the parenchymal and airway disease in COPD with much more clarity. Advancements in phenotyping in conjunction with genetics have provided better understanding about the genetic susceptibility in COPD. The fact that several of the GWAS results for lung function and COPD susceptibility are also associated with distinct emphysema patterns is encouraging, whereas the question of whether these loci are associated with COPD or emphysema remains unanswered. Methods for quantification of local emphysema and airway disease patterns are also evolving. This will provide more opportunities to integrate these phenotypes with genetics and genomics for systems biology analyses and determination of molecular phenotypes in COPD. Localization of emphysema on treatment outcomes is also emerging. A large multicenter study comparing lung volume reduction surgery with medical treatment has shown that patients with upper lobe emphysema and low exercise capacity who received the surgery had a greater survival rate than similar patients who received medical therapy (15). In a recent randomized control trial evaluating the efficacy of a γ selective retinoid agonist in the treatment of emphysema, placebo patients with lower lung emphysema deteriorated faster than those with predominantly upper lobe disease. In addition, patients with lower lung emphysema appeared to respond better to the treatment (16). Adding more granularity using LHE and other regional emphysema measurements will definitely help advance this field. This makes us wonder, is COPD like the GOLDen rule of real estate . . . location, location, location? ■

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New Asthma Biomarkers: Shorter Telomeres, Longer Disease?

Asthma is a disease characterized by large variability in its natural history and clinical course. Patients can experience clinical manifestations that go from mild, sporadic wheezing episodes to life-threatening attacks, and anything in between. Once the disease has occurred, the clinical course can follow any combination of persistence, remission, and relapse, with a substantial and hardly predictable interpatient variability. This difficulty in predicting the natural history of asthma and, for that matter, the individual

response to treatment and tertiary prevention is partly related to our limited understanding of the molecular mechanisms that underlie the disease and its sequelae.

In this framework, biomarker research holds the promise—or at least the potential—to provide, on one side, new insights into the molecules and pathways that drive the disease processes and, on the other, to improve our ability to predict individual outcomes, persistence of disease, and, in turn, to "personalize" intervention strategies.

In this issue of the *Journal*, Belsky and colleagues (pp. 384–391) provide an additional contribution to the field by using longitudinal data from the Dunedin birth cohort to investigate the potential role of a newly proposed biomarker of persistent asthma: leukocyte telomere length (1). Telomeres are repetitive DNA sequences located at chromosomal ends that are critical for the maintenance of genomic integrity. Their progressive shortening with cell divisions leads to cellular senescence and apoptotic death and, as such, reduced telomere length has been proposed as a general marker of aging and linked to morbidity and mortality in several degenerative and age-related diseases (2, 3).

Two recent cross-sectional studies (4, 5) have first reported that leukocyte telomere length may also be shorter in subjects with asthma as compared with healthy control subjects and correlate inversely with disease severity. These previous findings are now confirmed and expanded by the study by Belsky and colleagues (1) in at least three ways. First—and most importantly—in this study the association between short telomere length and asthma is investigated within a longitudinal study design. Participants were followed from 9 to 38 years of age, and leukocyte telomere length at ages 26 and 38 years was found to be shorter in the group of subjects who had persistent asthma from childhood into adult age but not among subjects who had childhood asthma that remitted in adulthood or among those who only had adult-onset asthma. These findings suggest one of two possible scenarios: either an accelerated "molecular clock"—which may be influenced by genetic factors and/or early developmental processes—predisposes to an early-onset, chronic form of the disease; or the persistence of active symptoms from childhood into adult life and their related inflammatory processes lead to significant telomere shortening. However, telomere shortening between ages 26 and 38 years was not accelerated in any of the asthma groups as compared with subjects with no asthma. Therefore, the telomere length deficits associated with childhood asthma that persists into adulthood are likely to be established by early adult life, if not in childhood already. No telomere length assessments were available from earlier ages in the Dunedin study, and the conundrum of whether short telomere length precedes or is rather a consequence of persistent asthma will need to be addressed in future studies. By assessing telomere length and asthma phenotypes from the early stages of life and, in turn, linking them to disease outcomes in adulthood, these studies will also contribute to establishing whether leukocyte telomere length can provide any useful information to identify, ahead of time, children with asthma who will go on to have persistent disease as adults.

A second important strength of the study by Belsky and colleagues (1) is the use of a population-based birth cohort with a remarkably low attrition rate. This study design allowed the authors to compare leukocyte telomere length between disease groups within the same age intervals (i.e., at 26 and 38 yr) and, therefore, to minimize the risk of potential confounding by age differences across asthma phenotypes. This issue had not been systematically addressed by previous research in the field and is particularly relevant in light of the established strong relation of aging to telomere length (6, 7). However, the price to be paid for the methodological strengths of this type of cohort study is that molecular investigations usually need to rely on biospecimens that are easy to collect and the least burdensome for participants (i.e., almost invariably blood samples). This was also the case for the Dunedin study. Thus, whether the association between short telomere length of leukocytes and chronic asthma that was found in this study also applies to (or may even be stronger for) other cell types remains to be determined. Previous studies support a direct correlation between telomere length measured in leukocytes and in samples from the lungs, skeletal muscle, skin, subcutaneous fat, and saliva (7–9). However, the strength of this correlation and its relevance in asthma for cells that may be directly involved with disease processes in the airways are unknown. Of note, in patients with chronic obstructive pulmonary disease (COPD), telomere length has been shown to be reduced both in leukocytes and other cells from lung tissue, including alveolar type II and endothelial cells (10). Answering this question in asthma will contribute to elucidating whether the role of telomere shortening in this disease is mediated by mechanisms that are shared across different tissues and whether this biomarker may have any value in molecular phenotyping.

Last but not least, it is worth noting that in the study by Belsky and colleagues (1) both persistent asthma and shorter telomere length were found to be associated with elevated blood eosinophils, suggesting that blood eosinophilia may be involved in the link between the two. This finding holds particular interest because eosinophilia has been shown to characterize the subgroup of subjects with asthma who are at increased risk of developing persistent airflow limitation (11), the hallmark of COPD. Indeed, severity and persistence of asthma—two disease characteristics associated with shorter telomere length (1, 4)—have been consistently linked to worse disease outcomes in terms of lung function deficits. For example, in this same cohort, individuals who had persistent wheezing symptoms between age 9 and 26 years also had the lowest levels of the ratio between FEV_1 and FVC throughout that age range (12). It is therefore tempting to speculate that accelerated aging processes that are reflected by telomere shortening may increase the risk of patients with persistent asthma to develop COPD and, in turn, an overlap syndrome that carries an elevated morbidity and mortality burden (13). Although this scenario is in line with the previously established relation of short telomere length to lung function deficits in asthma (5) and to risk, morbidity, and mortality in COPD (3, 14, 15), at the present time it remains an untested hypothesis.

Indeed, as evidence for the relation of leukocyte telomere length to asthma has begun to build up, many of the above questions will need to be tested before the robustness and possible clinical implications of this association can be established and before some, undoubtedly needed, light can be shed on its nature and implicated mechanisms. ■

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The Child Is Father of the Man?

Establishing the origins of diseases such as asthma is one of the most important goals of research today.

Asthma affects hundreds of millions of people worldwide. It is the most frequent disease in childhood for which parents visit their doctors, yet the origins of asthma are still mainly unclear. In past decades, epidemiologic studies have provided better insights into the etiology of asthma and provided several risk factors that can contribute to this airway disease. Both developmental risk factors in utero and in early childhood, such as environmental tobacco smoke exposure, and genetic factors contribute to disease development, and these risk factors may interact (1).

Early childhood risk factors in the first years of life are especially important during the time of rapid lung development and growth. During that period, all children are exposed to viruses that are inhaled in the respiratory tract and that can affect epithelial cells, underlying tissues, and the immune system. As a consequence, many respiratory wheezing episodes occur in that time of life after an early-life lower respiratory illness (LRI). It has been shown that these LRIs, especially when induced by respiratory syncytial virus (RSV), can be followed by asthma-like symptoms (2), and later on, by a physician diagnosis of asthma with additional lung function measurements in childhood (3), a risk that tends to diminish toward adolescence (4, 5). This risk is especially increased in children with severe RSV-LRI who needed hospitalization in early life (6).

Gern and Busse distinguished two nonexclusive relationships between RSV-LRI and wheezing (7). They postulated that RSV bronchiolitis, as can occur after RSV infection, may interfere with normal lung development or immune maturation. This then leads to recurrent episodes of wheezing. Alternatively, RSV infection might constitute the first stimulus for wheezing in children who are predisposed to wheeze by genetic susceptibility or preexisting abnormal lung function at birth (7). However, observational studies cannot determine whether RSV infection is the cause of recurrent wheeze or the first indication of preexistent pulmonary vulnerability in preterm infants. Therefore, a prospective study was designed by Blanken and colleagues (8). A double-blind study with palivizumab, an RSV immunoprophylactic agent, during the RSV season showed that active treatment resulted in a significant reduction in wheezing days during the first year of life in preterm children, a finding that remained present even after the end of treatment. These findings implicate RSV infection as an important causal mechanism of recurrent wheeze during the first year of life in such infants. It remains to be determined whether these protective effects on wheeze are also present in term infants at risk for the development of asthma; a study to investigate this was recently recommended (9).

Of interest, wheezing episodes after an RSV-LRI have been shown to reduce by adolescence, suggesting this is a childhood risk only (3–6). This also would suggest that RSV-LRI is not an asthma risk but, instead, a wheezing risk in the first decade of life. In this issue of the *Journal*, Voraphani and colleagues (pp. 392–398) showed that this is indeed the case; that is, objectified RSV-LRI in children of the Tucson birth cohort followed up to 29 years of age did not relate to an increased risk for asthma at that age when RSV-LRI had taken place in the first years of life (10). However, the authors