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⊗ The Origins of Chronic Obstructive Pulmonary Disease: Sometimes the Journey Matters More than the Destination

Fundamentally, chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder, and over the past 40 years, there have been great advances in clarifying this heterogeneity to the point that we now have a number of candidates that can be considered veritable COPD endotypes (1). Despite this progress, spirometry is still required to diagnose COPD, and the constraint to meet this spirometric criteria has obscured an important truth: a post-bronchodilator FEV₁/FVC ratio less than 0.70 only defines a destination but does not reveal how the patient arrived there (2). After all, one of the main goals of COPD research is to help clinicians predict how their patients' diseases will evolve and to map out individual natural histories such that timely interventions can be applied to slow or halt lung function decline. In reality, these paths and roads stretch both forward and backward, and thus it is perhaps prudent to examine where we came from as well as where we are going.

A discussion of the natural history of COPD necessarily begins with the work of Charles Fletcher and Richard Peto, but the dogma of accelerated FEV₁ decline was challenged in 2015 when Lange

and colleagues demonstrated that the inability to attain maximal lung function in early adulthood contributes significantly to COPD development (3, 4). In that landmark study, an analysis of pooled participants from three large longitudinal cohorts revealed distinct lung function trajectories when the results were stratified based on whether the study participant had normal FEV₁ at cohort inception (4). Four divergent trajectories were modeled, of which two outlined markedly different pathways to COPD: some subjects with normal FEV₁ at study onset developed COPD as a result of accelerated lung function decline, whereas an equal number had low or submaximal FEV₁ at study onset and developed COPD despite having a normal rate of decline. In this issue of the *Journal*, Marott and colleagues (pp. 210–218) provided an insightful update on one of these three cohorts, the Copenhagen City Heart Study (5). After 20 years of follow-up, 144 of 1,170 participants in this cohort developed COPD, including 79 who were in the “normal maximally attained FEV₁” trajectory and 65 in the “low maximally attained FEV₁” trajectory. These two subpopulations were equivalent in age, smoking habits, asthma history, and FEV₁ at the time of diagnosis, but predictably, participants who attained normal maximal FEV₁ had a FEV₁ rate of decline that was twice as high as those who had low maximal FEV₁. After another 10 years of follow-up, the rate of FEV₁ decline in these two COPD subgroups converged, but their mortality curves separated, with individuals in the normal maximally attained FEV₁ trajectory having increased all-cause mortality as well as nonmalignant respiratory mortality. There were several limitations to this study, the most important of which being the dwindling of the study population

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over the four decades of follow-up, especially in those with COPD. This resulted in large confidence intervals in the hazard ratio estimates and potentially prevented detection of other differences, such as severe exacerbation risk because of inadequate power. Detractors may also suggest that it was overly simplistic to dichotomize patients into these two trajectories of normal and low maximally attained FEV₁ and that, in reality, there is likely a spectrum of different lung function trajectories (6). Nevertheless, at least two other longitudinal studies of children, one starting at birth and another at a young age, have modeled similar lung function trajectories, with both demonstrating an association between early low lung function and COPD development later in life (7, 8). Any single patient's natural history of disease is affected by a collection of genetic and environmental factors, but grouping individuals into these trajectories is a valuable cognitive construct for thinking about COPD pathogenesis and progression. Furthermore, the fact that this study showed that these trajectories are associated with differences in mortality suggests that this "low maximal lung function" trajectory is more than just a developmental component to COPD and may represent a biologically distinct COPD subtype altogether.

These ideas have important implications for future research. Clinical COPD studies are already shifting their attention toward "early COPD" and focusing on younger smokers (9). However, practical cutoffs for age and cigarette smoke exposure are still required for recruitment into studies, and depending on the stringency of individual studies, some cutoffs may not attack the root of COPD aggressively enough, as multiple studies have already demonstrated that selected smokers as young as in their 20s can have an increased risk for developing COPD (10, 11). This is particularly relevant as the at-risk population shifts younger, as evidenced by the high prevalence of tobacco and electronic cigarette use among high school students and even middle school students; the biological underpinnings of COPD may be developing in these very young smokers, even when they have smoked well short of 10 pack-years (12, 13). Notably, previous studies have not shown that there is a difference in the rate of exposure to maternal smoking during gestation or early active smoking between young adults in the normal lung function trajectory and those in the low lung function trajectory (7, 8). Alternative risk factors to smoke, such as early respiratory viral infections (and the potential resultant changes to the lung microbiome), childhood asthma, and exposure to pollution, have all been connected to COPD development, but more work in these areas is needed. There is also a critical need for innovative models that explore COPD pathogenesis at a mechanistic level. Current animal models of COPD, including elastase and cigarette smoke-exposure models, target animals at an age when lung development has already completed (14). In addition, these studies frequently focus on airspace enlargement or emphysema development as a primary outcome, which, though impressive histologically, does not adequately represent the biological processes that occur in early COPD. Likewise, animal models of abnormal lung development or bronchopulmonary dysplasia have similar limitations: they are challenging to apply to very young postnatal animals and often result in phenotypes such as acute lung injury or fibrosis, which are not reflective of problems in lung development (15). Novel approaches, such as applying machine learning techniques to younger smoker cohorts to improve the clustering of trajectories or using three-dimensional organoids to model lung morphogenesis and disease, can potentially complement conventional clinical and animal studies (16, 17).

As outlined in this study and others, if the low maximal lung function trajectory is the road taken by nearly half of patients with COPD, then considerable additional effort is required to explore this road on a foundational level; tracing this path back to its beginning will not only add to our understanding of the origins of COPD but also provide us with new tools for tracking and treating its progression. ■

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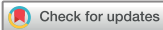
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ACE2: The Only Thing That Matters?

In December 2019, cases of a respiratory disease were reported in Hubei Province, China, caused by a positive-sense RNA virus from the family *Coronaviridae* (1). Subsequently, the disease was called coronavirus disease (COVID-19) and the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outcome of infection with SARS-CoV-2 is highly variable; on one hand, the virus has been responsible for more than 360,000 deaths worldwide, and on the other hand, there is a diverse range of clinical outcomes in different people (2). For any virus, infection depends on the ability to 1) enter, 2) evade cellular defenses, 3) hijack host machineries to express viral genes, 4) replicate new genomes, 5) assemble viral particles, and 6) exit. Virus tropism, the ability to infect particular cell types, is defined by the differential expression of host factors the virus subverts or evades during these processes. The earliest determinant is binding and entry via a cell surface receptor.

For SARS-CoV-2 entry, the primary receptor is ACE2 (angiotensin I-converting enzyme 2), which serves as receptor for SARS-CoV and a human seasonal coronavirus, human coronavirus NL63 (HCoV-NL63) (1). The physiological role of ACE2 is the regulation of the renin-angiotensin hormone system, regulating blood volume, systemic vascular resistance, and cardiovascular homeostasis (3). ACE2 is abundantly expressed in intestine, liver, kidney, and testis (proteintlas.org). Because COVID-19 is primarily a respiratory disease with obvious virally induced lesions in the lung, there has been intense interest to characterize ACE2 expression in the respiratory tract.

In the current issue of the *Journal*, Zhang and colleagues (pp. 219–229) have analyzed a broad range of preexisting RNA expression microarray data from human trachea and small and large airway epithelium (SAE/LAE) (4). They confirm ACE2 expression in these tissues and report higher levels of ACE2 in the trachea and LAE as compared with SAE. Similarly, Sungnak and colleagues recently reported at a single-cell level that upper airway cell types, including ciliated cells, express ACE2 mRNA (5). Lee and colleagues confirmed this at the protein level, showing ACE2 expression on the motile cilia by immunofluorescent staining (6). Together, these findings imply that because of abundant ACE2 expression, respiratory cells in the upper respiratory tract, particularly ciliated cells, can be infected by SARS-CoV-2 and that they may be more susceptible to infection than those in deep lung. Indeed, Hou and colleagues employed an elegant

reverse genetic approach in which recombinant SARS-CoV-2 viruses expressing GFP (green fluorescent protein) were used to infect cells from different levels of the respiratory tract and showed that the gradient of decreased expression of ACE2 from nose to alveolus is mirrored by a decrease in permissiveness to virus infection (7).

However, ACE2 expression may not be the only factor determining SARS-CoV-2 permissivity.

Not all cells that express ACE2 are susceptible to SARS-CoV-2 infection. Re-evaluating single-cell RNA sequencing allowed Zhang and colleagues to identify expression of ACE2 in all SAE cell types (even if at reduced expression relative to LAE), including club cells. Others have confirmed the presence of ACE2 protein and the surface activating protease TMPRSS2 (transmembrane protease, serine 2) in club cells (7). Nevertheless, club cells do not get productively infected by SARS-CoV-2 (7). Club cells have a stem cell-like function in the respiratory epithelium and potentially express intrinsically high levels of some antiviral IFN-stimulated genes, such as IFITMs (IFN-induced transmembrane proteins) and Ly6E (lymphocyte antigen 6E) (8), both described as coronavirus restriction factors (9, 10).

Just as expression of cell surface proteins used for SARS-CoV-2 entry does not always confer susceptibility to infection, different expression levels of ACE2 between individuals do not necessarily determine disease outcome. One key question in the field is why children are less affected by SARS-CoV-2 infection despite similar seroprevalence rates. Some studies have shown an age-dependent direct correlation between levels of ACE2 expression in nasal epithelium and age (11), but in other studies, this pattern did not hold up (6).

Another example is the effect of smoking. When the pandemic first started, smoking was considered a risk factor for COVID-19, as it is for many other respiratory virus infections. Zhang and colleagues were able to categorize their analysis of SAEs according to the smoking status and identified that male smokers had an increased expression of ACE2. This is complementary with other studies that have reported the same observations at the protein level (12). Strikingly, numerous epidemiological reports have found that smokers are actually underrepresented for COVID-19 complications (2, 13). Notably, a study with 1,099 individuals showed that smokers represented only 12.6% of COVID-19 cases while representing 30% of the Chinese population (2). These observations are inconsistent with the increased expression of the virus receptor and emphasize that receptor abundance is not the only factor important for severe disease progression.

Understanding the wide spectrum in severity of COVID-19 disease in different individuals infected by SARS-CoV-2 is important but challenging because disease outcome is determined by a combination of exposure levels, virus, and host responses. A first and crucial step is to understand how expression levels of genes we know

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