

EDITORIAL

COPD 2020: new directions needed

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INTRODUCTION

World COPD Day organized by GOLD (Global Initiative for Chronic Obstructive Lung Disease) is celebrated on November 18th this year to again raise awareness of this common but still neglected disease. It seems barely credible that COPD is so poorly recognized by the general public and even many health-care professionals, especially as it is the only common chronic disease that has steadily increased over the last 50 years and is now the third ranked cause of death after cardiovascular disease and stroke (18). The costs of COPD, which affects over 400 million people in the world, are mind-blowing—the World Economic Forum has estimated that the global costs of COPD will reach US\$50 trillion/yr by 2030, making it more costly than cardiovascular disease (13). Yet not only is COPD largely ignored, there is very little research funding available compared with cancer, cardiovascular disease, and neurological diseases. We do have more effective therapies, and particularly long-acting inhaled bronchodilators, and GOLD has been very successful in promoting more effective assessment and management of the disease, but we still do not have any therapy that has been shown to reduce its relentless progression and no drugs that have a major impact on mortality or comorbidities. This may reflect the fact that there is still a poor understanding of the underlying disease mechanisms.

HETEROGENEITY OF COPD

It has long been apparent that there are different clinical phenotypes of COPD and various approaches have been taken to subdividing patients, but there are often inconsistent groups that may not be stable and they have not been linked to specific underlying disease mechanisms or molecular pathways (6). It was hoped that with the discovery of α_1 -antitrypsin deficiency in the 1960s that other genetic causes of COPD would be discovered using new genetic approaches in large patient populations, but this has turned out to be disappointing, apart from rare polymorphisms of telomerase. Some genetic associations, such as polymorphisms in the hedgehog signaling pathway, FAM13A, and iron-responsive element-binding protein-2 (IREB2) binding have some biological plausibility, but so far have not been linked to distinct endotypes.

The most convincing biomarker that predicts a therapeutic response in COPD patients is increased blood eosinophils, which have consistently predicted a greater reduction in acute exacerbations with inhaled corticosteroids (2). However, it is not understood how blood eosinophils, which are not well related to lung and sputum eosinophils, are such a useful biomarker.

Surprisingly, increased blood eosinophils do not appear to be very predictive of a response to an anti-IL-5 treatment that specifically and markedly reduces blood eosinophils (16).

Although asthma and COPD are distinct clinical syndromes, some patients share features of both diseases. Originally termed asthma-COPD overlap syndrome (ACOS), this term was abandoned as it is clear that asthmatic patients with features of COPD (neutrophilic inflammation, fixed airway obstruction) are different from COPD patients with features of asthma (history of asthma, greater reversibility, increased eosinophils), so the term ACO was introduced. However, it has not been clinically useful and it is best to consider that asthma and COPD are distinct diseases that may coincide in some patients and that both may need to be treated (5).

NONSMOKING COPD: NEGLECTED BUT VERY IMPORTANT

Almost all of the emphasis has been placed on cigarette smoking as a risk factor for COPD and smoking cessation as an important component of clinical management. Almost all of the research on disease mechanisms and clinical trials of therapy has been conducted in smoking COPD patients, as this is the predominant risk factor in high income countries. Yet about half of COPD patients in the world are never-smokers, particularly in low- and middle-income countries (LMIC), where other risk factors, such as exposure to household air pollution (biomass smoke) and occupational dust exposure, are more important than smoking as risk factors (27). There is a great need to understand the nonsmoking phenotypes of COPD in terms of their underlying mechanisms, disease progression, clinical manifestations, and comorbidities. In rural India, COPD in women is related to wood smoke exposure in poorly ventilated houses and, although similar to smoking COPD, is less likely to be associated with emphysema. The sputum inflammatory profile and defective bacterial phagocytosis by alveolar macrophages are similar to smoking COPD, perhaps indicating that there is a common susceptibility (17, 24). There is a great need for clinical trials of therapy in nonsmoking COPD, although these may be challenging in resource-poor settings (26). COPD may occur with pulmonary tuberculosis and sometimes many years after treatment—so called tuberculosis obstructive pulmonary disease (TOPD); although this is very common in LMIC, there is little research on underlying mechanisms and no therapeutic trials (25).

THE PRESSING NEED FOR DISEASE-MODIFYING THERAPIES

Almost all of the new drugs approved for COPD therapy are known classes of drug. We now have a choice of several long-acting β_2 -agonists and muscarinic antagonists that are similarly effective and in fixed combination inhalers have additive

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bronchodilator effects, which improve symptoms and reduce exacerbations but do not target the underlying chronic disease process and therefore fail to reduce disease progression or mortality. There is a very large unmet need to find treatments that target the underlying inflammation and immune dysfunction. Many anti-inflammatory treatments have now been tested in COPD patients, including several mediator antagonists and broad-spectrum anti-inflammatory therapies. The only novel anti-inflammatory treatment so far developed is the oral phosphodiesterase-4 inhibitor roflumilast, which is effective in animal models of COPD, but poorly effective in COPD patients as the oral dose is limited by systemic side effects, such as headache, diarrhea, and nausea, so is not popular with patients (7). Attempts to reduce side effects of phosphodiesterase-4 (PDE4) inhibitors by inhaler delivery or development of more selective inhibitors have been unsuccessful. Several other anti-inflammatory treatments are in development, but most have failed either because of lack of efficacy or because of unacceptable side effects. It is also likely that they are too specific and do not target the complexity of the underlying disease process.

THE NEED FOR BETTER UNDERSTANDING OF DISEASE MECHANISMS

We need a much better understanding of the cellular and molecular mechanisms driving the pathology of COPD and to understand the different endotypes of disease. Patients are treated relatively late in the course of this progressive disease when any differences between different endotypes may have been lost. There is growing evidence that small airway disease may be the earliest abnormality, with loss of small airways and narrowing and fibrosis of others, but the mechanisms of small airway disease are poorly understood (22). Animal models of COPD, such as smoke exposure in mice and guinea pigs, have focused on emphysema and the mechanisms of lung parenchymal destruction and have largely ignored small airway fibrosis, which is not prominent in rodent models. We need to understand the mechanisms of small airway fibrosis and the role of small airway fibroblasts, which may be regulated by mediators released from small airway epithelial cells and may involve new therapeutic approaches that target mechanisms of fibrosis and repair (8).

The chronic inflammatory process in COPD involves many inflammatory cells, particularly macrophages, neutrophils, eosinophils, and various subtypes of lymphocyte (Tc1, Th1, Th17, ILC2, ILC3, NK cells) and over a hundred different inflammatory mediators, suggesting that treatments that are upstream in the inflammatory cascade are more likely to be useful. Cigarette and biomass smoke, and oxidative stress may drive this chronic low-grade inflammation, which eventually becomes self-perpetuating (1). There appears to be an amplification of lung inflammation in COPD patients compared with smokers with the same tobacco exposure who do not have airflow obstruction. One molecular mechanism for this amplification is a loss of the key regulator histone deacetylase-2 (HDAC2), which normally terminates inflammatory gene expression and is reduced to a much greater extent in COPD patients than in normal smokers and nonsmokers (21).

ACCELERATED AGING AS A KEY MECHANISM

There is increasing support for the view that COPD represents accelerated lung aging, resulting in the accumulation of

senescent cells in the lungs of COPD patients (10). Most cell types in the lungs of COPD patient show senescence and this may be accelerated by a loss of endogenous anti-aging molecules, such as sirtuin-1 and sirtuin-6, which are markedly reduced in the lungs of COPD patients (4, 23). Senescent cells are in cell cycle arrest and lose their ability to repair damage. They are also metabolically active (“zombie cells”) and secrete a characteristic pattern of inflammatory proteins known as the senescence-associated secretory phenotype (SASP), which corresponds very closely to the pattern of inflammatory mediators secreted by COPD cells. Oxidative stress is a major driving mechanism for cellular senescence (stress-induced senescence) and induces micro-RNA-34a which inhibits sirtuins-1 and -6, leading to accelerated aging (4). MicroRNAs may be transported from cell to cell via extracellular vesicles, resulting in disease progression and spread to other organs (14). This may account for the high frequency of comorbidities in COPD patients, many of which are also diseases of accelerated aging. Cellular senescence is associated with mitochondrial dysfunction and defective autophagy; dysfunctional mitochondria may be the major source of oxidative stress in COPD patients (12, 15). The molecular pathways of senescence in COPD are now being elucidated and have highlighted the critical role of increased phosphoinositide 3-kinase-mammalian target of rapamycin (PI3K-mTOR) signaling (20). Several therapies to target cellular senescence (senotherapies), including drugs that inhibit the PI3K-mTOR pathway (senostatics), are now in development, including repurposing existing treatments, such as metformin and rapamycin, as well as novel drugs (3). Removal of senescent cells with senolytic drugs that promote cell apoptosis and removal are also in development and have already been tested in humans (19). Senotherapies may be useful not only in COPD, but also in its comorbidities in which the same molecular pathways of accelerated aging are also involved.

FUTURE DIRECTIONS

The development of new therapies for COPD has been very disappointing so new approaches are needed. Drugs that target the underlying disease process are required and these may be more effective if used in early disease before major structural and irreversible changes occur. This will involve finding patients at an earlier stage in the disease process and long before spirometry becomes abnormal, as we currently define this disease. This means that we need to redefine COPD in the future and use more sensitive tests of small airway function and lung structure (11). By understanding the disease process better it may even be possible to develop therapeutic approaches with drugs and cell therapies that can restore the repair mechanisms of the lung which are lost early in COPD patients and this might even reverse the disease process in the future (9). World COPD Day is important for highlighting the importance of better recognition and management of COPD, but also for raising awareness of the need for much more research on this devastating and lethal global disease.

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AUTHOR CONTRIBUTIONS

P.J.B. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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