

Lipid metabolism in chronic obstructive pulmonary disease

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

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Abstract: Dysregulated lipid metabolism plays crucial roles in various diseases, including diabetes mellitus, cancer, and neurodegeneration. Recent studies suggest that alterations in major lipid metabolic pathways contribute to pathogenesis of lung diseases, including chronic obstructive pulmonary disease (COPD). These changes allow lung tissue to meet the energy needs and trigger anabolic pathways that initiate the synthesis of active molecules directly involved in the inflammation. In this review, we summarize the changes of catabolism and anabolism of lipids, lipid molecules including lipid mediators, lipid synthesis transcription factors, cholesterol, and phospholipids, and how those lipid molecules participate in the initiation and resolution of inflammation in COPD.

Keywords: COPD, lipid metabolism, airway inflammation

Introduction

Lipids are hydrophobic molecules with three general functions, which include energy storage, membrane building, and signal transduction.¹ Lipids can be divided into different classes, including triglycerides, cholesterol, phospholipids, and glycolipids. Metabolism of lipids includes anabolism and catabolism, which involves the synthesis of new lipids from smaller molecules and oxidation of lipids to supply energy or generate other lipids mediators, respectively.²

Lipid metabolism has been implicated in diabetes mellitus, cancer, neurodegeneration, and cardiovascular diseases.^{3,4} Lipid metabolism contributes to the pathogenesis of diabetes mellitus by modulating the insulin resistance and inflammation.⁵ As highly proliferating cells, tumor cells need lipids for synthesis of membranes and signaling molecules.^{6,7} Recent evidence suggests that lipid metabolism in lung disease might also be altered.^{8–10}

Once considered as static metabolic energy reserves, lipids have emerged as important components of cellular signal transduction pathways. Their roles in modulating host inflammatory responses, either promotion or resolution, are of clinical interests.¹¹ At present, there are rapidly expanding insights into novel lipid mediators that function to regulate inflammation.

Chronic obstructive pulmonary disease (COPD) is a pulmonary dysfunction characterized by irreversible and progressive airflow obstruction, chronic airway inflammation, and systemic effects or comorbidities. Several studies have suggested that COPD is a disease associated with derangement of lipids. A study conducted in the Warsaw Ghetto during World War II showed that a high percentage of people who died of starvation had emphysema.¹² Furthermore, rats with restricted caloric

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intake for a few weeks showed changes in pulmonary mechanics and lung structure that were described as “emphysema-like”.^{13–18} Besides, there are increasing evidence suggesting that obesity is associated with declined lung function and increased morbidity in moderate to severe COPD.^{19,20}

More recent studies have suggested that alterations in major metabolic pathways contribute to pathogenesis of COPD.^{21,22} The lung is a complex organ composing a large number of cell types. Same lipid molecules might be differentially modulated in various cells in COPD, and they may exert differential effects on the eventual COPD pathogenesis. Thus, studying the cell-specific alterations and functions of lipid molecules in COPD is of great importance. In this review, we will discuss the role of lipid metabolism, focusing on the alterations of various lipids molecules, and the consequences of these changes in COPD.

Lipid catabolism in COPD

As a mechanism for the utilization of fatty acids, fatty acid oxidation (FAO) (Figure 1) is a major bioenergetic pathway that is upregulated under conditions of prolonged fasting, exercise, or metabolic stress.²³ The mitochondrial membrane

is impermeable to fatty acids. They must be conjugated to carnitine to enter mitochondria. Carnitine forms a high-energy ester bond with fatty acids by the action of carnitine palmitoyl transferase 1 (CPT1), located in the inner aspect of the outer mitochondrial membrane, with the formation of acylcarnitines. Carnitine acylcarnitine translocase (CACT) exchanges acylcarnitines and carnitine between outer and inner membranes of mitochondrial and finally acylcarnitines are converted back into acyl-CoAs for oxidation by CPT2.^{24,25} Fatty acids are an important source of energy, as FAO produces 2.5 times as much ATP per mole as oxidation of glucose.²⁶

Although several factors, including genetic or environmental ones, may contribute to the development of COPD, cigarette smoking (CS) is still the highest risk factor.²⁷ Glucose metabolism decreased in lung alveolar cells after subchronic cigarette smoke exposure (8 weeks). This impairment was compensated by enhanced FAO to maintain cellular energy homeostasis, accompanied by an increased expression of CPT1. Increased utilization of palmitate (most likely from dipalmitoyl-phosphatidylcholine) was found in alveolar type 2 cells.^{21,28} Consistently, cigarette smoke exposure promoted FAO and increased mitochondrial respiration in human bronchial epithelial cells.²⁹

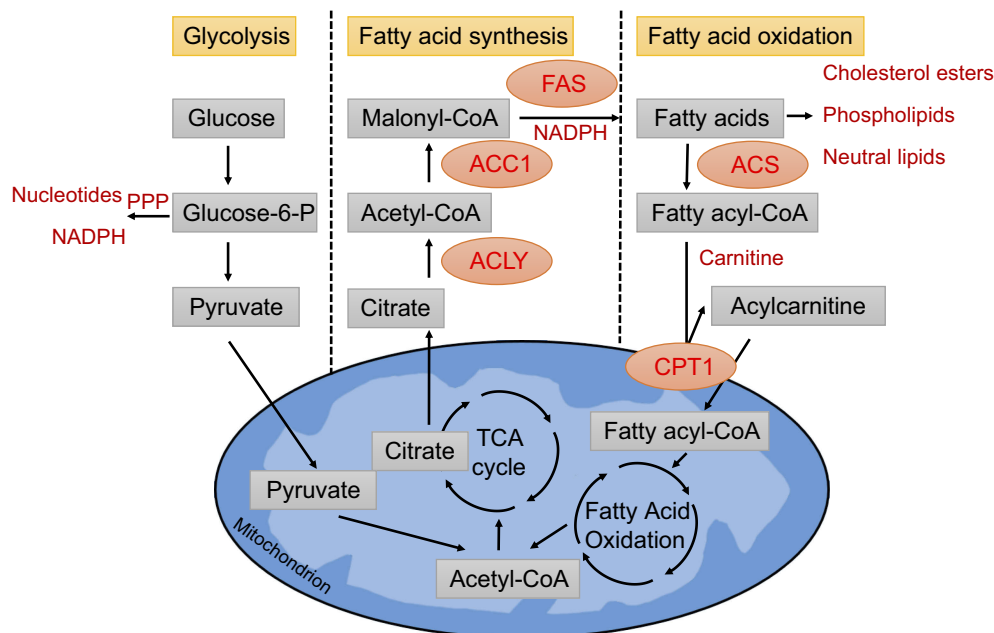


Figure 1 Metabolic pathway of glycolysis, FAS and FAO. Glycolysis converts glucose into pyruvate, which can enter the tricarboxylic acid (TCA) cycle. Glycolysis also feeds the pentose phosphate pathway (PPP), which generates ribose for nucleotides and NADPH. Citrate can be fully oxidized to generate ATP or transported to the cytoplasm where it is converted back to acetyl-CoA by ATP citrate lyase (ACLY). A portion of the acetyl-CoA is carboxylated to malonyl-CoA by acetyl-CoA carboxylase I (ACC1). Fatty acid synthase (FAS) performs the condensation of acetyl-CoA and malonyl-CoA to produce the 16-carbon saturated fatty acid palmitate and other saturated long-chain FAs. In the cytosol, fatty acyl-CoA synthases (ACS) activate fatty acids by converting them to fatty acyl-CoA. Fatty acyl-CoA is converted to acylcarnitine by CPT1 on the outer mitochondrial membrane and transported to the mitochondrial matrix. In the mitochondrial matrix, fatty acyl-CoA is oxidized to acetyl-CoA through fatty acid oxidation.

Abbreviations: ACC1, acetyl-CoA carboxylase α ; ACLY, ATP citrate lyase; ACS, acyl-CoA synthase; CPT1, carnitine palmitoyltransferase I; FAS, fatty acid synthase; TCA cycle, tricarboxylic acid cycle.

This switch might be important to maintain adenosine triphosphate (ATP) levels and delay CS-induced cellular damage. Metabolomics screening showed that reduced L-carnitine, a metabolite critical for transporting long-chain fatty acids into the mitochondrial for their subsequent β -oxidation, was associated with impaired lung function.³⁰

However, sustained elevation in FAO may also aggravate CS-induced ROS accumulation, mitochondrial damage, and cell death.²⁹ As phosphatidylcholine represents approximately 80% of the surfactant phospholipid, continuously increased FAO may lead to surfactant deficiency, which had been observed in smokers and patients with COPD.^{31,32}

The FAO level might vary according to cell types as showed by reduced FAO capacity in airway smooth muscle cell (ASMC) of COPD patients. Changes in fatty acid metabolism may contribute to increased biosynthesis, supporting ASMC hypertrophy and/or hyperplasia.³³ Future studies are required to fully clarify the metabolic responses of other cells, including those immune cells.

Catabolic lipid mediators in COPD

Eicosanoids are a family of very potent biological signaling molecules that act as short-range messengers, affecting tissues near the cells that produce them. In response to inflammation, phospholipase A_2 attacks membrane phospholipids, releasing arachidonic acid (AA) from the middle carbon of glycerol. Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is a primary target of regulated PLA₂ hydrolysis, and is the precursor to a vast array of lipid signaling molecules.³⁴ Cyclooxygenases (COX) 1/2 oxidize AA to generate the prostaglandin family of oxidized fatty acids. In general, these lipid species can be proinflammatory, propagating their signaling actions via receptor-mediated mechanisms, and are responsible for many of the phenomena of inflammation.^{35,36}

Prostanoids are a family of metabolites of the fatty acid arachidonic acid, which include PGD₂, PGE₂, PGF₂, and PGI₂, as well as thromboxane A.³⁷ PGE₂ levels were increased in respiratory secretions from patients with COPD, which could contribute to airway inflammation and the impaired lung repair.^{38–40}

Leukotrienes are a family of eicosanoid inflammatory mediators, which are synthesized in the cell from arachidonic acid by arachidonate 5-lipoxygenase. In COPD, activated macrophages, neutrophils, and epithelial cells produce cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄)

and Leukotriene B₄ (LTB₄).⁴¹ Leukotriene B₄ (LTB₄), a neutrophil and T-cell chemoattractant, is a potent inflammatory mediator. LTB₄ concentrations were increased in induced sputum and were further increased in sputum and exhaled breath condensate during acute exacerbations.^{42,43}

The role of oxidized lipids as proinflammatory mediators is well established. However, in the past decades several classes of lipid mediators have been discovered whose signaling actions act to resolve rather than to promote inflammation. These bioactive lipid mediators are called pro-resolving lipid mediators (SPMs).⁴⁴ SPMs are mainly biosynthesized from omega-3 essential fatty acids, including eicosapentaenoic and docosahexaenoic acids, and are generally categorized into five families: lipoxins, D-series resolvins, E-series resolvins, protectins, and maresins. These molecules are currently the subject of intense research, as they represent an emerging generation of investigational new drugs to address inflammatory diseases.

Pro-resolving pathways were disrupted in lung tissue from patients with COPD. Supplementation with resolvin D1 was associated with a reduced development of cigarette-smoke-induced increase of neutrophils and total cell counts, emphysema and airspace enlargement, with concurrent reductions in inflammation, oxidative stress, and cell death. D-series resolvins decreased inflammatory cytokines and enhanced phagocytosis in human alveolar macrophages from COPD patients. Thus, these results suggest that supplementation with SPMs might reduce the development of emphysema by controlling chronic inflammation.^{45–47}

Nitrated fatty acids (NFAs), endogenous products of nonenzymatic reactions of NO-derived reactive nitrogen species with unsaturated fatty acids, exhibit substantial anti-inflammatory activities. NFA treatment downregulated expression and activity of the inflammatory transcription factor NF- κ B while upregulated PPAR- γ . It also downregulated production of inflammatory cytokines and chemokines and of the protease cathepsin S (Cat S), a key mediator of emphysematous septal destruction.⁴⁸

The progression of COPD is often accelerated by its exacerbation.⁴⁹ A primary goal of treatment is to reduce the frequency of exacerbation. Thus, a specific biomarker for detection and diagnosis of exacerbations is needed. Considering the role of those lipid mediators in COPD, whether they could become a biomarker of exacerbations need further investigation.

It is now clear that the lipid mediators play an important role in regulating generation and resolution of inflammation by modulating the balance between proinflammatory and

anti-inflammatory mediators; however, it remains mysterious how lung shift from the secretion of proinflammatory to anti-inflammatory molecules. More studies are needed to directly assess the impact of lipid metabolic genes on COPD development, which are important for production of various lipid mediators.

Lipid anabolism in COPD

Fatty acid synthesis (FAS) (Figure 1) uses products derived from several other metabolic pathways, notably glycolysis, the TCA cycle, and pentose phosphate pathway. These metabolic pathways cross-talk with FAS by providing precursors and NADPH. Glycolysis feeds the pentose phosphate pathway, which generates ribose for nucleotides and NADPH.⁵⁰ TCA cycle-derived citrate may be exported from the mitochondria into the cytosol via the citrate carrier, where ATP citrate lyase converts it into acetyl-CoA. FAS takes place in the cytoplasm of the cell, commencing with the ATP-dependent carboxylation of acetyl-CoA to malonyl-CoA. This committed step of FAS is catalyzed by acetyl-CoA carboxylase 1 (ACC1).⁵¹ The next step is performed by FA synthase (FAS), a key multifunctional enzyme that acts in an NADPH-dependent manner to catalyze the condensation of acetyl-CoA and malonyl-CoA to produce the 16-carbon saturated FA palmitate and other saturated long-chain FAs (LCFAs).⁵² Saturated LCFAs can be further modified by elongases or desaturases to form more complex lipids, which are then used for the synthesis of phospholipids, triglycerides, and cholesterol esters.

Viral infections can provoke acute worsening of disease in patients with COPD.⁵³ Study showed that the activity of FAS was enhanced when infected with rhinovirus in bronchial epithelial cells, and that inhibition of FAS reduced the rhinoviral infections.⁵⁴ Therefore, FAS might be a potential target for exacerbation of COPD.

Prolonged cigarette smoke may lead to different metabolic changes. Warburg effect is the phenomenon that tumor cells consume glucose at a surprisingly high rate compared to normal cells and secrete most of the glucose-derived carbon as lactate rather than oxidizing it completely. Similar to the role of “Warburg effect” in cancer cells, glucose consumption and lactate production were increased in human bronchial epithelial BEAS₂B cells treated with cigarette smoke condensate for 7 months. Besides, lipid biosynthetic capacity and net reductive carboxylation were enhanced, suggesting a profound anabolic reprogramming in the airway epithelium.^{55,56} Although

speculative, lipid metabolism changes may help us understand why COPD patients tend to get lung cancer.⁵⁷

Lipid synthesis transcription factors in COPD

Transcriptional mechanisms regulating lipid synthesis are known to be dependent on a number of transcription factors, including peroxisome proliferator activated receptors (PPARs), liver X receptor (LXR), and SREBPs.^{58–61} Although transcriptional networks regulating lipid homeostasis have been extensively studied in other cell types, including hepatocytes and adipocytes, less is known regarding the transcriptional control of lipid homeostasis in the respiratory system. Those transcription factors might be pathophysiologically or therapeutically relevant to COPD if their potential roles in COPD are well characterized.

PPAR- γ is a member of the PPAR subfamily of nuclear hormone receptors that function as transcription factors, modulating glucose and lipid metabolism, inflammation, and cell proliferation. PPAR- γ forms heterodimers with retinoid X receptors, which bind to PPAR response elements and regulate transcription of target genes.⁶¹ PPAR- γ was down-regulated in lung tissue, epithelial cells, and myeloid dendritic cells in COPD patients.^{62,63} Mice lacking PPAR specifically in airway epithelial cells displayed increased susceptibility to chronic CS-induced emphysema, with excessive macrophages accumulation.⁶⁴ Conditional knock-out of PPAR- γ in antigen-presenting cells (APC) led to spontaneous lung inflammation and emphysema that resembled the phenotype of smoke-exposed mice.⁶³ Treating epithelial cells with synthetic (rosiglitazone) or endogenous PPAR- γ agonists strongly up-regulated PPAR- γ expression and activity, suppressed CSE-induced production and secretion of inflammatory cytokines.⁶² Later study showed that PPAR- γ ligands reduced proinflammatory cytokine production, including tumor necrosis factor- α and CCL5 in COPD alveolar macrophages. Rosiglitazone, one of PPAR- γ agonist, increased the levels of M2 genes that are involved in anti-inflammatory effects and tissue repair and enhanced the clearance of apoptotic neutrophils. Moreover, Rosiglitazone attenuated airway neutrophilia in a corticosteroid-resistant mouse model of pulmonary inflammation, without leading to an increase in the pulmonary bacterial burden, unlike dexamethasone.^{65,66} These data suggest that activation of PPAR- γ in local airways might be an effective therapeutic strategy for COPD.

LXR is a sensor of cellular cholesterol load, which regulates the transcription of genes involved in cholesterol efflux and low-density lipoprotein receptor degradation.⁶⁰ The levels of LXR were significantly increased in whole lung tissue extracts of COPD patients and smokers, and those increases were located in small airway and alveolar epithelium.⁶⁷

Sterol-response element-binding proteins (SREBPs) are transcription factors that regulate the expression of genes encoding enzymes required for synthesis of cholesterol and unsaturated fatty acids.⁵ Conditionally deleting the SREBP cleavage-activating protein gene, *Scap*, in alveolar epithelial cells decreased the phospholipid synthesis while lipid storage, synthesis, and transfer by lung lipofibroblasts were increased.⁶⁸ Second-hand smoke stimulates lipid accumulation in the liver by modulating AMPK and SREBP1.⁶⁹ Further studies are needed to investigate the role of SREBPs in lung diseases.

Cholesterol in COPD

Cholesterol is an essential component of cellular membranes that is therefore required for cell proliferation.⁷⁰ Several intermediates of the cholesterol biosynthetic pathway, as well as oxidized cholesterol products such as oxysterols, modulate immune cell functions by affecting signaling molecules or by binding to cellular receptors.⁷¹ Cholesterol is produced from acetyl-CoA via cytosolic HMG-CoA reductase (HMGCR) pathway. The activity of this enzyme is regulated by the levels of intracellular cholesterol by means of feedback inhibition, control of gene expression via SREBPs, and cholesterol-induced polyubiquitination and proteasomal degradation.⁷² In addition, the activity of HMGCR is regulated through phosphorylation by AMP-activated protein kinase (AMPK).

Patients with very severe COPD exhibited higher level of cholesterol and serum Apolipoprotein M in blood.^{73,74} Oxidized cholesterol products 27-hydroxycholesterol (27-HC) and 25-hydroxycholesterol (25-HC) were elevated in the airways of COPD patients compared with those in healthy subjects.^{75,76} Inhibition of HMGCR by statin attenuated key genes involved in inflammatory processes, immune response, and leukocyte activation in lung tissues of COPD patients.⁷⁷ Studies in animal models revealed that treatment with statin prior to and continued throughout smoke exposure reduced the total influx of leukocytes, neutrophils, and macrophages into the lung and airways.⁷⁸ Treatment with the concentration of 27-HC detected in COPD airways significantly augmented expression of senescence-associated proteins and senescence-

associated β -galactosidase activity, and delayed cell growth through the prostaglandin E2-reactive nitrogen species pathway.⁷⁹ Moreover, 25-HC in airway epithelial cells regulated CS-induced B-cell migration and inducible bronchus-associated lymphoid tissue (iBALT) formation, a tertiary lymphoid organ that develops in the lungs during infection, autoimmunity, or chronic inflammation. Mice deficient with 25-hydroxylase, the key enzyme for 25-HC production, or the oxysterol receptor Epstein-Barr virus-induced gene 2 exhibited decreased iBALT and subsequently attenuated CS-induced emphysema.⁷⁶

The upregulation of cholesterol can be interpreted as smoking has an adverse impact on the lipoprotein. Cholesterol is insoluble in water, which is carried in blood plasma as plasma lipoproteins. Much of the cholesterol synthesis takes place in the liver. Low-density lipoprotein (LDL) carries cholesterol to extrahepatic tissues, and high-density lipoprotein (HDL) transports cholesterol to the liver. Smoking is associated with an increase in circulating LDL, and a decrease in plasma HDL levels.^{80,81} Apolipoprotein A1 (ApoA1) is the major protein in HDL that plays an important role in reverse cholesterol transport by extracting cholesterol and phospholipid from various cell types, including lung cells, and transferring them to the liver. ApoA1 levels were significantly decreased in the lungs of patients with COPD and in the lungs of mice exposed to CS. ApoA1 overexpression attenuated lung inflammation, oxidative stress, metalloprotease activation, and apoptosis in CS-exposed mouse lungs. Mechanistically, ApoA1 prevented CSE-induced translocation of Fas and downstream death-inducing signaling complex into lipid rafts, thereby inhibiting Fas-mediated apoptosis.⁸²

Observational studies suggested that statin use was associated with reduced morbidity and/or mortality in COPD, whereas a large randomized controlled trial concluded that simvastatin did not reduce exacerbations in patients with COPD that had no cardiovascular indication for statin treatment.⁸³ Therefore, it is possible that a subgroup of COPD patients with cardiovascular indications and/or systemic inflammation may obtain clinical benefit from statin treatment.

Phospholipid in COPD

Phospholipids are a class of lipids that are major component of all cell membranes, composed of sphingomyelin and glycerophospholipids. Sphingolipids were significantly higher expressed in smokers with COPD than in smokers

without COPD in sputum using untargeted lipidomic analysis.⁸⁴ A recent study found that sphingomyelins were strongly associated with emphysema and glycosphingolipids were associated with COPD exacerbations.⁸⁵

Ceramide is a component of sphingomyelin, which is found in the cell membrane and is associated with a wide variety of cellular functions, including growth, differentiation, and apoptosis. Ceramide is *de novo* generated by serine palmitoyl transferase, ceramide synthase, or via membrane sphingomyelin hydrolysis by sphingomyelinase. It can be directly phosphorylated by ceramide kinase to ceramide-1-phosphate (C1P).⁸⁶

Studies have shown that ceramide triggered apoptosis of pulmonary epithelial cells and was involved in the destruction of alveolar structure in emphysema.^{87,88} Cigarette smoke exposure could increase the level of C16-Cer, and C16-Cer accumulation contributed to mitochondrial damage and PINK1-mediated necroptosis.⁸⁹ While C1P reduced CS-induced acute and chronic lung inflammation and development of emphysema in mice, which was associated with a reduction in neutral sphingomyelinase (nSMase) and NF- κ B activity in the lungs, nSMase can hydrolyze the phosphodiester bond of sphingomyelin to release the ceramide, whose activity in human serum was correlated negatively with lung function decline.⁹⁰

Conclusion remarks

Though current literature have addressed certain parts of lipid metabolism in COPD pathogenesis (summarized in Table 1), future studies are encouraged to address the following concerns.

Although COPD is a lung disease, it is associated with systemic manifestations and comorbid conditions, including skeletal muscle wasting, cachexia, and lung cancer.^{91,92} It will be interesting to determine whether lipid metabolism alteration in organs like liver or adipose tissue is consistent with changes in lung. The detailed effects and mechanisms of cigarette smoke putting on lipid metabolism in those organs will enhance our understanding of the relations between COPD and comorbidities.

Most of the currently available studies about energy metabolism in COPD focused on epithelial cells and ASMCS, while few advances have been made to unveil the metabolic changes in those immune cells. Macrophages function in host defense, tissue homeostasis and repair, pathology, and development. To accommodate this function, macrophages usually undergo a metabolism reprogramming to adopt an activation state.⁹³ Alveolar

macrophages play a key role in sensing and eliminating microbial agents early in the course of an infection, while cigarette smoke compromises the ability of alveolar macrophages to phagocytose bacteria.^{94,95} Activation of PPAR- γ is able to reduce cigarette-smoke-induced inflammation and to decrease the magnitude of bacterial exacerbations.⁶⁶ Thus, it can be estimated that macrophages might have a dysregulated lipid metabolism that have a compromised function to phagocytose bacteria. Targeting those metabolism pathways in macrophages might be an effective therapeutic approach to improve COPD management.

Little is known about the changes of FAS in COPD, as balance of FAS and FAO is a key molecular integrator of energy homeostasis. Understanding how the balance between FAS and FAO is regulated under conditions of inflammation, and examining the external and intracellular signaling pathways regulating this balance, are also challenges in COPD research. In addition, it will be necessary to address the role FAS and coordinating transcription regulators in COPD using conditional knock-out mice. Pulmonary surfactant consists of lipids and related surfactant protein, and it is also not clear whether dysregulated lipid metabolism will affect the homeostasis of pulmonary surfactant and eventually contribute to the development of emphysema.

Lipidomics should be applied to the study in COPD. Lipidomics is an emerging field of biomedical research which includes complex lipidome analysis. Lipidomics involves system-level identification and quantitation of thousands of pathways and networks of cellular lipid molecular species.⁹⁶⁻⁹⁸ Pilot study employing lipidomic analysis have uncovered that sphingolipid pathways are highly expressed in smokers with COPD in sputum.⁸⁴ Nevertheless, such lipidomic analyses need to be extensively employed in COPD research.

In conclusion, lipid metabolic pathways and molecules are clearly altered in COPD, and these alterations may in turn modulate the functions of specific cells, such as production of inflammatory mediators, immune regulation, or cell death, eventually contributing to COPD development. However, deeper metabolic studies of different lipid species in various lung cell types are required *in vitro* as well as in COPD patients and in animal models. Also, cell specifically genetic modification of certain lipid metabolic molecules in mouse lung cells are critical to clarify the cell-type-dependent functions of lipid metabolism in COPD pathogenesis. With such efforts, lipid metabolic

Table 1 Lipids alterations in COPD

Lipids metabolic events	Targets	Major outcome(s)	References
Fatty acid oxidation pathway	Alveolar type 2 cells	Oxidative metabolism was activated after subchronic cigarette smoke exposure. Enhancement of FAO affected the surfactant biosynthesis pathway in lung type 2 cells.	21, 28
	Bronchial epithelial cells	Cigarette smoke exposure promoted fatty acid oxidation, and sustained elevation in FAO may aggravate ROS accumulation, mitochondrial damage, and cell death.	29
	Airway smooth muscle cell	Fatty acid oxidation capacity was reduced under unstimulated conditions.	33
Catabolic lipid mediators			
Prostanoids	Fibroblasts	Increased PGE ₂ contributed to airway inflammation and the impaired lung repair.	38–40
Leukotrienes	Sputum	LTB ₄ increased in induced sputum.	42, 43
Resolvins	Lung tissue	D-series resolvins altered in human lung samples of COPD. Treatment of resolving DI decreased inflammatory cytokines and enhanced phagocytosis of macrophages.	45–47
Nitrated fatty acids	Macrophages	NFA treatment downregulated production of inflammatory cytokines and chemokines in macrophages.	48
Fatty acid synthesis pathway	Bronchial epithelial cells	Long-term cigarette smoke exposure might lead to increased glucose consumption and enhanced lipid biosynthesis.	55, 56
Transcription factors			
PPAR-γ	Lung tissue, epithelial cells, and myeloid cells	PPAR-γ was downregulated in those targets, which increased susceptibility to chronic CS-induced emphysema and expression of chemokines.	62–64
LXR	Lung tissue	LXR increased in lung tissue, located in small airway and alveolar epitheliums.	67
Cholesterol or oxidized cholesterol	Serum, bronchial epithelial cells	The level of cholesterol was higher in serum of patients with very severe COPD. Oxidized cholesterol products were elevated in the airway of COPD patients. Hydroxycholesterol contributed to the inflammation and CS-induced emphysema.	73–78
Phospholipids	Sputum, Plasma, lung tissue	Sphingolipids was higher in COPD patients in sputum. Plasma sphingolipids associated with chronic obstructive pulmonary disease phenotypes. Upregulation of ceramide in lung tissue implicated in alveolar cell apoptosis.	84, 85, 87

Abbreviations: COPD, chronic obstructive pulmonary disease; CS, cigarette smoke; FAO, fatty acid oxidation; FAS, fatty acid synthesis; LXR, liver X receptor; LTB₄, leukotriene B₄; PGE₂, prostaglandin E₂; PPAR-γ, peroxisome proliferator activated receptors-γ; ROS, reactive oxygen species.

signals might represent some novel therapeutic targets for COPD.

Acknowledgments

This work was supported by the National Key R&D Program of China (Grant 2016YFA0501602 to ZC) and the Major and General Projects from the National Natural Science Foundation of China (Grant 81670031 to ZC).

Disclosure

The authors report no conflicts of interest in this work.

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