

## An Official American Thoracic Society Workshop Report: Obesity and Metabolism

### An Emerging Frontier in Lung Health and Disease

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#### Abstract

The world is in the midst of an unprecedented epidemic of obesity. This epidemic has changed the presentation and etiology of common diseases. For example, steatohepatitis, directly attributable to obesity, is now the most common cause of cirrhosis in the United States. Type 2 diabetes is increasingly being diagnosed in children. Pulmonary researchers and clinicians are just beginning to appreciate the impact of obesity and altered metabolism on common pulmonary diseases. Obesity has recently been identified as a major risk factor for the development of asthma and for acute respiratory distress syndrome. Obesity is associated with profound changes in pulmonary physiology, the development of pulmonary hypertension,

sleep-disordered breathing, and altered susceptibility to pulmonary infection. In short, obesity is leading to dramatic changes in lung health and disease. Simultaneously, the rapidly developing field of metabolism, including mitochondrial function, is shifting the paradigms by which the pathophysiology of many pulmonary diseases is understood. Altered metabolism can lead to profound changes in both innate and adaptive immunity, as well as the function of structural cells. To address this emerging field, a 3-day meeting on obesity, metabolism, and lung disease was convened in October 2015 to discuss recent findings, foster research initiatives, and ultimately guide clinical care. The major findings arising from this meeting are reported in this document.

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Obesity is a complex disorder characterized by changes in dietary intake, physical activity, the microbiome, innate and adaptive immunity, neuromuscular function, and cellular metabolism. Obesity also leads to dramatic changes in lung health and disease: Obesity is a major risk factor for the development of asthma (1) and acute

respiratory distress syndrome (ARDS) (2, 3), and it is associated with changes in pulmonary physiology (4), chronic obstructive pulmonary disease (COPD) outcomes (4), the development of pulmonary hypertension (4), sleep-disordered breathing (5), and lung transplant failure (6). Obesity and the metabolic syndrome are associated with chronic low-grade systemic inflammation, a process that is thought to drive many of the related complications. Recent evidence suggests that this inflammatory state may also lead to impairment of pulmonary immune responses and consequently affect the onset and progression of respiratory diseases. Indeed, obesity increases susceptibility to respiratory infections (7, 8) and worsens outcomes of ARDS (9). Therefore, investigations into the role of obesity and metabolism in the pathophysiological processes of pulmonary diseases are needed.

To address this emerging field, we convened the third biennial University of Vermont Conference on Obesity and the Lung, bringing together experts in various aspects of obesity, metabolism, and lung diseases to outline a state-of-the-art understanding of the field, to help achieve consensus, and to establish future research priorities for this field. The take-home messages from the meeting were as follows:

- Common genetic risk variants may be important contributors to the obesity-asthma relationship.
- Environmental factors, such as air pollution and certain dietary components, contribute to obesity-associated morbidity associated with lung disease.
- Obesity-mediated metabolic dysregulation contributes to the pathogenesis of asthma in obese persons.
- Altered mitochondrial function can contribute to increased susceptibility to lung diseases.
- Obesity-associated dyslipidemia has profound effects on the pulmonary immune response and appears to play a key role in the pathogenesis of lung diseases.

We are in the midst of an escalating global epidemic of overweight and obesity (10). The increased prevalence of overweight and obesity conveys not only greater morbidity and mortality to the population but also substantial associated medical

costs. Obesity affects multiple organ systems, including the respiratory system. Furthermore, altered metabolism and mitochondrial function can lead to profound changes in both innate and adaptive immunity, as well as in pulmonary function. Pulmonary researchers and clinicians are just beginning to appreciate the impact of obesity on common pulmonary diseases.

This transdisciplinary symposium was focused on emerging concepts and data pertaining to metabolic disease and lung health. The goals were to (1) develop research priorities and collaborations and (2) disseminate this knowledge to the wider scientific and medical community.

## Methods

This symposium was organized by a four-person planning committee (B.T.S., A.E.D., S.A.S., and R.S.S.). This committee met four times by teleconference to identify experts in the field who would present relevant data and act as discussants. The planning committee focused on recent advances in the understanding of the relationship between obesity and lung disease, and also on identifying themes that had emerged over the 2 years since the prior conference. For this cycle, the committee chose to focus on recent advances related to understanding genetic and epigenetic changes in obesity and asthma; work linking the microbiome, lung disease, and obesity; the role of lipids in pulmonary immune responses; and new insights into the central role of mitochondrial and cellular metabolism in diseases of the lung. The planning committee based programming and selection of speakers on careful review of the literature and knowledge of the important areas in the field. Speakers were asked to develop their presentations on the basis of a current review of published literature in their respective areas of expertise and also to include recent, as-yet-unpublished work done at their own laboratories. The format of the meeting included focused presentations followed by discussions and poster sessions presented by both senior and junior investigators. All participants submitted conflict-of-interest disclosures according to the policies and procedures of the American Thoracic Society. The symposium was convened in Burlington, Vermont, in October of 2015 and spanned

3 days. After the symposium, the writing committee drafted a workshop report based on an outline developed by the co-chairs. All speakers were given the opportunity to view and comment on the report.

## Obesity and Airway Diseases

### Insights Derived from Omics Approaches

Perhaps the best-described effect of obesity and changes in systemic metabolism are on the airway diseases, especially asthma. In this report, we summarize a session dedicated to the various “omics” approaches that are being used to understand the mechanistic basis for this relationship.

Asthma and obesity are both complex diseases that have a heritable component. Dr. Kelan Tantisira (Harvard Medical School, Boston, MA) reviewed evidence supporting the hypothesis that genetics may contribute to the relationship between obesity and asthma. First, there are Mendelian disorders (e.g., Bardet-Biedl syndrome) in which both obesity and asthma are present. Second, twin studies support some common heritability of obesity and asthma (11, 12). Third, both family-based linkage studies and genome-wide association studies indicate that colocalization of genomic regions for obesity and asthma (see Table 1 in Reference 13), and obesity and asthma share common candidate genes (14, 15). Genetic changes that protect against the common occurrence of asthma and obesity, such as a 0.45-Mb genomic inversion on chromosome 16p11.2, have also been identified (16). Functional validation of these regions, such as with gene expression studies, will be an important next step; some gene expression studies have already produced several promising findings (17). Researchers in a genome-wide epigenetic study have also identified several genes and pathways differentially methylated in obese versus nonobese children with asthma. These differences in methylation likely impact gene expression (18).

MicroRNAs (miRs) circulate in the blood, modify gene expression, and have the capacity for long-range signaling between cells. Certain miRs are consistently linked to asthma (19, 20) or to obesity (21). Many miRs altered in the asthmatic lung have also been found in the sera of children in the Childhood Asthma Management Program, and the expression

of some of these miRs is associated with body mass index. Obesity also appears to modify the relationship between miRs and asthma severity. These data suggest that circulating miRs may play a role in the obesity–asthma relationship.

In addition to genetic and epigenetic associations, alterations in the gut and lung microbiomes are observed in obesity and asthma. Dr. Benjamin Marsland (University of Lausanne, Lausanne, Switzerland) reviewed data supporting a role for the microbiome in asthma (*see also* Reference [22]). Colonization of the human gastrointestinal tract with bacteria begins at birth. Asthma often has its origins early in life, and two exposures associated with increased microbial exposure—residence on a farm and consumption of unpasteurized milk—protect against the development of allergic diseases, including allergic asthma (23). In mice, airway microbial colonization begins at birth, and its composition shifts drastically during the first month of life. This shift is associated with a reduced disposition toward allergic airway inflammation and coincides with increases in a regulatory T-cell population that requires programmed death ligand 1 (PD-L1) for its development. Indeed, blocking PD-L1 prevents this aging-related tolerance to allergic inflammation. Similarly, germ-free mice raised from birth without bacterial exposure do not demonstrate an age-related increase in PD-L1<sup>+</sup> regulatory T cells and maintain their predisposition toward allergic inflammation even as they age (24). Thus, early development of an airway microbiome appears key in preventing allergic asthma.

Furthermore, alterations in the gut microbiome induced by varying dietary fiber also impact allergic airway disease in mice. In particular, diets rich in fiber are associated with reduced allergic airway inflammation (25). The effect of dietary fiber is the result of microbial production of short-chain fatty acids that enter the circulation from the gut and act on bone marrow to impact dendritic cell populations that participate in the allergic process, suggesting important microbiome–metabolome interactions in the regulation of allergic airway disease.

Obesity also alters the microbiome and impacts the metabolomes of a variety of tissues, including the blood. Dr. Stephanie

Shore (Harvard T. H. Chan School of Public Health, Boston, MA) discussed ways in which microbiome–metabolome interactions might contribute to asthma in obese individuals. Both in humans and in mice, obesity alters the distal gut microbiota, increasing the ratio of Firmicutes to Bacteroidetes, the two most abundant phyla in the gastrointestinal tract (26, 27). These shifts have profound influences on host physiology because the typical adipose tissue inflammation observed with the induction of obesity is not observed if mice are treated with antibiotics (28). Exposure to the air pollutant ozone is an important trigger for asthma, and in female mice, treatment with a cocktail of antibiotics virtually abolishes obesity-related increases in the magnitude of ozone-induced airway hyperresponsiveness, indicating an important role for the microbiome in these events. Consistent with these observations, in lean mice in which the gut microbiome was first depleted with antibiotics and then reconstituted by repeated gavage with feces from untreated mice, the magnitude of ozone-induced airway hyperresponsiveness was greater in the reconstituted mice if the feces were derived from obese than from lean murine donors. Lung and blood metabolomic profiling was used to identify bacteria-derived moieties that might contribute to these changes in airway responsiveness. Changes in bile acids were among the metabolic pathways most affected. In particular, ozone exposure resulted in a marked increase in taurine-conjugated bile acids in antibiotic- but not vehicle-treated mice. Because bile acid binding to a G protein–coupled receptor, TGR5, causes relaxation of gut smooth muscle in a cAMP-dependent manner (29), it is conceivable that there are similar effects of bile acids on airway smooth muscle.

Metabolomic studies are also contributing to the understanding of COPD. Dr. Irina Petrache (National Jewish Health, Denver, CO) discussed her work on metabolomic derangements in COPD with an eye to better defining phenotypes using an unbiased approach. These studies demonstrated that mouse plasma metabolites are altered by chronic cigarette smoke (CS) exposure, and that some of these changes persist after CS cessation, including changes in sphingolipid metabolites (30). Metabolomic examinations of plasma from

approximately 130 smokers with or without COPD participating in the COPDGene Study (31) revealed phenotype-specific sphingolipid signatures. In emphysema, the pattern indicated accelerated sphingolipid metabolism with depletion of plasma sphingomyelin and ceramides, suggesting activation of the sphingomyelinase pathway. In participants with frequent COPD exacerbations, there was significant accumulation of complex glyceroceramides and signs of *de novo* synthesis. Similar to results obtained in mice (32), metabolomic analysis suggested an inverse correlation of sphingosine-1-phosphate in subjects with emphysema and COPD exacerbations, but not in those with chronic bronchitis. The accelerated ceramide catabolism in human plasma was supported by genomic identification of abnormal *ASAH1* (ceramidase) expression (33). These findings indicate that metabolomics is a promising tool to discover phenotypic biomarkers in COPD.

#### Insights Derived from Other Approaches

Dr. Janice Allen (National Institute of Environmental Health Sciences, Durham, NC) discussed how there is a consistent positive association of obesity with both the incidence and the prevalence of asthma; in both adults and children, obesity precedes and “predicts” the development of asthma (34). Researchers have noted that people with asthma tend to weigh more than people without asthma, and a large prospective cohort study suggested that obesity may explain much of the current asthma epidemic (35).

Authors of a 2011 National Institutes of Health asthma report identified 374 different substances, both naturally occurring and man-made, linked to asthma etiology; air pollution is an overarching factor. Variable factors such as land-use conditions (sprawl) and social context (crime) were specified as potential confounders of locally built environmental influences that might contribute to obesity and then asthma. Physical activity is affected by many variables, some of which may limit activities and contribute to the development of obesity and asthma (36). Environmental exposures may also contribute to the development of obesity: certain chemicals (termed *obesogens*) are endocrine disrupters that increase

sensitivity to weight gain and obesity. One example is fetal exposure to CS, an exposure that can increase the risk of developing asthma and obesity. There are multiple other recognized obesogens (e.g., components of plastics, including bisphenol A and diethylhexyl phthalate) that may contribute to obesity and lung disease, but this requires further study.

Obesity does not affect all people with asthma alike. There are at least two major phenotypes of asthma noted in obesity: a later-onset, nonallergic type with airway reactivity that tends to improve with weight loss and an earlier-onset type typically associated with increased markers of allergic inflammation. It is likely that obesity has distinct effects on these two asthma phenotypes.

The severity of asthma-related health effects in obese people may be based on whether asthma started early (<12 yr old) or later in life. Obese people with early-onset asthma had more airway obstruction and greater increases in bronchial responsiveness, and they were more likely to have asthma-related medical treatment or admissions (37). Patients with early-onset allergic asthma and obesity appear to represent a distinct phenotype with airway reactivity that does not necessarily improve with weight loss (although symptoms certainly do improve) (38). Dr. Anne Dixon (University of Vermont) discussed how those with early-onset allergic asthma and increased markers of allergic inflammation appear to be at significantly higher risk of morbidity related to asthma than their lean counterparts (37). The reasons for this are not clear but may be related to differences in airway allergic responses (metabolic dysfunction and related mediators might affect cell trafficking and inflammation), altering the nature of the allergic response in these individuals.

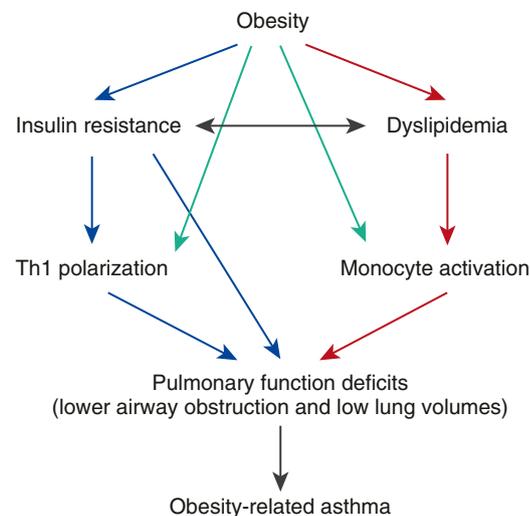
Dr. Dixon also discussed how in the later-onset patients improvements in airway reactivity with weight loss are related to reductions in sensitivity to airway closure (39) and improvements in baseline peripheral lung function (40). These patients also appear to have airway reactivity that is associated with visceral adipose tissue inflammation but not airway inflammation. Dr. Jason Bates (University of Vermont) discussed additional insights derived from modeling studies which suggest that

either an increase in airway wall thickness or a decrease in airway wall stiffness might contribute to the development of lung function abnormalities typically detected in these obese patients with asthma (41).

Metabolic derangements in adipose tissue manifest clinically as metabolic syndrome, a syndrome characterized by abdominal obesity, insulin resistance, hypertriglyceridemia, hypertension, and low high-density lipoprotein (HDL) cholesterol levels. The metabolic syndrome likely alters the pathogenesis of asthma through both nonimmune and immune pathways. Dr. Fernando Holguin (University of Pittsburgh, Pittsburgh, PA) discussed data showing that in obese patients with late-onset asthma, a reduction in L-arginine coupled with increased asymmetric dimethylarginine leads to uncoupling of nitric oxide synthase, consequent reductions in the bioavailability of nitric oxide in the airways, and increased oxidative stress. Reduced L-arginine/asymmetric dimethylarginine ratios are associated with reduced lung function, reduced exhaled nitric oxide, and increased respiratory symptoms (42). The metabolic syndrome may lead to long-term effects on the airways, refractory even to weight loss; in

the Longitudinal Assessment of Bariatric Surgery study, obese patients with asthma and the metabolic syndrome were less likely to achieve significant improvements in asthma control than those without the metabolic syndrome (43).

The metabolic syndrome may also alter the pathogenesis of asthma in obesity through effects on immune function. Dr. Deepa Rastogi (Albert Einstein College of Medicine, Bronx, NY) discussed how obese children with asthma have evidence of non-atopic Th1 polarization and increased activation of circulating monocytes, rather than atopic Th2 polarization. Importantly, components of the metabolic syndrome associate differentially with these two aspects of immune dysregulation: Insulin resistance is associated with Th1 polarization, whereas dyslipidemia with low HDL is associated with monocyte activation. Moreover, insulin resistance mediates the association of Th1 polarization with pulmonary function, particularly with lower lung volumes (44). Thus, immune responses in obese children with asthma are both altered and complex; these changes appear to be associated with changes in pulmonary function and are closely related to metabolic dysregulation (44). Importantly, obesity and/or metabolic



**Figure 1.** The complex interactions between obesity-mediated metabolic dysregulation, systemic inflammation, and pulmonary function deficits in association with obesity-related asthma. Obesity-mediated metabolic dysregulation includes (1) insulin resistance and its downstream effects (blue arrows) and (2) dyslipidemia and its downstream effects (red arrows). Insulin resistance and dyslipidemia frequently coexist. Obesity is also associated with systemic inflammation, Th-cell polarization and monocyte activation (green arrows). Inflammation mediated by metabolic dysregulation and obesity is associated with pulmonary function deficits specific to obesity-related asthma. Insulin resistance itself is associated with reduced pulmonary function.

syndrome appear to impair lung function through mechanisms independent of Th2-related inflammation, and thus are not likely to be steroid responsive (Figure 1).

Environmental factors may also contribute to the morbidity of lung disease in obesity; one such factor may be increased susceptibility to the effects of air pollution. Dr. Meredith McCormack (Johns Hopkins University, Baltimore, MD) discussed a number of studies which suggest that obesity worsens asthma control in response to air pollution. Dong and colleagues found that overweight and obese children have increased symptoms in response to nitrogen dioxide and particulate matter less than or equal to 10 μm in diameter (PM<sub>10</sub>), as well as increased risk of doctor-diagnosed asthma in response to sulfur dioxide and PM<sub>10</sub> (45). Lu and coworkers also found that being overweight or obese could increase susceptibility to indoor PM<sub>2.5</sub> and nitrogen dioxide in children with asthma living in urban environments (46). Similar findings have been reported in those over the age of 65 years. Epstein and colleagues found that traffic-related air pollution was associated with poor asthma control in obese individuals (47). McCormack and coworkers found that obesity also increased symptoms and exacerbations in response to PM in patients with COPD (48). The reasons for this increased susceptibility to PM are not known but could be related to altered breathing patterns in obesity (49), increased oxidative stress (50), or perhaps corticosteroid resistance with increasing weight (51).

Another environmental factor that may contribute to pulmonary morbidity in the setting of obesity is dietary composition. There are data to suggest that a Western dietary pattern (i.e., that characterized by high intake of processed foods, high-fat dairy produce,

and sugary desserts and drinks) is associated with asthma morbidity (52). Wood and coworkers have shown that intake of a high-fat diet increases airway inflammation and reduces bronchodilator responsiveness in patients with asthma (53). A pilot trial of a healthy eating intervention improved asthma outcomes (54), supporting the need for studies investigating the role of diet in improving asthma control. Together, current studies of the mechanisms underlying the links between obesity and airway disease suggest that physiological derangements and altered immune responses related to metabolic dysfunction contribute to the pathogenesis of airway disease in obesity and may increase susceptibility to environmental factors such as air pollution and high-fat diets.

### Mitochondrial and Cellular Metabolism in Lung Disease

#### Pulmonary Circulation

The maintenance of cellular metabolism is a fundamental aspect of all living organisms, and mitochondria play a central role in orchestrating these biological processes. As such, it is not surprising that alterations in mitochondrial function are now linked to a wide range of respiratory diseases, including COPD, asthma, pulmonary hypertension, and lung fibrosis (55–58). In the third session, presentations were focused on recent advances in the understanding of the biological mechanisms by which mitochondrial pathology contributes to the development of vascular and fibrotic disorders of the lung (Table 1).

In the first presentation, Dr. Evangelos Michelakis (University of Alberta, Edmonton, AB, Canada) discussed his work

linking mitochondrial pathology to the development of pulmonary arterial hypertension (PAH). Although his presentation introduced a variety of novel concepts, the major focus of the discussion was on the metabolic theory of PAH (59). This theory states that PAH is caused by a global metabolic defect in mitochondrial function that affects many tissues but manifests predominately in smooth muscle cells in the pulmonary circulation. His data indicate that central to this defect is the inhibition of pyruvate dehydrogenase as a result of increased pyruvate dehydrogenase kinase activity; this leads to a suppression of glucose oxidation and to an increase in dependence on glycolysis for driving cellular metabolism. Like many cancer cells that exhibit a similar predilection for aerobic glycolysis, smooth muscle cells in PAH also display a cancer-like hyperproliferative and antiapoptotic phenotype. Dr. Michelakis and colleagues speculated that metabolic events might drive the hyperproliferative phenotype in smooth muscle cells. To test this hypothesis, they administered a small-molecule inhibitor of pyruvate dehydrogenase kinase called *dichloroacetate* in a monocrotaline rat model of pulmonary hypertension. Remarkably, they found that dichloroacetate was effective not only in reversing the glycolytic shift but also in attenuating vascular remodeling in the lung. On the basis of these novel findings, his group is now planning studies to evaluate the safety, and ultimately the efficacy, of dichloroacetate in reducing vascular remodeling in patients with PAH.

In the second presentation, Dr. Stephen Black (University of Arizona, Tucson, AZ) extended this discussion by presenting his work on the role of mitochondrial endothelial nitric oxide synthase (eNOS)

**Table 1.** Summary of Mitochondria and Cellular Metabolism Session

Speaker	Mitochondrial Defect	Cell Type	Pathobiology	Disease Association
Michelakis	Decreased oxidative phosphorylation	Pulmonary vascular smooth muscle cells	Antiapoptotic, hyperproliferative phenotype	Pulmonary arterial hypertension
Black	Decreased carnitine transport	Pulmonary vascular endothelial cells	Impaired endothelial relaxation	High-flow pulmonary vascular disease
Jain	Increased mitochondrial oxidative stress	Lung fibroblasts	Increased TGF-β production	Idiopathic pulmonary fibrosis
Mora	Decreased mitophagy	Type II epithelial cells	Endoplasmic reticulum stress and increased cell death	Idiopathic pulmonary fibrosis
Natarajan	Decreased cardiolipin synthesis	Type II epithelial cells	Increased cell death	Idiopathic pulmonary fibrosis

Definition of abbreviation: TGF-β = transforming growth factor-β.

in regulating endothelial function in the pulmonary circulation (60). He showed that eNOS translocates to mitochondria in lung endothelial cells under high-flow conditions (61) as a result of post-translational modifications in the serine/threonine-specific protein kinase Akt (62). Moreover, he showed that mobilization of eNOS impairs mitochondrial function by disrupting key components of the carnitine shuttle and that L-carnitine supplementation could preserve nitric oxide signaling and restore endothelial function in a lamb model of high-output pulmonary vascular disease. Collectively, these findings provide additional support for the concept that mitochondria-targeted therapies might be effective in the treatment of pulmonary vascular diseases.

### Fibrotic Remodeling

Several presentations were focused on the role of mitochondrial dysfunction in the pathogenesis of fibrotic remodeling in the lung. In the first presentation related to this topic, Dr. Manu Jain (Northwestern University, Chicago, IL) presented data showing that transforming growth factor- $\beta$ -induced mitochondrial reactive oxygen species (ROS) regulate production of extracellular matrix (63). His group demonstrated that mitochondrial ROS generated at complex III of the electron transport chain plays a particularly important role in driving transforming growth factor- $\beta$  gene expression in human lung fibroblasts, which can be modulated effectively by mitochondria-targeted antioxidant therapies. Next, Dr. Ana Mora (University of Pittsburgh) discussed her work on the effects of aging on mitochondrial function in the alveolar epithelium. Her findings demonstrated that aging has profound effects on mitochondrial quality control mechanisms as a result of downregulation in the mitophagy-associated protein phosphatase and tensin homolog-induced putative kinase 1 (PINK) in type II alveolar epithelial cells (58). This decrease in PINK1 expression was associated with an accumulation of dysmorphic and abnormally functioning mitochondria, as well as an increase in the susceptibility of the alveolar epithelium to injury. Importantly, Dr. Mora showed that reduced PINK1 expression and abnormal mitochondrial morphological characteristics were also observed in type II alveolar epithelial cells in patients with

idiopathic pulmonary fibrosis, suggesting that similar pathological mechanisms contribute to fibrotic remodeling in both the rodent and human lung. In the last presentation of this session, Dr. Viswanathan Natarajan (University of Illinois, Chicago, IL) presented his data on the cardiolipin remodeling enzyme lysocardiolipin acyltransferase (LYCAT) in pulmonary fibrosis (64). Cardiolipin is a unique, mitochondria-specific tetra-acyl lipid that serves as an essential component of the inner mitochondrial membrane. Dr. Natarajan demonstrated that LYCAT is downregulated in fibrotic lung tissue and is associated with a disruption in mitochondrial function as a result of profound disturbances in the electron transport chain. He also showed that increasing LYCAT expression can ameliorate fibrotic remodeling in the mouse lung, in large part through its ability to enhance mitochondrial membrane potential and reduce ROS production. These findings highlight the importance of mitochondrial structure-function relationships and suggest that targeting cardiolipin synthesis could be an effective approach in the treatment of idiopathic pulmonary fibrosis.

### Lipid Handling and Mishandling: Lung Inflammation and Remodeling

Recent work has shown that complex interactions exist between lipids and lipid metabolism, pulmonary homeostasis, and the inflammatory response. The final session of the conference was introduced by Dr. Benjamin Suratt (University of Vermont), who reviewed current understanding of these interactions. Obesity and the metabolic syndrome are associated with the development of dyslipidemia, typically in the form of elevated circulating triglycerides, LDL, and free fatty acids, with a concomitant lowering of HDL. These alterations have been shown to affect many tissues of the body and to drive a variety of pathologies, including a systemic inflammatory state. How dyslipidemia may affect the lung is not yet well understood, but clinical evidence suggests that obesity and the metabolic syndrome are associated with an increased risk of ARDS (3) and asthma (35) and also that, at least in the case

of asthma, dyslipidemia may play a key role (44, 65, 66).

Atherosclerosis research has demonstrated that lipid species (particularly LDL and free fatty acids) drive immune activation and vascular injury through both direct interactions (e.g., oxidized LDL-mediated activation of the Toll-like receptor 4 [TLR4] complex [67, 68]) and indirect actions (e.g., macrophage cholesterol efflux-dependent control of granulopoiesis [69]). Recent research in which researchers examined the interactions between dietary lipid intake and the gut microbiome suggested discrete mechanisms through which such interactions may also activate the immune system (70). Such interactions may be considered in the greater context of a nutrient-immune interface in which homeostatic levels of lipids are handled primarily by metabolic mechanisms, whereas higher levels begin to inappropriately engage pathogen-sensing pathways because of homology between endogenous lipid species and pathogen-associated molecular patterns, ultimately leading to immune activation and derangement (71, 72).

Animal models of obesity- and dyslipidemia-associated effects on lung inflammation indeed suggests “priming” of the lung for both ARDS and asthma (73–75), and this may reflect not only systemic immune activation but also activation of lung-resident cells, including alveolar macrophages, endothelial cells, and alveolar type II cells (76). Animal studies suggest that the airspace and its lining cells are partly susceptible to fatty infiltration. What remains less clear is how dyslipidemia might directly affect the airspace lipid milieu of the lung, especially surfactant production, function, and clearance, perturbations of which have been shown to participate in a wide range of pulmonary pathology. In the aggregate, it is clear that the dyslipidemic state may participate in the pathogenesis of an array of lung diseases, but more work is required to establish both conclusive evidence and strong mechanistic links.

Dyslipidemia has been strongly associated with a systemic inflammatory state, and Dr. Yury Miller (University of California, San Diego, La Jolla, CA) highlighted the role of cholesterol in the regulation of inflammation. Oxidized cholesteryl esters (including “minimally modified” LDL) may act as ligands, binding

to leukocyte surface MD-2 to induce TLR4 dimerization and activation of proinflammatory pathways (77). Conversely, limiting cholesterol levels in the plasma membrane reduces inflammation, as shown in a zebrafish model, in which secreted apolipoprotein A1-binding protein can accelerate cholesterol efflux from both endothelial cells (78) and macrophages. The resulting targeted destruction of cholesterol-rich lipid rafts in the plasma membrane precludes TLR4 dimerization and inhibits inflammatory responses. Dr. Miller presented preliminary results suggesting that inhalation of apolipoprotein A1-binding protein has the potential to reduce pulmonary inflammation and lung injury.

The lung relies upon circulating lipoproteins as the source for more than 80% of its cholesterol. Dr. Michael Fessler (National Institute of Environmental Health Sciences) discussed the role of lipoproteins and cholesterol handling in lung inflammation. Abnormal cholesterol-laden macrophage “foam cells” have been documented in multiple chronic human lung diseases, suggesting that dysregulated

**Table 2.** Key conceptual advances

#### Key Conceptual Advances

- Obesity is associated with changes in dietary and environmental exposures, gut microbiome, systemic and cellular metabolism, immune function, and lung physiology. Each of these factors may contribute to the development of lung disease in any one patient.
- Mitochondrial dysfunction and oxidative stress are key pathological features in a wide range of lung diseases.
- Defective mitochondrial turnover may underlie the pathogenesis of age-related lung diseases.
- The lung and gut microbiome can impact both allergic and nonallergic airway hyperresponsiveness.
- Metabolomic and microRNA analyses of serum have the capacity to identify obesity-related events that contribute to lung disease.
- Obesity-mediated metabolic dysregulation is associated with pulmonary function deficits, likely by mediating systemic inflammation.
- Different aspects of metabolic dysregulation—insulin resistance as compared with dyslipidemia—affect pulmonary function by different immune alterations.

cholesterol homeostasis may be a common event in lung disorders. In support of this, mice with genetic deletion of the cholesterol efflux transporter ATP-binding cassette G1 display coordinated cholesterol overload of pulmonary macrophages and chronic pulmonary inflammation. Oxysterols (i.e., oxidized cholesterol) are lipids with dual roles in inflammation/immunity and cholesterol homeostasis. Intriguingly, oxysterol synthetic enzymes such as cytochrome P450 family 27 subfamily A member 1 (CYP27A1; human) and cholesterol 25-hydroxylase (Ch25h; mouse) are very highly expressed in the lung, suggesting that cholesterol metabolism and its dynamic regulation by oxysterols may be specifically relevant to lung biology. 25-Hydroxycholesterol in particular, an oxysterol produced by Ch25h in alveolar macrophages, has been described to have both pro- and antiinflammatory functions through activity on multiple protein targets, including liver X receptor, activating protein 1, C-X-C chemokine receptor type 2, and inflammasomes. Furthermore, it appears that 25-hydroxycholesterol is upregulated in the murine and human lung following inhalation of bacterial lipopolysaccharide, and that Ch25h-null mice have deficiencies in resolution of innate inflammation in the lung. These findings suggest coupling of cholesterol and immune homeostasis in the lung.

Oxidized phospholipids (OxPLs) generated during oxidation of low-density lipoprotein (LDL) can contribute to lung injury (79). Dr. Konstantin Birukov (University of Chicago, Chicago, IL) discussed the role of OxPLs in lung injury and endothelial barrier regulation. Oxidation of a natural cell membrane phospholipid component, 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine (OxPAPC), by enzymatic and nonenzymatic mechanisms can generate two major species: fragmented and full-length oxygenated OxPLs. These two groups exhibit contrasting effects on the lung endothelial barrier and inflammatory response (80). Fragmented OxPL species produce rapid, dose-dependent barrier disruption in pulmonary endothelial cells (81). In contrast, full-length cyclopentenone-containing OxPAPC products exhibit potent barrier-protective and antiinflammatory properties (80, 82, 83); this appears to be related to activation of small GTPases Rac1 and Rap1, which promote activation of

peripheral actin cytoskeleton assembly and enhancement of adherens junction and tight junction cell-adhesive complexes. Full-length OxPAPC species also protect against endothelial barrier dysfunction caused by vasoactive contractile agonists such as thrombin (84). Studies done over the last 10 years have revealed barrier-protective and antiinflammatory effects of OxPLs, which lay the foundation for the development of novel treatments for ARDS and other inflammatory syndromes.

Dr. Ross Summer (Thomas Jefferson University, Philadelphia, PA) discussed how dysregulated lipid synthesis may promote fibrotic responses in the lung. In previous work, his group has demonstrated that diverse types of profibrotic insults to the lung cause profound metabolic changes in the distal pulmonary epithelium, which include an increase in lactic acid production and a suppression of lipid synthesis (85). Because *de novo* lipid synthesis is believed to be important for enabling endoplasmic reticulum (ER) membrane expansion in the setting of increased protein load, Dr. Summer's group hypothesized that

**Table 3.** Key unanswered questions

#### Key Unanswered Questions

- What is the basis for mitochondrial dysfunction in different cell types in the lung?
- Is mitochondrial dysfunction a cause or consequence of lung disease?
- Will mitochondria-directed therapies be effective for the treatment of lung disease?
- What is the role of different obesity phenotypes and endotypes in the pathogenesis of pulmonary disease?
- How do we determine optimal treatment of obese patients with lung disease, since these patients are often excluded from clinical trials?
- Do obesity-related changes in the gut or lung microbiome underlie the effects of obesity on airway disease?
- Are there metabolomic signatures that can identify obese patients at risk for lung disease?
- What are the mechanisms underlying obesity's effects on the pulmonary immune response, and could understanding these contribute to the development of novel treatments for inflammatory lung diseases?
- What are the organ-specific mechanisms by which metabolic dysregulation-mediated systemic inflammation impacts pulmonary function?

inhibition of lipid synthesis might promote fibrotic responses through disruption of key elements of the unfolded protein response. Consistent with this hypothesis, instillation of the ER stress-inducing agent tunicamycin in the lung markedly increased lipid synthesis while having no effect on fibrotic remodeling. In contrast, inhibition of lipid synthesis with a compound that blocked the activity of stearoyl-coenzyme A desaturase 1 both increased ER stress and promoted fibrotic remodeling in the lung. Moreover, by either enhancing lipid synthesis through increasing stearoyl-coenzyme A desaturase 1 activity or supplying the alveolar epithelium with additional metabolic intermediates used for lipid synthesis, one can effectively decrease ER stress and reduce fibrotic remodeling to silica in the lung. Taken together, these findings indicate an essential role for lipid synthesis in the resolution of ER stress and in limiting fibrotic remodeling in the lung.

## Conclusions

The meeting highlighted key aspects of the links between pulmonary disease and obesity, the metabolic syndrome, cellular metabolism, and environmental exposures (Table 2). Obesity can disrupt normal cellular and systemic metabolism. In particular, studies have highlighted the critical role of normal metabolic processes for normal physiological functioning of cells and systems. In addition, native human metabolic processes interact with the microbiome and its related metabolome, which can affect development of immune responses. Normal lipid metabolism has emerged as a fundamental regulator of immune function. Whereas changes in cellular metabolism contribute to the pathogenesis of diseases such as PAH, changes in mitochondrial function are critical for the pathogenesis of fibrotic lung

disease. Tremendous challenges remain in furthering understanding of the roles of cellular and systemic metabolism in lung disease (Table 3). Only through continued development of this field will fundamental insights be gained into the biology of lung function and how it can become altered with extreme metabolic disturbance in obesity. ■

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