matter (PM)	Source of particles	Molecular/Target Molecules	Dose/Exposure Level	Exposure Duration	Impact/Outcome
1	PM2.5 (35)	Ambient urban PM collected from an urban environment	15-Lipoxygenase-1 (15-LOX1); 15-Lipoxygenase-2 (15-LOX2); Cancer stem cell (CSC) markers: CD133, ALDH1A1, Nanog, Notch1, Hes1; EMT markers: Vimentin; Wnt/β-catenin signaling pathway (β-catenin, p-GSK3β, TCF4); Proliferation/apoptosis regulators: Bcl-2, Bax, Caspase-3	5, 10, 25, 50, 75 μg/m	Short-term: 1–72 hr; Medium-term: 6 hr; Long-term: 28 days of continuous exposure	↓15-LOX1 and 15-LOX2 expression; ↑Bcl-2 expression; ↑ALDH1A1 expression; ↑CD133; ↑Nanog, Notch1, Hes1; ↑Vimentin; ↑β-catenin, pGSK3β, TCF4 expression; ↑miRNA targets of 15-LOX1 (miR-18, miR-203) and 15-LOX2 (miR-17, miR-20a, miR-20b, miR-93, miR-106a, miR-106b, miR-590-3p); DNA hypermethylation of the 15-LOX1 promoter
2	Carbon Black (CB nanoparticles); Diesel Exhaust Particles (DEP); PM2.5; Elemental Carbon (EC) (63)	Actual Occupational Exposure in Carbon Black Industry Workers	Inflammatory biomarkers: IL-1β, IL-6, IL-8, TNF-α, MIP-1β, CRP; PAH metabolites; Transcriptomics (RNA-seq); Hub genes: CDC20, PLK1, FOS, JUN; CBMN assay	PM2.5 control: ~130 μg/m^3; CB: ~637.4 μg/m^3; DEP: ~430.8 μg/m^3	CB exposure: average 16.2 years; DEP exposure: average 10.2 years	CB group: ↑IL-1β, IL-6, IL-8, TNF-α, MIP-1β, CRP. DEP group: ↑1-OHP, 1-OHNa, 2-OHNa, 2-OHFlu, 2-OHPh. CBMN strongly correlated with CDC20 expression. CB: 81 DEGs; DEP: 220 DEGs. CB activated the G2/M checkpoint and E2F targets. DEP activated ROS and DNA damage pathways. ↑ROS in DEP exposure
3	PM; heavy metals (Fe, Cu, Zn, Pb, Ni, Cd, Mn); PAHs including Benzo(a)pyrene (36)	Atmospheric Environment of the Industrial Area	Proteomics; oxidative stress proteins (SOD2, PRDX1); DNA repair proteins (TP53BP1, NSMCE4A); carcinogenesis-related proteins (CAV1, CEBPZ, C1QBP); metabolic proteins (MDH2, UGP2)	50 and 100 μg/ml	24 hr	↓SOD2, PRDX1, GSTP1, GSTO1; ↑TP53BP1, NSMCE4A, TOP1/2A/2B, PARN; ↓USP5. ↑C1QBP, EWSR1, CAV1, RBM39; ↓UBQLN1 and annexins. ↓MDH2, PGLS, UGP2, mitochondrial proteins. ↑Ribosomal proteins and RNA processing proteins. ↑Actin and actin-binding proteins
4	PM2.5 (47)	Ambient air in urban environments, especially in areas with high levels of traffic activity and industrial emissions	Oxidative stress biomarkers: MDA, SOD, GSH, GSH-Px; Differential proteins: MT2A, MT1X, SLC39A10, PRSS23	50 μg/ml	24 hr	L02 + PM2.5 group: ↑MDA, ↓SOD, ↓GSH, ↓GSH-Px; ↑MT2A, ↑MT1X, ↑MT1E; ↓SLC39A10; ↓PRSS23; ↓LDLR; ↑COX17. c-Myc silenced + PM2.5 group: ↑MDA, ↓SOD, ↓GSH, ↓GSH-Px; ↑MT2A, ↑MT1X, ↑MT1E; ↓SLC39A10; ↑PRSS23; ↑Apolipoprotein family proteins
5	$PM_{2.5-0.3}$ (55)	Urban areas and rural areas	Cytotoxicity: MDH & LDH; PAH metabolism genes; γH2AX; telomerase activity; miRNA expression; 8-oxodG	≥6 μg/cm^2; ≥1.5 μg/cm^2; 12 μg/cm^2; 3 μg/cm^2	24, 48, or 72 hr	↑LDH; ↓MDH; ↑H2AX phosphorylation; ↑γH2AX; ↑Telomerase activity; ↑miR-21; slight ↑miR-26b; ↑CYP1A1 and CYP1B1; ↑AhRR; no significant change in AhR and ARNT; ↑NQO1
6	PM_{10} (56)	Ambient air pollutants collected from the urban and surrounding environments of Jeddah, including emissions from traffic, fossil fuel combustion, and environmental dust.	BMP4 mRNA; Hsp90 mRNA; Fibronectin pre-mRNA; siLuc	N/A	48 hr	PM_{10} induced alternative splicing of BMP4. ↑4–5-fold increase in long 5′UTR BMP4 isoforms. ↓Total BMP4 mRNA and protein levels. Inhibited RNA Polymerase II elongation and delayed FN1 transcription recovery. ↓SR protein expression. CPT inhibited FN1 pre-mRNA synthesis and induced BMP4 alternative splicing. No significant changes in Hsp90 expression
7	PM10–2.5 (57)	Building demolition site	FAK, p-FAK(Y925), p38, ERK1/2, JNK, PI3K, AKT1/2/3; migration and invasion markers; BCL2; Aurora B	200, 400, and 600 μg/ml	24–48 hr	↑p-FAK-Y925; ↑PI3K expression; ↑AKT activation; ↑Aurora B kinase; ↑Bcl-2; ↑β-catenin; ↑N-cadherin; ↑Vimentin; ↑MMP-9; ↑Cathepsin D; ↓E-cadherin. ERK, JNK, and p38 MAPK showed no significant changes
8	PM2.5 (58)	Commercially available pure NPAHs (9-nitroanthracene and 1-nitronaphthalene)	MST1/MST2, LATS1/LATS2, YAP, phospho-YAP, phospho-MST1/2, phospho-LATS1/2; E-cadherin; ICAM	0.1, 3, and 10 μM	24 hr	↓E-cadherin; ↑ICAM-1; ↓phospho-MST1/2 and phospho-LATS1/2; activation of oncogenic YAP and YAP–TEAD complex formation, facilitating migration, adhesion, and metastasis of A549 lung cancer cells
9	PM2.5 (59)	National Institute of Standards and Technology (NIST, Gaithersburg, MD, United States)	Rad51, RAD54L, EME1, RMI2, GAPDH, MDA, DNA damage	0, 25, 100, 200 μg/ml	24 hr	↓Cell proliferation; ↑Apoptosis with increasing PM2.5 concentration; ↑Tail DNA %, Tail Length, and Olive Tail Moment; ↑MDA; 1,702 significantly altered mRNAs; ↓16 DNA repair genes; ↓Rad51, Rad54L, EME1, RMI2 expression. Rad51 overexpression reduced DNA damage
10	PM2.5 and PM10 (60)	Ambient air in urban areas	E-selectin, P-selectin, ICAM-1, VCAM-1, PECAM-1, sLex, PSGL-1, LFA-1, VLA-4, αVβ3	0.03, 0.3, 1, 3, 10, and 30 μg/cm^2	3 hr for early adhesion molecules; 24 hr for late adhesion molecules	↑E-selectin and P-selectin; ↑sLex and PSGL-1; ↑ICAM-1, VCAM-1, PECAM-1; ↑LFA-1, VLA-4, αVβ3; PM2.5 had stronger effects on LFA-1 and αVβ3 at high concentrations; PM10 increased VLA-4 and αVβ3 from 10 μg/cm^2 onward; ↑cellular adhesion between A549 and U937 cells
11	PM2.5 (61)	Ambient air in urban areas	ADM (Adrenomedullin); CYP1B1; EREG (Epiregulin); IL1A & IL1B; ITGB3; MMP1; MT1X; PGM3; PPP1R14A; RND3; SPHK1; LAMA5; TGFB2; TNFRSF1A; TP53; GAPDH	50 μg/cm^2	72 hr	↑ADM (Adrenomedullin); CYP1B1 (Cytochrome P450 Family 1 Subfamily B Member 1): significantly induced; ↑EREG (Epiregulin); ↑IL1A & IL1B (Interleukin-1α and Interleukin-1β); ↑ITGB3 (Integrin Beta 3) expression; ↑MMP1 (Matrix Metalloproteinase-1); MT1X (Metallothionein 1X): induced by heavy metal exposure in PM2.5; ↑PGM3 (Phosphoglucomutase 3); ↑PPP1R14A (Protein Phosphatase 1 Regulatory Subunit 14A); ↑RND3 (Rho Family GTPase 3); ↑SPHK1 (Sphingosine Kinase 1); ↓LAMA5 (Laminin Subunit Alpha 5); ↓TGFB2 (Transforming Growth Factor Beta 2); ↓TNFRSF1A (TNF Receptor Superfamily Member 1A); ↓TP53 (Tumor Protein p53)
12	PM10 (37)	Environmental airborne particles (source not specified)	Knockdown of lncRNA NORAD using siRNA; SAC genes: MAD1L1, MAD2L1, BUB1B, AURKB, BIRC5; PUM1 protein; mitotic index; cell cycle; micronucleus assay	10 μg/cm^2 in culture medium	24 hr	↑NORAD (lncRNA); ↑MAD1L1; ↑MAD2L1; ↑BUB1B; ↑AURKB (Aurora Kinase B); ↑BIRC5 (Survivin); ↓PUM1 (Pumilio RNA Binding Protein 1); ↓Mitotic index; ↑Aneuploidy / micronucleus formation; ↑MN CEN$^+$ (centromere-positive micronucleus); altered cell cycle progression
13	PM1 (38)	Urban ambient PM and tobacco smoke particulates (TSP)	Peroxidasin (PXDN); HOCl; HOBr; sulfilimine bond; type IV collagen; CD8+ T cells; IFN-γ; ITGB1, CXCR3, ROCK	0–500 μg/ml FPM	24–48 hr	↑PXDN enzymatic activity; adsorption/accumulation on FPM; phase separation activation. ↑HOCl and HOBr production. ↑Type IV collagen crosslinking; increased insoluble collagen fraction and matrix thickening. ↑Sulfilimine bond formation; ↑allysine levels. ↑NC1 dimer; ↓NC1 monomer. ↓Migration of cytotoxic T lymphocytes (CTLs)
14	PM2.5 (39)	Collection of urban ambient aerosols	ROS; NRF2; HO1; NQO1; GPX1; SOD2; GSTP1; BCL2; BAX; p53; GSH/GSSG; ΔΨm	10 μg/cm^2	4-hour pretreatment, 20-hour apoptosis induction	↑ROS; ↓GSH/GSSG ratio. ↑NRF2 activation and nuclear translocation; ↑HO-1; ↑NQO1; ↑GPX1; ↑SOD2; ↑GSTP1. ↑BCL-2; ↓BAX; ↑BCL-2/BAX ratio; ↓p53; ↓apoptosis activation. ↑Mitochondrial membrane potential (ΔΨm). ↑Cell viability
15	PM10 (40)	Commercial urban area	AhR; AP-1 family proteins; MMP-9; Histone H3; GAPDH	10 μg/cm^2 PM10; 1 μM BaP	48 hr	PM10 ↑AhR protein expression; BaP ↑AhR levels; AhR silencing ↓AhR expression. AhR nuclear translocation observed after PM10 and BaP exposure. ↑c-Jun and JunB activity; ↓after AhR silencing. JunD unchanged, but ↓after AhR silencing. ↓FosB activity after PM10; c-Fos ↓with PM10 and ↑with BaP. ↑Fra-1 after PM10 and BaP exposure. PM10 ↑MMP-9 expression and enzymatic activity. PM10 ↑A549 cell invasion by 40%; invasion abolished after AhR silencing

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Continued Table 3.

16	PM2.5 (41)	An area surrounded by residential neighborhoods, schools, subway stations, railway stations, intercity bus terminals, and urban bus terminals	MTT assay; cell morphology; RNA-seq; GO and KEGG pathway analysis	400 µg/ml	24 hr	↑MMP1; ↑SNX31; ↑IL1R2; ↓NEDD9; ↓CPA4; ↓RBMS3. Significant transcriptomic dysregulation with 712 altered genes, predominantly up-regulated. GO and KEGG analyses confirmed systemic molecular pathway alterations induced by PM2.5
17	PM2.5 (62)	Urban ambient PM	MTT assay; cell morphology; RNA-seq; GO and KEGG pathway analysis	400 µg/ml	24 hr	↑MMP1; ↑SNX31; ↑IL1R2; ↓NEDD9; ↓CPA4; ↓RBMS3. Significant transcriptomic dysregulation with 712 altered genes, predominantly up-regulated. GO and KEGG analyses confirmed systemic molecular pathway alterations induced by PM2.5.
18	PM2.5 (54)	Urban background air monitoring site	FTSJ1; PGK1; lactate and pyruvate; ECAR and OCR; qRT-PCR; WB; RNA-seq; ChIP assay	0–400 µg/ml	24 days	↓FTSJ1 mRNA and protein expression. ↓tRNA Am modification. FTSJ1 knockdown ↑lactate, pyruvate, and ECAR. ↑PGK1 expression. FTSJ1 suppresses PGK1 translation and glycolytic activity. ↑H3K27ac modification at the PGK1 promoter. ↑Translation efficiency and LDHA expression. FTSJ1 negatively correlated with SUVmax in NSCLC patients, while PGK1 positively correlated.
19	PM10 (43)	Urban areas predominantly influenced by motor vehicle emissions and rural areas with PM primarily derived from natural sources	DNA damage; ROS	75, 150, 300 µg/ml	24 hours	↑DNA damage in a dose-dependent manner (75 → 150 → 300 µg/ml). DNA damage was higher in urban PM compared to rural PM and higher during autumn than spring. ↑ROS production
20	PM2.5, PAHs, LMW, MMW, HMW-PAHs, ions, heavy metals (42)	Vehicular emissions	IL-6; CYP1A1; HO-1; NQO-1; ROS	±10 µg/ml	6 hr and 48 hr	↑IL-6; EGCG significantly ↓IL-6. ↑CYP1A1; EGCG ↓CYP1A1 expression. ↑ROS; EGCG ↓ROS. ↑HO-1 and ↑NQO-1; EGCG normalized HO-1 and NQO-1 expression
21	$PM_{2.5}$ (44)	Traffic-derived	EMT markers: E-cadherin, N-cadherin, fibronectin 1, vimentin; EMT transcription factors: SNAIL1, SNAIL2, ZEB1, ZEB2; MMPs and integrins: MMP1, MMP2, MMP9, integrin β1, β3, αv; Cancer stem cell markers: CD44, CD133, ALDH1A1, ABCG2; Pluripotency factors: SOX2, OCT4, NANOG, KLF4; MicroRNAs: let-7a, miR-15, miR-16, miR-34a, miR-143, miR-145	Acute exposure: 0, 5, 25, 50, 100, 200 µg/ml; Chronic exposure: 0, 5, 50, 100 µg/ml	Acute exposure: 24 hr; Chronic exposure: 24–48 hr	Acute vs chronic exposure: ↑MMP9, MMP1, MMP2 vs ↑migration and invasion effects; ↑Integrin β1, β3, αv; ↓E-cadherin vs ↓E-cadherin; ↑N-cadherin & vimentin vs ↑N-cadherin & vimentin; ↑ZEB1 & ZEB2; SNAIL1 & SNAIL2 showed minimal changes vs SNAIL1 & ZEB2; ZEB1 increased at the protein level; CD133, CD44, ALDH1A1, ABCG2 showed no significant changes vs ↑CD44 & ABCG2; SOX2, OCT4, NANOG, KLF4 showed no changes vs ↑SOX2 & OCT4; SP cells (%) unchanged vs ↑SP cells (%); let-7a, miR-15, miR-16, miR-34a, miR-143, miR-145 not measured vs ↓let-7a, miR-15, miR-16, miR-34a (especially let-7a & miR-16); miR-143 & miR-145 unchanged
22	$PM_{2.5}$ (45)	Ambient air from an industrial area comprising machinery manufacturing, chemical industries, boilers, and power plants	Cytotoxicity: LDH release; Oxidative stress: intracellular ROS; Pro-inflammatory response: TNF-α, IL-1β	0; 12.5; 25; 50; 100 µg/ml	24 hr (cytotoxicity and inflammation); 4 hr (ROS assay); NAC pretreatment: 8 hr before $PM_{2.5}$ exposure	↑LDH release; highest cytotoxicity during winter; ↑ROS production; spring, summer, and autumn produced lower cytotoxic effects; ↑TNF-α expression, strongest during winter; Sulforaphane (SFN) significantly inhibited ROS production, reduced TNF-α expression during winter, and suppressed IL-1β release during winter; ↑IL-1β release predominantly during winter
23	PM2.5 (46)	Ambient PM (source not specified)	VEGFA; p-ERK/ERK; CD31; CD133; VEGFB; ANG1; PDGFA/PDGFB; FGF family	12.5–25 µg/ml (*in vitro*; ambient PM2.5 exposure in epidemiological studies)	30–60 days (long-term exposure)	↑VEGFA mRNA and protein expression; ↑VEGFA concentration in conditioned medium; xenograft tumor tissues showed higher VEGFA expression. ↑ERK phosphorylation (p-ERK); ERK inhibition or ERK siRNA ↓VEGFA expression and angiogenesis. c-Jun overexpression ↑VEGFA mRNA expression. ↑CD31 and CD133 expression in xenograft tissues; ↑recruitment of endothelial progenitor cells (EPCs); ↑tumor angiogenic activity. Other angiogenic factors (VEGFB, ANG1, PDGFA/B, FGF) showed no significant increase
24	PM2.5 (48)	Standard Reference Material (SRM) 1650b Diesel PM obtained from the National Institute of Standards and Technology (NIST) and purchased through Sigma-Aldrich	EGFR/pEGFR; AKT/pAKT; STAT3/pSTAT3; ERK/pERK; AhR; TMPRSS2; IL-18; Ki-67; qRT-PCR; Western blot; ChIP-qPCR; RNA-seq	Main concentration: 50 µg/ml	Short-term: 24 hr; Long-term: 60 days (PC9), 90 days (A549 and H1975)	↑Persistent EGFR/pEGFR activation; ↑pAKT in EGFR-mutant cells; ↑pSTAT3 in EGFR wild-type cells; ERK changes not significant; ↑AhR nuclear translocation; ↑TMPRSS2 expression; ↑IL-18 expression; EGFR–AKT axis promoted cancer cell proliferation and survival
25	PM2.5 (49)	Urban ambient air	Inflammation: IL-17a, IL-6, TNF-α; EMT: MMP2, MMP9, TGF-β1, α-SMA, Fibronectin, Vimentin; Oncogenes & stemness markers: Kras, c-Myc, ABCG2, OCT4, SOX2, Aldh1a1; Tumor suppressors: p53, PTEN	±168.5 µg/m³	N/A	↑IL-17a, ↑IL-6, ↑TNF-α; ↑TGF-β1, ↑MMP2, ↑MMP9, ↑α-SMA, ↑Fibronectin, ↑Vimentin; ↑Kras, ↑c-Myc, ↑ABCG2, ↑OCT4, ↑SOX2, ↑Aldh1a1; ↓p53 and ↓PTEN
26	PM2.5 (50)	Urban PM from National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 16… (Gaithersburg, MD, USA)	Differentially expressed genes (DEGs); GO, KEGG, Reactome pathways; CYP1A1; CYP1B1; SLC16A6; AC007622.2; LINC01085; CBS	200 µg/ml	24 hr (acute exposure)	↑CYP1A1; ↑CYP1B1; ↑SLC16A6; ↑AC007622.2 (lncRNA); ↑CYSRT1; ↓LINC01085; ↓CBS; ↓BDKRB2; ↓ATP8A1; ↓DIO2; ↓AC092279.2; ↓AC131649.2; ↓SIMM11; ↓MEMO1P1; ↓CKMT1B
27	PM2.5 (51)	National Institute of Standards and Technology (NIST), Standard Reference Material (SRM) 1648a, Maryland, Amerika Serikat	DLAT; eIF4E; Sp1; lactate; pyruvate; acetyl-CoA; ECAR; OCR; Ki-67; Caspase-3; γH2AX	100, 200, 400 µg/ml	24–48 hr	↑DLAT expression; ↑lactate; ↑pyruvate; ↑ECAR; ↓acetyl-CoA; ↑lung cancer cell proliferation; ↓apoptosis. ↑eIF4E expression and DLAT translation; ↑Sp1 expression and promoter binding. OCR unchanged. ↓Caspase-3 expression/activity; ↑γ-H2AX expression
28	PM2.5 (52)	Traffic-originated PM organic extract (tPo)	lncRNA loc107985872; Notch1 pathway; ADAM17; PSEN1; DLL1; EMT markers; CSC markers	A549: 5 mg/ml; H1299: 2 mg/ml	Chronic exposure over 10 cell passages	↑loc107985872 expression; ↑Notch1; ↑ADAM17; ↑PSEN1; ↑DLL1; ↑E-cadherin; ↑ZO-1; ↑N-cadherin; ↑Vimentin; ↑CD44; ↑OCT4; ↑SOX2; ↑ALDH1A1; ↑ABCG2
29	PM2.5 (53)	Ambient dust	EMT markers: E-cadherin, N-cadherin, Vimentin, Fibronectin; Transcription factors: Snail, Slug, Twist; PI3K/Akt pathway; CXCL12/CXCR4; CCL3; MMP-2; MMP-9	190 µg/ml	24, 48, and 72 hr	E-cadherin ↓ with PM2.5 and ↑ with PM2.5+BCA; β-catenin ↓ with PM2.5 and ↑ with PM2.5+BCA; N-cadherin, Vimentin, Fibronectin ↑ with PM2.5 and ↓ with PM2.5+BCA; Snail, Slug, Twist ↑ with PM2.5 and ↓ with PM2.5+BCA; CXCL12, CXCR4, TGF-β1, TGF-β2 ↑ with PM2.5 and ↓ with PM2.5 + BCA; MMP-2 and MMP-9 ↑ with PM2.5 and ↓ with PM2.5 + BCA; PM2.5 activated PI3K/Akt signaling; proliferation ↓ with PM2.5 and ↑ with PM2.5+BCA; migration and invasion ↑ with PM2.5 and ↓ with PM2.5+BCA

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Health Sciences–National Toxicology Program–Office of Health Assessment and Translation (OHAT) to evaluate the risk of bias in each experimental study, including *in vitro* investigations (31). The assessment used eight criteria: exposure assessment, outcome assessment, confounding bias, selection bias, attrition/exclusion bias, selective reporting bias, conflicts of interest, and other potential sources of bias (32). Two independent reviewers conducted the assessment and resolved disagreements through discussion or by involving a third reviewer. Each risk-of-bias domain was rated using four response categories: "++" (+2, definitely low risk), "+" (+1, probably low risk), "–" (-1,

probably high risk), or "−−" (-2, definitely high risk). The scores for each study were summed and divided by the total number of questions assessed. Numerical values ranging from -2 to +2 were assigned to each item. Studies were subsequently categorized as having a low risk of bias (Tier 1), moderate risk of bias (Tier 2), or high risk of bias (Tier 3). The cut-off values were >0.7 for Tier 1, -0.6 to 0.7 for Tier 2, and <-0.6 for Tier 3 (33, 34).

Results

Literature search and study characteristics

The initial literature search identified 5,962 articles. After removing 1,547 duplicate records, we screened 4,415 articles by title and abstract, excluding 4,209 records. Subsequently, 206 full-text articles were retrieved and assessed for eligibility. During this eligibility assessment stage, 176 articles were excluded for the following reasons: ineligible samples (n=134), non-intervention studies (n=28), animal studies (n=11), review articles (n=2), and study protocols only (n=1). Ultimately, 29 studies met the inclusion criteria and were included in this systematic review for further analysis (Figure 1).

Study characteristics

The majority of the studies employed an *in vitro* design (n=27, 93.1%)(35-61), while one study used a combined *in vitro–in vivo–clinical* design (n=1, 3.4%) (62), and one study applied an *ex vivo* approach (n=1, 3.4%)(63). The included studies were predominantly conducted by institutions in Greater China (n=17, 58.6%), including China, Hong Kong, and Taiwan (35, 41, 42, 44, 45, 47-49, 51-54, 58, 61-63). North America (United States and Mexico) contributed 7 studies (24,1%)(36, 37, 39, 40, 53, 57, 60). The remaining 5 studies (17,2%) originated from the Middle East, Europe, and other Asian countries (39, 43, 50, 55, 56). The primary biological target investigated was lung cancer/non-small cell lung cancer (NSCLC)(n=24, 82.8%)(35-44, 46, 48-53, 55, 58-63). Two studies focused on leukemia (n=2, 6.8%) (45, 54), while one study each (3.3%) focused on breast cancer (57), colon cancer (56), and hepatocarcinogenesis (47). The A549 cell line was the most frequently used *in vitro* model (n=20, 69%)(36-38, 44, 46, 48-53, 58-62). The normal cell lines used as comparative controls (e.g., BEAS-2B) were reported in six studies (n=6, 20.7%)(37, 39, 51, 55, 59, 62). Other lung cancer cell lines (H1299, H1975, H460, PC9) were employed in seven studies (n=7, 24.1%)(35, 46, 48, 50, 51, 61). Non-lung cells (representing other cancer models) were used in six studies (n=6, 20.7%)(45, 47, 54, 56, 57, 63). All studies implemented stringent negative controls. Validation using positive controls (established carcinogens) was conducted in 3 studies (n=3, 10,3%)(45, 56, 63)(Supplementary Table 1).

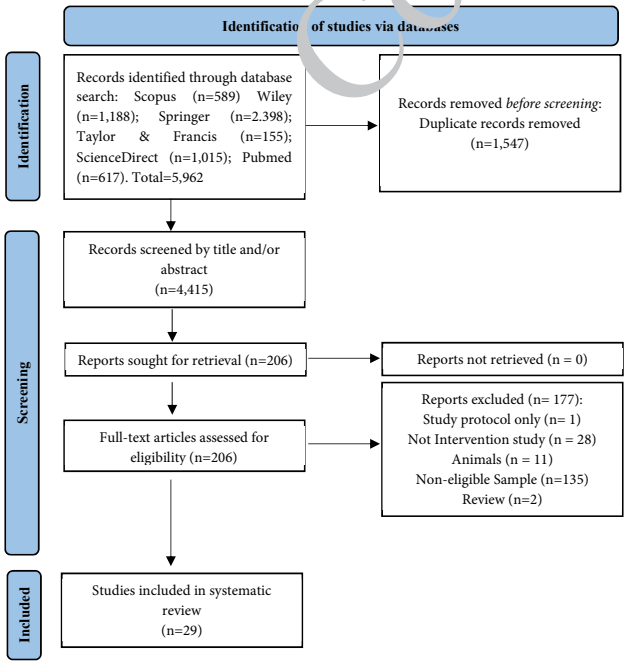


Figure 1. Study selection process according to the PRISMA flow diagram

Study quality assessment

Overall, the methodological quality of the evaluated literature was good, with generally strong internal validity. Based on the overall risk-of-bias classification, no studies were categorized as high risk of bias (Tier 3). A total of 22 studies were classified as Tier 1 (low risk of bias), indicating high methodological quality and reliable reporting (35, 37-43, 46-48, 51, 52, 54-57, 60-62). Meanwhile, seven studies were classified as Tier 2 (moderate risk of bias), mainly because of limitations in reporting randomization procedures or internal validity. However, they still met the inclusion criteria for this systematic review (36, 44, 49, 50, 53, 58, 63).

Domain-based risk-of-bias analysis demonstrated methodological consistency across most studies. All included studies exhibited a definitely low or probably low risk of bias in allocation, maintenance of experimental conditions, data completeness, outcome assessment, and outcome reporting. These findings indicate that most *in vitro* studies were conducted under well-controlled experimental conditions, and cellular parameters were measured and reported transparently. Regarding PM exposure characterization, most studies also demonstrated adequate quality. However, Zhang *et al.* (63) and Omran *et al.* (46) were considered to have a probably high risk of bias because they reported insufficient information on PM dosage and exposure characterization.

The most common methodological limitations involved exposure randomization and investigator blinding. Most studies demonstrated a high risk of bias in these domains. This limitation is common in molecular *in vitro* studies because investigators are generally aware of the exposure type and dose administered to cell cultures. In contrast, blinding procedures are rarely implemented or clearly reported (64-66). Nevertheless, Wang *et al.* (62) and Cheng *et al.* (57) implemented blinding procedures more rigorously than other studies. Regarding internal validity, most studies met acceptable methodological standards. However, several studies (36, 44, 47, 50, 57) still showed a higher risk of bias due to suboptimal control of confounding variables or limitations in the use of specific controls (Supplementary Table 2).

Molecular landscape of PM-induced carcinogenesis

Analysis of the 29 included studies demonstrated that carcinogenesis research was predominantly focused on exposure to fine PM ($PM_{2.5}$)(n=20, 66.7%)(35, 39, 41,

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42, 44, 45, 47-52, 54, 55, 57, 59-62). Coarse particles (PM_{10})(n=4, 13,8%)(37, 40, 43, 56), PM_1 (n=1, 3.4%) (38), Carbon Black (CB) and Diesel Exhaust Particles (DEP)(n=1, 3,4%)(63), and mixed/general PM extracts or specific particulate variants (n=5, 17,2%)(40, 42, 43, 55, 57, 60). Exposure duration ranged from acute phases (1-72 hr) to chronic exposure models (up to 90 days or 10 cell passages) designed to simulate long-term cellular transformation (Table 3). Based on the findings, the molecular mechanisms describing how air pollution promotes the transformation of normal cells into malignant cells at the DNA and protein levels can be summarized into six major carcinogenic phases: 1) Oxidative Stress and Chronic Inflammation; 2) Genotoxicity and Dysregulation of DNA Repair; 3) Epigenetic Modifications and Non-Coding RNA Regulation; 4) Epithelial–Mesenchymal Transition (EMT) and Metastasis; 5) Apoptosis Evasion and Metabolic Reprogramming; 6) Deregulation of Cell Proliferation and Evasion of Growth Suppressors. Table 4 summarizes the findings, and Figure 2 illustrates the cellular mechanisms triggered by PM exposure. These mechanisms include reactive oxygen species (ROS) generation, NLRP3 inflammasome activation, long non-coding RNA (lncRNA) dysregulation, and the induction of EMT.

Table 4. Molecular distribution across different phases of particulate matter–induced carcinogenesis

Carcinogenic Mechanism Category	Related Molecular Markers	Studies
Oxidative Stress and Chronic Inflammation	Inflammatory biomarkers: IL-1β, IL-6, IL-8, TNF-α, MIP-1β, CRP; Reactive Oxygen Species (ROS) pathway Oxidative stress markers: SOD2, PRDX1, GSTP1, GSTO1 Oxidative stress biomarkers: MDA, SOD, GSH, GSH-Px Peroxidasin (PXDN), Hypochlorous acid (HOCl), Hypobromous acid (HOBr) ROS, NRF2, HO-1, NQO1, GPX1, GSH/GSSG ratio Inflammation: IL-1β, IL-6, iNOS, COX-2; Oxidative stress: ROS, NADPH oxidase (NOX); Signaling pathways: NF-κB (p65), STAT3 Inflammation: IL-6; Oxidative stress: HO-1, NQO-1, ROS	36, 39, 42, 47, 54, 62, 63)
Genotoxicity and Dysregulation of DNA Repair	Micronucleus (CBMN assay), genomic instability, DNA damage response DNA damage and repair-related proteins: TP53BP1, NSMCE4A, Topoisomerases (TOP1, TOP2A, TOP2B), PARN, USP5 Genotoxicity markers: γH2AX, 8-oxo-2'-deoxyguanosine (8-oxodG) DNA repair markers: Rad51, RAD54L, EME1, RMI2; DNA damage indicators (Tail DNA %, OTM) Aneuploidy/Micronucleus (MN) Dose-dependent DNA damage	(36, 37, 43, 55, 59, 63)
Epithelial–Mesenchymal Transition (EMT) and Metastasis	miRNA targets of 15-LOX1 (miR-18, miR-203) and 15-LOX2; DNA promoter hypermethylation of 15-LOX1 Epigenetic alterations: Telomerase activity; miRNA expression: miR-21, miR-26b, miR-17a Alternative splicing changes in EMP4 and FN1 pre-mRNA genes Long non-coding RNA (lncRNA) NORAD tRNA Am modification, Histone modification H3K27ac MicroRNAs: let-7a, miR-15b, miR-16, miR-34a, miR-143, miR-145	(35, 37, 44, 55, 56, 62)
EMT and Metastasis	EMT marker: Vimentin Migration/invasion markers: Vimentin, N-cadherin, β-catenin, cathepsin D, MMP9; Signaling proteins: FAK, PI3K, AKT Adhesion markers: E-cadherin, ICAM; YAP-TEAD complex (migration, adhesion, and metastasis) Early and late adhesion molecules: E-selectin, P-selectin, ICAM-1, VCAM-1, PECAM-1, LFA-1, VLA-4, αVβ3 Increased secretion and activity of MMP-9 (cell invasion) EMT markers: E-cadherin, N-cadherin, fibronectin 1, vimentin; EMT transcription factors: SNAIL1, SNAIL2, ZEB1, ZEB2; Metastatic enzymes: MMP1, MMP2, MMP9	(35, 40, 44, 57, 58, 60)
Apoptosis Evasion and Metabolic Reprogramming	Metabolic proteins: MDH2, UGP2, PGLS; Glycolytic and TCA cycle enzymes; Mitochondrial proteins Apoptotic pathways: BCL2 (anti-apoptotic), BAX (pro-apoptotic), p53, caspases; Mitochondrial function (ΔΨm) Glycolytic biomarkers: FTSJ1, PGK1, lactate, pyruvate, ECAR (Extracellular Acidification Rate), OCR	(36, 39, 53, 62)
Deregulation of Cell Proliferation and Evasion of Growth Suppressors	Cancer stem cell (CSC) markers: CD133, ALDH1A1, Nanog, Notch1, Hes1; Proliferation regulators: Bcl-2, Bax, Caspase-3; Wnt/β-catenin signaling pathway Hub genes: CDC20, PLK1, FOS, JUN; E2F targets (cell cycle); Expression of CCND1 and E2F1 (G2/M phase) Proliferation/survival markers: BCL2, Aurora B Spindle Assembly Checkpoint (SAC) genes: MAD1L1, MAD2L1, BUB1B, AURKB, BIRC5 (Survivin); Mitotic index and cell cycle Cancer stem cell markers: CD44, CD133, ALDH1A1, ABCG2; Pluripotency factors: SOX2, OCT4, NANOG, KLF4	(35, 37, 44, 57, 63)

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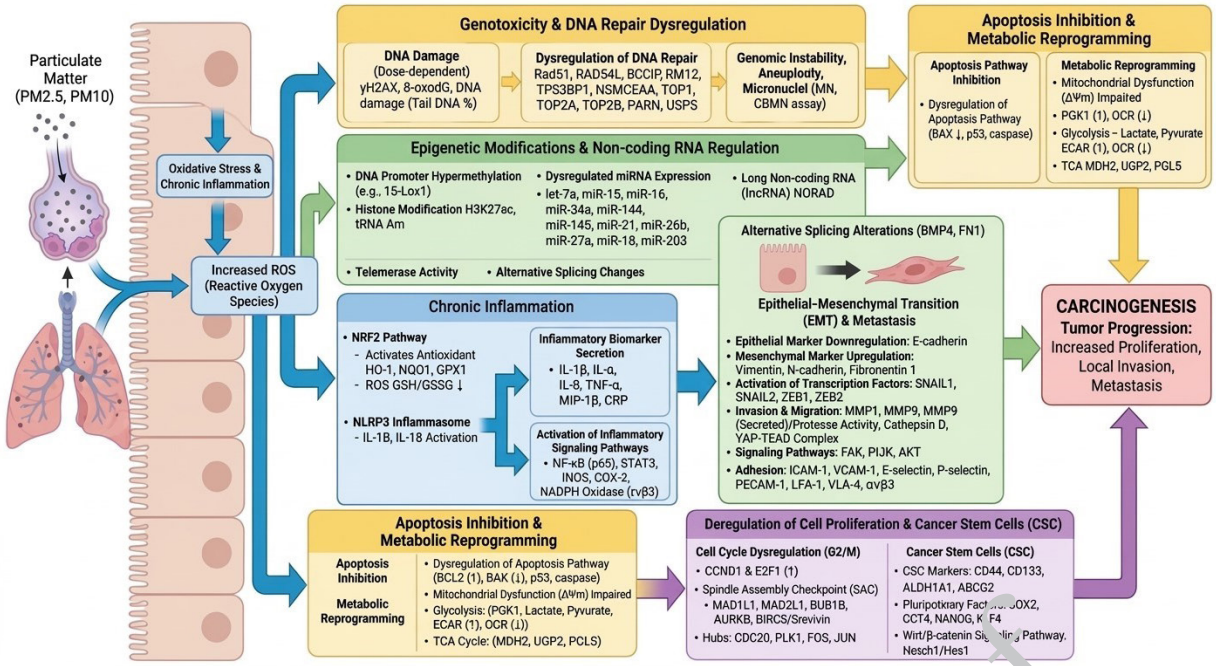


Figure 2. Schematic representation of the cellular pathways following PM exposure, encompassing ROS production, NLRP3 inflammasome activation, lncRNA dysregulation, and subsequent induction of EMT
PM: Particulate matter; ROS: Reactive oxygen species; EMT: Epithelial–mesenchymal transition

Discussion

Airborne PM ($PM_{2.5}$ and PM_{10}) has consistently been shown to play a significant role in carcinogenesis through multiple interconnected molecular pathways. Based on the synthesis of the 29 included *in vitro* studies, several major mechanistic links were identified connecting oxidative stress and chronic inflammation; genotoxicity and dysregulation of DNA repair; epigenetic modifications and non-coding RNA regulation; EMT and metastasis; evasion of apoptosis and metabolic reprogramming; as well as deregulation of cell proliferation and evasion of growth suppressors.

Oxidative stress and chronic inflammation

Exposure to PM is a major environmental risk factor for carcinogenesis initiation through excessive ROS generation, which induces oxidative stress and disrupts cellular homeostasis (1, 67). Under physiological conditions, redox balance is maintained by endogenous antioxidant systems, including superoxide dismutase (SOD2), NAD(P)H quinone dehydrogenase 1 (NQO1), glutathione peroxidase 1 (GPX1), and the glutathione (GSH)/glutathione disulfide (GSSG) ratio, which collectively function to neutralize ROS and prevent oxidative damage (68, 69). However, PM exposure can suppress or alter the expression of these antioxidant systems through gene modulation and activation of oxidative stress-sensitive transcription factors, ultimately leading to the failure of cellular defense mechanisms (15, 67).

Several PM components, particularly polycyclic aromatic hydrocarbons (PAHs), activate the aryl hydrocarbon receptor (AhR) pathway and cytochrome P450 enzymes, thereby enhancing ROS production and inflammatory responses (13). Uncontrolled ROS accumulation causes oxidative damage to DNA, proteins, and lipids, contributing to genotoxicity, genomic instability, and the initiation of carcinogenic processes (9, 45). Furthermore, oxidative stress and inflammation interact through a pathological feedback loop that amplifies cellular damage while simultaneously promoting tumorigenesis and cancer progression (42, 70).

ROS also plays a critical role in activating pro-inflammatory transcription factors, particularly NF-κB and STAT3, which are major regulators of chronic inflammation and cancer development. Activation of these pathways increases secretion of pro-inflammatory mediators, including IL-1β, IL-6, IL-8, TNF-α, and MIP-1β, sustaining a cycle of chronic inflammation and oxidative stress (42, 70). This inflammatory environment not only induces direct cellular damage through DNA injury and apoptosis but also promotes the establishment of a tumor microenvironment (TME) that supports cancer cell proliferation, migration, angiogenesis, and immune evasion. The inflammatory TME has been implicated across several cancer types, including triple-negative breast cancer (TNBC), where interactions between adipocytes and cancer cells via STAT3/NF-κB signaling increase IL-6 production, facilitating tumor invasion and progression (71). Additionally, TNF-α can promote macrophage and epithelial cell migration. Moreover, ROS–TNF-α interactions induce chemokine expression, including IL-8 and MCP-1, thereby recruiting immune cells into the TME and reinforcing chronic inflammation (72, 73). Collectively, these findings indicate that the oxidative stress–inflammation axis plays a central role in PM-induced carcinogenesis and represents a promising therapeutic target for inhibiting cancer progression (Supplementary Table 3).

Genotoxicity and dysregulation of DNA repair

Oxidative stress induced by PM, particularly $PM_{2.5}$, is a major mechanism contributing to genotoxicity and the dysregulation of DNA repair systems. PM exposure markedly increases ROS production, resulting in direct DNA damage, as evidenced by elevated levels of γH2AX and 8-oxoDG biomarkers, which indicate double-strand breaks

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and oxidative DNA lesions, respectively (13, 15). ROS accumulation beyond the buffering capacity of endogenous antioxidant systems promotes chronic cellular damage and accelerates both the initiation and promotion phases of carcinogenesis (15).

In response to this damage, cells activate multiple DNA repair pathways. However, persistent oxidative stress disrupts repair mechanisms, thereby compromising DNA repair efficiency. Key proteins and pathways involved in DNA repair, including TP53BP1, Rad51, and topoisomerases (TOP1/TOP2A/TOP2B), are activated but frequently fail to resolve the extensive DNA damage induced by chronic PM exposure (74, 75). This condition is exacerbated by the down-regulation of genes involved in base excision repair (BER) and double-strand break repair, a phenomenon similarly observed following oxidative stress induced by polystyrene nanoparticles (74). Consequently, cells increasingly rely on error-prone alternative repair pathways, thereby increasing mutation rates and genomic instability (76). PM exposure has also been associated with the activation of the cGAS-STING pathway, which promotes cellular senescence and further impairs DNA repair processes (77).

Failure of DNA repair systems contributes directly to genomic instability, a major hallmark of cancer, characterized by micronucleus formation and aneuploidy. Micronuclei arise from chromosomal mis-segregation and function not only as biomarkers of genetic damage but also as active mediators of DNA damage signaling through mechanisms such as chromothripsis and the activation of antiviral cellular pathways (78). These processes are further intensified by oxidative stress-induced replication stress and chromosomal instability, as demonstrated in aging murine fibroblasts (79). One of the primary biomarkers of oxidative DNA damage is 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), which is generated by free-radical attack on DNA and repaired through the BER pathway (80, 81). Accumulation of 8-oxodG, especially within enhancer regions, is associated with the activation of DNA damage responses and chromatin loop fragility, thereby accelerating genomic instability. Collectively, the complex interplay between oxidative stress, DNA damage, repair failure, and genomic instability strongly supports the role of PM exposure as a critical factor in carcinogenesis and aging-related diseases. A more comprehensive understanding of these mechanisms may provide a scientific basis for developing targeted cancer therapies and environmentally focused preventive strategies (Supplementary Table 4).

Epigenetic modifications and non-coding RNA regulation

PM exposure can induce epigenetic alterations that affect gene expression without modifying the DNA sequence, thereby contributing to cancer development and other chronic diseases. One major mechanism involves DNA hypermethylation within promoter regions, such as that of the 15-LOX1 gene, resulting in gene silencing that contributes to the pathogenesis of both cancer and cardiovascular disease (82, 83). PM exposure also induces histone modifications, including increased H3K27ac levels, which alter chromatin structure and transcriptional accessibility, thereby modulating global gene expression patterns (83, 84).

Dysregulation of non-coding RNAs, particularly miRNAs and lncRNAs, represents another important consequence of PM exposure. Several miRNAs, including miR-21, let-7a, and miR-34a, exhibit altered expression profiles and influence the activity of tumor suppressor genes and oncogenes, including 15-LOX1/2, thereby affecting inflammation, cell proliferation, and cancer progression (84, 85). Meanwhile, lncRNAs such as NORAD are involved in DNA damage responses and have been associated with both cardiovascular disease and cancer, with PM exposure further exacerbating their dysregulation (86, 87). In lung cancer, PM-induced up-regulation of lncRNAs such as lnc-MTPAP-1 has been shown to suppress apoptosis and promote tumor progression (88). Overall, epigenetic alterations and non-coding RNA dysregulation highlight the complex interaction between environmental pollutants and genetic regulation, while also offering opportunities to develop targeted epigenetic therapies (86, 89).

Beyond altering gene expression, PM-induced epigenetic modifications also contribute to the establishment of cellular epigenetic memory, defined as the ability of cells to maintain transcriptional changes through cell division without changes to the DNA sequence. This process is mediated by DNA methylation, histone modifications, and non-coding RNAs through feedback loops and reader-writer systems that preserve epigenetic inheritance during mitosis (90-93). These epigenetic alterations also influence the alternative splicing of genes such as BMP4 and FN1, as well as telomerase activity, both of which are associated with genomic stability and cellular transformation. Moreover, chromatin state plays a crucial role in regulating splicing outcomes through histone modifications and DNA methylation in response to environmental exposure (94). Because PM-induced epigenetic alterations may persist for extended periods and be transmitted across successive cell generations, they hold substantial potential as novel biomarkers of environmental exposure and early disease detection (95). Therefore, a comprehensive understanding of epigenetic memory and chromatin dynamics is essential for developing biomarkers and therapeutic interventions for environmentally associated diseases.

Epithelial–mesenchymal transition (EMT) and metastasis

EMT is a crucial biological process in cancer progression, characterized by the loss of epithelial polarity and cell-cell adhesion and the acquisition of mesenchymal properties that enhance cancer cell migration, invasion, and metastasis. EMT enables tumor cells to detach from the primary tumors and colonize distant tissues, thereby playing a central role in metastatic dissemination (96, 97). At the molecular level, EMT is characterized by reduced expression of epithelial markers including E-cadherin and increased expression of mesenchymal markers, including vimentin, N-cadherin, and fibronectin. This process is regulated by key transcription factors including SNAIL1/2, ZEB1/2, and TWIST (97, 98).

EMT does not occur as a binary event but rather exists along a spectrum of epithelial–mesenchymal plasticity (EMP), allowing cancer cells to maintain hybrid epithelial-mesenchymal phenotypes. This plasticity contributes to tumor initiation, cancer progression, metastasis, and therapeutic resistance (96, 99). EMT regulation involves multiple signaling pathways, particularly TGF-β/SMAD, Wnt/β-catenin, PI3K/AKT/mTOR, YAP-TEAD, and focal adhesion kinase (FAK), which collectively regulate cancer cell proliferation, migration, adhesion, and survival (98,

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100). The PI3K/AKT and FAK pathways, for example, play critical roles in enhancing cell motility and invasive capacity during metastatic progression (101).

The tumor microenvironment (TME) also plays an important role in EMT induction through interactions among cancer cells, stromal cells, inflammatory mediators, and environmental factors, including the microbiota and PM exposure (102). In certain cancers, such as oral squamous cell carcinoma, increased expression of N-cadherin and SNAIL2 has been correlated with lymph node metastasis and advanced disease stages (98). Furthermore, PM exposure of the airway epithelium can induce EMT, thereby potentially facilitating cellular transformation and systemic dissemination of malignant cells (103).

EMT is also strongly influenced by extracellular matrix (ECM) remodeling. Matrix metalloproteinases (MMPs), especially MMP1, MMP2, and MMP9, facilitate cancer cell invasion by degrading ECM components and disrupting tissue barriers (104, 105). MMP9 has both proteolytic and non-proteolytic functions that help regulate cancer cell adhesion and migration (105). Additionally, adhesion molecules such as ICAM-1, VCAM-1, and E-selectin are dynamically regulated during EMT to support cell detachment, migration, and metastatic colonization (106).

Evasion of apoptosis and metabolic reprogramming

PM exposure can induce metabolic reprogramming and apoptosis evasion, thereby promoting adaptive responses that enhance cellular survival, particularly in cancer cells. A principal metabolic alteration is the Warburg effect, a shift from oxidative phosphorylation to aerobic glycolysis despite sufficient oxygen. This adaptation enables cells to meet the energy and biosynthetic demands of rapid proliferation. It is characterized by increased expression of glycolytic enzymes such as phosphoglycerate kinase 1 (PGK1) and pyruvate kinase isozyme M2 (PKM2), which play critical roles in promoting glycolytic flux, oncogenesis, and therapeutic resistance (62, 107). PM-induced metabolic reprogramming extends beyond glycolysis to include the pentose phosphate pathway and lipid metabolism, which contribute to redox homeostasis and provide precursors for biomolecule synthesis (108, 109). In non-small cell lung cancer (NSCLC), PM exposure has been shown to suppress tRNA methyltransferase FTSJ1 expression, thereby increasing PGK1 expression and enhancing glycolysis and tumor malignancy (62). Similar metabolic dysregulation has also been observed in non-neoplastic diseases such as pulmonary arterial hypertension, indicating that PM-induced metabolic dysfunction contributes broadly to disease progression through mitochondrial dysfunction and altered glucose metabolism (110).

Mitochondrial dysfunction is a central component of this metabolic adaptation. Alterations in mitochondrial dynamics, oxidative phosphorylation, and reactive oxygen species (ROS) production support cellular survival under genotoxic stress and facilitate resistance to apoptosis (111, 112). In prostate cancer, for instance, acetylation of cytochrome c at lysine 53 (K53) reduces mitochondrial respiration while increasing glycolytic activity, thereby enhancing cancer cell invasiveness and apoptosis resistance (113). This adaptation is frequently accompanied by decreased mitochondrial membrane potential and reduced superoxide levels, which further enhance cellular tolerance to oxidative stress (113, 114).

Apoptosis evasion is also mediated by altered regulation of pro- and anti-apoptotic proteins. Up-regulation of anti-apoptotic proteins such as BCL2, together with suppression of pro-apoptotic factors including BAX and p53, preserves mitochondrial membrane integrity and inhibits caspase activation, both required for intrinsic apoptosis (115). In acute lymphoblastic leukemia, increased sphingomyelin levels have been reported to inhibit caspase activation and promote apoptosis resistance (116). Conversely, disrupting lipid–mitochondrial homeostasis in melanoma cells can activate intrinsic apoptosis via mitochondrial dysfunction, suggesting this pathway is a promising therapeutic target (117). The interaction between metabolic reprogramming and mitochondrial dysfunction therefore represents a major mechanism by which cancer cells survive, proliferate, and adapt to unfavorable microenvironments. Consequently, targeting metabolic pathways and mitochondrial function may provide promising therapeutic strategies for developing therapies against both cancer and PM-related diseases.

Deregulation of cell proliferation and evasion of growth suppressors

Deregulation of cell proliferation and evasion of growth suppressors are central mechanisms underlying cancer development, particularly in cancer stem cells (CSCs), which play crucial roles in tumor initiation, disease progression, metastasis, and therapeutic resistance. Genetic and epigenetic alterations that fail to trigger apoptosis result in uncontrolled cellular proliferation by disrupting cell-cycle checkpoints and activating oncogenic signaling pathways. In this context, the spindle assembly checkpoint (SAC) is essential for maintaining genomic stability during cell division. Dysregulation of SAC genes, including MAD1L1, MAD2L1, and BUB1B, can induce abnormal mitosis and promote tumorigenesis (118).

MAD2L1, for example, is frequently up-regulated in hepatocellular carcinoma and is associated with aggressive tumor growth and poor prognosis. Conversely, silencing MAD2L1 suppresses cellular proliferation, highlighting its potential as a therapeutic target (118). Similarly, BUB1B contributes to the maintenance of stemness and the progression of lung adenocarcinoma through activation of the PI3K/AKT pathway (119). The Wnt/β-catenin pathway is another major regulator of CSCs, promoting self-renewal, cellular plasticity, and resistance to anticancer therapy (120). Cell-cycle progression is further driven by the activation of Cyclin D and E2F target genes, such as CCND1, thereby accelerating G2/M phase progression and sustaining continuous CSC proliferation (121).

Additionally, Polo-like kinase 1 (PLK1) promotes chromosomal instability by bypassing cell-cycle checkpoints, thereby increasing the risk of tumorigenesis and cancer progression (122). The complex interactions among these molecular pathways highlight the remarkable adaptive capacity of CSCs, particularly through their interactions with the tumor microenvironment (TME), which remains a major barrier to the development of effective cancer therapies (123-125).

Relative strength of evidence across mechanistic pathways

Multiple mechanisms have been proposed to explain PM-induced carcinogenesis; however, the strength of

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the evidence supporting each mechanism varies. Based on the available evidence, oxidative stress and chronic inflammation represent the mechanistic pathways supported by the most consistent evidence. Numerous studies consistently report increased concentrations of inflammatory biomarkers, including IL-1β, IL-6, IL-8, TNF-α, and C-reactive protein (CRP), enhanced production of reactive oxygen species (ROS), alterations in endogenous antioxidant defense systems, such as superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPX), and malondialdehyde (MDA), as well as activation of key signaling pathways, including NF-κB, STAT3, and the NRF2/HO-1/NQO1 axis (34, 37, 40, 45, 51, 60, 61). Evidence from *in vitro* experiments, *in vivo* studies, human biomarker investigations, and epidemiological research consistently shows that PM exposure increases ROS generation, inducing cellular damage, persistent inflammation, and molecular alterations that contribute to multiple stages of carcinogenesis, from tumor initiation to progression (1, 15, 126). Within the tumor microenvironment (TME), ROS further activates downstream NF-κB and STAT3 signaling pathways, promoting cancer cell proliferation and survival, stimulating pro-inflammatory cytokine production, and enhancing therapeutic resistance (127-131). Collectively, oxidative stress and chronic inflammation can therefore be regarded as the core mechanistic pathway underlying PM-induced carcinogenesis.

Genotoxicity and dysregulation of DNA repair represent another major mechanistic pathway, supported by substantial experimental evidence, that is closely linked to oxidative stress. Multiple studies have consistently demonstrated increased DNA damage, as indicated by micronucleus formation, elevated expression of γH2AX and 8-oxo-dG, genomic instability, and alterations in DNA repair-related proteins, including TP53BP1, RAD51, RAD54L, ERCC1, and topoisomerases (40, 51, 60, 132, 133). Several studies show that DNA damage occurs alongside increased ROS production, suggesting that oxidative stress is a major driver of genomic instability and impaired DNA repair (60). Furthermore, redox imbalance resulting from depletion of endogenous antioxidant systems further accelerates cellular dysfunction and facilitates malignant transformation (134). Collectively, these findings indicate that the oxidative stress–inflammation axis and genotoxicity are the principal mechanistic pathways with the strongest body of evidence supporting the carcinogenic effects of PM.

In contrast, other proposed mechanisms—including EMT and metastasis progression, apoptosis evasion, metabolic reprogramming, deregulation of cell proliferation, epigenetic alterations, immune dysfunction, and microbiome perturbation—remain supported by relatively limited evidence. Although several studies have demonstrated alterations in EMT-related biomarkers (E-cadherin, N-cadherin, vimentin, MMP-1, MMP-2, MMP-9, SNAIL, and ZEB)(37, 41, 53, 55, 57, 59), regulators of metabolism and apoptosis (BCL2, BAX, caspases, MDH2, PGK1, lactate, oxygen consumption rate [OCR], and extracellular acidification rate [ECAR])(40, 59, 63), as well as biomarkers of cell proliferation and cancer stemness (CD44, CD133, ALDH1A1, SOX2, OCT4, NANOG, CDC20, PLK1, and Wnt/β-catenin signaling)(41, 53, 60, 132), the available evidence remains heterogeneous with regard to the biomarkers evaluated, experimental models, and study designs. Similarly, epigenetic alterations, immune dysfunction, and microbiome dysbiosis may accelerate cancer progression and influence therapeutic responses; however, their causal roles and biological significance require further confirmation through *in vivo* investigations, longitudinal studies, and integrated multi-omics approaches (135-140). Therefore, these mechanisms are best regarded as complementary pathways that amplify the carcinogenic effects of PM, whereas oxidative stress–mediated inflammation and genotoxicity remain the mechanistic pathways supported by the strongest and most consistent evidence.

Case studies linking specific toxins to cancer

To illustrate the biological and clinical relevance of airborne PM exposure in cancer development, it is important to examine specific examples with robust mechanistic evidence. These case studies provide mechanistic insights into how PM exposure contributes to particular cancer types by highlighting the underlying molecular mechanisms and their implications for cancer risk assessment and public health. The following subsection summarizes well-characterized particulate pollutants, including $PM_{2.5}$ (encompassing organic extracts/tPo and co-exposure with heavy metals, PAHs, and NNK), PM_{10} (including co-exposure with benzo[a]pyrene/BaP), and other particulate fractions (PM_1, $PM_{2.5\text{-}0.3}$, size-segregated particles 0.4–10 μm, carbon black, diesel exhaust particles, tobacco smoke, heavy metals, and PAHs). This section discusses these particulate pollutants to elucidate the molecular mechanisms by which they contribute to cancer risk and progression. Evidence from studies across diverse populations shows how different exposure routes—such as inhalation, ingestion, and dermal contact—influence pollutant-specific carcinogenic outcomes (Supplementary Table 5). Figure 3 summarizes the mechanistic relationships between airborne PM exposure, oxidative stress, epigenetic reprogramming, and carcinogenesis.

Critical evaluation of existing research

Recent research on PM exposure has progressed considerably through multidisciplinary approaches that integrate genomic, proteomic, and epigenetic data to elucidate the complex molecular mechanisms induced by PM. Numerous studies have demonstrated that PM exposure triggers oxidative stress, inflammation, DNA damage, and epigenetic dysregulation, thereby contributing to the development of respiratory diseases, cardiovascular disorders, cancer, and skin abnormalities (126, 141). These multi-omics approaches provide a more comprehensive understanding of the relationships between environmental exposures and the molecular alterations that underlie disease pathogenesis. Another major strength lies in recent methodological advances, particularly the use of advanced *in vitro* models such as three-dimensional (3D) cell cultures and high-throughput exposure systems. These models more accurately recapitulate tissue architecture, cell–cell interactions, and realistic exposure conditions than conventional two-dimensional cultures, thereby improving physiological relevance and biological fidelity (142–144).

Despite these advances, several methodological limitations remain. Approximately 69% of the included studies used the A549 lung carcinoma cell line as the

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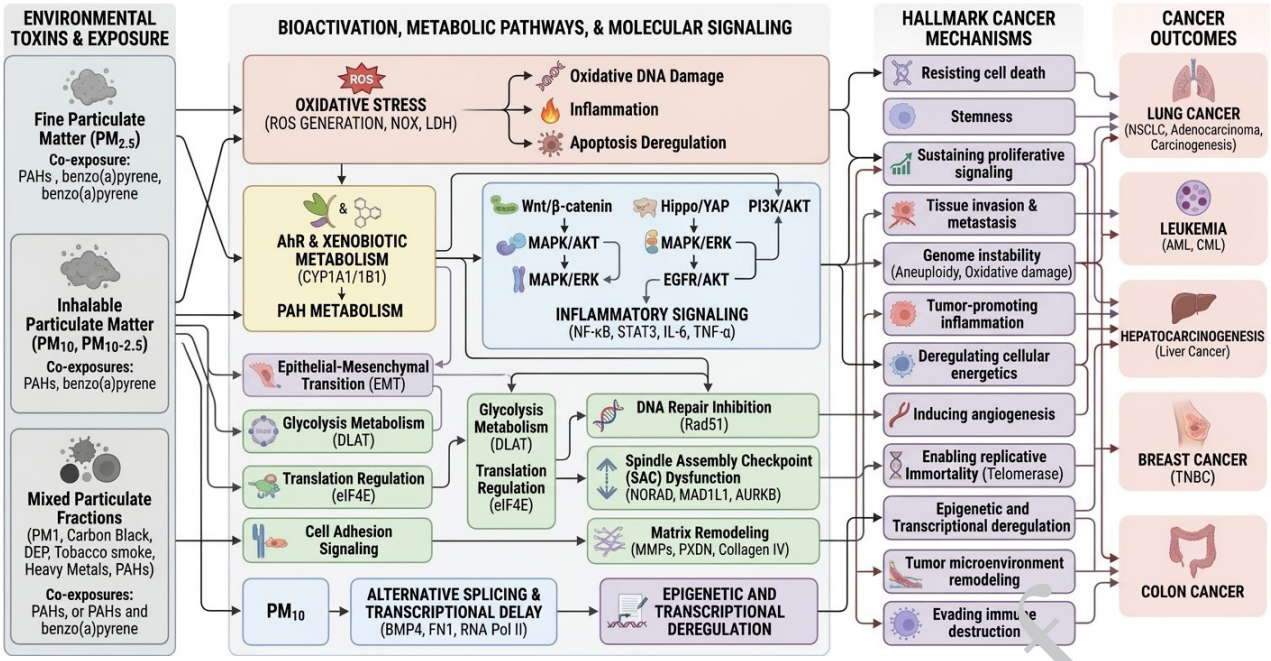


Figure 3. Mechanistic interrelationships among environmental toxins, oxidative stress, epigenetic reprogramming, and carcinogenic processes

experimental model. While useful, A549 cells harbor intrinsic malignant characteristics that limit their suitability for investigating the early stages of carcinogenesis, thereby potentially limiting the interpretation of findings (17) the molecular mechanisms underlying the PM-induced increases in lung cancer progression remain unclear. We applied the lung cancer cell line A549 (Parental; A549.Par. In contrast, normal bronchial epithelial cell lines such as BEAS-2B offer a more physiologically relevant model for investigating early cellular transformation (145, 146).

Many *in vitro* studies used high PM concentrations over short exposure periods, which may not accurately reflect chronic low-dose human exposure, thereby limiting the translation of findings to human health outcomes (147, 148). Furthermore, the heterogeneity of PM composition across geographic locations, emission sources, and seasonal factors limits the generalizability of findings as different PM components may induce distinct biological responses (142,148). Therefore, the findings should be interpreted with caution.

Strengths and limitations

This literature review followed the PRISMA guidelines to ensure methodological transparency and rigor throughout the review process. The major strengths of this review include a comprehensive search strategy across multiple databases, the inclusion of studies published over the past two decades, and comprehensive eligibility criteria that facilitated the identification of relevant scientific evidence. Although independent dual screening was not fully implemented, the moderation process supports the reliability and consistency of the study selection process. However, several limitations should be acknowledged. First, restricting the search to English-language publications may have introduced language bias and excluded relevant evidence from non-English sources. The literature search was restricted to publications published between 1 January 2015 and 31 December 2025. Consequently, studies published before or after this period were excluded from the present review; thus, earlier evidence and the most recent findings may not be represented. Second, as a secondary study, this review is inherently dependent on the quality and completeness of existing publications and does not provide primary experimental evidence. Third, the complexity of PM-induced carcinogenic mechanisms may have been oversimplified, potentially overlooking biological heterogeneity and diverse exposure scenarios. Fourth, Embase and Web of Science could not be included because of access limitations. Google Scholar was also excluded due to its limited search reproducibility, limited transparency in its indexing processes, and reduced precision of search results compared with curated bibliographic databases. Selection and publication biases may also limit the generalizability of associations between PM exposure and cancer risk across populations. Finally, a meta-analysis was not feasible due to substantial methodological and clinical heterogeneity among the included studies, encompassing differences in study models, participant characteristics, interventions, measured outcomes, and reporting methods. This heterogeneity limited the feasibility of quantitatively synthesizing effect estimates; therefore, the findings of this review are presented using a narrative synthesis approach.

Conclusion

PM-induced carcinogenesis is initiated by PM penetration into deep lung tissues, triggering oxidative stress and chronic inflammatory signaling cascades through activation of the NF-κB and STAT3 signaling pathways. These processes create a pro-tumorigenic microenvironment in which persistent DNA damage and impaired DNA repair mechanisms promote tumor initiation. This review highlights that the carcinogenic effects of PM extend beyond conventional genetic mutations; particulate exposure induces widespread epigenetic alterations, including dysregulation of microRNA and long non-coding RNA profiles, which act as critical regulators of

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oncogenic gene expression without altering the underlying DNA sequence. Moreover, PM exposure further promotes tumor progression through EMT, enabling cancer cells to acquire migratory and invasive phenotypes that facilitate metastasis. Furthermore, metabolic reprogramming and apoptosis evasion underscore that chronic air pollution exposure supports malignant cell survival and adaptation. Collectively, these findings provide a mechanistic foundation for developing early-detection biomarkers and novel therapeutic targets.

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Authors' Contributions

L S conceptualized the study, led the research design and development, supervised data collection and analysis, prepared the initial manuscript draft, interpreted the data, critically reviewed manuscript drafts, finalized the manuscript, and conducted revisions. FP provided expert input, contributed to data interpretation, and critically reviewed manuscript drafts. NH H provided expert guidance throughout the research process, contributed to data interpretation, and critically reviewed multiple manuscript versions. AH K contributed to draft preparation, visualization, and critical revision. AN S contributed to data processing, data collection, and experiment execution. N L contributed to data interpretation and critically reviewed multiple manuscript versions. YS N contributed to the research design, co-led data collection, and helped prepare both the initial and revised manuscript versions.

Conflicts of Interest

The authors declare that there are no conflicts of interest

Declaration

The lead author guarantees the integrity of this manuscript, including the originality, accuracy, and transparency in the presentation of the research findings. It is emphasized that no essential elements of the study have been omitted. During preparation, the authors used Grammarly to ensure proper grammar and used ChatGPT and Gemini AI to improve sentence structure. Figures 2 and 3 were created with Gemini AI assistance solely to generate the initial schematic illustrations. The authors subsequently reviewed, verified, and manually revised the illustrations to ensure scientific accuracy, consistency with the manuscript content, and overall quality. Following the use of these tools/services, the authors carefully reviewed and edited the manuscript as necessary and assume full responsibility for the content of this publication.

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