MINIREVIEW

Multiple Roles of Phospholipase A\textsubscript{2} during Lung Infection and Inflammation\textsuperscript{\textdagger}

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Inflammation of the lung marked by excessive recruitment of neutrophils from circulation to the airway is a common feature among several pathological lung disorders, particularly those involving infection (13, 17, 64, 69, 73, 76). Although neutrophils serve a protective role by targeting and eliminating bacterial invaders, excessive neutrophil recruitment and accumulation can cause overactivity of the nonspecific neutrophil destructive capabilities, resulting in severe host lung tissue damage (127). Inflammation associated with bacterial pneumonia results from direct infection of the upper airway by either gram-positive pathogens, such as 

\textit{Streptococcus pneumoniae}, or gram-negative species, such as 

\textit{Pseudomonas aeruginosa} (73). \textit{P. aeruginosa} is also the major pathogen colonizing the lung resulting in an influx of inflammatory cells, largely consisting of neutrophils, resulting in increased permeability of the capillary/alveolar barrier and severely impairing oxygenation (76). Although ARDS is not necessarily associated with infection by a specific pathogen, it is often a consequence of sepsis and frequently associated with nosocomial infections (76). Asthma causes reversible airway obstruction involving an aberrantly regulated inflammatory response (64). Eosinophils are the effector immune cells during the asthmatic process and allergens more so than infectious organisms serve as the trigger for an asthmatic attack (64). Severe asthmatic attacks can be exacerbated by respiratory infections, and the pathological process in these severe attacks involves a significant neutrophil presence (13). Chronic obstructive pulmonary disease (COPD) results in airway obstruction that is not fully reversible and is generally brought on by environmental exposure to pollutants, such as cigarette smoke and asbestos (111). Inflammation and airway remodeling are key features in the progression of COPD (13). Since inflammation is a key common component characterizing the pathology of many clinically distinct lung diseases, understanding the mechanisms governing the inflammatory process in the lung may reveal versatile treatment options that could have a beneficial impact on multiple lung disorders.

It has become increasingly appreciated over the past couple of decades that the enzyme phospholipase A\textsubscript{2} (PLA\textsubscript{2}) is an important factor in lung diseases that involve inflammation (106). The defining enzymatic function of PLA\textsubscript{2} is the cleavage of membrane phospholipids into smaller bioactive molecules that can then participate in a plethora of cellular processes (Fig. 1). Determining the particular role of PLA\textsubscript{2} in the setting of lung inflammation has proven quite challenging, because this enzyme represents a family of over 20 distinct proteins with various structural and biochemical characteristics (106). For the purposes of this review, the PLA\textsubscript{2} enzymes are segregated into six major classes based on biochemical properties: secretory PLA\textsubscript{2}\textsubscript{s} (sPLA\textsubscript{2}s), cytoplasmic PLA\textsubscript{2}\textsubscript{s} (cPLA\textsubscript{2}s), calcium-independent PLA\textsubscript{2}\textsubscript{s} (iPLA\textsubscript{2}s), lysosomal PLA\textsubscript{2}s, platelet-activating factor acetylhydrolases (PAF-AHs), and PLA\textsubscript{2}\textsubscript{s} of bacterial origin (Table 1). PLA\textsubscript{2}s isoforms representing each of these major groups have been reported to contribute to either the promotion or the resolution of inflammation occurring in the lung during various disease processes (106). A unifying principle for the role of PLA\textsubscript{2}s in lung disease remains elusive owing to the numbers of PLA\textsubscript{2}s isoforms that are expressed in the lung combined with the multiple and distinct functions attributable to each isoform. These circumstances represent a significant challenge for the design of anti-inflammatory therapeutics based on modulating the PLA\textsubscript{2} enzymatic activity. The purposes of this review are to highlight findings of the roles various PLA\textsubscript{2}s take part in during lung infection and inflammation and to illustrate the importance of PLA\textsubscript{2} in lung disease.

sPLA\textsubscript{2}s

The sPLA\textsubscript{2}s encompass a family of small (14 to 18 kDa) proteins with multiple disulfide bonds whose activity depends on millimolar concentrations of calcium (80, 119). There are more than 10 distinct isoforms included in the sPLA\textsubscript{2} group, including the toxic enzymes present in poisonous venoms of snakes and bees (80, 106, 119). Mammalian sPLA\textsubscript{2}s that have been identified include groups IB, IIA, IIC (pseudogene in humans), IID, IIE, IIIF, IIF, V, X, and XII (Table 1) (80, 106, 119). The most-widely studied sPLA\textsubscript{2} isoforms include group IB and group IIA. Group IB is known to be produced by the pancreas and is thought to be mainly involved in digestion, although other functions have been demonstrated (80, 119). Group IIA sPLA\textsubscript{2} was initially discovered in synovial fluid and...
classified as an acute-phase protein (80, 106, 119). Other group II isoforms, including IID, IIE, and IIF, have been identified by sequence homology analysis using the group IIA gene sequence (Table 1). Although group I and II sPLA2s have received the majority of attention to date, the more-recent discoveries of novel isoforms have led to the establishment of unique and prominent roles for both group V and group X in innate immunity (7, 80, 106, 119). The group V and X sPLA2 enzymes have also been cloned based on sequence similarity to group IIA. As will be discussed in detail below, many of these mammalian sPLA2 isoforms are expressed in the lung and play significant roles in human inflammatory lung disease. The mechanism of action of each sPLA2 depends not only on the isoform but also on the particular functional context. Certain functions require the direct PLA2 enzymatic activity, while others are mediated indirectly through the engagement of signaling cascades upon the binding of sPLA2 to a specific cell surface receptor (43, 80, 119). Notable functions of the various sPLA2s in the lung include the stimulation of chemokines and cytokines, generation of bioactive eicosanoids, perturbation of lung surfactant, and direct bactericidal activity against bacterial species infecting the airway (119). Each of these functions is discussed in more detail below.

Expression of sPLA2 in the lung. Several studies have detected the presence of sPLA2 in the lung (5, 88). In conditions such as asthma, ARDS, and bronchial pneumonia, elevated amounts of sPLA2 are found in the bronchial/alveolar lavage fluid (BALF) and lung tissue of patients (5, 7, 18, 50, 72, 88, 108). In fact, a positive correlation exists between increased levels of sPLA2 and a poor clinical outcome (5, 88). A major source of sPLA2 is the alveolar macrophage (5). Group IIA sPLA2 expression in the alveolar macrophage is induced by inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), as well as bacterial products, including lipopolysaccharide (LPS) (4, 5, 133). Increased expression of sPLA2 co-localizes with areas of intense inflammation (5). In addition to macrophages, the epithelial cells along the respiratory tract may be an important source of sPLA2s, as these cells express many sPLA2 isoforms (44, 65, 66, 109). Human bronchial and nasal cell lines, as well as primary nasal mucosa, have displayed detectable mRNA expression of all sPLA2 isoforms (65, 66). Increased expression of group IIA and IID is observed when epithelial cells are treated with gamma interferon (IFN-γ) (66). In a study investigating mRNA expression in the nasal mucosa, group X sPLA2 displayed the highest expression level among the sPLA2 isoforms (65). In studies examining human whole-lung tissue, groups V and X are generally highly ex-
pressed in the epithelium (72, 109). The results of one study comparing the protein expression levels of various sPLA2 isoforms in normal lung tissue to the levels in lung tissue from patients having infectious bronchial pneumonia displayed discrete isoform localization in both control and diseased states (72). Under normal conditions, staining of group II isoforms is negligible, whereas group V displays a scattered expression pattern in the bronchial epithelium. Group X is strongly expressed in the alveolar epithelium and the interstitial tissue below the bronchial epithelium (72). In patients with pneumonia, group V is enhanced, with strong expression in the bronchial epithelium, lung fibroblasts, and macrophages. Group X remains highly expressed in the epithelium and the fibroblasts of patients with pneumonia. Group IIA, which is undetectable in control healthy lungs, is significantly expressed in the pulmonary arterial walls and the chondrocytes from pneumatic patients (72). The group IID isoform is increased in both pulmonary arterial walls and the chondrocytes from pneumatic patients having infectious bronchial pneumonia displayed distinctive functions have been ascribed to certain sPLA2 isoforms.

**Induction of cytokines and chemokines.** Cytokines and chemokines are critical to the inflammatory and immune responses by serving as signals that orchestrate the actions of immune cells. Lung microvascular endothelial cells produce various CXC neutrophil chemokines, such as interleukin-8 (IL-8), Gro, and ENA-78, in response to LPS treatment (12). Group IB and IIA potentiate this pathway through the activation of NF-κB and the mitogen-activated protein kinase extracellular signal-regulated kinase (ERK) pathway (12). Taken together, it is clear from data obtained from both humans and mice that various sPLA2 isoforms are produced by multiple lung cell types in response to a diversity of stimuli. The role of each distinct isoform in a given lung cell type during inflammatory disease is not entirely clear; however, significant progress has been made over the past decade, and multiple distinctive functions have been ascribed to certain sPLA2 isoforms.

### TABLE 1. Phospholipase A2s involved in lung disease

<table>
<thead>
<tr>
<th>Biochemical class</th>
<th>Isoform</th>
<th>Alternative name</th>
<th>Primary role(s) in lung disease</th>
<th>Reference</th>
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<tr>
<td>sPLA2s</td>
<td>IB</td>
<td>Pancreatic sPLA2</td>
<td>Cytokine/chemokine production</td>
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<td></td>
<td>IIA</td>
<td>Synovial sPLA2</td>
<td>Antibacterial activity</td>
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<td></td>
<td>IID</td>
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<td>65, 66, 72, 116</td>
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<tr>
<td></td>
<td>IIE</td>
<td>Unknown; mRNA expressed in lung cells</td>
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<tr>
<td></td>
<td>IIF</td>
<td>Eicosanoid generation</td>
<td>72</td>
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<tr>
<td></td>
<td>III</td>
<td>Cell signaling/adaptive immunity</td>
<td>94, 97</td>
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<td></td>
<td>V</td>
<td>Eicosanoid generation, surfactant degradation</td>
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<td>X</td>
<td>Eicosanoid generation, PAF hydrolysis</td>
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<td></td>
<td>XII</td>
<td>Antibacterial activity</td>
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<td>Eicosanoid generation, apoptosis</td>
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<td>Lysosomal PLA2s</td>
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<td>LPLA2</td>
<td>Surfactant degradation</td>
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<td></td>
<td></td>
<td>aiPLA2, prdx6</td>
<td>Surfactant degradation</td>
<td>26, 27, 28, 71, 135</td>
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<td>PAF-AHs</td>
<td>VIIA</td>
<td>Plasma PAF-AH or LpPLA2</td>
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<td>VIIB</td>
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<td>VIII</td>
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<td>Bacterial PLA2s</td>
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<td>Lung cell necrosis</td>
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<td>PlaB</td>
<td>Surfactant degradation, hemolysis</td>
<td>30, 31</td>
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<tr>
<td></td>
<td>PlaC</td>
<td>Surfactant degradation</td>
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<tr>
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<td>OMPLA</td>
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</tr>
<tr>
<td></td>
<td>SlaA</td>
<td>Promotes colonization</td>
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* Bacterial PLA2 enzymes are of bacterial origin.

* Classified by sequence homology (106). Only isoforms found in humans are listed.
group X can induce TNF-α and IL-6 expression in macrophages (39). Interestingly, stimulation of cytokines by group IB and X may not require sPLA₂ enzymatic activity. Instead, certain sPLA₂ isoforms bind to a specific receptor known as M-type receptor (or PLA₂R) and activate kinase signaling pathways through engagement of this mannose-type receptor (43).

A recent study investigating single-nucleotide polymorphisms (SNPs) has revealed an association between an SNP in the gene for sPLA₂, group IID and increased weight loss contributing to a worse prognosis in COPD. This SNP in group IID results in a single amino acid change which may modify the activity of the group IID enzyme and, as speculated by the authors, alter the inflammatory process by enhancing sPLA₂-mediated cytokine production (116). Induced expression of chemokines and cytokines likely contributes to the process of immune effector cell recruitment. Consistent with this notion, studies have demonstrated a dramatic influx of neutrophils into the lung upon intratracheal administration of sPLA₂ (38). Diseases where sPLA₂ levels are elevated, such as ARDS, asthma, and pneumonia, are marked by excessive neutrophil influx.

Certain PLA₂ groups also impact the adaptive immune system through the ability to activate signaling pathways that result in the generation of cytokines (94, 97). The maturation of dendritic cells (DCs) from monocytes has been demonstrated to occur as a result of treatment with group III sPLA₂s (94, 97). Group III sPLA₂ can activate transcription factors, such as NF-κB, AP-1, and NFAT, in DCs which likely generate a diversity of bioactive molecules involved in organizing the effector immune response. DCs matured by sPLA₂ group III display increased migratory capacity and, when mixed with T cells, cause T-cell release of IFN-γ. T-cell production of IFN-γ is an important step in the generation of an inflammatory Th1-type adaptive immune response. Interestingly, this ability of sPLA₂ to induce maturity of DCs, which can modulate T-cell activity, is dependent on sPLA₂ enzymatic activity rather than involving binding to a receptor (94). Clearly, sPLA₂ stimulation of cytokines and chemokines in various cell types involves multiple distinct mechanisms and these processes have dramatic effects on immune and inflammatory processes.

**Generation of eicosanoids.** The enzymatic function of PLA₂ is to cleave phospholipids into free fatty acids and lysophospholipids (Fig. 1). In the case where arachidonic acid (AA) is the free fatty acid in the sn-2 position of the phospholipid target, AA release from phospholipids can subsequently be converted into a variety of functionally diverse lipid mediators collectively known as eicosanoids (Fig. 2) (106). Eicosanoids are a class of bioactive lipids derived from AA, which includes prostaglandins (PGs), leukotrienes (LTs), hepoxilins, and lipoxins (LXs), as well as several others that are synthesized by the actions of lipooxygenases and cyclooxygenases on the common substrate, AA (Fig. 2) (110). Eicosanoids, such as the leukotriene LTB₄ and the hepoxilin HXA₄, serve as neutrophil chemotactants, playing a key role in the inflammatory process. On the other hand, PGs, including PGE₂, and LXs, such as LXA₄, can protect against excessive inflammation in the lung, as well as participate in lung tissue repair (110, 122). The generation of AA by PLA₂ is considered to be the rate-limiting step in the synthesis of eicosanoids, and thus, PLA₂ plays a critical role in the generation of all eicosanoids. Unlike other PLA₂ families, sPLA₂s do not selectively target phospholipids that possess AA at the sn-2 position, which has led many to speculate on a less-prominent role for sPLA₂ in eicosanoid synthesis. Nevertheless, there are numerous cases where sPLA₂ isoforms are fully capable of independently generating AA for conversion to eicosanoids, in addition to possessing the ability to cooperate with other PLA₂s to mediate this important function (32, 99).

Group IB and group II sPLA₂ are capable of inducing AA release in both bronchial epithelial cells and mast cells, with group IB displaying greater efficiency than group II (6). When group IIF, V, and X sPLA₂ are transfected into bronchial lung epithelial cells and lung fibroblasts, significant AA release and subsequent PGE₂ production occurs. This is not observed for groups IIA, IID, and IIE. The catalytic activity of the sPLA₂ is required for the increased AA to occur in these transfection studies, suggesting direct enzymatic involvement of these sPLA₂s in this process (72). Group V and X are much more efficient than group IIA at hydrolyzing phosphatidylcholine (PC), which potentially accounts for the greater effectiveness of group V and X at generating AA from mammalian cell membrane targets. High levels of eicosanoids have been reported in the BALF of CF patients (75). Baseline and LPS-induced sPLA₂ group IIA expression, as well as production of PGE₂, are enhanced in CF epithelial cells. Increased AA and subsequent PGE₂ release precedes sPLA₂ group IIA expression, suggesting that the enzymatic source of increased AA and PGE₂ in CF epithelial cells is likely the result of sPLA₂, rather than sPLA₂ activity (75). In some instances it has been reported that sPLA₂s induce AA release indirectly by binding to its receptor and stimulating kinase pathways that lead to the phosphorylation and activation of cPLA₂, which is known to be directly responsible for the generation of AA (32, 99).

Neutrophils treated with group V, but not group IIA phospholipases, release AA and demonstrate increased LTB₄ synthesis (57). The mechanism mediating increased LTB₄ synthesis does not simply involve the hydrolysis of neutrophil extracellular-membrane phospholipids by group V sPLA₂. Instead, the extracellular-membrane hydrolysis products resulting from group V sPLA₂ activity, lysophospholipids, and AA serve to stimulate cPLA₂ activity in the perinuclear region of neutrophils. The actions of cPLA₂ generate a discrete pool of FIG. 2. Represents a simplified schematic of some eicosanoid synthesis pathways occurring within a mammalian cell. PLA₂ hydrolyzes membrane phospholipids, releasing AA. AA can then be converted to eicosanoids, such as LTs, LXs, and hepoxilins, through the actions of lipooxygenases (LOs), or PGs, through the actions of cyclooxygenases (COX). Enzymes are depicted within boxes.
AA derived from perinuclear phospholipids that can then be converted to LTβ by 5-lipoxygenase, also located in the perinuclear region. Furthermore, LTβ4 produced by the neutrophils is also released, causing a second wave of cPLA2 activation by an autocrine positive feedback mechanism. LTβ4 interacts with LTβ1 receptors on the neutrophil surface and further activates cPLA2 through calcium influx and activation of the ERK pathway, which leads to further LTβ4 production (57). For this complex mechanistic process to occur in vivo, the initial group V sPLA2 activation of neutrophils requires an alternative, nonneutrophil cell source of group V sPLA2, which is speculated to be provided by other inflammatory cells, such as mast cells or macrophages (57). Indeed, transcellular sPLA2 activity for the purposes of eicosanoid generation has been reported in other studies (77, 79, 128). Bronchial epithelial cells produce group V sPLA2 in response to endothelin-1, which is then capable of directly hydrolyzing eosinophil membranes to produce AA for subsequent conversion to cysteinyl LTs, such as LTC4, LTC, as well as other eicosanoids, are frequently found to be enhanced in the BALF of asthmatic patients (64, 77, 128). Of particular note, AA release leading to LTC synthesis in eosinophils was shown to occur independently of cPLA2, demonstrating the ability of sPLA2 group V to directly generate AA for eicosanoid synthesis (77, 79, 128).

A mouse model where the sPLA2 group V gene has been knocked out results in significantly reduced eicosanoid generation in in vivo-stimulated macrophages, further emphasizing the role of group V in eicosanoid generation (102). A more recent study exploring the role of group V sPLA2 in a mouse model of airway hyperresponsiveness has further established the importance of group V sPLA2 to the lung inflammatory process in vivo (78).

Group X sPLA2 appears to possess the ability to act directly on the extracellular-membrane surface for mediating AA release and PGE2 production (99). A recent study exploring the role of group X sPLA2 in a mouse model of asthma establishes a critical role for group X in immune cell recruitment, cytokine production, and airway remodeling (45). sPLA2 group X-knockout mice produce significantly less PGs and LTs upon challenge with antigen, and this appears to underlie the much-attenuated asthmatic response to allergen of group X-knockout mice compared with the response of wild-type mice (45).

Evidence for the ability of sPLA2 group III to facilitate the production of PGE2 has recently been reported (81). Group III exhibits a lack of sequence homology with other members of the sPLA2 group, except in the catalytic site and the calcium binding loop where significant sequence homology exists between group III and the other sPLA2 isoforms (81). The role of group III sPLA2s in contributing to the synthesis of eicosanoids in the setting of lung inflammation is largely unexplored.

Eicosanoids are major contributors to the lung inflammatory process, and as described above, many of the sPLA2 isoforms are capable of generating their common substrate, AA. Significant evidence establishes a role of sPLA2 in eicosanoid synthesis, either by direct enzymatic action on membrane phospholipids or through receptor signaling leading to activation of the cPLA2 group.

Effects on lung surfactant. Surfactant is a complex combination of lipids and proteins that is secreted by airway epithelial cells into the airspace for the purpose of reducing surface tension, thereby preventing alveolar collapse during the breathing process (101). Lung inflammatory conditions, such as ARDS and asthma, are marked by surfactant dysfunction (101). Surfactant provides a barrier to pathogens as well, and thus, deficiencies in surfactant may predispose individuals to infectious pneumonia (101). As discussed above, various sPLA2 isoforms are produced in the lung, mainly by macrophages and epithelial cells, and they appear to have direct affects on lung surfactant.

The lipid component of surfactant predominantly consists of PC, but also contains a small percentage of phosphatidylglycerol, phosphatidylinositol, and phosphatidylethanolamine (PE) (51). Various sPLA2 isoforms have different specificities for hydrolyzing particular phospholipid substrates with particular head groups. Hydrolysis of surfactant phospholipids results in a buildup of free fatty acids and lysophospholipids (Fig. 1). Both a reduction in surfactant phospholipid content and the accumulation of released lysophospholipids can be detrimental to surfactant function. Groups IB and V favor hydrolysis of PC, whereas group IIA is far more effective at hydrolyzing phosphatidylglycerol. Thus, it appears that different sPLA2 isoforms act on distinctive regions of the lipid portion of surfactant (50, 52). Mice that are transgenic for group V expire immediately after birth due to an inability to breathe resulting from a marked reduction in lung surfactant (87). Thus, group V, at least in mice, is quite effective at hydrolyzing surfactant.

In addition to serving as a target of sPLA2 activity, surfactant appears to exert a certain degree of control over sPLA2 (133, 134). Both lipid constituents and protein components of surfactant, such as the collectin protein SP-A, can cause a major reduction in the expression of sPLA2 group IIA in alveolar macrophages (134). In fact, SP-A has been shown to specifically bind to group IIA sPLA2 and to reduce the ability of sPLA2 group IIA to hydrolyze phosphatidylglycerol (5, 18). Decreased SP-A levels in BALF are observed in ARDS patients, where sPLA2 activity is more abundant (18). Thus, during inflammatory lung disease processes, a counterbalance between sPLA2 and surfactant appears to be deranged, ultimately manifesting in surfactant degradation. The degradation of surfactant and subsequent loss of phospholipids and collectins, such as SP-A, relieves their repressive effects on sPLA2 further exacerbating surfactant function and perpetuating the lung inflammatory process.

Bactericidal activity. In addition to the numerous contributions toward the enhancement of the inflammatory response attributable to sPLA2s, several isoforms exert an innate defensive role by virtue of their inherent bactericidal activity (15). Gram-positive organisms, such as *Listeria monocytogenes*, *Staphylococcus aureus*, and *Bacillus anthracis*, appear to be directly susceptible to sPLA2 activity both in vitro and in vivo owing to the ability of sPLA2 to hydrolyze bacterial-membrane phospholipids (36, 41, 42, 61, 96). Interestingly, lethal factor produced by *B. anthracis* is capable of down-regulating sPLA2 group IIA expression by alveolar macrophages, a potential virulence mechanism utilized by anthrax to protect itself from destruction by host defenses (36). Gram-negative bacteria, such as *Escherichia coli*, are also susceptible to sPLA2 bactericidal activity; however, additional factors, such as bactericidal permeability-increasing protein or components of complement, are required for effective sPLA2-mediated bacterial de-
struction (60, 62). Interestingly, not all gram-negative bacteria require cofactors, as the gram-negative lung pathogen *P. aeruginosa* is potently susceptible to direct sPLA₂-mediated killing. *P. aeruginosa* killing by sPLA₂ occurs even under the high salt or acidic conditions that are found in the lungs of individuals with CF. This is in contrast to other bactericidal factors that are less effective under the conditions present in the CF lung (24). Bacterial membranes exhibit a different phospholipid composition than mammalian cell membranes, with a greater presence of PE and phosphatidylglycerol and a lesser presence of PC (42). This attribute of bacterial membranes likely accounts for the observation that group IIA exerts the greatest bactericidal activity among the sPLA₂ isoforms against gram-positive bacteria (59). Groups V and X possess bactericidal activity against gram-positive pathogens, albeit to a lesser extent than group IIA, and group IB has minimal bactericidal activity to gram-negative bacteria, such as *E. coli*. Group XII represents an exception, however, and is able to directly kill *E. coli* without need of additional factors (59). The bactericidal activity of sPLA₂ isoforms represents a defense mechanism against infectious lung diseases through the ability of sPLA₂ to eliminate bacterial pathogens prior to initiating or exacerbating the inflammation process.

**cPLA₂s AND iPLA₂s**

The isoforms of the cPLA₂ and iPLA₂ families of PLA₂ are significantly larger than the members of the sPLA₂ family, ranging in size from approximately 61 to 110 kDa (106). Both cPLA₂ and iPLA₂ isoforms possess a patatin domain in their primary sequence that includes a highly conserved active-site serine. The patatin domain was originally identified from the primary sequence that includes a highly conserved active-site calcium, in contrast to sPLA₂s, which require millimolar calcium for enzyme action. However, the translocation of cPLA₂ from the cytosol to the membrane does require calcium, making calcium-mobilizing agents potent activators of cPLA₂ (33, 106).

Stimulants of cPLA₂ in lung epithelial cells include cytokines, such as TNF-α, IFN-γ, and IL-1α, as well as oxidative stress (93, 130, 131, 132, 136). Oxidative stress is also a source of cPLA₂ stimulation in lung fibroblasts (68). The results of several studies suggest that protein signaling kinases, such as ERK1/2, protein kinase C, and p38, play a prominent role in cPLA₂ activation by mediating cPLA₂ phosphorylation (93, 129). These protein kinase signaling pathways are frequently activated by cytokines, such as TNF-α, in many cell types. Cytokines are also capable of stimulating cPLA₂ by inducing mRNA and protein expression, as observed in both lung epithelial cells and lung fibroblasts (23, 131, 132).

cPLA₂ has been proposed to play a significant role in airway inflammatory diseases, such as ARDS, as cPLA₂ is significantly elevated in lung tissues in response to multiple pathological stimuli (83). The primary function of cPLA₂ in lung tissues is considered to be the generation of AA from membrane phospholipids for the synthesis of eicosanoids (106). Since multiple eicosanoids have divergent functions during lung inflammation, cPLA₂ serves as a key enzyme in mediating many aspects of the lung inflammatory process. AA metabolites produced by cPLA₂ also appear to be involved in mediating the transcription of genes involved in lung inflammation, such as IL-8, through interaction with the ligand-associated nuclear transcription factor peroxisome proliferator-activated receptor (91, 92). A role for cPLA₂ in promoting apoptosis has also been reported (58).

A number of studies have supported the notion of cPLA₂ as a key enzyme in the synthesis of eicosanoids during lung inflammation (83, 84, 98, 121). cPLA₂-α-knockout mice have been generated and exploited in the context of airway disease models (83, 84, 98, 121). An evaluation of the role of cPLA₂-α during the pathological process of ARDS has been conducted whereby both wild-type and cPLA₂-α-knockout mice are subjected to intratracheal installation of LPS, zymosan, or HCl. Treatment of wild-type mice with the various insults results in a significant enhancement of the quantity of eicosanoids, including trioxilins and Cys-LTs, in the BALF (83). In parallel to the increase in the quantity of eicosanoids, severe lung edema, neutrophil infiltration, and exacerbation of gas exchange occur in wild-type mice subjected to treatment. The pathological findings are markedly less prominent in the cPLA₂-α-knockout mice, with low levels of detectable eicosanoids present in the BALF after insult. Such results suggest that cPLA₂ plays a critical role in facilitating this robust inflammatory process in the airway, likely through the generation of eicosanoid mediators (83). In a model of acute allergy, antigen challenge of the mouse airway, which normally causes a severe anaphylactic response, results in reduced anaphylaxis in cPLA₂-α-knockout mice compared with the anaphylaxis in wild-type mice (121). Macrophages from cPLA₂-knockout mice are completely unable to produce PGE₂, Cys-LTs, and PAF in response to LPS or calcium ionophors. Thus, data from studies employing cPLA₂-α-knockout mice support a mechanistic model in which cPLA₂ facilitates the production of eicosanoids in the lung (121).
As predicted from the results of the knockout studies, inhibitors of cPLA₂ can partially reduce the neutrophil infiltration observed in LPS-induced lung injury in normal mice and thus may represent potential therapeutics for pathological lung inflammatory processes (84). However, despite the seemingly detrimental role cPLA₂-α plays in certain pathological lung situations, such as ARDS and acute allergy, it likely exhibits a protective role in other situations. Tracheal instillation of live E. coli, rather than LPS alone, in the cPLA₂-α-knockout mice, has revealed a severe defect in the ability of cPLA₂-deficient neutrophils to eradicate the bacteria, suggesting the importance of cPLA₂ in the clearance of bacterial infection (98). The inability of cPLA₂-α-knockout mice to eliminate infection appears to be directly due to the inability of cPLA₂-α-deficient neutrophils to generate sufficient AA for the production of eicosanoids. Although the administration of cPLA₂ inhibitors may aid in relieving overly active and potentially detrimental aspects of inflammation, in the context of an active infection, such treatment may cause more harm by allowing an infection to thrive (98).

A role for cPLA₂ in multiple animal models of asthma has also been reported (20, 21, 82). Both mast cells and eosinophils appear to require cPLA₂ in order to exert their effector functions in the lung (20, 21, 82). Both cell types are important sources of eicosanoids, and eicosanoids, such as Cys-LTs, are critical modulators of asthmatic disease.

The heritable condition CF, which results in bouts of severe lung inflammation associated with chronic bacterial infection over the life span of afflicted individuals, appears to involve cPLA₂ dysregulation in the lung. CF epithelial cells have been reported to produce more eicosanoids and have a higher amount of cPLA₂ activity than normal epithelial cells (14). Heightened cPLA₂ activity leading to overproduction of eicosanoids may exacerbate the inflammatory process, leading to severe lung injury as is observed in CF (14). Our group and others have demonstrated that the bacterial pathogen most relevant to CF, P. aeruginosa, can induce activation of cPLA₂ in lung epithelial cells (53, 58), perhaps further enhancing cPLA₂-mediated eicosanoid generation. Clearly, cPLA₂ is central to numerous lung diseases that are marked by a severe inflammatory process.

Although the majority of research regarding the involvement of cPLA₂ in lung inflammation has focused on cPLA₂-α, group IVC cPLA₂-γ has recently been implicated in airway inflammation in certain cases as well (70). Alveolar macrophages pretreated with the hormone leptin produce PGE₂ and LTβ when challenged with zymosan or calcium ionophors through a mechanism that is completely independent of cPLA₂-α but is associated with an increased expression of cPLA₂-γ (70). Leptin is believed to be increased during lung inflammatory conditions, including pneumonia and asthma (70). Thus, cPLA₂-γ should also be considered as a potential contributor to eicosanoid generation during lung disease.

Clearly the PL₂ group known as cPLA₂ plays a significant role in many lung inflammatory diseases, including pneumonia, asthma, ARDS, and CF. Its main function as a key enzyme in eicosanoid synthesis make it an attractive target for therapeutics, but it should always be considered that other PL₂ groups are also capable of generating eicosanoids. A better understanding of the role played by individual PL₂ isoforms in the generation of distinct eicosanoids by certain tissues and cell types during particular stages of disease processes will be crucial information for designing effective therapeutic intervention.

iPLA₂s. iPLA₂s have many characteristics in common with cPLA₂s, including the facts that both groups are of comparable size, both groups possess a similar active-site structure involving a key serine residue, both groups are expressed in the cytosol, and both groups act on phospholipids derived from internal membranes (8, 106). One crucial difference between the two groups is that the activation of iPLA₂ does not require calcium (8, 106). Also, unlike cPLA₂s, iPLA₂ isoforms do not show a substrate preference for phospholipids with AA at the sn-2 position (8, 106). The two known isoforms that represent the iPLA₂ group are VIA and VIB, or iPLA₂-β and iPLA₂-γ, respectively. Group VIA has five identified mRNA splice variants, with two of the splice variants lacking enzymatic activity and possibly serving an inhibitory role (8). Group IVA has been more widely investigated, and much of the information gathered regarding the iPLA₂ group is based on studies with group IVA. In addition to enhanced gene expression, alternative splicing, and/or enhanced protein expression of iPLA₂ upon stimulation, posttranslational mechanisms of iPLA₂ activation have been described (8). For example, the activity of iPLA₂ has been demonstrated to be modulated by interaction with calmodulin, the presence of ATP, phosphorylation, oligomerization via ankyrin repeats, proteolytic processing, and substrate availability (8). The mechanism of activation of iPLA₂ depends greatly on the particular stimulus, as well as the cell type involved. Alveolar macrophages and airway epithelial cells are capable of expressing iPLA₂, and activity in both cell types appears to be inducible (8, 65, 106, 124).

During cell growth, iPLA₂ serves to facilitate membrane remodeling by decylation and reacylation of membrane phospholipids (8, 106, 124). In studies examining alveolar epithelial cells, the bioactive lipid sphingosine 1-phosphate (Sph-1-P) has been associated with regulation of cell proliferation (124). Treatment of alveolar epithelial cells with Sph-1-P results in the release of AA, which has also been shown to contribute to cell proliferation (124). Interestingly, specific inhibitors of iPLA₂ prevent AA release in response to Sph-1-P but did not prevent AA release in response to alternative stimuli, such as calcium-mobilizing agents (124). This observation allows one to speculate that the specific PL₂ used to generate AA may depend on the stimulus and the intended consequence of the AA (i.e., inducing cell proliferation versus being metabolized for eicosanoid generation).

Despite the notion that iPLA₂ mainly serves a housekeeping role in cells, more-recent studies have pointed to the involvement of iPLA₂ in eicosanoid generation during inflammation (8, 35, 106). Using an in vivo rat model of acute pleurisy, the inflammatory process was investigated in discrete stages: influx of inflammatory cells, persistence of inflammatory cells, and resolution (35). It was observed that both the eicosanoids present, as well as the PL₂ enzymes operating, were altered from one stage of the inflammatory process to the next. In this model, iPLA₂ appeared to act exclusively at the onset of inflammation, generating eicosanoids, such as LTβ, to recruit inflammatory cells. At later stages in the inflammatory process, sPLA₂ and cPLA₂ were the predominant generators of eicosanoids, synthesizing the distinct anti-inflammatory eico-
sanoids LXA₄ and PGD₂, respectively. Pro-resolving eicosanoids, such as LXA₄ and PGD₂, aid in the repair of tissue damage resulting from inflammatory cell influx (35). The results of this study suggest not only that iPLA₂ is capable of participating in eicosanoid generation but also that certain cell types involved in inflammation possess specific and distinct mechanisms for activating the appropriate PLA₂ group or isoenzyme. The regulation of surfactant concentration in the lung remains to be determined. Also, the relative contributions of LPLA₂ and aiPLA₂ in surfactant homeostasis are currently unknown.

**LYSOSOMAL PLA₂S**

Two distinct iPLA₂s that are located within the lysosome have been recently described (48, 71). Lysosomal PLA₂s include the enzyme termed lysosomal PLA₂ (LPLA₂) and the enzyme referred to as acidic iPLA₂ (aiPLA₂) (48, 71). Both enzymes operate at an optimal pH of approximately 4 and possess a catalytically active serine. LPLA₂ and aiPLA₂ are highly expressed in the lung and are believed to participate in surfactant catabolism (49, 71). The major contribution of the enzyme regarding LPLA₂ and aiPLA₂ has been acquired using mouse surfactant catabolism (49, 71). The majority of information regarding LPLA₂ and aiPLA₂ has been achieved using mouse and rat models of lung disease, although the expression of aiPLA₂ in human tissue has been observed (65).

LPLA₂, recently designated as group XV PLA₂, is a mannose-rich, Ca²⁺-independent, acidic-pH-optimal, single-polypeptide-chain enzyme of approximately 45 kDa (1, 2, 106). In addition to PLA₂ activity, LPLA₂ also possesses PLA₁ and transacylase activity (Fig. 1) (1, 2, 48). N-Linked glycosylation of LPLA₂ causes enhanced activity, further implicating a connection between apoptosis and iPLA₂ (8, 106). The consequences of apoptotic processes mediated by iPLA₂ in lung inflammatory disease have not been widely explored; however, several lung cell types, including alveolar macrophages, alveolar epithelial cells, and the nasal mucosa, appear to express iPLA₂, and these cells routinely experience apoptosis under normal and inflammatory conditions (8, 65, 106, 124).

LPLA₂, like, LPLA₂, aiPLA₂ appears to play a significant role in surfactant homeostasis (26, 56, 71). The aiPLA₂ enzyme lacks significant glycosylation, has 224 amino acids (26 kDa), and displays no PLA₁ or lyso-phospholipase activity (Fig. 1) (71). Like LPLA₂, aiPLA₂ is expressed in alveolar macrophages, but unlike LPLA₂, aiPLA₂ is also expressed at high levels in the airway epithelium (65, 71). In addition to being expressed in the lysosome, aiPLA₂ is present in lamellar bodies, the cytosol, and extracellular fluids (71). The degradation and resynthesis of dipalmitoylphosphatidylcholine (DPPC), the major lipid component of surfactant, is believed to be an important activity of aiPLA₂ (71). aiPLA₂ can hydrolyze DPPC for further degradation in the lysosome or for the generation of lyso-PC for resynthesis of surfactant in the lamellar bodies (71). The regulation of surfactant concentration in the lung must be strictly controlled, and aiPLA₂ appears to play a significant role in this regard. The surfactant protein SP-A has been shown to bind directly to aiPLA₂ and inhibit PLA₂ activity, demonstrating a further layer in the control and maintenance of surfactant homeostasis (135).

An interesting property of aiPLA₂ is that it is a multifunctional enzyme (71). In addition to possessing PLA₂ activity, aiPLA₂ possesses glutathione-mediated peroxidase activity (19, 54). As a consequence of this, aiPLA₂ has been described under multiple names, including antioxidant protein 2, single-cysteine peroxiredoxin, and peroxiredoxin 6 (prdx6), among others (71), prdx6, or aiPLA₂, functions as a nonredundant antioxidant protein that protects membrane phospholipids from excessive oxidation (71). The active sites for PLA₂ activity and peroxidase activity are completely separate, and the elimination of PLA₂ activity by mutation of key active-site residues has no effect on peroxidase activity and vice versa (28, 71).

Both aiPLA₂-knockout mice and aiPLA₂-transgenic-overexpressing mice have been generated and investigated for surfactant defects (27, 28). Knockout mice display increased lung phospholipid content with decreased ability to degrade DPPC (28). Overexpressing aiPLA₂-transgenic mice, on the other hand, exhibit a smaller phospholipid pool size in the lung with an increase in DPPC degradation (27). Although aiPLA₂ also facilitates DPPC resynthesis through a pathway involving lyso-PC reacylation, the degradation of DPPC appears to be the more-prominent fate of DPPC hydrolysis by aiPLA₂ (27). When each of these mouse models is exposed to hyperoxia in order to evaluate the antioxidative role of the aiPLA₂ (prdx6) enzyme, the aiPLA₂ (prdx6)-knockout mice are significantly more susceptible to oxidative damage than the wild-type mice, whereas overexpressing transgenic mice are significantly less susceptible than wild-type mice (125, 126). The question of whether it is the PLA₂ activity or the antioxidative activity that represents the dominant role for aiPLA₂ (prdx6) in the human lung remains to be determined. Also, the relative contributions of LPLA₂ and aiPLA₂ in human surfactant homeostasis are currently unknown.

**PAF-AHs**

Groups VIIA, VIIB, and VIII are collectively termed PAF-AHs and are unique among the PLA₂s in that they act on small, water-soluble phospholipids rather than membrane phospholipids or surfactant (3, 9, 55, 114, 118). The bioactive
lipid mediator PAF is the predominant substrate of these calcium-independent enzymes, and since PAF serves an inflammatory role in several diseases, PAF-AH enzymes are thought to mainly serve an anti-inflammatory role, as PAF-AH hydrolyzes the inflammatory PAF molecule into the relatively inert lyso-PAF (118). Group VIIIA is secreted into bodily fluids, such as plasma, urine, and milk, and is also referred to as plasma PAF-AH or LpPLA₂, because of its association with lipoproteins in the bloodstream (55). Group VIIIA plasma PAF-AH has been observed to play an anti-inflammatory role in lung inflammatory conditions, such as asthma and ARDS (55). Group VIIIB and VIII are intracellular and have also been referred to as isoform II and isoform I, respectively (3, 55, 114). Group VIIIB PAF-AH shares 43% amino acid sequence identity with plasma PAF-AH, but VIIIB is not secreted; rather, this enzyme can translocate from the cytosol to the membrane as a consequence of a change in the activation state (3, 118). Both VIIIA plasma PAF-AH and VIIIB PAF-AH possess similar substrate specificities and operate as a single polypeptide chain. In addition to acting on PAF, group VII PAF-AHs are capable of neutralizing “PAF-like” molecules, such as oxidized fragments of PC, which also possess potent biological activity and can mimic PAF (3, 118). A discrete role for group VIIIB (PAF-AH isoform II) in lung disease has not been described, but it is generally thought to be involved in protecting cells against oxidative stress (3, 118).

Group VIII (PAF-AH isoform I) is structurally quite different from the group VII PAF-AHs, as it consists of three polypeptides, two catalytic subunits (VIIIA and VIIIB), and a regulatory subunit that combine to form a heterotrimmeric protein. This particular PAF-AH isoform has strict substrate specificity and is only capable of hydrolyzing PAF. Group VIII PAF-AH appears to play a role in brain development (3, 118). To our knowledge, evidence for the involvement of group VIII PAF-AH in lung inflammatory processes has not been described.

PAF is a lipid mediator involved in the pathogenesis of inflammatory lung diseases, such as ARDS, asthma, and COPD (55, 115, 118). Some effects ascribed to PAF include bronchoconstriction, airway hyperreactivity, mucus secretion, increased vascular permeability, and immune cell recruitment (55, 118). The ability to strictly control the plasma concentration of PAF appears to be crucial to avoiding pathological consequences. Plasma PAF-AH (group VIIIA) plays a key role in PAF homeostasis by mediating PAF elimination. Plasma PAF-AH is produced by cells of hematopoietic origin, predominantly macrophages, and its expression can be downregulated by LPS and certain cytokines (3, 118). A deficiency of PAF-AH in the BALF of asthmatic patients compared to the level in healthy patients may prolong PAF activity and represent an underlying mechanism contributing to the asthmatic pathology (120). A point mutation in the plasma PAF-AH gene (V279F) results in an inactive enzyme and has been identified in patients from Japan. This mutation is associated with an increased likelihood for the development of asthma, as well as being correlated with a higher prevalence among individuals experiencing more-severe attacks. Mice that are experimentally induced to exhibit asthma symptoms upon allergen exposure and then treated by injection of recombinant PAF-AH (rPAF-AH) display a significant reduction in symptoms, including a decrease in eosinophil recruitment, mucus secretion, and airway hyperreactivity (46). Despite strong evidence that rPAF-AH exhibits therapeutic benefits in the lung, no major diminution of the asthmatic response is observed in humans after the administration of recombinant plasma PAF-AH. Only a slight reduction in neutrophils present in the sputum of patients receiving rPAF-AH was noted (47). Furthermore, patients with the V279F mutation in their plasma paf-ah gene do not display hyperactivity toward PAF inhalation (86).

ARDS patients experience an increase in PAF-AH during the acute phase of the disease and a reduction at later stages, suggesting that plasma PAF-AH may be important for the resolution of ARDS (40, 85). In a rat model of ARDS, rPAF-AH administration serves to blunt alveolar macrophage inflammatory responses (16). Again, despite evidence suggesting a role for PAF-AH in ARDS resolution, clinical studies using rPAF-AH have yet to exhibit a significant amount of promise as a therapeutic treatment to minimize the onset or severity of ARDS (89, 107). A recent discovery which has challenged the central role of plasma PAF-AH in PAF hydrolysis is from a study whose results demonstrate that sPLA₂-X, which strongly hydrolyzes membrane PC, is also capable of hydrolyzing water-soluble PAF (37). A better understanding of the regulation of PAF levels in the plasma and BALF under normal circumstances and during pathological inflammatory lung episodes will bring about superior strategies for therapeutic intervention.

**BACTERIAL PLA₂S**

In recent years, several bacterial species have been discovered to possess mammalian-like PLA₂ enzymes (10, 31, 103, 113). Bacterial PLA₂S that have been described include ones that are secreted, as well as PLA₂S that are surface expressed by pathogens (113). Certain of these bacterial PLA₂S are known to serve as potent virulence factors that target host phospholipid membranes, resulting in host cell destruction (10, 31, 103, 113). In fact, bacterial PLA₂ virulence factors have been investigated as potential targets for therapeutic intervention to alleviate the suffering of patients with severe bacterial pneumonia (63).

*Pseudomonas aeruginosa.* The lung pathogen *P. aeruginosa* produces a toxin known as ExoU that is extremely cytotoxic to a diverse range of eukaryotic host cells (103). ExoU is injected directly into host cells in the lung by *P. aeruginosa* via a bacterial type III secretion system (103). Once inside the cell, ExoU interacts with a cofactor, Cu²⁺-Zn²⁺-superoxide dismutase 1, and translocates to the cell membrane, where it encounters phospholipid substrates (105). ExoU has broad substrate specificity, also possessing the ability to hydrolyze lysosphospholipids and operate in a calcium-independent manner (117). Like cPLA₂ and iPLA₂, ExoU contains a patatin domain with an active-site serine (95, 104). ExoU is incapable of acting on the extracellular surface because interaction with the intracellular enzyme superoxide dismutase 1 is required for PLA₂ activity (105). In the lung, ExoU is thought to target epithelial cells, endothelial cells, and macrophages (100, 117).

ExoU is not present in all pathogenic clinical isolates of *P. aeruginosa*; however, infection with ExoU-positive strains of *P. aeruginosa* is strongly associated with a significantly more-se-
vere pneumonia with a much higher rate of complications and a greater degree of mortality (103). Animal models of acute pneumonia have clearly demonstrated that ExoU plays a significant role in virulence by directly mediating acute lung injury and bacterial dissemination, resulting in the development of septic shock (90, 103, 112). The pathology associated with ExoU can be dramatically reduced by infection with a P. aeruginosa strain expressing a catalytically inactive (S142A or D344A) ExoU mutant (90, 103, 112). In vitro cell culture models have revealed that the PLA2 activity of ExoU is responsible for rapid, necrotic host cell lysis through disruption of lipid metabolism, phospholipid membrane cleavage, and loss of cell membrane integrity (90, 103, 112). This phenomenon is believed to account for the invasive nature of ExoU-positive P. aeruginosa clinical isolates in both animal models and human disease (90, 103, 112).

Although the destruction of host cells through membrane hydrolysis is considered to be the main consequence of the PLA2 activity of ExoU, several other PLA2-dependent processes have been attributed to ExoU (22, 74, 100, 103). The alteration of host cell signaling pathways by ExoU has been observed to occur in respiratory epithelial cell lines with ExoU-specific activation of c-fos and c-jun, leading to the initiation of AP-1-mediated gene expression (22, 74). These alterations in cell signaling pathways can lead to ExoU-specific induction of cytokines, such as IL-6 and IL-8 (22, 74). The consequence of these processes may be to instigate an inflammatory response upon intoxication with ExoU, which likely contributes to the disease process. The results of a recent report have demonstrated that ExoU is also capable of mediating eicosanoid production in mammalian cells (100). PGF2α and PGI2 release from P. aeruginosa-infected endothelial cells is ablated when the active-site serine of ExoU is mutated, and less PGE2 is recovered in the BALF of mice infected with ExoU-deficient P. aeruginosa (100). Whether it is through cytokine induction, eicosanoid generation, or direct host cell lysis, ExoU is a bacteria-derived PLA2 that can clearly have an impact on human lung disease.

Legionella pneumophilia. Legionnaires’ disease manifests as severe pneumonia frequently accompanied by ARDS (31). Legionella pneumophilia, the bacterial pathogen responsible for Legionnaires’ disease, is inhaled and infects and destroys lung epithelial cells and macrophages. PLA2 activity originating from L. pneumophilia is believed to be important in the destruction of airway cells, as well as a contributor to the disruption of lung surfactant (31). Several enzymes have been characterized as being responsible for the lyticolytic activity observed in L. pneumophilia, including PlaA, PlaB, and PlaC (11, 29, 30). All three enzymes possess lysosphospholipase (LPLA) activity, but only PlaB and PlaC possess PLA1 and PLA2 activity (Fig. 1) (11, 29, 30). The PLA activity of PlaB is bacterial cell associated, whereas PlaC-derived PLA activity is secreted into the external environment (11, 30). Although PLA2s from L. pneumophilia have been shown to be capable of hydrolyzing surfactant, the individual roles of PlaB and PlaC in this process or in other aspects of disease pathogenesis have not been definitively characterized. PlaB does exhibit hemolytic activity, and this may contribute to the disease process (30). Of note, a recently identified protein of L. pneumophilia called VipD displays significant homology to the P. aeruginosa toxin ExoU. Both VipD and ExoU share the patatin domain with a conserved active-site serine. Whether VipD functions as a PLA2 awaits further study (123).

Other lung bacterial pathogens. Several bacterial pathogens in addition to P. aeruginosa and L. pneumophilia that are noted to cause lung inflammation have been observed to possess functional PLA2 enzymes (113). Gram-negative bacterial species implicated in cases of bacterial pneumonia, including Escherichia coli and Klebsiella pneumoniae, produce an approximately 31-kDa enzyme referred to as OMPLA and encoded by the plaA gene (113). This enzyme has broad specificity, is calcium dependent, and is expressed on the outer membrane of the bacterial cell surface of lung, as well as enteric pathogens (113). OMPLA is believed to contribute to the cytolytic properties of bacterial pathogens; however, a role for OMPLA in the pathogenesis of lung disease has yet to be elucidated. Functional PLA2 enzymes have also been described for gram-negative pathogens with relevance to respiratory disease (113). Various species of group A Streptococcus (Streptococcus pyogenes) bacteria secrete a small (19 kDa) enzyme with significant sequence similarity to sPLA2s that include pancreatic bovine sPLA2 and sPLA2s found in snake venom (113). This enzyme, termed SlaA, plays a key role in upper respiratory tract colonization during group A Streptococcus infection of monkeys (113). As more bacterial pathogens are sequenced, it is likely that several novel bacterial PLA2 enzymes will be discovered. Future challenges include determining the extent to which these enzymes play a role in the disease process, the molecular mechanisms underlying their involvement in lung disease, and whether targeting such factors represents a useful strategy for treatment.

SUMMARY AND CONCLUSIONS

There exists a substantial diversity of PLA2 enzymes present in the airway that are capable of influencing the inflammatory process during the course of lung diseases, such as ARDS, pneumonia, CF, asthma, and COPD (Fig. 3). Many types of host cells, as well as bacterial invaders, are capable of synthesizing PLA2 enzymes that, as a whole, represent a large family of enzymes with a broad range of structure and specificity. The functional consequences of each distinct PLA2, operating in the lung are quite heterogeneous and can be beneficial or damaging to the host, depending on the context. Certain PLA2s are bactericidal and serve to eradicate invading pathogens, while others are immunomodulatory and can neutralize potent soluble bioactive lipids, such as PAF. Several PLA2 enzymes participate in various aspects of surfactant production and degradation which must be tightly orchestrated or severe lung pathology ensues. PLA2 involvement in eicosanoid synthesis and modulation of cell signaling and cytokine production may have beneficial or detrimental consequences, depending on the particular eicosanoid generated, as well as the context, location, and stage of disease in which the eicosanoid or modulated cytokine is produced. It is also important to reiterate that overlapping functions exist among the various PLA2 enzymes, making investigation of the roles of individual PLA2 enzymes challenging. Targeting PLA2s as a means to treat lung disease holds tremendous promise and represents a worthy pursuit; however, a more-thorough appreciation of the considerable
diversity of lung-associated PLA2 enzymes, their specificity, and their cell sources, as well as their discrete role in various lung diseases, will be necessary to ensure the efficacy, as well as the safety, of any PLA2-based therapeutic.

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