Review paper

The oxidative stress in emphysema and Chronic Obstructive Pulmonary Disaease (COPD)

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Abstract

The paper describes the current knowledge about the role of oxidative stress in the pathogenesis of chronic obstructive pulmonary disease and its role in the development of emphysema. The basic mechanisms leading to overproduction of free oxidant radicals in tobacco smokers' airways are underlined.

Key words: *COPD, emphysema, oxidative stress.*

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Introduction

Chronic obstructive pulmonary disease (COPD) has been defined as a disease characterized by progressive, not fully reversible, airflow limitation, associated with an abnormal inflammatory response of the lungs to noxious particles and gases, especially to tobacco smoke [1]. COPD is characterized by chronic cough due to excessive mucus production (chronic bronchitis) and/or alveolar destruction leading to increased airspaces, known as emphysema.

Emphysema is a pathologic term defined as the abnormal permanent enlargement of airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis [2, 3]. Emphysema may be associated with cigarette smoke–induced COPD. The exposure to tobacco smoke elicits a chronic inflammatory response which leads to the tissue destruction associated with pulmonary emphysema and chronic bronchitis [2, 3]. This inflammatory response is characterized by pulmonary infiltration, for the most part involving macrophages, neutrophils and CD8+ T cells [4]. Smoke – activated phagocytic cells are potent source of oxidants in the lungs.

Oxidative stress

Cigarette smoke may activate some of the molecular signaling pathways involved in cellular sensing of environmental stresses, such as those triggered by starvation, radiation, or hypoxia, leading to progressive disruption of organ maintenance, with the undesirable activation of apoptotic and inflammatory responses that characterize the alveolar destruction observed in emphysema [5, 6]. Cigarette smoke exposes the lung to extreme levels of oxidative stress [7]. It is estimated that each cigarette puff contains 1014 free radicals [7]. These smoke-derived oxidants damage epithelial cells of the lower respiratory tract by causing direct injury to membrane lipids, proteins, carbohydrates and DNA. The importance of oxidative stress has been confirmed by several studies that have identified the presence of markers of free radical damage in patients with COPD. Increased levels of 8-hydroxy-deoxyguanosine were detected in the urine of COPD patients and elevated levels of 3-nitrotyrosine and lung lipid peroxidation products were noted in the airway cells and epithelium of COPD patients and these markers demonstrated a strong correlation with disease severity as measured by FEV_1 [8-11]. Cigarette smoke exposure induced the expression of IL-1β, IL-8 and GM-CSF in human bronchial epithelial cells via the activation of both the NF-κB and MAPK pathways [8, 12]. Importantly, the smoke-mediated induction of MAPK and NF-κB signaling in these cells was blocked by the administration of the antioxidant epigallocatechin gallate [8, 13]. This data indicates that redox factors have a vitally important role in modulating intracellular signaling events that regulate the inflammatory responses to cigarette smoke exposure. In addition to its inflammatory effects, oxidative stress promotes alveolar cell apoptosis and emphysema formation by blocking the binding of vascular endothelial cell growth factor to its receptor [8, 14]. Thus, the oxidant/anti-oxidant balance in the lung has

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critical effects on the inflammatory and apoptotic responses that are involved in this disease. The binding of TNF to the TNF receptor (TNFR) has been linked to apoptosis, proliferation and the activation of NF-κB and c-Jun N-terminal kinase [8, 15]. By affecting these key cell-signaling processes, TNF is able to induce the development of smoking related lung diseases [8, 16-18]. TNF-α levels are elevated in the lungs of smokers and COPD patients and the absence of the TNF receptor renders mice resistant to smoke-induced inflammation [8, 16, 19, 20]. Moreover, animal studies have shown that mice lacking the TNF receptors are protected against both elastase and cigarette smoke-induced emphysema [8, 21-23]. Though TNF is critical in the pathogenesis of COPD, the mechanisms by which cigarette smoke alters TNF signaling remain to be determined. Several studies, however, indicate that oxidants have a central role in this process [8, 24, 25]. These smoke-derived oxidants trigger TNF signaling by directly stimulating the receptor or by activating TNF-receptor associated proteins and TRAF2 (TNF receptor associated factor-2) [8, 25, 26]. In addition, reactive oxygen species cause apoptosis signaling kinase-1 (ASK-1), a MAP kinase that is triggered by TNF, to dissociate from thioredoxin thus freeing it to activate c-Jun N-terminal kinase [8, 27-29]. Aside from enhancing the phosphorylation of c-Jun N-terminal kinase, oxidants are capable of sustaining this signaling by inactivating MAPK phosphatases (MKPs) that return c-Jun N-terminal kinase to its basal state [8, 30]. Importantly, oxidants can cooperate with TNF in the activation of both NF-κB and AP-1 [31, 32]. This is critical since the activation of these transcription factors have been linked to cigarette smoke-induced lung inflammation [8, 18, 33]. The lung has a rich network of enzymatic antioxidants to protect itself from this oxidative burden including superoxide dismutase (SOD) and glutathione peroxidase (GPX) [8, 34]. SOD1 which is located in the cytosol and is the primary SOD of the lung detoxifies superoxide by converting it to hydrogen peroxide [8, 35]. This can then be further detoxified by enzymes like GPX which convert hydrogen peroxide into water [8, 36]. Indeed, the classical GPX, GPX1, has anti-inflammatory properties in mice [8, 37, 38]. and can prevent the stress-induced activation of MAPK proteins *in vivo* [8, 39]. The major consequence of the oxidative stress is the activation of the transcription factor nuclear factor-κB, which activates proinflammatory cytokine transcription [40-42]. Recent evidence suggests that cigarette smoke inhibits histone deacetylase, further promoting the release of proinflammatory cytokines [43]. Therefore, oxidant injury and lung inflammation act in concert to increase alveolar destruction or compromise maintenance and repair of alveolar structure.

Conclusion

Over the past decade, we realized that emphysema is not caused by a single cell type or proteinase but that multiple inflammatory and immune cells including oxidative stress mediators are involved and we are now trying to determine how they interact in a complex network of interactions and relationships between immune function, inflammation, proteolytic burden, infection and apoptosis to contribute to lung destruction in COPD. Inflammation in COPD is marked by the presence of increased numbers of macrophages and neutrophils in the lung [44] and lymphocyte infiltration with enhanced accumulation of CD8+ T cells is a prominent finding [45-47]. Macrophages and neutrophils have been well studied and appear to play a role in the pathogenesis of COPD through the release of proteinases that alter the extracellular matrix [44]. Macrophages and neutrophils are prominent in chronic inflammatory conditions of the lung including emphysema [45, 46]. Investigators demonstrated that macrophages have the capacity to produce both cysteine proteinases (cathepsins) and matrix metalloproteinases (MMPs) capable of elastolysis [45, 46]. The chronic pulmonary inflammation of COPD is believed to result in progressive respiratory disorders. The pathogenesis of inflammation, airway remodeling, and destruction of the alveolar unit in COPD is complex and not completely understood. Human emphysema develops over decades of ongoing cigarette smoking or exposure to environmental pollutants Further studies are needed to solidify and define a complex network of inflammatory and immune cell interactions in chronic destructive lung disease and may allow therapeutic targeting to interrupt this pathologic process in humans.

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