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Editorial

Particulate Air Pollution and Chronic Obstructive Pulmonary Disease: The Role of Protein Oxidation

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Editorial

Chronic Obstructive Pulmonary Disease (COPD) is an important worldwide public health issue. Cigarette smoking and air pollution have been considered to be risk factors for developing COPD; however, there is a paucity of studies investigating the role of particulate matter (PM)-oxidised protein in patients with COPD and the damage to protein degradation systems. Here, the gaps in environmental health and clinical research will be discussed and we will provide novel insights into the role of PM in COPD.

Increasing epidemiological and clinical evidence has led to heightened concerns over the potential deleterious effects of particulate air pollutants on human health. Particulate air pollutants [e.g., PM of ≤ 2.5 μm aerodynamic diameters ($PM_{2.5}$) are associated with increased hospital admissions and mortality due to pulmonary and cardiovascular diseases [1]. For example, COPD is associated with exposure to air pollution [2]. Air pollution is one of the risk factors for COPD; however, its exact role in the development of COPD is difficult to demonstrate. Its physiological effects on lung function have been studied only since the nineties in long and tedious cohort studies. The report of Schikowski and colleagues (2013), who showed chronic effects of air pollution on the prevalence and incidence of COPD, was revealing [3]. Kumar *et al.* (2013) observed that the risk of acute exacerbation of COPD increased by 2.3% with a unit increase in exposure to $PM_{2.5}$, and the exposed groups (who experienced exposure to $PM_{2.5}$ >15.4 μg/m^3) were 54% more likely than the reference group to be admitted for acute exacerbation of COPD [4] action of particle constituents capable of reaching the systemic circulation on the vasculature [5]. The lung is the primary port of entry for airborne agents; therefore, Oxidative stress and inflammatory reactions were thought to be common biological mechanisms resulting from the inhalation of particulate air pollutants. Difficulties arise from the heterogeneity of air pollution (gas and particles); thus, respiratory effects must be examined for every component separately and in different populations. It is also necessary to determine the short and long term effects of particulate air pollution in view of the fact that physiological, clinical and toxicological effects occur from childhood through to adulthood. These factors make it difficult to obtain statistically significant results. Nevertheless, the majority of studies appear to point to a role for air pollution in the development of COPD via oxidative stress; however, further studies are required to confirm the exact consequences of each component of air pollution, such as PM, on the respiratory tract.

Toxicological experiments of controlled exposure to animals or humans show that several biological mechanisms may be affected by the inhalation of PM into the pulmonary environment, such as oxidative stress and systemic inflammation, alterations in autonomic balance and also the direct clearance of deposited foreign materials from the lung is critical for whole-body defence. Furthermore, most diseases associated with PM exposure are initiated within the respiratory system. Seaton and colleagues (1995) demonstrated that particles deposited in the lung provoke low-grade alveolar inflammation and a secondary systemic inflammatory response that exacerbates pulmonary and cardiovascular conditions in susceptible individuals [6]. Lung inflammation is believed to occur in response to increased oxidative stress. Two principal pathways of inflammation occur following deposition of PM in the airways: the generation of pro-inflammatory cytokines by macrophage-governed phagocytosis [7] and the release of pro-inflammatory mediators from epithelial cells in response to macrophage-derived cytokines [8]. Moreover, lung epithelial cells may also phagocytose deposited PM and synthesise pro-inflammatory cytokines and chemokines that influence local and systemic inflammatory reactions [9].

COPD is characterised by air flow limitation, which is not fully reversible and by pathologic changes in the proximal and peripheral airways, lung parenchyma and pulmonary vasculature [10]. Chronic inflammation in COPD occurs structural modifications to and narrowing of the small airways. The destruction of the lung parenchyma, which is also caused by inflammatory responses, leads to the loss of alveolar attachments to the small airways. Smoking, an important risk factor for COPD, appears to cause an abnormal inflammatory response of the lung to PM, which plays an important role in COPD pathogenesis [11].

Oxidative stress is recognised as a major predisposing factor in the pathogenesis of COPD. Antioxidant capacity in COPD is substantially reduced due to cigarette smoke and consequent exacerbations, with oxidative stress persisting after the cessation of cigarette smoking or the occurrence of exacerbations due to the continued production of Reactive Oxygen Species (ROS) from endogenous sources. ROS act as intracellular second messengers as inflammatory stimuli induce micro-oxidative imbalances essential for cellular activation [12]. Carbonyl stress in the form of electrophilic carbonyls may also impact many different signalling pathways. Oxidative stress biomarkers and carbonyl stress in COPD include elevated concentrations of nitro tyrosine [13] and lipid per oxidation products an increase in carbonyl adducts indicates systemic exposure to oxidative stress in COPD [14].

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The continued presence of oxidative stress most likely arises from endogenous sources, such as mitochondrial respiration. In addition to the intracellular production of ROS, there are several extracellular sources that also directly or indirectly provoke oxidative stress. Many pollutants in ambient air are either free radicals or promote the synthesis of free radicals. For example, oxidative stress caused by PM and organics may arise from a combination of sources [15]. These free radicals attack tissue and cause cell injury (e.g., mitochondrial and DNA damage), cell death (e.g., necrosis and apoptosis) and increase tissue permeability [17]. Oxidative stress results in enhanced inflammatory responses and the phenotype of a rapidly ageing lung in COPD with increased risk of developing emphysema.

A major etiologic factor driving COPD is likely to be oxidative and carbonyl stress in the lungs following long-term exposure to cigarette smoke or combustion-derived products, such as those that occur following the burning of biomass. Oxidative stress arises from endogenous antioxidant defences that lead to carbonyl stress. Oxidative damage to the surrounding tissue leads to the formation of highly reactive organic molecules that can modify proteins non-enzymatically and that target specific peptide residues, such as lysines, arginines, cysteinesor histidines. The major outcome is the formation of reactive carbonyls and their reaction with proteins (to cause "protein carbonylation"). This accumulation of reactive carbonyls and subsequent protein carbonylation has been typically referred to as carbonyl stress, and it is associated predominantly with chronic disease and ageing.

Carbonylation and nitration reduce the activity and expression of the important transcriptional corepressor Histone Deacetylase 2 (HDAC2), which is essential for the suppression of activated inflammatory genes and the anti-inflammatory actions of corticosteroids. Loss of HDAC2 activity in COPD patients has been shown to lead to the loss of Nrf2 activity due to increased Nrf2 acetylation. Nrf2 acetylation decreases Nrf2 stability and expression. Protein oxidation and carbonylation may modify protein function, which leads to a disruption in normal cell function and physiologic mechanisms [18].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines reported that high levels of air pollution are harmful to individuals with existing heart or lung disease; however, the role of outdoor air pollution in causing COPD remains unclear [10,13] suggested that chronic effects of air pollution on the prevalence and incidence of COPD require further biological and mechanistic evidence despite long-term epidemiological associations [3]. Moreover, they suggested specific definitions of particular COPD phenotypes and that more refined and source-specific exposure assessments are required. Previous studies have shown oxidative and carbonyl stress in patients with COPD [17,19], and protein oxidation could be a biomarker of the severity of COPD. Previous studies have shown that exposure to cigarette smoke impairs proteasomal degradation of modified and misfolded proteins [20]. Therefore, investigation of mechanisms underlying PM-driven protein oxidation in COPD patients is an emgerency public health issue.

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