

Air Pollution and Epigenetics

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ABSTRACT

Air pollution is a global problem with far-reaching environmental impacts. Exposure has been linked to a number of different adverse health effects. Understanding the impact of ambient air pollution is complicated given the diversity of both the pollutants involved as well as the complexity of associated diseases. While we see a positive correlation between levels of exposure and health issues, the mechanisms of pathogenesis are still under investigation. The study of epigenetic regulation as it relates to disease is emerging as an exciting new way to interpret the possible effects of ambient air pollution on DNA. In this review we provide an overview of epigenetic modifications as well as an analysis of how epigenetic mechanisms are involved in the adverse effects associated with the most common components of ambient air pollution.

Keywords: Air Pollution; Epigenetics; DNA Methylation; Histone Acetylation; microRNA; PAH; DEP; Ozone

1. Introduction

Recent epidemiological studies have shown that ambient air pollution exposure is associated with increased mortality and higher incidence of respiratory diseases such as asthma, chronic obstructive pulmonary disease, and cancer [1]. Adverse impacts of air pollutant exposure have a profound effect on morbidity and mortality; according to one study, ambient air pollution caused 6% of total mortality, or more than 40,000 attributable cases, per year [2].

In general, the worldwide trend is towards a reduction in the concentrations of air pollutants because of increasingly strong restrictions from local governments and international organizations. In developing countries, rising concentrations of air pollutants pose an imminent threat to public health, and even in countries that have made the improvements necessary to meet World Health Organization (WHO) air quality standards, the adverse health effects of air pollutants remain problematic [3,4].

Major air pollutants that have been linked to adverse health outcomes include polycyclic aromatic hydrocarbons (PAH), ozone, particulate matter (PM) and diesel exhaust particles (DEP), and cigarette smoke [5-8]. Although studies have found an associative link between ambient air pollution and the incidence of respiratory diseases, the exact, causative mechanisms of these air

pollutants are not yet fully understood. Recently, numerous publications have linked induction of diseases such as asthma via ambient air pollution exposure to epigenetic mechanisms, among others [9-12]. Epigenetics is defined as the study of heritable changes in gene expression that do not affect underlying DNA sequences. The most common epigenetic mechanisms include DNA methylation, histone modifications, and microRNA (miRNA) [13]. This review aims to provide a brief overview of epigenetic modifications (summarized in **Figure 1**) and explain the mechanisms through which the primary types of ambient air pollution can lead to adverse health effects.

2. Epigenetic Mechanisms

2.1. DNA Methylation

DNA methylation is necessary for regulating normal gene expression and can be greatly impacted by environmental factors. Methylation changes are reversible and mediated by DNA methyltransferase (DNMT) and demethylase. The addition of methyl groups generally occurs at cytosine residues adjacent to guanine nucleotides (CpG sites) within enhancer regions of candidate genes. The addition of methyl groups (methylation) prevents transcription, silencing gene expression. By contrast, the removal of methyl groups (demethylation) allows transcription

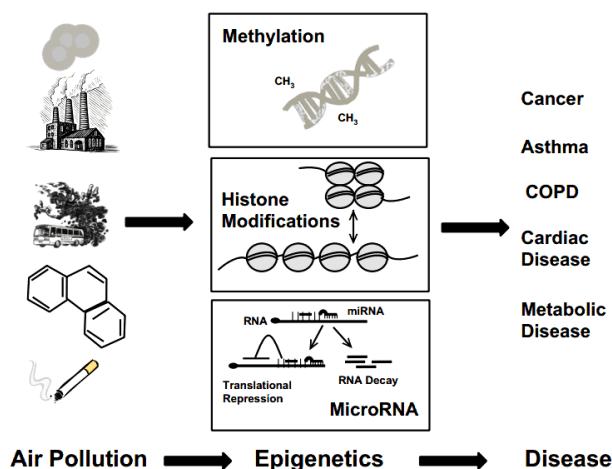


Figure 1. Epigenetic mechanisms involved in air pollutant induced adverse health effects.

factor binding, activating and enhancing gene expression. Methylation changes are dynamic and have been implicated in the natural course of mammalian development [14]. Environmental factors like ambient air pollution can affect global methylation patterns. Some of these epigenetic changes have been linked to disease.

2.2. Histone Acetylation

Histones are highly alkaline proteins that arrange DNA into structures known as nucleosomes. These nucleosomes function like spools around which the DNA coils, playing an important role in the regulation of gene accessibility [15]. Modifications to the histones therefore alter this regulation. Several potential modification mechanisms exist, including: 1) Acetylation, whereby acetyltransferases add an acetyl group to lysine residues in the histone tail, neutralizing their positive charge and therefore decreasing histones' affinity for DNA and increasing transcription; 2) Methylation, which—similarly to DNA methylation—involves the transfer of a methyl group by methyltransferases to or from lysine or arginine to create an unmodified, mono-, di-, or tri-methylated state, with certain modifications (H3K4me and H3K36me) associated with activation of transcription and others associated with repression of transcription (H3K9 and H3K27); 3) Phosphorylation, the addition of a phosphate group, which increases the negative charge of the histone and therefore increases repulsion between the histone and the DNA strand, increasing accessibility of the DNA; and 4) Ubiquitylation, in which a ubiquitin protein (76 amino acids) is added to a lysine side chain, with varying effects on transcription that seem to be context-dependent [15] [16]. There appears to be cross-talk not only between these mechanisms of histone modification, but also between histone modification and other epigenetic mechanisms, *i.e.*, DNA methylation and micro RNA [15,16].

2.3. microRNAs

MicroRNAs (miRNAs) are an abundant class of single-stranded small non-coding RNAs, approximately 19 - 22 nucleotides long, which regulate gene expression post-transcriptionally. miRNAs typically function by negatively regulating mRNA processing, stability, and translation and thereby represent a novel layer in regulation of flow of genetic information and cellular functions. miRNAs are encoded in genomic DNA and are transcribed by RNA polymerase II into long primary transcripts called pri-miRNA. This pri-miRNA is sequentially processed in the cell nucleus and then in the cytoplasm to generate mature active miRNA [17]. Recent evidence suggests that miRNA expression maybe implicated in several developmental, inflammatory, apoptotic, and cellular signal transduction pathways affecting multiple disease pathogenesis, including cardiovascular disease, cancer, metabolic diseases, lung development, and respiratory disease, etc. [18-25].

3. Common Air Pollutants

3.1. Polycyclic Aromatic Hydrocarbons (PAH)

Polycyclic aromatic hydrocarbons (PAHs) represent a complex class of environmental pollutants derived from the incomplete combustion of organic compounds. These relatively stable compounds are comprised of multiple, fused, benzene rings. The major sources of PAH include burning of biomass, wildfires, and vehicular emissions [26,27]. The primary sources of PAH production vary from country to country, with developing nations responsible for greater emissions than developed nations due in large part to disparities in production technology [27]. Exposure to PAH is most significant in urban regions marked by high levels of both industrial development as well as traffic [26,27]; significant global contributors include China, India, and Brazil [27].

Several studies have assessed occupational health risks in individuals exposed to disproportionate levels of PAHs, such as traffic controllers and industrial workers [28-31]. These studies show that PAH can be a potent carcinogen and has also been linked to adverse respiratory effects [26,27,32,33]. Additionally, PAH exposure has been associated with the activation of DNA damage signaling, with multiple PAHs exerting more extensive damage than one polycyclic compound alone [34].

PAH exposure can begin in the womb and, through epigenetic modifications, can have long-lasting effects. Increased maternal exposure to PAH has been associated with increased DNA methylation of the asthma related gene *acyl-CoA synthetase long-chain family member 3* (*ACSL3*) and subsequent increases in the prevalence of childhood asthma [8]. In another study, *in vitro* exposure was associated with hypermethylation of the asthma-

related gene interferon-gamma (*IFN- γ*) and consequent decreases in its expression. *IFN- γ* is thought to play a protective role in asthma and allergic disease; thus, decreases in expression may be pathogenic [35]. Exposure to ambient air pollution (which includes PAHs) has been linked to increased methylation in the forkhead box protein 3 (*FOXP3*) locus of regulatory T cells (Treg), and subsequent functional deficits that could contribute to asthma pathogenesis [36]. High levels of PAH exposure in coke oven workers has been correlated with hypomethylation of the O6-methyl-guanine-DNA methyltransferase (MGMT), contributing to genomic instability in lymphocytes [28], which may in turn increase the risk of carcinogenesis.

PAH appears to alter methylation patterns, which could account for the far-reaching impact of both pre- and postnatal chronic exposure to PAH. However, it is still not clear how PAH actually alters methylation. One hypothesis is that these epigenetic changes are mediated via the aryl hydrocarbon receptor (AhR). AhRs are expressed on several cell types and act as an environmental sensor for toxicity. Activation of AhR signals a number of pathways involved in inflammation and the immune response [37]. The effects of AhR activation appear to be ligand-dependent; thus, different PAHs may have varied effects. Binding of the PAH phenanthrene to AhR on the surface of Treg cells results in increased methylation of the *FOXP3* locus. This methylation diminishes the suppressive function of Treg and appears to convert them to T helper type 2 cells (Th2) [38], producing an inflammatory response. Overactivation of Th2 cells and deficits in natural regulatory mechanisms have both been linked to allergic disorders [39]. This imbalance may be induced through PAH-mediated activation of AhR.

3.2. Ozone

Ground-level ozone is one of six criteria pollutants for which National Ambient Air Quality Standards (NAAQS) are set by the United States Environmental Protection Agency, with the current standard set at 0.075 ppm/8h. Epidemiological studies have demonstrated a clear pathologic association between ambient ozone levels and respiratory health, including respiratory allergies, lung function deficits, increased prevalence of asthma, and hospital admissions [40-42]. A recent study showed that ozone inhalation contributed to both human morbidity and mortality and each 10 parts per billion (ppb) increase in ozone was associated with approximately a 0.52% increase in mortality [43].

Despite the non-antigenic nature of ozone, recent evidence suggests that ozone may indirectly modulate adaptive immunity by promoting the activation of antigen presenting cells [44-46]. Toll-like Receptor (TLR) 4 has been identified as an essential susceptibility gene for the

inflammatory and physiologic effects of ozone exposure in certain mouse strains, and is an important clue to the link between ozone and microbial immunity [47,48]. Recent evidence in intestinal epithelial cells suggests that TLR4 gene expression downregulated via epigenetic modifications including histone deacetylation and DNA methylation to prevent excessive inflammatory responses [49]. Although, a similar mechanism of regulation of TLR responses post ozone exposure might be at play in the lung epithelial cells no studies thus far have demonstrated this. More recently multiple miRNAs have been implicated in the regulation of TLR4 signaling pathway [50-56]. TLR signaling pathways consist of both MyD88 dependent and independent pathways [57]. MyD88 dependent pathway signals through IRAK1 and TRAF6 leading to nuclear translocation of NF κ B and activation of AP-1. Both IRAK1 and TRAF6 are targets of miR-146 [51]. The MyD88 independent pathway signals through TRIF, inducing IRF transcription factors resulting in type 1 interferon production. TRIF and another adaptor TAB2 in this pathway have known to be regulated by miR-155 [50,58].

3.3. Particulate Matter (PM) and Diesel Exhaust Particles (DEP)

Ambient PM has been associated with adverse health outcomes but the mechanisms linking PM inhalation to adverse health are not completely understood. A mouse model study using intranasal sensitization to *Aspergillus fumigatus* and inhaled DEP exposure showed changes in DNA methylation involved in two important genes involved in asthma, *IL-4* and *IFN- γ* , which positively correlated with increased total IgE secretion, which is involved in asthma pathogenesis [59]. In humans, a recent profiling study of 141 subjects showed that exposure to airborne PM, particularly black carbon and sulfate were significantly associated with changes in DNA methylation pattern of genes involved in asthma [60]. In a study of steel plant workers exposed to PM < 10 μ m, researchers showed significant alterations in blood DNA methylation both globally in the Alu and LINE-1 repetitive elements, involved in immune inflammatory response, as well as gene-specific methylation of iNOS promoter [10]. Oxidative and nitrosative stress have been implicated in mediating airway inflammation involved in asthma development and fractional concentration of exhaled nitric oxide (FeNO) has been used a biomarker to predict airway inflammation and asthma development.

Multiple studies show evidence of PM with ozone exposure linked to higher levels of FeNO, particularly in children [61-63]. The first study to show evidence linking PM exposure induced epigenetic modification with phenotype expression showed a significant association between exposure to short term (7 days) of PM < 2.5 μ m

with lower NOS2 methylation and correlation with FeNO levels [64]. A global methylation profiling study, using mice to mimic long term exposure of humans to ambient particulate air pollution near steel mills and major highways, showed hypermethylation in sperm DNA, which persisted even after exposure ceased. These mice also showed more DNA damage and higher frequencies in DNA mutations compared to mice exposed to filtered air, indicating potential increase in mutagenicity [65]. In vitro studies of bronchial epithelial cells using the BEAS-2B cell line showed that exposure to DEP resulted in histone modification including selective degradation of histone deacetylase (HDAC) 1 and activation of histone acetyltransferases (HAT) p300 as well as increased acetylation of histone H4 in the promoter region of cyclooxygenase-2 (COX-2), an inflammatory mediator. Expression of COX-2 was increased with DEP exposure indicating that DEP exposure resulted in histone modifications resulting in increased inflammation [66]. In another profiling study evaluating PM exposure effects on miRNA expression using a microarray approach, researchers found four PM-sensitive miRNAs that were expressed differentially post exposure compared to baseline (miR-421, miR-146a, miR-29a, and miR-let7g). Upon further analyzing miRNA expression and candidate inflammatory genes, the authors concluded that exposure to PM for 3 days resulted in inflammatory gene regulation through PM responsive miRNAs [67].

3.4. Cigarette Smoke

Cigarette smoke, both primary and secondary, is one of the more widely studied environmental exposures, particularly with regard to gene-environment interactions. Exposure to cigarette smoke has been associated with the development and exacerbation of several diseases, most prominently respiratory diseases such as COPD, asthma, and lung cancer, as well as cardiovascular disease and other cancers [68]. The mechanisms of these relationships are not fully understood, but it seems that epigenetics may play a major role in mediating the effects of cigarette smoke on human health.

A landmark study published in 2005 found that increased maternal and grandmaternal smoking was associated with increased asthma in children [69], suggesting a generational effect consistent with epigenetic modification. Indeed, several studies have associated *in utero* exposure to cigarette smoke via maternal smoking with global changes to DNA methylation [70-72] as well as with alterations in the methylation of specific genes implicated in growth [73], processing of toxicants and carcinogens [74,75], and cancer and immune functions [76]. Maternal smoking during pregnancy has also been associated with downregulation of miRNA implicated in growth and development [77].

Cigarette smoke exposure, both primary and secondary, has also been associated with alterations in DNA methylation, with global changes observed [78] as well as changes in genes relevant to asthma [13,79], cardiovascular disease [80], lung cancer [81-83], COPD [80], bladder cancer [84,85], and colorectal cancer [86] among others, with some suggestions of differences between current and former smokers [87].

Similar alterations due to smoke exposure have also been observed in histone modifications, including reduction of histone deacetylases (specifically histone deacetylases 2 and 3) that have implications in COPD and asthma [88-91], and phosphorylation associated with generation of double-stranded DNA breaks [92,93], as well as methylation [82], and acetylation and phosphorylation [94,95]. Many histone modifications have been studied in the context of changes in behavior of the protein complex NF- κ B, which is important for control of DNA transcription and has been found to be upregulated when histone deacetylases are reduced [96].

Smoke exposure has also been found to be associated with changes in micro RNA expression. Differences in plasma miRNA expression have been found between smokers and nonsmokers [97], as well as decreases in global miRNA expression in smokers versus nonsmokers [98,99]. Exposure to cigarette smoke condensate in culture has been associated with increased oncomir miRNA [100], and decreased tumor suppressor miRNA [101]; nicotine exposure has also been found to alter miRNA expression in adult human stem cells, with detrimental effects on regenerative potential [102]. Overall, these changes seem to suggest a potential mechanistic link to cancer more than any other disease associated with cigarette smoking.

It is important to note that cigarette smoke contains hundreds of compounds, including such common environmental pollutants as PM_{2.5}, PM₁₀, PAHs, cadmium, lead, and arsenic. This suggests that it is important to consider potential modulating effects of cigarette smoke exposure on the impacts of these other pollutants. Various studies have found that cigarette smoke exposure modulates both clinical symptoms and methylation patterns associated with air pollution exposures, exacerbating disease phenotypes [103,104].

4. Conclusion

Recent efforts have been made to curb the global production of air pollutants, but we are only beginning to uncover their impact. Here we outline the adverse health effects associated with ambient air pollution and suggest the involvement of epigenetic modifications, including DNA methylation, histone acetylation, and microRNAs. Many of these epigenetic changes are thought to be heritable; thus, adverse events associated with ambient air

pollution can have long-lasting, transgenerational impacts. Genetics have already been implicated in the pathogenesis of many disorders, like asthma and cancer that are also subsequently linked to ambient air pollution exposure. The study of genetics and epigenetics is vital to the understanding of ambient air pollution and could be useful in identifying biomarkers for those individuals most likely to develop health problems in response to exposure.

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