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Mini review

Convergence of air pollutant-induced redox-sensitive signals in the dendritic cells contributes to asthma pathogenesis

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HIGHLIGHTS

- Ambient particulate matter promotes asthma by targeting dendritic cells.
- This review summarizes the impact of particulate pollutants on dendritic cells.
- Inhaled particles induce oxidative stress in airway epithelial and dendritic cells.
- Redox-sensitive signals polarize dendritic cells towards T-helper 2 immunity.
- Airway epithelial cells mediate dendritic cell function through their own cytokines.

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ABSTRACT

Exposure to airborne particulate matter (PM) is a major risk factor for allergic airway inflammation such as asthma. Many of the PM components (i.e., polycyclic aromatic hydrocarbons and metals) are redox-active and capable of inducing cellular oxidative stress and injuries including inflammation and cell death. Airway epithelial cells and antigen-presenting dendritic cells (DC) are the major and direct targets of inhaled PM. The epithelial cells can further enhance the DC response to allergen and PM through several immune regulatory cytokines including thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. Among these cytokines TSLP is particularly relevant to the mechanisms by which particulate air pollutants contribute to asthma pathogenesis. Studies have found that TSLP released by PM-exposed human airway epithelial cells could polarize the DC towards a T-helper 2 immune response, which is one of the key immunological mechanisms in asthma pathogenesis. The convergence of regulatory signals generated by PM-induced oxidative stress in DC and the interactions among them may be one of the major mechanisms that are specifically related to the contribution of PM towards asthma pathogenesis.

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1. Introduction

A sudden surge in the level of ambient particulate matter (PM) has been associated with increased morbidity and mortality due to respiratory illness. It has been established by epidemiological evidence that exposure to PM is a major risk factor for the exacerbation of allergic airway inflammation such as asthma (Guarnieri and Balmes, 2014; D'Amato et al., 2010). Many PM components including polycyclic aromatic hydrocarbons (PAHs), quinones, and metals are redox-active and capable of generating reactive oxygen species (ROS) (Li et al., 2008; Jeng, 2010). Excessive accumulation of ROS can further result in cellular oxidative stress. To date, in vitro and in vivo studies have identified oxidative stress as one of the major mechanisms by which PM exerts its adverse health effects (Guarnieri and Balmes, 2014; Li et al., 2008; Viera et al., 2009). PM-induced oxidative stress can activate cellular inflammatory signaling pathways, alter cellular functions, and cause cell death in the respiratory and immune system; thereby, contributing to the pathogenesis and/or exacerbation of airway inflammatory diseases such as asthma (Guarnieri and Balmes, 2014; Kumar et al., 2013; Mazzoli-Rocha et al., 2010). In this review, we will discuss ROS generation by particle components, airway epithelial cell and antigen-presenting dendritic cell (DC) responses, and the convergence of these responses at the DC level as a potential mechanism by which PM contributes to asthma pathogenesis.

2. Generation of oxidative stress by PM components

Ambient particles are divided into three fractions based on their aerodynamic diameters. While the coarse and fine PM are $<10\ \mu m$ (PM_{10}) and $<2.5\ \mu m$ ($PM_{2.5}$) respectively, the aerodynamic diameter for ultrafine particles (UFP) is $<0.1\ \mu m$ (Heal et al., 2012). The major components that are responsible for the adverse respiratory effects of PM include organic carbon (OC) such as PAHs and quinones, metals (e.g., iron and copper), and endotoxin (Li et al., 2008; Mazzoli-Rocha et al., 2010; Araujo and Nel, 2009; Shiraiwa et al., 2012; Ghio et al., 2012; Totlandsdal et al., 2013). Many of the organic compounds and metals on the PM surface have strong oxidant potential and can produce ROS inside cells. ROS generated by PM components includes superoxide ($O_2^{\bullet -}$), alkoxy ($RO^{\bullet}$), peroxy ($ROO^{\bullet}$) and hydroxyl ($OH^{\bullet}$) radicals, hydrogen peroxide (H_2O_2), and hydroperoxides (ROOH). ROS accumulation and the subsequent oxidative stress, a result of decreased cellular antioxidant capacity, is a major underlying mechanism responsible for the adverse cardiopulmonary effects of ambient PM (Huang et al., 2015; Rui et al., 2015; Shen and Anastasio, 2012). One group of compounds that can directly produce ROS is the redox-active quinones. These quinones can undergo one-electron reduction catalyzed by NADPH cytochrome P450 reductase to form semi-quinones. The semiquinone is then converted back to the original quinone with concomitant generation of $O_2^{\bullet -}$. In addition, many PAHs can be converted to quinones through biotransformation involving cytochrome P450 1A1, epoxide hydrolase, and dihydro-diol dehydrogenase (Li et al., 2008). Transition metals (e.g., Fe, Cu, Co, Ni and Cr) can also generate ROS such as highly reactive $OH^{\bullet}$ inside cells via the Fenton reaction (Li et al., 2008; Bertazzi et al., 2014; Ghio and Cohen, 2005; Yi et al., 2014; Yang et al., 2014). Intracellular ROS accumulation induced by the organic compounds and metals can alter cellular redox homeostasis and lead to oxidative stress if it is not promptly restored.

That all three types of PM (coarse, fine and UFP) can induce cellular oxidative stress has been well documented. Electron spin resonance studies revealed that all of the possible sized PM fractions are capable of generating $OH^{\bullet}$ in suspension (Donaldson et al., 2003). Shen and Anastasio, (2012) have shown that H_2O_2 from fine and coarse PM is generated 30 times faster than $OH^{\bullet}$ in suspension, indicating that the time of ROS classification is pertinent to identifying the exact species that was generated. Furthermore, several PM constituents can contribute to ROS generation either intracellularly or through interactions among themselves and these constituents for each PM sized fraction vary from a day-to-day basis, even when the samples are collected from the same area (Huang et al., 2015; Rui et al., 2015; Yi et al., 2014; Rodriguez-Cotto et al., 2015). Due to the variability in PM constituents, even among the same size fraction, it is difficult to pinpoint the association between PM size and a specific type of ROS. A screening of the PM samples at question, revealing the possible combinations of the aforementioned constituents, will provide the best possible explanation as to what PM component is responsible for which form of ROS.

Cellular exposure to PM can lead to increased intracellular ROS and a decrease in the ratio of reduced to oxidized glutathione (GSH/GSSG) (Yi et al., 2014; Yang et al., 2014; Marchini et al., 2014). Mild oxidative stress can be alleviated by the activation of the antioxidant defense system that is mediated by the nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a transcription factor that is the master regulator of cellular antioxidant and detoxification enzymes. Several Nrf2-mediated antioxidant enzymes including heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase (NQO-1), and glutamate–cysteine ligase catalytic subunit (GCLC) can be effectively activated by pro-oxidative PM in human airway epithelial cells and macrophages (Totlandsdal et al., 2013; Li et al., 2004, 2013a; Val et al., 2011; Deng et al., 2013; Shinkai et al., 2013). However, when this protective mechanism fails, either due to a high level of oxidative stress that overwhelms the antioxidant response or a defect in the defense system, escalation of oxidative stress can lead to cellular injuries including inflammation and cell death (Li et al., 2008, 2013a; Manzo et al., 2010; Nel et al., 2006). For example, Manzo et al. (2010) have shown that healthy mouse airway epithelial cells were able to develop an antioxidant response to diesel exhaust particle (DEP)-induced oxidative stress by increasing HO-1 expression and thereby maintaining the ratio of GSH/GSSG and avoiding cellular injury, whereas the lack of this adaptive response in mildly inflamed cells led to significant cytotoxicity. In the same notion, Li et al. (2013c) reported that compared with their wild-type counterpart, Nrf2 knockout mice were much more susceptible to the adjuvant effect of ambient UFP on ovalbumin (OVA) sensitization and developed more severe allergic airway inflammation upon secondary OVA exposure.

3. Airway epithelial cells are a major target of PM

Airway epithelial cells, as the barrier of the respiratory system, are one of the major targets of inhaled particulate pollutants. Several studies using BEAS-2B as an in vitro system have shown that DEP-induced oxidative stress can activate redox-sensitive pro-inflammatory signaling pathways, including MAPK and NFκB, leading to increased expression of inflammatory cytokines/chemokines (e.g., IL-6, IL-8 and GM-CSF) (Totlandsdal et al., 2010, 2012, 2013; Wang et al., 2005; Tal et al., 2010; Li et al., 2013b; Baulig et al., 2009; Reibman et al., 2002; Ramgolam et al., 2008). The OC (e.g., PAHs and quinones) on DEP appears mainly responsible for these effects because they were only observed in the cells exposed to the crude DEP extract or quinone-enriched polar fraction (Wang et al., 2005). Moreover, Totlandsdal et al. (2013) compared DEP with contrasting PAH and metal content for their pro-oxidant and pro-inflammatory effects on BEAS-2B cells and found that the DEP with the highest PAH and lowest metal content had stronger oxidant potential and was more potent in activating p38 MAPK and inducing the expression of inflammatory mediators. A similar response has also been observed in the