Lipids in Chronic Obstructive Pulmonary Disease: A Target for Future Therapy?

Cigarette smoking is one of the leading preventable causes of mortality and morbidity worldwide, and in the United States alone it causes more than 480,000 deaths each year (1). Cigarette smoking is the principal cause of chronic obstructive pulmonary disease (COPD), a major incurable global health burden, which is currently the fourth largest cause of death in the world (2). Much of the disease burden and healthcare use in COPD is associated with the management of its comorbidities (2). It is now emerging that a significant proportion of patients with COPD have metabolic syndrome (MetS) as a comorbidity, but the mechanisms linking MetS to COPD are poorly understood (3).

There is evidence showing that lipids play an important role in respiratory diseases and could potentially link MetS to COPD. Much of this work has focused on the role of sphingolipids in the pathogenesis of COPD, cystic fibrosis, asthma, and acute lung injury (4, 5). This is perhaps due to sphingolipids having diverse functions, ranging from membrane constituents to intracellular second messengers and extracellular mediators. However, the role of sphingomyelins (SGMs) has not been fully evaluated, and this is surprising given that SGM is one of the major lipids in the mammalian plasma membrane, accounting for 2% to 15% of the total phospholipids (6), and regulates a plethora of physiological cellular responses (7–9). The biosynthesis of SGM involves the enzyme SGM synthase (SGMS), which is composed of two isoforms, SGMS1 and SGMS2 (10), of which SGMS2 is predominantly located in the plasma membrane (11). Surprisingly, the role of SGMS has not been evaluated in cigarette smoke (CS)-induced lung disease, and it is unclear how metabolic factors such as lipids affect airway resistance.

In this issue of the *Journal*, Gupta and colleagues (pp. 342–353) report on their studies of the effect of chronic CS exposure on SGMS activity and whether the deficiency of *Sgms2* affects pulmonary function (12). The authors found reduced SGMS activity in whole lungs of C57BL/6 mice exposed to CS for 6 months; they also found that CS exposure decreases *Sgms2* expression but not *Sgms1*. The authors excluded a strain-dependent effect, given that BALB/c mice also had CS-induced loss of SGMS activity and *Sgms2* gene expression. Collectively, the data suggest that reductions in *Sgms2* expression caused by CS may account for the observed reductions in SGMS activity.

Because CS reduces SGMS activity and *Sgms2* gene expression, the authors then went on to investigate whether this alters pulmonary function and airway and tissue resistance. The authors show that although CS exposure altered a plethora of lung function parameters (pressure–volume loops, total lung capacity, lung compliance, quasistatic compliance, tissue elastance, forced expiratory volume in 0.05 s/forced vital capacity), *Sgms2* deficiency did not influence any of these variables. This was not surprising, given that histological analysis of lung sections showed that *Sgms2* deficiency did not influence airspace enlargement or ductal/destructive fraction compared with wild-type (WT) CS-exposed mice. What is interesting, though, is that CS-exposed *Sgms2*$^{-/-}$ mice had an exponential increase in respiratory system resistance, Newtonian resistance, and tissue damping after methacholine challenge and that this was likely due to increased collagen deposition in peribronchial regions of the lungs of CS-exposed *Sgms2*$^{-/-}$ mice, as mucus production or smooth muscle cell area was not altered by the loss of *Sgms2* expression.

Changes in airway function can be associated with altered inflammatory responses in BAL fluid (BALF), and it is well known that CS exposure increases macrophages and neutrophils in BALF from mice and humans (13, 14). It is interesting that CS-exposed *Sgms2*$^{-/-}$ mice had more BALF macrophages and neutrophils than WT CS mice, but whether this was due to increased chemotactic factor levels for these cell types was not explored. However, the authors do show that the elevated immune cell infiltration was not due to Th2 cytokine levels.

Bozinovski and colleagues have previously proposed that Akt represents an attractive therapeutic target for the treatment of COPD because it functions as an intermediate linked to multiple signaling programs involved in survival, inflammation, and growth (15). Moreover, Akt is closely associated with key membrane-bound receptors and represents a convergent integration point for multiple stimuli implicated in COPD pathogenesis (15). Akt is also implicated in the systemic manifestations of COPD, such as skeletal muscle wasting and metabolic disturbances (15). In this study, CS exposure increased Akt phosphorylation in WT CS-exposed mice, which was further enhanced by *Sgms2* deficiency. It is conceivable that the increased immune cell infiltration in *Sgms2*-deficient mice could be due to increased levels of phosphorylated Akt, which in turn was acting on signaling pathways involved in inflammation and cell survival.

To explore the role of *Sgms2* in human COPD, the authors assessed SGMS2 levels in human bronchial tissue. Using immunofluorescence, they found that SGMS2 is expressed in bronchial tissue but that its levels were reduced in bronchial tissue from subjects with COPD. Moreover, primary human bronchial epithelial cells (HBE) isolated from subjects with COPD had lower SGMS2 gene expression and reduced SGMS protein levels than cells from nonsmoking counterparts. In addition, HBE cells isolated from nonsmokers exposed to CS exhibited suppressed SGMS2 expression compared with control subjects. The reduced

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SGMS gene and protein expression seemed to correspond with elevated Akt phosphorylation. Moreover, Akt inhibition reduced MMP-2 activity and secretion in HBE cells and both MMP-2 and -9 activity and secretion in monocyte-derived monocytes. Collectively, the data suggest that SGMS2, at least in part, regulates MMP2 and -12 responses by mediating Akt responses.

There are some possible limitations to this study that deserve discussion. The first relates to the *in vivo* studies where the authors only examined outcomes at one time point (i.e., 6 mo of CS exposure). More time points could have been explored to determine the contribution of Sgms2 deficiency to induction (i.e., acute inflammatory events) and progression (i.e., pathological consequences of chronic inflammation) of disease. Similarly, human lung and cell samples could have been obtained from various stages of COPD severity to determine the role of this pathway in COPD progression. Also, samples from healthy smokers could have been used, and better age-matching of the various populations should have been performed. It is intriguing that modulation of Akt responses in HBE cells and monocyte-derived monocytes can mediate MMP responses. However, the mechanism by which SGMS2 deficiency promotes Akt signaling needs to be determined using approaches that include lipidomic, proteomic, and genomic assessments. Despite these potential limitations, this valuable study will inform and prompt future studies in the field that will verify and expand on the results presented here.

In summary, the study by Gupta and colleagues shows that CS inhibits SGMS activity at least partially because of reduced SGMS2 expression, resulting in enhanced Akt phosphorylation, MMP production, and airway restriction (12). This study has important implications for CS-induced lung disease in humans, as it illustrates the importance of lipid mediators in pulmonary diseases and that their regulation may pave the way for novel treatments for COPD. ■

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