



Air pollution-induced epigenetic changes: disease development and a possible link with hypersensitivity pneumonitis

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Abstract

Air pollution is a serious threat to our health and has become one of the major causes of many diseases including cardiovascular disease, respiratory disease, and cancer. The association between air pollution and various diseases has long been a topic of research interest. However, it remains unclear how air pollution actually impacts health by modulating several important cellular functions. Recently, some evidence has emerged about air pollution-induced epigenetic changes, which are linked with the etiology of various human diseases. Among several epigenetic modifications, DNA methylation represents the most prominent epigenetic alteration underlying the air pollution-induced pathogenic mechanism. Several other types of epigenetic changes, such as histone modifications, miRNA, and non-coding RNA expression, have also been found to have been linked with air pollution. Hypersensitivity pneumonitis (HP), one of the most prevalent forms of interstitial lung diseases (ILDs), is triggered by the inhalation of certain organic and inorganic substances. HP is characterized by inflammation in the tissues around the lungs' airways and may lead to irreversible lung scarring over time. This review, in addition to other diseases, attempts to understand whether certain pollutants influence HP development through such epigenetic modifications.

Keywords Air pollution · Particulate matter · Epigenetic modifications · Hypersensitivity pneumonitis · Epigenetic biomarkers

Introduction

Air pollution has become a global threat to human health as it predisposes the risks of various diseases including cancers. In today's world, a whole range of industries such as petrochemical firms, chemical factories, fertilizer units, and metallurgical setups contribute to air pollution. Apart from the industrial sector, the main emissions from certain types of power stations, cars, railways, airways, combustion engines also cause air pollution. Certain field-cultivation techniques release ammonia in the air from heavily fertilized fields and consequently pollute the environment. Even natural disasters like forest

fire, volcanic erosion, and dust storms pollute the air. Other than these, biomass fuel uses, agricultural burning and utilization of adulterated fuels are some of the sources of air pollution (Manisalidis et al. 2020). The use of wood and charcoal for cooking and the operation of computers, printers, and photocopy machines, among others, contribute to indoor air pollution. Rapid urbanization also contributes to air pollution as it involves huge construction works. Moreover, some people are exposed to air pollution due to their professions—for instance, mining workers, traffic police and drivers are exposed to large amounts of air pollutants (Shukla et al. 2019).

Air pollution is linked with a range of diseases like asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), cardiovascular disease, metabolic disorders, various reproductive conditions, dysregulation in immune response, neurodegenerative disorders, and cancer (Breton and Marutani 2014; Kurt et al. 2016). In 2013, World Health Organization (WHO) declared outdoor air pollution as a leading environmental cause of death associated with cancer (WHO 2013). A new study has indicated that air pollution may increase the risk of death due to COVID-19, an infectious disease that emerged in 2019 and is caused by novel coronavirus SARS-CoV-2. It has been suggested that 15% deaths

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across the world due to covid-19 could be linked with long-term exposure to air pollution (Poizzer et al. 2020). Outdoor air is contaminated with various chemicals such as engine exhausts, solvents, metals, dusts, and particulate matter (PM). Although air pollution is linked with numerous diseases, the impact of pollutants at both cellular and molecular levels has not been explored in detail. At the cellular level, exposure to different air pollutants or other toxic elements may lead to apoptosis by targeting mitochondria either directly or indirectly. Airborne particles have been found to induce apoptosis associated with ROS production, cellular stress, and DNA fragmentation (Andreau et al. 2012). Air pollution also induces inflammation in tissues by influencing specific cytokines and may also impact our endocrine system and metabolism processes (Prada et al. 2020). Moreover, recent studies indicate that epigenetic alterations could be an important pathway through which environmental factors exert their effects (Alfano et al. 2018). Epigenetic is the alteration at the gene expression level without changing the underlying DNA sequence such as DNA methylation, histone modification, miRNA, and non-coding RNA expression (Weinhold 2006; Jin et al. 2011). Cancers and many other diseases are often associated with epigenetic modifications (Weinhold 2006). Exposure to environmental stimuli may result in epigenetic changes, which, in turn, can impact gene expression and predisposition to disease risk (Breton and Marutani 2014). Little is known about how specific air pollutants generate specific epigenetic marks associated with a particular disease. Understanding epigenetic alterations due to specific pollutants may lead to the development of biomarkers to assess the disease risk due to air pollution.

This narrative review provides an overview of the association between air pollution-induced epigenetic modification and disease development. It also explores whether such modification plays a role in HP pathogenesis. We have searched the PubMed and MEDLINE databases using the keywords ‘air pollution’, ‘air pollutant’, ‘air pollution-associated diseases’, ‘epigenetics’, and ‘hypersensitivity pneumonitis’. We have included all the original research articles published on the topic in the last 20 years. Overall, this review paper summarizes the findings of 235 articles, including 145 original research papers, 76 review articles, 6 systematic review and meta-analyses, 6 clinical trials, and 2 comparative studies. We have only included the studies where disease development is associated with air pollutants as well as with epigenetic changes. We have not included studies in which air pollution induces mutations or other alterations at the genetic level or causes other physiological changes associated with disease pathogenesis.

The objective of this review is to discuss the association between certain air pollutants, epigenetic modifications, and diseases linked with those pollutants. These epigenetic alterations could be the mechanisms underlying the diseases

associated with air pollution. Such knowledge may guide the prevention and treatment of the diseases. We also discuss HP pathogenesis because certain pollutants could influence HP development, and epigenetic modifications could be a mechanism involved in this process. Moreover, this review will help researchers to develop epigenetic biomarkers for early detection and monitoring prognosis of diseases associated with air pollution. Other mechanisms involved in air pollution-associated disease development have not been discussed in this review article.

Air pollution: an overview

Ambient air pollution is a mixture of many different components comprising airborne PM, ozone, nitrogen dioxide (NO₂), and volatile organic compounds, including benzene, carbon monoxide (CO), and sulfur dioxide (SO₂). Primary pollutants are emitted directly into the air, while secondary pollutants are formed in the atmosphere from other components. Industrial sources, traffic, and residential heating are the major sources of air pollution (Breton and Marutani 2014; WHO 2013). In 2013, the International Agency for Research on Cancer (IARC) declared outdoor air pollution and the associated PM as a potential risk factor for lung cancer. Globally, the mutagenic potential of outdoor air exceeds the normal range over six orders of magnitude (revertants/m³) (Loomis et al. 2014; Cohen 2000). There is increasing evidence to suggest that both acute and chronic exposure to air pollution is detrimental to human health and pregnant women, infants, and individuals with existing diseases, as they are more susceptible to the adverse effects of ambient air pollution (Kloog et al. 2012; Vieira 2015).

Particulate matters (PM)

PM is the sum of hazardous solid and liquid particles suspended in the air. They comprise both organic and inorganic particles such as dust, pollen, and liquid droplets. PM can be classified as coarse (diameter 10 μm; PM₁₀), fine (diameter 2.5 μm; PM_{2.5}), and ultrafine (0.1 μm; PM_{0.1}) particles on the basis of their sizes (Ji and Khurana Hershey 2012). Coarse PM is generally produced from dust on roads, dust generated from construction works and industrial emissions, while combustion processes form fine particles composed of metals, organic molecules, sulfate, nitrate etc. These fine particles are capable of travelling long distances, at times more than 100 km (WHO 2006). However, PM concentration varies by location and is generally more toxic during working hours due to heavy traffic. PM-induced diseases are listed in detail in Table 1. Other than inducing diverse diseases, PM_{2.5} also alters epigenetic age, which is a marker of mortality and disease risk (White et al. 2019). Another work

has shown that PM_{2.5} exposure promotes circadian rhythm disruption and metabolic dysfunction by downregulating histone deacetylases 2, 3, and 4, thereby altering the chromatin dynamics (Palanivel et al. 2020). Air pollution-induced changes in the transcriptomic profile has also been reported. PM_{2.5} exposure at birth is linked with differential gene expressions in early stages of life, which is relevant for complex diseases (Merid et al. 2021). It was observed that depending on the concentration and duration of PM_{2.5} exposure, a distinct transcriptomic and DNA methylomic profile is generated in bronchial epithelial cells (Huang et al. 2021).

Persistent organic pollutants (POPs) and polycyclic aromatic hydrocarbons (PAHs)

In early 1900s, the entire biosphere started to become contaminated with toxic man-made substances called persistent organic pollutants (POPs) (Jones and de Voogt 1999). Only recently, there has been much concern about POPs as many of these chemicals cause perturbations in the endocrine and reproductive health of mammals (Gregoraszczuk and Ptak 2013). Once produced, these chemicals remain in our ecosystem for several years and continue to exert their harmful effect on human health in the form of diseases like cancer, birth defects, and neurological and immunological disorders (El-Shahawi et al. 2010). Certain POPs are associated with immunodeficiency in infants, while a few others are substantial risk factors for breast cancer (Toms et al. 2016; Mouly and Toms 2016). Brain development in infants may get affected due to exposure to POPs, as it has been shown that children exposed to POPs during infancy scored comparatively lower in intelligence and concentration measurements (Tran and Miyake 2017). POPs are also associated with gynecological disorders such as endometriosis, pre-term birth, and other diseases like learning disabilities and an increased incidence of diabetes (Gregoraszczuk and Ptak 2013; Ngwa et al. 2015).

The US Environmental Protection Agency (US EPA) suggests that among the POPs, dioxin-related cancer risk is greater than 1 in 1000 for current background levels of exposure. However, the quantitative cancer risk assessment information for dioxin is of varying ranges (Institute of Medicine (US) Committee on the Implications of Dioxin in the Food Supply 2003). Integrated Risk Information System (IRIS) has been providing quantitative cancer risk assessments for several other POPs including chlordane, DDE, DDT, dieldrin, hexachlorobenzene, alpha-hexachlorocyclohexane, and toxaphene (Gehlhaus et al. 2011). In the US, a number of pesticides have been banned or restricted in terms of usage due to their carcinogenic potential. Some of them are DDT, dimethylhydrazine, hexachlorobenzene,

hexamethylphosphoramide, chlordecone, lindane, mirex, and nitrofen (Gunier et al. 2001). People with high exposure to pesticides have been identified with many different types of cancers including lung, brain, prostate, skin as well as blood and lymphatic system cancers (Blair and Freeman 2009).

Polycyclic aromatic hydrocarbons (PAHs) in the air are produced mainly by the burning of carbon-containing compounds like wood and fuel. They are also present in gasoline and diesel exhaust, cigarette smoke, and charcoal-broiled food. A number of studies have shown that exposure to PAHs is also linked with an increased incidence of lung, skin, and urinary tract cancers (Abdel-Shafy and Mansour 2016). A recent study has shown that PAH contributes to the biological age by changing the leukocyte telomere length and the mitochondrial DNA copy number, as well as by forming anti-benzo[a]pyrene diolepoxide adducts (Pavanello et al. 2020).

Effect of air pollution on human health

The most detrimental effect of air pollution is associated with lung cancer (Cohen and Pope 3rd. 1995). It was found that the incidence of lung cancer is correlated with urbanization variables other than smoking in a national Swedish cohort (Boffetta et al. 2001). Smoking was responsible for 85% and 20–40% of lung cancer incidences in men and women, respectively (Tomatis 1993). A study had shown that 4.3% of the lung cancer incidents in men and 10.5% in women in the Cracow region were due to the air pollution (Hemminki and Pershagen 1994). The nitroarenes from diesel exhaust which can be converted to aromatic amines are a threat to bladder cancer (Latifovic et al. 2015). Air pollution is also associated other type of cancers such childhood leukemia and breast cancer (Lien et al. 2017; Callahan et al. 2019). WHO has estimated that the air quality for 91% of the global population exceeds the pollution limit (WHO 2018). Ambient air pollution was responsible for 4.2 million deaths worldwide, contributing to 7.6% of all deaths in 2016. In 2018, ambient air pollution was responsible for 29% of all deaths and diseases due to lung cancer. It is well realized that air pollution remains one of the major causes for many diseases. In a study in 1994, more than 40% of COPD incidents was attributed to air pollution, while it was responsible for nearly 30% of ischemic heart disease, stroke, and other respiratory infections (Hemminki and Pershagen 1994). A recent study has indicated that air pollution can also bring out interstitial lung diseases (ILDs) (Goobie et al. 2020).

Air pollution and epigenetic modifications

Epigenetics is the process where changes occur in gene functions without changing their underline DNA sequences. Such

changes, which may get reflected in cellular and physiological traits, can be generated by environmental factors, besides being a part of the normal developmental phenomena (Sharma et al. 2010; Feil and Fraga 2012). DNA methylation and histone modifications are two key processes which alter gene functions without changing the DNA sequences (Fuks 2005). DNA methylation is a reversible process and are mediated by DNA methyltransferase (DNMT) and demethylase (Jin et al. 2011). Several studies indicated that a DNA methylation pattern can be greatly influenced by environmental factors like ambient air pollution, and these epigenetic changes are linked with diverse diseases (Plusquin et al. 2017; Ding et al. 2016; Xu et al. 2018). Histones can also be modified by several ways, such as acetylation, methylation, phosphorylation, and ubiquitylation. Micro-RNAs and ncRNAs play critical role in gene expression and contribute to epigenetic control in the process (Chuang and Jones 2007).

MicroRNAs are capable of regulating post-transcriptional gene expression including the expression of epigenetic factors like DNA methyltransferases, histone deacetylases, and polycomb group genes (Macfarlane and Murphy 2010; Filipowicz et al. 2008). Expression of miRNAs are associated with several developmental processes and may contribute to the onset of many diseases like cardiovascular diseases, cancer, metabolic diseases, and developmental disorders (Ha 2011). A diverse class of ncRNAs, such as snoRNAs, miRNAs, siRNAs, exRNAs, piRNAs, and long ncRNAs, can influence transcription and translation processes and play significant roles in health and diseases. They generally do not code proteins but are capable of regulating gene expression through the regulation of the chromatin structure and DNA methylation (Hombach and Kretz 2016). Moreover, mitochondrial DNA (mtDNA) is also regulated at the epigenetic level in the form of mtDNA methylation (van der Wijst et al. 2017). Mitochondrial epigenetics are capable of influencing diverse cellular activities such as transcription regulation, cell division, cell cycle regulation, physiological homeostasis, bioenergetics, and disease pathologies (Stimpfel et al. 2018) (Fig. 1).

Chronic exposure to air pollution causes cytogenetic damage, DNA-strand breakage, epigenetic changes, and altered gene expression—all these changes are associated with higher risk factors for many diseases, especially for cancers (Ghorani-Azam et al. 2016). Studies have shown that organic extracts of outdoor PM induce changes in the DNA morphology in mammalian cell culture. Several cytotoxic effects, such as oxidative DNA damage, breakage in the DNA strand, altered telomere length, and mutation formation have been observed in human peripheral monocytes when exposed to such organic extracts (Cimino et al. 2014). DNA methylation pattern in the genome also gets altered upon exposure to certain pollutants (Martin and Fry 2018). Asbestos is not an essentially mutagenic substance; it may, however, impose the risk of

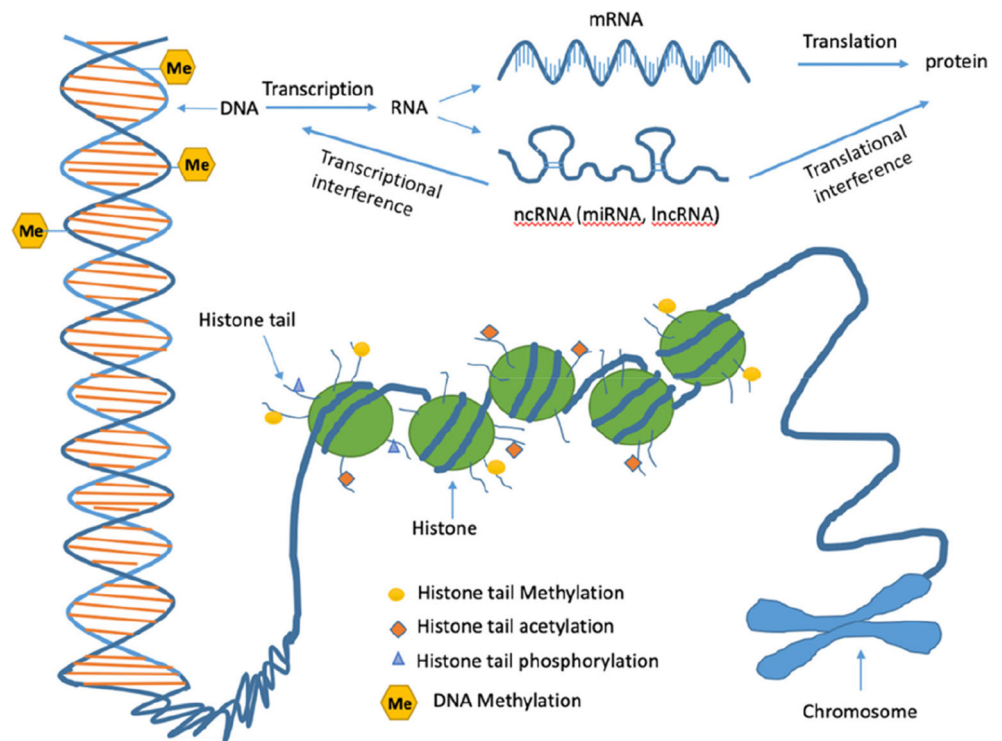
cancer through an epigenetic mechanism (Kettunen et al. 2017). In addition, it is to be noted that an altered miRNA expression profile has been reported as an effect of PM exposure (Jardim 2011).

Epigenetic mechanisms are also involved in regulating many genes that are involved in inflammation and immune responses (Suárez-Álvarez et al. 2013). Therefore, aberrant environmental signals that may induce epigenetic changes could generate an imbalance in immunity. It was found that exposure to PM_{2.5}, CO, and O₃ altered the methylation pattern in many CpG sites for the immunoregulatory gene Foxp3, IL-4, IL-10, and IFN- γ , thereby altering the immune response (Prunicki et al. 2021). Air pollution has also been found to have been associated with autoimmune diseases. Such pollutants may trigger pulmonary inflammation by altering the lung microenvironment and inducing epigenetic changes (Zhao et al. 2019). Besides abnormal immune responses, air pollution-induced epigenetic modifications could directly contribute to disease pathogenesis and such epigenetic changes could be inherited across generations.

Air pollution and DNA methylation

Emerging evidences suggest that air pollutants modulate epigenetic states, ranging from DNA methylation to miRNAs expression (Breton and Marutani 2014; Alfano et al. 2018). Epithelial cells from the aerodigestive tract of heavy smokers exhibit aberrant methylation of multiple genes associated with the pathogenesis of lung cancer (Zö Zöchbauer-Müller et al. 2003). Several genes that are related with cancer progression have also been found to be hypermethylated in the bronchial epithelium and peripheral lymphocytes of smokers (Sridhar et al. 2008). Exposures to metals induce DNA methylation as well as histone modifications (Martinez-Zamudio and Ha 2011). Metal-rich air particles generate H3K4me₂ and H3K9ac patterns in specific promoters of transcriptionally active genes (Cantone et al. 2011). Mitochondrial DNA also gets methylated upon metal exposure (Byun et al. 2013). It is to be noted that fine PM is strongly pro-oxidant in nature, and mitochondrial DNA is more susceptible to oxidative damage due to lack of introns and histone proteins (Bhargava et al. 2018b). DNA from the sperm of mice exposed to steel plant air has been shown in a persistent hypermethylated state long after the exposure ended (Yauk et al. 2008). Epidemiological studies reveal that PM_{2.5} and PM₁₀ exposures induce the hypomethylation of Alu and/or LINE1 (Long Interspersed Nuclear Element-1) elements in leukocytes and buccal cells (Terry et al. 2011; De Nys et al. 2018). PM exposure also alters DNA methylation in the NOS2A gene involved in nitric oxide production, which is important for cardiovascular and respiratory health (Breton et al. 2012; Breton et al. 2014). During pregnancy, especially in the first trimester, PM_{2.5} exposure is linked with global DNA hypomethylation in the placental

Fig. 1 Epigenetic alterations in the mammalian system. (a) DNA methylation at the DNA bases, (b) different types of modifications at the histone tails, and (c) interference of the non-coding RNAs (ncRNAs) with the gene expression process



tissue (Janssen et al. 2013). High levels of PM and ozone exposures are associated with hypermethylation of the FOXP3 gene in regulatory T cells (Nadeau et al. 2010). Direct exposure to PM_{2.5} also induces methylation of the p16 promoter (a tumor-suppressor gene) in alveolar epithelial cells as well as in the lungs of mice. The expression level of DNA methyltransferase 1 (DNMT1) is reported to be elevated in PM-exposed patients—this could be a mechanism to induce methylation in the p16 promoter region (Soberanes et al. 2012). In an attempt to establish a link between childhood asthma and air pollution, studies have demonstrated that exposure to PM_{2.5} induces DNA methylation in several CpG loci of inducible nitric oxide synthase (iNOS) genes, the major enzyme for nitric oxide production in the airways (Breton et al. 2012). Another study has shown that short-term exposure to air pollution alters DNA methylation at the promoter region of the iNOS gene (Salam et al. 2012). All these studies indicate distinct pathways through which air pollution exerts its phenotypic expression.

Expressions of many inflammatory and immune response genes are found to be altered due to DNA methylation linked with air pollution (Vawda et al. 2014). Air pollution-induced DNA methylation is often found to be associated with poor respiratory health outcomes (Rider and Carlsten 2019). Both short- and long-term exposures to NO₂, CO, and PM_{2.5} lead to changes in the differentially methylated region (DMR) of the Foxp3 promoter region and the IL10 intronic region. These changes are long-lasting and significantly associated with asthma pathogenesis (Prunicki et al. 2018). The

hypermethylation of interferon-gamma (IFN- γ) in effector T-cells and Foxp3 in regulatory T-cells has been observed as an effect of ambient air pollution (Kohli et al. 2012). In another trial, 15 healthy adult participants were exposed to concentrated ambient particles (CAPs). Exposure to fine CAPs reduced Alu methylation, while coarse CAPs reduced Toll-like receptor-4 (TLR4) methylation—a gene involved in asthma pathogenesis (Bellavia et al. 2013). Among other air pollutants, SO₄ has been associated with altered methylation patterns in genes associated with asthma (Sofer et al. 2013). In addition to DNA repetitive elements, PM exposures alter the DNA methylation pattern for specific genes, including p53, p15, p16, APC, RASSF1A, HIC1, iNOS, hTERT, and IL-6, and such alterations influence the development of diverse diseases. However, each different gene and subfamily of repetitive DNA sequence responds independently to different exposure conditions (Pacchierotti and Spanò 2015).

PAH is also associated with DNA methylation. Neonatal exposure to PAH causes hypermethylated ACSL3 in the DNA of the white blood cells of the umbilical cord (Perera et al. 2009). PAHs can also cause a hypermethylation state in the LINE1 repetitive element (Lee et al. 2017). Airborne benzene exposure in humans also generates hypomethylation of the repetitive elements and specific genes (Bollati et al. 2007). The measurement of Alu and LINE-1 methylation gives an estimation of the global genomic DNA methylation content. Global hypomethylation and hypomethylation of transposable repetitive sequences are associated with reduced chromosomal stability and altered gene functions (Lisanti et al. 2013). It is

possible that DNA methylation makes individuals susceptible to pollutant exposure. A study has shown that exposure to various pollutants alters ICAM-1 and VCAM-1 levels in blood and these effects are dependent on Alu, LINE-1, or TLR-2 methylation status (Bind et al. 2012).

Exposure to POPs such as DDT, DDE, HCH, chlordane, mirex, and PCBs also induce altered methylation in Alu and LINE1 sequences (Rusiecki et al. 2008). In a similar study, a healthy Korean cohort shows that the blood concentrations of different organochlorine pesticides are inversely associated with the Alu methylation level (Kim et al. 2010). Perfluoroalkyl substances (PFASs), a new class of POPs, are industrial wastes and have been found to be epigenetically active. A study has revealed that an increased level of serum perfluorooctanesulfonate (PFOS) is associated with LINE-1 methylation, while prenatal PFOS exposure could be associated with the hypomethylation in Alu repeats in cord blood (Watkins et al. 2014; Liu et al. 2018). Moreover, black carbon exposure was found to generate hypomethylation in the Alu region (Madrigano et al. 2011). Only a few studies have revealed the effect of PM10 or PM1 on epigenetic modifications. A combination of PM10, PM1, zinc, and iron exposures has been negatively associated with NOS3 methylation, while only zinc exposure has reduced endothelin-1 (EDN1) methylation. The reduced NOS3 and EDN1 methylation has led to an increase in the endogenous thrombin potential (ETP), a measurement of global coagulation, thereby providing a mechanism for environmental exposures on coagulation through epigenetic modifications (Tarantini et al. 2013). Overall, exposure to diesel exhaust particles (DEP) and other air pollutants may result in epigenetic changes at repeat elements and specific candidate genes, which in turn is likely to influence gene expression levels and contribute to disease pathogenesis. All these observations suggest that changes in the methylation pattern could be diverse and depend on several factors like the duration and length of exposure, co-exposure, targets, route of exposure, and the genetic makeup of hosts. Further investigations are required to establish a direct correlation between methylation patterns and specific pollutants.

Air pollution and histones

The effect of air pollution on histone modification is well established. However, measurement of histone modifications due to air pollution in large population studies remains unexplored. One study shows that inhaled nickel, arsenic, and iron are associated with increased histone3-lysine4 dimethylation (H3K4Me2) and histone3-lysine9 acetylation (H3K9Ac) on histones from blood leukocytes (Martinez-Zamudio and Ha 2011). PAH exposure also induces histone modifications in mice—for instance, exposure to benzo[a]pyrene (BaP), a type of PAH, decreases the acetylation of H3K14 in the steroidogenic acute regulatory protein (StAR) gene promoter, which is

important for testosterone production (Liang et al. 2012). BaP exposure to HeLa cells generates H3K4Me3 and H3K9Ac modifications along with a reduced association of DNMT1 with the LINE-1 promoter. Cytosine methylation within the CpG island of the LINE-1 promoter is also reported to be reduced (Teneng et al. 2011). A knockout mice study shows that Sirt1, a member of class III histone deacetylase, can control the adverse effect of PM exposure on cardiopulmonary functions through the regulation of inflammation/coagulation responses in lungs following the exposure (Wu et al. 2012). Cigarette smoke exposure is also associated with an increased expression level of DNMT1 and a decreased level of DNMT3B (Xiao et al. 2015; Liu et al. 2007). Another study reveals that cigarette smoke exposure decreases histone deacetylase (HDAC) activity and reduces HDAC1, HDAC2, and HDAC3 expressions in macrophages, thereby leading to an inflammatory response generation (Yang et al. 2006). Exposures to PM10 and DEP may cause an imbalance between histone acetyltransferase (HAT) and HDAC expression levels, as well as increase histone H4 acetylation in the promoter region of the specific genes, thereby generating inflammatory responses in human bronchial epithelial (HBE) cells (Gilmour et al. 2003; Cao et al. 2007).

Air pollution and miRNA

It is controversial whether to include miRNAs as an epigenetic mark. Almost two-thirds of the human genes are regulated by miRNAs and are thought to play a critical role in mediating biological responses to air pollution (Jardim 2011; Tomankova et al. 2011). In one study, human airway epithelial cells had been incubated with DEP and the miRNA expression profile was determined using miRNA microarray technique. In total, 197 miRNAs were found to be down or upregulated in response to the exposure, and a few among them involved in inflammatory and tumorigenic processes (Jardim et al. 2009). Exposure to PM also alters miRNA expression levels in the microvesicles derived from A549 alveolar cells and from the plasma of healthy steel plant workers (Bollati et al. 2015). These PM-induced changes often impose the risk of cardiovascular diseases. Literatures showing an association between ambient air pollution and miRNA is emerging. A small change in a single miRNA has the potential to influence a large number of genes working on its downstream mechanism (Catalanotto et al. 2016).

It is to be noted that miRNAs are involved in important cellular functions such as cell growth, differentiation, development, apoptosis, and metabolism. Dysregulations in miRNA expression are associated with diverse diseases including cancers (Mahmoud et al. 2021). A recent study has shown that a total of 25 miRNAs are deregulated in lung cancer as well as associated with air pollution exposure. It was suggested that miR-222, miR-21, miR-126-3p, miR-

155, and miR-425 may serve as biomarkers for the assessment of risk factors for lung cancer in individuals who have been exposed to air pollution (Sima et al. 2021). Besides various types of cancers, miRNAs are also deregulated in different diseases such as stroke, Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Mahmoud et al. 2021). All these diseases are also associated with air pollution (Kasdagli et al. 2019; Esmacel Mousavi et al. 2017; Wu et al. 2017b). The presence of miRNAs in body fluids such as urine and serum as well as in tissues makes them suitable candidates for developing disease biomarkers.

Air pollution and non-coding RNA

Only a small number of known lncRNAs have been functionally characterized so far. lncRNAs are already emerging as potential regulators of air pollution-associated diseases (Karlsson and Baccarelli 2016). A recent work has shown that cigarette smoke extracts and PM_{2.5} treatment alter the expression level of a particular lncRNA, lung cancer progression-association transcript 1 (LCPAT1), in lung cancer cells and knockdown of LCPAT1 impairs the effect of treatment (Lin et al. 2018). An experiment reveals that lncRNA LOC101927514 is linked with the PM_{2.5}-induced inflammation in bronchial 16HBE cells that are used as a respiratory inflammation model. RNAi inhibition of lncRNA LOC101927514 reduces inflammation induced by PM_{2.5}. Moreover, lncRNA LOC101927514 binds with STAT3, a protein which is known to influence the inflammatory state of the cells. This indicates the possibility that lncRNA LOC101927514 could be a potential target for the treatment of PM_{2.5}-induced respiratory inflammation (Tan et al. 2020). In another study, more than 500 lncRNAs have shown altered expression levels in rat embryos exposed to air pollution. Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses of the deregulated lncRNAs indicate their involvement in neurological processes and congenital defects (Li et al. 2019). Smoking is another common risk factor for many diseases like COPD, asthma, lung cancer, and cardiovascular diseases; it influences the expression of lncRNAs in lung tissues (Wang et al. 2017). GO and KEGG pathway analysis show that these lncRNAs are linked with the pathways involved in the pathogenic processes of COPD (Zhang et al. 2018a). Another lncRNA, MALAT1 is involved in cigarette smoke extract-induced malignant changes in HBE cells (Ji et al. 2003).

lncRNA can influence miRNA expressions. In many cases, the crosstalk between lncRNAs and miRNAs are important regulators of gene expression. Sometimes intragenic miRNA sequences are embedded within lncRNA sequences, thus suggesting a post-transcriptional regulatory role of lncRNAs in miRNA regulations (Dykes and Emanuelli 2017). These findings suggest that lncRNAs may function as novel biomarkers

of environmental exposure—they are involved in interactions with various environmental factors and can regulate many cellular processes, thereby influencing disease pathogenesis associated with air pollution.

Air pollution and transgenerational epigenetic inheritance

Epigenetic changes may persist through several cell cycles or may get transmitted to subsequent generations without impacting the underlying DNA sequences (Henikoff and Greally 2016). Transgenerational epigenetic inheritance deals with epigenetic marks—i.e. DNA methylation, histone modifications, and non-coding RNAs—that are acquired in one generation and get stably transferred to the next generation through the gametes (Trerotola et al. 2015; Blake and Watson 2016). Transgenerational epigenetic inheritance is not a very common phenomenon. However, epigenetic changes can be inherited when they occur in gametes and are not completely erased due to reprogramming (Wei et al. 2015). Tumor-suppressor mismatch repair genes MLH1 and MSH2 are examples where epimutations are inherited through the germ lines (Hitchins et al. 2007; Chan et al. 2006). Imprinted genes provide another example of epigenetic inheritance. Generally, there are two functional copies (alleles) for each gene—one inherited from the mother and another from the father. One copy of the alleles which is heavily methylated is called the imprinted gene and it remains transcriptionally silenced (Barlow and Bartolomei 2014). miRNA is a regulatory molecule for gene expression in response to environmental stimuli, and such changes in miRNA expression may alter the gene expression so as to influence the gene expression even in the future generations.

It has been found that 5-methylcytosine (5mC) is the predominant DNA methylation in mammals. Methylation marks could be inherited if they are mitotically and meiotically stable and are capable to avoid epigenetic reprogramming in primordial germ cells as well as postfertilization embryos (Stenz et al. 2018). Recently, it has been thought that histone modifications and their regulatory enzymes can transfer the epigenetic signatures across generations. In *C. elegans*, histone3-lysine27 trimethylation (H3K27me3) marks can transfer the memory of repressing X-chromosome transgenerationally (Gaydos et al. 2014). The role of non-coding RNAs in transgenerational epigenetic inheritance is currently being researched (Larriba and del Mazo 2016).

In Table 1, we have summarised the connection between various air-pollutants, subsequent epigenetic modifications, and different disease risks. A few pollutants are associated with immune modulation through epigenetic changes and thus could play as a risk factor for HP development. It would be interesting to study whether there is direct correlation between HP development and exposure to those pollutants.

Table 1 Diverse disease risks due to air pollution-mediated epigenetic changes

Air pollutants	Epigenetic mark	Diseases/Symptoms	References
1 PM2.5	Promoter methylation of the tumor suppressor p16 gene	Lung cancer	Soberanes et al. 2012
2 PM2.5	SOX2 promoter hypermethylation	Lung Cancer	Tantoh et al. 2019
3 PM2.5	miRNA mediated deregulation in gene expression	Lung Cancer	Ning et al. 2019
4 PM2.5	H3K27ac (histone 3 lysine 27 acetylation)	Inflammatory responses	Liu et al. 2015
5 PM2.5	Alterations in LINE-1 methylation, methylation at CpG loci of TNF- α	Inflammation	Wang et al. 2020a
6 PM2.5	Altered global DNA methylation, P16 gene promoter methylation, and DNMT activity, altered post-translational histone modification.	COPD	Leclercq et al. 2017
7 PM2.5	Mitochondrial DNA methylation	Heart rate variability	Byun et al. 2016
8 PM2.5	miRNA	Cardiovascular diseases	Chen et al. 2018
9 PM 2.5	Methylation at candidate CpGs in monocytes	Atherosclerosis	Chi et al. 2016
10 PM 2.5	Genome-wide DNA methylation	Cardiometabolic diseases	Li et al. 2018a
11 PM 2.5	ICAM-1 promoter methylation	Glucose dysregulation	Peng et al. 2016
12 PM2.5	Regulation of extracellular vesicle-enriched miRNA (evmiRNAs) expression by DNA methylation	Altered systolic blood pressure	Rodosthenous et al. 2018
13 PM2.5	Altered methylation in clock genes (CRY1, CRY2, NPAS2)	Ischemic stroke	Cantone et al. 2020
14 Prenatal exposure to PM2.5	Cord blood DNA methylation of IGF2/H19 gene	Disease risk in later life	Wang et al. 2020b
15 Prenatal exposure to PM2.5	Lower expression levels of the miR-17/92 cluster in cord blood	Cancer risk, disease predisposition in later life	Tsamou et al. 2020
16 PM2.5, metals from traffic sources (Cd, Fe, Mn, and Ni)	DNA methylation in imprinted control regions(L3MBTL1, NNAT, PEG10, GNAS Ex1A, MCTS2, SNURF/SNRPN, IGF2R, and RB1)	Risk associated with non-small cell lung cancer, glioma, and bladder cancer	Liang et al. 2021
17 PM2.5 and PM10	Hypomethylation of tandem repeats <i>SATα</i>	Inflammation	Guo et al. 2014
18 Ambient air pollutant: PM2.5, PM10, PAH, O3	Hypermethylation of Foxp3 locus	Asthma	Janssen et al. 2013
19 PM2.5, NO _x	CpG-methylation, DMRs in circulating monocytes	Atherosclerosis pathogenesis	C Chi et al. 2021
20 PM2.5, NO2	DNA methylation on cytosine-phosphate-guanine (CpG) sites and differentially methylated regions (DMRs).	Inflammation and immune responses	Eze et al. 2020
21 Traffic-related air pollution (TRAP) – PM2.5, PM10, NO2 and SO2	DNA methylation and histone H3K9 acetylation	Respiratory disorders	Ding et al. 2017
22 Exposure to PM2.5, PM10 during pregnancy	DNA methylation on CpG sites and on differentially methylated regions (DMRs)	Respiratory health	Gruzjeva et al. 2019
23 Ambient air pollutants: PM2.5, PM10, SO ₂ , NO ₂ , CO.	Genome-wide analysis of differential DNA methylation	Pulmonary disorders and cancers	Wang et al. 2020c
24 Traffic-related pollutants: PM2.5, black carbon, NO2, CO	LINE-1, Alu, and gene-specific DNA methylation tissue factor (F3), Toll-Like Receptor 2 (TLR-2), and ICAM-1)	Cardiovascular disease	Lisanti et al. 2013
25 Prenatal exposures to PM2.5, PM10	Altered DNA methylation in specific gene promoters	Childhood cardio-respiratory health	Breton et al. 2016
26 Prenatal exposures to PM2.5, PM10	Placental global DNA methylation	Placental adaptation at the level of global DNA methylation	Maghbooli et al. 2018
27 PM10	microRNA-101	Blood pressure	Motta et al. 2016
28 PM10 (most abundant elements: Al, Fe, water soluble organic fraction)	Alterations in DNA methylation in macrophages	Inflammation	Miousse et al. 2014
29 Iron-rich combustion- and friction-derived nanoparticles (CFDNPs) that are	Lower H3K9me2/me3 and higher γ -H2A.X	Alzheimer's disease (AD)	Calderón-Garcidueñas et al. 2020

Table 1 (continued)

Air pollutants	Epigenetic mark	Diseases/Symptoms	References
abundantly present in airborne particulate matter			
30 Airborne PM and PM metallic components	Extracellular vesicle (EV) miRNAs	Inflammation and coagulation	Pavanello et al. 2016
31 Ambient ultrafine particles (UFP, diameter Dp < 0.18 μm)	Noncoding RNAs	Neurodevelopmental and neurodegenerative disorders	Solaimani et al. 2017
32 Ozone (O3)	miRNAs, namely miR-132, miR-143, miR-145, miR-199a*, miR-199b-5p, miR-222, miR-223, miR-25, miR-424, and miR-582-5p	Inflammatory diseases	Fry et al. 2014
33 Ozone (O3)	DNA methylation of the apelin gene	Pulmonary edema	Miller et al. 2018
34 Traffic-related air pollution (TRAP)	Nasal DNA methylation	Childhood asthma	Zhang et al. 2018b
35 Traffic-related air pollution	Differentially methylated CpG positions (DMPs) and differentially methylated regions (DMRs)	Asthma severity	Zhu et al. 2021
36 Diesel exhaust particles (DEP) from traffic and house dust mite (HDM)	Changes in 5-methyl-cytosine (5mC) and 5-hydroxy-methylcytosine (5hmC) in the regulatory regions associated with transcription factors in airway epithelial cells	Airway diseases, asthma	Zhang et al. 2018a, 2018b, 2018c (July)
37 Diesel Exhaust (DE)	CpG site methylation	Allergic disease	Clifford et al. 2017
38 Diesel Exhaust (DE)	CysLT-related gene methylation	Asthma, poor lung function	Rabinovitch et al. 2021
39 Diesel Exhaust (DE)	CpG site methylation, DMRs in bronchial epithelial cells	Pulmonary pathologies	Cardenas et al. 2021
40 Gestational exposure to Diesel Exhaust (DE)	DNA methylation in global regulatory regions	Cardiac hypertrophy, fibrosis and susceptibility to heart failure	Goodson et al. 2019
41 Polycyclic aromatic hydrocarbons (PAHs)	Methylation in the FOXP3 locus	Asthma, allergic rhinitis	Hew et al. 2015
42 PAH	Higher expression of let-7a, miR-146a-5p, and miR-155-5p and lower expression of IL-6, CXCL8, and TLR2 mRNAs	Inflammation	Li et al. 2020
43 PAH, Nitro-PAH, PM2.5	Promoter methylation of CDKN2A, APC, and MLH1 genes and hypomethylation of the LINE-1	Cancer risk	Silva et al. 2019
44 Phenanthrene (Phe)	CpG island methylation of FOXP3 gene	Atopic conditions	Liu et al. 2013
45 Coke oven emissions (COE), PAHs	Hypomethylation of LINE-1 and AhRR gene	Lung cancer	Yang et al. 2018
46 Air pollutants	Histone modifications (H3K9ac, H3K9me3, H3K27me3, and H3K36me3)	Blood pressure	Kresovich et al. 2017
47 Air pollution	Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism	Alzheimer’s disease (AD)	Wu et al. 2017b
48 Environmental tobacco smoke	Alteration in gene-specific and global DNA methylation	Allergic asthma	Christensen et al. 2017
49 Tobacco smoke exposure	CD14 methylation	Allergic diseases	Munthe-Kaas et al. 2012
50 Environmental tobacco smoke	Alterations in methylation pattern of IFN-γ and Thy-1 promoters	Respiratory diseases	Cole et al. 2017
51 Prenatal exposure to tobacco smoke	Alterations in DNA methylation of LINE1 and AluYb8. Changes in the methylation on CpGs in the promoter region of AXL and PTPRO genes.	Disease risk in later life	Breton et al. 2009
52 Cigarette smoke	Hypomethylation on the glutamate-cysteine ligase catalytic subunit (GCLC) gene	COPD	Cheng et al. 2016
53 Cigarette smoke	CpG methylation Of gene AIRE, PENK and SLC6A3	Non-small cell lung cancer	Ma et al. 2019
54 Cigarette smoke	DNA methylation in white blood cells	Cardiovascular diseases	Chatziioannou et al. 2017
55 Cigarette smoke	DNA methylation	Schizophrenia	Ma et al. 2020

Table 1 (continued)

Air pollutants	Epigenetic mark	Diseases/Symptoms	References
56 Indoor air pollution caused by smoky coals with high benzo(a)pyrene (BaP) and quartz levels	CDKN2A, DLEC1, CDH1, DAPK, RUNX3, APC, and WIF1	Primary non-small cell lung cancer (NSCLC)	Huang et al. 2018a
57 Biomass smoke	DNA methylation in the promoter region	Cardiovascular diseases	Ruiz-Vera et al. 2019
58 Second-hand smoke	miR-126 and miR-155	Lung cancer	Tommasi et al. 2012
59 Second-hand smoke	Altered methylation of major repetitive DNA elements including LINE L1, IAP LTR and SINE B1	Bladder carcinoma	Wilhelm-Benartzi et al. 2011
60 Second-hand smoke	DNA methylation of several CpG loci	Asthma	Runyon et al. 2012
61 Smoke and second-hand smoke	CpG methylation within FOXP3 and IFN γ loci	Breast cancer	Callahan et al. 2019
	Altered methylation of GSTP1, FHIT, and CDKN2A, SCGB3A1 and BRCA1 genes		

Air pollution and epigenetic modifications in hypersensitivity pneumonitis (HP)

Airborne pollutants have adverse effects in the lungs. Recent studies find an association between air pollution exposure and increased incidence of poor lung function and mortality in interstitial lung diseases (ILDs) (Johansson et al. 2015). In idiopathic pulmonary fibrosis (IPF), air pollution is associated with increased incidence and harmful effects on health (Harari et al. 2020). ILDs comprise an array of heterogeneous parenchymal lung diseases that occur due to fibrosis and inflammation of lung parenchyma. Considerable heterogeneity exists among ILDs, depending on a variety of causative agents, while in some cases the cause is unknown and therefore the disease is classified as idiopathic. Prevalence of ILDs depends largely on geographical locations and incumbent environmental conditions. IPF, sarcoidosis, and HP are the most regularly observed disorders amongst ILDs (Kalchier-Dekel et al. 2018). According to data from Indian registry, HP accounts for 47.3% of all ILD cases and is the most frequent type of ILD in India. HP, also known as extrinsic allergic alveolitis (EAA), is a heterogeneous and immunologically-mediated lung disease. It results from the inhalation of certain organic substances of animal or plant origin and inorganic substances like low molecular weight chemical isocyanates. The most prevalent forms of HP are farmer's lung disease, developed from bacterial and fungal exposure, and bird fancier's lung that occur due to the inhalation of avian antigen found in bird droppings. Interestingly, the inhaled offending antigen does not induce the disease in every exposed individual. It is reported that nearly 5–10% of the exposed individuals will develop HP. Prevalence of chemical worker's lung is only 1–4.7% of the isocyanate-exposed workers, while farmer's lung is reported to have developed in 1–19% of the mouldy hay-exposed individual. It is also estimated that only about 6–20%

of the avian antigen-exposed people develop bird fancier's lung. Such variations in disease incidence can be traced to the presence of predisposed genetic and epigenetic factors. Individuals who are genetically susceptible (first hit) develop HP when exposed to an inciting antigen (second hit). The second hit—i.e. the exposure to causative antigen—alone cannot induce HP development (Spagnolo et al. 2015). A recent study has indicated an association between air pollution level and HP occurrence in India (Singh et al. 2019). It is apparent that air pollution could be a risk factor for HP, but how air pollution could influence HP pathogenesis is largely unknown. It has been observed that exposure to specific air pollutants leads to inflammation and altered immune responses. Such exposure is also associated with epigenetic modifications. Therefore, we hypothesize that air pollution-induced epigenetic alterations influence immune responses, thereby making exposed individuals susceptible to the development of HP. The following section outlines the pathophysiology of HP in connection with epigenetic modifications induced by air pollution.

Immunopathogenesis of HP

HP is an inflammatory lung disease caused by the inhalation of organic or inorganic antigens (summarized in Table 2) less than 5 μm in diameter. According to the 'two-hit' hypothesis, the coexistence of inducing factors, such as antigen and promoting factors like genetic abnormalities or additional environmental exposures, may lead to an exaggerated immune reaction in the lungs and thereby causes inflammation. HP is characterized by alveolitis, which eventually results in granuloma formation and the development of fibrosis. The development of fibrosis leads to respiratory insufficiency, and finally, to the death of the patient (Selman et al. 2012).

Table 2 Common HP-inducing antigens

Name of the Disease	Origin	Antigen	Source of Antigen
1. Farmer’s lung	Bacterial	<i>Micropolyspora faeni</i> , <i>Thermoactinomyces vulgaris</i>	Moldy hay
2. Summer-type HP	Fungal	<i>Penicillium frequentans</i>	Contaminated old houses
3. Hot tub lung	Mycobacterial	Mycobacterium avium complex (MAC), composed of <i>M. avium</i> and <i>M. intracellulare</i>	Contaminated water
4. Bird fancier’s lung	Animal fur protein	Avian proteins	Feather bloom, avian serum(pigeons, chicken, turkey, goose, avian proteins), and excrement (mainly due to pigeon intestinal mucin)
5. Chemical worker’s lung	Low-molecular weight chemicals	Diisocyanates, trimellitic anhydride	Polyurethane foams, spray paints, dyes, glues

The pathogenesis of HP is complex and involves both Type III (immune complex-mediated) and Type IV (T cell-mediated) hypersensitivity reaction. Several studies have suggested that the alveolitis, (inflammation in alveoli branches) initiates with almost an exclusive predominance of neutrophils, eventually involving lymphocytes and becoming solely lymphocytic at later stages. The human lung contains approximately 10^{11} alveolar macrophages which play a major role in granuloma and fibrosis formation in HP. In the susceptible individual with repeated exposures, the disease-causing antigen forms an immune complex with the pre-existing antigen-specific antibody (IgG). This event triggers the activation of the complement cascade and results in the recruitment of macrophages, neutrophils, and lymphocytes at the site infection to induce the formation of granuloma (Patel et al. 2001). These immune cells also secrete several molecular mediators that induce the migration and stimulation of fibroblast to induce fibrosis. It is reported that chronic forms of HP are regulated by the T cells. Analyses of the bronchoalveolar lavage fluid (BALF) of chronic HP patients have suggested an involvement of Th2 T cells with a higher CD4+ / CD8+ ratio and a concomitant reduction in the number of $\gamma\delta$ T cells in disease development (Caillaud et al. 2012; Simonian et al. 2009). It is likely that the CD4 to CD8 ratio varies according to the type of the inhaled antigen. Activation of alveolar macrophages in the acute and sub-acute phases also promotes CD8+ T cells accumulation, granuloma formation, and subsequent development of fibrosis. Natural killer cells are also reported to be involved in HP pathogenesis (Korosec et al. 2007). Various reports have demonstrated that Th1 cytokine plays an essential role in disease pathogenesis (Barrera et al. 2008). The induction and perpetuation of the inflammatory responses in HP, including the recruitment of the different inflammatory cells, are mediated by a myriad of cytokines and chemokines. The pathophysiology of HP is not dependent on any one component of cellular immunity, but it is developed due to a multimodal

interaction between these components, each of which may play a crucial role in disease progression.

Neutrophils are the body’s first line of defence against foreign bodies and plays a crucial role in inflammatory diseases like HP. After inhalation of the causative antigen, neutrophils accumulate in the alveoli and small airways of the lungs. Upon stimulation, neutrophils secrete various cytokines that are implicated in the pathogenesis of HP (Pardo et al. 2000). The secretion of IFN β , IL-10, and IL-6 by neutrophil is regulated by epigenetic modifications. The binding of two transcription factors, PU.1 and C/EBP β , favours activation of the transcription of these three cytokines (Ostuni et al. 2016). Additionally, the matrix metalloproteinases (MMPs), collagenase-2 (MMP 8), and gelatinase B (MMP 2) produced by neutrophils are also reported to play a key role in the disease progression (Pardo et al. 2000). An epigenetic study on MMP2 reveals that its expression is dominated by DNA and histone modifications (Santiago-Ruiz et al. 2019). Patients with chronic HP have an increase of neutrophils loaded with MMP8 and MMP9, and many studies show that the expressions of MMPs are regulated by histone and DNA methylation (Campos et al. 2016).

Macrophages are predominantly involved in granuloma formation in HP (Suga et al. 1997). The lncRNA MEG3-4 has been identified as a tissue-specific regulator of inflammatory responses in alveolar macrophages during bacterial infection through the transcriptional regulation of immune response genes. It has been confirmed that the lncRNA MEG3-4 binds to the microRNA miR-138 in a competitive manner, with mRNA encoding the proinflammatory cytokine IL-1 β , thereby increasing the abundance of IL-1 β and enhancing the inflammatory response to bacterial infection in alveolar macrophages (Li et al. 2018b). A recent study on epigenome analysis has revealed that DNA methylation is involved during macrophage differentiation by changing the binding sites of transcription factors (Dekkers et al. 2019). T

cells are also considered to be important regulators of HP development (Simonian et al. 2009). Epigenome maps combined with mechanistic studies, have demonstrated that T cells undergo extensive epigenome remodelling in response to signals, which has a strong effect on phenotypic stability and function of the lymphocytes (Schmidl et al. 2018). Moreover, it was shown that the second-hand smoke and ambient air pollution, which deteriorate respiratory health, were associated with DNA hypermethylation and a decreased expression of IFN- γ and Foxp3 in T cells population (Runyon et al. 2012).

External influence on HP development

Recently, Singh et al. have reported that ambient air pollution is a promoting factor in the development of HP. The study demonstrates that the odds of developing HP is 7% greater for every 10 $\mu\text{g}/\text{m}^3$ increase in air pollution (PM2.5 level). The authors hypothesize that fine-particulate air pollutants lead to airway inflammation, reduce mucociliary clearance in the alveoli, and lead to an immune-mediated response that ultimately leads to the development of HP (Singh et al. 2019). It is apparent that more rigorous studies are necessary to establish this hypothesis. It is evident from the 'Table 1' that exposures to PM2.5, PM10, NO2, SO2, CO, and O3 were found to be associated with epigenetic changes like alteration in LINE-1 methylation, methylation on CpG sites of many immunoregulatory genes, histone modifications, and miRNA regulations. These epigenetic changes were again associated with inflammation and poor respiratory health. Therefore, exposure to those pollutants may alter immune responses, which could influence HP development. Moreover, HP pathogenesis involves many components of our immune systems that are under epigenetic regulations (Fernández-Morera et al. 2010). Wu et al. have reported methylation of EBF3 gene in peripheral blood samples of a Turkic ethnic group (Uygurs) with bird fancier's lung. The authors hypothesized that EBF3 hypomethylation might be associated with IL 10 dysregulation in HP subjects (Wu et al. 2018). In another study on Chinese Uygur population by the same group, methylation of the gene Smad3 is reported. Smad 3 protein is one of the key players in the formation of fibrosis; it is likely that Smad3 gene hypomethylation promotes pulmonary fibrosis by increasing Smad3 mRNA expression (Wu et al. 2017a).

Diagnosis and effective management of HP often pose to be a challenge to the pulmonologists. HP is curable if diagnosed correctly in its early stages, i.e. before occurrence of irreversible lung damage. The prognosis of HP is not dependent only on the dose and duration of exposure to the causative agents; the genetic and environmental factors also play a major role in disease pathogenesis. Recent studies have shown that HP development is associated with ambient air pollution, which is known to be linked with inflammation and other lung

diseases. An understanding of epigenetic alterations associated with air pollution has emerged in recent times and in many cases, such alterations are associated with diverse diseases including ILDs (Fig. 2).

Future perspective: development of risk assessment biomarkers

Epigenetic signatures reflect changes in the cellular environment and can also be found in the human circulatory system in case of several diseases (Ladd-Acosta 2015; Bhargava et al. 2018a). These signatures seem promising and can be explored to identify robust biomarkers to monitor clinical outcomes as well as early detection of diseases. An ideal biomarker should show a high degree of specificity and sensitivity and ease of measurement; it should also be capable of detecting a disease in its early stage (Byrnes and Weigl 2018). Although the plasticity of the human epigenome makes it difficult to establish true epigenetic marks for a particular condition, diverse diseases show alterations in their epigenetic signatures. A recent study reports that epigenetic alterations take place even on seasonality and weather influence (Ricceri et al. 2014; Xu et al. 2020). A significant number of studies have been conducted to understand the epigenome during cancer. The cancer-specific hypermethylation of CpG islands shows clinical importance (Jin et al. 2011; Wilhelm-Benartzi et al. 2011). Epigenetic marks, which are established as an effect of air pollution, can also be used as biomarkers for risk assessments for diseases associated with air pollution.

Methylation in DNA sequences has several advantages. DNA is a relatively stable molecule. It can be collected from a large number of sources and stored for a long time after being collected from patients. Moreover, DNA methylation is a widespread change throughout the cancer genome and hence many points in the genome can be used for the assay to generate highly predictive models (Huang et al. 2018a, 2018b; Tommasi et al. 2012). Sophisticated techniques such as methylation-specific PCR (MSP), mass spectrometry-based methylation detection (EpiTYPER), MethyLight, and pyrosequencing etc, allow determination of the methylation state of a specific DNA location even from a minimum sample volume (Olkhov-Mitsel and Bapat 2012). This makes it feasible to evaluate the diagnostic and prognostic potential of the methylation state of a large number of DNA sequences for many cancer types. The Cancer Genome Atlas project (TCGA) provides a platform for information regarding DNA methylation changes in cancers (Lee 2016). A case control study in 2008 utilized a series of methylated genes to predict disease recurrence after surgery in Stage I lung cancer patients. The promoter hypermethylation of just four genes—CDH13, RASSF1A, APC, and CDKN2A (p16) was reported to predict tumor recurrence, thus establishing a link between

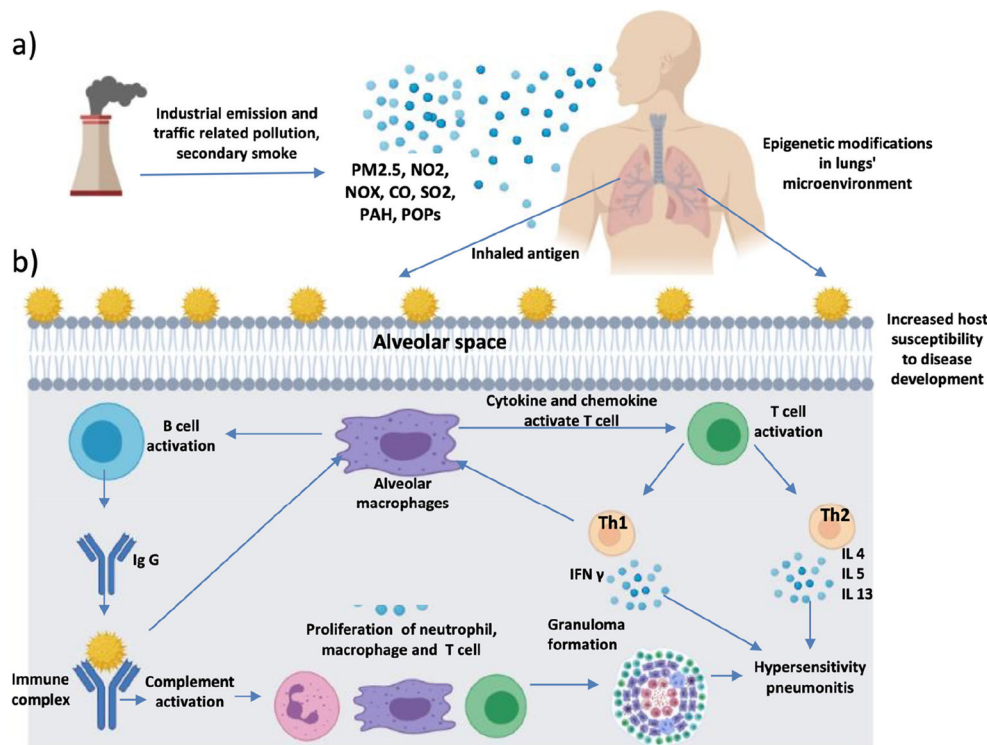


Fig. 2 Mechanism showing HP development by increasing host susceptibility through air pollution exposure. a) Emission of industrial and traffic-related air pollution. Pollutants reach the alveolar spaces in the lungs and induce epigenetic changes in the lungs’ microenvironment, thereby influencing host susceptibility to disease development. b) The interaction between the causative antigen deposited in alveolar spaces and the circulating IgG antibody forms precipitating antigen-antibody immune complexes in interstitial spaces.

Immune complexes trigger activation of both complement and pulmonary macrophages. Activated macrophages secrete the cytokines IL-1 and TNF- α that promote adhesion of leukocytes to activated endothelium. Complement activation enhances vascular permeability and attracts inflammatory cells. As a consequence of recruitment and activation, inflammatory cells release toxic mediators that promote acute lung injury, which eventually leads to HP development

gene methylation and tumor recurrence in lung cancer patients (Brock et al. 2008). This study established that the epigenetic status of tumors plays a critical role in clinical outcomes as well as in determining the aggressiveness of tumor development. MGMT (O6-methylguanine-DNA methyltransferase)-promoter methylation has been used to determine the treatment response among patients with glioblastoma (Butler et al. 2020). MGMT is a DNA-repair enzyme, and the efficiency of DNA repair in cancer cells plays an important role in therapeutic resistance. Thus, MGMT inactivation can sensitize such cells to therapeutic drugs (Verbeek et al. 2008). Many other epigenetic changes have started to emerge as predictive markers for the response to chemotherapy. BRCA1 hypermethylation is common in breast and ovarian cancers (Esteller et al. 2000). It has been found that BRCA1 methylation status can predict chemosensitivity and treatment response to cisplatin (Stefansson et al. 2012). The methylation of GSTP1 and MLH1 also predicts therapeutic outcomes in many cancer types (Shivapurkar and Gazdar 2010). Another oncogene, KRAS is itself capable of mediating epigenetic alterations, which are essential for cell transformation. KRAS has been found to promote DNA methylation by facilitating the recruitment of DNMT1 in the promoter regions of

the specific genes (Serra et al. 2014). In H-Ras-transformed rat fibroblasts, MMP2 and clusterin gene expressions are suppressed by promoter DNA hypermethylation (Lund et al. 2006).

Aberrant histone modifications can also be utilized as predictive biomarkers to evaluate the progression and treatment outcomes in cancers. A significant number of proteins that regulate histone modifications are themselves mutated in tumors. The polycomb group protein Enhancer of Zeste 2 (EZH2) acts as a critical regulator in prostate cancer development. EZH2 is involved in chromatin silencing by methylating histone3 on lysine27 (H3K27me3). EZH2 has been found to be overexpressed in metastatic prostate cancer, and tumors that express a higher level of EZH2 are associated with poorer prognosis (Gan et al. 2018; Liu et al. 2019). In addition, EZH2 overexpression has shown poor clinical outcomes in other cancers such as esophageal cancer, breast cancer, head and neck cancer, and glioblastoma (He et al. 2010). Lysine-specific demethylase 1 (LSD1) is another histone-modifying protein, which is linked with cancer development. LSD-1 removes the mono- and di-methyl groups from H3K4 and functions as a transcriptional repressor (Majello et al. 2019). The role of LSD1 in breast cancer has not been clearly

established. A study has shown that inactivation of LSD1 by both genetic and pharmacological approaches leads to aggressiveness in luminal breast cancer, while another study shows that LSD1 mediates chemoresistance in the disease (Verigos et al. 2019; Hu et al. 2019).

Bioinformatics, as a new emerging discipline, combines mathematics, information science, and biology and helps answer biological questions. There are several bioinformatics tools for DNA methylation analyses, but only a few platforms can correlate DNA methylation and gene expression for customized analyses. Several bioinformatics tools like COHCAP (Warden et al. 2013), PiIL tool (Moghadam et al. 2017), ViewBS (Huang et al. 2018a, 2018b), correlate DNA methylation with gene expression. MethHC databases can also be utilized to visualize DNA methylation and gene expression on a web platform (Huang et al. 2015). MethGET is another web-based bioinformatics platform that correlates genome-wide DNA methylation and gene expression (Teng et al. 2020). The Gene-Ontology (GO) database provides a useful tool to analyse the functions of all dysregulated genes (Harris et al. 2004). Database for Annotation, Visualization, and Integrated Discovery (DAVID) is another online bioinformatics tool that provide biological meaning behind gene profile (Dennis Jr et al. 2003). In addition to that, Reactome also provides intuitive bioinformatics tools for visualisation, interpretation and analysis of pathways associated with genes (Fabregat et al. 2017).

We anticipate that this review will provoke further investigation on the potential association between HP and air pollution, considering epigenetic modifications as a potential threat by which air pollution exerts its effect on disease development. It would be useful to identify a set of predictive biomarkers to assess the risk factors for the development and progression of the diseases associated with air pollution. However, in this review article we did not explore whether air pollution directly affects our genome by generating novel mutation, deletion, DNA breakage or chromosomal aberrations. We also did not discuss the genetic and immunological basis of HP development, although it could be crucial to understand the impact of air pollution in disease pathogenesis and may lead to the development of novel biomarkers to assess the risk of HP development due to air pollution.

Conclusion

The adverse effect of air pollution on our health is a matter of increasing concern. PM and other chemicals associated with air pollution pose various disease risks through both genetic and epigenetic alterations. Although the link between environmental exposure and disease risk due to epigenetic modifications is clearly established, little is known about the signaling pathways that connect the pollutants to the epigenome. Here

we summarize the air pollutants that are associated with epigenetic modifications linked with increasing risk factors for several diseases. This discussion prompts the question whether these epigenetic changes could be utilized as risk assessment biomarkers for specific diseases associated with air pollution. Further research may identify more robust epigenetics marks that are associated a particular disease induced by specific pollutants. Moreover, such modifications may pass through several generations and predispose an individual to disease risks even without any direct exposure. These epigenetic alterations may serve as biomarkers for disease susceptibility for the next generation.

Recently, it has been indicated that HP is associated with ambient air pollution. Pollution-mediated epigenetic changes in HP is yet to be explored. Such changes may sensitize the immune system, thereby making individuals susceptible to developing HP when exposed to the causative agents. Future research may use the findings of this paper to more comprehensively understand HP pathogenesis as well as to develop biomarkers for early detection and disease prognosis.

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