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Oxidative stress in chronic lung disease: From mitochondrial dysfunction to dysregulated redox signaling

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ABSTRACT

The lung is a delicate organ with a large surface area that is continuously exposed to the external environment, and is therefore highly vulnerable to exogenous sources of oxidative stress. In addition, each of its approximately 40 cell types can also generate reactive oxygen species (ROS), as byproducts of cellular metabolism and in a more regulated manner by NOX enzymes with functions in host defense, immune regulation, and cell proliferation or differentiation. To effectively regulate the biological actions of exogenous and endogenous ROS, various enzymatic and non-enzymatic antioxidant defense systems are present in all lung cell types to provide adequate protection against their injurious effects and to allow for appropriate ROS-mediated biological signaling. Acute and chronic lung diseases are commonly thought to be associated with increased oxidative stress, evidenced by altered cellular or extracellular redox status, increased irreversible oxidative modifications in proteins or DNA, mitochondrial dysfunction, and altered expression or activity of NOX enzymes and antioxidant enzyme systems. However, supplementation strategies with generic antioxidants have been minimally successful in prevention or treatment of lung disease, most likely due to their inability to distinguish between harmful and beneficial actions of ROS. Recent studies have attempted to identify specific redox-based mechanisms that may mediate chronic lung disease, such as allergic asthma or pulmonary fibrosis, which provide opportunities for selective redox-based therapeutic strategies that may be useful in treatment of these diseases.

1. Introduction

The lung represents the human body's largest interface with the external environment, with an estimated surface area of ~150 m^2. This large surface area is critical for effective uptake and delivery of oxygen (O_2) to all organs, but also renders the lung vulnerable to airborne pathogens and pollutants, and the respiratory tract is therefore equipped with elaborate antimicrobial and antioxidant defense systems to minimize infection or injury and maintain appropriate lung function. Epithelial cells that coat the entire lung surface form a critical component of such defense, as they form a physical barrier that prevents entry of inhaled antigens and pathogens and also act as a source of antimicrobial factors, high-molecular weight glycoproteins (mucins), iron-binding proteins (e.g. lactoferrin and transferrin), and various secreted antioxidant enzymes and low-molecular weight antioxidant molecules (e.g. ascorbic acid, GSH), which are deposited into the airway surface fluids to provide a first-line defense network against inhaled pathogens or oxidant pollutants. While lung host defense against most airborne pathogens largely relies on resident inflammatory cell types, such as alveolar macrophages, dendritic cells, and innate lymphoid cells, the respiratory epithelium also plays a critical role in mediating acute responses to these pathogens by regulating innate or adaptive inflammatory responses to these common environmental challenges (Holgate et al., 2004; Hammad and Lambrecht, 2008). Chronic diseases of the lung, such as asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, have diverse etiologies but also share common traits in that they often involve repetitive cycles of injury to the respiratory epithelium (due to inhaled pollutants such as tobacco smoke or pathogens), combined with dysregulated epithelial repair pathways and chronic activation of inflammatory processes, collectively leading to inappropriate production of airway mucus, increased fibroblast activation, myofibroblast differentiation, smooth muscle proliferation, etc, thereby resulting in airway remodeling and decline in lung function. In addition, these various processes are further compromised by diverse genetic factors and chronic bacterial or viral infections due to loss of host defense pathways.

Many commonly encountered environmental pollutants, such as tobacco smoke, particulate matter, or ozone or nitrogen dioxide from photochemical smog, are oxidizing in nature and are thus thought to cause lung injury by oxidative stress. In addition, reactive oxygen

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species (ROS) are produced by phagocytic cells by activation of NADPH oxidase (NOX) enzymes in their efforts to kill pathogens, and inappropriate ROS production during acute or chronic lung inflammation is commonly thought to contribute to impaired lung cell function and progression of lung disease (Andreadis et al., 2003; Jacobsen et al., 2007; Shaw et al., 2007; Fahy, 2009; Wedes et al., 2009). Mitochondria, present in all lung cell types, also produce ROS during incomplete reduction of O_2 to water (H_2O) in the electron transport chain, and mitochondrial ROS formation is typically increased due to mitochondrial dysfunction during chronic disease, potentially contributing to disease pathology. Contrasting these presumed damaging effects of NOX- or mitochondria-derived ROS, NOX-family enzymes are widely expressed in other lung cells, and participate in other cell functions such as cell proliferation, differentiation, etc., illustrating more widespread physiological properties of ROS (van der Vliet, 2011; Segal et al., 2012). Similarly, mitochondrial ROS (mtROS) are also increasingly appreciated to serve important functions in cell biology, for example in basal and adaptive responses that control homeostasis and promote health span (Sena and Chandel, 2012; Ristow, 2014; Shadel and Horvath, 2015). Based on these considerations, the mechanisms by which ROS contribute to lung disease (as well as diseases of other organs) may be related to dysregulated redox signaling rather than by non-discriminate oxidative biomolecular damage ("oxidative stress"). Because of the diverse biological functions of ROS in many diverse cell types, in both physiological and pathological outcomes, it is perhaps not surprising that generic antioxidant-based approaches to quench ROS have so far been minimally effective in mitigating chronic disease, including lung disease, and have in some cases even promoted adverse outcomes (Nadeem et al., 2008; Fortmann et al., 2013; Kirkham and Barnes, 2013; Ristow, 2014; Sayin et al., 2014; Ghezzi et al., 2017). Therefore, recent research efforts have focused on identifying specific redox-based post-translational mechanisms that may mediate lung disease pathology, by addressing the involvement of specific cellular ROS sources and by characterizing critical protein targets and their redox-dependent modifications that induce functional alterations and mediate adverse biological outcomes. This review will briefly summarize the current evidence supporting dysfunctional ROS homeostasis in lung disease, and discuss some recent developments illustrating how selective targeting of specific ROS sources or redox signaling events may be more beneficial in combating chronic lung disease.

2. Sources of ROS in the lung – location matters

2.1. Mitochondria

All cells in the body derive at least some of their energy from oxidative phosphorylation (OXPHOS) in mitochondria, during which O_2 is reduced to H_2O, typically leading to production of intermediate ROS ($O_2^{\bullet-}$ and H_2O_2) at complex I and III in the mitochondrial respiratory chain, the major site of cellular O_2 consumption (Drose and Brandt, 2012; Lenaz, 2012; Wong et al., 2017). Since the lung is the organ exposed to the highest O_2 concentrations, such mitochondrial ROS (mtROS) production may be especially relevant to lung biology. The lung contains over 40 different cell types, which all contain varying mitochondrial densities. Among these, ciliated epithelial cells and secretory club cells that line the airways and alveolar type II cells that secrete surfactant are highly metabolically active cells and rich in mitochondria (Agrawal and Mabalirajan 2016). Most lung cells depend on aerobic glycolysis to supply carbon in the form of pyruvate to support OXPHOS and provide ATP as a constant supply of energy. Oxygen consumption rates in the lung are comparable to those in most other organs, and ATP content is also similar to that of other organs and mostly dependent on mitochondrial sources (Cloonan and Choi, 2016; Piantadosi and Suliman, 2017). Well-oxygenated tissues such as lung contain high levels of a unique isoform of the electron transport chain cytochrome oxidase complex IV subunit, COX IV isoform 2, which affects oxygen sensitivity, although the precise mechanisms and consequences are still not clear (Huttemann et al., 2012; Pierron et al., 2012; Sommer et al., 2017).

Production of mtROS has typically been considered as a leak resulting from incomplete reduction of O_2, but more recent studies indicate that such mtROS release may function as a cytosolic signal to support mitochondrial integrity and organismal homeostasis (Sena and Chandel, 2012; Shadel and Horvath, 2015; Topf et al., 2018). The diverse nature of mtROS production, which originates from up to 11 different sites depending on bioenergetic conditions (Wong et al., 2017), further illustrates the complex and variable biological functions of mtROS. Moreover, mitochondria are engaged in dynamic networks throughout the cell, and factors that impact on mitochondrial fission/fusion dynamics or subcellular mitochondrial trafficking dictate the subcellular location of mitochondrial ATP or ROS to support specific cell functions (Schuler et al., 2017; Lopez-Domenech et al., 2018). Indeed, mitochondria in airway epithelial cells are not distributed randomly, but are localized primarily near the apical surface, and also in the basolateral region, indicating their specific functions in localized responses to e.g. external (apical) triggers (Ribeiro et al., 2003; Xu et al., 2014). Thus, production of mtROS is a highly localized event, and likely effects cellular outcomes in a specific manner depending on location.

2.2. NADPH oxidases

A well-known major source of ROS during conditions of infection and inflammation is the activation of the so-called respiratory burst in phagocytic cells and other immune cells, due to assembly and activation of the NADPH oxidase complex within their phagosomes to generate intraphagosomal ROS to kill ingested microorganisms by oxidative mechanisms (Babior et al., 2002; Winterbourn et al., 2006; Bedard and Krause, 2007). We now know that multiple homologs of NADPH oxidase (NOX) exist that are more widely distributed across virtually all cell types, with a variety of biological functions beyond host defense (Bedard and Krause, 2007; van der Vliet, 2008). Similarly, NOX enzymes are widely distributed throughout the lung, with major roles in inflammatory/immune cells (alveolar macrophages, dendritic cells, T and B lymphocytes) as well as structural cell types (airway and alveolar epithelial cells, endothelial cells, fibroblasts, smooth muscle cells), each with distinct functional properties (van der Vliet, 2011; Bernard et al., 2014). Activation of NOX enzymes generates superoxide anion ($O_2^{\bullet-}$) and/or hydrogen peroxide (H_2O_2) as primary products (Geiszt and Leto, 2004; Ameziane-El-Hassani et al., 2005; Martyn et al., 2006), which in some specialized cases interact with locally secreted heme peroxidases (e.g. myeloperoxidase, lactoperoxidase) to generate secondary oxidants (e.g. nitrogen dioxide, hypochlorous acid, hypobromous acid) (Wijkstrom-Frei et al., 2003; Geiszt and Leto, 2004; El Hassani, Benfares et al., 2005). In addition, $O_2^{\bullet-}$ or H_2O_2 can also react directly with alternative susceptible cell targets, including redox-sensitive proteins, by which NOX enzymes control a variety of biological processes ranging from cell proliferation, differentiation, to inflammatory signaling and immune regulation. NOX-mediated signaling mechanisms are often related to regulation of common signaling processes involving protein phosphorylation and Ca^{2+} signaling (Finkel, 2003; Forman et al., 2004; Terada, 2006; Janssen-Heininger et al., 2008; van der Vliet, 2008). Specificity in such oxidative signaling is typically achieved by strict spatial localization of NOX activation and its target proteins, e.g. in endosomes or membrane lipid rafts (Terada, 2006; van der Vliet, 2008; Ushio-Fukai, 2009). In fact, ROS can have opposing effects on biological processes, depending on the location or extent of ROS production, as illustrated by the ability of ROS to promote as well as inhibit activation of transcription factors such as nuclear factor (NF)-κB or HIF-1 (Brar et al., 2003; Li et al., 2006; Janssen-Heininger et al., 2008).

Recent observations also indicate the presence of reciprocal interactions between different NOX enzymes e.g. (Heppner et al., 2016; Kim