REVIEW ARTICLE

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Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease

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N Engl J Med 2019;381:1248-56.
DOI: 10.1056/NEJMra1900475

For almost 50 years, since Fletcher and Peto reported their seminal observations in young working men in London,[1] chronic obstructive pulmonary disease (COPD) has been widely accepted as a self-inflicted condition caused by tobacco smoking. The classic concept was that in susceptible persons, smoking elicits an abnormal inflammatory response[2] that damages the airways (bronchitis–bronchiolitis) and alveoli (emphysema), accelerates the physiologic decline of lung function with age, and leads to airflow limitation and chronic respiratory symptoms, which are difficult to reverse and may periodically be manifested as exacerbations.[3] As a result, today the diagnosis of COPD relies on the presence of airflow limitation in smokers that is difficult to reverse, and treatment is largely directed toward improving airflow and ameliorating symptoms and exacerbations with the use of bronchodilators with or without inhaled glucocorticoids.[3] Several recent observations, however, challenge this traditional and seemingly straightforward pathogenic paradigm.

First, although tobacco smoking is the key environmental risk factor for COPD, about a third of affected patients worldwide are nonsmokers; other environmental pollutants, such as smoke from biomass fuel used for cooking and heating, are also major environmental risk factors for COPD in many places around the globe.[4] Second, comorbid conditions are highly prevalent among patients with COPD but are largely unrelated to lung function.[5] Therefore, COPD can be seen as the pulmonary component of a systemic and multimorbid syndrome.[6]

Third, we now know that COPD is not always a self-inflicted disease. In healthy persons, lung function, as measured by the forced expiratory volume in 1 second (FEV_1), reaches a peak at about 20 years of age, followed by a relatively short plateau and a steady decline thereafter. Yet there is a range of lung-function trajectories throughout life (Fig. 1).[7-9] For instance, between 4% and 12% of persons in the general population do not have an FEV_1 peak that is in the predicted normal range for their age and sex, and many of those persons have chronic airflow limitation later in life, even though the rate of decline in FEV_1 after its peak is similar to that observed in people without disease.[10] These persons also have a higher prevalence and an earlier incidence, by about a decade, of coexisting cardiac and metabolic disorders, as well as an increased risk of premature death.[10] These observations indicate that a failure to reach the predicted level of peak lung function (as measured by FEV_1) in early adulthood identifies a group of high-risk persons with disordered development of lung function (and other organ systems), which might have been preventable or treatable had it been better understood.[11]

Finally, the diagnosis of COPD currently requires spirometric confirmation of airflow limitation. Therefore, smokers with normal spirometric findings but chronic respiratory symptoms and exacerbations[12] or computed tomographic (CT) evidence of lung disease such as emphysema are not considered to have COPD and

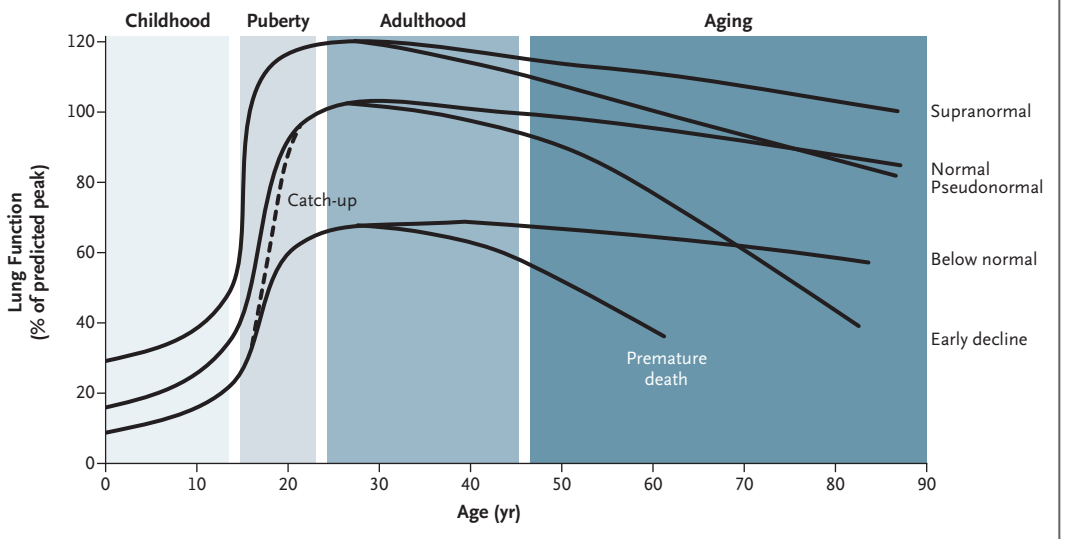

Figure 1. Lung-Function Trajectories from Birth to Death.

Two main biologic mechanisms can lead to chronic obstructive pulmonary disease (COPD) in adulthood: abnormal lung development and an increased rate of lung-function decline with age. These mechanisms can coexist. In some persons with below-normal lung function in childhood, a catch-up phase may occur during puberty. Persons with supranormal lung function in early adulthood may lose lung function over time (e.g., by smoking) but nonetheless in late adulthood may have pseudonormal spirometric findings (i.e., findings that appear normal despite the presence of symptoms or evidence of structural lung damage such as emphysema). Adapted from Agusti and Faner.[9]

hence do not receive evidence-based treatment for it.[3] These persons may well belong to the supranormal lung-function trajectory (Fig. 1), in which substantial lung damage may have occurred before it is reflected on spirometry, and the spirometric findings are therefore "pseudonormal." This hypothesis, though, requires formal validation.

In this review, we treat COPD as a clinical syndrome characterized by chronic respiratory symptoms, structural pulmonary abnormalities, impaired lung function, or a combination of these findings and often accompanied by multiple, clinically significant comorbid disorders.[13] We propose that COPD derives from various lifelong, dynamic, and cumulative gene–environment interactions (e.g., smoking, inhalation of other pollutants, prematurity, respiratory infections, and dietary insufficiency), that modulate the development, maintenance, and function of the lungs, and probably other systemic organs too, through complex and varied biologic mechanisms, including but not limited to inflammation.[11,14] Here, within this conceptual framework, we focus on the mechanisms of smoking-induced lung injury. Our review does not include the roles of abnormal lung development and mucus hypersecretion in COPD, since these disorders have been covered by recent reviews in the *Journal*.[15,16] The clinical aspects of COPD are discussed in a companion article by Celli and Wedzicha in this issue of the *Journal*.[17]

SMOKING-INDUCED LUNG INJURY

It is difficult to imagine a better way to deliver chronic, repetitive inhalational injury to lung tissue than smoking 20 or more cigarettes a day for many years. A puff of cigarette smoke contains millions of water droplets with a median aerodynamic diameter of 0.45 μm, each containing a complex mixture of toxic chemicals derived from the various types of raw tobacco plus toxic chemicals added to achieve the blend of aroma and taste that defines a particular brand of cigarette.

In the nose, mouth, larynx, and central conducting airways, large inhaled particles have sufficient momentum to leave the flowing stream of gas and collide with the airway walls. In the lung periphery, the total cross-sectional area available for gas flow is much larger than it is in

the central airways,[18] so the momentum of the inhaled gas and particles slows substantially. Intermediate-size particles settle on the surface of the larger airways, whereas fine and ultrafine particles reach the terminal, transitional, and respiratory bronchioles located near the center of the lobule. Toxic gases diffuse throughout the lung. At all these anatomical sites, smoking can induce tissue damage both directly, through oxidative stress, and indirectly, by eliciting an inflammatory response.

PATHOLOGICAL FEATURES OF SMOKING-INDUCED COPD

The severity of airflow limitation in COPD is associated with the extent to which the lung tissue is infiltrated by neutrophils, macrophages, and lymphocytes (Fig. 2). In severe COPD, lymphocytes form tertiary lymphoid organs, indicating the presence of an adaptive immune response. Airway remodeling thickens the airway walls in a manner that involves the epithelium, lamina propria, smooth muscle, and adventitia of the walls of airways that are less than 2 mm in diameter. Studies using microCT have confirmed that the number of patent terminal and transitional bronchioles is reduced by 40% in mild-to-moderate COPD[19] and by 80% in severe-to-very-severe COPD[20] (Fig. 3A), findings that are consistent with Mead's hypothesis that these airways represent a "quiet zone" within the lungs where damage can accumulate without being noticed.[18] The question of whether smoking-induced injury leads to a decrease in the number of airways, which may precede the development of emphysema (Fig. 3B),[19,20] or whether the reduction in airway number reflects abnormal lung development in early life cannot be answered on the basis of currently available data,[11,15] and the two mechanisms might coexist.

Emphysema, the destruction of alveolar airspaces, is another key component of COPD.[3] An imbalance between protease and antiprotease activity due to lung infiltration by activated neutrophils, reduced antiprotease activity, or both, with the classic example being alpha$_1$-antitrypsin deficiency, was originally considered the key pathogenic mechanism in emphysema.[21] More recently, additional factors have been proposed, including enhanced apoptosis[22] and lung-maintenance failure,[23] as well as oxidative stress, autoimmunity, malnutrition, or a combination of these factors.[24-26] In addition, abnormal alveolarization during lung development in early life (due to maternal smoking, prematurity, or other reasons) probably contributes to the lifetime burden of emphysema.[10]

The pulmonary circulation can also be altered in COPD. Historically, cor pulmonale was explained by the decrease in the capillary surface area associated with emphysema, increased hypoxic pulmonary vasoconstriction, or both in patients with severe disease.[27] Other observations point to the presence of pulmonary vascular inflammation and endothelial dysfunction in patients with milder airflow limitation.[28] For unclear reasons, some patients may have pulmonary hypertension that is more prominent than airflow limitation.[29] The potential role of lung developmental abnormalities in such patients has not been determined.[29]

The nature of lung disease associated with inhaled pollutants other than cigarette smoke, including vapors from electronic cigarettes, is mostly unknown. It has been established that patients exposed to biomass fumes have less severe emphysema, a lower incidence of emphysema, more airway involvement, a smaller decline in lung function over time, less systemic inflammation, and higher IgE levels than those exposed to cigarette smoke.[30,31] The pathogenesis of chronic airflow limitation due to other diseases, such as tuberculosis, bronchiectasis, rheumatoid arthritis, and human immunodeficiency virus infection, is even less well understood, so whether these disorders should be included within the COPD syndrome requires further research.[13]

REPAIR AND REMODELING OF LUNG TISSUE DAMAGED BY SMOKING

The type of healing that follows tissue injury depends on both the type of injury and the context in which it occurs. Normally, the repair process begins with activation of the coagulation system, which initiates the damage control required to stop bleeding.[32] This is followed by the infiltration of inflammatory immune cells, primarily neutrophils and macrophages, which protect the site of injury from infection and participate in a demolition process that removes dead and damaged tissue.[32] Subsequently, fibroblasts, myofibroblasts, and endothelial precursor

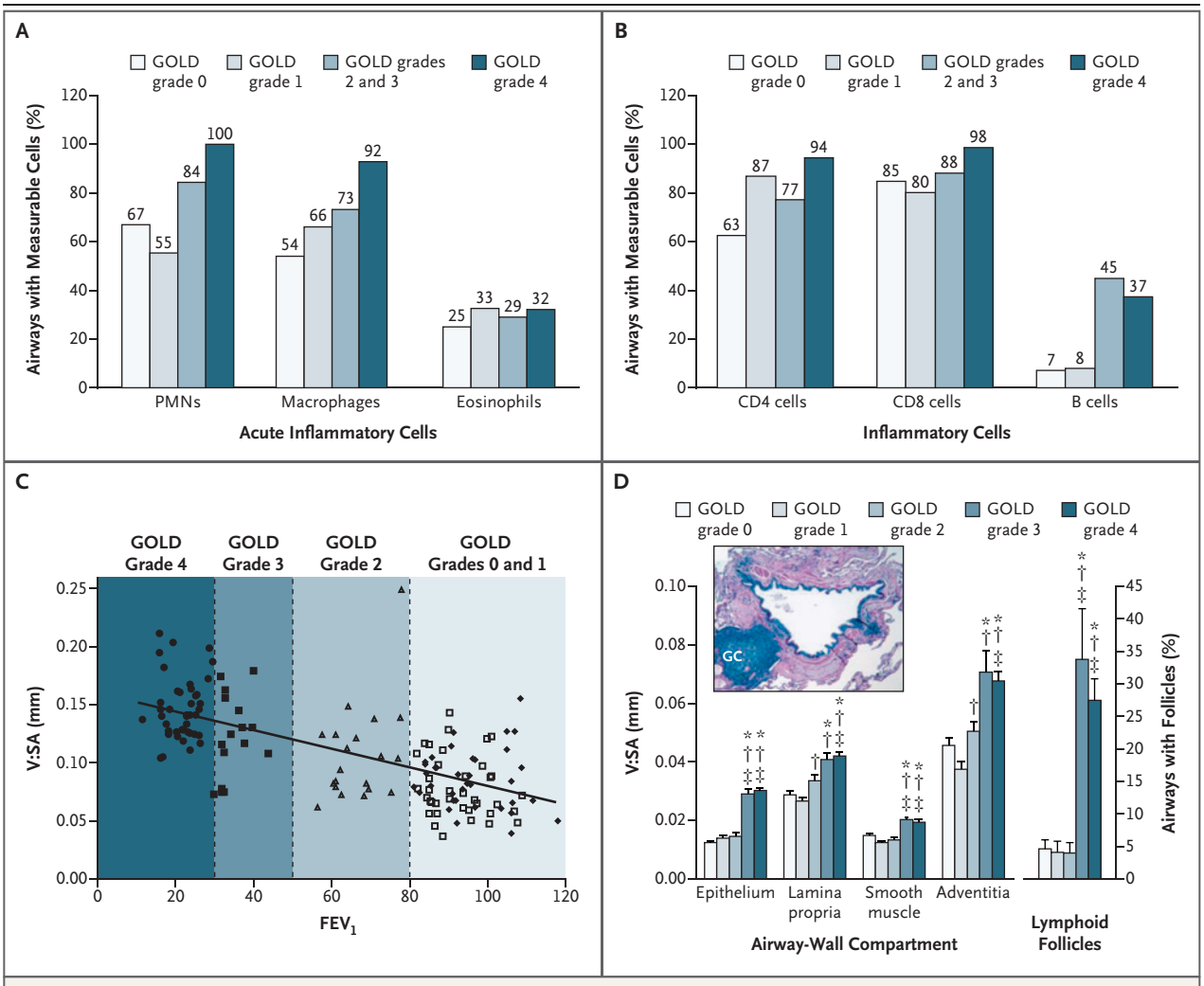

Figure 2. Pathological Features of COPD According to the Severity of Airflow Limitation.

Shown are the proportion of airways containing polymorphonuclear neutrophils (PMNs), macrophages, and eosinophils (Panel A) and the proportion containing CD4 cells, CD8 cells, and B cells (Panel B) in patients with different GOLD (Global Initiative for Chronic Obstructive Lung Disease) grades of airflow limitation. GOLD grade 0 (no longer in use) identifies persons with chronic respiratory symptoms but normal spirometric findings. GOLD grades 1, 2, 3, and 4 identify patients with COPD who have mild, moderate, severe, and very severe airflow limitation, respectively. In Panels A and B, GOLD grades 2 and 3 have been combined so that there is a similar number of patients in each group. In Panel C, the inverse relationship between total wall thickness, measured as the ratio of the volume to the surface area (V:SA), and forced expiratory volume in 1 second (FEV_1) is shown. The solid circles denote GOLD 4, the solid squares GOLD 3, the triangles GOLD 2, the open squares GOLD 1, and the diamonds GOLD 0; the dotted lines indicate the boundaries of the GOLD grades. Panel D shows the mean (±SE) volume of epithelium, lamina propria, smooth muscle, and adventitia expressed per unit of V:SA (left y axis) and the percentage of airways containing lymphoid follicles (right y axis); in the inset, Movat's staining highlights a lymphoid follicle containing a germinal center (GC) surrounded by a rim of darker-staining lymphocytes that extend to the epithelium of both the small airway and the alveolar surface. Asterisks indicate P<0.001 for the comparison with GOLD grade 0, daggers indicate P<0.001 for the comparison with GOLD grade 1, and double daggers indicate P<0.001 for the comparison with GOLD grade 2. Adapted from Hogg et al.[2]

cells appear and create a provisional matrix that allows the microvascular network to reconnect and supports the restoration of the epithelial surface, which under ideal circumstances can restore the tissue to a healthy state.[32] Repetitive injury, such as that induced by smoking, elicits a more complex form of tissue repair that combines tissue destruction with scar formation.[33]

Once the inflammatory stimulus ceases, resolution of inflammation (i.e., catabasis) begins.

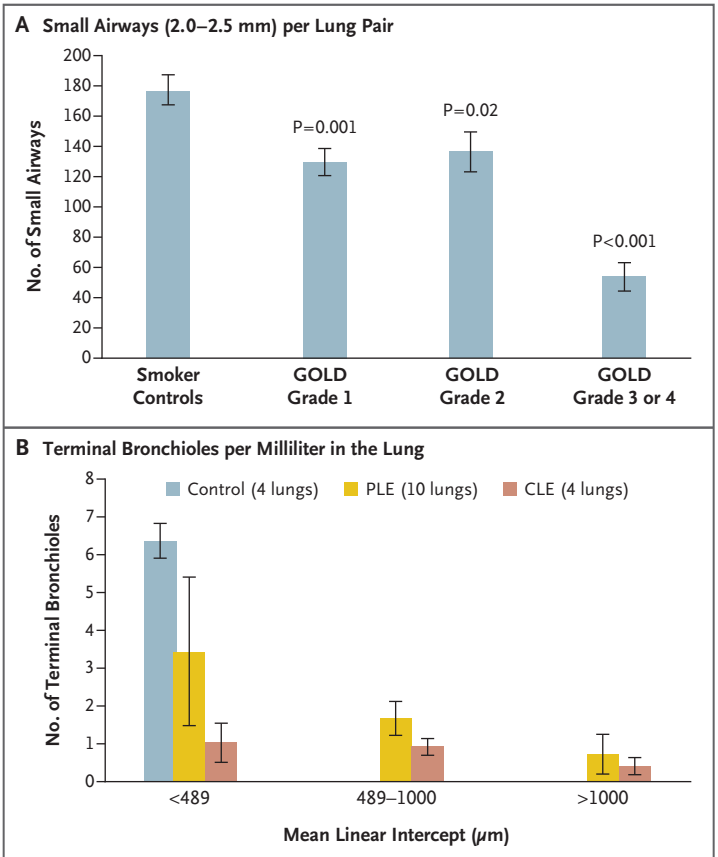

Figure 3. Number of Small Airways According to Severity of Airflow Limitation and Amount of Emphysema.

Panel A shows that the number of airways measuring 2.0 to 2.5 mm in diameter per lung pair is lower in patients with COPD than in smokers with normal spirometric findings (control smokers), in proportion to the severity of airflow limitation (GOLD grade 1, 2, 3, or 4); P values are for the comparison with control smokers. Panel B shows that the number of terminal bronchioles is reduced in patients with COPD in relation to the amount of emphysema present (as determined by the mean linear intercept), both in patients with panlobular emphysema (PLE) and in those with centrilobular emphysema (CLE). This reduction also occurs in patients with COPD but without emphysema (mean linear intercept, <489 μm). The I bars indicate standard errors. Adapted from McDonough et al.[20]

This is a highly regulated process that requires the active participation of many different molecules, including lipid mediators (e.g., lipoxins, protectins, and resolvins) and repair factors (e.g., transforming growth factor β, vascular endothelial growth factor, hepatocyte growth factor, and peroxisome proliferator–activated receptors), as well as the elimination of apoptotic neutrophils and epithelial cells by macrophages (efferocytosis), which prevents secondary necrosis of apoptotic cells with liberation of the proinflammatory cytoplasmic content.[34] A key macrophage efferocytosis receptor, CD44, is down-regulated in patients with COPD.[35]

An adaptive immune response to either self antigens[36] or foreign antigens (bacterial, viral, or fungal)[2] can also contribute to the pathogenesis of COPD. Patients with COPD have greater numbers of T lymphocytes and B lymphocytes than healthy persons (Fig. 2),[2] as well as B-cell infiltration (with the formation of lymphoid follicles) in the walls of terminal bronchioles and alveolar tissue (Fig. 2, inset), which correlates with a reduced number of alveolar attachments to the airway walls,[37] and patients who have COPD with emphysema have a distinct B-cell transcriptomic signature.[38] These findings constitute circumstantial evidence of autoimmunity in patients with COPD.[39] The presence of circulating antibodies against elastin and pulmonary epithelium and endothelium (which may be deposited with complement in the lungs of patients with COPD), the observation that CD4+ T cells cultured from the lungs of patients with COPD recognize and respond to elastin by secreting interferon-γ and interleukin-10,[36] and the presence of increased numbers of type 1 and type 17 helper T cells secreting their canonical cytokines interferon-γ and interleukin-17 in patients with severe disease[40] constitute indirect evidence of an acquired immune response in COPD. Finally, experimental models have shown that injection of human umbilical-vein endothelial cells into rats leads to the production of antibodies against these cells and to the development of emphysema[41]; furthermore, when these antibodies are transferred to rats that have not been injected with endothelial cells, emphysema results,[41] providing direct evidence of an abnormal acquired immune response in COPD.[39]

GENETIC AND EPIGENETIC REGULATORS OF SMOKING-INDUCED LUNG INJURY

The well-established observation that COPD develops in only a proportion of smokers[1,42] provides support for the role of a person's genetic or epigenetic background in the pathogenesis of the disease. So far, the best-known genetic risk factor for COPD is alpha$_1$-antitrypsin deficiency,[3] but there are others. Hobbs et al. identified 22 genetic loci associated with COPD in a large cohort (see Table S1 in the Supplementary Appen-

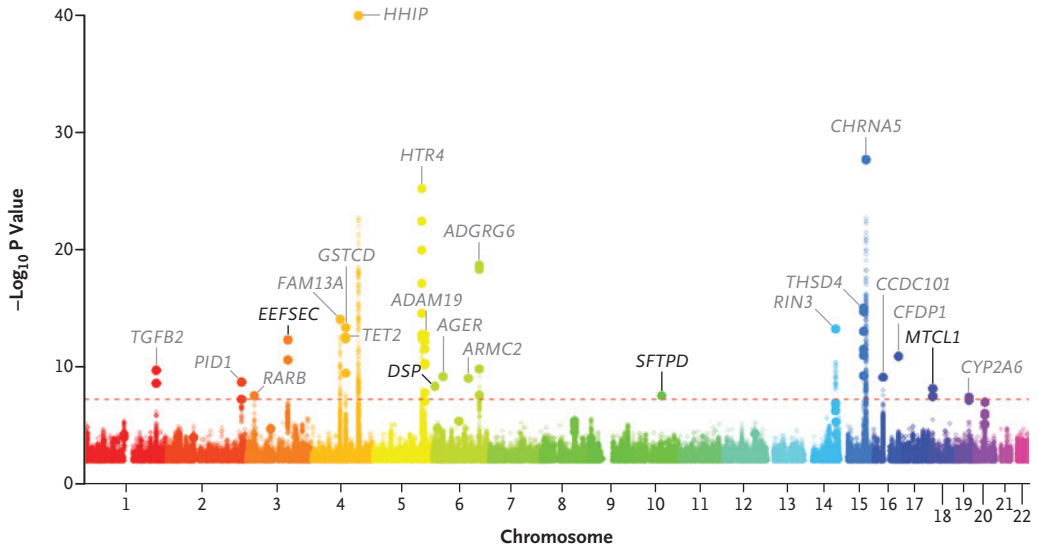

Figure 4. Genetic Loci Associated with COPD.

Shown is a Manhattan plot of P values ($-\log_{10}$) for associations between COPD and genetic loci in 22 chromosomes. The 18 gene names in gray indicate genes previously identified as associated with COPD or lung function, and the 4 names in black indicate loci newly identified in a recent study.[43] The horizontal dashed line shows the threshold for genomewide significance ($P<5\times10^{-8}$). Adapted from Hobbs et al.[43]

dix, available with the full text of this article at NEJM.org)[43]; 13 represented new associations with COPD. Although 9 of these 13 loci had previously been associated with measures of lung function in the general population, the remaining 4 represented new associations with both COPD and lung function (Fig. 4). Two of the loci (*FAM13A* and *DSP*) were previously reported to be related to pulmonary fibrosis (albeit with opposite risk alleles for COPD), and none to asthma.[43] The odds ratios for these 22 loci ranged from 1.05 to 1.25, indicating that individual genetic variation explains a small fraction of COPD susceptibility. Wain et al. developed a polygenic risk score for COPD susceptibility, also in a very large cohort, and reported that the odds ratio for COPD between the highest and lowest risk-score deciles differed by a factor of 3.7.[44] A discussion of the specific ontologies of the genetic loci identified in these two large studies is beyond the scope of this review, but it is notable that both studies identified functional annotation enrichment for fetal lung cells,[43,44] supporting a role of early life events in the risk of COPD. So far, however, studies investigating the genetic basis of COPD have included elderly patients without considering the potential influence of early life events. It is possible that the stratification of patients according to their vital lung-function trajectories (Fig. 1) may uncover more solid genetic associations.[9]

Epigenetic changes can also contribute to individual susceptibility to COPD.[44,45] For example, genomewide studies profiling DNA methylation in lung tissue from patients with COPD have revealed differences in methylation loci that are related to lung function, a diagnosis of asthma, nicotine dependence, T-cell development, and other factors.[46,47] These changes appear to be directly related to smoking exposure and may not resolve after cessation of smoking.[48] Likewise, the activity of histone deacetylase (HDAC), another epigenetic mechanism, is reduced in the lungs of affected patients in proportion to the severity of airflow limitation.[49] Given that HDAC downregulates the production of proinflammatory cytokines, this change can contribute to the enhanced inflammatory response that characterizes COPD.[2] Finally, several changes in microRNAs (miRNAs), which are another epigenetic regulator, have also been reported in patients with COPD.[50] A better understanding of the effects of these genetic and epigenetic modulators is necessary before they can be translated into clinical

practice for the purposes of diagnosis, prognosis, disease stratification, and treatment guidance.

MECHANISMS OF DISEASE PROGRESSION

Disease progression in COPD has traditionally been equated with loss of lung function, as manifested by an accelerated decline in FEV_1 over time.[51] This view needs to be reconsidered for several reasons.[52] First, COPD is a heterogeneous disease with components that can progress independently of one another.[53] For instance, frequent exacerbations, each of which is associated with a decline in FEV_1 and an effect on health status and prognosis, occur predominantly in a subgroup of patients.[54] Second, multimorbid conditions can contribute to disease progression independently of lung function.[3,5] Third, given that various lung-function trajectories lead to COPD in adulthood[7,9] (Fig. 1), it is possible that patients with severe disease have not had the mild and moderate stages of disease. For obvious ethical and practical reasons, it is not possible to study the progression of lung disease by obtaining sequential lung samples from the same person at regular intervals. The available evidence (Figs. 2 and 3) is therefore based on comparisons of single lung-tissue samples obtained from patients with different degrees of airflow limitation.[2] Although these cross-sectional observations are compatible with the hypothesis that the progression of COPD is associated with increased inflammation and an abnormal tissue-repair process, they cannot exclude the possibility that the pathogenic mechanisms of disease with a mild effect on lung function differ from those of disease with a severe effect on lung function. Thus, it is possible that these stages actually result from different pathogenic mechanisms and have different natural histories.[9,11] Finally, the traditional view that COPD is always a progressive disease also needs to be revised because lung function often remains stable or may even improve with time in some patients.[55,56]

LUNG AGING AND CELL SENESCENCE

Because lung function normally declines with age owing to lung aging, the accelerated decline in lung function that occurs in COPD after the FEV_1 peaks in early adulthood[42] may be interpreted as accelerated lung aging.[57] Yet the cycle of injury, repair, and remodeling, reviewed above, can also increase the loss of lung function without truly being a mechanism of lung aging. Alternatively, there is evidence that true accelerated lung aging can contribute to the progression of COPD, since most hallmarks of aging are altered in persons with COPD; these alterations include genomic instability,[58] telomere attrition[59] and telomerase mutations,[60] loss of proteostasis,[61] increased autophagy,[62] increased apoptosis of epithelial[63] and endothelial[64] cells, mitochondrial dysfunction[65] and mitophagy,[66] stem-cell exhaustion and dysfunction,[67-69] and dysregulation of the extracellular matrix.[70] In addition, the increased prevalence of comorbid conditions among patients with COPD could also support a generalized process of aging in such patients.[10] However, the observation that these conditions are prevalent among persons with low lung function in early adulthood[10] raises questions about the relationship between multimorbid conditions and aging in COPD.

The term "cell senescence" is often used in the discussion of lung aging in COPD and refers to a functional state of the cell characterized by irreversible replicative arrest, apoptosis resistance, and acquisition of a senescence-associated secretory phenotype (SASP) with proinflammatory and tissue-destructive effects.[71] This phenotype includes the secretion of cytokines, chemokines, bradykinin, prostanoids, proteases, miRNAs, hemostatic factors, damage-associated molecular patterns (DAMPs), and factors that cause stem-cell dysfunction and loss of tissue resilience.[71] It is clear that senescent cells accumulate in aged tissues, but it has also been shown that younger cells can be induced into a senescent state in vitro[71]; therefore, the term senescence is not always synonymous with aging. It is important to keep this caveat in mind when considering the evidence of senescence in alveolar epithelial cells, endothelial and pulmonary-artery smooth-muscle cells, and fibroblasts in COPD.[72] On the other hand, immune senescence (i.e., progressive, age-related impairment of the immune system) impairs the response to new antigens, favors the development of autoimmunity (discussed above), and increases susceptibility to infection and, perhaps, to changes in the airway microbiome.[73] Excessive senescence can therefore also be a pathogenic mechanism of COPD, and senolytic therapies aimed at reducing the senescent-cell burden in a number of human diseases merit investigation.[71]

CONCLUSIONS

Once believed to be a single disease caused by smoking and characterized by a progressive loss of lung function with age,[1] COPD should currently be considered a clinical syndrome with many causes in addition to smoking.[13,17] This does not mean that health care professionals should refrain from encouraging all their patients who smoke to quit, but it does mean that the pathogenic mechanisms in mild-to-moderate COPD may differ from those in severe-to-very-severe cases of airflow limitation.[11] In fact, the assumption that COPD is always a progressive disease also requires careful reconsideration. Currently available evidence indicates that COPD is the end result of a series of dynamic, interactive, and cumulative gene–environment interactions from conception to death that determine the development, maintenance, and function of the lungs, as well as other systemic organs.[11,14] This realization inevitably leads to the conclusion that the pathogenesis of COPD is complex and heterogeneous and that several mechanisms coexist and interact.[11] It is therefore imperative to identify and validate biomarkers associated with specific endotypes (i.e., mechanisms of disease) that underlie the various lung-function trajectories in patients and rigorously evaluate them to determine which ones are causative. This approach could represent the first step toward the development of specific, effective, and safe preventive and therapeutic strategies, which most likely will have to be implemented earlier in life.[9]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank R. Rodriguez-Roisin, M.D., Ph.D. (Barcelona), B. Celli, M.D. (Boston), and R. Faner, Ph.D. (Barcelona) for their careful reading of and helpful contributions to an earlier version of the manuscript.

REFERENCES

1. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1977;1:1645-8.
2. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 2004;350:2645-53.
3. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Am J Respir Crit Care Med 2017;195:557-82.
4. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374:733-43.
5. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32:962-9.
6. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007;370:797-9.
7. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med 2015;373:111-22.
8. Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. Lancet Respir Med 2018;6:535-44.
9. Agusti A, Faner R. Lung function trajectories in health and disease. Lancet Respir Med 2019;7:358-64.
10. Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. Lancet Respir Med 2017;5:935-45.
11. Agustí A, Faner R. COPD beyond smoking: new paradigm, novel opportunities. Lancet Respir Med 2018;6:324-6.
12. Woodruff PG, Barr RG, Bleecker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. N Engl J Med 2016;374:1811-21.
13. Celli BR, Agustí A. COPD: time to improve its taxonomy? ERJ Open Research 2018;4(1):00132-2017.
14. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta: Centers for Disease Control and Prevention, 2010 (https://www.ncbi.nlm.nih.gov/books/NBK53017/).
15. Martinez FD. Early-life origins of chronic obstructive pulmonary disease. N Engl J Med 2016;375:871-8.
16. Boucher RC. Muco-obstructive lung diseases. N Engl J Med 2019;380:1941-53.
17. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. N Engl J Med 2019;381:1257-66.
18. Mead J. The lung's quiet zone. N Engl J Med 1970;282:1318-9.
19. Koo H-K, Vasilescu DM, Booth S, et al. Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study. Lancet Respir Med 2018;6:591-602.
20. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med 2011;365:1567-75.
21. Barnes PJ. Chronic obstructive pulmonary disease. N Engl J Med 2000;343:269-80.
22. Tuder RM, Petrache I, Elias JA, Voelkel NF, Henson PM. Apoptosis and emphysema: the missing link. Am J Respir Cell Mol Biol 2003;28:551-4.
23. Tuder RM, Yoshida T, Fijalkowka I, Biswal S, Petrache I. Role of lung maintenance program in the heterogeneity of lung destruction in emphysema. Proc Am Thorac Soc 2006;3:673-9.
24. Coxson HO, Chan IHT, Mayo JR, Hlynsky J, Nakano Y, Birmingham CL. Early emphysema in patients with anorexia nervosa. Am J Respir Crit Care Med 2004;170:748-52.
25. Sharafkhaneh A, Hanania NA, Kim V. Pathogenesis of emphysema: from the bench to the bedside. Proc Am Thorac Soc 2008;5:475-7.
26. Taraseviciene-Stewart L, Douglas IS, Nana-Sinkam PS, et al. Is alveolar destruction and emphysema in chronic obstructive pulmonary disease an immune disease? Proc Am Thorac Soc 2006;3:687-90.
27. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J 2008;32:1371-85.
28. Peinado VI, Barberá JA, Abate P, et al. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1605-11.
29. Kovacs G, Agusti A, Barberà JA, et al. Pulmonary vascular involvement in chronic obstructive pulmonary disease: is there a pulmonary vascular phenotype? Am J Respir Crit Care Med 2018;198:1000-11.
30. Olloquequi J, Jaime S, Parra V, et al. Comparative analysis of COPD associated

with tobacco smoking, biomass smoke exposure or both. Respir Res 2018;19:13.
31. Golpe R, Martín-Robles I, Sanjuán-López P, et al. Differences in systemic inflammation between cigarette and biomass smoke-induced COPD. Int J Chron Obstruct Pulmon Dis 2017;12:2639-46.
32. Kumar V, Abbas AK, Fausto N, eds. Robbins and Cotran pathologic basis of disease. 7th ed. Philadelphia: Elsevier Saunders, 2005.
33. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 2004;364:709-21.
34. Serhan CN. Resolution phase of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. Annu Rev Immunol 2007;25:101-37.
35. Noguera A, Gomez C, Faner R, et al. An investigation of the resolution of inflammation (catabasis) in COPD. Respir Res 2012;13:101.
36. Cosio M, Saetta M, Agusti A. Immunological aspects of COPD. N Engl J Med 2009;360:2445-54.
37. Tanabe N, Vasilescu DM, Kirby M, et al. Analysis of airway pathology in COPD using a combination of computed tomography, micro-computed tomography and histology. Eur Respir J 2018;51:51.
38. Faner R, Cruz T, Casserras T, et al. Network analysis of lung transcriptomics reveals a distinct B-cell signature in emphysema. Am J Respir Crit Care Med 2016; 193:1242-53.
39. Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunol Today 1993; 14:426-30.
40. Kheradmand F, Shan M, Xu C, Corry DB. Autoimmunity in chronic obstructive pulmonary disease: clinical and experimental evidence. Expert Rev Clin Immunol 2012;8:285-92.
41. Taraseviciene-Stewart L, Scerbavicius R, Choe KH, et al. An animal model of autoimmune emphysema. Am J Respir Crit Care Med 2005;171:734-42.
42. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham Offspring cohort. Am J Respir Crit Care Med 2009;180:3-10.
43. Hobbs BD, de Jong K, Lamontagne M, et al. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis. Nat Genet 2017;49:426-32.
44. Wain LV, Shrine N, Artigas MS, et al. Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. Nat Genet 2017;49: 416-25.
45. Morrow JD, Glass K, Cho MH, et al. Human lung DNA methylation quantitative trait loci colocalize with chronic obstructive pulmonary disease genome-wide association loci. Am J Respir Crit Care Med 2018;197:1275-84.
46. Morrow JD, Cho MH, Hersh CP, et al. DNA methylation profiling in human lung tissue identifies genes associated with COPD. Epigenetics 2016;11:730-9.
47. Selman M, Martinez FJ, Pardo A. Why does an aging smoker's lung develop idiopathic pulmonary fibrosis and not chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2019;199:279-85.
48. Qiu W, Wan E, Morrow J, et al. The impact of genetic variation and cigarette smoke on DNA methylation in current and former smokers from the COPDGene study. Epigenetics 2015;10:1064-73.
49. Ito K, Ito M, Elliott WM, et al. Decreased histone deacetylase activity in chronic obstructive pulmonary disease. N Engl J Med 2005;352:1967-76.
50. Du Y, Ding Y, Chen X, et al. MicroRNA-181c inhibits cigarette smoke-induced chronic obstructive pulmonary disease by regulating CCN1 expression. Respir Res 2017;18:155.
51. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-55.
52. Agustí A, Celli B. Natural history of COPD: gaps and opportunities. ERJ Open Research 2017;3(4):00117-2017.
53. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010; 11:122-36.
54. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
55. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med 2011;365:1184-92.
56. de-Torres JP, Marín JM, Pinto-Plata V, et al. Is COPD a progressive disease? A long term Bode cohort observation. PLoS One 2016;11(4):e0151856.
57. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. Chest 2009;135: 173-80.
58. Brody JS, Spira A. State of the art: chronic obstructive pulmonary disease, inflammation, and lung cancer. Proc Am Thorac Soc 2006;3:535-7.
59. Morlá M, Busquets X, Pons J, Sauleda J, MacNee W, Agustí AG. Telomere shortening in smokers with and without COPD. Eur Respir J 2006;27:525-8.
60. Stanley SE, Chen JJ, Podlevsky JD, et al. Telomerase mutations in smokers with severe emphysema. J Clin Invest 2015; 125:563-70.
61. Min T, Bodas M, Mazur S, Vij N. Critical role of proteostasis-imbalance in pathogenesis of COPD and severe emphysema. J Mol Med (Berl) 2011;89:577-93.
62. Chen ZH, Kim HP, Sciurba FC, et al. Egr-1 regulates autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. PLoS One 2008;3(10):e3316.
63. Ryter SW, Lee SJ, Choi AM. Autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. Expert Rev Respir Med 2010;4:573-84.
64. Kasahara Y, Tuder RM, Cool CD, Lynch DA, Flores SC, Voelkel NF. Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. Am J Respir Crit Care Med 2001;163:737-44.
65. Prakash YS, Pabelick CM, Sieck GC. Mitochondrial dysfunction in airway disease. Chest 2017;152:618-26.
66. Mizumura K, Cloonan SM, Nakahira K, et al. Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. J Clin Invest 2014;124:3987-4003.
67. Staudt MR, Buro-Auriemma LJ, Walters MS, et al. Airway basal stem/progenitor cells have diminished capacity to regenerate airway epithelium in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;190:955-8.
68. Ghosh M, Miller YE, Nakachi I, et al. Exhaustion of airway basal progenitor cells in early and established chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2018;197:885-96.
69. Palange P, Testa U, Huertas A, et al. Circulating haemopoietic and endothelial progenitor cells are decreased in COPD. Eur Respir J 2006;27:529-41.
70. Meiners S, Eickelberg O, Königshoff M. Hallmarks of the ageing lung. Eur Respir J 2015;45:807-27.
71. Kirkland JL, Tchkonia T. Cellular senescence: a translational perspective. EBioMedicine 2017;21:21-8.
72. Houssaini A, Breau M, Kebe K, et al. mTOR pathway activation drives lung cell senescence and emphysema. JCI Insight 2018;3(3):93203.
73. Faner R, Rojas M, Macnee W, Agustí A. Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012;186:306-13.