Lung inflammation in COPD: why does it matter?

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Abstract

COPD is characterized by lung inflammation, which intensifies with disease progression. Recent studies suggest that COPD has multiple phenotypes, each with a distinct molecular pathway. Proteolytic enzymes may have a prominent role in the emphysematous phenotype, while nitric oxide pathways may be more relevant for pulmonary vessel remodelling in COPD. This article provides a synopsis of the possible role that lung inflammation plays in the pathogenesis of COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a global epidemic, affecting nearly 300 million people worldwide and killing 3 million individuals each year. It is the only major cause of mortality that is increasing such that by 2030 the mortality rate will reach 7 to 8 million per annum [1]. Regrettably, however, there are no drugs currently available that can reduce COPD mortality and very few promising compounds in the pipeline. Clinically, COPD is characterized by shortness of breath (usually with mild to moderate exertion) and chronic (productive) cough that persists for weeks to months [2]. All patients demonstrate airflow limitation on lung function tests with reduced expiratory flow rates. The international Global initiative for chronic Obstructive Lung Disease (GOLD) committee defines COPD on the basis of spirometric criteria with forced expiratory volume in one second to forced vital capacity ratio of less than 70% following administration of a bronchodilator [2]. Morphologically, COPD lungs show, in most cases, a combination of emphysema (i.e. destruction of alveoli) and bronchiolitis (i.e. airway wall thickening of bronchioles less than 2 mm in diameter) [3]. Worldwide, the most common cause of COPD is cigarette smoking, accounting for approximately 50% of the overall cases. Other putative causes of COPD include bronchial hyperresponsiveness, family history of asthma, air pollution, biomass exposure, severe childhood infections, malnutrition and genetic abnormalities, such as α-1-antitrypsin deficiency [2]. The main commonality in these environmental and genetic triggers is that they promote lung inflammation, which, in susceptible individuals, leads to lung injury and damage. In this article, we will provide a brief overview of the importance of lung inflammation in the pathogenesis and progression of COPD and some inflammatory targets for future drug and biomarker discovery to combat the growing epidemic of COPD across the world.

Recent advances

Acute effects of cigarette smoke on lung inflammation

Acute exposure to cigarette smoke is associated with a rapid up-regulation of innate immunity, characterized by a large influx of neutrophils into the airways, which in turn release a variety of proteolytic enzymes including myeloperoxidase, serine proteases (e.g. elastase, cathepsin G) and bactericidal/permeability-increasing proteins that can injure the lungs. This acute process is largely mediated by Toll-like receptor 4 (TLR4) and interleukin (IL)-1R1 (receptor) signaling pathways that are dependent on an adaptor protein, MyD88 [4,5]. Upon stimulation, this receptor complex activates the "inflammasome" (a multiprotein oligomer that is located in the cytoplasm and consists of caspase 1 and nucleotide-binding, oligomerization domain [NOD]-like receptor and other proteins),

which in turn converts pro-IL-1 into its active form. Specific blockage of IL-1 or the TLR-4 receptor markedly attenuates cigarette smoke-related lung inflammation [5]. Interestingly, however, in the chronic cigarette smoke exposure model, elimination of TLR-4 (using transgenic mice) does not abrogate cigarette smoke-related emphysema, suggesting that acute inflammatory changes related to smoking are not responsible for COPD [4].

Chronic effects of cigarette smoke in lungs

COPD begins in the small airways (less than 2 mm in internal diameter) in response to long-term exposure to toxic gases and particles, most often related to cigarette smoking. Over time, the disease process spreads to the gas exchanging units, resulting in emphysema [6]. The initial response is orchestrated by the innate immune system, which includes the epithelium, mucociliary elevator, and inflammatory cells, such as macrophages and neutrophils, which patrol the airways for irritants and microbes. The second line of defense is adaptive immunity, which is largely mediated by T lymphocytes. Nearly all inflammatory cells are increased in the small airways of COPD lungs in a severity-dependent manner. In patients with GOLD class 4 COPD (the most severe) defined on the basis of lung function (forced expiratory volume in one second less than 30% of predicted), nearly all small airways contain neutrophils, alveolar macrophages, and CD4 and CD8 lymphocytes (vs. ~50-85% of small airways in lungs of smokers without COPD) [7]. The one notable exception is eosinophils, whose numbers remain relatively constant in the airways across the full spectrum of disease severity. One of the most striking histological features of the COPD lung is the marked increase in the number of lymphoid follicles, especially in patients whose forced expiratory volume in one second is less than 50% of predicted. In these lungs, approximately a third of the small airways are surrounded by a lymphoid follicle (vs. less than 5% of small airways in lungs of smokers without COPD) [7]. Interestingly, the use of inhaled or oral corticosteroids is associated with a marked reduction in the number of lymphoid follicles in COPD lungs [8]. However, these medications are also associated with an increased risk of pneumonia, raising the possibility that the lymphoid follicles may be involved in regulating microbial flora (and preventing overgrowth of pathogenic microbes) in the small airways of COPD patients [9]. This hypothesis will need to be tested in experimental studies.

Another striking histological feature of COPD lungs is expression of mucus in the small airways, which increases with disease progression. In GOLD class 4 lungs, mucus occupies on average ~15% of the total luminal area of small airways; whereas, in healthy smokers, less than 5% of the luminal area is occupied by mucus [7].

Most importantly, the extent of mucus expression in the small airways is the single most important histological risk factor for mortality in patients with severe disease [8]. Neither inhaled nor oral corticosteroids materially alter mucus expression in the airways [8], which may explain why these medications do not appear to modify mortality in COPD.

Autoimmunity

One unresolved conundrum in COPD is the persistence of lung inflammation even years following smoking cessation [10]. Some have postulated that lymphocytes (especially T lymphocytes) play a pivotal role by inducing "auto-immunity" [11,12]. This theory has been fueled recently by the observation that some breakdown products of the lung extracellular matrix, especially N-acetyl Pro-Gly-Pro (PGP), share structural homology with α chemokines causing attraction and activation of neutrophils in the lungs. This process can be abrogated by neutralizing collagen breakdown products [13,14]. Other matrikines (i.e. bioactive extracellular matrix fragments), such as SIKVAV-containing laminin α-1 and α-5 peptides and certain elastin fragments, have also been implicated in amplifying the inflammatory process in lungs [15]. Further support of this theory has been the observation of tertiary lymphoid follicles in the walls of small airways in COPD lungs, containing oligoclonal B cells without any traces of viral or bacterial antigens, similar to those observed in joints of patients with rheumatoid arthritis or Crohn's Disease [16]. Consistent with the autoimmunity theory, some epidemiological studies have reported that patients with COPD harbor anti-elastin antibodies and autoreactive T cells against bronchial epithelium and pulmonary artery endothelium in the plasma [17,18]. However, a more recent (and larger) study failed to replicate these findings and demonstrated no significant differences in the plasma levels of anti-elastin or anti-PGP antibodies between COPD patients and healthy control subjects [19]. Moreover, large clinical trials of inhaled corticosteroids, which significantly attenuate lymphoid follicles in COPD lungs, have failed to demonstrate a disease-modifying effect of these drugs, arguing against a prominent role of lymphocytes in the pathogenesis of COPD [20]. Thus, the role of "autoimmunity" in COPD remains uncertain.

Lung microbiome

Recent advances in molecular techniques (e.g. sequencing) have shown that lungs, contrary to traditional teaching, are not "sterile". Indeed, there appears to be a rich (and distinct) microbial flora that is present in healthy subjects [21]. With COPD, however, this flora changes with a reduction in diversity in microbial communities and overgrowth of certain bacteria, such as lactobacillus [9].

Although the clinical relevance of this observation is unknown, some have speculated that alterations in the lung microbiome with COPD may perpetuate the inflammatory response observed in these lungs (despite smoking cessation). Additional studies will be needed to address this hypothesis.

Innate immunity

While it is unlikely that TLR-4 is directly involved in the pathogenesis of COPD (see above), there are suggestions that other parts of the innate immune response may play a significant role in disease progression. In patients with α-1-antitrypsin deficiency, elastase (a peptidase that is released by neutrophils) induces tissue destruction in the lungs by breaking down elastin, which, when unleashed and unimpeded, leads to emphysema and mild bronchiectasis. Consistent with this notion, individuals in the general community who harbor a functional polymorphism in the α-1 antitrypsin gene, resulting in reduced α-1 antitrypsin levels in serum, experience an accelerated decline in lung function compared to those with normal serum α-1 antitrypsin levels, especially among those who smoke [22]. Elastase is also released by activated alveolar macrophages (also called matrix metalloproteinases) and its expression in lungs (in response to cigarette smoke) from macrophages can induce emphysema. Inhibition of elastase abrogates this process [23]. Indeed, mice containing macrophages deficient in elastase do not develop emphysema despite smoking [23].

Neutrophils and macrophages also release myeloperoxidase upon activation. Myeloperoxidase is a small enzyme that catalyzes the reaction of chloride ions with hydrogen peroxide that results in the production of hypochlorous acid, which is cytotoxic to microbes. Cigarette smoke up-regulates myeloperoxidase expression in lungs, and chronically this leads to pulmonary hypertension, airway remodeling and emphysema. All of these features can be halted by inhibiting myeloperoxidase expression [24]. Thus, enzymatic products of neutrophils and macrophages (e.g. myeloperoxidase, elastase and metallomatrix proteins) appear to play very important roles in COPD pathogenesis and are potential targets for drug discovery.

Nitric oxide

Whereas the role of macrophage- and neutrophil-mediated enzymes as key regulators of COPD has been known for years, the possible role of nitric oxide synthase in this process has been elucidated only recently. Cigarette smoke up-regulates cellular synthesis of nitric oxide in the lungs by up-regulating predominantly the expression of inducible nitric oxide synthase. Inducible nitric oxide synthase is expressed widely in human lungs including airway epithelium [25], alveolar macrophages [26], neutrophils and pulmonary endothelial cells [27]. Inducible nitric oxide synthase is up-regulated in response to environmental stressors, especially in response to lipopolysaccharide (LPS), and converts L-arginine to nitric oxide, which in turn reacts with superoxide ions to form a very potent oxidant, peroxynitrite. A recent study suggests that cigarette smoking induces emphysema by up-regulating inducible nitric oxide synthase and causing oxidative stress in the lungs. Inhibition of inducible nitric oxide synthase with a selective inhibitor abrogates these changes and "reverses" emphysema and pulmonary vessel remodelling related to smoking [27]. Interestingly, adoptive transfer of bone marrow from inducible nitric oxide synthase-deficient mice to wildtype mice failed to protect these mice from emphysema or vessel remodelling; whereas, the reverse (i.e. adoptive transfer of bone marrow cells from wildtype animals to mice deficient in inducible nitric oxide synthase) protected mice from smoking-related emphysema and pulmonary hypertension. These data suggest that while cigarette smoke up-regulates inducible nitric oxide synthase in both resident and inflammatory cells in the lungs, inducible nitric oxide synthase up-regulation in the resident cells (e.g. epithelial or endothelial cells) appears to be more important in the pathogenesis of COPD [27]. Although the exact mechanisms by which inducible nitric oxide synthase regulates emphysema is not known, it is postulated that cigarette smoke up-regulates inducible nitric oxide synthase, which in turn unleashes oxidant stress in lungs, causing large scale damage and destruction of vulnerable cells, such as endothelial cells. This in turn leads to microvascular changes, which over time cause changes in pulmonary parenchyma. Consistent with this notion, the earliest morphologic lesions in the smoking mice model are found in pulmonary vessels, characterized by increases in right ventricular heart pressures and "disappearance" of pulmonary vessels months before emphysematous or small vessel changes are observed [27].

Future directions

Despite the large ongoing public health burden of COPD, its pathophysiology has not been fully resolved. COPD lungs show a variable mixture of bronchiolitis, emphysema, and pulmonary hypertension, and in all of these processes inflammation appears to play a pivotal role. However, the inflammatory mediators involved in each of these processes may be different. For instance, neutrophil elastase may affect emphysema but spare pulmonary vessels and the airways; whereas, inducible nitric oxide synthase may be involved in pulmonary hypertension and emphysema but not bronchiolitis. COPD may thus be a collection of many different pathological processes, with each involving different mediators. This may explain why so many promising therapeutic targets in animals have failed in drug development – because drug companies

have considered COPD as a single pathologic entity. In the future, with the use of highly sensitive macro and micro imaging techniques and the advent of novel biomarkers, we may be able to tease out which of the pathologic processes are predominantly present in certain patients (i.e. phenotyping). This will enable development of "smart" drugs that can be used to treat patients with phenotypes that match the therapeutic target of the drug.

Abbreviations

COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for chronic Obstructive Lung Disease; IL, interleukin; LPS, lipopolysaccharide; NOD, nucleotide-binding oligomerization domain-containing protein; PGP, N-acetyl Pro-Gly-Pro; TLR-4, Toll-like receptor 4.

Disclosures

DDS has received honoraria for speaking engagements and lectures from GlaxoSmithKline, AstraZeneca, Merck, Pfizer, Grifols, and Nycomed and has served on advisory boards for Novartis, Nycomed, Merck, AstraZeneca and GlaxoSmithKline.

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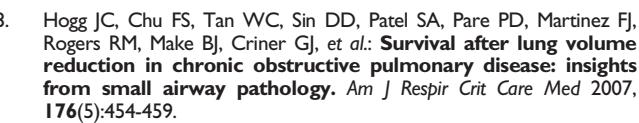
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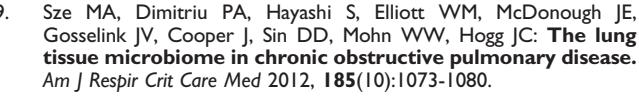
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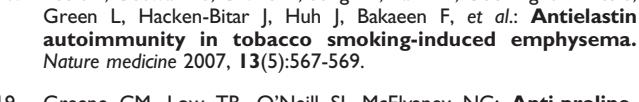
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