Environmental Research 197 (2021) 111155

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

Epigenetic related changes on air quality

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ARTICLE INFO

Keywords:
Epigenetic
Particulate matter
Air pollution
Health
Human diseases
Epigenetic mechanisms

ABSTRACT

The exposure to airborne particulate matter (PM) increases the risk of developing human diseases. Epigenetic mechanisms have been related to environmental exposures and human diseases. The present review is focused on current available studies, which show the relationship between epigenetic marks, exposure to air pollution and human's health. Air contaminants involved in epigenetic changes have been related to different specific mechanisms (DNA methylation, post-translational histone modifications and non-coding RNA transcripts), which are described in separate sections. Several studies describe how these epigenetic mechanisms are influenced by environmental factors including air pollution. This interaction between PM and epigenetic factors results in an altered profile of these marks, in both, globally and locus specific. Following this connection, specific epigenetic marks can be used as biomarkers, as well as, to find new therapeutic targets. For this purpose, some significant characteristics have been highlighted, such as, the spatiotemporal specificity of these marks, the relevance of the collected tissue and the specific changes stability. Air pollution has been related to a higher mortality rate due to non-accidental deaths. This exposure to particulate matter induces changes to the epigenome, which are increasing the susceptibility of human diseases. In conclusion, as several epigenetic change mechanisms remain unclear yet, further analyses derived from PM exposure must be performed to find new targets and disease biomarkers.

1. Introduction

Human needs and activities along their whole history have resulted in the abuse of natural resources to improve their quality of life by making a more practical and productive lifestyle. This abuse has led to an impact in the environment and air quality, which is being worse because of a greater air pollution and causing an imbalance in the ecosystem (Shukla et al., 2019). Air (with all its components) is constantly in contact with humans and directly involved in breathing. This daily contact with air and its contents, increases the contingency of damage to healthiness and it does not distinguish between age, gender, social-status or education level (Hernández-Escamilla et al., 2015).

Epidemiological studies have associated the impact of air pollution with a higher mortality rate due to non-accidental, cardiovascular and respiratory deaths (Huang et al., 2018). Air pollution causes more than 350,000 bronchial, tracheal or lung cancer deaths globally, in 2017, as shown by the Global Burden of Disease Study (GBD, 2017) Results (Available from http://ghdx.healthdata.org/gbd-results-tool). Remarkably, the risk of lung cancer is positively correlated with the air pollution levels, and the mortality of this type of cancer related to with air pollution levels is higher in regions with elevated air contamination (Brauer et al., 2016; Loomis et al., 2013). For example, in Xuanwei and Fuyuan, which are located in the Yunnan province (southwest of China), present a high incidence of lung cancer caused by indoor and outdoor airborne polycyclic aromatic hydrocarbons (PAHs) due to coal combustion (Lv et al., 2009; Xiao et al., 2012). The Environment Protection Agency (EPA) has set National Ambient Air Quality Standards for six principal pollutants (carbon monoxide, lead, nitrogen dioxide, ozone, sulfur dioxide and Particulate Matter), which are called "criteria" air pollutants (NAAQS Table | Criteria Air Pollutants | US EPA). Particulate Matter (PM) is being widely investigated and it increases the impact on air quality and therefore on human's health.

Understanding most diseases requires a multifactorial approach, addressing genetic, epigenetic, stochastic, and environmental factors.

While genetics has the study of genes as its main objective, epigenetics deals with the study of their expression (i.e. the creation of proteins from the instructions within genes). For didactic purposes, DNA has traditionally been compared to an encyclopedia in which genes contain the instructions of life, with epigenetics determining whether or not the different sections of the encyclopedia are possible to be read

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https://doi.org/10.1016/j.envres.2021.111155
Received 17 November 2020; Received in revised form 12 March 2021; Accepted 7 April 2021
Available online 21 April 2021

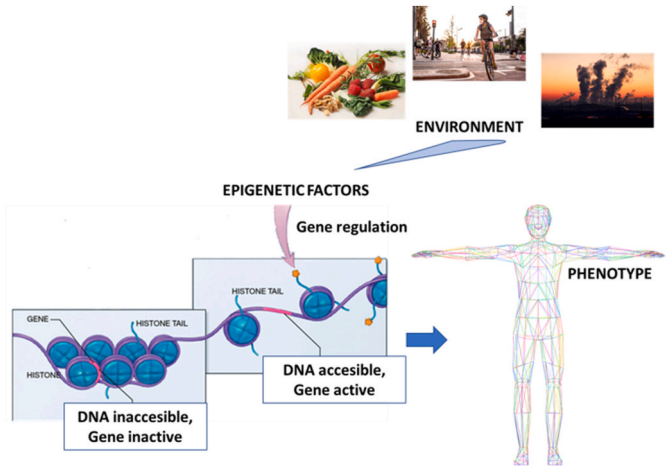

Fig. 1. A model of the connections between environmental and epigenetic factors in the gene expression regulation, resulting in a specific phenotype.

(Fig. 1).

In this work we will pay special attention to epigenetic alterations produced by exposure to air pollution.

2. Particulate matter and health

PM is the term used for a mixture of liquid and solid particles suspended in the air. It is composed by any type of particle (organic or inorganic) including dust, dirt, soot or smoke. Some of these particles are large enough to be detected with the naked eye, but others are very small, and they can be only detected with a precise technology, such as an electron microscope. PM also includes some other biological components as endotoxins, bacteria, pollen, fungal spores and viruses (Cevallos et al., 2017). The composition of the particulate material will determine its effects on health; for example, anthropogenic particles tend to be more harmful than natural ones.

These particles are divided into three principal categories based on their diameter: There are coarse particles (PM10) with a diameter between 2.5 and 10 μm; Fine particles (PM2.5) with a diameter less than 2.5 μm; And the last groups known as ultrafine particles (PM0.1), with a less than 0.1 μm diameter (Cevallos et al., 2017; Hernández-Escamilla et al., 2015). Exposition to these contaminants is linked not only to respiratory diseases, but also to others such as, cardiovascular and neurological diseases. As PM diameter decreases, the risk of damage in an organism increases, both due to differences in composition (primary emissions from industrial sites and traffic mainly produce PM2.5) and also because smaller particles can penetrate further into the lungs (Kassomenos et al., 2012).

Additionally, fine and ultrafine particles can be incorporated into the bloodstream through alveolar capillaries causing lung and systemic inflammation (Fiordelisi et al., 2017). A PM2.5 and smaller is considered as an important risk (Hernández-Escamilla et al., 2015; Particulate Matter (PM) Basics | Particulate Matter (PM) Pollution | US EPA). Several biological mechanisms have been associated between PM and their effects over different human systems, such as the cardiovascular or respiratory. Indeed, PM induces inflammatory and immune responses, oxidative stress, mutagenicity and cancer, heart rate variability and changes in gene expression (Mukherjee and Agrawal 2018; Thompson 2018).

Focusing on the cardiovascular system, the inhalation of PM causes distinct events, from acute to chronic cardiovascular effects, so that they may occur within hours or days after exposure, especially to PM2.5 in people with aging and previous coronary or heart diseases (Fiordelisi et al., 2017). Accordingly, acute exposure to PM has been significantly associated with an increase in myocardial infarction risk (Mustafić et al., 2012) and atrial fibrillation (Link et al., 2013). Moreover, chronic exposure to PM has been analyzed in 11 cohorts participating in the European Study of Cohorts for Air Pollution Effects (ESCAPE). They have found that long term exposure to PM is related to a higher frequency of coronary events (Cesaroni et al., 2014).

In terms of the respiratory system, the particles that reach the lung parenchyma remain there for years, determining various pulmonary chronic diseases (Siroux and Crestani 2018). These effects of PM in the pathogenesis of pulmonary diseases include infectious diseases, chronic obstructive pulmonary disease (COPD) and other reduction of their functionality as idiopathic fibrosis (Losacco and Perillo 2018). Apart from cardiovascular and respiratory effects caused by PM exposure, there are some recent meta-analyses, which have found a strong association between PM2.5 exposure and neurological disorders, such as Alzheimer (Fu et al., 2019; Tsai et al., 2019). This opens a new field of study, but this review will focus on both cardiovascular and respiratory diseases caused by PM exposure and related to with epigenetic changes.

3. Epigenetics, adaptation and disease

The epigenome is conceived as the heritable changes during cell division that do not modify the DNA primary sequence. Thus, it alters the phenotype without genotype modifications. This nuclear information controls cellular functions, development and tissue differentiation processes. Briefly, epigenetic mechanisms or marks regulate gene activation or gene suppression needed for cell activities and the adaptation to changing environments. These mechanisms are modified by internal or external factors, such as, genome sequence, lifestyle, aging, environmental exposure and disease. But, at the same time, they participate in the pathogenesis of several pathologic conditions. As previously mentioned, the environment and lifestyle alter epigenetic marks, thereby predisposing/to different pathologies throughout life. Most epigenetic marks are reversible, so, unlike what occurs in the genome, the epigenome varies. Epigenetic mechanisms are influenced by both, the environment and disease. Hence, the environment can cause diseases through epigenetic changes. Also, the environment induces changes in epigenetic marks through disease processes (Feinberg 2018). In other words, the relationship may be: environment > epigenetic-changes > disease or environment > disease > epigenetic-changes.

A remarkable property of the epigenome is that these marks have a spatio-temporal specificity, so that, epigenetic patterns vary across tissues. In addition, variations in the metabolism of the same tissue are guided by changes of the epigenetic mechanisms. Therefore, the cell or tissue to study environmental influences must be carefully chosen and relevant to the specific factor studied.

Epigenetic marks can be analyzed in a global view or also locus-specific. Thus, genome-wide studies are mostly used to relate a specific phenotype to with a variation by searching in the entire human genome. Whereas, locus-specific studies are focused on a specific variation related to the aim of identifying its association with an observable trait. Furthermore, another strategy used for example by Fraga and collaborators, is a large cohort of monozygotic twins' analyses. They have shown that different phenotypes originate from the same genotype by altering epigenetic marks (Fraga et al., 2005).

Epigenetic marks are stable and heritable through cell division. Also, several studies have confirmed that environmental factors can influence the epigenome of offspring during pregnancy. However, it is still unclear whether epigenetic marks are truly heritable through generation in humans, thus escaping the demethylation waves (Cantone and Fisher 2013; Zeng and Chen 2019).

Environmental factors have been widely related to epigenetic alterations and at the same time associated to certain pathological conditions. External conditions impact over the epigenome throughout the whole life and during pregnancy in the utero. Maternal nutrition has been associated with influencing the epigenome later in lifetime. The

first study providing evidence for the relationship between early-life environmental conditions and epigenetic changes in humans was performed in the Dutch Famine Birth Cohort. It consisted in the study of individuals who were prenatally exposed to hunger during the Dutch Hunger Winter (1944–1945). This study shows that these individuals present specific epigenetic alterations, predisposing to a high body mass index and an insulin resistance, 60 years later (Heijmans et al., 2008).

Similarly, several studies have demonstrated the influences of maternal smoking during pregnancy (Knopik et al., 2012). Suter and collaborators have proven that specific CpG sites, associated to a transcription factor binding element, were hypomethylated in smokers. This hypomethylation is directly related to a higher placental gene expression of CYP1A. They conclude that prenatally smoking exposure significantly diminishes DNA methylation at a transcription factor binding element, which increases placental CYP1A1 expression (Suter et al., 2010). Moreover, the same group has have studied the transcriptome and methylome of prenatally smoking exposures. They showed an altered placental site-specific CpG methylation at different sites that produce differential gene expression and cause a reduction in infant birth weight, among smokers (Suter et al., 2011).

When focusing on postnatal external factors, the impact of environmental influences are also easily observed. Cigarette smoking has been widely related to Chronic Obstructive Pulmonary Disease (COPD) through the epigenetic regulation of genes involved in the pathogenesis of this disease and its complications, such as, lung cancer. For instance, cigarette smoking induces the hypermethylation of the GCLC promoter, causing its downregulation and the initiation and progression of COPD (Cheng et al., 2016). Similarly, an altered DNA methylation pattern contributes to distinct cancer development providing a connection between smoking and gene expression variations pointing to cancer progression. There are several published manuscripts proving the smoking-epigenetics-cancer interconnection (Callahan et al., 2019; Conway et al., 2017; Zhang et al., 2016).

Thus, epigenetics mechanisms link environmental factors to with genome information, by regulating gene expression activity and consequently cell functions. An altered epigenetic pattern could be found in both, environmental and/or pathologic conditions.

4. Epigenetic mechanisms and human diseases

Among epigenetic mechanisms there are three main groups, including DNA methylation, post-translational histones modification (PTMs) and non-protein coding RNAs (ncRNAs). These mechanisms impact gene activity acting at different levels of the genetic code: at the chromatin packaging level; at the pre-transcriptional as marks that either allow or inhibit transcription; And at the post-transcriptional level, by modulating protein translation.

PTMs regulate chromatin packaging and DNA methylation marks regulate the transcription, so that both are crucial for controlling pre-transcriptional processes. The methylation of cytosines at gene promoters is particularly important. In general, promoter methylation tends to inhibit gene transcription, whereas promoter demethylation tends to activate gene expression. In general, ncRNAs have been related to with post-transcriptional processes. However, there is a big family of ncRNAs transcripts which are also involved in the genome integrity and other pre-transcriptional processes, as described below.

These mechanisms are essential for cell differentiation during its development and for the maintenance of their gene-expression profiles. They do not play a role in an independent manner, but they interact one with another so that they are closely related. For example, DNA methylated CpG sites of a specific loci could be associated with a concrete histone mark which is repressing the gene expression of a Non-Coding RNA. Principal functions and interactions between all epigenetic marks are summarized in Fig. 2. In addition, commonly used terms and definitions in epigenetics are shown in Table 1.

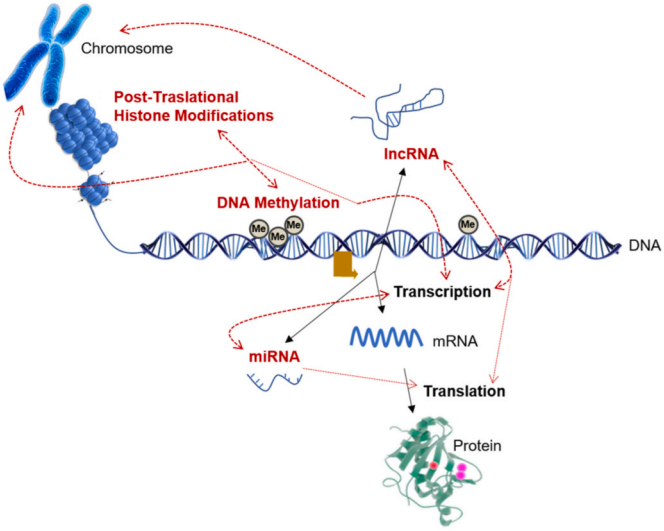

Fig. 2. Principal functions and interactions between epigenetic marks.

Table 1
Commonly used terms and definitions in epigenetics.

Terms	Definition
DNA methylation	DNA methylation consists in a covalent addition of a methyl group at the 5-carbon of the Cytosine (5-methylcytosine). It almost occurs in cytosines that precede a guanine, called CpG site.
CpG islands	Short CpG rich DNA sequences that break the pattern significantly from the average genomic basis.
Histone	Proteins which are bound to the DNA and are therefore influencing chromatin conformation and gene transcription.
Nucleosome	Basic functional unit of the chromatin, composed by 147 nucleotides of DNA wrapped around a histone octamer.
Post-translational Histone Modifications (PTMs)	Histones are chemically modified in their N and C tails by different types of enzymes, and thereby regulating chromatin's state. These covalent modifications consist in phosphorylation, methylation, acetylation, ubiquitylation or sumoylation of their aminoacids.
Chromatin	Chromatin is the basis of a chromosome, composed of DNA, RNA, and protein, which is found in the nucleus of eukaryotic cells.
Noncoding RNAs	Functional RNA molecules that are transcribed but not translated into proteins. They are classified as short noncoding RNAs (<200 nucleotides) and long noncoding RNAS (>200 nt).
Locus	A locus is a fixed position on a chromosome at which a gene, mutation or other genetic marker is located.
Genomic Imprinting	Genomic imprinting is a genetic process where a specific genomic domain is marked pointing out its parental origin. This process is performed by DNA methylation marks or by interactions with proteins and RNA molecules. It must be maintained after each cell cycle.
Transcription factors	Transcription factors are proteins involved in the transcription process. Thus, transcription factors are involved in the gene expression regulation.

4.1. DNA methylation

DNA methylation consists of the covalent addition of a methyl group in the 5′-position of the cytosine ring. It almost occurs in cytosines which precede a guanine, denominated as CpG sites. This CpG sites are abundant in singular regions of the genome such as, gene promoter regions.

These regions with a high density of CpG sites are known as CpG islands. DNA methylation is a dynamic process, for cells to have a biochemical machinery with enzymes able to methylate DNA and other enzymes involved in the demethylation of DNA. Depending on their methylation degree and their specific localization in the genome, gene expression activity is activated or deactivated. However, whereas the methylation of many regions changes through the life span, others tend to be rather stable. A particular case is that of imprinted genes, which remain methylated or unmethylated depending on the origin of the gametes, either paternal or maternal.

Moreover, DNA methylation marks are tissue and state-specific, so that each tissue has a different methylation profile, but also an altered profile can be found in the same tissue because of environmental or pathologic conditions (Varley et al., 2013). Hence, environmental factors affect several cell types at the same time, which cause alterations in the chromatin structure and DNA methylation marks aiming to a modified gene expression pattern (Dor and Cedar 2018). That is the reason why external factors (e.g. diet, trauma, pollution, lifestyle or disease) may produce specific DNA methylation patterns through various mechanisms such as, hormone concentrations (Reizel et al. 2015, 2018), obesity or caloric restriction (Gensous et al., 2019; Horvath et al., 2014; Maegawa et al., 2017), among others.

These characteristics make DNA methylation useful for human diagnosis, for example in cell-free DNA (cfDNA). Dead cells with different tissue of origin release DNA fragments (cfDNA) into blood, which can be used as a valuable diagnostic tool (Dor and Cedar 2018). Thus, cfDNA is being used to identify fetal chromosome aberrations in maternal plasma (Christina Fan et al., 2012) or in non-invasive detection of transplanted organ rejection (Snyder et al., 2011). Moreover, the analysis of tissue-specific methylation patterns in cfDNA can be used to detect particular tissue cells with an elevated specificity in several human diseases (Lehmann-Werman et al., 2016).

4.2. Post translational histone modifications

Histones are basic proteins with positive charges that allow them to interact with the DNA sequences, which present negative charges. They are chemically modified in their N and C tails by different types of enzymes, and thereby regulating chromatin's state. The most common modifications are acetylation and/or methylation of lysine and arginine and phosphorylation of serine and threonine residues. However, there are also other modifications, including ribosylation, ubiquitination and sumoylation of lysines. Additionally, methylation marks are especially complicated because they may appear in three different forms, as mono-, di- or trimethyl for lysines and mono or di-methyl for arginines. Among all modifications, some of them promote gene expression (H3K27ac and H3K4me1), while other marks repress gene expression (H3K9me3 and H3K27me3) by changing the chromatin state to an 'opened state' that permit the union of specific transcription factors or a dense state, respectively (Kouzarides 2007).

Numerous enzymes are implicated in these post translational histone modifications (PTMs), which are firmly regulated and very dynamic. PTMs are related to both fast and slow effects on the cellular functions, in return to nutrients, hormones, environmental factors, cell cycle, cell differentiation or many other physiological conditions (Fan et al., 2015). An altered pattern of PTMs may be related to pathological conditions including cancer (Chrun et al., 2017), pulmonary diseases (Sundar et al., 2014) and neurodegeneration (Cobos et al., 2019), among others.

4.3. Non-protein-coding RNAs

RNA molecules that are not translated into proteins are known as non-coding RNA (ncRNA). They are classified in two main groups. Long non-coding RNAs (lncRNA), which exceed 200 nucleotides in length, and small ncRNAs that are those with less than 200 nucleotides.

Small ncRNAs can be further classified into different subgroups depending on their origins and mechanisms of action. Nevertheless, the most studied class of small ncRNAs are micro RNAs (miRNAs) which are single stranded RNA molecules with about 20–23 nucleotides. They are very important gene expression regulators and contribute to control several physiological cell processes (Ghildiyal and Zamore 2009). More than 2000 miRNAs have been reported in humans and a half of them are transcribed from non-protein-coding genes, in humans. Known miRNAs are expected to regulate a third of all genes of the genome. Therefore, this type of ncRNAs is involved in cell development, differentiation and metabolism. Alterations related to their gene expression (hyper- or hypo-expression), have been associated with different human diseases (Hammond 2015; Iswariya et al., 2019).

However, lncRNAs are transcribed RNAs that are not translated into proteins because they do not have a protein coding sequence. They are longer than 200 nucleotides in length. LncRNAs were originally thought to be transcriptional noise and defined as 'junk' DNA. However, several studies support their critical role in the chromatin structure regulation and gene expression processes in the cell. LncRNAs have the characteristic of being tissue specific and of a specific cellular state, so that their gene expression is different in distinct tissues and it is also different in variable states of the same tissue. They are classified into various types according to their location with respect to the nearest protein coding gene, so that, they can be classified as: sense, antisense or intergenic (Jarroux et al., 2017; Yao et al., 2019). LncRNAs have distinct mechanisms of action, for example, they may act as guides between DNA, RNA and proteins, as scaffolds in protein complexes or as molecular decoys (Balas and Johnson 2018). The aberrant expression of these transcripts has been linked to multiple human diseases and that is the reason why lncRNAs are being used as both disease biomarkers and as potential therapeutic targets (Beermann et al., 2016; Boon et al., 2016).

5. Particulate matter and epigenetic mechanisms

5.1. DNA methylation

Particulate matter exposure and associated DNA methylation changes have been widely studied in both, the epigenetic alteration occurring in PM-related disease and epigenetic alteration linking PM exposure and disease development. Numerous studies have analized connecting proofs between long- and short-term PM exposure on different life stages and DNA methylation alterations. The most vulnerable life stages are pregnancy, childhood and old age when considering PM exposure and DNA methylation changes. These changes affect several biological mechanisms and consequently human's health (Ferrari et al., 2019). In terms of preconception, some systematic review has assessed the impact of air pollution on semen quality. They summarized that most studies support that outdoor air pollution affects at least one of the four most used semen quality parameters (Jurewicz et al., 2018; Lafuente et al., 2016). These sperm affections due to air pollution have been related to a sperm DNA hypermethylation in mice studies (Yauk et al., 2008). Additionally, environmental pollutants have been found to be probably a cause of Premature Ovarian Insufficiency (Vabre et al., 2017) and once more some studies are reporting the epigenetic changes related to these female gametes alterations due to air pollution (Menezo et al., 2019). However, there are not exist any studies that relate PM female gametes insufficiency and DNA methylation. Hence, further studies should be done in this field. Nevertheless, several studies relate PM and DNA methylation changes during pregnancy. A particular study shows the association between ambient air pollution (PM10) with differences in placental DNA methylation levels by using a Whole-genome DNA-methylation analysis in the placenta of 668 newborns from the EDEN cohort. They showed 27 differential methylated regions significantly connected with air pollutants exposure (Abraham et al., 2018). Moreover, another meta-analysis proved that several significantly differentially methylated sites and/or regions are linked to prenatal PM exposure, especially in particular genes, which were

previously implicated in lung-related outcomes (Gruzieva et al., 2019). Interestingly, Nawrot and collaborators identified some DNA methylated sites altered in the placental CLOCK due to PM2.5 exposure, which might affect fetal development (Nawrot et al., 2018). The same group used data from the Environmental Influence On Early Ageing (ENVIRONAGE) birth cohort. They focused their DNA methylation study over the promoter of DNA repair and tumor suppressor genes and confirmed that prenatal exposure to PM is directly associated with DNA methylation alterations in key DNA repair and tumor suppressor genes, compromising fetal and neonatal DNA repair capacity (Neven et al., 2018).

Focusing on the postnatal effects of PM on the epigenome, the DNA methylation changes are more relevant when considering childhood and old age, rather than adulthood. However, the major part of studies conducted nowadays are focused on adults (excluding the elderly). The reason is because samples from adult populations are generally easier to recruit than newborns or children (Ferrari et al., 2019). These studies are almost distributed depending on the affected tissue or certain human diseases. Practically, respiratory and cardiovascular deficiencies in which this review is focused on.

When centering on human respiratory alterations, the Foxp3 promoter region was found to be significantly more methylated (hypermethylated) in asthma. This also occurs after 90 day period, in blood samples, so that Foxp3 promoter was significantly hypermethylated after the exposure of PM2.5, as well as NO2 and CO exposures (Prunicki et al., 2018). Some human cohort studies have analyzed the blood-derived DNA methylation in long-term exposures to PM and other contaminants. The 454 Italian and 159 Dutch participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) study found some CpG sites differentially methylated in fine PM exposures, but the highest methylation changes in adults were associated with exposure to higher ambient outdoor concentrations of NO2 and NOx (Plusquin et al., 2017). However, the DNA methylation analysis related to with fine particulate matter in three populations (KORA F3, KORA F4 and the Normative Aging Study) disclosed that the pathways associated to the PM-related CpG sites differentially methylated are exposing adverse health effects through DNA methylation variations (Panni et al., 2016). At the same time, an epigenome-wide study about Korean chronic obstructive pulmonary disease cohort identified 12 differentially methylated positions and 27 differentially methylated regions associated with PM10, with enriched metabolic pathways related to cardiovascular and respiratory diseases. They conclude that the impact of long-term air pollution exposure can be used as potential air pollution biomarkers (Lee et al., 2019).

However, following the same strategies, there are several examples of published evidence associating PM exposures with epigenetic changes in cardiovascular alterations. Along the way a new association between fine PM exposure and DNA methylation levels in purified monocytes was found. This opened new insights into molecular mechanisms underlying this connection in atherosclerosis (results from the Multi-Ethnic Study of Atherosclerosis (MESA)) (Chi et al., 2016). Furthermore, a randomized, double-blind, crossover trial among 36 healthy young adults was performed in Shanghai to scrutinize the impact off short-term PM2.5 on DNA methylation levels. They determined that PM2.5 exposure is linked to DNA methylation variations causing adverse alterations in cardiometabolic diseases (Li et al., 2018a).

It is important to note that these human cohort studies analyze blood samples and as we showed before the epigenetic marks are very tissue and state specific. Thus, many relevant alterations are not elucidated because of the tissue studied. That is the reason why multiple PM exposure experiments must be done in cell lines (in vitro) and animal models (in vivo) studies. In vivo studies permit to obtain other tissues such as –the directly affected organs, like such as lungs or heart. Hence, the inflammatory response and lung toxicity of PM2.5 could be analyzed for example in mice or rats. The PM exposure can be assured due to direct intratracheal instillation. Moreover, DNA methylation and gene expression analyses are performed on the tissue of interest (lungs). In addition, some studies use human cell lines, such as, human bronchial epithelial cells (BEAS-2B) to investigate the alterations in vitro (Shi et al., 2019). The previous study demonstrated DNA methylation and gene expression variations after PM2.5 exposure directly involved in pulmonary toxicity and pathological processes.

The epidemiological evidence of human diseases and possibly related molecular mechanisms in their progression need to be rigorously confirmed through in vitro and in vivo investigations (Cho et al., 2018).

5.2. Histones

Histone marks have also been related to PM exposure, which cause altered patterns of these marks, from early life exposure (prenatally) to adult state. An analysis performed with data from the Environmental Influence on Aging (ENVIRONAGE) birth cohort study from pregnancies related to a geographical PM2.5 exposure, exposed that trimethylated H3K4 and total histone H3 were incremented with gestational PM2.5 exposure. Thus, they affiliated ambient air pollution with cord plasma H3 alterations during early life, which seems to show that circulating histones are a risk factor in the development of air pollution-associated disease later in life (Vrijens et al., 2020). Some recent studies in mice models have implicated levels of acetylated histone 3 lysine 9 (H3K9ac) in GATA4 promoter region in the hearts of PM2.5 exposed female mice. They proposed that maternal exposure to PM2.5 cause cardiac injury in childness through histone modifications regulating the transcription factor GATA4 (Li et al., 2020; Wu et al., 2019). In an adult's lifetime an analysis has been performed with the Beijing Truck Driver Air Pollution Study data and they found that global histone H3 modifications are due to traffic-derived PM exposures (Zheng et al., 2017). Once again, previous human studies were performed with blood tissue samples. Therefore, some in vitro and in vivo studies focusing on other cell tissues are described below.

Histone H4 acetylation after PM10 exposure has been found in an in vitro study, concretely, in A549 cells (human alveolar basal epithelial cell line) after 24 h with PM10 exposure in the media. This treatment enhanced acetylated histone 4 (H4) levels in the promoter region of the IL-8 gene and thereby increasing IL-8 release. These data show a histone remodeling mechanism (Histone acetylation) in PM10 mediated responses in epithelial lung cells (Gilmour et al., 2003). Furthermore, ultrafine PM exposure (PM0.1) gives rise to NF-κβ inflammatory responses, which implicates epigenetic modifications, such as, an increase in H3K4me3, H3K9me3, H3K9me27, H3K9me36, and H3K79me3 levels of human lymphocytes (Bhargava et al., 2019). Additionally, aiming to get closer to human in vivo conditions without the direct implication of human healthiness, Leclercq and collaborators have differentiated primary human bronchial epithelial cells derived from normal subjects (NHBE) or sensitive chronic obstructive pulmonary disease (COPD)-diseased patients (DHBE) and exposed them repeatedly to PM2.5. They found specific epigenetic changes including histone H3 modifications (i.e., H3K4me3, H3K9ac, H3K27ac, and H3S10 ph). The genetic and epigenetic changes they found were already described in distinct pulmonary diseases. However, they have found all these similar epigenetic events following repeated exposure of air pollution-derived PM2.5 (Leclercq et al., 2017).

Despite all the clinically and epidemiologically provided evidence providing evidences of PM-derived epigenetic changes and health effects, in vitro and in vivo studies are still needed to provide new involved cell tissue mechanisms. Thus, as shown above there are many studies focused on cell lines and mice models to find the closest mechanisms involved in human pathologic conditions.

5.3. Non-protein-coding RNAs

The transcriptome is a step beyond below in the genetic code when compared with the previous epigenetic marks (DNA methylation and

post-translational histone modifications). It shows the expression of specific cell in each state. However, the transcriptome is a very complex system with protein coding and non-protein coding genes, which interact with each other as well as with other epigenetic marks, to regulate both transcription and translation activities. Moreover, depending on their type, non-protein coding RNAs have several molecular mechanisms. That is the reason why this review will focus on some evidence relating PM-derived respiratory alterations to with small and long ncRNAs, independently But not on their specific mechanisms and pathways.

In terms of lncRNAs, all published evidences are executed experimentally in cell lines, primary cells or animal models. There do not exist clinical or epidemiological human studies related to with lncRNA gene expression and PM-pollution. Some analyses have been performed with gene expression microarrays, for mRNA and lncRNAs, in human cell lines exposed to PM2.5. Particularly, in human bronchial epithelial cells (HBECs) exposed to arterial traffic ambient and wood smoke PM2.5, with the objective to look for new therapeutic targets for chronic obstructive pulmonary disease/s. They found numerous lncRNAs differentially expressed between the different groups, involved in diverse pathways (Li et al., 2018c). Similarly, to demonstrate the association with cardiovascular adverse effects, the expression patterns of a human endothelial cell line (EA.hy926) were analyzed after a treatment with PM2.5. They found several lncRNAs implicated in the PM2.5 toxicity, engaged in inflammatory processes and co-expression with other genes, suggesting that they can be used as new biomarkers in cardiotoxicity (Wang et al. 2018, 2019a; Wang and Tang 2019). Moreover, 885 lncRNAs were differentially expressed in lung tissues of PM2.5 exposed BALB/c Mice with a higher pulmonary inflammation score (Zhong et al., 2019b).

In addition, PM2.5 exposure causes cell cycle arrest, at G2/M phase, in human bronchial epithelial cells (16HBE) mediated by lncRNAs LINC00341 gene expression. Furthermore, after LINC00341 knockdown PM2.5-induced G2/M phase cell cycle arrest and p21 expression is reversed, suggesting that this lncRNA is implicated in the cell cycle arrest mediated by PM2.5 exposure (Xu et al., 2017). There are many other interesting mechanisms discovered by different authors. As an example, Deng and collaborators showed the toxicological effects of PM2.5 in lung cancer cells progression and metastasis. They demonstrated that internalized PM2.5 in lung cancer cells upregulates loc146880 expression through reactive oxygen species (ROS), and that loc146880 is further related to with autophagy. Thus the downstream sequence is that PM2.5 exposure activate ROS generation, which activates loc146880 gene expression, initializing autophagy processes in lung cancer (Deng et al., 2017).

In line with the lncRNA studies There is plenty of miRNAs evidence relating PM2.5 to these transcriptome changes. Almost all miRNA studies associated with PM consist of cell lines or animal model experiments. However, there is a pilot study in old older population, where 800 miRNAs were analyzed in 22 randomly selected participants from the Normative Aging Study cohort. Interestingly, it consisted of the analysis of extracellular vesicle encapsulated miRNAs (evmiRNAs) isolated from serum samples. They found a significant association between long-term ambient PM2.5 exposures and the levels of multiple evmiRNAs circulating in serum, which are affiliated to cardiovascular diseases pathways such as, oxidative stress, inflammation, and atherosclerosis (Rodosthenous et al., 2016). These evmiRNAs can be used as biomarkers, for therapeutic strategies and the miRNA underlying mechanisms in diverse pathologies (Liu et al., 2018).

In addition, another study was implemented in 55 healthy students, in Shanghai. It consisted of a double-blind randomized crossover study with air identical purifiers, except for the removal of the filter in the sham group. Air purifiers were used to reduce indoor PM2.5 pollution for two weeks, to analyze later the gene expression of 10 serum cytokines and possibly related miRNAs. They suggest that effects of PM2.5 on cardiovascular diseases are positively associated with the some cytokines expression (IL1, IL6, TNF, TLR2, F3 and EDN1), and negatively associated with miRNAs (miR-21–5p, miR-187–3p, miR-146a-5p, miR-1-3p, and miR-199a-5p) (Chen et al., 2018). Furthermore, there exist several in vitro studies and in vivo supporting miRNA roles in the cardiovascular (Wang et al., 2019b; Zhong et al., 2019a) and pulmonary (Li et al., 2018b; Zhou et al., 2018) effects caused by PM.

6. Future perspectives

Studies targeting epigenetic changes may likely find a place in the diagnosis and therapy of environmental driven disorders, such as, the above mentioned cardiovascular and respiratory diseases. Because of the epigenetic mechanisms specificity, the target tissue is very relevant to ensuring significant results. In the near future, more epigenome-wide studies have to be implemented in different tissues with a specific environmental exposure. Mice models exposed to certain PM will help to learn more about their affection in the respiratory and cardiovascular system. Whereas, human studies are very helpful to detect new blood markers of PM exposure. Subsequently, epigenome-wide studies must be replicated in locus-specific analyses on the target tissues. The knowledge generated in this area, will help us to find new genetic/epigenetic markers which could be the target for both, prevention or treatment therapies.

7. Conclusions

Overall, epigenetic changes have been highly associated with PM-derived effects on human's health. These epigenetic marks can be used as potential biomarkers, as therapeutic targets for disease and also to find other implicated genes, pathways or molecules involved in the disease processes. Because of their spatiotemporal specificity, it is important to consider the tissue collected for the study. Blood tissue is the preferred sample used for human exposure analyses due to the search for new biomarkers with non-invasive procedures. Specific tissue changes are usually experimented in certain cell lines derived from the tissue of interest, and in organs isolated from mice models. Epigenetic modifications or alterations are reversible, but some environmentally induced changes can be detected long time after the exposure. Thus, epigenome-wide analyses are the perfect connection between PM exposure and human cardiovascular and pulmonary diseases. From these studies new involved pathways and disease biomarkers are being found. However, several mechanisms remain unclear, so that further investigations must be performed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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