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Review

DNA methylation: A critical epigenetic mechanism underlying the detrimental effects of airborne particulate matter

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ABSTRACT

Exposure to airborne particulate matter (PM) does great harm to the health of human beings. To date, PM exposure has been closely associated with respiratory and cardiovascular diseases, as well as some types of cancer. As the associations of PM with the adverse health effects are well documented in literatures, the underlying mechanisms have not been completely clarified. With the field of epigenetics rising in recent years, PM-associated epigenetic alterations have gradually turned into the hot research topic. DNA methylation is one of the earliest-discovered and best-studied epigenetic mechanisms, of which the alteration can influence the transcription initiation of genes. A number of studies have been published to demonstrate that PM exposure is linked with DNA methylation patterns in the human genome. DNA methylation is the potential regulator of the biological effects of PM exposure. In the present review, DNA methylation related to PM exposure was elaborated on genome-wide and gene-specific methylation. In particular, genome-wide DNA methylation was composed of the alterations in global methylation content and genome-wide methylation profile; gene-specific methylation included the methylation changes in mechanism-related and disease-specific genes. Representative epidemiological and experimental studies were cited to elucidate the viewpoints, focusing on both PM-related methylation changes and the mediating effects of DNA methylation between PM and the health impacts. This review will provide advantageous clues for subsequent studies on the DNA methylation in relation to PM exposure.

1. Introduction

Airborne particulate matter (PM) is the most health-harmful substance among air pollutants, which is a complex mixture of many different chemical species deriving from a variety of sources (Colbeck and Lazaridis, 2010). PMs are highly variable in composition and particle size. The major compositions of PM are organic and elemental carbon, crustal elements, inorganic ions (such as sulfate, nitrate and ammonium), trace heavy metals (such as zinc, vanadium, and nickel), polycyclic aromatic hydrocarbons (PAHs), and particle-bound water (Cheung et al., 2011; Gao et al., 2018). PMs with an aerodynamic diameter less than 10 μm (PM_{10}) are defined as inhalable particles, which can penetrate deep inside the lungs (Pipal et al., 2011). In detail, PMs above 2.5 μm and below 10 μm can penetrate into the bronchi, while PMs below 2.5 μm ($PM_{2.5}$) are respirable and can get to the alveoli (Heyder, 1986). This property makes PM_{10} and $PM_{2.5}$ strongly bound up with human health and morbidity. Nowadays, the rising exposure levels of PM and the impacts on global health conditions have emerged as public concerns all over the world. Globally, according to the WHO report of ambient air pollution in 2016, approximately 84% of the assessed population around the world is exposed to PM_{10} or $PM_{2.5}$ of which the annual mean levels overstep the limits of the WHO air quality guidelines (World Health Organization, 2016). Furthermore, annual PM levels are estimated to have a global increase of 8% during the five-year period (2008–2013) in the assessed cities (World Health Organization, 2016). The Global Burden of Disease Study 2015 reported that the amount of deaths attributable to ambient particulate matter pollution increased by 7.8% to over 4 million from 2005 to 2015, while

Abbreviations: 5-mC, 5-methylcytosine; ACE, Angiotensin I converting enzyme; APEX, Apurinic/apyrimidinic endodeoxyribonuclease; BC, black carbon; CD40LG, CD40 ligand; EDN1, Endothelin 1; F3, coagulation factor III; Foxp3, Forkhead box protein 3; ICAM-1, Intercellular adhesion molecule-1; IFN-γ, Interferon-gamma; IL, Interleukin; LINE-1, Long interspersed nuclear element-1; MAPK, Mitogen-activated protein kinase; NF-κB, Nuclear factor-kappa B; OGG1, 8-oxoguanine DNA glycosylase; p16, Cyclin-dependent kinase inhibitor 2A; p53, Tumor suppressor p53; PARP1, Poly(ADP-ribose) polymerase 1; RASSF1A, Ras association domain family member 1A; SERPINE1, Serpin family E member 1; TNF-α, Tumor necrosis factor-alpha

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DALYs declined by 4.2% during the ten years (GBD, Risk Factors Collaborators, 2015, 2016). In addition, International Agency for Research on Cancer (IARC) has listed PM in outdoor air pollution as a confirmed human carcinogen (IARC, 2016). To date, exposure to PM is associated with a number of negative health effects mainly in respiratory and cardiovascular system (Hamra et al., 2014; Nelin et al., 2012; Ristovski et al., 2012). While the health impacts of PM are well described in the existing studies, the biological mechanisms mediating these impacts have not been fully elucidated.

Evidences are accumulating to demonstrate that epigenetic modifications play a role in environmental-exposure-associated detrimental health effects and adverse biological outcomes (Herceg and Vaissiere, 2011; Marsit, 2015). The epigenetics rising in recent decades has provided a new regulatory relationship among gene, gene product and phenotype, mainly including DNA methylation, histone modifications, chromatin remodeling and non-coding RNAs (Tammen et al., 2013). Among them, DNA methylation is an important mechanism which is studied earliest and most completely. It refers to the process of transferring the methyl to cytosine in CpG dinucleotide (5-mC), which is catalyzed by DNA methyltransferase, with s-adenosyl methionine (SAM) as the methyl donor (Singal and Ginder, 1999). Gene transcription can be prevented by DNA methylation through inhibiting the binding of transcription machinery or being recognized by repressors such as methyl-CpG-binding domain (MBD) family (Klose and Bird, 2006). DNA methylation is a dynamic and reversible process (Bhutani et al., 2011), which can be easily altered in response to exogenous stimuli. PMs have been shown to exert an impact on global gene expression profiling in human body, which is reflected by the changes in peripheral blood of exposed individuals and specific cell lines (Huang, 2013; Wang et al., 2005). Such disturbance in gene expression related to PM exposure is likely to be mediated by DNA methylation, which may further contribute to a variety of disorders in human organs and systems. Therefore, exploration on whether DNA methylation involves in the pathogenic process of PM holds great significance for the revelation of in-depth mechanisms beneath PM toxicity. In the present review, we summarized the scientific evidences of DNA methylation associated with PM exposure, focusing on both genome-wide and gene-specific methylation (Fig. 1).

2. Genome-wide DNA methylation and PM

The exploration of genome-wide DNA methylation in relation to PM exposure mainly include two aspects, the alterations in global methylation content and genome-wide methylation profile, respectively aiming at overall methylation status and PM-associated CpG sites.

2.1. Global methylation content alteration

Global DNA hypomethylation has been identified in the blood of subjects with cardiovascular disease and cancer (Robertson, 2005). Reduction of global methylation content has been associated with extensive alterations in gene expression and chromatin packaging, as well as the increase of genomic instability (Dean et al., 2005). However, the explicit mechanisms linking global DNA methylation to PM toxicity still remain unclear. In spite of this, global methylation changes can be treated as a kind of response of organisms or cells to various stimulations. To estimate the level of global DNA methylation, the methylation of repeated elements, LINE-1 and Alu, can be applied as surrogate markers (Yang et al., 2004). This approach has been adopted in most PM-related global methylation studies. In addition, the measurement of global 5-mC content is another accurate method, but seldom used.

2.1.1. Epidemiological studies on global DNA methylation

To date, whether exposure to PM can cause hyper- or hypomethylation all over the genome has not been settled. Baccarelli et al. (2009) found the decreased blood LINE-1 methylation which was significantly associated with exposure to higher $PM_{2.5}$ and BC for the time windows from 4 h to 7 days. Further in the same population, the increase in sulfate and BC exposures over 90 days were respectively associated with a decrease of 5-mC in LINE-1 and Alu, pointing to the influence of PM compositions (Madrigano et al., 2011). However, no significant association was observed in the 90-day $PM_{2.5}$ exposure with the repetitive element methylation. As to one-year average exposure, LINE-1 and Alu methylation in monocytes was not associated with $PM_{2.5}$ in the multi-ethnic study of atherosclerosis (MESA) (Chi et al., 2016). The fundamental cause of the distinct global methylation related to PM exposure of different time frames is obscure.

Moreover, the effects of occupational PM exposure on global methylation also reveal inconsistency with that of environmental exposure. In contrast with the above findings of different time frames, Tarantini et al. (2009) reported that methylation in both LINE-1 and Alu was negatively associated with PM_{10} exposure level among steel workers according to their long-term effect estimate. At the same time, methylation of LINE-1 and Alu showed no change after 3 days of work (Tarantini et al., 2009). Kile et al. (2013) found that either acute or chronic exposure to welding fume $PM_{2.5}$ was not associated with methylation in LINE-1 or Alu. Fan et al. (2014) found the positive correlation of welding $PM_{2.5}$ with blood methylation level of LINE-1.

A handful of relevant human trials have been carried out to demonstrate the impact of PM on global DNA methylation. In a crossover trial, fifteen healthy adult participants underwent 130-min exposure to fine concentrated ambient particles (CAPs), coarse CAPs, or HEPA-filtered medical air in randomized order, with a minimum 2-week washout period (Bellavia et al., 2013). This trial indicated that exposure

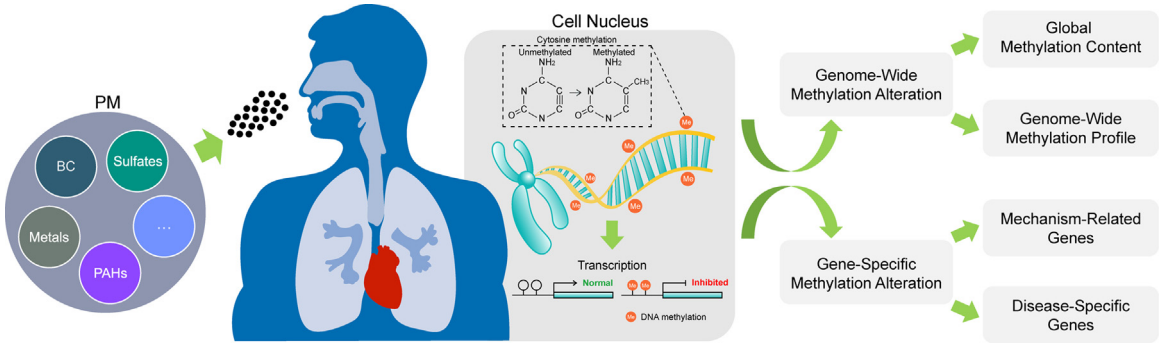

Fig. 1. Overview of DNA methylation alterations associated with PM exposure. Exposure to PM and its components such as BC, sulfates, metals and PAHs can result in disorders in respiratory and cardiovascular system, which may be mediated by DNA methylation. DNA methylation is an epigenetic mechanism which can inhibit the transcription of genes. PM-related methylation changes mainly include genome-wide and gene-specific methylation alterations. PM: Airborne particulate matter; BC: Black carbon; PAHs: Polycyclic aromatic hydrocarbons; Me: DNA methylation.