Nonrespiratory Functions of the Lung

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Key Points

- Pulmonary endothelial cells metabolize endogenous substances and xenobiotics via ectoenzymes on their luminal surface and caveolae as well as enzyme systems within their cytosol.
- Pulmonary metabolism results in the activation of several endogenous substances and medications of importance to the anesthesiologist.
- Pulmonary uptake is often not associated with metabolism, but still markedly affects pharmacokinetics by initially attenuating peak concentrations and then returning unchanged substance to the circulation.
- The lung's ability to serve as a vascular reservoir is directly related to the capacitance of the pulmonary vessels.
- The lung serves as a physical filter, but this function may be compromised with high cardiac output and in several disease states.
- The respiratory epithelium's functions include humidification and trapping of particles and pathogens.
- The airway surface film has antimicrobial capacity beyond its mechanical removal of debris from the airway.

Introduction

For nearly two millennia of Western medicine, the lungs were thought to primarily protect the heart from overheating by exhaling warm air and from direct injury both by their position and cushioning structure. These views are ascribed to the teachings of Galen and, to some extent, Aristotle [1, 2]. Traditional Chinese medicine emphasized the interconnectedness of the organ groupings of the five phases, but within this construct, the lung was seen as a minister to the emperor heart and in partnership with the bowel to have the responsibility of maintaining the boundary of the body and outside world. In the thirteenth century, Ibn-an-Nafis of Cairo described the purification of blood by mixing with air in the lungs in one of the earliest known descriptions of gas exchange [3].

Over the last sever-al centuries, however, the biochemistry and physiology of respiration have become essentially synonymous with the lungs. From the work of pioneers such as Boyle, Lower, Priestly, Haldane, and others, most clinicians now think of the lung first and foremost as an organ of gas exchange. In more recent years, other important roles of the lung have emerged, roles that are largely in keeping with the concepts of our medical heritages.

In this sense, we now return to historic views of the lung as protector and modulator. Specifically, nonrespiratory functions of the lung including its metabolic processes, endocrine role, mechanical filtration of venous blood, warming of inspired gasses, and protection against inhaled pathogens and toxins are discussed. Focused aspects of organ structure and cellular function are reviewed as required by this discussion.

Uptake and Metabolism Within the Lung

The lungs are particularly suited for critical metabolic activities. They continuously receive essentially the entire cardiac output, and their vascular area, depending upon the

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degree of recruitment, is an enormous 70–100 m^2. Further, the lungs contain nearly half of the body's endothelium [4] and have an extraordinarily high perfusion of 14 mL/min/g tissue (as opposed to the next-highest renal perfusion of 4 mL/min/g tissue). Thus, there is ample blood–endothelial interface for surface enzyme activity as well as uptake and secretion. The largest population of cells involved in pulmonary metabolism of blood-borne substances is, as might be expected, the pulmonary endothelium. Consistent with high metabolic activity, endothelial cells have both extensive cytoplasmic vesicles and prominent caveolae. The caveolae are tiny membrane invaginations and near-membrane vesicles similar to those found elsewhere in the body, measuring 50–100 nm, associated with caveolin proteins, and derived from lipid rafts within the membrane. The predominant activities of these caveolae, thought to include endocytosis [5] and signal transduction, have not been fully delineated and may be pleiotropic [6]. The endothelial cells structurally have large luminal projections and invaginations, providing an even greater interface area at the microscopic level.

Metabolism by the endothelial cell occurs either on the surface of the cell via enzymes associated with the membrane ("ectoenzymes") or by cytosolic processing after the substances are taken up by the cell. Some surface enzymes are distributed along the luminal membrane [7], while others are associated exclusively with the caveolae [8]. Figure 7.1 schematically depicts these processes with example substances and pathways. Metabolism may be further divided into exogenous vs. endogenous substances as well as deactivated vs. activated products. Regardless of these considerations, it should be remembered that intensive investigation of pulmonary metabolism has developed only over the last several decades [9]. Much remains to be discovered, and conflicting data exist for drugs as central to clinical anesthesiology as propofol [10, 11].

The literature's terminology of pulmonary metabolism can be confusing and sometimes inconsistent. The careful reader must sometimes deduce the actual processes described and investigated through context. In general, "pulmonary uptake" or "extraction" is simply used to describe transfer from blood to the lung and does not indicate whether the substance of interest is subsequently metabolized or returned back into the blood with or without alteration. "First-pass" uptake is used to describe the amount of substance removed from the blood on the first cycle through the lungs, although data from techniques such as tissue slices have been used to infer this behavior. "Extraction" is also sometimes used synonymously with first-pass uptake. "Clearance" may be used to describe a substance undergoing actual elimination, either in terms similar to renal clearance as volume of blood from which the substance would be completely removed (mL/min or mL/kg min) or as a comparison of pulmonary arterial concentration vs. systemic arterial concentration. Terms used for isolated lung studies include "accumulation," the percentage of substance retained in the lungs after equilibrium, and "persistence," percentage of substance retained after washout.

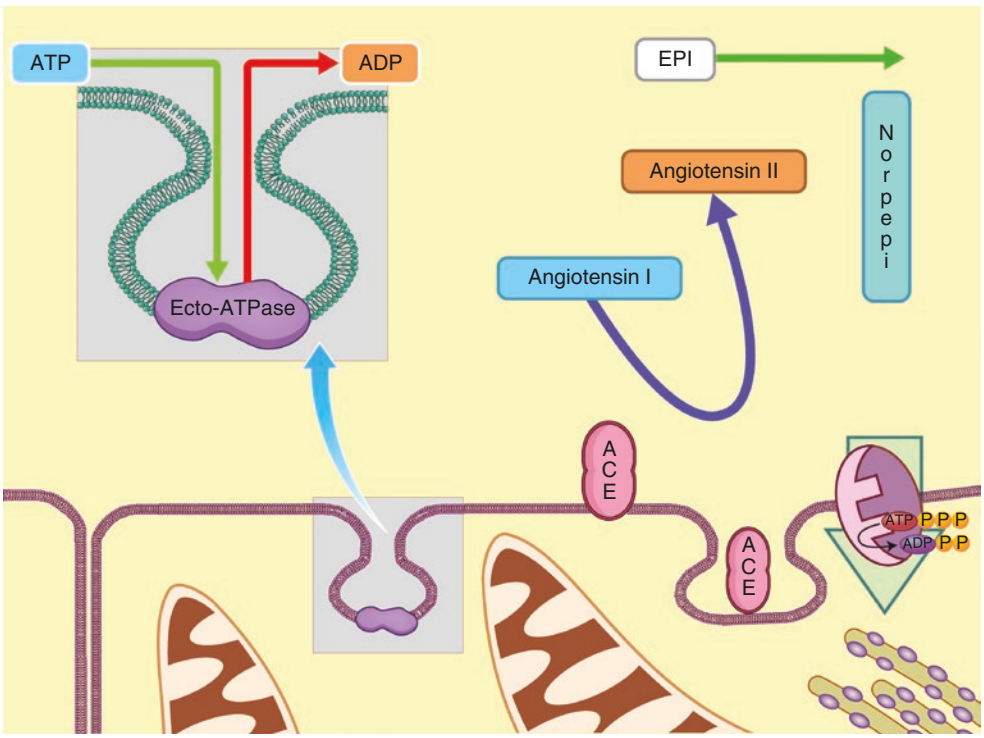

Fig. 7.1 Schematic examples of pulmonary endothelial metabolism. Surface enzymes may be restricted to the caveolae (Ecto-ATPase in the inset above is an example) or present on both the luminal surface and caveola (e.g., angiotensin-converting enzyme [ACE]). Another characteristic of pulmonary endothelium is selective uptake, here exemplified by the ATP-dependent uptake of norepinehrine (NOREPI), while epinephrine (EPI) is not taken up. See text for details

It is beyond the scope of this discussion to fully detail the experimental methods used in the investigation of pulmonary metabolism, but the challenges of investigation and data interpretation merit at least mention. As implied above, lung metabolism has been investigated in vitro and in vivo. In vitro techniques include the use of cellular fractionates, tissue homogenates, and tissue slices. Recent advances in uniform preparation and cryoprotection have made tissue slices an attractive, cost-efficient option [12] despite concerns regarding the impact of processing on enzyme behavior. Tissue slices have a particular advantage in lung research because they include all cell types. The isolated and perfused animal lung model represents the next level of fidelity. The lung can remain within the animal or be explanted, and the uses of various perfusion managements (e.g., nonpulsatile vs. pulsatile, blood vs. crystalloid, and one-pass vs. recirculation) have been described with little standardization. Further, various investigators commonly subject the lung to no inflation, constant airway pressure, or positive pressure ventilation. The impact of these differences in ventilation on resultant data is unknown. In the next level of modeling, in intact animals and human subjects, the pulmonary uptake is assessed by measurements of the difference between pulmonary arterial and pulmonary venous (animals) or systemic arterial (human) concentrations of the substance in question, typically after a controlled bolus and/or infusion when possible. These invasive requirements do not lend themselves to large volunteer studies. In fact, most human subjects are critically ill and/or undergoing complex procedures. This variation in disease and treatment may produce data that in turn has great variance [13]. Conversely, inclusion criteria rigorous enough to provide consistent results produce a patient population in which the results are of limited general applicability [14]. A variation of the method just described is the double-indicator dilution technique [15]. In this technique, the substance of interest and a substance with no (or no known) pulmonary uptake are injected, typically into the right atrium. Samples are then taken from a systemic artery, with the known substance serving as the control to which the investigated substance's concentration curve is compared. This technique is more practical in terms of decreased frequency of sampling and somewhat decreased invasiveness.

It is important to reemphasize that the lung has a profound impact on the blood concentration of substances even when it does not ultimately metabolize or secrete them. This is because of the simple uptake and retention of substances, often followed by release back into the blood. This "capacitor effect" [16] of the lungs in which any rapid rise or fall in concentration is attenuated will be revisited in the discussion below as it pertains to local anesthetic toxicity.

With these limitations in mind, we shall first review the current understanding of drug metabolism with focus on medications of particular interest to the anesthesiologist, and then look at metabolism of endogenous substances. Even though they are also administered therapeutically and duplicated in the summary of medications, endogenously produced substances such as catecholamines will be included in the latter discussion (Table 7.1).

Table 7.1 The lung and medications of interest to anesthesiologists

Drug class	Impact of passage through the pulmonary circulation	
	Minimal or none	First-pass uptake and/or metabolism
Hypnotics		Thiopental +
		Ketamine ++
		Propofol ++
Benzodiazepines		Diazepam ++
Nondepolarizing muscle relaxants	Rocuronium	
	Vecuronium	
	Rapacuronium	
	d-tubocurarine	
Opiates	Morphine	Fentanyl ++
		Sufentanil +
		Alfentanil ±
Catecholamines	Dopamine	Norepinephrine +
	Epinephrine	
	Isoproterenol	
Local anesthetics		Bupivacaine +
		Lidocaine ++

Drugs

The cytochrome P-450 monooxygenase enzyme systems are the most studied metabolic pathways for medications. The lungs have substantial concentrations of P-450 isoenzymes, particularly within type II pneumocytes, Clara cells, and endothelial cells [17]. This implies that the lung has the capacity for drug metabolism via P-450 systems. While P-450 and other enzyme systems have long been known to exist in the human lung (Table 7.2), the actual activity of lung enzymes ranges from negligible to 33% of that of the liver [19]. The difference between organ enzyme activity of different species is large (lung to liver activity varying from a few percent to 111%) and mandates caution when interpreting animal data [20].

Opioids

Fentanyl has been shown to have a markedly variable first-pass uptake of up to 90% in humans [21]. The same investigators found that significant amounts of fentanyl are returned from the lungs into the blood with a biphasic pattern, equilibrating after about a minute in the fast phase and nearly 25 min for the slow phase. The uptake of fentanyl is higher than expected even for this basic and lipophilic drug. In fact,

Table 7.2 Enzyme systems of the lung [18]

Cytochrome P-450 oxygenase
Sulfotransferase
Nitroreductase
N-Methyltransferase
Glutathione-*S*-epoxide transferase
Glutathione-*S*-aryl transferase
Glucuronyl transferase
Epoxide hydrolase
Amine oxidase

active uptake of fentanyl has been demonstrated in human lung endothelial cells [22].

The study of alfentanil has led to widely variant first-pass uptake data. Uptakes of 67% have been reported [21], although more commonly uptakes of approximately 10% are reported [23]. Of note, these studies included other medications (sufentanil and morphine in one study and fentanyl in the other) that were found to behave similarly to accepted data for those drugs. This makes the discrepancy for alfentanil behavior particularly hard to interpret.

Sufentanil demonstrates uptake that is a little more than half that of fentanyl. A study in which patients had received alfentanil for induction followed by a sufentanil infusion of 50 μg/min for 10 min showed sufentanil first-pass uptake of about 50% with a 20-min retention of about 20% [24]. The investigators incidentally noted that smokers had a statistically higher retention of the infused dose.

Early work with morphine in the perfused rabbit lung model showed about 30% first-pass uptake [25]. Interestingly, subsequent work in intact animals and in humans has found much lower uptake of about 10% [23, 26], including postoperative bolus and infusion [27]. Metabolism has generally been found to be negligible.

Muscle Relaxants

There is a paucity of data on pulmonary pharmacokinetics of muscle relaxants. This may be because the agents studied, including vecuronium, rocuronium, d-tubocurarine, rapacuronium, and Org 7617, demonstrated no first-pass uptake or metabolism in the intact porcine model [28]. This would appear to have generated little enthusiasm for further investigation of this class of drugs.

Local Anesthetics

Lidocaine has a long history of investigation in terms of pulmonary uptake and metabolism. The general consistencies across species include a first-pass uptake of approximately 50% with significant retention at 10 min [29–31]. The uptake of lidocaine has also been examined in a variety of physiological circumstances. Under extremes of metabolic acidosis and alkalosis [30], lidocaine demonstrates increased uptake with higher blood pH. It is postulated that this finding is the consequence of increased drug lipophilicity, since, in a less acidic environment, more of the drug is in its nonionized form. Under extremes of FiO_2 in in vivo isolated lobes of dogs under nitrous oxide and halothane anesthesia, there were no differences demonstrated in lidocaine uptake [32]. Of interest, the prolonged retention in all groups was less than that commonly reported in other studies, raising the issue of the effects of this particular model on uptake.

Bupivacaine has been investigated less extensively than lidocaine with less consistent results. In most animal species, peak extraction has been reported as high with variable first-pass retention between species and methodology [33–35]. In humans, however, the effective first-pass extraction appears to be lower when studied by epidural dosing [36, 37]. As in the case of lidocaine, the pulmonary pharmacokinetics of bupivacaine have also been investigated in acidosis. In a rabbit model, animals with a pH of 7.0–7.1 demonstrated decreased maximum pulmonary extraction as a group [38] with resultant higher peak systemic concentrations of drugs.

Two recent areas of interest in the practice of clinical anesthesia are intimately linked with the pulmonary uptake of local anesthetics. The first is the relative safety of levobupivacaine and ropivacaine in comparison to bupivacaine. These drugs have, in fact, been the subject of several investigations. Early animal studies suggested decreased toxicity of these newer preparations [39, 40]. The discussion continues, however, with more recent work regarding the pulmonary uptake of these drugs. In rabbits, for example, the uptake of levobupivacaine is higher than ropivacaine with resultant lower systemic blood concentrations of levobupivicaine [41]. The authors thus caution that the lower absolute toxicity of ropivacaine may be tempered by the lung's greater attenuation of peak levobupivacaine levels in inadvertent intravenous injections. A recent review of the pharmacodynamics and pharmacokinetics of local anesthetics [42] focuses on the challenges of comparing toxicities in clinical practice [43–45]. Animal models, with the limitations already discussed among many more [46], must be utilized since clinical toxicity is an uncontrolled, rare, and dangerous event [47]. Other questions are raised by the relative central nervous system and cardiovascular toxicity between drugs and study variation in drug administration and measurement. The inconsistencies in the data of pulmonary uptake are thus one of many challenges in understanding the clinical toxicities of local anesthetics.

A second, related, area of great contemporary interest is the treatment of local anesthetic toxicity with lipid emulsion [48, 49]. A recent case report, in particular, is germane to the

discussion of pulmonary uptake [50]. Briefly, a patient undergoing brachial plexus block with bupivacaine demonstrated evidence of toxicity by progressive symptomatology, seizures, widening QRS tachycardia, and asystole. Successful emulsified lipid "rescue" was followed nearly an hour later by recurrence of episodic ventricular tachycardia. The authors believe that this represented the first reported recurrence of toxic bupivacaine levels after lipid treatment. Several possible causes were postulated for this phenomenon, including postresuscitation hepatic dysfunction, reversal of generalized peripheral ion trapping of bupivacaine, and, appropriately, release of bupivacaine from the pulmonary vasculature. Thus, it seems that the issue of pulmonary uptake and release of local anesthetics must be considered in the treatment of suspected local anesthetic toxicity with emulsified lipid.

Hypnotics

There are limited, and sometimes dated, data regarding the pulmonary metabolism of intravenous induction agents. Thiopental has been found to have nearly 15% first-pass uptake in humans [51] with little or no metabolism. Ketamine shows marked species variation in its metabolism. In rabbit homogenate, the eventual complete disappearance of ketamine with only half being metabolized to norketamine implies the production of other metabolite(s) [52]. Lung tissue homogenate was more quickly saturated than liver tissue. As previously mentioned, the applicability of this homogenate data to intact animals, and certainly to humans, is unknown. In dogs under halothane anesthesia, the pulmonary uptake of ketamine was found to be slightly less than 10% without subsequent metabolism [53]. Human data are lacking.

The clarification of propofol uptake and metabolism by the lungs has taken many turns. One of the earliest studies in sheep with propofol administered as the sole medication demonstrated an apparent steady-state pulmonary clearance of 1.21 L/min [54] with negligible drug accumulation in the lung tissue, while a later study in sheep demonstrated a similar 1.14 L/min pulmonary clearance [55]. Other early works found that propofol uptake in cats was nearly 60%, but this uptake was particularly decreased in the presence of halothane or fentanyl [56]. Microsomal fractions from rat, rabbit, and human lung showed no glucuronidation of propofol [57]. Turning to data from human clinical studies, most recent work shows about 30% first-pass uptake and negligible metabolism of propofol by the lungs [11, 58]. It is interesting that a recently developed model of propofol pharmacodynamics and pharmacokinetics [59] has produced a very good fit with data from human studies [60, 61]. In this work, the lung is modeled as three tanks in series with the full cardiac output sequentially flowing to each, a model previously proven effective [62] in simulating the behavior of markers indocyanine green and antipyrine as well as the narcotic alfentanil.

Inhaled Medications

A number of medications include inhaled formulations. The inhaled route offers multiple benefits for drug delivery including a large absorptive surface area, high epithelial permeability, increased vascularity, avoidance of first-pass metabolism, and fast onset [63]. The majority of inhaled medications are used to treat the lungs directly, offering localized, targeted delivery and avoidance of systemic absorption. However, several drugs to treat illnesses from migraine headaches to diabetes are currently under development [63].

The handling of aerosolized drugs occurs via four processes including deposition, dissolution, absorption, and clearance. The site of deposition in the respiratory tract determines the treatment of most inhaled medications and is determined by the size of the particle. Chronic lung diseases including asthma, chronic bronchitis, and emphysema affect the deposition of aerosolized particles by narrowing the smaller airways resulting in deposition in larger airways [64]. The epithelial lining fluid has direct contact with the aerosolized particles, and the thickness and composition of the layer vary according to the site of deposition. Dissolution of particles into the fluid layer is controlled by the hydrophilicity of the particle. Water-soluble particles (e.g., albuterol, insulin) dissolve into the fluid and are freely absorbed [65]. In poorly water-soluble drugs (e.g., budesonide, fluticasone), the dose exceeds the aqueous solubility and the absorption is determined by dissolution-controlled kinetics [65]. Once dissolved, the speed of absorption depends on the size of the particle with smaller drugs quickly absorbed within minutes. The absorption of larger proteins is more complex but typically slower with more variable bioavailability [66]. Absorption occurs via several mechanisms. Passive diffusion occurs primarily via intercellular junction pores for hydrophilic compounds and transcellular diffusion for hydrophobic compounds. Drugs with low passive permeability utilize drug carrier transporters for uptake and transfer across cell membranes [67]. Like deposition, absorption may be impacted by chronic pulmonary disease due to deposition in the diseased upper airways, thickened mucous, and reduced surface area of diseased lungs. This may be beneficial in the treatment of chronic pulmonary diseases by preventing systemic absorption and increasing local drug effects. Hydrophilic substances may have increased absorption in the presence of chronic inflammation due to decreased epithelial barrier function and tight junction dysregulation with

increased permeability [67]. Clearance of aerosolized drugs occurs via mucociliary clearance and macrophage uptake, both of which will be discussed later.

Pulmonary Handling of Endogenous Substances

Angiotensin-Converting Enzyme

This section will discuss the activity of angiotensin-converting enzyme (ACE) and two important substrates, angiotensin I and bradykinin. The lung plays a critical role in the renin–angiotensin system because of the pulmonary endothelium's high concentration of ACE. When the kidney responds to changes in physiologic parameters including vascular volume, blood pressure, and adrenergic stimulation by the cleaving of prorenin, the resultant renin catalyzes the formation of angiotensin I from angiotensinogen. ACE then converts angiotensin I to the critically important vasoconstrictor, angiotensin II. Although ACE can be found on vascular endothelium throughout the body as well as in the plasma, the pulmonary endothelium has an abundance of ACE as a surface or ectoenzyme on the vascular membrane [68, 69], including the caveolae (Figs. 7.1 and 7.2). The newly formed angiotensin II is not, in health, taken up or further metabolized by the endothelial cell, but rather immediately returns to the blood. Clinically, ACE inhibitors have been useful drugs in the management of systemic hypertension. As will be

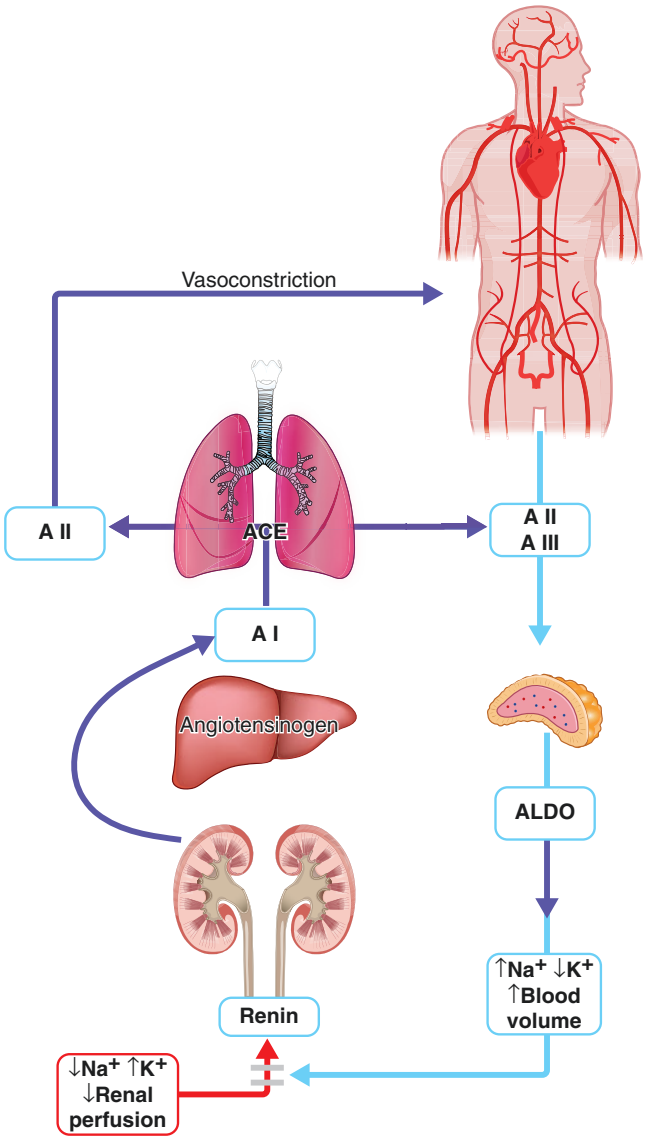

Fig. 7.2 An example of the lung's central role in the body's endocrine processes, in this case the renin–angiotensin–aldosterone axis. In response to sodium, potassium, and renal perfusion changes, renin is secreted by the kidneys. Renin cleaves angiotensinogen (renin substrate) from the liver to form angiotensin I (AI). The lung then converts AI to AII through the action predominately of endothelium-associated angiotensin-converting enzyme (ACE). AII causes vasoconstriction and is involved in stimulation of aldosterone (ALDO) secretion by the adrenal gland, resulting in retention of sodium and volume by the kidney

discussed below, the effects of these drugs are not limited simply to decreased levels of angiotensin II.

Bradykinin is a nine-amino-acid peptide produced in multiple sites throughout the body from kininogen through the action of plasma kallikrein. It is in turn metabolized by several peptidases. Pertinent to this discussion, bradykinin is degraded by ACE, and, in fact, more than 90% of bradykinin is eliminated on first-pass through the lungs [70]. Bradykinin's effects are wide-ranging, including antithrombotic and profibrinolytic activity in the coagulation system, as well as modulation of nitric oxide and prostacyclin release. Specific to the lung, bradykinin was shown some time ago to have vasodilating effects on normal pulmonary vessels but to be vasoconstrictive when the pulmonary endothelium was destroyed in animal models [71, 72]. Bradykinin has also been long described as a bronchoconstrictor [73, 74] and is still considered a prototypical bronchoconstricting substance [75]. The complexities of the kallikrein–kinin system's effect on endothelial cells, the myocardium, and vascular smooth muscle and its role in phenomena of cardiovascular injury are beyond the scope of this discussion, and the interested reader is referred to extensive reviews elsewhere [66, 76].

ACE is probably best known to clinicians through the drugs that block its activity, and, in fact, ACE inhibitors remain one of the most commonly prescribed group of drugs in the United States [77]. They are effective antihypertensive medications and have been shown to decrease the incidence of congestive heart failure after myocardial infarction [76]. It is now believed that some side effects of ACE inhibitors, such as angioedema and cough, and some of the beneficial impact, such as decreased myocardial infarctions and improved renal function, involve modification of bradykinin metabolism [66].

Biogenic Amines

Histamine, serotonin (5-hydroxytryptamine or 5-HT), and the three naturally occurring catecholamines (dopamine, norepinephrine, and epinephrine) comprise the group commonly termed biogenic amines. Studies looking into the uptake and metabolism of serotonin by the pulmonary circulation were among the earliest investigations of pulmonary pharmacokinetics [9, 78]. Subsequent work has made the behavior of this compound among the best understood in terms of pulmonary uptake and metabolism.

5-HT is produced predominately by the gastrointestinal tract's chromaffin cells. Ingested tryptophan undergoes a two-step conversion first by tryptophan-5-hydroxylase and then by L-amino acid decarboxylase to serotonin. Mast cells and neuroendocrine cells in the lung are also capable of producing serotonin by uptake of tryptophan along the same enzymatic pathway. However, the lung normally contributes minimally to systemic 5-HT production because of lesser tryptophan availability and much slower reaction rates [79]. Once released from the gastrointestinal tract, there is avid uptake of 5-HT, particularly by nerve endings and platelets. These cells do not metabolize 5-HT to any great extent. The remainder of 5-HT is extracted by the lung and, to a lesser degree, the liver. In the case of these organs, the 5-HT is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by cytosolic monoamine oxidase and aldehyde dehydrogenase. 5-HIAA is, of course, a clinically useful marker of carcinoid syndromes associated with increased histamine turnover. It has been found that monoamine oxidase inhibitors block the cytosolic metabolism of 5-HT but not its uptake, while several drugs, including volatile anesthetic agents, block uptake but not intracellular metabolism [80].

Because it is not lipophilic, the pulmonary uptake of 5-HT is an active process, predominately via endothelial cells, with some variability between species. Several details of this uptake have been delineated as an ATPase-dependent active carrier process [81]. The pulmonary uptake of 5-HT by the lung is typically reported to be 90% or greater with little 5-HT reaching the systemic vasculature under normal circumstances. This model of production and uptake of 5-HT plays a pivotal role in several pathological processes relevant to clinical anesthesiology. In carcinoid syndrome, for example, the right heart receives a high concentration of 5-HT (and other substances) before being extracted and metabolized by the pulmonary circulation. This is thought to be the reason that the right heart shows the greatest myocardial and valvular injury in this syndrome [82–84]. This model is supported by other clinical observations. The valvular injury of substances related to 5-HT such as methysergide and ergotamine, those that increase 5-HT such as the infamous fenfluramine, and more recently the recreational drug "ecstasy" (3,4-methylenedioxymethamphetamine), known to activate 5-HT receptors, are all similar to carcinoid cardiac disease [85, 86]. Moreover, when an intracardiac right-to-left shunt is present in the carcinoid patient with bypass of the pulmonary circulation, the left heart demonstrates valvular injury similar to that of the right heart [18].

Pulmonary embolism presents another clinical situation pertinent to 5-HT activity. It has long been appreciated that the mass effect of embolism does not, in itself, account for the typical cardiopulmonary consequences including pulmonary hypertension. The platelet aggregation and activation associated with acute pulmonary embolism results in degranulation with the release of 5-HT, well known to be a potent vasoconstrictor and to increase bronchial smooth muscle tone. This release of 5-HT and, perhaps, decreased local uptake of 5-HT are postulated to cause local and regional vascular changes [87]. Other actions of elevated 5-HT, such as promotion of further platelet aggregation and inhibition of the vasodilating prostacyclin, likely also play a role in the

full response to pulmonary embolism [88]. The infusion of a serotonin antagonist in animals was found to attenuate the increase in pulmonary pressures associated with pulmonary embolism [89], supporting the role of 5-HT in this response.

Histamine, in contrast to 5-HT, has almost no uptake in the pulmonary circulation. Lung homogenates are capable of histamine metabolism [90], but the intact lung appears to lack an uptake mechanism for histamine.

Just as the lung has the enzymes to metabolize both histamine and serotonin but the ability to take up only serotonin, its uptake of catecholamines also demonstrates marked selectivity. Norepinephrine demonstrates a 35–50% first-pass uptake with subsequent metabolism by catechol-O-methyltransferase (COMT), MAO, aldehyde reductase, and aldehyde dehydrogenase [91]. Dopamine and epinephrine, however, have essentially no uptake although they would be susceptible to the cytosolic enzymes, as again proven by cell homogenates. The synthetic catecholamine isoproterenol also has no appreciable uptake by the lung.

Arachidonic Acid Metabolites

Extensive production and metabolism of arachidonic acid derivatives occur in the lung. The term eicosanoids refers to the 20-carbon carboxylic acids derived from the metabolism of the lipid membrane component icosatetraenoic acid, more commonly known as arachidonic acid. The action of phospholipase A_2 converts the esterified form, as found in the membrane, and releases arachidonic acid from structural glycerol. Once free, arachidonic acid may follow three main metabolic pathways in the lung. The lipoxygenase pathway produces leukotrienes, lipoxins, and some of the hydroxyeicosatetraenoic acids (HETEs). The cyclooxygenase (COX) pathway produces prostaglandins, thromboxane, and prostacyclin. The cytochrome P-450 monooxygenase system produces cis-epoxyeicosatrienoic acids and HETEs that are different than the products of the lipoxygenase pathway.

The lipoxygenase pathways produce leukotrienes and lipoxins. The formation of all leukotrienes starts from a common precursor. 5-Lipoxygenase, located in the perinuclear cytosol, responds to increased calcium in concert with its activating protein to generate 5-hydroperoxyeicosatetraenoic acids (5-HPETE) from arachidonic acid. A dehydrase then yields the relatively unstable leukotriene A_4 (LTA_4), which may undergo transformation by epoxide hydrolase (LTA_4 hydrolase) to LTB_4 which leaves the cell via a transport protein. The alternative pathway for LTA_4 is via LTC_4 synthase to form LTC_4, which is converted by nonspecific interstitial peptidases to the leukotrienes LTD_4 and LTE_4 (commonly referred to as slow-reacting substance of anaphylaxis). Whereas closely related prostanoids (see below) demonstrate opposing biological actions, the leukotrienes uniformly promote inflammatory responses in the lung. They are responsible for bronchoconstriction and increased pulmonary vascular permeability, are chemotactic and chemokinetic for neutrophils, and facilitate eosinophil degranulation [92–94]. They are produced by activated inflammatory cells within the lung as well as those arriving in response to inflammation. It should be no surprise that leukotrienes have been the subject of investigation in processes ranging from hypoxic pulmonary vasoconstriction in normal as well as damaged lungs [95, 96] to the pathogenesis of adult respiratory distress syndrome (ARDS) [97–99] and asthma [100]. This work has been especially fruitful in the case of asthma, for which leukotriene modifiers are a mainstay of treatment [101–103].

There appears to be little specialized pulmonary uptake or metabolism of the leukotrienes beyond the inactivation of LTB_4 and LTC_4 by neutrophils in the lung. Nonspecific hydroxylation and carboxylation of leukotrienes also occur in the interstitium, similar to that of other tissues [104].

The lipoxins have been identified as critical factors in the resolution of inflammation throughout the body, now seen more as an active process than the simple "burnout" of pro-inflammatory processes [105, 106]. There are three main synthetic routes of lipoxin formation, involving interactions of products from 5-lipoxygenase, 15-lipoxygenase, and/or 12-lipoxygenase, with the eventual formation of the two lipoxins, the positional isomers lipoxin A_4 (LxA_4) and B_4 (LxB_4). The lipoxins have a variety of antiinflammatory effects. They inhibit eosinophil and neutrophil chemotaxis and adhesion, as well as natural killer cell activation [107–110]. They are endothelium-dependent vasodilators of both pulmonary and systemic vasculature [111]. The lipoxins have been investigated extensively for their role in lung physiology and disease. Asthma, in particular, has received a great deal of attention [112]. Work thus far indicates that lipoxins are decreased in the sputum [113] and blood [114] of patients with severe asthma. The balance between leukotriene and lipoxin activity, in particular, has been found related to disease severity [115], raising the possibility of inducing lipoxin activity [116] as an adjunct to leukotriene modifiers. The role of lipoxins has also been considered in the active resolution of acute lung injury [117].

The lipoxins are predominately taken up by circulating monocytes with subsequent dehydrogenation [118]. No specific pulmonary uptake or metabolism of lipoxins has been described.

As implied by its name, COX catalyzes the cyclization and oxygenation of arachidonic acid, producing prostaglandin PGG_2, which is converted by nonspecific peroxidase(s) to the unstable precursor PGH_2. There are subtypes of COX, most notably COX-1 and COX-2. There has been great interest in COX-2 since its discovery in the 1990s because its inhibition was hoped to be more specific in controlling pain and inflammation without injury to the gastroduodenal mucosa [119,

120]. Although effective, the emergence of a small but real increase in cardiovascular risk of COX-2 inhibitors [121] has tempered their use. Complicating this issue further is that many of the "traditional" COX inhibitors such as acetaminophen, salicylates, and the nonsteroidal antiinflammatory agents ibuprofen and naproxen show only slightly less COX-2 avidity than some of the newer COX-2 inhibitors.

Following the production of PGH_2, the metabolic pathway divides into branches producing the various bioactive prostanoids; the enzymes of particular interest here are PGD synthase, PGE synthase, prostacyclin synthase, and thromboxane synthase. The final products of these pathways typically have oppositional or balancing effects locally and regionally. Prostaglandin E_2 (PGE_2) and PGI_2 are bronchodilators, for example, while $PGF_{2\alpha}$, PGD_2, and thromboxane A_2 (TXA_2) cause bronchoconstriction. Similarly, PGD_2, PGE_2, $PGF_{2\alpha}$, and TXA_2 are potent vasoconstrictors, while PGE_1 and PGF_2 are vasodilators.

Pulmonary endothelial cell cultures demonstrate virtually all COX pathway products to some extent, but the level of in vivo production is less clear. PGI_2 appears to be continuously produced, with modulation by vascular flow [122]. PGD_2, PGE_1, PGE_2, PGI_2, $PGF_{2\alpha}$, and TXB_2 have all been found to be produced by human lungs, although under varying circumstances [123, 124].

The discussion of the pulmonary metabolism of COX products includes the now familiar theme of a broad range of intracellular enzymes (by cell culture and cellular homogenate investigation) but selective uptake. In this way, at least 80–90% of PGD_1, PGE_2, and $PGF_{2\alpha}$ are taken up and metabolized in a first-pass through intact pulmonary circulation; but PGA_1, PGA_2, and PGI_2 demonstrate essentially no uptake [24, 125, 126]. TXA_2, a relatively unstable compound, presents a special case in the discussion of pulmonary uptake. TXA_2 undergoes hydrolysis in the blood, forming TXB_2. It is TXB_2 that is taken up by a carrier for cytosolic metabolism and is often utilized as an investigative marker of TXA_2 activity [127].

The P-450 monooxygenase system provides three pathways of arachidonic acid metabolism which results in epoxyeicosatetraenoic acids (EETs), HETEs, or dihydroxyeicosatetraenoic acids (dHETEs). These pathways are not unique to the endothelium, epithelium, and smooth muscle of the lung, being found in several other organs including the gastrointestinal tract, liver, and kidney [128]. Subfamilies of cytochrome P-450 systems have been identified within the lung. The CYPA4 family produces 20-HETE, while the CYP2J family is found in epithelial, bronchial, and vascular smooth muscle cells, as well as endothelial and alveolar macrophages [129].

The HETEs and EETs have been shown experimentally to affect pulmonary vascular and bronchomotor tone. 20 HETE and 5, 6, 11, and 12-EETs all have relaxing effects on both the lung vasculature and airways [130, 131]. They are further known to have general antiinflammatory effects, to modulate reperfusion injury, and to inhibit platelet aggregation. Within the lung, 15-HETE and 20-HETE may both modify hypoxic vasoconstriction [132].

Natriuretic Peptides

The natriuretic peptides currently consist of, in order of their discovery during the 1980s, atrial natriuretic peptide (ANP), brain natriuretic peptide, and C-type natriuretic peptide. ANP has received the most attention in terms of pulmonary pharmacokinetics. It is a pulmonary artery (and to a lesser extent, venous) vasodilator whose action is independent of endothelial function. ANP is known to interact with the renin–angiotensin–aldosterone system at several points. Best described are suppression of renin release, decrease in angiotensin-converting enzyme activity, and blocking of aldosterone release. These actions promote natriuresis and diuresis. ANP is mainly produced in the cardiac atria, but both ANP and its prohormone have been found in the human fetal lung [133] and adult pulmonary veins [134]. Lung production is suppressed by hypovolemia and increased with hypoxemia, hypervolemia, and in the presence of glucocorticoids. In terms of elimination, the rabbit lung demonstrates a 25% first-pass uptake of ANP [135].

Other Endogenous Substances

The number of substances handled by the lung and the intricacies of their metabolism precludes full discussion here. For the interested reader, several historically and/or clinically important substances are listed in Table 7.3, and references

Table 7.3 Lung effects on endogenous substances relevant to the anesthesiologist

Group	Impact of passage through the pulmonary circulation		
	Activated	Minimal or none	First-pass uptake and/or metabolism
Peptides	Angiotensin I	Angiotensin II	Endothelins
		Vasopressin	Bradykinin
		Oxytocin	
		Atrial natriuretic peptide	
Steroids	Cortisone		Beclomethasone
			Progesterone
Purine family			Adenosine phosphates (AMP, ADP, ATP)
Arachidonic acid family		PGA_2	PGD_2
		Prostacyclin (PGI_2)	PGE_2
			PGF_2
			Leukotrienes
Biogenic amines		Dopamine	5-HT
		Epinephrine	Norepinephrine
		Histamine	

are provided for the activation of cortisone to cortisol in health [136, 137] and disease [138], the behavior of endothelin in several clinical circumstances [76, 139, 140], and new perspectives on purine metabolism by endothelial ectoenzymes [138].

The Lung as Vascular Reservoir and Filter

The volume of blood within the lungs under various conditions has been a subject of investigation for over 80 years [141]. What is known is that the pulmonary vasculature in health has remarkable capacitance, allowing it to accept wide ranges of right ventricular output with minimal change in pressure. This ability to load and offload volume allows the lungs to serve as a vascular reservoir to meet the preload needs of the left heart as they change due to factors such as posture, exercise, changes in intrathoracic pressure (e.g., Valsalva maneuver), and daily volume shifts [142]. The role of pulmonary vascular capacitance is also emerging in our understanding of disease processes relevant to clinical anesthesiology. Models of heart failure, for example, now incorporate the role of vascular compliance in general and the pulmonary vasculature capacitance and permeability specifically [143]. Also of interest to anesthesiologists, researchers have found that following the release of the tourniquet in total knee arthroplasty, there is an actual decrease in pulmonary vascular resistance. A clue to the mechanism of this finding was metabolic evidence of increased endothelial recruitment with this obligatory microembolism [144].

The unique anatomical position of the lungs as they receive the entire right heart output allows them to serve as physical filters, in much the same way that they metabolically play a pivotal role in the uptake of endogenous substances and xenobiotics. Particles normally filtered by the lung before reaching the systemic circulation include small blood clots, fat droplets, agglutinated white blood cells, and amniotic fluid in the case of pregnancy. The literature commonly alludes to the ability of 350 and even 500 μm glass beads to pass through the pulmonary vasculature in animal models. Given that normal pulmonary capillaries have a diameter of 7–10 μm, this implies other arteriovenous communications under normal conditions. Recent work in isolated, but normally ventilated, animal and human lungs and, especially, exercised human subjects implies a more complicated picture. It now appears that, indeed, arteriovenous passage of particles larger than 50 μm occurs in isolated lungs, although more than 99% of such glass microspheres are trapped by the lungs [145]. In human volunteers, aggregated albumin tagged with technetium-99 and with diameters of 7–25 μm was found to have about 0.7% transpulmonary passage at rest. This rose to 3% passage with exercise, as demonstrated by aggregate trapping in systemic capillaries. This implies the recruitment of intrapulmonary arteriovenous pathways with exercise which presumably allow decreased resistance to flow but also compromise the lung's competence as a mechanical filter [146]. The lung's protection of systemic circulation from embolus can also, of course, be completely subverted by anatomic variants and pathological states. The latter is exemplified by the hepatopulmonary syndrome's intrapulmonary vascular dilatations, which have been associated with patient injury from embolism [147]. The patent foramen ovale and its potential for catastrophic embolic phenomena in the perioperative period [18, 146, 148] have long been appreciated and feared by anesthesiologists as the classic anatomic variant which bypasses the protective filtration of the pulmonary vasculature.

The Respiratory Epithelium

The lung defends the body not only by mechanical filtration and metabolism of substances from the blood but also from airborne agents. In this way, the constantly renewing airway epithelium is responsible for helping to maintain normal gas exchange from the trachea to the terminal alveoli. The respiratory epithelium represents a huge surface area that is a gateway from the outside world to the exquisitely delicate alveoli, a path taken by both life-sustaining oxygen and potentially damaging particles and gasses. This defensive challenge is especially impressive when considering both the wide range of conditions to which the modern human is exposed and the simple fact that even a somewhat sedentary adult can be expected to inhale well over 10,000 L of gas from his/her environment in a day. The discussion below will briefly review the structure and function of this system and then the way in which it provides protection through the mucociliary apparatus, trapping of particles, and response to particles and pathogens.

The Cells of the Respiratory Epithelium

While some 50 distinct cell types have been identified in the human airway [149], our discussion will focus on those most important to the lung's nonrespiratory functions.

Ciliated Columnar Cells

These cells are the most common of the respiratory epithelium. Their most obvious defining feature is several hundred cilia moving at a rate of about 12 cycles per second, always toward the trachea. As might be expected, this

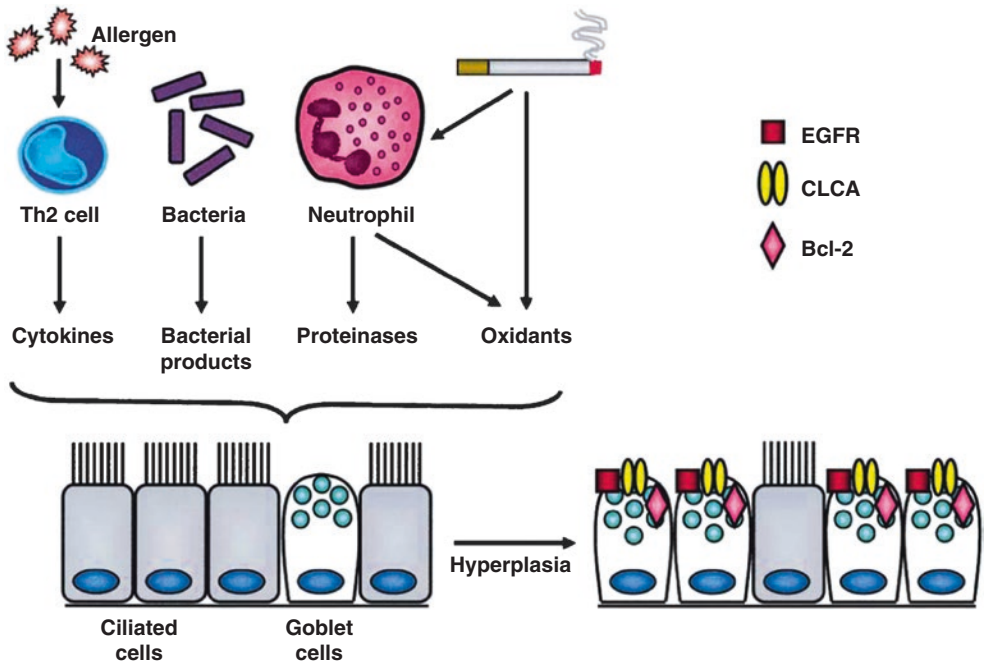

Fig. 7.3 Airway goblet cell hyperplasia. Simplified schematic outlining selected pathways generating increased epithelial mucin production. Cytokines (e.g., interleukin-4, interleukin-9 and interleukin-13), bacterial products (e.g., lipopolysaccharide and lipoteichoic acid), proteinases (e.g., elastase and cathepsin G), and oxidants from T helper-2 (Th2) lymphocytes, bacteria, neutrophils, and cigarette smoke upregulate mucin production and/or induce goblet cell hyperplasia with associated increases in expression of epidermal growth factor receptors (EGFR), calcium-activated chloride channels (CLCA), and the anti-apoptotic factor Bcl-2. Note: not all stimuli have yet been shown to induce expression of each of EGFR, CLCA, and Bcl-2. In addition, production of new goblet cells appears to involve differentiation of non-granulated epithelial cells rather than goblet cell division. (Reproduced with permission. Rogers [150]. Copyright Elsevier)

process requires large energy expenditures, and, in fact, the cells have extensive populations of mitochondria for energy production. The cellular architecture and shape change according to position in the respiratory tract. In the nose, pharynx, and large airways, the columnar cells are pseudostratified, layered over the basal cells which are thought to be the stem cells for both ciliated and goblet cells. Moving down the bronchi, they gradually thin to a single layer. Further still, in the bronchioles, the columnar cells transition to a layer of cuboidal cells and then, approaching the terminal airways, they mix with type I alveolar cells.

Goblet Cells

These specialized columnar epithelial cells can rapidly secrete mucins (high molecular weight mucous glycoproteins) which provide a protective layer over the epithelium when it combines with other lipid, glycoconjugate, and protein components [150]. Mucin is released by exocytosis in response to a variety of stimuli such as dust, microorganisms, fumes, and debris within the airway. Hyperplasia in response to chronic stimulation is a hallmark of the goblet cell population (Fig. 7.3) and typical of disease processes such as asthma, bronchitis, and cystic fibrosis [151].

Submucosal Secretory Cells

There are actually two types of submucosal secretory cells. Both are associated with the submucosal glands of the trachea and large bronchi. These glands are innervated by cholinergic fibers from the vagus [152] and are located in the submucosa between the smooth muscle and cartilage plate. The serous-type cells account for more than half of the submucosal gland in health and contain multiple secretory granules. Proteoglycans, lysozyme, lactoferrin, IgA receptor complex, peroxidase, and antiproteases are among the contents of these granules. The mucous-type cells are columnar cells with a high density of cell granules containing mucin. It is thought that serous cells transdifferentiate to mucous cells in response to injury from inhaled agents and the resulting predominance of mucous cells plays a role in the change of the character of mucus in response to injury. While it is accepted that both the submucosal secretory cells and goblet cells contribute to airway mucus, there

is apparent variability in the relative contribution of these cells on the basis of airway level, experimental model, and species [153–156].

Clara Cells

Clara cells (nonciliated bronchial secretory cells) are normally found predominately in the terminal bronchioles (Fig. 7.4). Their granules secrete Clara cell secretory protein (CCSP), the function of which is poorly defined. In an animal model, antigenic challenge results in proliferation of tracheobronchial Clara cells that secret not only CCSP but also demonstrate secretion of mucin [156]. Conversely, in normal humans, bronchiolar goblet cells have been found to secrete CCSP, leading to speculation that Clara cells may be goblet cell precursors [158], as well as progenitors of the epithelium [157].

Mast Cells

Mast cells are located throughout the lung, from typical locations under the airway epithelium and in the alveolar septum to those freely positioned in the airway. They have traditionally been associated with acquired immunity, but recent evidence indicates that mast cells also have important roles in innate immunity and inflammatory regulation [159]. Specifically, their role as sentinel for innate immunity seems to bridge the classic with the more recently appreciated roles [160].

Macrophages and Monocytes

Macrophages and monocytes can be categorized as (1) airway and alveolar macrophages, (2) interstitial macrophages, and (3) pulmonary vascular monocytes. This scheme does not include the monocyte derivative dendritic cells. There are limited data regarding the sparse interstitial macrophage population, mostly from animal preparations. There is no evidence that the intravascular monocytes of the lung are particularly different from monocytes throughout the body's vascular system, transforming into macrophages within the tissue to which they migrate.

The alveolar macrophages must routinely phagocytize a dizzying array of invaders of the airspace. These include dust and particulates as well as bacteria, yeasts, and other organic and inorganic debris. Phagosomes initially envelope the ingested target and then are merged with lysosomes. The latter contain hydrolytic enzymes, which efficiently destroy the majority of bacteria, yeasts, and debris encountered. For some

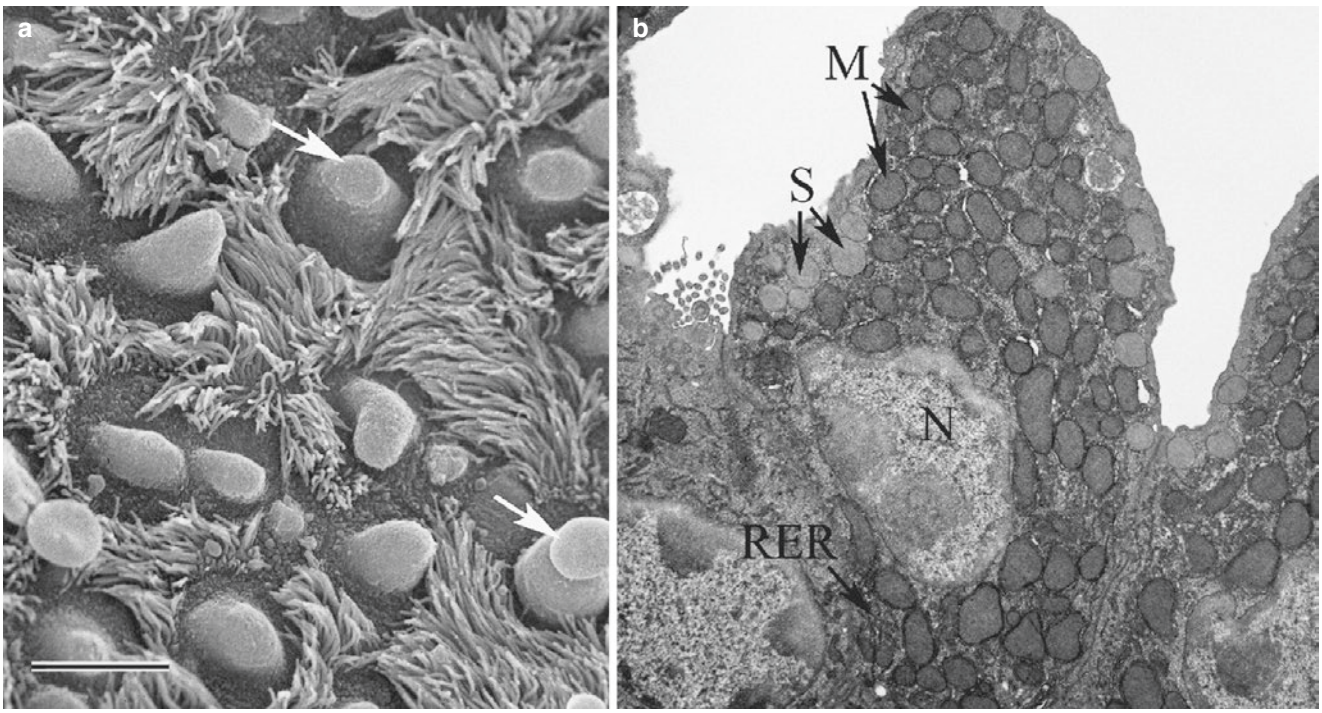

Fig. 7.4 (**a**) Scanning electron micrograph of the lining of the proximal bronchiole of a rat showing Clara cells, some of which are undergoing apocrine secretion (*arrows*), surrounded by ciliated cells (bar = 10 μm). (**b**) Transmission electron micrograph of a terminal bronchiolar Clara cell. Numerous mitochondria (M), secretory granules (S), rough endoplasmic reticulum (RER), and the basal nucleus (N) are indicated. (Reproduced with permission. Reynolds and Malkinson [157]. Copyright Elsevier)

microorganisms (e.g., mycobacteria and many gram-negative bacteria) and materials, the lysosomal system is not effective. In this case, secondary lysosomes are now used essentially as storage areas, where the material is isolated for the life of the macrophage. The fate of these laden cells is not uniform. It appears that some are swept away by the mucociliary apparatus for mechanical elimination and others remain in the lung for as long as months before dying and releasing their sequestered contents for uptake by successor macrophages. There has been recent attention to the translocation of particles from the lung to lymph nodes and other organs [161, 162], presumably in conjunction with alveolar macrophage activity.

Alveolar Epithelial Cells

Alveolar epithelial type I and type II cells (also referred to as type I and II pneumocytes) line the terminal alveoli. Type I cells are thin sheets lining the alveoli with each covering several capillaries. Type I cells cover approximately 90% of lung surface area and are responsible for maintaining lung fluid homeostasis. The tight junctions between cells are well described and thought to provide only a 1-μm gap under normal circumstances. Historically thought to serve as a barrier to the movement of solutes and water into the alveoli, more recent work with sodium and chloride transporters has found evidence of active epithelial mechanisms for fluid transport in both health and diseased states [163, 164]. Additionally, the presence of caveolae and intracellular vacuoles suggests that type I cells may also have endocytic function and participate in metabolic activities [165]. Type II alveolar epithelial cells tend to be clustered at alveolar junction points. They are cuboidal cells with lamellar bodies in the cytoplasm and numerous mitochondria. The lamellar bodies are inclusions of variable size and composed of stacked layers of membrane-like material. It is this material which is processed and released as surfactant by the type II cell [166]. Four types of surfactant proteins A, B, C, and D (SP-A through SP-D) have been identified. SP-A and SP-D modulate surfactant release, while SP-B and SP-C stabilize the surfactant monolayer discussed below [167]. SP-B is the protein absolutely required for survival, but important contributions have been discovered for the other SP proteins. SP-A and SP-D, for example, play immune roles by direct antimicrobial activity and enhancement of macrophage recognition of microorganisms.

Functions of the Respiratory Epithelium

The functions of the respiratory epithelium that will be reviewed here include maintenance of the complex liquid film of the airway, humidification, removal of inhaled materials, and response to inhaled pathogens.

Airway Surface Film

The surface liquid of the airway, in health, is about 10 μm thick. It consists of two layers, namely, the periciliary sol underneath a second layer of mucus gel. The sol is a low-viscosity watery liquid that surrounds the cilia. The mucus, as discussed previously, is produced by the submucosal glands and goblet cells in response to a variety of irritants. The complex gel-aqueous becomes progressively thinner from the trachea (100 μm) to the bronchi (8 μm) and then to terminal bronchioles (3 μm) [168]. The cilia are too tightly arranged for the mucus gel to find its way between cilia, thus the gel layer contacts only the ciliary tips along its bottom edge. The cilia, then, are free to move in their well-characterized rhythmic pattern with relatively less resistance from the minimally viscous sol. In this manner, the cilia propel the mucous layer toward the trachea at a rate of 3–4 mm/min [169]. The thickness of the layers of this system, especially the sol, must be maintained within very narrow tolerances for mechanical efficiency. This is achieved in large extent by simple osmotic gradient and probably accounts for much of the adjustment that occurs as larger amounts of mucus converge in the larger airways. Adjustments of sol osmolarity to effect this mechanism occur through the activity of the amiloride-sensitive chloride channel, more commonly referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Indeed, the ravages of cystic fibrosis are now thought to start at least in part because of the relative depletion of the sol, emphasizing the delicate nature of the system just described [170]. The antimicrobial capabilities of the mucociliary apparatus will be discussed below.

Humidification

The respiratory system has enormous capacity to humidify inspired gas. At rest, air is completely saturated with water vapor as it passes through the nose and upper airway, before it reaches the trachea. As minute ventilation (MV) increases, smaller and smaller airways are required to contribute to humidification, such that at a MV of 50 L min^{-1}, airways of only a few millimeters in diameter receive incompletely humidified gas [171]. The airways do reclaim some of the heat and moisture imparted on the inhaled gas during its exhalation. Thus, bypassing of the nasopharyngeal passages and upper trachea by devices such as endotracheal tubes not only decreases humidification of the gasses delivered to the distal airways but also cheats the opportunity to recoup heat and moisture on exhalation.

Removal of Inhaled Particles

The regions of the respiratory tract in which particles are deposited depend upon respiratory pattern, environmental conditions, and the nature of the particles themselves. Accepting these variations, it is possible to generalize particle behavior under normal circumstances. Particles larger than 10 μm (e.g., dust and particulates from low-grade petroleum combustion) are often trapped at the level of the nose or pharynx. Those that enter the airway of the lung, and particles of 3–10 μm, are caught on the liquid film layer and transported out of the lung for swallowing or expectoration as previously described. They tend to be deposited in higher concentration in areas of high turbulence such as airway bifurcations. Particles smaller than 3 μm may reach the alveoli. They will either be subsequently exhaled or settle in the alveolus, where they will be subject to the activity of macrophages as discussed in a previous section. There are, of course, particular substances that instigate a detrimental response from the body, for example, asbestos with resultant pulmonary fibrosis.

Response to Inhaled Organisms

There are several mechanisms with which the airway defends the body against inhaled microorganisms. The first is simple impact and capture by the nasal and pharyngeal mucosa with subsequent swallowing and destruction in the hostile gastrointestinal tract or expectoration. Those organisms that enter the lung may be similarly trapped on the surface film and moved out of the lung by ciliary action. The surface film is more than a simple transport mechanism, having a variety of antimicrobial mechanisms. These capabilities make teleological sense, because the potentially damaging agents are not immediately removed.

Surfactants, consisting of 80% phospholipids, 5–10% proteins, and 5–10% other lipids, are best known for their ability to reduce surface tension and thus equalize pressures within airspaces of differing sizes [168]. Less appreciated is the fact that SP-A and SP-D (following terminology introduced in the discussion of type II alveolar cells) are members of the collectin protein family. Collectins have an N-terminal collagen-type region and a C-terminal lectin region that bind carbohydrates. The C-terminal's preferential binding site is nonhost oligosaccharides, giving them the ability to opsonize bacterial and viral pathogens and to facilitate macrophage phagocytosis [172]. SP-A and SP-D are also known to be directly antimicrobial, without immune cells, against a variety of pathogens [173, 174].

The surface films of the large bronchi (and the mucosa of the nasopharynx) have generous amounts of IgA, which acts as an opsonin and has a role in complement induction. In smaller airways and alveoli, IgG becomes the predominant surface antibody in normal circumstances.

The airway epithelium also acts as an immune barrier via interactions between Fas receptors (CD95/Apo-1) and Fas ligand (FasL, CD95L, CD178), found on airway epithelium, in response to immune reactions and infection [175, 176]. The interaction between Fas and FasL activates intracellular caspases leading to apoptosis of infiltrating immune cells, protecting against tissue injury [177, 178]. FasL appears to be cleaved and made inactive in asthma, contributing to the chronic inflammation and damage to the epithelium seen in chronic lung diseases [179]. Toll-like receptors are also found in airway epithelial cells, upregulating the production of cytokines, chemokines, and other antimicrobial peptides in response to bacteria and viruses [180, 181]. Epithelial cells also secrete antimicrobial peptides including ß-defensins and LL-37, preventing the growth of inhaled microorganisms prior to clearance or phagocytosis [181].

Lung epithelial cells can release soluble factors including IL-1ß and IL-8, while alveolar macrophages release TNF-α and IL-6 resulting in the release of neutrophils from bone marrow as well as neutrophil chemotaxis in response to pollutants, including cigarette smoke, and pathogens [182, 183]. Once present at the source of infection, neutrophils secrete granules containing lactoferrin, lysozymes, defensins, and other proteolytic enzymes as well as generate oxygen free radicals to destroy pathogens [184]. Stimulated bronchial epithelial cells can also secrete and/or facilitate adhesion molecules, growth factors, and collagen. Epithelial cells produce high levels of nitric oxide (NO), and production is increased in the presence of respiratory viruses acting to inhibit viral replication [185]. The absence of upregulation of nitric oxide synthase-2 in cystic fibrosis is implicated in increased viral susceptibility in these patients [186].

Summary

Historically, practitioners of the medical arts from around the globe viewed the lung as a defender of the body from a hostile outside world and as a trusted modulator of its internal processes. More recently, respiratory function became the focus of attention with advances that have been central to the development of anesthesiology and upon which modern clinicians base much of our practice in cardiopulmonary medicine. The purpose of this discussion, which returns to the concepts of lung as protector and minister, has been to highlight important nonrespiratory lung functions in terms of both current areas of discovery and clinical implications. It is hoped that the reader will agree that familiarity with these aspects of pulmonary function is pivotal to a complete understanding of the lung and to the advancement of clinical practice.

References

1. Major R. A history of medicine. Springfield: Thomas; 1954.
2. Lumb AB. The history of respiratory physiology. In: Lumb AB, editor. Nunn's applied respiratory physiology. 6th ed. Oxford: Buttterworth-Heinemann; 2005.
3. Shoja MM, Tubbs RS. The history of anatomy in Persia. J Anat. 2007;210(4):359–78.
4. Simionescu M. Lung endothelium: structure-function correlates. In: Crystal RG, editor. Lung: scientific foundations. New York: Raven Press; 1991. p. 301–21.
5. Klein IK, Predescu DN, Sharma T, Knezevic I, Malik AB, Predescu S. Intersectin-2L regulates caveola endocytosis secondary to Cdc42-mediated actin polymerization. J Biol Chem. 2009;284(38):25953–61.
6. Parat M, Kwang WJ. The biology of caveolae: achievements and perspectives. In: International review of cell and molecular biology, vol. 273. Amsterdam: Academic; 2009. p. 117–62.
7. Ryan US, Ryan JW. Relevance of endothelial surface structure to the activity of vasoactive substances. Chest. 1985;88(4 Suppl):203S–7.
8. Ryan JW, Smith U. Metabolism of adenosine 5′-monophosphate during circulation through the lungs. Trans Assoc Am Phys. 1971;84:297–306.
9. Vane JR. The release and fate of vaso-active hormones in the circulation. Br J Pharmacol. 1969;35(2):209–42.
10. Dawidowicz ALP, Fornal EPD, Mardarowicz MPD, Fijalkowska APD. The role of human lungs in the biotransformation of propofol. Anesthesiology. 2000;93(4):992–7.
11. Hiraoka H, Yamamoto K, Miyoshi S, et al. Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain. Br J Clin Pharmacol. 2005;60(2):176–82.
12. de Graaf IAM, Koster HJ. Cryopreservation of precision-cut tissue slices for application in drug metabolism research. Toxicol In Vitro. 2003;17(1):1–17.
13. Klem C, Dasta JF, Reilley TE, Flancbaum LJ. Pulmonary extraction of dobutamine in critically ill surgical patients. Anesth Analg. 1995;81(2):287–91.
14. Hayashi Y, Sumikawa K, Yamatodani A, Kamibayashi T, Mammoto T, Kuro M. Quantitative analysis of pulmonary clearance of exogenous dopamine after cardiopulmonary bypass in humans. Anesth Analg. 1993;76(1):107–12.
15. Matot I, Pizov R. Pulmonary extraction and accumulation of lipid formulations of amphotericin B. Crit Care Med. 2000;28(7):2528–32.
16. Upton RN, Doolette DJ. Kinetic aspects of drug disposition in the lungs. Clin Exp Pharmacol Physiol. 1999;26(5–6):381–91.
17. Serabjit-Singh CJ, Nishio SJ, Philpot RM, Plopper CG. The distribution of cytochrome P-450 monooxygenase in cells of the rabbit lung: an ultrastructural immunocytochemical characterization. Mol Pharmacol. 1988;33(3):279–89.
18. Mizuguchi KA, Fox AA, Burch TM, Cohn LH, Fox JA. Tricuspid and mitral valve carcinoid disease in the setting of a patent foramen ovale. Anesth Analg. 2008;107(6):1819–21.
19. Pacifici GM, Franchi M, Bencini C, Repetti F, Di Lascio N, Muraro GB. Tissue distribution of drug-metabolizing enzymes in humans. Xenobiotica. 1988;18(7):849–56.
20. Litterst CL, Mimnaugh EG, Reagan RL, Gram TE. Comparison of in vitro drug metabolism by lung, liver, and kidney of several common laboratory species. Drug Metab Dispos. 1975;3(4):259–65.
21. Taeger K, Weninger E, Schmelzer F, Adt M, Franke N, Peter K. Pulmonary kinetics of fentanyl and alfentanil in surgical patients. Br J Anaesth. 1988;61(4):425–34.
22. Waters CM, Krejcie TC, Avram MJ. Facilitated uptake of fentanyl, but not alfentanil, by human pulmonary endothelial cells. Anesthesiology. 2000;93(3):825–31.
23. Boer F, Bovill JG, Burm AG, Mooren RA. Uptake of sufentanil, alfentanil and morphine in the lungs of patients about to undergo coronary artery surgery. Br J Anaesth. 1992;68(4):370–5.
24. Boer F, Olofsen E, Bovill JG, et al. Pulmonary uptake of sufentanil during and after constant rate infusion. Br J Anaesth. 1996;76(2):203–8.
25. Davis ME, Mehendale HM. Absence of metabolism of morphine during accumulation by isolated perfused rabbit lung. Drug Metab Dispos. 1979;7(6):425–8.
26. Roerig DL, Kotrly KJ, Vucins EJ, Ahlf SB, Dawson CA, Kampine JP. First pass uptake of fentanyl, meperidine, and morphine in the human lung. Anesthesiology. 1987;67(4):466–72.
27. Persson MP, Wiklund L, Hartvig P, Paalzow L. Potential pulmonary uptake and clearance of morphine in postoperative patients. Eur J Clin Pharmacol. 1986;30(5):567–74.
28. Beaufort TM, Proost JH, Houwertjes MC, Roggeveld J, Wierda JM. The pulmonary first-pass uptake of five nondepolarizing muscle relaxants in the pig. Anesthesiology. 1999;90(2):477–83.
29. Bertler A, Lewis DH, Lofstrom JB, Post C. In vivo lung uptake of lidocaine in pigs. Acta Anaesthesiol Scand. 1978;22(5):530–6.
30. Post C, Eriksdotter-Behm K. Dependence of lung uptake of lidocaine in vivo on blood pH. Acta Pharmacol Toxicol (Copenh). 1982;51(2):136–40.
31. Krejcie TC, Avram MJ, Gentry WB, Niemann CU, Janowski MP, Henthorn TK. A recirculatory model of the pulmonary uptake and pharmacokinetics of lidocaine based on analysis of arterial and mixed venous data from dogs. J Pharmacokinet Biopharm. 1997;25(2):169–90.
32. Hasegawa K, Yukioka H, Hayashi M, Tatekawa S, Fujimori M. Lung uptake of lidocaine during hyperoxia and hypoxia in the dog. Acta Anaesthesiol Scand. 1996;40(4):489–95.
33. Sjostrand U, Widman B. Distribution of bupivacaine in the rabbit under normal and acidotic conditions. Acta Anaesthesiol Scand Suppl. 1973;50:1–24.
34. Irestedt L, Andreen M, Belfrage P, Fagerstrom T. The elimination of bupivacaine (Marcain) after short intravenous infusion in the dog: with special reference to the role played by the liver and lungs. Acta Anaesthesiol Scand. 1978;22(4):413–22.
35. Rothstein P, Cole JS, Pitt BR. Pulmonary extraction of [3H] bupivacaine: modification by dose, propranolol and interaction with [14C]5-hydroxytryptamine. J Pharmacol Exp Ther. 1987;240(2):410–4.
36. Kietzmann D, Foth H, Geng WP, Rathgeber J, GundertRemy U, Kettler D. Transpulmonary disposition of prilocaine, mepivacaine, and bupivacaine in humans in the course of epidural anaesthesia. Acta Anaesthesiol Scand. 1995;39(7):885–90.
37. Sharrock NE, Mather LE, Go G, Sculco TP. Arterial and pulmonary arterial concentrations of the enantiomers of bupivacaine after epidural injection in elderly patients. Anesth Analg. 1998;86(4):812–7.
38. Palazzo MG, Kalso EA, Argiras E, Madgwick R, Sear JW. First pass lung uptake of bupivacaine: effect of acidosis in an intact rabbit lung model. Br J Anaesth. 1991;67(6):759–63.
39. Chang DH, Ladd LA, Wilson KA, Gelgor L, Mather LE. Tolerability of large-dose intravenous levobupivacaine in sheep. Anesth Analg. 2000;91(3):671–9.
40. Ohmura S, Kawada M, Ohta T, Yamamoto K, Kobayashi T. Systemic toxicity and resuscitation in bupivacaine-, levobupivacaine-, or ropivacaine-infused rats.[see comment]. Anesth Analg. 2001;93(3):743–8.
41. Ohmura S, Sugano A, Kawada M, Yamamoto K. Pulmonary uptake of ropivacaine and levobupivacaine in rabbits. Anesth Analg. 2003;97(3):893–7.

42. Mather LE, Copeland SE, Ladd LA. Acute toxicity of local anesthetics: underlying pharmacokinetic and pharmacodynamic concepts [see comment]. Reg Anesth Pain Med. 2005;30(6):553–66.
43. Heavner JE. Let's abandon blanket maximum recommended doses of local anesthetics [comment]. Reg Anesth Pain Med. 2004;29(6):524.
44. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept [see comment]. Reg Anesth Pain Med. 2004;29(6):564–75; discussion 524.
45. Reynolds F. Maximum recommended doses of local anesthetics: a constant cause of confusion [comment]. Reg Anesth Pain Med. 2005;30(3):314–6.
46. Groban L. Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in the intact animal model. Reg Anesth Pain Med. 2003;28(1):3–11.
47. Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: incidence and preventive measures. Reg Anesth Pain Med. 2002;27(6):556–61.
48. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest [see comment]. Anesthesiology. 2006;105(1):217–8.
49. Felice K, Schumann H. Intravenous lipid emulsion for local anesthetic toxicity: a review of the literature. J Med Toxicol. 2008;4(3):184–91.
50. Marwick PC, Levin AI, Coetzee AR. Recurrence of cardiotoxicity after lipid rescue from bupivacaine-induced cardiac arrest [see comment]. Anesth Analg. 2009;108(4):1344–6.
51. Roerig DL, Kotrly KJ, Dawson CA, Ahlf SB, Gualtieri JF, Kampine JP. First-pass uptake of verapamil, diazepam, and thiopental in the human lung. Anesth Analg. 1989;69(4):461–6.
52. Pedraz JL, Lanao JM, Hernandez JM, Dominguez-Gil A. The biotransformation kinetics of ketamine "in vitro" in rabbit liver and lung microsome fractions. Eur J Drug Metab Pharmacokinet. 1986;11(1):9–16.
53. Henthorn TK, Krejcie TC, Niemann CU, Enders-Klein C, Shanks CA, Avram MJ. Ketamine distribution described by a recirculatory pharmacokinetic model is not stereoselective. Anesthesiology. 1999;91(6):1733–43.
54. Mather LE, Selby DG, Runciman WB, McLean CF. Propofol: assay and regional mass balance in the sheep. Xenobiotica. 1989;19(11):1337–47.
55. Kuipers JA, Boer F, Olieman W, Burm AG, Bovill JG. First-pass lung uptake and pulmonary clearance of propofol: assessment with a recirculatory indocyanine green pharmacokinetic model. Anesthesiology. 1999;91(6):1780–7.
56. Matot I, Neely CF, Katz RY, Neufeld GR. Pulmonary uptake of propofol in cats. Effect of fentanyl and halothane. Anesthesiology. 1993;78(6):1157–65.
57. Le Guellec C, Lacarelle B, Villard PH, Point H, Catalin J, Durand A. Glucuronidation of propofol in microsomal fractions from various tissues and species including humans: effect of different drugs. Anesth Analg. 1995;81(4):855–61.
58. Bulger EM, Maier RV. Lipid mediators in the pathophysiology of critical illness. Crit Care Med. 2000;28(4 Suppl):N27–36.
59. Upton RN, Ludbrook G. A physiologically based, recirculatory model of the kinetics and dynamics of propofol in man. Anesthesiology. 2005;103(2):344–52.
60. Kazama T, Ikeda K, Morita K, Ikeda T, Kikura M, Sato S. Relation between initial blood distribution volume and propofol induction dose requirement [see comment]. Anesthesiology. 2001;94(2):205–10.
61. Kazama T, Morita K, Ikeda T, Kurita T, Sato S. Comparison of predicted induction dose with predetermined physiologic characteristics of patients and with pharmacokinetic models incorporating those characteristics as covariates. Anesthesiology. 2003;98(2):299–305.
62. Krejcie TC, Jacquez JA, Avram MJ, Niemann CU, Shanks CA, Henthorn TK. Use of parallel Erlang density functions to analyze first-pass pulmonary uptake of multiple indicators in dogs. J Pharmacokinet Biopharm. 1996;24(6):569–88.
63. Wang WB, Watts AB, Peters JI, Williams RO III. The impact of pulmonary disease on the fate of inhaled medicines- a review. Int J Phram. 2014;461:112–28.
64. Sweeney TD, Skornik WA, Brain JD, Hatch V, Godleski JJ. Chronic bronchitis alters the pattern of aerosol deposition in the lung. Am J Respir Crit Care Med. 1995;151:482–8.
65. Patton JS, Brain JD, Davies LA, et al. The particle has landed-characterizing the fate of inhaled pharmaceuticals. J Aerosol Med Pulm Drug Deliv. 2010;23(Suppl 2):S71–87.
66. Patton JS, Fishburn CS, Weers JG. The lungs as a portal of entry for systemic drug delivery. Proc Am Thorac Soc. 2004;1:338–44.
67. Olsson B, Bodesson E, Borgstom L. Pulmonary drug metabolism, clearance, and absorption. In: Smyth HDC, Hickey AJ, editors. Controlled pulmonary drug delivery. 1st ed. New York: Springer; 2011.
68. Ryan JW. Processing of endogenous polypeptides by the lungs. Annu Rev Physiol. 1982;44:241–55.
69. Orfanos SE, Langleben D, Khoury J, et al. Pulmonary capillary endothelium-bound angiotensin-converting enzyme activity in humans. Circulation. 1999;99(12):1593–9.
70. Skidgel RA. Bradykinin-degrading enzymes: structure, function, distribution, and potential roles in cardiovascular pharmacology. J Cardiovasc Pharmacol. 1992;20(Suppl 9):S4–9.
71. Chand N, Altura BM. Acetylcholine and bradykinin relax intrapulmonary arteries by acting on endothelial cells: role in lung vascular diseases. Science. 1981;213(4514):1376–9.
72. Skidgel RA, Erdos EG. Angiotensin converting enzyme (ACE) and neprilysin hydrolyze neuropeptides: a brief history, the beginning and follow-ups to early studies. Peptides. 2004;25(3):521–5.
73. Simke J, Graeme ML, Sigg EB. Bradykinin induced bronchoconstriction in guinea pigs and its modification by various agents. Arch Int Pharmacodyn Ther. 1967;165(2):291–301.
74. Collier HO. Humoral factors in bronchoconstriction. Sci Basis Med Annu Rev. 1968:308–35.
75. Suguikawa TR, Garcia CA, Martinez EZ, Vianna EO. Cough and dyspnea during bronchoconstriction: comparison of different stimuli. Cough. 2009;5:6.
76. Enseleit F, Hurlimann D, Luscher TF. Vascular protective effects of angiotensin converting enzyme inhibitors and their relation to clinical events. J Cardiovasc Pharmacol. 2001;37(Suppl 1):S21–30.
77. Muntner P, Krousel-Wood M, Hyre AD, et al. Antihypertensive prescriptions for newly treated patients before and after the main antihypertensive and lipid-lowering treatment to prevent heart attack trial results and seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure guidelines [see comment]. Hypertension. 2009;53(4):617–23.
78. Alabaster VA, Bakhle YS. Removal of 5-hydroxytryptamine in the pulmonary circulation of rat isolated lungs. Br J Pharmacol. 1970;40(3):468–82.
79. Gonmori K, Rao KS, Mehendale HM. Pulmonary synthesis of 5-hydroxytryptamine in isolated perfused rabbit and rat lung preparations. Exp Lung Res. 1986;11(4):295–305.
80. Cook DR, Brandom BW. Enflurane, halothane, and isoflurane inhibit removal of 5-hydroxytryptamine from the pulmonary circulation. Anesth Analg. 1982;61(8):671–5.
81. Junod AF. Uptake, metabolism and efflux of 14 C-5-hydroxytryptamine in isolated perfused rat lungs. J Pharmacol Exp Ther. 1972;183(2):341–55.

82. Righi L, Volante M, Rapa I, Scagliotti GV, Papotti M. Neuroendocrine tumours of the lung. A review of relevant pathological and molecular data. Virchows Arch. 2007;451(Suppl 1):S51–9.
83. Shah PM, Raney AA. Tricuspid valve disease. Curr Probl Cardiol. 2008;33(2):47–84.
84. Sandmann H, Pakkal M, Steeds R. Cardiovascular magnetic resonance imaging in the assessment of carcinoid heart disease. Clin Radiol. 2009;64(8):761–6.
85. Bernheim AM, Connolly HM, Pellikka PA. Carcinoid heart disease. Curr Treat Options Cardiovasc Med. 2007;9(6):482–9.
86. Droogmans S, Cosyns B, D'Haenen H, et al. Possible association between 3, 4-methylenedioxymethamphetamine abuse and valvular heart disease. Am J Cardiol. 2007;100(9):1442–5.
87. Utsunomiya T, Krausz MM, Shepro D, Hechtman HB. Prostaglandin control of plasma and platelet 5-hydroxytryptamine in normal and embolized animals. Am J Phys. 1981;241(5):H766–71.
88. Stratmann G, Gregory GA. Neurogenic and humoral vasoconstriction in acute pulmonary thromboembolism [see comment]. Anesth Analg. 2003;97(2):341–54.
89. Huval WV, Mathieson MA, Stemp LI, et al. Therapeutic benefits of 5-hydroxytryptamine inhibition following pulmonary embolism. Ann Surg. 1983;197(2):220–5.
90. Said SI. Metabolic functions of the pulmonary circulation. Circ Res. 1982;50(3):325–33.
91. Philpot RM, Andersson TB, Eling TE. Uptake, accumulation, and metabolism of chemicals by the lung. In: Bakhle YS, Vane JR, editors. Metabolic functions of the lung. New York: Marcel Dekker; 1977. p. 123–71.
92. Garcia JG, Noonan TC, Jubiz W, Malik AB. Leukotrienes and the pulmonary microcirculation. Am Rev Respir Dis. 1987;136(1):161–9.
93. Samuelsson B, Dahlen SE, Lindgren JA, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science. 1987;237(4819):1171–6.
94. Haeggstrom JZ, Kull F, Rudberg PC, Tholander F, Thunnissen MMGM. Leukotriene A4 hydrolase. Prostaglandins Other Lipid Mediat. 2002;68–69:495–510.
95. Yang G, Chen G, Wang D. Effects of prostaglandins and leukotrienes on hypoxic pulmonary vasoconstriction in rats. J Tongji Med Univ. 2000;20(3):197–9.
96. Caironi P, Ichinose F, Liu R, Jones RC, Bloch KD, Zapol WM. 5-lipoxygenase deficiency prevents respiratory failure during ventilator-induced lung injury [see comment]. Am J Respir Crit Care Med. 2005;172(3):334–43.
97. Leitch AG. The role of leukotrienes in asthma. Ann Acad Med Singap. 1985;14(3):503–7.
98. Sprague RS, Stephenson AH, Dahms TE, Lonigro AJ. Proposed role for leukotrienes in the pathophysiology of multiple systems organ failure. Crit Care Clin. 1989;5(2):315–29.
99. Orfanos SE, Mavrommati I, Korovesi I, Roussos C. Pulmonary endothelium in acute lung injury: from basic science to the critically ill. Intensive Care Med. 2004;30(9):1702–14.
100. Huang SK, Peters-Golden M. Eicosanoid lipid mediators in fibrotic lung diseases: ready for prime time? Chest. 2008;133(6):1442–50.
101. Del Giudice MM, Pezzulo A, Capristo C, et al. Leukotriene modifiers in the treatment of asthma in children. Ther Adv Respir Dis. 2009;3(5):245–51.
102. O'Byrne PM, Gauvreau GM, Murphy DM. Efficacy of leukotriene receptor antagonists and synthesis inhibitors in asthma. J Allergy Clin Immunol. 2009;124(3):397–403.
103. Tantisira KG, Drazen JM. Genetics and pharmacogenetics of the leukotriene pathway. J Allergy Clin Immunol. 2009;124(3):422–7.
104. Murphy RC, Gijon MA. Biosynthesis and metabolism of leukotrienes [erratum appears in Biochem J. 2007 Sep 15;406(3):527]. Biochem J. 2007;405(3):379–95.
105. Romano M. Lipid mediators: lipoxin and aspirin-triggered 15-epi-lipoxins. Inflamm Allergy Drug Targets. 2006;5(2):81–90.
106. Romano M, Recchia I, Recchiuti A. Lipoxin receptors. Sci World J. 2007;7:1393–412.
107. Soyombo O, Spur BW, Lee TH. Effects of lipoxin A4 on chemotaxis and degranulation of human eosinophils stimulated by platelet-activating factor and N-formyl-L-methionyl-L-leucyl-L-phenylalanine. Allergy. 1994;49(4):230–4.
108. Raud J, Palmertz U, Dahlen SE, Hedqvist P. Lipoxins inhibit microvascular inflammatory actions of leukotriene B4. Adv Exp Med Biol. 1991;314:185–92.
109. Le Y, Li B, Gong W, et al. Novel pathophysiological role of classical chemotactic peptide receptors and their communications with chemokine receptors. Immunol Rev. 2000;177:185–94.
110. Colgan SP, Serhan CN, Parkos CA, Delp-Archer C, Madara JL. Lipoxin A4 modulates transmigration of human neutrophils across intestinal epithelial monolayers. J Clin Invest. 1993;92(1):75–82.
111. Brezinski ME, Gimbrone MA Jr, Nicolaou KC, Serhan CN. Lipoxins stimulate prostacyclin generation by human endothelial cells. FEBS Lett. 1989;245(1–2):167–72.
112. Wenzel SE, Busse WW, The National Heart, Lung, Blood Institute's Severe Asthma Research Program. Severe asthma: lessons from the Severe Asthma Research Program. J Allergy Clin Immunol. 2007;119(1):14–21; quiz 22–13.
113. Vachier I, Bonnans C, Chavis C, et al. Severe asthma is associated with a loss of LX4, an endogenous anti-inflammatory compound. J Allergy Clin Immunol. 2005;115(1):55–60.
114. Levy BD, Bonnans C, Silverman ES, et al. Diminished lipoxin biosynthesis in severe asthma. Am J Respir Crit Care Med. 2005;172(7):824–30.
115. Kupczyk M, Antczak A, Kuprys-Lipinska I, Kuna P. Lipoxin A4 generation is decreased in aspirin-sensitive patients in lysine-aspirin nasal challenge in vivo model. Allergy. 2009;64(12):1746–52.
116. Van Hove CL, Maes T, Joos GF, Tournoy KG. Chronic inflammation in asthma: a contest of persistence vs. resolution. Allergy. 2008;63(9):1095–109.
117. Bonnans C, Levy BD. Lipid mediators as agonists for the resolution of acute lung inflammation and injury. Am J Respir Cell Mol Biol. 2007;36(2):201–5.
118. Serhan CN. Lipoxins and novel aspirin-triggered 15-epi-lipoxins (ATL): a jungle of cell-cell interactions or a therapeutic opportunity? Prostaglandins. 1997;53(2):107–37.
119. Ramalho TC, Rocha MVJ, da Cunha EFF, Freitas MP. The search for new COX-2 inhibitors: a review of 2002–2008 patents. Expert Opin Ther Pat. 2009;19(9):1193–228.
120. Grosser T. Variability in the response to cyclooxygenase inhibitors: toward the individualization of nonsteroidal anti-inflammatory drug therapy. J Investig Med. 2009;57(6):709–16.
121. Funk CD, FitzGerald GA. COX-2 inhibitors and cardiovascular risk. J Cardiovasc Pharmacol. 2007;50(5):470–9.
122. Frangos JA, Eskin SG, McIntire LV, Ives CL. Flow effects on prostacyclin production by cultured human endothelial cells. Science. 1985;227(4693):1477–9.
123. Eling TE, Ally AI. Pulmonary biosynthesis and metabolism of prostaglandins and related substances. Environ Health Perspect. 1984;55:159–68.
124. Robinson C, Hardy CC, Holgate ST. Pulmonary synthesis, release and metabolism of prostaglandins. J Allergy Clin Immunol. 1985;76(2 Pt 2):265–71.
125. McGiff JC, Terragno NA, Strand JC, Lee JB, Lonigro AJ, Ng KK. Selective passage of prostaglandins across the lung. Nature. 1969;223(5207):742–5.
126. Dusting GJ, Moncada S, Vane JR. Recirculation of prostacyclin (PGI2) in the dog. Br J Pharmacol. 1978;64(2):315–20.
127. Gardiner PJ. Eicosanoids and airway smooth muscle. Pharmacol Ther. 1989;44(1):1–62.

128. Regner KR, Connolly HM, Schaff HV, Albright RC. Acute renal failure after cardiac surgery for carcinoid heart disease: incidence, risk factors, and prognosis. Am J Kidney Dis. 2005;45(5):826–32.
129. Zeldin DC, Foley J, Ma J, et al. CYP2J subfamily P450s in the lung: expression, localization, and potential functional significance. Mol Pharmacol. 1996;50(5):1111–7.
130. Salvail D, Dumoulin M, Rousseau E. Direct modulation of tracheal cl – channel activity by 5, 6- and 11, 12-EET. Am J Phys. 1998;275(3 Pt 1):L432–41.
131. Birks EK, Bousamra M, Presberg K, Marsh JA, Effros RM, Jacobs ER. Human pulmonary arteries dilate to 20-HETE, an endogenous eicosanoid of lung tissue. Am J Phys. 1997;272(5 Pt 1):L823–9.
132. Jacobs ER, Zeldin DC. The lung HETEs (and EETs) up. Am J Physiol Heart Circ Physiol. 2001;280(1):H1–10.
133. Sirois P, Gutkowska J. Atrial natriuretic factor immunoreactivity in human fetal lung tissue and perfusates. Hypertension. 1988;11(2 Pt 2):I62–5.
134. Di Nardo P, Peruzzi G. Physiology and pathophysiology of atrial natriuretic factor in lungs. Can J Cardiol. 1992;8(5):503–8.
135. Turrin M, Gillis CN. Removal of atrial natriuretic peptide by perfused rabbit lungs in situ. Biochem Biophys Res Commun. 1986;140(3):868–73.
136. Tomlinson JW, Walker EA, Bujalska IJ, et al. 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. Endocr Rev. 2004;25(5):831–66.
137. Garbrecht MR, Klein JM, Schmidt TJ, Snyder JM. Glucocorticoid metabolism in the human fetal lung: implications for lung development and the pulmonary surfactant system. Biol Neonate. 2006;89(2):109–19.
138. Baker RW, Walker BR, Shaw RJ, et al. Increased cortisol: cortisone ratio in acute pulmonary tuberculosis. Am J Respir Crit Care Med. 2000;162(5):1641–7.
139. Huang CH, Huang HH, Chen TL, Wang MJ. Perioperative changes of plasma endothelin-1 concentrations in patients undergoing cardiac valve surgery. Anaesth Intensive Care. 1996;24(3):342–7.
140. Dupuis J, Cernacek P, Tardif JC, et al. Reduced pulmonary clearance of endothelin-1 in pulmonary hypertension. Am Heart J. 1998;135(4):614–20.
141. Drinker CK, Churchill ED, Ferry RM. The volume of blood in the heart and lungs. Am J Phys. 1926;77(3):590–622.
142. Campbell I, Waterhouse J. Fluid balance and non-respiratory functions of the lung. Anaesth Intensive Care Med. 2005;6(11):370–1.
143. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure – re-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail. 2008;10(2):165–9.
144. Jules-Elysee K, Blanck TJJ, Catravas JD, et al. Angiotensin-converting enzyme activity: a novel way of assessing pulmonary changes during total knee arthroplasty. Anesth Analg. 2004;99(4):1018–23.
145. Lovering AT, Stickland MK, Kelso AJ, Eldridge MW. Direct demonstration of 25- and 50-microm arteriovenous pathways in healthy human and baboon lungs. Am J Physiol Heart Circ Physiol. 2007;292(4):H1777–81.
146. Lovering AT, Haverkamp HC, Romer LM, Hokanson JS, Eldridge MW. Transpulmonary passage of 99mTc macroaggregated albumin in healthy humans at rest and during maximal exercise. J Appl Physiol. 2009;106(6):1986–92.
147. Abrams GA, Rose K, Fallon MB, et al. Hepatopulmonary syndrome and venous emboli causing intracerebral hemorrhages after liver transplantation: a case report. Transplantation. 1999;68(11):1809–11.
148. Colohan AR, Perkins NA, Bedford RF, Jane JA. Intravenous fluid loading as prophylaxis for paradoxical air embolism. J Neurosurg. 1985;62(6):839–42.
149. Breeze RG, Wheeldon EB. The cells of the pulmonary airways. Am Rev Respir Dis. 1977;116(4):705–77.
150. Rogers DF. The airway goblet cell. Int J Biochem Cell Biol. 2003;35(1):1–6.
151. Huffmyer JL, Littlewood KE, Nemergut EC. Perioperative management of the adult with cystic fibrosis. Anesth Analg. 2009;109(6):1949–61.
152. Nadel JA. Neural control of airway submucosal gland secretion. Eur J Respir Dis Suppl. 1983;128(Pt 1):322–6.
153. Reid L. Measurement of the bronchial mucous gland layer: a diagnostic yardstick in chronic bronchitis. Thorax. 1960;15:132–41.
154. Gallagher JT, Kent PW, Passatore M, Phipps RJ, Richardson PS. The composition of tracheal mucus and the nervous control of its secretion in the cat. Proc R Soc Lond B Biol Sci. 1975;192(1106):49–76.
155. Heidsiek JG, Hyde DM, Plopper CG, St George JA. Quantitative histochemistry of mucosubstance in tracheal epithelium of the macaque monkey. J Histochem Cytochem. 1987;35(4):435–42.
156. Evans CM, Williams OW, Tuvim MJ, et al. Mucin is produced by clara cells in the proximal airways of antigen-challenged mice. Am J Respir Cell Mol Biol. 2004;31(4):382–94.
157. Reynolds SD, Malkinson AM. Clara cell: progenitor for the bronchiolar epithelium. Int J Biochem Cell Biol. 2009;42(1):1–4.
158. Boers JE, Ambergen AW, Thunnissen FB. Number and proliferation of clara cells in normal human airway epithelium. Am J Respir Crit Care Med. 1999;159(5 Pt 1):1585–91.
159. Krishnaswamy G, Ajitawi O, Chi DS. The human mast cell: an overview. Methods Mol Biol. 2006;315:13–34.
160. Taube C, Stassen M. Mast cells and mast cell-derived factors in the regulation of allergic sensitization. Chem Immunol Allergy. 2008;94:58–66.
161. Peters A, Veronesi B, Calderon-Garciduenas L, et al. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol [Electronic Resource]. 2006;3:13.
162. Jakubzick C, Tacke F, Llodra J, van Rooijen N, Randolph GJ. Modulation of dendritic cell trafficking to and from the airways. J Immunol. 2006;176(6):3578–84.
163. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev. 2002;82(3):569–600.
164. Matthay MA, Clerici C, Saumon G. Invited review: active fluid clearance from the distal air spaces of the lung. J Appl Physiol. 2002;93(4):1533–41.
165. Dobbs LG, Johnson MD. Alveolar epithelial transport in the adult lung. Respir Physiol Neurobiol. 2007;159:283–300.
166. Andreeva AV, Kutuzov MA, Voyno-Yasenetskaya TA. Regulation of surfactant secretion in alveolar type II cells. Am J Physiol Lung Cell Mol Physiol. 2007;293(2):L259–71.
167. Weaver TE, Conkright JJ. Function of surfactant proteins B and C. Annu Rev Physiol. 2001;63:555–78.
168. Ungaro F, d'Angelo I, Miro A, La Rotonda MI, Quaglia F. Engineered PLGA nano- and micro-carriers for pulmonary delivery: challenges and promises. J Pharm Pharmacol. 2012;64:1217–35.
169. Wanner A, Salathe M, O'Riordan TG. Mucociliary clearance in the airways. Am J Respir Crit Care Med. 1996;154(6 Pt 1):1868–902.
170. Boucher RC. Evidence for airway surface dehydration as the initiating event in CF airway disease. J Intern Med. 2007;261(1):5–16.
171. McFadden ER Jr. Heat and water exchange in human airways. Am Rev Respir Dis. 1992;146(5 Pt 2):S8–10.
172. Crouch E, Wright JR. Surfactant proteins a and d and pulmonary host defense. Annu Rev Physiol. 2001;63:521–54.
173. Wu H, Kuzmenko A, Wan S, et al. Surfactant proteins a and D inhibit the growth of gram-negative bacteria by increasing membrane permeability [see comment]. J Clin Invest. 2003;111(10):1589–602.

174. Wright JR. Pulmonary surfactant: a front line of lung host defense [comment]. J Clin Invest. 2003;111(10):1453–5.
175. Hamann KJ, Dorscheid DR, Ko FD, et al. Expression of Fas (CD95) and FasL (CD95L) in human airway epithelium. Am J Respir Cell Mol Biol. 1998;19:537–42.
176. Fine A, Anderson NL, Rothstein TL, Williams MC, Gochuico BR. Fas expression in pulmonary alveolar type II cells. Am J Phys. 1997;273:L64_L71.
177. Muzio M, Salvesen GS, Dixit VM. FLICE induced apoptosis in a cell-free system. Cleavage of caspase zymogens. J Biol Chem. 1997;272:2952–6.
178. Griffith TS, Brunner T, Fletcher SM, Green DR, Ferguson TA. Fas ligand-induced apoptosis as a mechanism of immune privilege. Science. 1995;270:1189–92.
179. Wadsworth SJ, Atsuta R, McIntyre JO, Hackett TL, Singhera GK, Dorscheid DR. IL-13 and T(H)2 cytokine exposure triggers matrix metalloproteinase 7-mediated Fas ligand cleavage from bronchial epithelial cells. J Allergy Clin Immunol. 2011;126(2):366–74, 374 e1–8.
180. Kaisho T, Akira S. Toll-like receptor function and signaling. J Allergy Clin Immunol. 2006;117:979–87.
181. Bals R, Hiemstra PS. Innate immunity in the lung: how epithelial cells fight against respiratory pathogens. Eur Respir J. 2004;23:327–33.
182. Mio T, Romberger DJ, Thompson AB, Robbins RA, Heires A, Rennard SI. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. Am J Respir Crit Care Med. 1997;155:1770–6.
183. Chung KF. Cytokines in chronic obstructive pulmonary disease. Eur Respir J. 2001;34(Suppl):50s–9s.
184. Russo RG, Liotta LA, Thorgeirsson U, Brundage R, Schiffmann E. Polymorphonuclear leukocyte migration through human amnion membrane. J Cell Biol. 1981;91:459–67.
185. Kao YJ, Piedra PA, Larsen GL, Colasurdo GN. Induction and regulation of nitric oxide synthase in airway epithelial cells by respiratory syncytial virus. Am J Respir Crit Care Med. 2001;163:532–9.
186. Zheng S, De SBP, Choudhary S, et al. Impaired innate host defense causes susceptibility to respiratory virus infections in cystic fibrosis. Immunity. 2003;18:619–30.