Bioactive Lipids in Emphysema

Decoding Fat to Reveal COPD Phenotypes

It is reassuring to know that in the 21st century, chronic obstructive pulmonary disease (COPD) is appropriately recognized not as a single disease but as a constellation of heterogeneous lung diseases with several distinct phenotypes (1, 2). Given how lipids and their bioactive metabolites provide essential structural and functional support in all living organisms (e.g., participating in cellular proliferation, apoptosis, senescence, migration, and organ vascularization), it is not surprising that their role has been actively investigated in the complex pathobiology of COPD. Specifically, among different classes of lipids, sphingolipids have been highlighted as key bioactive metabolites and potential biomarkers in COPD (3).

Ceramides (Cer), sphingomyelins (SM), and sphingosine-1-phosphate (S1P) are among the most common bioactive lipid mediators, some of which act as the extracellular ligands for G-protein-coupled receptors (4). S1P and its receptor, S1PR1 (expressed on lymphocytes), have been shown to be required for cell egression from the lymphoid system and into tissue under normal conditions (5). The discovery of S1P-mediated gradient formation and lymphocyte trafficking has stimulated the development of novel therapeutic agents (e.g., fingolimod) that suppress the immune system and treat some of the most recalcitrant autoimmune inflammatory diseases (6). Whether S1P or other bioactive lipids specifically promote acquired immune responses in smoke-induced lung inflammation, and whether their modulation could be used as novel therapeutics in different COPD phenotypes, remains unclear.

Smoking has been linked to increased lung Cer concentrations. This increase in Cer level has in turn been linked to the activation of apoptosis, impaired efferocytosis, and abnormal tissue repair that could collectively culminate in emphysema (7). Further, sphingolipids have been shown to be elevated in the sputum of smokers with COPD (8), suggesting that various sphingolipids might be associated with different COPD phenotypes.

In this issue of the *Journal,* Bowler and colleagues (pp. 275–284) examined the association between sphingolipids and different phenotypes in COPD (9). The authors used biological samples (plasma and peripheral blood mononuclear cells) collected from the COPDGene cohort to show that several sphingolipids found in the plasma are strongly associated with emphysema and COPD exacerbation phenotypes, but not with airflow obstruction and chronic bronchitis. They arrive at their conclusion by first performing a targeted study of 69 distinct sphingolipid species that were used for quantitative comparison in 129 current and former smokers. After adjusting for multiple covariates (e.g., age, sex, body mass index, and current smoking) and false discovery rate, they found that concentrations of Cer, SM, and gangliosides were strongly and inversely associated with emphysema phenotype in smokers (Figure 1). Employing receiver operating characteristic curves, they demonstrated that several sphingolipids improved diagnosis of moderate to severe emphysema beyond clinical and physiological covariates. Using a similar strategy, they identified 11 sphingolipids including four trihexosylceramides, three dihexosylceramides, sulfatide, and ganglioside that were positively, whereas S1P and SM were negatively, associated with severe COPD exacerbations. In support of these findings, receiver operating characteristic curve analyses showed that these 11 sphingolipids improved the ability to diagnose severe exacerbations beyond just clinical and physiologic covariates. The authors explored gene–metabolite association with their phenotypic analysis and show that sphingnosine–CYR61 is associated with severe emphysema whereas Cer–Acer is associated with severe COPD exacerbations.

The strength of the work includes the study population (the well-phenotyped COPDGene cohort), as well as replication of some of the markers using untargeted mass spectrometry in an independent laboratory. Some of the caveats of the study include using plasma samples that were not collected at the time of COPD exacerbation to measure trihexosylceramide levels. Given this limitation, which could significantly affect their findings, this biomarker might not support the conclusion that a rapid flux of sphingosine-to-ceramide-to-glycosylated ceramide metabolism occurs in smokers with COPD exacerbation. Further, a large study using the Multi-Ethnic Study of Atherosclerosis (MESA) and mixed-effect models reported that higher plasma concentrations of sphingomyelin predicted increased annual progression of emphysema (10). These findings appear to be contradictory to the current report that found a negative correlation between most of the sphingolipid species and emphysema severity (9). However, there are several differences between these reports that might provide insight to the seemingly divergent results.

First, the report by Bowler and colleagues is based on cross-sectional analysis of many highly bioactive lipids; in contrast, the MESA study examined plasma SMs to evaluate longitudinal changes in emphysema progression using serial chest computed tomography scans (9, 10). Second, the sample size in the MESA study was much larger, and the cohort was drawn from the general population (never and ever smokers) without selecting for lung disease *per se*, whereas the COPDGene cohort was designed to recruit smokers with and without COPD. Finally, the current report measured a large number of SMs in relation to several clinical endpoints in a relatively small cohort, whereas the MESA study used a large cohort, and its single endpoint was focused on changes in emphysema progression. Barring differences in the

Am J Respir Crit Care Med Vol 191, Iss 3, pp 241–254, Feb 1, 2015
Internet address: www.atsjournals.org

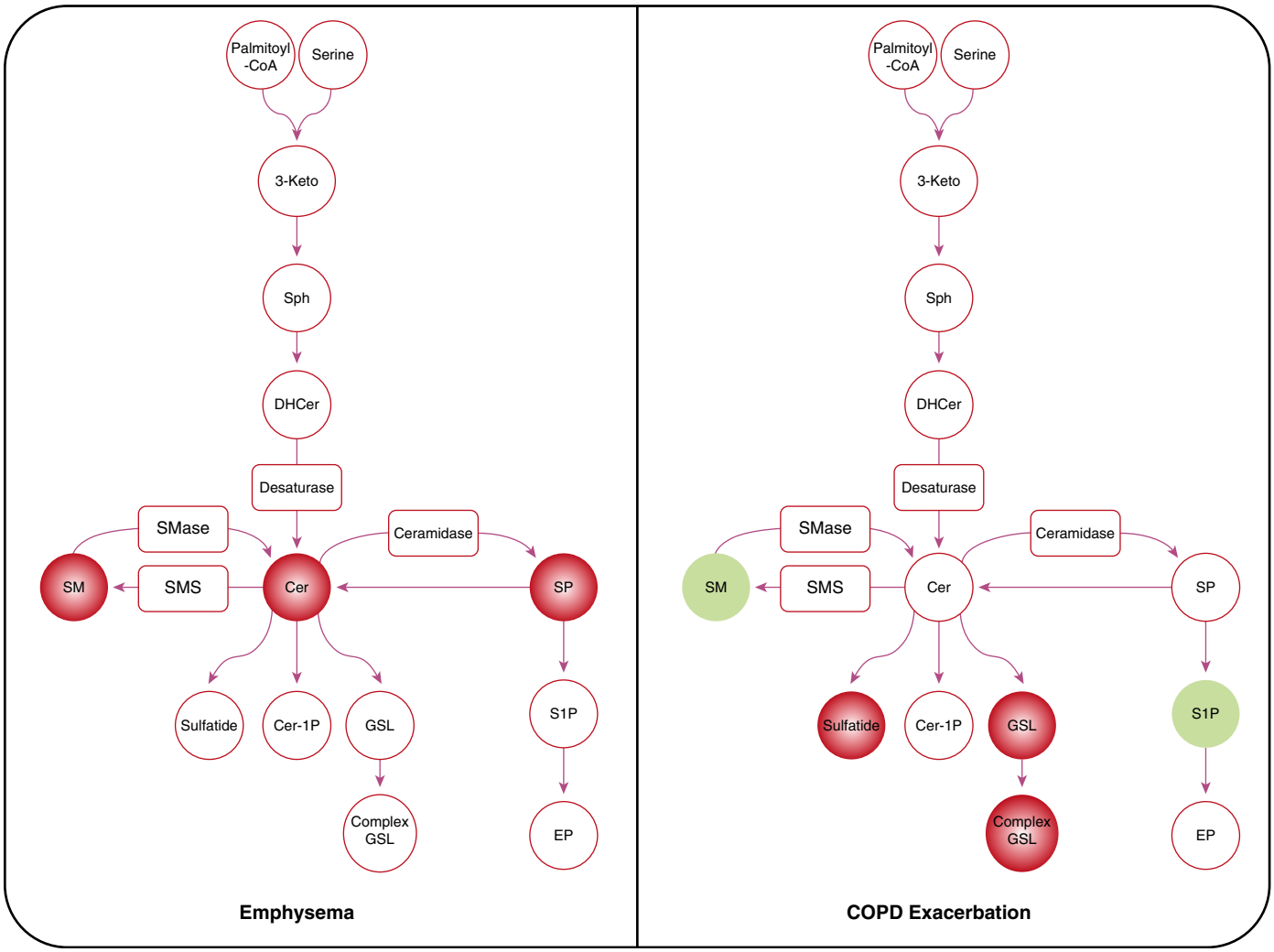

Figure 1. The sphingolipid metabolic pathway associated with emphysema (*left*) and COPD exacerbation (*right*). *Circles* and *rectangles* represent the metabolites and enzymes, respectively. *Red* and *green* colors indicate positive and negative associations, respectively. Concentration of Cer, SM, and gangliosides are strongly and inversely associated with emphysema phenotype and glycolipids (trihexosylceramides, dihexosylceramides, ganglioside). Sulfatides are positively and S1P and SM are negatively associated with severe COPD exacerbation phenotype. 3-Keto = 3-ketosphinganine; Cer = ceramide; Cer-1P = ceramide-1 phosphate; COPD = chronic obstructive pulmonary disease; DHCer = dihyroceramide; EP = ethanolamine phosphate; GSL = glycosphingolipid; SM = sphingomyeline; SMase = sphingomyelinase; SMS = sphingomyelin synthase; SP = sphingosine; S1P = sphingosine-1-phosphate; Sph = sphinganine.

methodology used to measure SMs (mass spectroscopy versus spectrophotometric assays), the differences in study design (cross-sectional versus longitudinal) could account for their divergent findings.

Overall, the current study adds significantly to our understanding of how metabolic pathways might be activated in smokers with different clinical phenotypes. Further, phenotypic characterization of this population in turn could identify novel bioactive lipids that could be linked to disease pathogenesis. More work is required to further clarify how quantitative measurement of bioactive lipids could be used to complement our current clinical and physiological assays to better diagnose emphysema and understand why patients with COPD exacerbate. Finally this work reminds us that ancillary studies in large, well-phenotyped cohorts (e.g., MESA, COPDGene, SPIROMICS, etc.) allow the testing of novel hypotheses to provide new insight into the conundrum of COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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An Old World's View on a New World's Solution

Improving quality of care and preventing avoidable complications is a priority to patients, healthcare providers, and policy makers (1, 2). Improvement, however, requires reliable measurement of the outcomes we wish to prevent. Accurate determination of the incidence of ventilator-associated pneumonia (VAP) is one of the major challenges in infection surveillance (3, 4). In an effort to improve the reliability of surveillance data and enhance their capability to guide quality improvement, the US National Healthcare Safety Network has shifted the focus of surveillance toward so-called ventilator-associated events (VAEs). A key entity within this paradigm is the ventilator-associated condition (VAC), a respiratory deterioration identified on the basis of ventilator settings that may in some cases subsequently be classified as infection-related VAC, or even as possible or probable VAP (5).

In this issue of the *Journal*, Klompas and colleagues (pp. 292–301) present the first multicenter study on prevention of VAE by using spontaneous breathing trials (SBTs) and spontaneous awakening trials (SATs) (6). The authors must be complimented in that they successfully implemented SATs and SBTs into routine clinical practice by transferring the responsibility for SAT and SBT initiation to nurses and respiratory therapists according to a predefined protocol. In intensive care units (ICUs) adopting the intervention, they achieved compliance rates higher than 75% of days when indicated and observed reduced duration of mechanical ventilation, shortened length of ICU and hospital stay, and lowered incidence of VAE per episode of mechanical ventilation, without a significant reduction of VAP incidence or an overall effect on in-hospital mortality (6). In addition, in a sophisticated multivariable analysis, they demonstrate an association between monthly performance rates of SBTs and SATs and VAE incidence. In the surveillance-only units, SBTs and SATs were not implemented actively, although their performance rates increased somewhat over the course of the study, and shortened durations of ICU and hospital stay were observed, along with a nonsignificant decrease in rates of VAP.

In accordance with other studies (7), SATs and SBTs are powerful interventions for reducing the duration of mechanical ventilation. As the authors point out, this reduction in time at risk could be the main mechanism in reducing VAE rates observed per episode of mechanical ventilation, but not per ventilator day. Importantly, the definition of VAE is closely linked to the duration of mechanical ventilation, as only patients ventilated for 4 or more days are eligible to develop a VAE (8). The current study includes all ventilated patients, of whom a considerable number were mechanically ventilated for less than 4 days and, hence, were not at risk for a VAE (25–49% in the intervention ICUs and $>$50% in the surveillance-only units). Yet the reduction in VAE incidence was also observed in a sensitivity analysis restricted to patients mechanically ventilated for at least 4 days. Nonetheless, it must be realized that the effect of SBTs and SATs is obfuscated by the inclusion of a considerable proportion of patients who could not benefit from the intervention from the perspective of VAE prevention, in particular in the surveillance-only units.

As the authors emphasize, the assignment of ICUs to either the collaborative or surveillance-only groups was not randomized, and the types of ICUs included in each group varied considerably, precluding direct comparison between both groups. Moreover, although the effect of concurrent quality improvement programs was excluded, confounding resulting from secular trends cannot be ruled out. The VAE paradigm was nationally adopted halfway through the study and gained considerable attention; this could have led to subtle changes in ventilator management policies and