

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 $<10\text{ }\mu\text{m}$ (PM_{10}) and $<2.5\text{ }\mu\text{m}$ ($\text{PM}_{2.5}$) respectively, the aerodynamic diameter for ultrafine particles (UFP) is $<0.1\text{ }\mu\text{m}$ (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 ($\text{O}_2^{\bullet-}$), alkoxy ($\text{RO}^{\bullet}$), peroxy ($\text{ROO}^{\bullet}$) and hydroxyl ($\text{OH}^{\bullet}$) 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 semiquinones. The semiquinone is then converted back to the original quinone with concomitant generation of $\text{O}_2^{\bullet-}$. In addition, many PAHs can be converted to quinones through biotransformation involving cytochrome P450 1A1, epoxide hydrolase, and dihydrodiol dehydrogenase (Li et al., 2008). Transition metals (e.g., Fe, Cu, Co, Ni and Cr) can also generate ROS such as highly reactive $\text{OH}^{\bullet}$ 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 $\text{OH}^{\bullet}$ 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 $\text{OH}^{\bullet}$ 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 NF κ B, 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

primary human airway epithelial cells. Tal et al. (2010) have shown that exposure of primary human airway epithelial cells to DEP with various OC content led to the activation of different signaling pathways that mediated IL-8 expression. The DEP with high OC content upregulated IL-8 gene expression through required AP-1 activation, whereas the same effect of DEP with low OC content involved a NF κ B-dependent mechanism. In the study assessing the impact of DEP on epidermal growth factor receptor (EGFR) expression Pourazar et al. (2008) showed that there was significantly more phosphorylated p38 and JNK in the bronchial epithelium of DEP-exposed healthy subjects compared to the control. The findings from DEP studies are corroborated by the evidence from research using PM from other sources (e.g., ultrafine carbon black particles and PM_{2.5} from wood burning process or urban areas) and in other types of airway epithelial cells (Reibman et al., 2002; Kim et al., 2005; Corsini et al., 2013). Studies on the cellular effects of wood smoke by Corsini et al. (2013) showed that similar to DEP, PM_{2.5} generated during wood combustion increased IL-8 production in human lung epithelial cell line A549; this effect could be completely blocked by p38 MAPK inhibitor. In the study by Reibman et al. (2002) it has been demonstrated that ambient quasi-UFP (<0.18 μ m) collected in New York City could increase the phosphorylation of ERK and p38 and this was required for the upregulation of GM-CSF in normal human bronchial epithelial cells (NHBE).

There has been increasing evidence showing that airway epithelial cells play a major role in regulating immunity through three major cytokines: thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 (Lambrecht and Hammad, 2014a,b). Among these cytokines TSLP is particularly relevant to the mechanisms by which PM contribute to the pathogenesis of asthma (Bleck et al., 2008, 2010, 2013; Segawa and Hirasawa, 2014; Hallstrand et al., 2014; Nakamura et al., 2008). A number of studies have revealed that environmental agents (e.g., DEP, cigarette smoke and aromatic chemical compounds) can increase TSLP expression in airway epithelial cells through a mechanism involving oxidative stress and activation of NF κ B and AP-1 (Bleck et al., 2008, 2010; Segawa and Hirasawa, 2014; Takai, 2012). Bleck et al. (2008, 2010) have shown that both DEP and ambient PM_{2.5} could increase TSLP expression in primary human bronchial epithelial cells (HBEC), which was accompanied by increased intracellular ROS production. The effect of these particles on TSLP could be strongly suppressed by the presence of antioxidant N-acetyl cysteine (NAC) indicating the involvement of oxidative stress. Another trigger for TSLP production is the disruption of the barrier function of the airway epithelium (Lambrecht and Hammad, 2012). Previously we have reported that ambient UFP, which had extremely high PAH content and strong oxidant potential, could penetrate into mitochondrion and cause its structural damage (Li et al., 2003). Thus, in addition to intracellular oxidative stress generated by the redox-active compounds on the particles, PM-induced epithelial cell injury (e.g., disruption of tight junction) may also increase TSLP production (Caraballo et al., 2011, 2013). One mechanism by which TSLP regulates the immunity is mediated through its interaction with the antigen presenting DC; this has been shown to play a key role in asthma pathogenesis (Lambrecht and Hammad, 2014a; Ziegler, 2012).

4. Antigen presenting DC as a major target of PM

Another major target of PM is DC, which plays a central role in regulating the immune response. PM can directly modulate the co-stimulatory molecule expression as well as interfere with the function of DC through the generation of oxidative stress. Exposure of bone marrow-derived dendritic cells (BMDC) to residual oil fly ash (ROFA) induced DC maturation along with increased

expression of co-stimulatory molecules (MHCII, CD40, CD80, CD86 and CD14) and IL-12p70 production. Oxidative stress played a role at least in part in the effect of these particles because ROFA-induced CD40 expression could be inhibited by NAC (Arantes-Costa et al., 2014). Environmentally persistent free radicals had similar effects in increasing the expression of functional molecules on BMDC along with a significant decrease of intracellular GSH/GSSG, a direct indicator of cellular oxidative stress (Wang et al., 2011). Studies assessing the effect of DEP on BMDC phenotype have shown that in addition to its suppressive effect on lipopolysaccharide (LPS)-induced DC maturation, DEP interfered with the T-helper 1 (Th1) priming of DC by inhibiting LPS-induced IL-12 production (Chan et al., 2006; Braun et al., 2010; Matthews et al., 2014). This led to a cytokine milieu that favored a T-helper 2 (Th2) response (Chan et al., 2006; Braun et al., 2010; Ohtani et al., 2005). Ambient particles (PM_{2.5} and UFP) also have a direct effect on DC (Li et al., 2013c; Williams et al., 2008). Williams et al. (2008) have shown that direct exposure of BMDC to the ambient PM_{2.5} collected in a major urban area resulted in a significant increase in intracellular H₂O₂ and the gene expression of Nrf2-mediated antioxidant enzymes including glutathione cysteine ligase and HO-1. These particles also up-regulated the expression of functional molecules on the DC surface as well as the production of several cytokines involved in allergic and inflammatory responses (i.e., IL-12p40, IL-6, IL-10, TNF α , and VEGF).

Toll like receptor (TLR) signaling plays an important role in regulating DC function and the subsequent T cell response (Iwamura and Nakayama, 2008; Schroder and Arditi, 2007). Several studies have demonstrated that environmental pollutants affect the DC response through interference with TLR-regulated signaling pathways. Porter et al. (2007) have shown that DEP could down-regulate TLR2 and TLR4 expression on human peripheral blood progenitor cell-derived DC, which led to a mixed pattern of T cell activation with increases in both Th1 (IFN γ and IL-12) and Th2 (IL-13) cytokines. The effect of DEP on DC TLR may be related to its OC content. For example, Chan et al. (2006) have reported redox-active organic DEP extract could inhibit LPS-induced DC surface molecule expression and IL-12p40 production through mechanisms involving the Nrf2-mediated protective pathway and NF κ B activation. Besides its inhibition on TLR4-regulated LPS effects, DEP extract also down-regulated CD86 expression and IL-12p40 production induced by TLR2 and TLR3 ligands. Moreover, ambient PM_{2.5} has also been found to down-regulate TLR2 and TLR4 expression on human DC, resulting in a Th2-like cytokine pattern with decreased IFN γ /IL-13 ratio in the coculture of DC and allogeneic naïve T cells (Williams et al., 2007a,b). These findings suggest that the suppression of TLR signaling followed by the down-regulation of MyD88 may be one of the major mechanisms by which PM weakens the innate immunity and creates a milieu that favors Th2 polarization (Schroder and Maurer, 2007).

Taken together, evidence to date clearly indicates that PM can directly interfere with the functions of both airway epithelial cells and DC, and PM-induced oxidative stress is one of the major mechanisms involved in both processes.

5. PM-induced redox-sensitive responses in the respiratory and immune systems converge in the DC

Communications between airway epithelial cells and DC through TSLP are considered one of the major mechanisms for the Th2 immune response; a key immunological basis of asthma (Lambrecht and Hammad, 2012; Ziegler and Artis, 2010; Liu, 2006, 2007). The importance of TSLP in asthma pathogenesis has been demonstrated by both human and cellular studies (Lambrecht and Hammad, 2012; Ziegler and Artis, 2010; Liu, 2006, 2007; Froidure et al., 2014; Shikotra et al., 2012). Patients with severe asthma have

increased TSLP expression in their airways, and genetic variants in TSLP may contribute to the susceptibility to asthma in urban populations (Shikotra et al., 2012; Liu et al., 2011). In the presence of cellular injury, danger signals, or allergens, TSLP is produced by airway epithelial cells (Lambrecht and Hammad, 2014a). Currently there is limited information on how signals generated by airway epithelial cells, upon contact with inhaled air pollutants, are passed to the immune system to contribute to asthma pathogenesis. Emerging data strongly suggest that TSLP may be a key regulator that links airway epithelial cells to the immune system for the pro-allergic effects of air pollutants. Bleck et al. (2010) have previously presented clear evidence demonstrating that both DEP and ambient PM could increase TSLP by HBEC through mechanisms that include oxidative stress. Subsequent dissection of the mechanisms led Bleck et al. (2013) to suggest that several regulatory pathways, which may converge on NF- κ B, are likely to be responsible for this effect. Moreover, through the action of TSLP DEP-treated primary HBEC increased the expression of OX40L and Jagged in DC, leading to a Th2 response in an allogeneic mixed lymphocyte reaction as evidenced by a significant increase in the ratio of IL-5/IFN γ . Using antioxidant NAC it was demonstrated that this bronchial epithelial cell–DC–T cell response axis was mediated through a process regulated by ROS (Bleck et al., 2010). In addition

to regulating DC via airway epithelial cell-derived TSLP, particulate pollutants can directly interfere with the phenotype and function of DC as discussed above (Li et al., 2013c; Arantes-Costa et al., 2014; Chan et al., 2006; Matthews et al., 2014; Williams et al., 2008; Bleck et al., 2006; de Haar et al., 2008; Riedl, 2008). Not only can the deficiency in Nrf2-regulated antioxidant defense enhance these effects, it can also create an intrinsic predilection to a Th2-favoring cytokine profile under resting conditions; characterized by a low level of IL-12p70 and a high level of IL-6 (Li et al., 2013c; Williams et al., 2008). Allergic sensitization by adoptive transfer of BMDC that are pulsed by OVA and pro-oxidative UFP led to significantly enhanced allergic airway inflammation compared to the animals sensitized by the DC exposed to OVA alone (Li et al., 2009, 2013c).

Thus, upon inhalation exposure the DC receives two sets of regulatory signals derived from redox-active PM; one set comes from the airway epithelial cells via TSLP and the other is directly from the particles. These signals may have an additive or synergistic effect in activating signaling pathways that skews DC toward priming a Th2 response. Moreover, Th2 cytokines (e.g., IL-4 and IL-13) and antibodies produced during allergic inflammation (e.g., IgE) can also increase TSLP production, therefore, forming an amplification cycle of the Th2 response (Takai, 2012). Increase of other redox-sensitive inflammatory

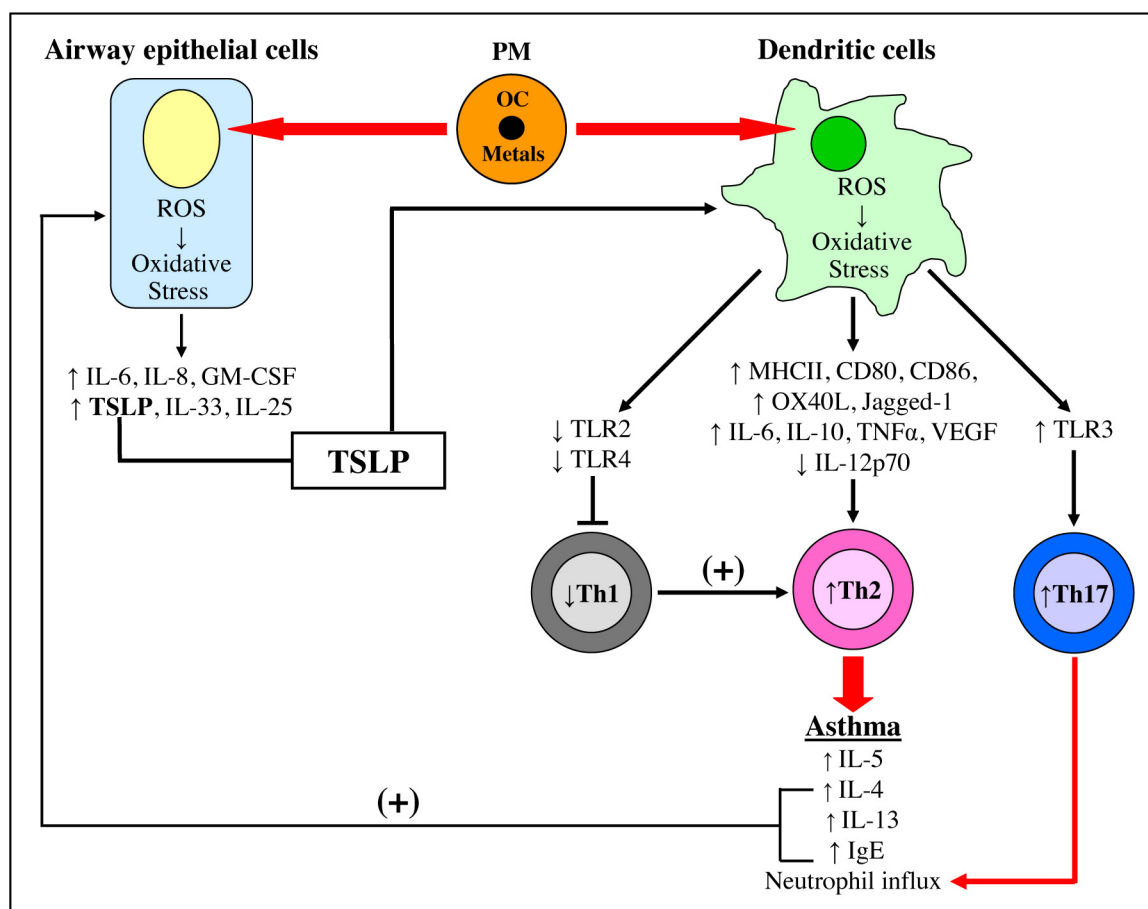


Fig. 1. PM contributes to asthma pathogenesis through its direct and indirect effects that converge in DC. PM directly interferes with DC function by increasing the expression of surface functional molecules (i.e., MHCII, CD80 and CD86) and the production of cytokines involved in the allergic and inflammatory response (i.e., IL6, IL10, TNF α and VEGF). It can also interfere with the Th1 priming of DC by suppressing LPS-induced IL-12p70 response. The indirect effect of PM on DC is mediated through TSLP. TSLP released by PM-exposed airway epithelial cells increases the expression of OX40L and Jagged-1 on DC, resulting in Th2 polarization. Th2 cytokines (e.g., IL-4 and IL-13) and antibodies (e.g., IgE) can further increase TSLP production by airway epithelial cells, resulting in an amplification cycle. In addition, a combination of TSLP and TLR3 ligand may enhance the ability of DC to prime a Th17 response. Both direct and indirect effects of redox-active PM on the immune system are mediated by mechanisms involving cellular oxidative stress. The Th2 polarization and the suppression of Th1 priming, together with increased local inflammatory mediators (e.g., IL-6, IL-8 and GM-CSF) produced by airway epithelial cells may provide an explanation to the association between ambient PM and asthma.

mediators (e.g., IL-6, IL-8 and GM-CSF) can strengthen the local inflammation, further contributing to the promoting effect of particulate air pollutants on asthma (Fig. 1).

Altered interactions between DC and T cells play an important role in asthma associated with PM exposure. One mechanism that has been identified by several studies is the inhibition of the Th1 response by PM-exposed DC, which is likely caused by the direct down-regulation of TLR signaling (Chan et al., 2006; Porter et al., 2007; Williams et al., 2007a,b). The suppression of the Th1 response favors Th2 polarization; thus, leading to the development and exacerbation of asthma. Moreover, weakened innate immunity also reduces an individual's ability to fight viral infection, which has been identified as one of the major triggers for asthma exacerbation (Yoo et al., 2013). Not only can PM alter Th1/Th2 balance, it has also been shown to promote the Th17 response. Wang et al. (2011) have reported that combustion-generated environmentally persistent free radicals could induce oxidative stress in DC, up-regulate their surface functional molecule expression, and induce a Th17 response. Tanaka et al. (2009) showed that human CD11c⁺ DC pulsed by TSLP and TLR3 ligand are significantly more efficient in priming naïve CD4⁺ T cells to differentiate into Th17-cytokine-producing cells compared to the DC pulsed by TLR3 ligand or TSLP alone and this action took place without interfering with the development of the Th2 response. In addition to their interactions with T cells, DC can also affect IgE production by B cells. Braun et al. (2010) have demonstrated that exposure of immature DC to highly polluted DEP led to the loss of their ability to suppress IgE isotype switching in co-cultured B cells. Collectively, PM-induced changes in DC can have a multifaceted effect on the immunological mechanisms involved in the pathogenesis and exacerbation of asthma (Fig. 1).

6. Conclusion

It has been established that allergens and PM are the two major risk factors for asthma. PM promote asthma pathogenesis or exacerbation by acting as an adjuvant for allergen-induced sensitization or enhancing the inflammatory response during allergen re-exposure. At the cellular level, signals generated by redox-active PM components (i.e., OC, PAHs and metals) can impact not only the airway epithelial cells per se, but also the DC either via the epithelial cytokine TSLP or through a direct effect on DC. The convergence of the direct and indirect effects of PM is likely a set of key signals responsible for the Th2 immune response observed in asthma that is linked to air pollution exposure. Currently, there is limited information on how inhaled particulate pollutants interfere with the immune response through TSLP. Further detailed studies focusing on redox-sensitive interactions between airway epithelial cell-derived mediators (e.g., TSLP) and DC may help to develop preventive and therapeutic strategies for air pollution-associated asthma pathogenesis and exacerbation.

Conflict of interests

The authors declare that they have no conflicts of interests.

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