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Emerging Roles for Cholesterol and Lipoproteins in Lung Disease

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Abstract

Dyslipidemia, the condition of elevated serum triglycerides, elevated low-density lipoprotein cholesterol, and/or low high-density lipoprotein cholesterol, is a public health problem of growing concern. Dyslipidemia clusters with other disorders of the metabolic syndrome that together influence, and may derive from, chronic inflammation. While best recognized as a risk factor for atherosclerotic cardiovascular disease, lipid dysregulation has recently been shown to influence a variety of disease processes in several organ systems. This review highlights our current understanding of the role of cholesterol and its homeostatic trafficking in pulmonary physiology and pathophysiology. Gene-targeted mice deficient in regulatory proteins that govern reverse cholesterol transport (e.g., ATP Binding Cassette transporter G1, apolipoprotein E) have recently been shown to have abnormal lung physiology, including dysregulated pulmonary innate and adaptive immune responses to the environment. It has also recently been shown that diet-induced dyslipidemia alters trafficking of immune cells to the lung in a manner that may have important implications for the pathogenesis of acute lung injury, asthma, pneumonia, and other lung disorders. Conversely, cholesterol-targeting pharmacologic agents, such as statins, apolipoprotein mimetic peptides, and Liver X Receptor agonists, have shown early promise in the treatment of several lung disorders. An improved understanding of the precise molecular mechanisms by which cholesterol and its trafficking modify pulmonary immunity will be required before the full implications of dyslipidemia as a lung disease modifier, and the full potential of lipid-targeting agents as pulmonary therapeutics, can be realized.

Keywords

Pulmonary disease; Dyslipidemia; Statins; Metabolic Syndrome; Inflammation; Cholesterol

1. Introduction

Dyslipidemia, a condition involving elevated serum triglyceride (TG), elevated serum low density lipoprotein cholesterol (LDL-C), and/or low serum high density lipoprotein cholesterol (HDL-C), has become a health problem of growing concern in many industrialized countries and developing nations (reviewed in [1]). Approximately 21% of adults in the United States have elevated serum LDL-C (reviewed in [2]). Dyslipidemia is

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often associated with metabolic syndrome, which increases the risk for atherosclerosis and type II diabetes mellitus. Hypercholesterolemia has been widely studied in the context of cardiovascular inflammation, but its role in pulmonary immunity has only recently been considered. The issue of cholesterol and its role in pulmonary immunity is potentially of tremendous public health impact given the high rates of dyslipidemia and respiratory tract infections in the United States, and recent reports that widely used cholesterol-active therapies impact pulmonary immunity [3]. This review addresses our current understanding of how cholesterol levels are regulated in the lung and how cholesterol itself regulates immune responses in the lung. Furthermore, we discuss emerging roles for cholesterol regulatory proteins as potential targets for therapeutic development in chronic pulmonary disease.

2. Cholesterol transport, uptake, and excretion

Cholesterol is essential for the integrity of cellular membranes, maintaining membrane fluidity and membrane functions, including signal transduction. Cholesterol and TG homeostasis have been extensively studied in cardiovascular disease progression and have been t he topic of recent scholarly reviews (reviewed in [4, 5]). While a comprehensive treatment of cholesterol trafficking is beyond the scope of the present review, a basic understanding of the mechanisms by which cell and serum cholesterol levels are maintained is necessary for examining how these events translate to lung physiology and pathophysiology.

Cholesterol is either absorbed from dietary sources or synthesized *in vivo* in both liver and peripheral cells by a pathway whose rate-limiting step is regulated by hydroxymethyl-glutaryl coenzyme A reductase (HMGCR). Hepatic cholesterol, deriving both from *de novo* synthesis and uptake of intestinal chylomicron remnants, is packaged with apolipoprotein B (ApoB) into very low-density lipoprotein (VLDL) particles for export into the systemic circulation. VLDL is then progressively metabolized into low density lipoprotein (LDL), which serves as the major vehicle supplying cholesterol to peripheral cells (e.g., tissue macrophages) via low density lipoprotein receptor (LDLR) and scavenger receptors (SRs). Cholesterol levels of peripheral cells are, in turn, controlled by LDLR and HMGCR downregulation as well as by the homeostatic pathway for disposal of cellular cholesterol, termed ‘reverse cholesterol transport’ (RCT) (reviewed in [6, 7]).

Following hydrolysis from its esterified form, free cholesterol (FC) is effluxed from peripheral cells to serum lipid-poor/free apolipoprotein A-I (apoA-I) via the ATP Binding Cassette (ABC) transporter A1 (ABCA1) (reviewed in [8]), thereby forming nascent high density lipoprotein (HDL) particles in the first step of RCT. HDL then serves as an acceptor for further cellular cholesterol efflux mobilized via scavenger receptor B type I (SR-BI) and ABCG1 [9], along with cholesterol mobilized by diffusion and by export with macrophage apoE. Serum HDL cholesterol is then cleared by the liver after binding to hepatic SR-BI; alternatively, cholesterol transferred from HDL to LDL in the circulation by cholesteryl ester transfer protein (CETP) is cleared by hepatic LDLR. The liver finally disposes of cholesterol, in the form of FC and bile acids, by export of these sterols into the biliary tract for excretion in the feces. Notably, ABCA1, ABCG1, apoE, and CETP (in humans) are all target genes of the nuclear receptor Liver X Receptor (LXR), a transcription factor that serves as a cellular sensor for elevated oxysterol levels. As RCT is thought to be anti-atherogenic, active efforts are underway to develop and validate apoA-I mimetic peptides as well as synthetic LXR agonists that might reduce human atherosclerotic cardiovascular disease by promoting RCT *in vivo* [10].

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Although cholesterol is essential for cellular integrity and metabolism, overloading of macrophages with cholesterol produces cytotoxic and inflammatory responses that are now known to contribute to atherosclerosis and other diseases. Overloading macrophages *in vitro* with exogenous cholesterol induces cytokine production via endoplasmic reticulum (ER) stress [11, 12]. Free cholesterol loading of membranes also activates Toll like Receptors (TLRs), as well as sensitizes TLRs to microbial ligands [13], while intracellular cholesterol overload activates the inflammasome [14]. The inflammasome is a large, multiprotein complex that activates caspase 1 to cleave pro-IL-1β and pro-IL-18 into a mature form [15, 16]. The activation of the inflammasome by cholesterol crystals has been shown to work through NLRP3 leading to the production of the proinflammatory cytokine IL-1 that has been implicated in cardiovascular disease pathogenesis [17, 18]. Thus, cholesterol homeostasis and inflammation are coupled in macrophages, with dysregulated cellular cholesterol loading inducing inflammatory responses. This 'spontaneous' activation of the innate immune system by cholesterol overload has been widely studied in the progression of chronic inflammatory diseases such as atherosclerosis, but has only recently been examined in the context of the lung.

3. Cholesterol and lipoproteins in lung physiology

Although the lung has not traditionally been considered an organ sensitive to circulating lipoproteins and their cholesterol cargo, several reports over the years have suggested an important and perhaps even unique role for lipoproteins and cholesterol in pulmonary physiology (summarized in Figure 1). Circulating LDL and HDL are both taken up by the lung through specific receptors, and supply cholesterol to lung-resident cells, thereby inhibiting local pulmonary cholesterol biosynthesis [19, 20]. HDL also serves as the major source of the antioxidant vitamin E for alveolar epithelial type II cells [21], and promotes surfactant production by type II cells [22], and growth of lung fibroblasts [23]. Although cholesterol is essential for type II cell function, excessive amounts of cholesterol impair surfactant function, suggesting the critical importance of alveolar cholesterol homeostasis to normal lung physiology [24]. Indeed, increased dietary cholesterol has been shown to alter surfactant synthesis, composition, and function [25, 26]. Whether lipoprotein particles comparable to those described in the serum exist in the alveolar compartment remains unclear.

As surfactant lipids are directly exposed to environmental oxidants, oxidation of alveolar lipids into cytotoxic and pro-inflammatory species poses a unique and perpetual problem for the lung. Ozone forms bioactive oxysterols that, if not properly cleared by type A scavenger receptors (i.e., MARCO, SR-AI/II) on alveolar macrophages [27], induce apoptosis and cytotoxicity [28–30]. Moreover, a broad array of acute lung injury exposures has been reported to oxidize surfactant phospholipids into proinflammatory species that trigger inflammation through secondary activation of the TLR4 cascade [31]. Thus, homeostatic maintenance of alveolar lipids is directly coupled to alveolar inflammatory homeostasis and represents a unique challenge for the lung.

Several proteins that play a central role in RCT, including apoA-I, apoE, ABCA1, and ABCG1 are expressed in the lung. For many of these targets, pulmonary phenotypes observed upon gene-deletion suggest the importance of cholesterol homeostasis to lung physiology. Mice with a deletion of the RCT-promoting, HDL-associated apolipoprotein apoA-I have increased airway resistance, inflammatory cell recruitment, and airway collagen deposition in the steady state [32], whereas apoE-deficient mice, a dyslipidemic strain commonly utilized in atherosclerosis research, have reduced developmental alveologenesis and abnormal pulmonary function with increased airway resistance and static compliance [33]. Mice deficient in either of the cholesterol efflux transporters ABCA1 or

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ABCG1, both of which are expressed in alveolar macrophages and alveolar epithelium, have a pulmonary phenotype characterized by lipid overload [11, 34, 35]. ABCA1 null mice have an accumulation of excess cholesterol in alveolar macrophages and type II cells, alveolar proteinosis, and respiratory distress [34]. Naïve *Abcg1*$^{-/-}$ mice have a similar yet more pronounced pulmonary phenotype of lipid-overloaded alveolar macrophages and alveolar epithelial cells that is further complicated by increased steady state recruitment of a wide array of leukocyte subtypes to the lung [11, 35]. *Abcg1*$^{-/-}$ alveolar macrophages appear to play a central role in this phenotype, displaying increased constitutive cytokine synthesis and apoptosis [35]. Interestingly, the lung phenotype of *Abcg1*$^{-/-}$ mice is highly reminiscent of the rare human lung disease pulmonary alveolar proteinosis, in which alveolar macrophage ABCG1 deficiency has been implicated [36]. While there is good evidence that loading of cultured macrophages with exogenous cholesterol activates multiple inflammatory pathways, there is nevertheless little direct evidence at present that cholesterol overload in ABCG1-deleted mice is causally responsible for their constitutive lung inflammation.

4. Effects of cholesterol regulators on pulmonary immune responses to the environment

Recent studies have revealed important roles for several endogenous cholesterol trafficking regulators, including ABCG1, apoE, and LXR in pulmonary immune responses. We recently reported that *Abcg1*$^{-/-}$ mice have an exaggerated pulmonary response to both LPS inhalation and *K. pneumoniae* infection, characterized by enhanced PMN recruitment to the airspace as well as elevated airspace cytokines [37]. Increased alveolar neutrophilia in the infected *Abcg1*$^{-/-}$ lung was associated with enhanced bacterial clearance, suggesting that ABCG1 regulates pulmonary host defense. Interestingly, this phenotype appeared to be tissue-selective as *Abcg1*$^{+/+}$ and *Abcg1*$^{-/-}$ mice had equivalent responses to intravenous bacteria and intraperitoneal LPS. Recently, our laboratory has also uncovered a novel role for ABCG1 in a murine model of allergic asthma involving ovalbumin (OVA) sensitization and challenge [38]. We find that ABCG1-deficient mice display reduced airway eosinophils, T helper (Th) 2 cytokines, and Th2 cells, and increased airway neutrophils and IL-17 after OVA sensitization and challenge, suggesting skewing of adaptive immune programs away from Th2 in the setting of ABCG1 deficiency. By contrast, the dyslipidemic murine strains *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ were recently reported to display increased airway hyperresponsiveness and mucus production but normal airway inflammatory cell counts in a house dust mite model of murine asthma [39].

Several studies have recently indicated that LXR, a nuclear receptor for oxysterols that induces ABCG1 and apoE among several other RCT target genes, also regulates pulmonary immunity. We and others have reported that treatment of mice with synthetic LXR agonists decreases influx of PMNs into the airspace, upregulates antioxidant enzymes, and decreases proinflammatory cytokines in the airspace in multiple models of acute lung injury and infection [40–43]. Our laboratory also reported that pharmacologic activation of LXR compromises host defense against *K. pneumoniae* lung infection, likely due to reduced alveolar neutrophil recruitment [43]. This contrasts with a recent study by Korf et al. [44], wherein it was reported that LXR expression contributes to clearance of, and T cell specific immunity against *Mycobacterium tuberculosis*. Taken together, these studies indicate that regulation of pulmonary host defense by LXR may be pathogen-specific. As the lung is a major source of the endogenous LXR agonist cholestenoic acid, and serum cholestenoic acid is decreased in various chronic lung diseases [45], we speculate that reduced LXR tone in the injured lung may feed back to dysregulate inflammation and host defense during chronic lung disease.

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5. Effects of diet-induced dyslipidemia on pulmonary immunity

Whereas metabolic syndrome and dyslipidemia have been clearly linked to several cardiovascular inflammatory phenotypes, little is known about the sensitivity of immune responses in the lung to systemic dyslipidemia. To address this knowledge gap, we recently reported the effects of diet-induced dyslipidemia on pulmonary innate immune responses in wild type (C57BL/6) mice [46]. We found that high cholesterol diet-fed mice displayed attenuated influx of PMNs into the airspace in response to LPS and *K. pneumoniae*, as well as compromised bacterial clearance from the lung. The reduced influx of PMNs in dyslipidemic mice stemmed from both deficient induction of airspace NF-κB-dependent cyto-/chemokines and impaired PMN chemotaxis, and could be recapitulated by intravenous injection of oxidized LDL into naïve normal diet-fed mice. Paradoxically, bacteria were cleared more effectively from the bloodstream during dyslipidemia. This was associated with basal circulating neutrophilia and serum cytokine induction in dyslipidemic mice, as well as hyperresponsiveness to systemically administered TLR ligands. Taken together, these data indicate that diet-induced dyslipidemia imparts a dysregulated compartmentalization of neutrophils, cytokines, and TLR responsiveness between serum and airspace, enhancing host defense in the former but compromising host defense in the latter.

In a report by Martens et al. [47], *Apoe* $^{-/-}$ mice were fed either a low cholesterol (LC) or high (HC) diet before infection with *M. tuberculosis. Apoe* $^{-/-}$ mice fed the LC diet were slightly more susceptible to *M. tuberculosis*, as evidenced by increased lung inflammation and bacterial lung burden. However, *Apoe*$^{-/-}$ mice fed the HC diet had a significant increase in *M. tuberculosis* susceptibility characterized by massive lung inflammation, heavy bacterial burden, and early mortality. The *Apoe*$^{-/-}$ HC diet-fed mice also had a defect in adaptive immunity with a failure to mount a protective Th1 immune response. The *M. tuberculosis* susceptibility of *Apoe*$^{-/-}$ mice increased with serum cholesterol, suggesting that their susceptibility was dependent upon cholesterol and not ApoE deficiency. Taken together, these studies indicate that dyslipidemia can alter pulmonary innate and adaptive immune responses, increasing susceptibility to pathogens in the lung.

The effect of diet-induced dyslipidemia has also been recently examined in adaptive immune responses in the lung. In a report by Yeh and colleagues [48], a HC diet in mice significantly increased airspace eosinophils, IL-5, and PGE_2 but not allergen-specific serum IgE in an OVA sensitization and challenge model. By contrast, we recently reported an inverse relationship between serum total and non-HDL cholesterol and asthma in the U.S. population, suggesting that human subjects with the highest serum cholesterol levels are least likely to have asthma [49]. Clearly, further investigation of the relationship between serum lipoprotein cholesterol and asthma is warranted.

6. Cholesterol as a potential pharmacologic target in lung disease

Given the connection between cholesterol dysregulation and pulmonary immunity, it has become of interest to examine the efficacy against pulmonary disease of drugs targeting cholesterol transport (Table 1). In addition to reduction of serum cholesterol through inhibition of HMGCR in the mevalonate synthesis pathway of the liver and other organs, statins have been shown to have pleiotropic anti-inflammatory actions. While some effects of statins on pro-inflammatory signaling likely stem from reduction of lipid raft cholesterol, statins also attenuate pro-inflammatory signaling through depleting HMGCR-derived isoprenoids, and may also have HMGCR-independent effects upon inflammation (reviewed in [3]). Most *in vivo* studies of statins have not distinguished among these mechanisms.

The benefits of statin therapy on inflammatory airway diseases have been demonstrated in multiple mouse models of lung disease, that together suggest wide-ranging potential for

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statins in therapy of human lung disorders. Both simvastatin and pravastatin reduced airspace inflammatory cells and Th2 cytokine production in mouse models of allergic asthma (OVA and house dust mite) [50, 51]. Lee et al. [52] reported that simvastatin inhibited lung parenchymal destruction and peribronchial and perivascular inflammatory cell infiltration in a murine model of smoking-induced emphysema through a reduction in levels of MMP-9, a major inflammatory mediator. Our group reported that lovastatin reduced airspace neutrophilia and protein leakage following LPS inhalation, a model of acute lung injury [53]. Beneficial effects of statins have also been observed in animal models of pulmonary hypertension and pulmonary fibrosis [54, 55].

Recently, the impact of statins on lung function has been examined in observational studies of human lung disease (Table 2). Several retrospective studies have reported that statins are independently associated with reduced risk of pneumonia and/or pneumonia-associated mortality [56–62]. However, a prospective study noted no significant relationship between statins and mortality or admission to an intensive care unit in a cohort of patients with community-acquired pneumonia [63]. In asthma, both simvastatin and atorvastatin treatment have been associated with reduced leukocytes and leukotrienes in sputum, as well an improvement in FEV1 [64–66], although not all studies have found a benefit in important clinical outcomes (reviewed in [67]). In COPD, statins were associated with reduced FEV1 decline, decreased intubations, and decreased mortality [68, 69]. Other observational studies have reported that statins may delay disease progression and improve survival in patients with pulmonary hypertension [70], and decrease the occurrence of acute rejection after lung transplant [71]. While varying results have been reported for statins in acute lung injury (ALI) [72, 73], a large NHLBI ARDS network study in progress, Statins for Acutely Injury Lungs from Sepsis (SAILS), will hopefully resolve the issue of statin efficacy in ALI and ARDS. Additional lipid-modifying agents that have been evaluated in cardiovascular disease include niacin and cholesterol ester transfer protein (CETP) inhibitors. Both niacin and CETP inhibitors have been successful in raising HDL levels and lowering LDL levels [74–76], however niacin failed to improve cardiovascular outcomes in a large trial (AIM-HIGH). While the CETP inhibitor torcetrapib has been associated with worsened clinical outcomes, more recently tested CETP inhibitors such as anacetrapib have shown more promise [75, 77]. Whether niacin and/or CETP inhibitors may have efficacy against lung disease remains an interesting, untested question.

Additional cholesterol-targeting agents that have been studied in models of lung disease include LXR agonists and apolipoprotein mimetic peptides. In addition to the aforementioned efficacy against LPS- and bacteria-induced pulmonary neutrophilia [43], LXR agonists also have been shown to reduce pro-inflammatory responses in human airway smooth muscle cell cultures, suggesting that they may hold some promise in treatment of airway disease [78]. Peptides have been designed that mimic the secondary structure (i.e., amphipathic α-helical repeats) and anti-inflammatory/antioxidant function of the apoA-I holoprotein, and that have been validated, like apoA-I, to have atheroprotective and RCT-promoting activity in animal models. Much like apoA-I, apoA-I mimetics bind oxidized lipids, promote cellular cholesterol efflux, and exert potent anti-inflammatory effects in cell culture (reviewed in [79]). While well characterized in attenuation of atherosclerosis, these peptides have only recently been examined in pulmonary disorders.

Administration of the apoA-I mimetic peptide 5A prior to house dust mite (HDM) sensitization and challenge in a mouse model of asthma resulted in a significant reduction in airspace eosinophils, lymphocytes, and neutrophils, as well as attenuated pulmonary histopathology [80]. The reduction in airway inflammation was associated with a decrease in Th2 and Th17 cytokines. 5A also abrogated the development of airway hyperresponsiveness, and reduced several key features of airway remodeling, including

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goblet cell hyperplasia and the expression of collagen genes (Col1a1 and Col3a1). Similar findings were noted for the alternate apoA-I mimetic D-4F in an OVA sensitization and challenge model of asthma, wherein D-4F decreased airway hyperresponsiveness, cellular inflammation, and markers of oxidative stress [81]. D-4F has also interestingly been reported to attenuate lung inflammation induced by influenza A infection in mice [82]. Recently, an apoE mimetic peptide modeled after the LDLR-binding region of apoE holoprotein was also shown to reduce eosinophilic airway inflammation, airway cytokines, airway hyperresponsiveness, and goblet cell hyperplasia in a house dust mite model of allergic asthma in mice [39]. Taken together, these studies highlight the strong potential for apolipoprotein mimetics in treatment of pulmonary diseases, although the precise mechanisms underlying the efficacy of these agents remain unclear.

7. Conclusions

Dyslipidemia is highly prevalent in modern society, and clusters with obesity and other disorders of the metabolic syndrome that together center upon disordered inflammation. Emerging studies using gene-deleted mice and pharmacological tools indicate that cholesterol trafficking plays a surprisingly important and perhaps unique role in lung physiology and lung immune homeostasis. This unique relationship likely arises from the distinct biology and cholesterol requirements of the lung. To what extent obesity modifies lung disease through dysregulated lipid trafficking in the lung remains an unanswered question. Future studies will be required to differentiate the various roles of cholesterol regulators in trafficking of leukocytes to the lung, clearance of pathogens, and maintenance of pulmonary function. This intriguing area of research holds the promise of uncovering novel determinants of, and treatments for, chronic lung disease.

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ABBREVIATIONS

ABCA1	ATP Binding Cassette transporter A1
ABCG1	ATP Binding Cassette transporter G1
AHR	Airway Hyperresponsiveness
ALI	Acute lung injury
Apo	apolipoprotein
BAL	Broncheoalveolar lavage
CETP	cholesteryl ester transfer protein
CTGF	connective tissue growth factor
COPD	Chronic obstructive pulmonary disease
eNOS	endothelial nitric oxide synthase
ER	endoplasmic reticulum
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity

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FC	free cholesterol
HD	hemodynamics
HDL-C	high density lipoprotein cholesterol
HMGCR	hydroxymethyl-glutaryl coenzyme A reductase
HSMC	human smooth muscle cells
ICS	inhaled corticosteroids
ICU	Intensive care unit
IL	interleukin
IPF	Idiopathic pulmonary fibrosis
LDL-C	low density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LPS	lipopolysaccharide
LTB4	leukotriene B4
LXR	Liver X Receptor
MCP-1	monocyte chemotactic protein-1
MMP	matrix metalloproteinase
NO	nitric oxide
OVA	ovalbumin
PAP	pulmonary artery pressure
PEF	peak expiratory flow
PGE2	prostaglandin E2
PH	pulmonary hypertension
PMN	polymorphonuclear leukocyte
RCT	reverse cholesterol transport
SMA	smooth muscle actin
SR	scavenger receptor
TG	Triglyceride
Th	T helper
TGF-β1	transforming growth factor β1
TLR	Toll-like Receptor
TNF	tumor necrosis factor
VEGF	vascular endothelial growth factor
VFD	ventilator-free days
VLDL	very low density lipoprotein.

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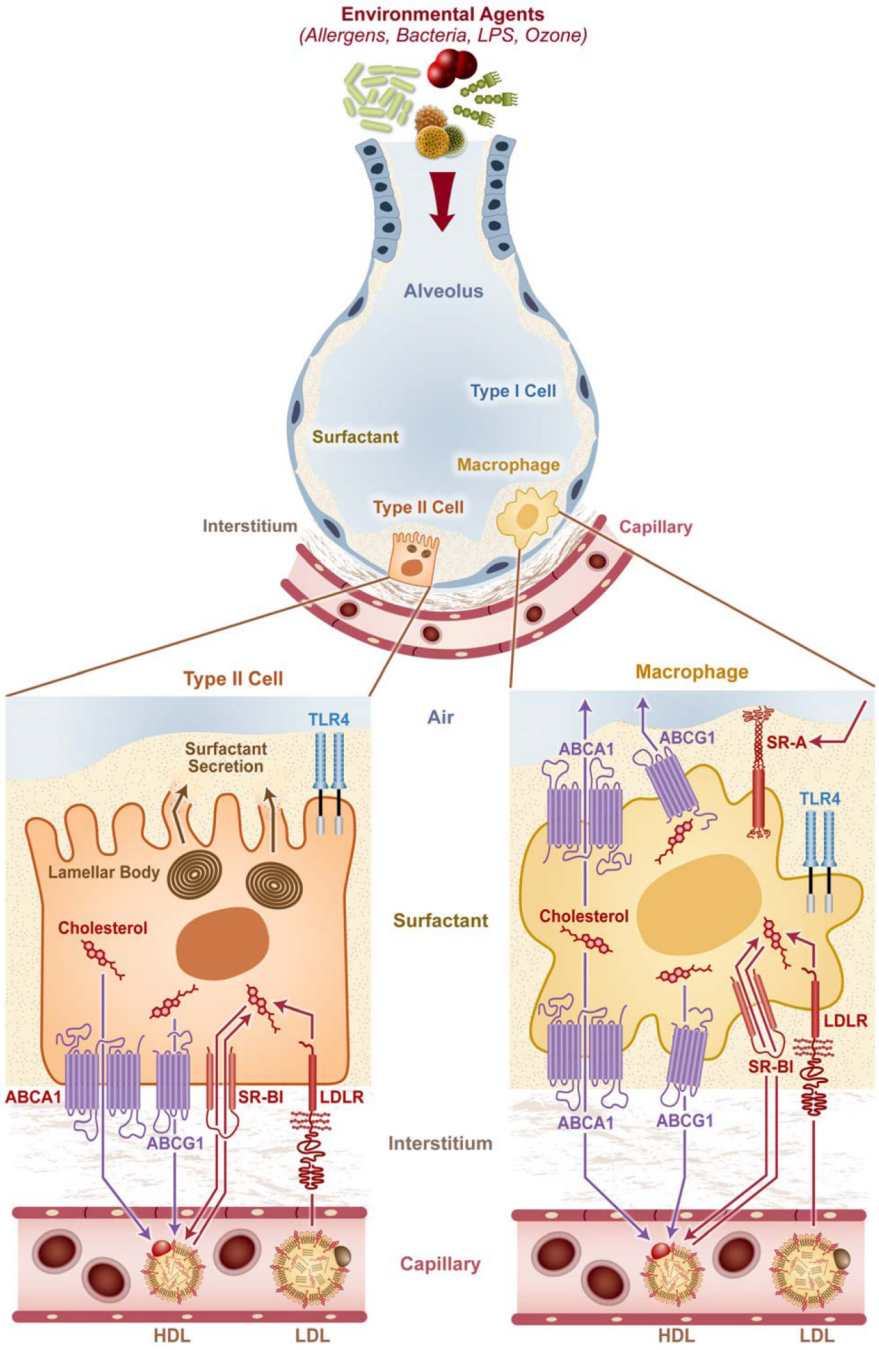

Figure 1. Cholesterol trafficking influences multiple cell types in the lung

Alveolar epithelial type II cells and alveolar macrophages likely receive cholesterol from circulating low density lipoprotein and high density lipoprotein (LDL, HDL) through the LDL receptor (LDLR) and scavenger receptor B type I (SR-BI), respectively. HDL is also the major source of the antioxidant vitamin E for type II cells. Class A scavenger receptors (SR-A) on macrophages play a role in clearance of oxidized alveolar lipids that may otherwise mediate cytotoxic and pro-inflammatory effects. The disposal pathway for cholesterol from type II cells and macrophages involves the cholesterol efflux transporters ATP Binding Cassette (ABC) A1 and ABCG1, and perhaps also SR-BI. ABCA1 also mediates basolateral surfactant efflux from type II cells; deletion of either ABCA1 or

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ABCG1 leads to severe surfactant proteinosis and lipidosis. Disordered cholesterol/phospholipid trafficking through the lung, such as with ABCG1 deletion, alters immune cell trafficking to the lung as well as the lung's immune responsiveness to a variety of environmental exposures, indicating that there is intimate crosstalk between lipid and immune homeostasis in the lung.

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Table I

Reported efficacy of cholesterol-targeted agents in experimental models of lung disease.

Lung disease model	Pharmacological agent	Outcomes	References
Asthma	**Simvastatin**	↓ BAL eosinophils, Th1 and Th2 cytokines ↓ AHR ↓ TGF-β1-induced fibronectin	[50, 83, 84]
	Pravastatin	↓ BAL eosinophils, IL-5, PGE_2, MCP-1	[51]
	LXR agonist	TO901317: ↓ HSMC migration/proliferation GW3965: ↔ BAL eosinophils or cytokines, ↑ AHR	[41, 78]
	ApoA-I mimetics	5A and D4F: ↓ BAL eosinophils, PMNs, lymphocytes, and Th2 and Th17 cytokines, ↓ AHR	[56, 80]
	ApoE mimetics	↓ BAL eosinophils, Th2 and Th17 cytokines, AHR, and IgE	[39]
Acute Lung Injury	**Simvastatin**	↓ LPS-induced lung permeability, PMN influx, and NF-κB activation	[85]
	Lovastatin	↓ BAL PMNs, proinflammatory cytokines, ↓ lung clearance of *K. pneumoniae.*	[53, 85]
	LXR agonist	TO901317: ↓ BAL PMNs and clearance of *K. pneumoniae*.	[43]
	ApoA-I mimetics	D-4F: ↓ influenza A-induced IL-6 and TNFα production by A549 cells, ↑ Type I interferon and viability	[86]
	ApoA-I protein	↓ IL-1B, IL-6, and TNF-a in BAL and lung injury after sepsis	[87, 88]
COPD/Emphysema	**Simvastatin**	↓ lung injury, ↓ BAL MMP-9, VEGF, eNOS ↑ alveolar cell proliferation	[52, 89]
Idiopathic Pulmonary Fibrosis	**Simvastatin**	↓ CTGF, SMA, and collagen production from fibroblasts from healthy and IPF patients	[90]
	ApoA-I mimetics	↓ BAL cellular influx, and lung collagende position	[91]

Abbreviations: AHR, Airway Hyperresponsiveness; BAL, Bronchoalveolar lavage; CTGF, connective tissue growth factor; eNOS, Endothelial NOS; HSMC, Human smooth muscle cells; IPF, Idiopathic Pulmonary Fibrosis; IL, Interluekin; LPS, Lipopolysaccharide; MCP-1, Monocyte chemotactic protein-1; MMP, Matrix metalloproteinase; PGE_2, prostaglandin E2; PMN, polymorphonuclear leukocyte; SMA, Smooth muscle actin; Th, T helper; TGF-β1, Transforming growth factor β1; TNF, Tumor necrosis factor; VEGF, *Vascular endothelial growth factor*.

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Table 2

Clinical outcomes of treatment of lung disease with statins.

Pulmonary Disease	Study Design	Outcome Associated with Statin Therapy	Reference
Age-related lung function decline	Observational study	↓ decline in FEV1 and FVC	[92]
	Retrospective study of current/former smokers	↓ decline in FEV1 and FVC	[93]
COPD	Retrospective cohort study	↓ exacerbations, ↓ intubations	[69]
	Retrospective cohort, case control studies	↓ COPD death	[94]
	Population-based analysis	↓ COPD death	[95]
	Nested case control study	↓ COPD hospitalization, ↓ death	[96]
	Retrospective cohort study	↑survival after exacerbation	[68]
Asthma	Prospective, randomized, placebo-controlled, crossover trial	↑ FEV1, ↓ sputum eosinophils and symptoms in patients discontinuing ICS	[64]
	Prospective, randomized, placebo-controlled, double-blind crossover trial	↔ PEF, asthma control ↓ sputum macrophage, LTB4	[66]
	Population-based study	↓ hospitalization for asthma	[97]
	Prospective, randomized, placebo-controlled, double-blind trial	↓ sputum eosinophil percentage in patients co-treated with ICS	[65]
	Prospective, randomized, placebo-controlled, double-blind crossover trial	↔ exhaled NO, lung function, sputum eosinophils	[98]
	Retrospective cohort study	↓ FEV1, ↑ medication requirement, ↑ symptoms compared with asthmatics not started on statins	[99]
	Prospective, randomized, placebo-controlled trial	↔ PEF ↑ quality of life score	[76]
ALI	Retrospective cohort study	↔ VFD, organ failures, mortality	[72]
	Prospective, randomized, placebo-controlled, double-blind trial	↓ nonpulmonary organ dysfunction ↓ BALF interleukin-8 ↔ ICU mortality	[73]
IPF	Retrospective cohort study	↔ survival	[100]
Pulmonary Hypertension	Prospective observational study	↑ exercise capacity / improved HD ↓ disease progression	[70]
	Prospective, randomized, placebo-controlled trial of COPD patients with PH	↑ exercise capacity ↓ dyspnea score, ↓ PAP	[101]

Abbreviations: ALI, *Acute lung injury; BALF,* Bronchoalveolar *fluid; COPD,* Chronic obstructive pulmonary disease; FEV1, Forced expiratory volume in 1 second; FVC, *Forced vital capacity; HD, hemodynamics; ICS, inhaled corticosteroids; ICU, Intensive care unit; IPF, Idiopathic pulmonary fibrosis; LTB4, leukotriene B4; NO, nitric oxide; PAP, pulmonary artery pressure; PEF, peak expiratory flow; PH, pulmonary hypertension; VFD, ventilator-free days.*