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Review

Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles

Peter Møller*, Pernille Høgh Danielsen, Dorina Gabriela Karottki, Kim Jantzen, Martin Roursgaard, Henrik Klingberg, Ditte Marie Jensen, Daniel Vest Christophersen, Jette Gjerke Hemmingsen, Yi Cao, Steffen Loft

Department of Public Health, Section of Environmental Health, University of Copenhagen, Øster Farimagsgade 5A, DK-1014 Copenhagen K, Denmark

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ABSTRACT

Generation of oxidatively damaged DNA by particulate matter (PM) is hypothesized to occur via production of reactive oxygen species (ROS) and inflammation. We investigated this hypothesis by comparing ROS production, inflammation and oxidatively damaged DNA in different experimental systems investigating air pollution particles. There is substantial evidence indicating that exposure to air pollution particles was associated with elevated levels of oxidatively damaged nucleobases in circulating blood cells and urine from humans, which is supported by observations of elevated levels of genotoxicity in cultured cells exposed to similar PM. Inflammation is most pronounced in cultured cells and animal models, whereas an elevated level of oxidatively damaged DNA is more pronounced than inflammation in humans. There is non-congruent data showing corresponding variability in effect related to PM sampled at different locations (spatial variability), times (temporal variability) or particle size fraction across different experimental systems of acellular conditions, cultured cells, animals and humans. Nevertheless, there is substantial variation in the genotoxic, inflammation and oxidative stress potential of PM sampled at different locations or times. Small air pollution particles did not appear more hazardous than larger particles, which is consistent with the notion that constituents such as metals and organic compounds also are important determinants for PM-generated oxidative stress and inflammation. In addition, the results indicate that PM-mediated ROS production is involved in the generation of inflammation and activated inflammatory cells can increase their ROS production. The observations indicate that air pollution particles generate oxidatively damaged DNA by promoting a milieu of oxidative stress and inflammation.

Contents

* Corresponding author at: Section of Environmental Health, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5A, Building 5B, 2nd Floor, DK-1014 Copenhagen, Denmark. Tel.: +45 3532 7654; fax: +45 3532 7686.
E-mail address: pemo@sund.ku.dk (P. Møller).

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1. Introduction

Epidemiological studies have indicated associations between exposure to ambient air particulate matter (PM) and increased mortality from cardiopulmonary diseases [1–3], including lung cancer, chronic obstructive lung disease and myocardial infarction. The concept that especially small size particles generate inflammation by oxidative stress has been used as a paradigm of the mechanism of action of particle-mediated health effects [4,5]. This concept has gained wide acceptance as mechanism of action for other types of particles such as nanomaterials and oxidatively generated biomolecules, recruitment of leukocytes and cytokine signaling are becoming standard tools in the hazard identification of various types of particles [6–8]. In addition, it has been suggested that the dose–response relationship between exposure to poorly soluble particles and pulmonary toxicity had two different thresholds where the first one was defined as a "dosimetric threshold" related to macrophage-mediated clearance and the second was a "mechanistic threshold" that was related to the inability of the antioxidant defense system to counterbalance the production of reactive oxygen species (ROS) by inflammatory cells [9]. This is in keeping with the hypothesis of a stratified hierarchical (three-tier) response where oxidative stress occurs at three levels with adaptive responses at first level and where inflammation does not occur unless the second level is reached, whereas cell death relates to the third level [10]. However, other researchers have regarded PM-mediated inflammation and oxidative stress as more independent phenomena [11–13]. It has actually been difficult to pinpoint whether inflammation, oxidative stress, or DNA oxidation products occur at the lowest dose threshold in animal and human studies. ROS production can increase rapidly after exposure to PM, whereas inflammation develops over time, suggesting that oxidative stress may come first during a bolus exposure to high doses of PM. This has been demonstrated in cultured cells where increased ROS production could be detected within 0.5–1 h of air pollution PM exposure, whereas increased secretion of cytokines was observed at 16–24 h of exposure [14–17]. It takes some time for DNA lesions to accumulate to a level that can be distinguished from the background levels of DNA damage by the methods that are typically used in particle toxicology. It means that oxidatively generated DNA lesions are typically measured at time points when inflammation also occurs. Thus, it is difficult to tease out whether the genotoxicity is caused by inflammation or oxidative stress. It has been proposed that PM-mediated DNA oxidation damage could originate from primary (ROS-mediated) or secondary (inflammation-mediated) pathways [18]. This concept has been further developed to distinguish two types of "primary genotoxicity" (characterized by the absence of inflammation) with PM-mediated ROS production either directly from the material or by activating endogenous ROS production by the target cells, or from "secondary genotoxicity" that depends on the ROS production of activated inflammatory cells [19–21]. The level of oxidatively damaged DNA may also depend on the DNA repair activity. Transition metals may damage proteins by direct oxidation, which may be associated with decreased DNA repair activity. In addition, the activity of DNA repair enzyme may be inhibited by some metals in PM. This effect has typically been attributed to non-cytotoxic concentrations of nickel(II), cobalt(II), cadmium(II) and arsenic(III) because they inhibit DNA repair activity in vitro [22]. However, carcinogenic metals such as cadmium(II), arsenic(III), and chromium(VI) have multiple effects on redox regulation and cell signaling [23]. It means that it is difficult to distinguish between effects of oxidative stress and inhibition of DNA repair enzymes in studies on metal-generated DNA damage.

In this review we have assessed whether PM-mediated oxidative stress, inflammation and DNA damage are independent phenomena, generated by a common cause (i.e. PM), or if there is a sequence of inter-related events potentially differing in a translational context from cell culture to human population. Fig. 1 outlines three possible relationships where DNA oxidation damage is a secondary phenomenon to ROS production or inflammation. It is possible that either PM-mediated oxidative stress stimulates inflammation (Relationship A) or PM-mediated inflammation causes oxidative stress (Relationship B). However, it is also possible that PM causes both oxidative stress and inflammation by different mechanisms of action (Relationship

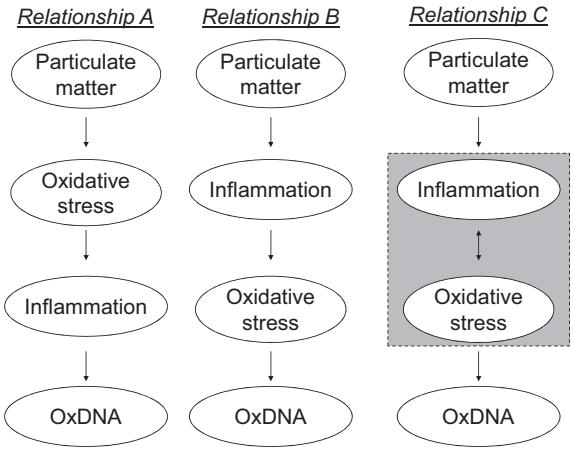

Fig. 1. Relationship between exposure to particulate matter (PM) and generation of oxidative stress, inflammation and DNA oxidation damage (OxDNA).