**Name of journal:** **World Journal of Respirology**

**ESPS Manuscript NO: 5326**

**Columns:** Review

**autotaxin and lysophosphatidic acid signalling in lung pathophysiology**

**Magkrioti C *et* *al*.** ATX/LPA in lung pathophysiology

Christiana Magkrioti, Vassilis Aidinis

**Christiana Magkrioti, Vassilis Aidinis,** Institute of Immunology, Biomedical Sciences Research Center Alexander Fleming, 16672 Athens, Greece

**Author contributions:** Magkrioti C and Aidinis V searched the literature, analyzed their results, wrote and revised the manuscript.

**Supported by** national grants from the Hellenic Ministry of Education, Lifelong Learning And Religious Affairs, No. 09SYN-12-679/680

**Correspondence to: Dr. Vassilis Aidinis, PhD,** **Researcher A’,** Institute of Immunology, Biomedical Sciences Research Center Alexander Fleming, 34 Fleming Street, 16672 Athens, Greece. [v.aidinis@fleming.gr](mailto:V.Aidinis@Fleming.gr)

**Telephone:** +30-210-9654382  **Fax:** +30-210-9654210

**Received:** August, 29, 2013  **Revised:** October 3, 2013

**Accepted:** November 18, 2013

**Published online:**

**Abstract**

Autotaxin (ATX or ENPP2) is a secreted glycoprotein widely present in biological fluids. ATX primarily functions as a plasma lysophospholipase D and is largely responsible for the bulk of lysophosphatidic acid (LPA) production in the plasma and at inflamed and/or malignant sites. LPA is a phospholipid mediator produced in various conditions both in cells and in biological fluids, and it evokes growth-factor-like responses, including cell growth, survival, differentiation and motility, in almost all cell types. The large variety of LPA effector functions is attributed to at least six G-protein coupled LPA receptors (LPARs) with overlapping specificities and widespread distribution. Increased ATX/LPA/LPAR levels have been detected in a large variety of cancers and transformed cell lines, as well as in non-malignant inflamed tissues, suggesting a possible involvement of ATX in chronic inflammatory disorders and cancer. In this review, we focus exclusively on the role of the ATX/LPA axis in pulmonary pathophysiology, analysing the effects of ATX/LPA on pulmonary cells and leukocytes *in vitro* and in the context of pulmonary pathophysiological situations *in vivo* and in human diseases.

©2013 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words:** Autotaxin; lysophosphatidic acid; lung; acute lung injury; pulmonary fibrosis; asthma; lung cancer

**Core tip:** In the lungs, autotaxin (ATX) is constitutively expressed in the bronchial epithelium, and all pulmonary cell types express some amount of lysophosphatidic acid (LPA) receptor. LPA affects all pulmonary cell types, mainly promoting a pro-inflammatory state. Increased ATX/LPA levels have been detected in various pathophysiological situations, both in mice and humans, including acute, allergic or chronic pulmonary inflammation; fibrosis; and lung cancer. Genetic or pharmacologic interventions targeting the ATX/LPA axis have proved beneficial for modelled disease management in animal models, establishing the ATX/LPA axis as a possible therapeutic target.

Magkrioti C, Aidinis V. autotaxin and lysophosphatidic acid signalling in lung pathophysiology. World J Respirol 2013;

**Available from:**

**DOI:**

**Introduction**

Autotaxin (ATX, ENPP2) is a secreted glycoprotein widely present in biological fluids, including the blood[[1](#_ENREF_1),[2](#_ENREF_2)]. It is a member of the exo/ecto- nucleotide/pyrophosphatase/phosphodiesterase family of ectoenzymes (NPPs) that hydrolyse phosphodiesterase bonds of various nucleotides and derivatives[[3](#_ENREF_3)]. However, ATX primarily functions as a plasma lysophospholipase D, and it is largely responsible for the bulk of lysophosphatidic acid (LPA) production in the plasma and at inflamed and/or malignant sites[[2](#_ENREF_2),[4](#_ENREF_4),[5](#_ENREF_5)]. LPA is a phospholipid mediator produced in various conditions both in cells and in biological fluids, and it evokes growth-factor-like responses, including cell growth, survival, differentiation and motility, in almost all cell types[[2](#_ENREF_2),[4](#_ENREF_4)]*.* The large variety of LPA effector functions is attributed to at least six G-protein coupled LPA receptors (LPARs) with overlapping specificities and widespread distribution[[6](#_ENREF_6),[7](#_ENREF_7)]. Finally, a group of transmembrane lipid-phosphate phosphatases have been suggested to act as negative regulators of LPA metabolism[[8](#_ENREF_8),[9](#_ENREF_9)]. Beyond the well-established role of the ATX/LPA axis in carcinogenesis[[10](#_ENREF_10),[11](#_ENREF_11)], high levels of ATX expression have been observed in non-malignant, inflamed tissues, suggesting a possible involvement of ATX in chronic inflammatory disorders[[12](#_ENREF_12),[13](#_ENREF_13)]. Given the role of the ATX/LPA axis in human disease, a large number of ATX inhibitors and LPAR antagonists are being developed[[14-17](#_ENREF_14)] in pursuit of a compound with likely therapeutic potential. The reviews cited above summarise the current knowledge on ATX, LPA and LPA receptors and their therapeutic relevance and targeting. In this review, we focus exclusively on the role of the ATX/LPA axis in pulmonary pathophysiology, analysing extensively the effects of ATX/LPA on pulmonary cells and leukocytes *in vitro,* as well as discussing these effects in the context of pulmonary pathophysiology *in vivo* and the pathogenesis of human diseases.

**The ATX/LPA axis in the healthy lung**

The gene encoding ATX consists of 27 exons and, through alternative splicing, gives rise to five protein isoforms, designated α-ε, that differ by the presence or absence of sequences encoded by exons 12, 19 and 21[[18](#_ENREF_18),[19](#_ENREF_19)]. All isoforms are catalytically active, and the polybasic insertion in ATXα has been suggested to confer specific binding to cell surface heparin sulphate (HS) proteoglycans[[20](#_ENREF_20)]. In the absence of proteomic data, ATX mRNA expression analysis indicates that ATXγ is brain specific and that ATXβ is the more abundant isoform, exhibiting a broad tissue distribution that includes the lungs[[18-21](#_ENREF_18)]. *In situ* hybridisation localised ATX mRNA expression to the basal cells of normal human bronchial epithelium[[22](#_ENREF_22)], and ATX can be detected in the bronchoalveolar lavage fluid (BALF) of healthy humans (unpublished data). Accordingly, immunohistochemical studies have indicated constitutive ATX expression predominantly in the mouse bronchial epithelium that could also be detected in the BALF of healthy mice[[23](#_ENREF_23)]. Moreover, with genome-wide linkage analysis coupled with expression profiling, ATX was identified as a candidate gene involved in the control of pulmonary functions (dead space volume, VD; total lung capacity, TLC; lung compliance, CL; and diffusing capacity for CO, DCO)[[24](#_ENREF_24)].

Because ATX is a constitutively active enzyme, the biological outcome of ATX’s enzymatic action - largely LPA production and signalling - will depend on its expression levels, the local availability of its substrates, and the abundance and activity of the different LPA receptors in the microenvironment.

Lysophosphatidylcholine (LPC), the main substrate of ATX, is a highly abundant bioactive lysoglycerophospholipid present at high concentrations (100-200 μmmol/L) in the circulation[[25](#_ENREF_25),[26](#_ENREF_26)] and is predominantly associated with albumin and lipoproteins[[12](#_ENREF_12)]. LPC can also be detected in the BALF of healthy mice (< 1 μmmol/L, unpublished data), whereas phosphatidylcholine (PC; mostly 16:0), one of the main precursors of LPC, is a major constituent of the surfactant, which is a macromolecular complex composed primarily of lipids (90%) and surfactant proteins (SPs A-D) and is largely responsible for maintaining minimal surface tension within the alveolar surfaces[[27](#_ENREF_27)]. It remains unknown if BALF LPC is synthesised from surfactant (or membrane) PC, if it diffuses from the circulation or if it is transported with albumin. Therefore, and given its abundance, LPC levels are not a limiting factor in ATX’s enzymatic activity and LPA production, although it is unknown whether LPC’s associations with other molecules (*e.g.*, carrier proteins) are masking the bioavailability of LPC as an ATX substrate.

A 50% reduction or a 100% increase in systemic (and BALF) ATX/LPA levels in genetically modified mice[[28](#_ENREF_28),[29](#_ENREF_29)] does not result in any appreciable effect on gross lung pathology[[23](#_ENREF_23)], although further pulmonary functional studies are needed. Conditional deletion of ATX from the bronchial epithelium results in significantly reduced (but not completely abrogated) levels of BALF ATX, which do not, however, affect lung development and gross pathophysiology in healthy, non-stimulated mice[[23](#_ENREF_23)]. Therefore, fluctuations in ATX levels in the lung seem to be well tolerated under normal, healthy conditions.

LPA can also be detected in the BALF of healthy human and mouse lungs[[23](#_ENREF_23),[30](#_ENREF_30),[31](#_ENREF_31)], the bulk of which is most likely synthesised from the enzymatic action of ATX on BALF (and most likely membrane) LPC.

LPA receptors are widely expressed throughout the body, and the lungs are no exception. All pulmonary cell types have been reported to express different LPARs, as summarised in Table 1. Compiled data analysis from multiple published works, including Northern analyses, real-time PCR and microarray data, suggest a slightly different expression profile in mouse (LPAR3 > LPAR1, LPAR2, LPAR5; no LPAR4) and human (LPAR3 > LPAR1; no LPAR2, 4, 5) lungs[[6](#_ENREF_6)]. Therefore, different LPA receptors are expressed in the lung tissue of healthy mice, although detecting their relative abundance in different cell types will have to wait for the emergence of specific antibodies and/or conditional KO mice. Interestingly, LPAR1 has been found to be dually sequestered in caveolin-1 and clathrin subcompartments of plasmalemmal fractions in porcine cerebral microvascular endothelial cells[[32](#_ENREF_32)], and LPAR1 has been reported to heterodimerise with CD97, an adhesion-linked GPCR[[33](#_ENREF_33)]. LPAR1 has also been reported to cluster with CD14, the LPS co-receptor, upon treatment of MEL12 pulmonary epithelial cells with LPS, an interaction abolished upon the disruption of lipid rafts[[34](#_ENREF_34)]. Further studies are needed to explore possible homo- and hetero-dimerisation of LPARs and the effect of their possible association with other GPCRs within lipid rafts.

Complete genetic deletion of LPAR1-5 does not result in any gross pathological signs in the lungs of non-stimulated mice[[6](#_ENREF_6)], with the exception of the development of pulmonary hypertension in aged LPAR1 and 2 double KO mice[[35](#_ENREF_35)], which is consistent with the proven role of ATX/LPA in vascular development[[6](#_ENREF_6),[28](#_ENREF_28),[36-38](#_ENREF_36)] and the effects of LPA on endothelial and smooth muscle cells physiology (see below).

ATX has been shown to be necessary for embryonic development, as complete genetic deletion results in aberrant vascular and neuronal development leading to embryonic lethality[[6](#_ENREF_6),[28](#_ENREF_28),[36-38](#_ENREF_36)]. However, preliminary studies with inducible complete genetic deletion of ATX in adult mice or long-term potent pharmacological ATX inhibition indicate no gross pathological signs (unpublished data). Moreover, and according to published reports, fluctuations in ATX/LPA levels and the abrogation of LPA receptor signalling are well tolerated in the lungs, with the exception of aged mice. Therefore, the ATX/LPA axis does not seem to have a major role in the pulmonary physiology of healthy adult mice. However, more studies are needed to determine the effect of lysophospholipid homeostasis on healthy pulmonary functions and vice versa.

**LPA effects on pulmonary cells**

The possible involvement of the ATX/LPA axis in pulmonary pathophysiology has been widely explored in *in vitro* studies, mainly upon LPA treatment of various cell types and lines, primary or established. The main findings, exclusively concerning cells of pulmonary origin, are summarised in Table 2, presented below together with major findings from cells of different origin, and are discussed later in the context of disease pathogenic mechanisms. Notably, all reported effects were observed at LPA concentrations much higher than the physiological LPA levels in the plasma and BALF, and thus, they address possible perturbed functions in pathophysiological situations involving the increased production of LPA at local sites. Finally, differential effects have been observed for different LPA species and in the presence of appropriate carriers (*e.g.*, albumin, gelsolin); however, the mechanisms regulating phospholipid homeostasis and LPA activity are far from being understood.

***Epithelial cells***

The airway epithelium, the first line of defence of the lungs against inhaled stimuli, plays a protective role through its barrier activity to inhaled insults. Increased epithelial apoptosis in response to injury is believed to play a major role in the initiation of pulmonary pathophysiological disorders, such as fibrosis. Moreover, damaged epithelial cells release a plethora of factors that contribute to repair mechanisms such as growth factors, chemokines, cytokines and prostaglandins[[39](#_ENREF_39)]. Mouse bronchial epithelial cells have been reported to be the major ATX-producing cell type in the mouse lung[[23](#_ENREF_23)], and transformed pulmonary epithelial cell lines (A549) have also been reported to express ATX[[40](#_ENREF_40)]. All pulmonary cell types have been reported (with some controversy) to express at least one LPA receptor, as indicated in Table 1.

LPA signalling through LPAR1 has been reported to induce anchorage-dependent apoptosis in cultured normal human bronchial epithelial cells (NHBEs)[[41](#_ENREF_41)], and the genetic deletion of LPAR1 or LPAR2 results in a decreased number of TUNEL+ bronchial epithelial cells *in vivo* post-bleomycin (BLM)-mediated lung injury, which specifically targets epithelial cells[[41](#_ENREF_41),[42](#_ENREF_42)]. ATX expression from epithelial transformed A549 cells has been reported to induce their LPA-dependent and LPA-independent migration[[40](#_ENREF_40)], a crucial step for re-epithelisation and tissue remodelling.

The stimulation of normal human bronchial epithelial cells (HBEpCs) with LPA increases stress fibre formation, reorganises αvβ6 at their ends and leads to increased TGF-β activity *via* LPAR2/Gaq and RhoA/Rho kinase[[43](#_ENREF_43)]. TGF-β plays crucial roles in tissue regeneration and cell differentiation, and integrin α5β6 has been shown previously to bind and activate TGF-β1, a mechanism that was suggested to regulate pulmonary inflammation and fibrosis[[44](#_ENREF_44)].

LPA induces IL (interleukin)-8 expression from HBEpCs, the major chemoattractant of neutrophils, through NFκB/AP1 and PKCδ/p38/ERK/JNK pathways[[45](#_ENREF_45),[46](#_ENREF_46)]. LPA levels and their effects on IL-8 expression have been reported to be regulated intracellularly by acylglycerol kinase (AGK)[[47](#_ENREF_47)] and extracellularly by lipid phosphatase-1 (LPP1)[[48](#_ENREF_48)] and ATX[[40](#_ENREF_40)]. Moreover, the stimulation of IL-8 expression is mediated, at least in part, by LPA-mediated phosphorylation and transactivation of the epidermal growth factor receptor (EGFR)[[49](#_ENREF_49)]. *In vitro* results were verified *in vivo*, where intratracheal LPA administration to mouse lungs stimulated the expression of MIP-2, the mouse homologue of IL-8, and neutrophil influx[[45](#_ENREF_45)]. Another pro-inflammatory action of LPA in HBEpCs *in vitro* is the induction of thymic stromal lymphopoietin (TSLP) and chemokine CCL20 through CARMA3-mediated NF-κB activation[[50](#_ENREF_50)]. TSLP stimulates dendritic cell maturation, leading to antigen presentation to T cells and the initiation of an adaptive immune response to an inhaled antigen[[51](#_ENREF_51)], whereas CCL20 induces the chemotaxis of T cells and dendritic cells (DCs)[[52](#_ENREF_52)]. Both cytokines are expressed in the airway of asthmatic patients and contribute to airway inflammation in mouse models of asthma[[52](#_ENREF_52),[53](#_ENREF_53)].

LPA has also been reported to induce IL-13 receptor α2 expression and to inhibit IL-13 signalling in HBEpCs *in vitro*[[54](#_ENREF_54)]. IL-13 is a Th2 cytokine and a mediator of allergic inflammation and disease, the levels of which were found to be increased in the BALF of asthma patients and ovalbumin-challenged mice[[55](#_ENREF_55)]. LPA levels were also found to be increased after segmental allergen challenge[[56](#_ENREF_56)]. Therefore, LPA-induced stimulation of IL-13Rα2 and abrogation of IL-13 signalling would conceivably abrogate the induction of allergic asthma in mice. Heterozygous LPAR2 knockout mice exhibit reduced neutrophil infiltration in the lungs upon treatment with *Schistosoma mansoni* soluble egg antigen (SEA)[[57](#_ENREF_57)]; however, the adoptive transfer of allergen-pulsed LPAR2-/-DCs induce substantially more lung inflammation, pointing to an anti-inflammatory role of LPA/LPAR2[[58](#_ENREF_58)]. Consistent with a potential anti-inflammatory role of LPA signalling, especially in the context of allergic inflammation, LPA has been found to inhibit the TNF/IFN-γ-induced production of CCL5/RANTES in an established human bronchial epithelial cell line (BEAS-2B)[[59](#_ENREF_59)]. RANTES is a chemoattractant for eosinophils, monocytes and T-cells and seems to exacerbate asthma[[60](#_ENREF_60)]. LPA has also been reported to induce the expression of soluble ST2 (sST2) from HBEpCs, a decoy receptor of IL-33 that attenuates IL-33 and endotoxin-induced inflammatory responses[[61](#_ENREF_61)]. The increased expression has also been verified *in vivo*, where the intratracheal administration of LPA increased sST2 levels in BALF[[61](#_ENREF_61)]. However, the physiological relevance of this finding remains unknown, as the abrogation of LPA signalling *in vivo, via* the genetic deletion of LPAR1 or LPAR2, attenuates LPS-induced responses[[34](#_ENREF_34),[62](#_ENREF_62)]. The controversial anti-inflammatory effects of LPA are exemplified by its stimulation of cyclo-oxygenase-2 (COX-2) expression and prostaglandin E2 (PGE2) release from HBEpCs[[63](#_ENREF_63)]. *In vivo*, LPAR2+/- mice express less COX-2 and secrete lower amounts of PGE2 compared to wild-type mice upon allergic stimulation[[57](#_ENREF_57)]. COX-2 and PGE2 are commonly considered potent proinflammatory mediators and are involved in several inflammatory diseases. However, in the lungs, as opposed to other parts of the body, PGE2 has a role in limiting the immune-inflammatory response and tissue repair processes[[64](#_ENREF_64),[65](#_ENREF_65)]. The generation of conditional knockouts for the different LPA receptors will be instrumental in dissociating the inflammatory effects of LPA in different cell types *in vivo*. Moreover, the possible differential effects of LPA in stromal and innate immune cells, as compared to adaptive immune cells, should be addressed with appropriate bone marrow transfer experiments.

LPA stimulates PGE2 production and IL-8 secretion in HBEpCs through EGFR phosphorylation and transactivation[[49](#_ENREF_49),[63](#_ENREF_63)] introducing the concept that LPA can also activate or modulate structurally distinct receptors. LPA induces a decrease in EGFR binding of EGF both in HBEpCs and established epithelial cell lines (BEAS-2B) *via* different signalling pathways, including transactivation of EGFR[[66](#_ENREF_66),[67](#_ENREF_67)]. The decrease in EGF binding to its receptor is sustained in normal cells but is rapidly reversed in cancer cell lines (H292, A549)[[67](#_ENREF_67)]. LPA has been found to transactivate receptor tyrosine kinases (RTKs) other than EGFR, such as platelet-derived growth factor receptor-β (PDGF) in lung epithelial cells. Specifically, in primary cultures of HBEpCs, LPA stimulates tyrosine phosphorylation of PDGF-Rβ and threonine/tyrosine phosphorylation of the downstream molecule ERK1/2, both through PDGF-R kinase, suggesting that PDGF-R is transactivated by LPA[[68](#_ENREF_68)]. As PDGF promotes cell proliferation[[69](#_ENREF_69)], PDGFR transactivation from LPA may have a proliferative role in airway epithelium.

In general, transactivation of RTKs by GPCRs induces tyrosine phosphorylation of RTKs, thereby resulting in further signal transduction. Similarly, LPA induces tyrosine phosphorylation of EGF-R and PDGF-Rβ in HBEpCs[[66](#_ENREF_66),[68](#_ENREF_68)]. By contrast, LPA has no effect on tyrosine phosphorylation of another RTK, c-Met, which is the receptor of hepatic growth factor (HGF)[[70](#_ENREF_70)]. Rather, LPA in HBEpCs induces serine phosphorylation of c-Met and its redistribution to the plasma membrane[[70](#_ENREF_70)]. Moreover, LPA has an inverse effect on c-Met compared to the c-Met ligand, HGF. HGF induces tyrosine phosphorylation of c-Met and its internalisation, whereas LPA reverses these effects and promotes the redistribution of the c-Met-E-cadherin complexes on the plasma membrane through PKCδ[[70](#_ENREF_70)]. The implication of LPA on c-Met signalling, which is involved in tumour invasion and metastasis, could be of importance in lung cancer (LC) in which c-Met is overexpressed[[71](#_ENREF_71)]. Conversely, the inhibition of HGF signalling by LPA is another link between LPA and fibrosis, in which HGF has an important protective role[[72](#_ENREF_72)].

The ATX/LPA axis is widely known to be implicated in cancer[[10](#_ENREF_10),[11](#_ENREF_11)]; however, limited studies have addressed the role of ATX/LPA in LC. A549 lung carcinoma epithelial cells express ATX, which localises to perinuclear and exocytotic vesicle-like bodies and is later secreted in the culture medium[[40](#_ENREF_40)]. ATX has been reported to induce the migration of A549 cells, most likely through the phosphorylation of PKCδ and of the actin-binding protein cortactin, which could be inhibited by an LPAR1/LPAR3 inhibitor or knock-down of LPAR1[[40](#_ENREF_40)]. Interestingly, mutant ATX or heat-inactivated cell supernatant were also reported to promote cell migration, proving that ATX-induced cell migration does not depend totally on ATX enzymatic activity and LPA[[40](#_ENREF_40)]. This LPA-independent pathway of cell migration could be mediated by the binding of ATX to cell-surface receptors, such as integrin β4, which, as shown by co-immunoprecipitations, takes place even after ATX has been heat inactivated[[40](#_ENREF_40)].

Moreover, in the context of carcinogenic epithelial cells, LPA has been shown to decrease the total cellular content of the tumour suppressor p53 in A549 lung epithelial cells, most likely through proteasomal degradation regulated by PI3K, and simultaneously to decrease the nuclear localisation of p53 and the p53-dependent transcription of cell-cycle arrest genes[[73](#_ENREF_73)]. Overexpression of LPA receptors 1, 2 or 3 in A549 cells was found to be sufficient to cause a severe reduction in p53-dependent transcription[[73](#_ENREF_73)]. Moreover, LPA protects A549 cells from genotoxic drugs, which normally cause nuclear accumulation of p53 and apoptosis, by reducing the total levels of p53 and preventing apoptosis[[73](#_ENREF_73)]. This may explain the protection that LPA offers to carcinoma cells against chemotherapeutic agents. In addition, the fact that p53 inhibition regulates transcription by LPA means that LPA suppresses the G1-S cell cycle arrest induced by p53 and favours tumour cell growth. The same A549 cell line, which predominantly expresses LPAR1, shows induction of cell motility by LPA[[74](#_ENREF_74)], whereas its migration and invasion are inhibited *in vitro* by 1-bromo-3(*S*)-hydroxy-4-(palmitoyloxy)butyl-phosphonate (BrP-LPA), a dual-function pan-antagonist of LPA receptors and inhibitor of the lysophospholipase D activity of ATX[[75](#_ENREF_75),[76](#_ENREF_76)]. Expression of LPAR1 seems to be crucial for motility, as another lung epithelial carcinoma cell line with no LPAR1 but significant LPAR2 levels is not susceptible to LPA-induced cell motility[[74](#_ENREF_74)]. Intriguingly, when A549 cells are injected along extracellular matrix (ECM) in nude mice, the resulting tumours are inhibited, and the number of vessels is decreased by BrP-LPA, an inhibitor of ATX and LPA signalling[[76](#_ENREF_76)]. Therefore, LPA regulates many of the aspects of A549 cells that promote carcinogenesis, such as cell cycle promotion, migration, invasion and survival.

Taken together, these results show that LPA seems to be involved in different aspects of pulmonary epithelial pathophysiology, including migration, apoptosis, pro-(and anti-) inflammatory gene expression and transactivation of RTK receptors. However, most of the reported LPA effects in epithelial cells described above were examined *in vitro*, in the absence of cell-to-cell interactions and a functional ECM, which are defining events especially in the case of epithelial cells. Their implication on pulmonary pathophysiological situations *in vivo* is discussed below.

***Fibroblasts***

Fibroblasts are ubiquitous cells found in connective tissue that provide mechanical strength to tissues by providing a supporting framework of ECM[[77](#_ENREF_77)]. Moreover, fibroblasts are important sentinel cells in the immune system, which have been suggested to play a critical role in the switch from acute inflammation to adaptive immunity and tissue repair[[78](#_ENREF_78)]. Fibroblasts from different anatomical regions exhibit characteristic phenotypes that are maintained even after prolonged culture *in vitro*, suggesting that many fibroblasts have an imprinted phenotype. They are extremely versatile cells that display a remarkable capacity to differentiate into other components of the connective tissue, such as cartilage, bone, adipocyte and smooth muscle cells. Their differentiation to myofibroblasts, under mechanical pressure from the ECM and/or pro-fibrotic TGF-β stimulation, regulates connective tissue remodelling by combining the ECM–synthesising features of fibroblasts with cytoskeletal characteristics of contractile smooth muscle cells. Myofibroblasts can have multiple origins, regress and disappear by apoptosis on wound epithelialisation, and may persist in fibrotic situations and cause organ dysfunction, such as pulmonary fibrosis[[79](#_ENREF_79)]. Moreover, fibroblasts are associated with cancer cells (cancer-associated fibroblasts) at all stages of cancer progression, and their functional contribution to this process is beginning to emerge[[80](#_ENREF_80)].

Fibroblast proliferation is required in wound healing to fill an open wound. In the lungs, LPA has been reported to promote the proliferation of established human normal lung fibroblasts (CCL151), along with ERK phosphorylation and the transcription of c-fos, *HB-EGF* and *amphiregulin* genes[[81](#_ENREF_81)]. In accordance, cell migration, rounding and proliferation in response to LPA are decreased in embryonic fibroblasts from LPAR1-null mice but are not absent, consistent with redundant signalling from LPA receptors[[82](#_ENREF_82)]. In support of a role of LPA in lung fibroblast proliferation, LPA stimulates proliferation of synovial fibroblasts mediated through the GPCR, ERK, p38 and Rho kinase signalling pathways[[83](#_ENREF_83)]. The proliferative effects of LPA in synovial fibroblasts correlates with the development of actin stress fibres[[83](#_ENREF_83)], in agreement with early reports on LPA effects in Swiss 3T3 fibroblasts, also indicating tyrosine phosphorylation of focal adhesion kinase (FAK), paxillin and p130[[84-86](#_ENREF_84)]. Moreover, LPA-induced cytoskeleton reorganisation in peritoneal mesothelial cells promotes connective tissue growth factor (CTGF) expression, which in turn promotes NIH3T3 fibroblast proliferation, an effect abolished upon silencing of CTGF or LPAR1 in mesothelial cells[[87](#_ENREF_87)].

LPA has also been shown to augment human foetal lung and human foreskin fibroblast-mediated contraction of collagen gels[[88](#_ENREF_88),[89](#_ENREF_89)] and to promote the contraction of human myofibroblasts, isolated from the palmar aponeurosis of patients with Dupuytren’s disease[[90](#_ENREF_90)]. LPA-mediated contraction of myofibroblasts has been suggested to involve Rho/Rho kinase inhibition of myosin light chain (MLC) phosphatase (MLCP)[[90](#_ENREF_90)]. In accordance, LPA has been found to increase the phosphorylation and thereby the inhibition of MLCP in Swiss 3T3 fibroblasts in a ROK-dependent manner[[91](#_ENREF_91)]. This would therefore suggest that MLCP inhibition could play a role in LPA-induced fibroblast contraction by enhancing the effect of MLC kinase (MLCK), leading to prolonged phosphorylation of MLC and, subsequently, an increase in actin/myosin cross-bridging and contraction. Moreover, LPA has also been shown to induce an MLC-independent pathway of cell contraction through rac, p21-activated kinase 1 (PAK1) and cofilin-1-mediated membrane ruffling[[92](#_ENREF_92)].

In addition to promoting Rho-dependent cell contraction, LPA is also a potent stimulator of Rac, leading to lamellipodia protrusion and cell migration[[74](#_ENREF_74),[93](#_ENREF_93)]. This involves Gi-dependent activation of PI3K that, in turn, activates the Rac-specific guanine nucleotide-exchange factor Tiam1[[93](#_ENREF_93)]. Moreover, LPA synergises with EGF, PDGF and β1Α integrins in the stimulation of cell migration[[94](#_ENREF_94)]. In the lung, it has been shown that LPA bound to albumin acts through LPAR1 as a chemoattractant for primary mouse lung fibroblasts. Chemotaxis induced by BALFs isolated from fibrotic mice is attenuated by more than 50% when the fibroblasts are deprived of LPAR1, suggesting that LPA is the predominant fibroblast chemoattractant in the airspaces of BLM-treated mice[[31](#_ENREF_31)]. In addition, a selective inhibitor for LPAR1, AM966, has been found to inhibit the chemotaxis of IMR-90 human lung fibroblasts mediated by LPA[[95](#_ENREF_95)]. The LPAR1-LPAR3 inhibitor Ki16425 inhibits chemotaxis of human foetal lung fibroblasts induced by BALF from IPF patients, showing the importance of LPAR1 in LPA-induced fibroblast chemotaxis[[31](#_ENREF_31)]. *In vivo,* LPAR1 deletion protects against BLM-induced fibrosis in mice, most likely due to the observed decrease in fibroblast accumulation. By contrast, fibroblast collagen production and differentiation to myofibroblasts remain unaffected by LPAR1 deletion[[31](#_ENREF_31)] but have been suggested to be regulated by LPAR2[[42](#_ENREF_42)]. In human lung fibroblasts, LPA induces the expression of α-smooth muscle actin (αSMA), fibronectin (FN), collagen I a2 and TGF-β1 protein expression, mediated through LPAR2[[42](#_ENREF_42)]. In support of an effect of LPA on the differentiation of lung fibroblasts to myofibroblasts, tumour-secreted LPA promotes the differentiation of peritumor fibroblasts to myofibroblasts and accelerates hepatocellular carcinoma progression[[96](#_ENREF_96)], as well as the expression of αSMA in human adipose tissue-derived mesenchymal stem cells[[97](#_ENREF_97),[98](#_ENREF_98)].

LPA signalling, specifically through LPAR1, has been found to completely suppress the apoptosis of adherent primary mouse lung fibroblasts induced by serum deprivation[[41](#_ENREF_41)]. Similar anti-apoptotic effects of LPA have also been reported in NIH3T3, Swiss 3T3 and Rat-1 fibroblasts[[99](#_ENREF_99)], as well as ATX-transfected NIH3T3 fibroblasts[[100](#_ENREF_100)], further supporting a role of ATX/LPA in mediating pathologic fibroblast accumulation.

Finally, signs of LPA-induced differential expression in fibroblasts can be extrapolated from an expression profiling study of mouse embryonic fibroblasts (MEFs)[[101](#_ENREF_101)]. LPA induces the transcription of more than 100 immediate-early genes associated with growth and cell cycle progression, growth regulatory kinases and secreted factors such as chemokines, pro-angiogenic factors and pro-fibrotic factors. Also very prominent is the activation of genes related to cytoskeletal organisation and integrin signalling, which is in line with the role of LPA in cell motility. Simultaneously, LPA-downregulated genes are associated with adhesion[[101](#_ENREF_101)]. Therefore, LPA seems to have a plethora of actions on fibroblasts concerning cell cycle, growth, motility and inflammation. However, when used at low concentrations, LPA enhances mostly genes associated with cell movement rather than cell growth, indicating that LPA acts predominantly as a motility factor than a growth factor at low concentrations[[101](#_ENREF_101)]. The effects of LPA on differential gene expression in MEFs have been suggested to be mediated by beta-arrestin 2 in an independent study[[102](#_ENREF_102)].

***Endothelial cells***

The endothelium is the thin layer of cells that lines the interior surface of blood vessels and lymphatic vessels forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall. Endothelial cells (ECs) are involved in many aspects of vascular biology, including barrier function, blood clotting, angiogenesis, vasoconstriction and vasodilation[[103](#_ENREF_103)]. Although endothelial dysfunction, or the loss of proper endothelial function, is a hallmark for vascular diseases and often regarded as a key early event in the development of atherosclerosis and cardiovascular diseases, chronic lung diseases such as COPD, pulmonary hypertension and interstitial lung diseases have all been reported to have a lung vascular disease component[[104](#_ENREF_104),[105](#_ENREF_105)]. Moreover, the interaction of endothelial cells with immune cells is instrumental for the extravasation of inflammatory cells at local sites.

LPA increases the permeability of an endothelial layer consisting of human pulmonary arterial ECs (HPAECs) to FITC-dextran (in transwell assays) and reduces their electrical impedance[[106](#_ENREF_106)]. The LPA-induced loss of endothelial barrier function is associated with changes in actin stress fibre formation[[106](#_ENREF_106)]. Similar observations have been made in human umbilical vein ECs, in which it has been shown that LPA induces endothelial hyperpermeability through the activation of RhoA and Rho kinase, master regulators of signals to the cytoskeleton[[107-109](#_ENREF_107)]. Therefore, and despite some conflicting reports on the effects of LPA on the permeability of other endothelial systems[[109-111](#_ENREF_109)], the increased levels of LPA in certain pulmonary pathophysiological conditions could increase endothelial permeability, thereby facilitating the influx of inflammatory cells and soluble factors. Indeed, genetic deletion of LPAR1 or LPAR2 and the resulting abrogation of LPA signalling attenuate the BLM-induced vascular leakage observed during the development of modelled pulmonary inflammation and fibrosis[[31](#_ENREF_31),[42](#_ENREF_42)].

Interestingly, ECs of high endothelial venules (HEVs), largely responsible for lymphocyte extravasation into secondary lymphoid organs, have been reported to express and secrete ATX, and chemokine-activated lymphocytes express receptors with enhanced affinity for ATX[[112](#_ENREF_112),[113](#_ENREF_113)]. Moreover, it has recently been shown that HEV-expressed HS plays a role in chemokine presentation and lymphocyte homing[[114](#_ENREF_114)], while the polybasic insertion in ATXα has been suggested to confer specific binding to cell surface HS proteoglycans[[20](#_ENREF_20)]. Impressively, intravenous injection of enzymatically inactive ATX attenuates T-cell homing to lymphoid tissues, suggesting that EC-bound-ATX is an adhesive substrate for homing lymphocytes [[112](#_ENREF_112)]. In the same homing cascade, LPA locally produced by HEV-ATX stimulates the polarisation, motility and transendothelial migration of naïve T-cells[[112](#_ENREF_112),[115](#_ENREF_115)] or the motility of the ECs[[116](#_ENREF_116)]. Furthermore, LPA stimulates the expression of IL-1β, IL-8 and MCP-1 from human ECs[[117-119](#_ENREF_117)] *via* the p38 and JNK pathways[[119](#_ENREF_119)], and it has been reported that LPA activates ECs to secrete chemokines which, in the presence of LPA, might modulate interactions between the endothelium and circulating monocytes[[120](#_ENREF_120)]. LPA increases ICAM-1 expression in HUVECs, which might also enhance interactions with leukocytes[[121](#_ENREF_121),[122](#_ENREF_122)] through ROCK2[[122](#_ENREF_122)] in an NF-κB dependent mechanism[[121](#_ENREF_121),[122](#_ENREF_122)]. A similar effect has also been reported in human aortic ECs, in which LPA stimulates E-selectin and VCAM-1 expression and increases the binding of monocytes and neutrophils[[123](#_ENREF_123)]. It has also been reported that LPA upregulates the expression of pentraxin-3 (PTX3) in a human artificial EC cell line[[124](#_ENREF_124)]. PTX3 is an acute-phase protein produced at the sites of infection and inflammation by various tissues and cells, in particular innate immunity cells, in response to proinflammatory signals and Toll-like receptor engagement. In addition, it has recently been reported that PTX3 regulates leukocyte recruitment upon acute lung injury (ALI)[[125](#_ENREF_125)], while genetic variation in PTX3 is associated with primary graft dysfunction after lung transplantation[[126](#_ENREF_126)]. Although the endothelial cells of HEVs (and other endothelial systems) differ substantially from pulmonary endothelial cells, similar mechanisms may be in play in the lung, further regulating inflammatory cell influx.

Beyond the effects of LPA in endothelial permeability and the possible regulation of the influx of inflammatory cells, LPA stimulates the migration of some (but not all) pulmonary EC types through ECM-dependent cytoskeletal rearrangements involving focal adhesions[[127-129](#_ENREF_127)]. The migration, proliferation and differentiation of ECs are all essential steps in angiogenesis, and LPA has been reported to be involved in all processes, in different EC systems and experimental conditions (reviewed in[[130](#_ENREF_130)]). Notably, LPA dramatically downregulates the surface expression of CD36, the receptor of thrombospondin-1 and other anti-angiogenic proteins in primary microvascular endothelial cells and promotes angiogenesis *via* a PKD-1-dependent signalling pathway[[131](#_ENREF_131)]. LPA enhances VEGF-C expression in human endothelial cell lines through LPAR1/3, COX-2, NF-kB and EGFR transactivation-dependent mechanisms[[132](#_ENREF_132),[133](#_ENREF_133)]. Therefore, the ATX/LPA axis might also stimulate angiogenesis, thereby exacerbating carcinogenesis and possibly chronic lung diseases that have been suggested to include a vascular component.

***Smooth muscle cells***

Smooth muscle cells (SMCs) play an important role in mediating a wide range of physiological processes, such as blood pressure regulation and airway responsiveness. Their principle function is to contract or relax in response to stimuli, and they are capable of major phenotypic changes in response to alterations in local environmental cues[[134](#_ENREF_134)]. LPA has been suggested to be such a phenotypic modulator of SMCs, and its possible involvement in vascular diseases and atherosclerosis have been extensively reviewed elsewhere[[13](#_ENREF_13),[135](#_ENREF_135)], suggesting that isolated vascular SMCs respond to LPA by proliferating and migrating. The early growth response-1 (Egr-1) transcription factor[[136](#_ENREF_136),[137](#_ENREF_137)], which regulates the transcription of a large variety of genes in SMCs implicated in vascular diseases and fibrotic genes in fibroblasts[[138](#_ENREF_138)], has been proposed to be central to LPA responses of vascular SMCs.

LPA has been reported to stimulate the proliferation of airway SMCs in marked synergism with EGF[[139](#_ENREF_139)] and to enhance their contraction in response to serotonin and methacholine[[140](#_ENREF_140)]. Moreover, LPA upregulates the expression of EGF receptors, increases EGF binding[[141](#_ENREF_141),[142](#_ENREF_142)] and induces integrin αvβ5-mediated TGF-β activation[[143](#_ENREF_143)], suggesting a possible involvement of LPA in asthma and obstructive lung diseases.

Remarkably, LPA has been suggested to target vascular and oncogenic pathways *via* the receptor for advanced glycation end products (RAGE)[[144](#_ENREF_144)]. LPA has been reported to bind avidly to RAGE, which is required for LPA effects in vascular SMCs, including Akt signalling, proliferation and migration[[144](#_ENREF_144)]. RAGE is a member of the immunoglobulin superfamily and has been shown to be a pattern recognition receptor that transduces the effects of multiple ligands, including advanced glycation end products (AGEs), advanced oxidation protein products, S100/calgranulins, high-mobility group box-1 (HMGB1) and amyloid-β peptide[[145](#_ENREF_145)]. RAGE is highly expressed in the lungs, suggesting a potentially important role in lung homeostasis, and the disruption of RAGE levels has been implicated in the pathogenesis of a variety of pulmonary disorders, including ALI, fibrosis and cancer[[145](#_ENREF_145)]. The discovery that it can be transactivated by LPA opens up novel research directions on the effects of LPA in the lung.

**LPA effects on leukocytes**

In addition to the different immunomodulatory effects of ATX/LPA in stromal cells presented above, including the modulation of barrier functions of endothelial cells, vascular remodelling and cytokine secretion from epithelial cells, LPA has been reported to have direct effects on leukocytes. As with every cell in the body, primary alveolar leukocytes all express some LPA receptors (Table 1)[[31](#_ENREF_31)].

***Granulocytes***

Eosinophils have a unique contribution in initiating inflammatory and adaptive responses due to their bidirectional interactions with DCs and T cells and to their large panel of secreted cytokines and soluble mediators[[146](#_ENREF_146)]. They are mainly involved in parasite infections and allergic diseases; however, they have significant contributing roles in a wide range of other diseases[[147](#_ENREF_147)]. LPA exhibits chemotactic activity towards human peripheral blood eosinophils, shown to express LPAR1,3 mRNA, both *in vitro*[[148](#_ENREF_148)] and in the lung *in vivo*[[149](#_ENREF_149)]. Moreover, LPA re-arranges the eosinophil actin cytoskeleton, upregulates the expression of the integrin CD11b on their surface and stimulates Ca++ mobilisation and the production of reactive oxygen intermediates[[148](#_ENREF_148)]. The observed effects of LPA in eosinophils, shown pharmacologically to be mediated through LPAR1/3-Gi/o, are comparable to those obtained from other well-known chemoattractants such as C5α, PAF, CCL5, CCL11 and CCL13[[148](#_ENREF_148)], suggesting that LPA is a potent chemoattractant and activator of eosinophils.

Like eosinophils, human peripheral blood neutrophils, the most abundant granulocytes or leukocytes in the blood and the major effectors of acute inflammation[[150](#_ENREF_150)], respond to LPA by calcium flux and oxidative burst[[151](#_ENREF_151)]. LPA has also been reported to stimulate neutrophil degranulation[[152](#_ENREF_152)] and to promote neutrophil chemotaxis both *in vitro*[[153](#_ENREF_153)] and in the lung *in vivo*[[149](#_ENREF_149)]. Despite the limited studies and some conflicting reports[[154](#_ENREF_154)], it seems that LPA might have a role in neutrophilic responses and therefore in acute inflammation and lung injury.

***Macrophages***

Macrophages(MΦs), the most plastic cells of the haematopoietic system and the predominant resident immune cells in the lungs, have well-established roles in lung homoeostasis, tissue repair and immunity[[155](#_ENREF_155),[156](#_ENREF_156)]. Peripheral blood monocytes and/or tissue MΦs in mice, humans and rats all express some of the receptors for LPA; however, different publications, all based on RT-PCR data, report different expression patterns[[31](#_ENREF_31),[157-159](#_ENREF_157)], while bone marrow-derived MΦs were found to express all 5 major LPARs (unpublished data and[[83](#_ENREF_83)]). All transformed monocytic cell lines (MM6, RAW, THP-1, J774A.1) have also been reported to express LPA receptors[[160-162](#_ENREF_160)]. However, a systematic study on LPAR expression during the differentiation of monocyte to MΦs and upon inflammatory activation of primary, resident or immigrating cells is still lacking.

The same is true for ATX, as there are limited reports on ATX expression in monocytes/MΦs. LPS-stimulated transformed monocytic THP-1 cells have been reported to express ATX mRNA[[163](#_ENREF_163),[164](#_ENREF_164)] that is inhibited by pharmacological inhibitors of PKR, JNK and p38 MAPK[[164](#_ENREF_164)]. More importantly, alveolar MΦs from BLM-challenged fibrotic mice and human IPF patients have been shown with immunocytochemistry to express ATX[[23](#_ENREF_23)]. Macrophage ATX expression has also been noted in LC patients (unpublished data). Therefore, ATX expression from inflammatory or tumour-associated MΦs would stimulate local LPA production and its plethora of effects.

As far as the effects of LPA on MΦs themselves are concerned, LPA has been shown to protect murine primary peritoneal MΦs from apoptosis induced by serum deprivation, suggested to be mediated through PI3K[[165](#_ENREF_165)]. By contrast, LPA has no effect on macrophage proliferation[[165](#_ENREF_165)]. In THP-1 cells, LPA significantly increases reactive oxygen intermediates (ROI) production and prostaglandin E2 release[[161](#_ENREF_161)]. In RAW264.7 cells, LPA stimulates cell survival and induces monocyte lipid accumulation from oxidised low-density lipoprotein (ox-LDL), suggested to be mediated through PPARγ activation, and CD36 scavenger receptor uptake[[166](#_ENREF_166)]. LPA in J774A.1 cells also induces ox-LDL uptake[[162](#_ENREF_162)] and IL-1 expression[[167](#_ENREF_167)]. In MM6 cells, LPA has been reported to increase cytosolic Ca++, a second messenger of cellular activation that regulates diverse biological processes such as the secretion of cytokines and the expression of proinflammatory genes[[160](#_ENREF_160)]. Therefore, the limited studies on the effects of LPA in MΦs point to a potential pro-survival and pro-inflammatory role of the ATX/LPA axis, although more studies are needed, especially in primary cells, employing flow cytometry analysis of surface expression markers.

***DCs***

DCs are the most potent antigen-presenting cells specialised in the activation of naive T-lymphocytes and the initiation of the immune response and are among the major immunological cells residing in the lungs. LPA (50 μmmol/L) has been shown to affect the differentiation of peripheral circulating monocytes to DCs *in vitro*, which, however, have impaired immunological functions[[168](#_ENREF_168)]. Interestingly, LPC, the precursor of LPA and the substrate of ATX, has also been reported to promote dendritic cell maturation from monocytes, with the ability to stimulate IL-2 and IFN-γ production by allogeneic T lymphocytes[[169](#_ENREF_169)]. Notably, LPC released from apoptotic cells has also been suggested to be a potent chemotactic signal to MΦs *via* the phagocyte receptor G2A[[170](#_ENREF_170),[171](#_ENREF_171)].

Both mature and immature DCs express LPARs[1-3] but respond differently to LPA[[172](#_ENREF_172)]. LPA induces calcium flux, actin polymerisation and chemotaxis of immature DCs, whereas LPS-exposed mature DCs are insensitive. However, LPA inhibits, in a PTX-insensitive manner, the secretion of IL-12, and TNF and enhances the secretion of IL-10 from LPS-exposed mature DCs[[172](#_ENREF_172)]. Other groups have suggested a predominance of LPAR2 in DCs[[173](#_ENREF_173),[174](#_ENREF_174)] and reported that LPA induces IL-6 and IL-8 in maturing DCs[[174](#_ENREF_174)] but does not have these effects in mature DCs[[174](#_ENREF_174)]. Moreover, LPA does not exert a dominant effect on the ability of DCs to stimulate Th cell polarisation but does inhibit LPS-induced responses[[173](#_ENREF_173)]. Similarly, unsaturated LPA species (as opposed to saturated ones) are able to induce the chemotaxis of immature but not LPS-exposed mouse bone marrow-derived DCs *in vitro*, attributed to LPAR3[[175](#_ENREF_175)]. Finally, LPAR2-/-DCs have been reported to induce the proliferation of and IL-13 secretion in co-cultured T cells more so than in wild-type DCs, suggesting that LPAR2 in DCs has a suppressive role in the Th2 inflammation and airway response to allergens[[58](#_ENREF_58)]. Indeed, adoptive transfer of LPAR2-/-DCs pulsed with ovalbumin (OVA) enhances lung inflammation in comparison with OVA-pulsed wild-type DCs[[58](#_ENREF_58)]. However, a different group reported that heterozygous LPAR2 KO mice are partially protected from allergic inflammation[[57](#_ENREF_57)].

Taken together, and despite the limited available information and observed discrepancies, LPA seems to have a pro-inflammatory role in immature DCs, promoting inflammatory cytokine secretion and their chemotaxis and maturation, whereas in mature cells, LPA has a potential anti-inflammatory role, which might depend on the allergen.

***Lymphocytes***

Lymphocytes, the major cellular components of the adaptive immune response, all express some LPARs, as assessed with RT-PCR and in some rare case with western blots, but the results have been somewhat conflicting[[176-178](#_ENREF_176)]. Moreover, the presence of recently identified LPARs remains to be examined. In one such study, LPAR5 was reported to be highly expressed in gastrointestinal lymphocytes[[179](#_ENREF_179)]. As with all cells, future FACS studies on primary cells are needed to clarify the constitutive and inducible regulation of LPA receptor expression in T- and B-cell subsets. By contrast, no ATX mRNA expression was detected in splenocytes, thymocytes and CD8+ T-cells, even upon their activation with phorbol myristate acetate (PMA) (unpublished data and[[83](#_ENREF_83)]), consistent with the expression of other NPP family members in these cells[[3](#_ENREF_3)]. However, a human transformed pre-B-cell line (Nalm-6) was reported to express and secrete ATX, the effects of which on LPA production were suggested to be counteracted by the simultaneous expression of LPP1[[180](#_ENREF_180)].

LPA stimulates Jurkat leukemic T cells, leading to calcium flux and proliferation[[181](#_ENREF_181)]. Similarly, immortalised human B lymphoblasts respond to LPA with calcium flux, MAPK activation, and immunoglobulin production[[182](#_ENREF_182)]. However, there is a wide variety of responses to LPA regarding calcium flux depending on the cell line[[183](#_ENREF_183)].

Jurkat cells also respond to LPA *in vitro* by migrating through a matrigel membrane, an experimental connective tissue-like barrier[[184](#_ENREF_184)]. As mentioned above, and despite opposing findings[[185](#_ENREF_185)], LPA produced locally by HEV-ATX has been shown to stimulate the polarisation, motility and transendothelial migration of naïve T-cells[[115](#_ENREF_115),[116](#_ENREF_116)], and ATX/LPA has also been shown to affect endothelial permeability and thus the regulation of lymphocyte influx[[112](#_ENREF_112),[113](#_ENREF_113)]. Similar mechanisms may also exist in B-cells, as LPA has been shown to enhance LFA-mediated adhesion of murine follicular and marginal zone B-cells to ICAM-1 *in vitro,* similar to the effects of CXCL12 and CXCL13 chemokines and PMA[[186](#_ENREF_186)], suggesting that LPA may be involved in B-cell homing within the spleen.

LPA has also been reported to inhibit the apoptosis induced by antibodies to Fas, CD2 or CD3/CD28 of a human T lymphoblast cell line (Tsup-1), accompanied with the suppression of the apoptotic protein Bax[[187](#_ENREF_187)]. Similarly, LPA protects B-cell lines (BJAB and I-83) and primary chronic lymphocytic leukaemia cells from apoptosis. By contrast, LPA does not protect normal B-cells from fludarabine- and etoposide-induced apoptosis[[188](#_ENREF_188)]. LPA protects transformed pre-B cells (Nalm-1) from spontaneous or staurosporine-induced apoptosis[[180](#_ENREF_180)]. However, indirect pro-apoptotic effects of LPA on T-cells have been reported through the upregulation of Fas in ovarian cancer cells[[189](#_ENREF_189),[190](#_ENREF_190)].

LPA, surprisingly in a PTX-insensitive manner, suppresses IL-2 secretion from anti-CD3/CD28-activated CD4+ T-cells, but not similarly activated CD8+ cells or non-activated CD4+ cells[[176](#_ENREF_176)], although opposing results on IL-2 expression have been reported in Jurkat cells[[181](#_ENREF_181)]. By contrast, LPA was reported to enhance PMA-induced IL-13 promoter activity and gene expression in Jurkat and human peripheral blood CD4+ lymphocytes *in vitro*, but only under submaximal conditions and not by itself[[178](#_ENREF_178)]. Therefore, it seems that LPA might co-stimulate the polarisation to Th2 responses, although both cultured human Th1 and Th2 cells responded to LPA by inducing calcium flux and chemotaxis[[191](#_ENREF_191)].

***Platelets and mast cells***

Platelets are the principle effector cells in haemostasis and have additional major functions in inflammation, vascular integrity, and tissue repair. In the lungs, platelets contribute to pulmonary vascular barrier function and are required for defence against pulmonary haemorrhage[[192](#_ENREF_192)]. Increased coagulation and depressed fibrinolysis, as a consequence of the activation of circulating quiescent platelets, result in diffuse alveolar fibrin deposition, which serves to amplify pulmonary inflammation, while the interaction of platelets with endothelial cells and leukocytes is critical in the pathogenesis of ALI[[193](#_ENREF_193)]. Moreover, asthma is associated with a procoagulant state in the bronchoalveolar space, further aggravated by impaired local activities of the anticoagulant protein C system and fibrinolysis[[194](#_ENREF_194)]. ATX has been reported to bind to integrins β1 and β3 on the surface of platelets[[195](#_ENREF_195)], consistent with the integrin-mediated binding of ATX to lymphocytes[[112](#_ENREF_112)] and insights from the crystal structure[[196](#_ENREF_196)]. ATX was found to inhibit fibrinogen-dependent platelet aggregation and enhance their thrombin-induced LPA production[[195](#_ENREF_195)], whereas systemic genetic overexpression of ATX in mice *in vivo* resulted in bleeding diathesis and attenuation of thrombosis[[29](#_ENREF_29)]. On the other hand, LPA levels in serum prepared from platelet-rich plasma are 5-10-fold higher than in platelet-poor plasma[[197](#_ENREF_197)], indicating that activated platelets are a major source of LPA in the circulation. Therefore, the recruitment of circulating ATX to the platelet surface could enhance the local LPA production during clotting, which in turn would exert its numerous effects in adjacent cells. The effects of LPA on platelets, which express the five major LPARs, include shape change, fibronectin matrix assembly, platelet-monocyte co-aggregate formation and synergism with other platelet agonists, such as epinephrine and adenosine diphosphate, and have been reviewed elsewhere[[135](#_ENREF_135)].

Mast cells, potent effector cells of the innate immune system, are mainly implicated in pro-inflammatory responses to allergens but can also contribute to protection against pathogens[[198](#_ENREF_198)]. LPA potently induces the proliferation and differentiation of mast cells, which also express LPARs[[199-201](#_ENREF_199)], providing a synergistic signal with the major mast cell growth factor, stem cell factor (SCF)[[199](#_ENREF_199)]. LPA strongly enhances the formation of secretory granules and the cell-surface expression of kit[[199](#_ENREF_199)]. Mast cells primed with IL-4 respond to LPA by the production of chemokines, including macrophage inflammatory protein (MIP)-1b, monocyte chemotactic protein (MCP)-1, and IL-8[[200](#_ENREF_200)]. Moreover, LPA induces histamine release from rat peritoneal mast cells and mouse skin fragments[[202](#_ENREF_202)], and the subcutaneous administration of LPA increases plasma exudation in the skin[[203](#_ENREF_203)]. Thus, LPA may both support reactive mastocytosis (a feature observed in several disease states) and serve as an amplifier of mucosal inflammation, in which mast cell hyperplasia is mediated by a Th2 cytokine-based mechanism.

**The ATX/LPA axis in lung pathophysiology**

***ALI***

ALI, or mild acute respiratory distress syndrome (ARDS), is a diffuse heterogeneous lung injury characterised by arterial hypoxemia, respiratory failure and low lung compliance, non-cardiogenic pulmonary oedema, and widespread capillary leakage leading to alveolar flooding[[204](#_ENREF_204)]. Bacterial or viral pneumonia is the most common cause of ALI and ARDS, but sepsis due to non-pulmonary infections, the aspiration of gastric contents, major trauma with shock and/or mechanical ventilation also commonly precipitate this type of injury[[204](#_ENREF_204)]. Altered permeability of epithelial and endothelial barriers, inappropriate accumulation of leukocytes and uncontrolled activation of coagulation pathways are among the main pathophysiological concepts in ALI and ARDS[[204](#_ENREF_204)], and LPA seems to affect all of them.

Elevated ATX/LPA levels have been detected in an animal model of LPS-induced ALI (unpublished data[[34](#_ENREF_34)]), and the genetic deletion of LPAR1 or LPAR2 has been reported to moderately attenuate inflammation but not the epithelial/vascular leakage induced by LPS[[62](#_ENREF_62),[205](#_ENREF_205)]. However, both pulmonary inflammation and vascular leakage in response to BLM are entirely abrogated in the absence of LPAR1 or LPAR2[[31](#_ENREF_31),[42](#_ENREF_42)]. The partial protection of LPAR1- and LPAR2-null mice and attenuation of inflammation from LPS-induced lung injury are consistent with the observed LPA stimulation of IL-8 secretion from pulmonary epithelial cells *in vitro*[[45](#_ENREF_45),[46](#_ENREF_46)]. IL-8 is the major chemoattractant of neutrophils[[206](#_ENREF_206)], which in turn predominate LPS-induced inflammatory responses in ALI/ARDS[[207](#_ENREF_207)]. LPA can also directly induce neutrophil chemotaxis *in vitro*, as well as neutrophil activation and degranulation[[153](#_ENREF_153),[208](#_ENREF_208)]. However, the exogenous administration of LPA to the lungs has been reported to both increase and decrease neutrophilic accumulation and LPS-induced lung injury[[149](#_ENREF_149),[209](#_ENREF_209)], highlighting the importance of assessing endogenous local control mechanisms of LPA production. Conclusive insights are expected to be obtained by the ongoing conditional genetic deletion of ATX and an examination of LPS-induced ALI severity, as well as by the creation of conditional knockouts for LPARs.

The ability of LPA to induce integrin-dependent activation of TGF-β in pulmonary epithelial cells[[43](#_ENREF_43)] points to another pro-inflammatory role of LPA. TGF-β activation has been reported to disrupt the alveolar epithelial barrier integrity, leading to alveolar flooding[[210](#_ENREF_210),[211](#_ENREF_211)]. Moreover, TGF-β is known to induce the expression of plasminogen activator inhibitor-1 (PAI11), a major inhibitor of fibrinolysis, whereas fibrin deposition is a hallmark of ALI[[212](#_ENREF_212)]. Therefore, by promoting TGF-β activation in the pulmonary epithelium, LPA could indirectly promote epithelial barrier disruption and inhibit fibrinolysis in an environment of high TGF-β content and in this manner promote lung injury.

Moreover, LPA has been shown to increase the permeability of endothelial systems[[106-108](#_ENREF_106)], which could facilitate the entry of inflammatory cells in the alveolar space, although there is much controversy on the issue[[109-111](#_ENREF_109)]. *In vivo*, genetic deletion of LPAR1 or LPAR2 attenuated the BLM-induced vascular leak[[31](#_ENREF_31),[42](#_ENREF_42)], indicating that LPA signalling indeed disrupts vascular endothelial barrier integrity, in turn promoting the infiltration of inflammatory cells and possibly ALI.

***Idiopathic pulmonary fibrosis***

Idiopathic pulmonary fibrosis**(**IPF) is a chronic, progressive, fibrotic form of diffuse lung disease that occurs mainly in older adults and is characterised by a progressive worsening of lung functions and a poor prognosis[[213](#_ENREF_213),[214](#_ENREF_214)]. Clinically, IPF is characterised by progressive, exertional dyspnoea and non-productive cough, worsening of pulmonary function and radiographically evident interstitial infiltrates (honeycombing). Histologically, IPF is associated with the appearance of Usual Interstitial Pneumonitis (UIP), which is characterised by patchy subpleural and/or paraseptal interstitial fibrosis alternating with areas of mild inflammation and normal lung. The hallmark of IPF/UIP is the presence of hyperplastic reparative epithelium overlying distinctive fibroblastic foci that deposit exuberant ECM components, leading to thickening of alveolar septa and the collapse of normal lung architecture[[213](#_ENREF_213)]. Although the aetiology and pathogenesis of IPF remain poorly understood, a number of conditions and risk factors are weakly associated with the disease: cigarette smoking, occupational/environmental factors, gastro-oesophageal reflux, latent viral infections, and age/gender/genetic predisposition[[213](#_ENREF_213)]. To study the pathogenetic mechanisms that govern disease activation and perpetuation, a number of animal models have been developed that reproduce the clinical features of IPF, although it remains unclear if they truly replicate the chronic and progressive forms of the disease[[215](#_ENREF_215)]. Among them, the BLM model is the most widely used and best characterised model and is responsible, together with the site-specific and/or temporal overexpression or ablation of candidate pathogenic genes, for most of our knowledge concerning IPF pathogenesis[[215](#_ENREF_215),[216](#_ENREF_216)]. In this context, current research suggests that the mechanisms driving IPF reflect abnormal, deregulated wound healing in response to repetitive pulmonary epithelial damage, involving increased vascular permeability of the endothelium, extravascular coagulation, TGF-β activation, fibroblast persistence and differentiation to myofibroblasts, leading to exaggerated collagen deposition[[214](#_ENREF_214),[217](#_ENREF_217)].

Deregulated phospholipid homeostasis seems to be an integral component of pulmonary fibrosis pathogenesis. Early studies have reported the altered composition of phospholipids in IPF[[218-221](#_ENREF_218)], whereas experiments with genetically modified mice implicate proinflammatory mediators, such as prostaglandins, thromboxanes and leukotrienes, in the pathogenesis of BLM-induced pulmonary fibrosis[[222-224](#_ENREF_222)]. These mediators derive from arachidonic acid, which is the product of phosphatidylcholine (PC) hydrolysis by PLA2[[225](#_ENREF_225)], with concurrent release of LPC, the substrate of ATX.

ATX shows strong staining intensity within the alveolar epithelium immediately adjacent to fibroblastic foci and lower intensity in interstitial MΦs, fibroblast-like cells and in areas of bronchiolar metaplasia in IPF lung samples[[23](#_ENREF_23)]. A similar expression profile was also demonstrated in fibrotic non-specific interstitial pneumonia (fNSIP) samples, a histopathological pattern sharing common pathologic features with UIP. By contrast, ATX has minimal expression within the inflammatory components of cellular NSIP lung samples and in areas of loose connective tissue, called Masson bodies, representing the pathogenetic hallmark of cryptogenic organising pneumonia (COP). The two latter pathologies represent two forms of idiopathic interstitial pneumonias (IIPs) with favourable prognoses and excellent treatment response to corticosteroids, indicating that ATX upregulation is closely associated with more progressive and irreversible forms of pulmonary fibrosis, such as IPF/UIP and fNSIP[[23](#_ENREF_23)]. In the mouse BLM-induced fibrotic lung, high constitutive ATX expression has been noted in the bronchial epithelium, the major source of ATX in the lungs, as well as in inflammatory alveolar MΦs, resulting in increased ATX BALF levels[[23](#_ENREF_23),[31](#_ENREF_31)]. However, the increase in ATX BALF closely follows BALF total protein levels, suggesting that additional ATX could be extravasated from the circulation. As a consequence of the increased ATX levels, LPA levels are also increased in the BALFs of fibrotic mouse and human lungs[[23](#_ENREF_23),[31](#_ENREF_31)], even at early time points[[41](#_ENREF_41)]. Pharmacological inhibition of ATX results in the attenuation of LPA levels, confirming that ATX is solely responsible for LPA production in the lung[[23](#_ENREF_23)].

Conditional genetic deletion of ATX from the majority of bronchial epithelial cells or MΦs results in the attenuation of BLM-induced pulmonary inflammation and fibrosis, as indicated by the improved lung architecture, reduced inflammation and collagen production, highlighting the importance of local pulmonary ATX production and verifying ATX as a major contributor to disease pathogenesis[[23](#_ENREF_23)]. Likewise, genetic deletion of either LPAR1 or LPAR2 also results in attenuation of the BLM-induced disease[[31](#_ENREF_31),[42](#_ENREF_42)], suggesting that the ATX/LPA axis is a candidate for therapeutic interventions. Indeed, pharmacological inhibition of either ATX or LPAR1 results in attenuation of BLM-induced disease symptoms[[23](#_ENREF_23),[95](#_ENREF_95)], and pharmacological inhibition of LPAR1/3 alleviates radiation-induced pulmonary fibrosis[[226](#_ENREF_226)]. However, the relative contribution of each receptor to pulmonary inflammation and fibrosis will have to be evaluated in head-to-head studies, with animals of the same genetic background and in comparison with littermate controls.

The apoptosis of alveolar epithelial cells is found both in the lungs of IPF patients and in animal models of the disease, correlating with the increased expression of “death-inducing” TNF/TNF receptor family members and various apoptotic markers[[227](#_ENREF_227)]. Furthermore, induction of epithelial apoptosis is sufficient to initiate a fibrotic response in animal models[[228](#_ENREF_228)], whereas genetic or pharmacological blocking of apoptotic signals can prevent a BLM-induced fibrotic response[[229](#_ENREF_229)]. These observations have contributed significantly to the prevailing hypothesis that the mechanisms driving IPF reflect abnormal, deregulated wound healing in response to multiple sites of on-going alveolar epithelial injury[[214](#_ENREF_214)]. LPAR1- and LPAR2-null mice, which are both protected from the development of the BLM-induced disease, exhibit significantly reduced numbers of TUNEL+ epithelialcells[[31](#_ENREF_31),[42](#_ENREF_42)], suggesting that LPA promotes epithelial apoptosis upon lung injury. In agreement, LPA signalling through LPAR1 was reported to induce anchorage-dependent apoptosis in cultured normal human bronchial epithelial cells[[41](#_ENREF_41)], although the intracellular mechanisms and the role of cell-to-cell and cell-to-ECM contacts need to be defined. Interestingly, BLM-induced, epithelial cells undergoing apoptosis *in vivo* express TNF[[230](#_ENREF_230)], which has been suggested to stimulate ATX expression[[83](#_ENREF_83),[231](#_ENREF_231)]. Therefore, stimulation of apoptosis in epithelial cells from BLM in mice or unidentified insults in humans can stimulate TNF expression, which in turn promotes ATX expression and the local production of LPA, perpetuating the damage. Moreover, the critical involvement of the cytoskeleton in epithelial apoptosis and BLM-induced disease[[232](#_ENREF_232)], as well as the reported ability of LPA to rearrange the cytoskeleton of bronchial epithelial cells[[43](#_ENREF_43)], argue for an additional intracellular pathway mediating the effects of LPA in epithelial cells.

Increased fibroblast accumulation, due to increased fibroblast proliferation and migration and to decreased fibroblast apoptosis, is a hallmark of IPF pathogenesis[[233](#_ENREF_233)]. Consistent with a role for ATX/LPA in disease pathogenesis, LPA stimulates lamellipodia protrusion and fibroblast cell migration[[74](#_ENREF_74),[93](#_ENREF_93)]. Moreover, LPA acts as a chemoattractant for primary mouse lung fibroblasts, and genetic deletion of LPAR1 attenuates lung fibroblast chemotaxis induced by BALF from fibrotic mice, proving that LPA is the predominant fibroblast chemoattractant in the airspaces of BLM-treated mice[[31](#_ENREF_31)]. In humans, BALFs from IPF patients with elevated LPA levels induce fibroblast chemoattraction, in contrast with BALF from healthy individuals, an effect abrogated by an LPAR1 inhibitor[[31](#_ENREF_31)], while LPA also induces the chemotaxis of human lung fibroblasts *in vitro*[[95](#_ENREF_95)]. Thus, the chemotactic effect of LPA on fibroblasts could be a determining factor for the development of IPF. Moreover, the ability of LPA to promote the proliferation of lung fibroblasts *in vitro* [[81](#_ENREF_81),[226](#_ENREF_226)] and its ability to completely suppress the apoptosis of adherent primary mouse lung fibroblasts[[41](#_ENREF_41)] or non-lung fibroblasts[[99](#_ENREF_99)] further indicate that LPA promotes pathologic fibroblast accumulation in the airspaces. Chronic fibrosis is characterised by the persistence of myofibroblasts, which promote tissue remodelling by expressing fibrogenic and extracellular mediators[[234](#_ENREF_234)]. LPA, through LPAR2, induces the differentiation of human lung fibroblasts to myofibroblasts by inducing αSMA, FN, collagen I a2 and TGF-β1 protein expression[[42](#_ENREF_42)], whereas LPA-mediated differentiation of peritumor fibroblasts to myofibroblasts in the liver has also been shown[[96](#_ENREF_96)]. Therefore, the ATX/LPA axis is also implicated in pulmonary fibrosis through fibroblast recruitment, proliferation and differentiation into myofibroblasts.

It is well accepted that inflammatory mediators play a role both in the initiation and progression of pulmonary fibrosis, despite the failure of anti-inflammatory treatments[[214](#_ENREF_214)]. A prominent effect of LPA in epithelial cells is the production of IL-8[[45](#_ENREF_45),[46](#_ENREF_46)], a potent neutrophil chemoattractant, suggesting that the observed increased levels of LPA in the early phases on BLM-induced lung injury[[41](#_ENREF_41)] can promote the initiation of the inflammatory cascade. LPA stimulation of ECs also result in the upregulation of inflammatory mediators, such as IL-1β, IL-8 and MCP-1[[117-119](#_ENREF_117)], and adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin, that might enhance interactions with leukocytes, facilitating their extravasation[[119](#_ENREF_119),[121](#_ENREF_121),[123](#_ENREF_123)]. Moreover, EC-bound-ATX has been shown to be an adhesive substrate for homing lymphocytes[[112](#_ENREF_112)], whereas LPA stimulates the polarisation, motility and transendothelial migration of naïve T-cells[[112](#_ENREF_112),[115](#_ENREF_115)]. Genetic deletion of LPAR1 or LPAR2 results in the attenuation of vascular leakage upon BLM treatment[[31](#_ENREF_31),[42](#_ENREF_42)], whereas LPA increases the permeability of an endothelial layer consisting of human pulmonary arterial ECs[[106](#_ENREF_106)]. Therefore, LPA can also affect the inflammatory component of pulmonary fibrosis through the stimulation of cytokine production, through the modulation of the endothelial barrier and through the promotion of inflammatory cells extravasation.

TGF-β is the major pro-fibrotic factor in several organs. In the lung, it is produced from a wide variety of cells, including alveolar MΦs and neutrophils, activated epithelial and endothelial cells, fibroblasts and myofibroblasts[[235](#_ENREF_235)]. When activated, TGF-β is a pleiotropic growth factor with chemotactic and proliferative properties, inducing macrophage and fibroblast recruitment and the secretion of a number of pro-inflammatory and pro-fibrotic cytokines[[235](#_ENREF_235)]. TGF-β levels are increased in the BALFs of fibrotic lungs in both BLM-challenged mice and human IPF patients[[236](#_ENREF_236)], whereas adenoviral delivery of TGF-β is sufficient to promote fibrosis in the absence of inflammation[[237](#_ENREF_237),[238](#_ENREF_238)]. LPA induces TGF-β expression in pulmonary fibroblasts *in vitro*[[42](#_ENREF_42)], and stimulation with LPA leads to increased TGF-β activity through integrin avβ6 in bronchial epithelial cells[[43](#_ENREF_43)] and through integrin avβ5 in smooth muscle cells[[143](#_ENREF_143)]. Therefore, LPA can indirectly promote pro-fibrotic responses by potentiating TGF-β activation and possibly expression.

HGF is a growth factor for epithelial and endothelial cells. It is activated only in injured tissues, the lungs included, and its expression increases post-lung injury[[239](#_ENREF_239)]. In patients with IPF, HGF levels in BALF are increased compared to healthy subjects; however, fibroblasts from IPF patients express less HGF and have a decreased activation capability of pro-HGF[[239](#_ENREF_239)]. In fact, the exogenous administration of HGF alleviates fibrosis and induces lung repair[[72](#_ENREF_72),[239](#_ENREF_239)]. The protective effect of HGF has been suggested to be mediated through the restriction of myofibroblast recruitment, the promotion of proliferation and the survival of lung epithelial and endothelial cells[[72](#_ENREF_72)] and the induction of myofibroblast apoptosis[[239](#_ENREF_239)]. Compared to HGF, LPA has the opposite effects on c-Met, the basic receptor of HGF, in normal human bronchial epithelial cells: LPA induces c-Met serine phosphorylation and its redistribution to the cell membrane, and it is also capable of abrogating HGF-induced c-Met activation[[70](#_ENREF_70)]. Therefore, LPA could indirectly have profibrotic consequences through the inhibition of HGF signalling.

Conclusively, the ATX/LPA axis may promote pulmonary fibrosis in several ways, such as the induction of vascular leakage, fibroblast migration, fibroblast differentiation, epithelial cell apoptosis, inflammatory cell influx, TGF-β signalling and HGF signalling suppression; however, anti-inflammatory effects have also been reported.

***Asthma***

Asthma, a common chronic inflammatory lung disease that leads to airflow obstruction[[53](#_ENREF_53)], has an onset usually early in life in association with sensitisation to common aeroallergens. Asthma can be divided into phases, such as acute or chronic, severe or not severe, with the pathophysiology of the disease differing among the distinct phases[[240](#_ENREF_240)]. Acute asthma, or allergic asthma, is triggered by allergens that lead to IgE reactions and the activation of mast cells located beneath the mucosa of the lower airways of the respiratory tract. Mast cells release their granules, thereby stimulating mucus production and airway smooth muscle contraction, which constricts the airway, causing the characteristic asthmatic wheezing. Furthermore, a Th2 lymphocyte response is also a predominant feature of acute asthma and, together with mast cells, lead to cytokine secretion, thus mediating inflammation in the form of eosinophil and other leukocyte recruitment[[240](#_ENREF_240),[241](#_ENREF_241)]. Eosinophils, key players in asthma, further promote inflammation and enhance airway hyper-responsiveness and airflow obstruction[[240](#_ENREF_240)]. Chronic asthma is a result of the inflammation obtained from acute asthma. The acquired chronic inflammation leads to mucosal epithelium hypersensitivity so that even simple environmental agents such as smoke can evoke asthma attacks. In persistent asthma, the lung epithelium is injured, and airway smooth muscle becomes hypertrophic[[242](#_ENREF_242)]; both these tissues secrete inflammatory mediators[[240](#_ENREF_240)]. Further changes in asthmatic lungs include mucus gland hypertrophy, collagen deposition and thickening of the basal lamina, increased matrix deposition and thickening throughout the airway walls[[242](#_ENREF_242),[243](#_ENREF_243)], all of which contribute to airflow obstruction.

The involvement of the ATX/LPA axis in asthma was first established when it was shown that allergen exposure leads to an increase in the LPA levels in the BALF of humans[[56](#_ENREF_56)] and a mouse model of asthma[[57](#_ENREF_57)]. Similar results were obtained more recently: allergen challenge in asthmatic patients leads to an increase in LPA levels, accompanied by an increase in BALF ATX levels[[244](#_ENREF_244)]. In a triple allergen asthmatic mouse model, ATX expression is localised in terminal bronchial epithelial cells and alveolar MΦs[[244](#_ENREF_244)]. Transgenic mice overexpressing ATX in the liver, which leads to systemic 100%-200% increases in the ATX levels in the serum[[29](#_ENREF_29)], develop increased pulmonary inflammation and higher levels of IL-4 and IL-5 in lung homogenates and BALFs upon triple allergen challenge[[244](#_ENREF_244)]. Accordingly, heterozygous ATX full knockout mice, with a 50% reduction of systemic/serum ATX and LPA levels[[28](#_ENREF_28)], exhibit reduced inflammation and IL-4/5 levels upon triple allergen challenge[[244](#_ENREF_244)], indicating a major role for ATX/LPA in asthma pathogenesis. Pharmacological treatment with an ATX inhibitor attenuates disease development[[244](#_ENREF_244)], establishing ATX as a potential drug target in the treatment of asthma.

Allergic inflammation in LPAR2-/- knockout mice is also attenuated[[244](#_ENREF_244)]. Surprisingly, heterozygous LPAR1 or LPAR2 knockout mice have also been reported to develop distinct aberrant responses upon *Schistosoma mansoni* egg sensitisation and challenge[[57](#_ENREF_57)]. However, and in a different mouse asthma model, using systemic immunisation with ovalbumin and alum, LPAR2-/- knockout mice showed greater allergic sensitisation, higher eosinophilia and Th2 inflammation[[58](#_ENREF_58)]. These observed discrepancies could be due to the different allergens utilised and/or the genetic backgrounds of the experimental and control groups of mice, urging further comparative, genetic or pharmacological studies.

As mentioned above, LPA has been reported to have mainly pro-inflammatory effects in pulmonary cell types and pulmonary inflammation, but anti-inflammatory effects have also been reported. In support of a pro-inflammatory role of the ATX/LPA axis in the development of asthma, LPA stimulates IL-8 secretion from HBEpCs *in vitro*[[45](#_ENREF_45),[46](#_ENREF_46)] and IL-8 levels are elevated in mouse lungs after intratracheal LPA administration[[45](#_ENREF_45)]. IL-8 is a major chemoattractant for neutrophils and eosinophils[[245](#_ENREF_245)], and its levels are elevated in the BALFs of asthma patients[[245](#_ENREF_245)]. In accordance, intratracheal administration of LPA stimulates neutrophil infiltration in mice[[57](#_ENREF_57)] and both eosinophil and neutrophil infiltration in guinea pigs[[149](#_ENREF_149)], although no significant association was found between LPA and eosinophil recruitment in humans[[56](#_ENREF_56)]. However, LPA has been shown to act chemotactically on human eosinophils *in vitro*[[148](#_ENREF_148)]. Eosinophils have a primary role in allergic inflammation, releasing upon activation cytokines and leukotrienes and their highly inflammatory granule components injuring the airway and causing persistent inflammation[[240](#_ENREF_240)]. The mast cell is another important cell type in the initiation and perpetuation of allergic inflammation through the release of leukotrienes and cytokines[[240](#_ENREF_240)], whereas the release of histamine from their granules activates the endothelium and increases blood vessel permeability. LPA potently induces mast cell proliferation and differentiation, formation of their secretory granules[[199](#_ENREF_199)], chemokine production[[200](#_ENREF_200)] and histamine release[[202](#_ENREF_202)]. Therefore, the LPA-mediated chemoattraction of eosinophils and mast cell activation, the impairment of EC barriers[[107-109](#_ENREF_107)] and the enhancement of EC-leukocyte interactions[[120-123](#_ENREF_120)] can all be deteriorating factors in the pathogenesis of asthma.

LPA has also been reported to stimulate lymphocyte homing[[112](#_ENREF_112),[116](#_ENREF_116)] and TSLP and CCL20 secretion from HBEpCs *in vitro*[[50](#_ENREF_50)]. TSLP is produced from the airway epithelium upon TLR activation and acts on dendritic cell motility and activation[[53](#_ENREF_53),[246](#_ENREF_246)], leading to the Th2 polarisation[[53](#_ENREF_53)] that is crucial in asthma. CCL20 contributes to airway inflammation in mouse models of asthma[[52](#_ENREF_52)] and is known to act on the recruitment of DCs and T cells on the airway and other mucosal surfaces[[52](#_ENREF_52),[247](#_ENREF_247),[248](#_ENREF_248)]. Therefore, these results suggest that ATX/LPA could also regulate adaptive immune responses in asthma.

Several other findings implicate LPA in other aspects of asthma. LPA is capable of promoting the proliferation of airway smooth muscle cells[[139](#_ENREF_139)] and enhancing the contraction of airway smooth muscle[[140](#_ENREF_140)], which could contribute to smooth muscle mass increase and airway hypercontractility, respectively, both of which are key features in asthma. Furthermore, by activating TGF-β in airway smooth muscle cells in an integrin αvβ5-dependent way[[143](#_ENREF_143)], LPA can again promote asthma, as TGF-β induces airway remodelling, smooth muscle thickening, ECM deposition and mucous production in an asthma model[[249](#_ENREF_249)]. Moreover, TGF-β is required for the differentiation of the Th17 cells that are linked to asthma[[250](#_ENREF_250),[251](#_ENREF_251)] and Th9[[252](#_ENREF_252)], a Th2 subtype that participates in the inflammatory and the remodelling aspect of airway allergy[[53](#_ENREF_53)]. TGF-β also drives the differentiation of fibroblasts to myofibroblasts, leading to the thickening of epithelial basal lamina and airway walls[[241](#_ENREF_241)] that follows chronic and severe asthma[[253](#_ENREF_253)]. The observed activation of TGF-β by LPA in the airway epithelium[[44](#_ENREF_44)] and smooth muscle[[143](#_ENREF_143)] could, thus, affect many aspects of the disease.

The reported exacerbated allergic (OVA) inflammation in LPAR2-/- knockout mice is correlated with an LPA-LPAR2 suppressive effect on dendritic cell activation, the subsequent T cell proliferation and Th2 allergen response[[58](#_ENREF_58)]. In support of this proposed anti-inflammatory role of LPA/LPAR2 in asthma development, LPA was found to inhibit the TNF-α/IFN-γ stimulated CCL5/RANTES[[241](#_ENREF_241),[254-256](#_ENREF_254)] production from HBEpCs *in vitro*[[59](#_ENREF_59)], whereas RANTES was found to increase in BALFs of asthmatic patients[[257](#_ENREF_257)], and the severity of asthma has been associated with a polymorphism in the promoter of the RANTES gene[[258](#_ENREF_258)]. LPA has also been shown to induce the expression of the decoy receptors for IL-13 and IL-33, IL13R2 and soluble ST2 in HBEpCs *in vitro*[[54](#_ENREF_54),[61](#_ENREF_61)]. Notably and concerning IL-13, LPA has been shown to have an opposite effect on T cells at submaximal activation, where it actually stimulates its gene expression[[178](#_ENREF_178)]. Airway IL-13, found at higher levels in BALF of asthma patients[[55](#_ENREF_55)], is implicated in asthma in many ways: it promotes survival and migration of eosinophils, activation of MΦs, mast cell maturation, permeability of airway epithelial cells, airway hyperresponsiveness, mucus production and transformation of airway fibroblasts to myofibroblasts leading to collagen deposition[[53](#_ENREF_53),[241](#_ENREF_241),[259](#_ENREF_259),[260](#_ENREF_260)]. In allergy, IL-13 is also necessary for the isotype switching of B cells from IgM to IgE, whereas it restricts the differentiation of Th17 cells, a subtype also implicated in asthma[[261](#_ENREF_261)], although these processes take place in secondary lymphoid tissues[[53](#_ENREF_53)]. IL33 is another cytokine expressed by the airway epithelium upon PRR activation that activates lung DCs and helps sustain the Th2 response in asthma[[53](#_ENREF_53),[262](#_ENREF_262)]. Therefore, LPA could attenuate asthmatic inflammation by suppressing IL-13 and IL-33 signalling. Finally, LPA has been shown to stimulate PGE2 expression from HBEpCs *in vitro*[[63](#_ENREF_63)], whereas epithelial cells from asthmatic patients cultured *in vitro* were shown to overproduce PGE2 compared to normal epithelium[[263](#_ENREF_263)]. In the lung, PGE2 is bronchoprotective and suppressive of inflammation in asthma[[64](#_ENREF_64),[262](#_ENREF_262),[264](#_ENREF_264)], although some indications that it promotes Th2 differentiation do exist[[265](#_ENREF_265),[266](#_ENREF_266)]. Therefore, the induction of PGE2 by LPA could have complex consequences, mostly protective of the pathology.

***LC***

LC is the most prevalent form of malignancy and the major cause of cancer-related deaths worldwide. The prognosis for patients with LC remains dismal, with a five-year survival rate of 14%. Current therapeutic options are limited to classical adjuvant therapy (a combination of radiation and chemotherapy with cytotoxic drugs) following surgery[[267](#_ENREF_267),[268](#_ENREF_268)]. Histopathologically, LC can be divided into two major histopathological groups: non-small-cell LC (NSCLC)[[269](#_ENREF_269)] and small-cell LC (SCLC)[[270](#_ENREF_270)]. Approximately 80% of LC are NSCLC, and they are subdivided into adenocarcinomas, squamous cell, bronchoalveolar, and large-cell carcinomas[[271](#_ENREF_271)]. SCLC, which accounts for close to 18% of all lung tumours, and large-cell neuroendocrine carcinomas both have a very high proliferative and metastatic potential. SCLC and NSCLC show major differences in histopathologic characteristics that can be explained by the distinct patterns of genetic lesions found in both tumour classes[[272](#_ENREF_272)]. The molecular origins of LC lie in complex interactions between the environment (tobacco smoke and/or inhaled carcinogens) and host genetic susceptibility. Lung tumourigenesis appears to conform to a multistep model in which 1) self sufficiency of growth signals; 2) insensitivity to anti-growth signals; 3) evasion of apoptosis; 4) increased replication potential; and 5) angiogenesis and metastasis dictate the tumorigenic process[[273](#_ENREF_273)].

ATX was originally isolated as an autocrine motility stimulation factor from the supernatant of highly metastatic melanoma cells[[274](#_ENREF_274)]. Since then, increased ATX expression has been detected in a large variety of cancers such as neuroblastoma, hepatocellular carcinoma, breast cancer, renal cell carcinoma, glioblastoma, thyroid carcinoma, B-cell lymphomas, and non-small cell LC (reviewed in[[10](#_ENREF_10)]). Moreover, the plethora of actions of LPA are concordant with many of the ‘hallmarks of cancer’, including proliferation, the evasion of apoptosis, angiogenesis and metastasis[[10](#_ENREF_10),[11](#_ENREF_11)]. LPA levels are significantly increased in malignant effusions, and its receptors are aberrantly expressed in several human cancers[[10](#_ENREF_10)]. Notably, overexpression of ATX and/or LPARs in the mammary gland was recently reported to result in spontaneous breast cancer in aged mice[[275](#_ENREF_275)], whereas the genetic deletion of LPAR2 attenuates tumour formation in an experimental model of colitis-associated cancer[[276](#_ENREF_276)].

Despite the established role of the ATX/LPA axis in carcinogenesis, little is known about its involvement in LC. Meta-analysis of datasets from seven different microarray studies on NSCLC for differentially expressed genes related to survival time identified ATX as one of the 64 genes predicting potential beneficial effects of aggressive therapy of stage I LC patients[[277](#_ENREF_277)]. ATX mRNA is overexpressed in poorly differentiated carcinomas in NSCLC patients[[22](#_ENREF_22)], while the conditional deletion of ATX from the lung attenuates chemically induced or k-ras-driven lung carcinogenesis (unpublished data and[[278](#_ENREF_278)]), suggesting a major contribution of ATX in lung carcinogenesis, although the related mechanisms are still not fully investigated.

In support of these data, BrP-LPA, a dual function pan-antagonist of LPA receptors and an ATX inhibitor[[75](#_ENREF_75),[279](#_ENREF_279)], inhibited tumour growth and angiogenesis in a engineered three-dimensional tumour xenograft NSCLC model composed of A549 lung carcinoma epithelial cells encapsulated in 3-D ECM injected in nude mice[[76](#_ENREF_76)]. Similarly, genetic or pharmacologic neutralisation of LPAR1 attenuates mesenchymal stem cell-dependent angiogenesis and tumour growth in a murine xenograft model of A549 human adenocarcinoma[[280](#_ENREF_280)]. In accordance, ATX was independently reported to induce the migration of A549 cells[[40](#_ENREF_40)], although, in the same cells, LPA was shown to decrease the nuclear localisation and cellular abundance of p53[[73](#_ENREF_73)].

The expression of LPA receptors seems to vary in different lung tumour cells (Table 1 and [[74](#_ENREF_74),[281](#_ENREF_281),[282](#_ENREF_282)]), possibly regulated by methylation[[283](#_ENREF_283)],[[284](#_ENREF_284)], and LPAR1 mutations were reported in a rat model of lung carcinogenesis correlating with advanced staging[[285](#_ENREF_285)]. Again, conditional knockout mice for the different LPARs are needed to examine their individual contribution to lung carcinogenesis.

Genetic deficiency of ATX and its associated effects on LPA production results in embryonic lethality due to aberrant circulation and neural tube closure[[28](#_ENREF_28),[36](#_ENREF_36),[38](#_ENREF_38)], suggesting a major effect of ATX/LPA in angiogenesis. Supporting *in vitro* studies have suggested that LPA stimulates the expression of a large number of angiogenic genes in different endothelial and cancer cells and regulates endothelial proliferation and migration (see above; reviewed in[[130](#_ENREF_130)]). The conditional deletion of ATX and/or LPA receptors in different endothelial systems is expected to dissect the involvement of ATX/LPA to angiogenesis, an obligatory component of carcinogenesis.

EGFR is overexpressed and functions aberrantly in various human cancers, including NSCLC in which it enhances cancer invasion and brain metastasis[[286](#_ENREF_286)], and has been extensively used as a target of therapeutic approaches[[287](#_ENREF_287)]. LPA has been shown to induce squamous cell carcinoma cell proliferation and motility[[288](#_ENREF_288)], ovarian cancer cell invasion[[289](#_ENREF_289)] and prostate cancer cell proliferation[[290](#_ENREF_290)] through EGFR transactivation, introducing the concept that LPA can amplify carcinogenic growth signals. Likewise, LPA has been reported to affect c-Met signalling[[70](#_ENREF_70),[291](#_ENREF_291)] and was found to be overexpressed and activated in NSCLC cell lines and tumour tissues[[292](#_ENREF_292)]. In addition, LPA has been suggested to provide resistance to EGFR targeted therapies[[293](#_ENREF_293)]. Therefore, suggested adjuvant therapies targeting simultaneously both EGFR and c-Met for the treatment of NSCLC[[294](#_ENREF_294)] could be possibly enhanced by inhibitors of the ATX/LPA axis.

**CONCLUSION**

ATX is a secreted glycoprotein widely present in biological fluids, including BALFs, largely responsible for the bulk of LPA production in the plasma and at inflamed and/or malignant sites. In turn, LPA evokes growth-factor-like responses in almost all cell types, including pulmonary cells, through its abundant GPCR receptors. ATX/LPA have an established role in inflammation and malignant transformation, and increased ATX and/or LPA levels in the lung have been detected in both humans with pulmonary diseases such as acute lung injury, IPF, asthma, and LC and/or the corresponding animal models. Genetic or pharmacologic interventions targeting the ATX/LPA axis have proven to be beneficial for disease management in animal models, establishing the ATX/LPA axis as a possible therapeutic target.

**References**

|  |
| --- |
| 1 **Boutin JA**, Ferry G. Autotaxin. *Cell Mol Life Sci* 2009; **66**: 3009-3021 [PMID: 19506801 DOI: 10.1007/s00018-009-0056-9]  2 **van Meeteren LA**, Moolenaar WH. Regulation and biological activities of the autotaxin-LPA axis. *Prog Lipid Res* 2007; **46**: 145-160 [PMID: 17459484 DOI: 10.1016/j.plipres.2007.02.001]  3 **Stefan C**, Jansen S, Bollen M. NPP-type ectophosphodiesterases: unity in diversity. *Trends Biochem Sci* 2005; **30**: 542-550 [PMID: 16125936 DOI: 10.1016/j.tibs.2005.08.005]  4 **Okudaira S**, Yukiura H, Aoki J. Biological roles of lysophosphatidic acid signaling through its production by autotaxin. *Biochimie* 2010; **92**: 698-706 [PMID: 20417246 DOI: 10.1016/j.biochi.2010.04.015]  5 **Aoki J**, Inoue A, Okudaira S. Two pathways for lysophosphatidic acid production. *Biochim Biophys Acta* 2008; **1781**: 513-518 [PMID: 18621144]  6 **Choi JW**, Herr DR, Noguchi K, Yung YC, Lee CW, Mutoh T, Lin ME, Teo ST, Park KE, Mosley AN, Chun J. LPA receptors: subtypes and biological actions. *Annu Rev Pharmacol Toxicol* 2010; **50**: 157-186 [PMID: 20055701 DOI: 10.1146/annurev.pharmtox.010909.105753]  7 **Yanagida K**, Kurikawa Y, Shimizu T, Ishii S. Current progress in non-Edg family LPA receptor research. *Biochim Biophys Acta* 2013; **1831**: 33-41 [PMID: 22902318]  8 **Brindley DN**, Pilquil C. Lipid phosphate phosphatases and signaling. *J Lipid Res* 2009; **50** Suppl: S225-S230 [PMID: 19066402 DOI: 10.1194/jlr.R800055-JLR200]  9 **Nanjundan M**, Possmayer F. Pulmonary phosphatidic acid phosphatase and lipid phosphate phosphohydrolase. *Am J Physiol Lung Cell Mol Physiol* 2003; **284**: L1-23 [PMID: 12471011]  10 **Houben AJ**, Moolenaar WH. Autotaxin and LPA receptor signaling in cancer. *Cancer Metastasis Rev* 2011; **30**: 557-565 [PMID: 22002750 DOI: 10.1007/s10555-011-9319-7]  11 **Liu S**, Murph M, Panupinthu N, Mills GB. ATX-LPA receptor axis in inflammation and cancer. *Cell Cycle* 2009; **8**: 3695-3701 [PMID: 19855166 DOI: 10.4161/cc.8.22.9937]  12 **Sevastou I**, Kaffe E, Mouratis MA, Aidinis V. Lysoglycerophospholipids in chronic inflammatory disorders: the PLA(2)/LPC and ATX/LPA axes. *Biochim Biophys Acta* 2013; **1831**: 42-60 [PMID: 22867755]  13 **Schober A**, Siess W. Lysophosphatidic acid in atherosclerotic diseases. *Br J Pharmacol* 2012; **167**: 465-482 [PMID: 22568609 DOI: 10.1111/j.1476-5381.2012.02021.x]  14 **Albers HM**, Ovaa H. Chemical evolution of autotaxin inhibitors. *Chem Rev* 2012; **112**: 2593-2603 [PMID: 22335786 DOI: 10.1021/cr2003213]  15 **Barbayianni E**, Magrioti V, Moutevelis-Minakakis P, Kokotos G. Autotaxin inhibitors: a patent review. *Expert Opin Ther Pat* 2013; **23**: 1123-1132 [PMID: 23641951 DOI: 10.1517/13543776.2013.796364]  16 **Im DS**. Pharmacological tools for lysophospholipid GPCRs: development of agonists and antagonists for LPA and S1P receptors. *Acta Pharmacol Sin* 2010; **31**: 1213-1222 [PMID: 20729877 DOI: 10.1038/aps.2010.135]  17 **Tigyi G**. Aiming drug discovery at lysophosphatidic acid targets. *Br J Pharmacol* 2010; **161**: 241-270 [PMID: 20735414 DOI: 10.1111/j.1476-5381.2010.00815.x]  18 **Giganti A**, Rodriguez M, Fould B, Moulharat N, Cogé F, Chomarat P, Galizzi JP, Valet P, Saulnier-Blache JS, Boutin JA, Ferry G. Murine and human autotaxin alpha, beta, and gamma isoforms: gene organization, tissue distribution, and biochemical characterization. *J Biol Chem* 2008; **283**: 7776-7789 [PMID: 18175805 DOI: 10.1074/jbc.M708705200]  19 **Hashimoto T**, Okudaira S, Igarashi K, Hama K, Yatomi Y, Aoki J. Identification and biochemical characterization of a novel autotaxin isoform, ATXδ, with a four-amino acid deletion. *J Biochem* 2012; **151**: 89-97 [PMID: 21994952 DOI: 10.1093/jb/mvr126]  20 **Houben AJ**, van Wijk XM, van Meeteren LA, van Zeijl L, van de Westerlo EM, Hausmann J, Fish A, Perrakis A, van Kuppevelt TH, Moolenaar WH. The polybasic insertion in autotaxin α confers specific binding to heparin and cell surface heparan sulfate proteoglycans. *J Biol Chem* 2013; **288**: 510-519 [PMID: 23150666 DOI: 10.1074/jbc.M112.358416]  21 **Lee HY**, Murata J, Clair T, Polymeropoulos MH, Torres R, Manrow RE, Liotta LA, Stracke ML. Cloning, chromosomal localization, and tissue expression of autotaxin from human teratocarcinoma cells. *Biochem Biophys Res Commun* 1996; **218**: 714-719 [PMID: 8579579 DOI: 10.1006/bbrc.1996.0127]  22 **Yang Y**, Mou Lj, Liu N, Tsao MS. Autotaxin expression in non-small-cell lung cancer. *Am J Respir Cell Mol Biol* 1999; **21**: 216-222 [PMID: 10423404 DOI: 10.1165/ajrcmb.21.2.3667]  23 **Oikonomou N**, Mouratis MA, Tzouvelekis A, Kaffe E, Valavanis C, Vilaras G, Karameris A, Prestwich GD, Bouros D, Aidinis V. Pulmonary autotaxin expression contributes to the pathogenesis of pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2012; **47**: 566-574 [PMID: 22744859 DOI: 10.1165/rcmb.2012-0004OC]  24 **Ganguly K**, Stoeger T, Wesselkamper SC, Reinhard C, Sartor MA, Medvedovic M, Tomlinson CR, Bolle I, Mason JM, Leikauf GD, Schulz H. Candidate genes controlling pulmonary function in mice: transcript profiling and predicted protein structure. *Physiol Genomics* 2007; **31**: 410-421 [PMID: 17804602 DOI: 10.1152/physiolgenomics.00260.2006]  25 **Croset M**, Brossard N, Polette A, Lagarde M. Characterization of plasma unsaturated lysophosphatidylcholines in human and rat. *Biochem J* 2000; **345** Pt 1: 61-67 [PMID: 10600639 DOI: 10.1042/0264-6021:3450061]  26 **Ojala PJ**, Hirvonen TE, Hermansson M, Somerharju P, Parkkinen J. Acyl chain-dependent effect of lysophosphatidylcholine on human neutrophils. *J Leukoc Biol* 2007; **82**: 1501-1509 [PMID: 17884992 DOI: 10.1189/jlb.0507292]  27 **Pérez-Gil J**. Structure of pulmonary surfactant membranes and films: the role of proteins and lipid-protein interactions. *Biochim Biophys Acta* ; **1778**: 1676-1695 [PMID: 18515069]  28 **Fotopoulou S**, Oikonomou N, Grigorieva E, Nikitopoulou I, Paparountas T, Thanassopoulou A, Zhao Z, Xu Y, Kontoyiannis DL, Remboutsika E, Aidinis V. ATX expression and LPA signalling are vital for the development of the nervous system. *Dev Biol* 2010; **339**: 451-464 [PMID: 20079728 DOI: 10.1016/j.ydbio.2010.01.007]  29 **Pamuklar Z**, Federico L, Liu S, Umezu-Goto M, Dong A, Panchatcharam M, Fulkerson Z, Berdyshev E, Natarajan V, Fang X, van Meeteren LA, Moolenaar WH, Mills GB, Morris AJ, Smyth SS. Autotaxin/lysopholipase D and lysophosphatidic acid regulate murine hemostasis and thrombosis. *J Biol Chem* 2009; **284**: 7385-7394 [PMID: 19139100 DOI: 10.1074/jbc.M807820200]  30 **Berdyshev EV**, Gorshkova I, Usatyuk P, Kalari S, Zhao Y, Pyne NJ, Pyne S, Sabbadini RA, Garcia JG, Natarajan V. Intracellular S1P generation is essential for S1P-induced motility of human lung endothelial cells: role of sphingosine kinase 1 and S1P lyase. *PLoS One* 2011; **6**: e16571 [PMID: 21304987 DOI: 10.1371/journal.pone.0016571]  31 **Tager AM**, LaCamera P, Shea BS, Campanella GS, Selman M, Zhao Z, Polosukhin V, Wain J, Karimi-Shah BA, Kim ND, Hart WK, Pardo A, Blackwell TS, Xu Y, Chun J, Luster AD. The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat Med* 2008; **14**: 45-54 [PMID: 18066075 DOI: 10.1038/nm1685]  32 **Gobeil F**, Bernier SG, Vazquez-Tello A, Brault S, Beauchamp MH, Quiniou C, Marrache AM, Checchin D, Sennlaub F, Hou X, Nader M, Bkaily G, Ribeiro-da-Silva A, Goetzl EJ, Chemtob S. Modulation of pro-inflammatory gene expression by nuclear lysophosphatidic acid receptor type-1. *J Biol Chem* 2003; **278**: 38875-38883 [PMID: 12847111 DOI: 10.1074/jbc.M212481200]  33 **Ward Y**, Lake R, Yin JJ, Heger CD, Raffeld M, Goldsmith PK, Merino M, Kelly K. LPA receptor heterodimerizes with CD97 to amplify LPA-initiated RHO-dependent signaling and invasion in prostate cancer cells. *Cancer Res* 2011; **71**: 7301-7311 [PMID: 21978933 DOI: 10.1158/0008-5472.CAN-11-2381]  34 **Zhao J**, He D, Su Y, Berdyshev E, Chun J, Natarajan V, Zhao Y. Lysophosphatidic acid receptor 1 modulates lipopolysaccharide-induced inflammation in alveolar epithelial cells and murine lungs. *Am J Physiol Lung Cell Mol Physiol* 2011; **301**: L547-L556 [PMID: 21821728 DOI: 10.1152/ajplung.00058.2011]  35 **Cheng HY**, Dong A, Panchatcharam M, Mueller P, Yang F, Li Z, Mills G, Chun J, Morris AJ, Smyth SS. Lysophosphatidic acid signaling protects pulmonary vasculature from hypoxia-induced remodeling. *Arterioscler Thromb Vasc Biol* 2012; **32**: 24-32 [PMID: 22015657 DOI: 10.1161/ATVBAHA.111.234708]  36 **Koike S**, Keino-Masu K, Ohto T, Sugiyama F, Takahashi S, Masu M. Autotaxin/lysophospholipase D-mediated lysophosphatidic acid signaling is required to form distinctive large lysosomes in the visceral endoderm cells of the mouse yolk sac. *J Biol Chem* 2009; **284**: 33561-33570 [PMID: 19808661 DOI: 10.1074/jbc.M109.012716]  37 **Tanaka M**, Okudaira S, Kishi Y, Ohkawa R, Iseki S, Ota M, Noji S, Yatomi Y, Aoki J, Arai H. Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. *J Biol Chem* 2006; **281**: 25822-25830 [PMID: 16829511 DOI: 10.1074/jbc.M605142200]  38 **van Meeteren LA**, Ruurs P, Stortelers C, Bouwman P, van Rooijen MA, Pradère JP, Pettit TR, Wakelam MJ, Saulnier-Blache JS, Mummery CL, Moolenaar WH, Jonkers J. Autotaxin, a secreted lysophospholipase D, is essential for blood vessel formation during development. *Mol Cell Biol* 2006; **26**: 5015-5022 [PMID: 16782887 DOI: 10.1128/MCB.02419-05]  39 **Crosby LM**, Waters CM. Epithelial repair mechanisms in the lung. *Am J Physiol Lung Cell Mol Physiol* 2010; **298**: L715-L731 [PMID: 20363851 DOI: 10.1152/ajplung.00361.2009]  40 **Zhao J**, He D, Berdyshev E, Zhong M, Salgia R, Morris AJ, Smyth SS, Natarajan V, Zhao Y. Autotaxin induces lung epithelial cell migration through lysoPLD activity-dependent and -independent pathways. *Biochem J* 2011; **439**: 45-55 [PMID: 21696367 DOI: 10.1042/BJ20110274]  41 **Funke M**, Zhao Z, Xu Y, Chun J, Tager AM. The lysophosphatidic acid receptor LPA1 promotes epithelial cell apoptosis after lung injury. *Am J Respir Cell Mol Biol* 2012; **46**: 355-364 [PMID: 22021336]  42 **Huang LS,** Fu P, Patel P, Harijith A, Sun T, Zhao Y, Garcia JG, Chun J, Natarajan V. Lysophosphatidic Acid Receptor 2 Deficiency Confers Protection Against Bleomycin-Induced Lung Injury and Fibrosis in Mice. *Am J Respir Cell Mol Biol* 2013; In press [PMID: 23808384]  43 **Xu MY**, Porte J, Knox AJ, Weinreb PH, Maher TM, Violette SM, McAnulty RJ, Sheppard D, Jenkins G. Lysophosphatidic acid induces alphavbeta6 integrin-mediated TGF-beta activation via the LPA2 receptor and the small G protein G alpha(q). *Am J Pathol* 2009; **174**: 1264-1279 [PMID: 19147812 DOI: 10.2353/ajpath.2009.080160]  44 **Munger JS**, Huang X, Kawakatsu H, Griffiths MJ, Dalton SL, Wu J, Pittet JF, Kaminski N, Garat C, Matthay MA, Rifkin DB, Sheppard D. The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 1999; **96**: 319-328 [PMID: 10025398 DOI: 10.1016/S0092-8674(00)80545-0]  45 **Cummings R**, Zhao Y, Jacoby D, Spannhake EW, Ohba M, Garcia JG, Watkins T, He D, Saatian B, Natarajan V. Protein kinase Cdelta mediates lysophosphatidic acid-induced NF-kappaB activation and interleukin-8 secretion in human bronchial epithelial cells. *J Biol Chem* 2004; **279**: 41085-41094 [PMID: 15280372 DOI: [10.1074/jbc.M404045200](http://dx.doi.org/10.1074/jbc.M404045200)]  46 **Saatian B**, Zhao Y, He D, Georas SN, Watkins T, Spannhake EW, Natarajan V. Transcriptional regulation of lysophosphatidic acid-induced interleukin-8 expression and secretion by p38 MAPK and JNK in human bronchial epithelial cells. *Biochem J* 2006; **393**: 657-668 [PMID: 16197369 DOI: [10.1042/BJ20050791](http://dx.doi.org/10.1042/BJ20050791)]  47 **Kalari S**, Zhao Y, Spannhake EW, Berdyshev EV, Natarajan V. Role of acylglycerol kinase in LPA-induced IL-8 secretion and transactivation of epidermal growth factor-receptor in human bronchial epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2009; **296**: L328-L336 [PMID: 19112101 DOI: [10.1152/ajplung.90431.2008](http://dx.doi.org/10.1152/ajplung.90431.2008)]  48 **Zhao Y**, Usatyuk PV, Cummings R, Saatian B, He D, Watkins T, Morris A, Spannhake EW, Brindley DN, Natarajan V. Lipid phosphate phosphatase-1 regulates lysophosphatidic acid-induced calcium release, NF-kappaB activation and interleukin-8 secretion in human bronchial epithelial cells. *Biochem J* 2005; **385**: 493-502 [PMID: 15461590 DOI: [10.1042/BJ20041160](http://dx.doi.org/10.1042/BJ20041160)]  49 **Zhao Y**, He D, Saatian B, Watkins T, Spannhake EW, Pyne NJ, Natarajan V. Regulation of lysophosphatidic acid-induced epidermal growth factor receptor transactivation and interleukin-8 secretion in human bronchial epithelial cells by protein kinase Cdelta, Lyn kinase, and matrix metalloproteinases. *J Biol Chem* 2006; **281**: 19501-19511 [PMID: 16687414 DOI: [10.1074/jbc.M511224200](http://dx.doi.org/10.1074/jbc.M511224200)]  50 **Medoff BD**, Landry AL, Wittbold KA, Sandall BP, Derby MC, Cao Z, Adams JC, Xavier RJ. CARMA3 mediates lysophosphatidic acid-stimulated cytokine secretion by bronchial epithelial cells. *Am J Respir Cell Mol Biol* 2009; **40**: 286-294 [PMID: 18757306 DOI: [10.1165/rcmb.2008-0129OC](http://dx.doi.org/10.1165/rcmb.2008-0129OC)]  51 **Ziegler SF**, Liu YJ. Thymic stromal lymphopoietin in normal and pathogenic T cell development and function. *Nat Immunol* 2006; **7**: 709-714 [PMID: 16785889 DOI: [10.1038/ni1360](http://dx.doi.org/10.1038/ni1360)]  52 **Weckmann M**, Collison A, Simpson JL, Kopp MV, Wark PA, Smyth MJ, Yagita H, Matthaei KI, Hansbro N, Whitehead B, Gibson PG, Foster PS, Mattes J. Critical link between TRAIL and CCL20 for the activation of TH2 cells and the expression of allergic airway disease. *Nat Med* 2007; **13**: 1308-1315 [PMID: 17934471 DOI: [10.1038/nm1660](http://dx.doi.org/10.1038/nm1660)]  53 **Holgate ST**. Innate and adaptive immune responses in asthma. *Nat Med* 2012; **18**: 673-683 [PMID: 22561831 DOI: [10.1038/nm.2731](http://dx.doi.org/10.1038/nm.2731)]  54 **Zhao Y**, He D, Zhao J, Wang L, Leff AR, Spannhake EW, Georas S, Natarajan V. Lysophosphatidic acid induces interleukin-13 (IL-13) receptor alpha2 expression and inhibits IL-13 signaling in primary human bronchial epithelial cells. *J Biol Chem* 2007; **282**: 10172-10179 [PMID: 17287216 DOI: [10.1074/jbc.M611210200](http://dx.doi.org/10.1074/jbc.M611210200)]  55 **Wynn TA**. IL-13 effector functions. *Annu Rev Immunol* 2003; **21**: 425-456 [PMID: 12615888 DOI: [10.1146/annurev.immunol.21.120601.141142](http://dx.doi.org/10.1146/annurev.immunol.21.120601.141142)]  56 **Georas SN**, Berdyshev E, Hubbard W, Gorshkova IA, Usatyuk PV, Saatian B, Myers AC, Williams MA, Xiao HQ, Liu M, Natarajan V. Lysophosphatidic acid is detectable in human bronchoalveolar lavage fluids at baseline and increased after segmental allergen challenge. *Clin Exp Allergy* 2007; **37**: 311-322 [PMID: 17359381 DOI: [10.1111/j.1365-2222.2006.02626.x](http://dx.doi.org/10.1111/j.1365-2222.2006.02626.x)]  57 **Zhao Y**, Tong J, He D, Pendyala S, Evgeny B, Chun J, Sperling AI, Natarajan V. Role of lysophosphatidic acid receptor LPA2 in the development of allergic airway inflammation in a murine model of asthma. *Respir Res* 2009; **10**: 114 [PMID: 19930563 DOI: [10.1186/1465-9921-10-114](http://dx.doi.org/10.1186/1465-9921-10-114)]  58 **Emo J**, Meednu N, Chapman TJ, Rezaee F, Balys M, Randall T, Rangasamy T, Georas SN. Lpa2 is a negative regulator of both dendritic cell activation and murine models of allergic lung inflammation. *J Immunol* 2012; **188**: 3784-3790 [PMID: 22427635 DOI: [10.4049/jimmunol.1102956](http://dx.doi.org/10.4049/jimmunol.1102956)]  59 **Matsuzaki S**, Ishizuka T, Hisada T, Aoki H, Komachi M, Ichimonji I, Utsugi M, Ono A, Koga Y, Dobashi K, Kurose H, Tomura H, Mori M, Okajima F. Lysophosphatidic acid inhibits CC chemokine ligand 5/RANTES production by blocking IRF-1-mediated gene transcription in human bronchial epithelial cells. *J Immunol* 2010; **185**: 4863-4872 [PMID: 20861350 DOI: [10.4049/jimmunol.1000904](http://dx.doi.org/10.4049/jimmunol.1000904)]  60 **Appay V**, Rowland-Jones SL. RANTES: a versatile and controversial chemokine. *Trends Immunol* 2001; **22**: 83-87 [PMID: 11286708 DOI: 10.1016/S1471-4906(00)01812-3]  61 **Zhao J**, Chen Q, Li H, Myerburg M, Spannhake EW, Natarajan V, Zhao Y. Lysophosphatidic acid increases soluble ST2 expression in mouse lung and human bronchial epithelial cells. *Cell Signal* 2012; **24**: 77-85 [PMID: 21871564 DOI: [10.1016/j.cellsig.2011.08.004](http://dx.doi.org/10.1016/j.cellsig.2011.08.004)]  62 **Zhao Y,** He D, Pendyala S, Berdyshev E, Goya J, Chun J, Natarajan V. Deletion of Lysophosphatidic acid Receptors 1 and 2 Protects Against Lipopolysaccharide-Induced Acute Lung Injury in Mice FASEB J meeting abstract supplement 2010; A24  63 **He D**, Natarajan V, Stern R, Gorshkova IA, Solway J, Spannhake EW, Zhao Y. Lysophosphatidic acid-induced transactivation of epidermal growth factor receptor regulates cyclo-oxygenase-2 expression and prostaglandin E(2) release via C/EBPbeta in human bronchial epithelial cells. *Biochem J* 2008; **412**: 153-162 [PMID: 18294142 DOI: [10.1042/BJ20071649](http://dx.doi.org/10.1042/BJ20071649)]  64 **Vancheri C**, Mastruzzo C, Sortino MA, Crimi N. The lung as a privileged site for the beneficial actions of PGE2. *Trends Immunol* 2004; **25**: 40-46 [PMID: 14698283 DOI: [10.1016/j.it.2003.11.001](http://dx.doi.org/10.1016/j.it.2003.11.001)]  65 **Nakata J**, Kondo M, Tamaoki J, Takemiya T, Nohara M, Yamagata K, Nagai A. Augmentation of allergic inflammation in the airways of cyclooxygenase-2-deficient mice. *Respirology* 2005; **10**: 149-156 [PMID: 15823178 DOI: [10.1111/j.1440-1843.2005.00687.x](http://dx.doi.org/10.1111/j.1440-1843.2005.00687.x)]  66 **Kassel KM**, Schulte NA, Parker SM, Lanik AD, Toews ML. Lysophosphatidic acid decreases epidermal growth factor receptor binding in airway epithelial cells. *J Pharmacol Exp Ther* 2007; **323**: 109-118 [PMID: 17640953 DOI: [10.1124/jpet.107.120584](http://dx.doi.org/10.1124/jpet.107.120584)]  67 **Kassel KM**, Dodmane PR, Schulte NA, Toews ML. Lysophosphatidic acid induces rapid and sustained decreases in epidermal growth factor receptor binding via different signaling pathways in BEAS-2B airway epithelial cells. *J Pharmacol Exp Ther* 2008; **325**: 809-817 [PMID: 18309089 DOI: [10.1124/jpet.107.133736](http://dx.doi.org/10.1124/jpet.107.133736)]  68 **Wang L**, Cummings R, Zhao Y, Kazlauskas A, Sham JK, Morris A, Georas S, Brindley DN, Natarajan V. Involvement of phospholipase D2 in lysophosphatidate-induced transactivation of platelet-derived growth factor receptor-beta in human bronchial epithelial cells. *J Biol Chem* 2003; **278**: 39931-39940 [PMID: 12890682 DOI: [10.1074/jbc.M302896200](http://dx.doi.org/10.1074/jbc.M302896200)]  69 **Ingram JL**, Bonner JC. EGF and PDGF receptor tyrosine kinases as therapeutic targets for chronic lung diseases. *Curr Mol Med* 2006; **6**: 409-421 [PMID: 16900664 DOI: [10.2174/156652406777435426](http://dx.doi.org/10.2174/156652406777435426)]  70 **Zhao Y**, He D, Stern R, Usatyuk PV, Spannhake EW, Salgia R, Natarajan V. Lysophosphatidic acid modulates c-Met redistribution and hepatocyte growth factor/c-Met signaling in human bronchial epithelial cells through PKC delta and E-cadherin. *Cell Signal* 2007; **19**: 2329-2338 [PMID: 17689924 DOI: [10.1016/j.cellsig.2007.07.005](http://dx.doi.org/10.1016/j.cellsig.2007.07.005)]  71 **Jafri NF**, Ma PC, Maulik G, Salgia R. Mechanisms of metastasis as related to receptor tyrosine kinases in small-cell lung cancer. *J Environ Pathol Toxicol Oncol* 2003; **22**: 147-165 [PMID: 14529091 DOI: [10.1615/JEnvPathToxOncol.v22.i3.10](http://dx.doi.org/10.1615/JEnvPathToxOncol.v22.i3.10)]  72 **Panganiban RA**, Day RM. Hepatocyte growth factor in lung repair and pulmonary fibrosis. *Acta Pharmacol Sin* 2011; **32**: 12-20 [PMID: 21131996 DOI: [10.1038/aps.2010.90](http://dx.doi.org/10.1038/aps.2010.90)]  73 **Murph MM**, Hurst-Kennedy J, Newton V, Brindley DN, Radhakrishna H. Lysophosphatidic acid decreases the nuclear localization and cellular abundance of the p53 tumor suppressor in A549 lung carcinoma cells. *Mol Cancer Res* 2007; **5**: 1201-1211 [PMID: 18025263 DOI: [10.1158/1541-7786.MCR-06-0338](http://dx.doi.org/10.1158/1541-7786.MCR-06-0338)]  74 **Hama K**, Aoki J, Fukaya M, Kishi Y, Sakai T, Suzuki R, Ohta H, Yamori T, Watanabe M, Chun J, Arai H. Lysophosphatidic acid and autotaxin stimulate cell motility of neoplastic and non-neoplastic cells through LPA1. *J Biol Chem* 2004; **279**: 17634-17639 [PMID: 14744855 DOI: [10.1074/jbc.M313927200](http://dx.doi.org/10.1074/jbc.M313927200)]  75 **Jiang G**, Xu Y, Fujiwara Y, Tsukahara T, Tsukahara R, Gajewiak J, Tigyi G, Prestwich GD. Alpha-substituted phosphonate analogues of lysophosphatidic acid (LPA) selectively inhibit production and action of LPA. *ChemMedChem* 2007; **2**: 679-690 [PMID: 17443831 DOI: [10.1002/cmdc.200600280](http://dx.doi.org/10.1002/cmdc.200600280)]  76 **Xu X**, Prestwich GD. Inhibition of tumor growth and angiogenesis by a lysophosphatidic acid antagonist in an engineered three-dimensional lung cancer xenograft model. *Cancer* 2010; **116**: 1739-1750 [PMID: 20143443 DOI: [10.1002/cncr.24907](http://dx.doi.org/10.1002/cncr.24907)]  77 **Tomasek JJ**, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol* 2002; **3**: 349-363 [PMID: 11988769 DOI: [10.1038/nrm809](http://dx.doi.org/10.1038/nrm809)]  78 **Buckley CD**, Pilling D, Lord JM, Akbar AN, Scheel-Toellner D, Salmon M. Fibroblasts regulate the switch from acute resolving to chronic persistent inflammation. *Trends Immunol* 2001; **22**: 199-204 [PMID: 11274925 DOI: 10.1016/S1471-4906(01)01863-4]  79 **Hinz B**, Phan SH, Thannickal VJ, Prunotto M, Desmoulière A, Varga J, De Wever O, Mareel M, Gabbiani G. Recent developments in myofibroblast biology: paradigms for connective tissue remodeling. *Am J Pathol* 2012; **180**: 1340-1355 [PMID: 22387320 DOI: [10.1016/j.ajpath.2012.02.004](http://dx.doi.org/10.1016/j.ajpath.2012.02.004)]  80 **Kalluri R**, Zeisberg M. Fibroblasts in cancer. *Nat Rev Cancer* 2006; **6**: 392-401 [PMID: 16572188 DOI: [10.1038/nrc1877](http://dx.doi.org/10.1038/nrc1877)]  81 **Shiomi T**, Boudreault F, Padem N, Higashiyama S, Drazen JM, Tschumperlin DJ. Lysophosphatidic acid stimulates epidermal growth factor-family ectodomain shedding and paracrine signaling from human lung fibroblasts. *Wound Repair Regen* ; **19**: 229-240 [PMID: 21362091 DOI: [10.1111/j.1524-475X.2010.00655.x](http://dx.doi.org/10.1111/j.1524-475X.2010.00655.x)]  82 **Contos JJ**, Ishii I, Fukushima N, Kingsbury MA, Ye X, Kawamura S, Brown JH, Chun J. Characterization of lpa(2) (Edg4) and lpa(1)/lpa(2) (Edg2/Edg4) lysophosphatidic acid receptor knockout mice: signaling deficits without obvious phenotypic abnormality attributable to lpa(2). *Mol Cell Biol* 2002; **22**: 6921-6929 [PMID: 12215548 DOI: [10.1128/MCB.22.19.6921-6929.2002](http://dx.doi.org/10.1128/MCB.22.19.6921-6929.2002)]  83 **Nikitopoulou I**, Oikonomou N, Karouzakis E, Sevastou I, Nikolaidou-Katsaridou N, Zhao Z, Mersinias V, Armaka M, Xu Y, Masu M, Mills GB, Gay S, Kollias G, Aidinis V. Autotaxin expression from synovial fibroblasts is essential for the pathogenesis of modeled arthritis. *J Exp Med* 2012; **209**: 925-933 [PMID: 22493518 DOI: [10.1084/jem.20112012](http://dx.doi.org/10.1084/jem.20112012)]  84 **Barry ST**, Critchley DR. The RhoA-dependent assembly of focal adhesions in Swiss 3T3 cells is associated with increased tyrosine phosphorylation and the recruitment of both pp125FAK and protein kinase C-delta to focal adhesions. *J Cell Sci* 1994; **107** ( Pt 7): 2033-2045 [PMID: 7527052]  85 **Wang F**, Nobes CD, Hall A, Spiegel S. Sphingosine 1-phosphate stimulates rho-mediated tyrosine phosphorylation of focal adhesion kinase and paxillin in Swiss 3T3 fibroblasts. *Biochem J* 1997; **324** ( Pt 2): 481-488 [PMID: 9182707]  86 **Seufferlein T**, Rozengurt E. Lysophosphatidic acid stimulates tyrosine phosphorylation of focal adhesion kinase, paxillin, and p130. Signaling pathways and cross-talk with platelet-derived growth factor. *J Biol Chem* 1994; **269**: 9345-9351 [PMID: 7510708]  87 **Sakai N**, Chun J, Duffield JS, Wada T, Luster AD, Tager AM. LPA1-induced cytoskeleton reorganization drives fibrosis through CTGF-dependent fibroblast proliferation. *FASEB J* 2013; **27**: 1830-1846 [PMID: 23322166 DOI: [10.1096/fj.12-219378](http://dx.doi.org/10.1096/fj.12-219378)]  88 **Mio T**, Liu X, Toews ML, Rennard SI. Lysophosphatidic acid augments fibroblast-mediated contraction of released collagen gels. *J Lab Clin Med* 2002; **139**: 20-27 [PMID: 11873241 DOI: [10.1067/mlc.2002.120650](http://dx.doi.org/10.1067/mlc.2002.120650)]  89 **Lee DJ**, Ho CH, Grinnell F. LPA-stimulated fibroblast contraction of floating collagen matrices does not require Rho kinase activity or retraction of fibroblast extensions. *Exp Cell Res* 2003; **289**: 86-94 [PMID: 12941607 DOI: 10.1016/S0014-4827(03)00254-4]  90 **Parizi M**, Howard EW, Tomasek JJ. Regulation of LPA-promoted myofibroblast contraction: role of Rho, myosin light chain kinase, and myosin light chain phosphatase. *Exp Cell Res* 2000; **254**: 210-220 [PMID: 10640419 DOI: [10.1006/excr.1999.4754](http://dx.doi.org/10.1006/excr.1999.4754)]  91 **Feng J**, Ito M, Ichikawa K, Isaka N, Nishikawa M, Hartshorne DJ, Nakano T. Inhibitory phosphorylation site for Rho-associated kinase on smooth muscle myosin phosphatase. *J Biol Chem* 1999; **274**: 37385-37390 [PMID: 10601309 DOI: [10.1074/jbc.274.52.37385](http://dx.doi.org/10.1074/jbc.274.52.37385)]  92 **Rhee S**, Grinnell F. P21-activated kinase 1: convergence point in PDGF- and LPA-stimulated collagen matrix contraction by human fibroblasts. *J Cell Biol* 2006; **172**: 423-432 [PMID: 16449192 DOI: [10.1083/jcb.200505175](http://dx.doi.org/10.1083/jcb.200505175)]  93 **Van Leeuwen FN**, Olivo C, Grivell S, Giepmans BN, Collard JG, Moolenaar WH. Rac activation by lysophosphatidic acid LPA1 receptors through the guanine nucleotide exchange factor Tiam1. *J Biol Chem* 2003; **278**: 400-406 [PMID: 12393875 DOI: [10.1074/jbc.M210151200](http://dx.doi.org/10.1074/jbc.M210151200)]  94 **Sakai T**, de la Pena JM, Mosher DF. Synergism among lysophosphatidic acid, beta1A integrins, and epidermal growth factor or platelet-derived growth factor in mediation of cell migration. *J Biol Chem* 1999; **274**: 15480-15486 [PMID: 10336439 DOI: [10.1074/jbc.274.22.15480](http://dx.doi.org/10.1074/jbc.274.22.15480)]  95 **Swaney JS**, Chapman C, Correa LD, Stebbins KJ, Bundey RA, Prodanovich PC, Fagan P, Baccei CS, Santini AM, Hutchinson JH, Seiders TJ, Parr TA, Prasit P, Evans JF, Lorrain DS. A novel, orally active LPA(1) receptor antagonist inhibits lung fibrosis in the mouse bleomycin model. *Br J Pharmacol* 2010; **160**: 1699-1713 [PMID: 20649573 DOI: [10.1111/j.1476-5381.2010.00828.x](http://dx.doi.org/10.1111/j.1476-5381.2010.00828.x)]  96 **Mazzocca A**, Dituri F, Lupo L, Quaranta M, Antonaci S, Giannelli G. Tumor-secreted lysophostatidic acid accelerates hepatocellular carcinoma progression by promoting differentiation of peritumoral fibroblasts in myofibroblasts. *Hepatology* 2011; **54**: 920-930 [PMID: 21674557 DOI: [10.1002/hep.24485](http://dx.doi.org/10.1002/hep.24485)]  97 **Jeon ES**, Heo SC, Lee IH, Choi YJ, Park JH, Choi KU, Park do Y, Suh DS, Yoon MS, Kim JH. Ovarian cancer-derived lysophosphatidic acid stimulates secretion of VEGF and stromal cell-derived factor-1 alpha from human mesenchymal stem cells. *Exp Mol Med* 2010; **42**: 280-293 [PMID: 20177148 DOI: [10.3858/emm.2010.42.4.027](http://dx.doi.org/10.3858/emm.2010.42.4.027)]  98 **Jeon ES**, Moon HJ, Lee MJ, Song HY, Kim YM, Cho M, Suh DS, Yoon MS, Chang CL, Jung JS, Kim JH. Cancer-derived lysophosphatidic acid stimulates differentiation of human mesenchymal stem cells to myofibroblast-like cells. *Stem Cells* 2008; **26**: 789-797 [PMID: 18065393 DOI: [10.1634/stemcells.2007-0742](http://dx.doi.org/10.1634/stemcells.2007-0742)]  99 **Fang X**, Yu S, LaPushin R, Lu Y, Furui T, Penn LZ, Stokoe D, Erickson JR, Bast RC, Mills GB. Lysophosphatidic acid prevents apoptosis in fibroblasts via G(i)-protein-mediated activation of mitogen-activated protein kinase. *Biochem J* 2000; **352** Pt 1: 135-143 [PMID: 11062066 DOI: [10.1042/0264-6021:3520135](http://dx.doi.org/10.1042/0264-6021:3520135)]  100 **Song J**, Clair T, Noh JH, Eun JW, Ryu SY, Lee SN, Ahn YM, Kim SY, Lee SH, Park WS, Yoo NJ, Lee JY, Nam SW. Autotaxin (lysoPLD/NPP2) protects fibroblasts from apoptosis through its enzymatic product, lysophosphatidic acid, utilizing albumin-bound substrate. *Biochem Biophys Res Commun* 2005; **337**: 967-975 [PMID: 16219296 DOI: [10.1016/j.bbrc.2005.09.140](http://dx.doi.org/10.1016/j.bbrc.2005.09.140)]  101 **Stortelers C**, Kerkhoven R, Moolenaar WH. Multiple actions of lysophosphatidic acid on fibroblasts revealed by transcriptional profiling. *BMC Genomics* 2008; **9**: 387 [PMID: 18702810 DOI: [10.1186/1471-2164-9-387](http://dx.doi.org/10.1186/1471-2164-9-387)]  102 **Gesty-Palmer D**, El Shewy H, Kohout TA, Luttrell LM. beta-Arrestin 2 expression determines the transcriptional response to lysophosphatidic acid stimulation in murine embryo fibroblasts. *J Biol Chem* 2005; **280**: 32157-32167 [PMID: 16027114 DOI: [10.1074/jbc.M507460200](http://dx.doi.org/10.1074/jbc.M507460200)]  103 **Pober JS**, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol* 2007; **7**: 803-815 [PMID: 17893694 DOI: [10.1038/nri2171](http://dx.doi.org/10.1038/nri2171)]  104 **Farkas L**, Kolb M. Pulmonary microcirculation in interstitial lung disease. *Proc Am Thorac Soc* 2011; **8**: 516-521 [PMID: 22052930 DOI: [10.1513/pats.201101-007MW](http://dx.doi.org/10.1513/pats.201101-007MW)]  105 **Voelkel NF**, Douglas IS, Nicolls M. Angiogenesis in chronic lung disease. *Chest* 2007; **131**: 874-879 [PMID: 17356107 DOI: [10.1378/chest.06-2453](http://dx.doi.org/10.1378/chest.06-2453)]  106 **Ren Y**, Guo L, Tang X, Apparsundaram S, Kitson C, Deguzman J, Fuentes ME, Coyle L, Majmudar R, Allard J, Truitt T, Hamid R, Chen Y, Qian Y, Budd DC. Comparing the differential effects of LPA on the barrier function of human pulmonary endothelial cells. *Microvasc Res* 2013; **85**: 59-67 [PMID: 23084965 DOI: [10.1016/j.mvr.2012.10.004](http://dx.doi.org/10.1016/j.mvr.2012.10.004)]  107 **van Nieuw Amerongen GP**, Vermeer MA, van Hinsbergh VW. Role of RhoA and Rho kinase in lysophosphatidic acid-induced endothelial barrier dysfunction. *Arterioscler Thromb Vasc Biol* 2000; **20**: E127-E133 [PMID: 11116077 DOI: [10.1161/01.ATV.20.12.e127](http://dx.doi.org/10.1161/01.ATV.20.12.e127)]  108 **Neidlinger NA**, Larkin SK, Bhagat A, Victorino GP, Kuypers FA. Hydrolysis of phosphatidylserine-exposing red blood cells by secretory phospholipase A2 generates lysophosphatidic acid and results in vascular dysfunction. *J Biol Chem* 2006; **281**: 775-781 [PMID: 16278219 DOI: [10.1074/jbc.M505790200](http://dx.doi.org/10.1074/jbc.M505790200)]  109 **Alexander JS**, Patton WF, Christman BW, Cuiper LL, Haselton FR. Platelet-derived lysophosphatidic acid decreases endothelial permeability in vitro. *Am J Physiol* 1998; **274**: H115-H122 [PMID: 9458859]  110 **Yin F**, Watsky MA. LPA and S1P increase corneal epithelial and endothelial cell transcellular resistance. *Invest Ophthalmol Vis Sci* 2005; **46**: 1927-1933 [PMID: 15914605 DOI: [10.1167/iovs.04-1256](http://dx.doi.org/10.1167/iovs.04-1256)]  111 **English D**, Kovala AT, Welch Z, Harvey KA, Siddiqui RA, Brindley DN, Garcia JG. Induction of endothelial cell chemotaxis by sphingosine 1-phosphate and stabilization of endothelial monolayer barrier function by lysophosphatidic acid, potential mediators of hematopoietic angiogenesis. *J Hematother Stem Cell Res* 1999; **8**: 627-634 [PMID: 10645770 DOI: [10.1089/152581699319795](http://dx.doi.org/10.1089/152581699319795)]  112 **Kanda H**, Newton R, Klein R, Morita Y, Gunn MD, Rosen SD. Autotaxin, an ectoenzyme that produces lysophosphatidic acid, promotes the entry of lymphocytes into secondary lymphoid organs. *Nat Immunol* 2008; **9**: 415-423 [PMID: 18327261 DOI: [10.1038/ni1573](http://dx.doi.org/10.1038/ni1573)]  113 **Nakasaki T**, Tanaka T, Okudaira S, Hirosawa M, Umemoto E, Otani K, Jin S, Bai Z, Hayasaka H, Fukui Y, Aozasa K, Fujita N, Tsuruo T, Ozono K, Aoki J, Miyasaka M. Involvement of the lysophosphatidic acid-generating enzyme autotaxin in lymphocyte-endothelial cell interactions. *Am J Pathol* 2008; **173**: 1566-1576 [PMID: 18818380 DOI: [10.2353/ajpath.2008.071153](http://dx.doi.org/10.2353/ajpath.2008.071153)]  114 **Tsuboi K**, Hirakawa J, Seki E, Imai Y, Yamaguchi Y, Fukuda M, Kawashima H. Role of high endothelial venule-expressed heparan sulfate in chemokine presentation and lymphocyte homing. *J Immunol* 2013; **191**: 448-455 [PMID: 23733868 DOI: [10.4049/jimmunol.1203061](http://dx.doi.org/10.4049/jimmunol.1203061)]  115 **Zhang Y**, Chen YC, Krummel MF, Rosen SD. Autotaxin through lysophosphatidic acid stimulates polarization, motility, and transendothelial migration of naive T cells. *J Immunol* 2012; **189**: 3914-3924 [PMID: 22962684 DOI: [10.4049/jimmunol.1201604](http://dx.doi.org/10.4049/jimmunol.1201604)]  116 **Bai Z**, Cai L, Umemoto E, Takeda A, Tohya K, Komai Y, Veeraveedu PT, Hata E, Sugiura Y, Kubo A, Suematsu M, Hayasaka H, Okudaira S, Aoki J, Tanaka T, Albers HM, Ovaa H, Miyasaka M. Constitutive lymphocyte transmigration across the basal lamina of high endothelial venules is regulated by the autotaxin/lysophosphatidic acid axis. *J Immunol* 2013; **190**: 2036-2048 [PMID: 23365076 DOI: [10.4049/jimmunol.1202025](http://dx.doi.org/10.4049/jimmunol.1202025)]  117 **Lin CI**, Chen CN, Lin PW, Chang KJ, Hsieh FJ, Lee H. Lysophosphatidic acid regulates inflammation-related genes in human endothelial cells through LPA1 and LPA3. *Biochem Biophys Res Commun* 2007; **363**: 1001-1008 [PMID: 17923111 DOI: [10.1016/j.bbrc.2007.09.081](http://dx.doi.org/10.1016/j.bbrc.2007.09.081)]  118 **Lin CI**, Chen CN, Chen JH, Lee H. Lysophospholipids increase IL-8 and MCP-1 expressions in human umbilical cord vein endothelial cells through an IL-1-dependent mechanism. *J Cell Biochem* 2006; **99**: 1216-1232 [PMID: 16795034 DOI: [10.1002/jcb.20963](http://dx.doi.org/10.1002/jcb.20963)]  119 **Shimada H**, Rajagopalan LE. Rho-kinase mediates lysophosphatidic acid-induced IL-8 and MCP-1 production via p38 and JNK pathways in human endothelial cells. *FEBS Lett* 2010; **584**: 2827-2832 [PMID: 20434448 DOI: [10.1016/j.febslet.2010.04.064](http://dx.doi.org/10.1016/j.febslet.2010.04.064)]  120 **Gustin C**, Van Steenbrugge M, Raes M. LPA modulates monocyte migration directly and via LPA-stimulated endothelial cells. *Am J Physiol Cell Physiol* 2008; **295**: C905-C914 [PMID: 18632732 DOI: [10.1152/ajpcell.00544.2007](http://dx.doi.org/10.1152/ajpcell.00544.2007)]  121 **Lee H**, Lin CI, Liao JJ, Lee YW, Yang HY, Lee CY, Hsu HY, Wu HL. Lysophospholipids increase ICAM-1 expression in HUVEC through a Gi- and NF-kappaB-dependent mechanism. *Am J Physiol Cell Physiol* 2004; **287**: C1657-C1666 [PMID: 15294853 DOI: [10.1152/ajpcell.00172.2004](http://dx.doi.org/10.1152/ajpcell.00172.2004)]  122 **Shimada H**, Rajagopalan LE. Rho kinase-2 activation in human endothelial cells drives lysophosphatidic acid-mediated expression of cell adhesion molecules via NF-kappaB p65. *J Biol Chem* 2010; **285**: 12536-12542 [PMID: 20164172 DOI: [10.1074/jbc.M109.099630](http://dx.doi.org/10.1074/jbc.M109.099630)]  123 **Rizza C**, Leitinger N, Yue J, Fischer DJ, Wang DA, Shih PT, Lee H, Tigyi G, Berliner JA. Lysophosphatidic acid as a regulator of endothelial/leukocyte interaction. *Lab Invest* 1999; **79**: 1227-1235 [PMID: 10532586]  124 **Gustin C**, Delaive E, Dieu M, Calay D, Raes M. Upregulation of pentraxin-3 in human endothelial cells after lysophosphatidic acid exposure. *Arterioscler Thromb Vasc Biol* 2008; **28**: 491-497 [PMID: 18162608 DOI: [10.1161/ATVBAHA.107.158642](http://dx.doi.org/10.1161/ATVBAHA.107.158642)]  125 **Deban L**, Russo RC, Sironi M, Moalli F, Scanziani M, Zambelli V, Cuccovillo I, Bastone A, Gobbi M, Valentino S, Doni A, Garlanda C, Danese S, Salvatori G, Sassano M, Evangelista V, Rossi B, Zenaro E, Constantin G, Laudanna C, Bottazzi B, Mantovani A. Regulation of leukocyte recruitment by the long pentraxin PTX3. *Nat Immunol* 2010; **11**: 328-334 [PMID: 20208538 DOI: [10.1038/ni.1854](http://dx.doi.org/10.1038/ni.1854)]  126 **Diamond JM**, Meyer NJ, Feng R, Rushefski M, Lederer DJ, Kawut SM, Lee JC, Cantu E, Shah RJ, Lama VN, Bhorade S, Crespo M, Demissie E, Sonett J, Wille K, Orens J, Weinacker A, Weill D, Arcasoy S, Shah PD, Belperio JA, Wilkes D, Ware LB, Palmer SM, Christie JD. Variation in PTX3 is associated with primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2012; **186**: 546-552 [PMID: 22822025 DOI: [10.1164/rccm.201204-0692OC](http://dx.doi.org/10.1164/rccm.201204-0692OC)]  127 **Avraamides C**, Bromberg ME, Gaughan JP, Thomas SM, Tsygankov AY, Panetti TS. Hic-5 promotes endothelial cell migration to lysophosphatidic acid. *Am J Physiol Heart Circ Physiol* 2007; **293**: H193-H203 [PMID: 17337598 DOI: [10.1152/ajpheart.00728.2006](http://dx.doi.org/10.1152/ajpheart.00728.2006)]  128 **Panetti TS**, Hannah DF, Avraamides C, Gaughan JP, Marcinkiewicz C, Huttenlocher A, Mosher DF. Extracellular matrix molecules regulate endothelial cell migration stimulated by lysophosphatidic acid. *J Thromb Haemost* 2004; **2**: 1645-1656 [PMID: 15333043 DOI: [10.1111/j.1538-7836.2004.00902.x](http://dx.doi.org/10.1111/j.1538-7836.2004.00902.x)]  129 **Panetti TS**, Nowlen J, Mosher DF. Sphingosine-1-phosphate and lysophosphatidic acid stimulate endothelial cell migration. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1013-1019 [PMID: 10764666 DOI: [10.1161/01.ATV.20.4.1013](http://dx.doi.org/10.1161/01.ATV.20.4.1013)]  130 **Chen Y**, Ramakrishnan DP, Ren B. Regulation of angiogenesis by phospholipid lysophosphatidic acid. *Front Biosci (Landmark Ed)* 2013; **18**: 852-861 [PMID: 23747852 DOI: 10.2741/4148]  131 **Ren B**, Hale J, Srikanthan S, Silverstein RL. Lysophosphatidic acid suppresses endothelial cell CD36 expression and promotes angiogenesis via a PKD-1-dependent signaling pathway. *Blood* 2011; **117**: 6036-6045 [PMID: 21441463 DOI: [10.1182/blood-2010-12-326017](http://dx.doi.org/10.1182/blood-2010-12-326017)]  132 **Lin CI**, Chen CN, Huang MT, Lee SJ, Lin CH, Chang CC, Lee H. Lysophosphatidic acid upregulates vascular endothelial growth factor-C and tube formation in human endothelial cells through LPA(1/3), COX-2, and NF-kappaB activation- and EGFR transactivation-dependent mechanisms. *Cell Signal* 2008; **20**: 1804-1814 [PMID: 18627789 DOI: [10.1016/j.cellsig.2008.06.008](http://dx.doi.org/10.1016/j.cellsig.2008.06.008)]  133 **Lin CE**, Chen SU, Lin CC, Chang CH, Lin YC, Tai YL, Shen TL, Lee H. Lysophosphatidic acid enhances vascular endothelial growth factor-C expression in human prostate cancer PC-3 cells. *PLoS One* 2012; **7**: e41096 [PMID: 22911748 DOI: [10.1371/journal.pone.0041096](http://dx.doi.org/10.1371/journal.pone.0041096)]  134 **Owens GK**, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. *Physiol Rev* 2004; **84**: 767-801 [PMID: 15269336 DOI: [10.1152/physrev.00041.2003](http://dx.doi.org/10.1152/physrev.00041.2003)]  135 **Smyth SS**, Cheng HY, Miriyala S, Panchatcharam M, Morris AJ. Roles of lysophosphatidic acid in cardiovascular physiology and disease. *Biochim Biophys Acta* 2008; **1781**: 563-570 [PMID: 18586114]  136 **Cui MZ**, Laag E, Sun L, Tan M, Zhao G, Xu X. Lysophosphatidic acid induces early growth response gene 1 expression in vascular smooth muscle cells: CRE and SRE mediate the transcription. *Arterioscler Thromb Vasc Biol* 2006; **26**: 1029-1035 [PMID: 16497989 DOI: [10.1161/01.ATV.0000214980.90567.b5](http://dx.doi.org/10.1161/01.ATV.0000214980.90567.b5)]  137 **Iyoda T**, Zhang F, Sun L, Hao F, Schmitz-Peiffer C, Xu X, Cui MZ. Lysophosphatidic acid induces early growth response-1 (Egr-1) protein expression via protein kinase Cδ-regulated extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) activation in vascular smooth muscle cells. *J Biol Chem* 2012; **287**: 22635-22642 [PMID: 22577133 DOI: [10.1074/jbc.M111.335695](http://dx.doi.org/10.1074/jbc.M111.335695)]  138 **Bhattacharyya S**, Fang F, Tourtellotte W, Varga J. Egr-1: new conductor for the tissue repair orchestra directs harmony (regeneration) or cacophony (fibrosis). *J Pathol* 2013; **229**: 286-297 [PMID: 23132749 DOI: [10.1002/path.4131](http://dx.doi.org/10.1002/path.4131)]  139 **Cerutis DR**, Nogami M, Anderson JL, Churchill JD, Romberger DJ, Rennard SI, Toews ML. Lysophosphatidic acid and EGF stimulate mitogenesis in human airway smooth muscle cells. *Am J Physiol* 1997; **273**: L10-L15 [PMID: 9252534]  140 **Toews ML**, Ustinova EE, Schultz HD. Lysophosphatidic acid enhances contractility of isolated airway smooth muscle. *J Appl Physiol* (1985) 1997; **83**: 1216-1222 [PMID: 9338431]  141 **Ediger TL**, Danforth BL, Toews ML. Lysophosphatidic acid upregulates the epidermal growth factor receptor in human airway smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 2002; **282**: L91-L98 [PMID: 11741820]  142 **Kassel KM**, Schulte NA, Toews ML. Modulation of epidermal growth factor receptor binding to human airway smooth muscle cells by glucocorticoids and beta2-adrenergic receptor agonists. *Am J Physiol Lung Cell Mol Physiol* 2009; **296**: L693-L699 [PMID: 19201814 DOI: [10.1152/ajplung.90446.2008](http://dx.doi.org/10.1152/ajplung.90446.2008)]  143 **Tatler AL**, John AE, Jolly L, Habgood A, Porte J, Brightling C, Knox AJ, Pang L, Sheppard D, Huang X, Jenkins G. Integrin αvβ5-mediated TGF-β activation by airway smooth muscle cells in asthma. *J Immunol* 2011; **187**: 6094-6107 [PMID: 22025551 DOI: [10.4049/jimmunol.1003507](http://dx.doi.org/10.4049/jimmunol.1003507)]  144 **Rai V**, Touré F, Chitayat S, Pei R, Song F, Li Q, Zhang J, Rosario R, Ramasamy R, Chazin WJ, Schmidt AM. Lysophosphatidic acid targets vascular and oncogenic pathways via RAGE signaling. *J Exp Med* 2012; **209**: 2339-2350 [PMID: 23209312 DOI: [10.1084/jem.20120873](http://dx.doi.org/10.1084/jem.20120873)]  145 **Buckley ST**, Ehrhardt C. The receptor for advanced glycation end products (RAGE) and the lung. *J Biomed Biotechnol* 2010; **2010**: 917108 [PMID: 20145712]  146 **Blanchard C**, Rothenberg ME. Biology of the eosinophil. *Adv Immunol* 2009; **101**: 81-121 [PMID: 19231593 DOI: 10.1016/S0065-2776(08)01003-1]  147 **Jacobsen EA**, Helmers RA, Lee JJ, Lee NA. The expanding role(s) of eosinophils in health and disease. *Blood* 2012; **120**: 3882-3890 [PMID: 22936660 DOI: [10.1182/blood-2012-06-330845](http://dx.doi.org/10.1182/blood-2012-06-330845)]  148 **Idzko M**, Laut M, Panther E, Sorichter S, Dürk T, Fluhr JW, Herouy Y, Mockenhaupt M, Myrtek D, Elsner P, Norgauer J. Lysophosphatidic acid induces chemotaxis, oxygen radical production, CD11b up-regulation, Ca2+ mobilization, and actin reorganization in human eosinophils via pertussis toxin-sensitive G proteins. *J Immunol* 2004; **172**: 4480-4485 [PMID: 15034064]  149 **Hashimoto T**, Yamashita M, Ohata H, Momose K. Lysophosphatidic acid enhances in vivo infiltration and activation of guinea pig eosinophils and neutrophils via a Rho/Rho-associated protein kinase-mediated pathway. *J Pharmacol Sci* 2003; **91**: 8-14 [PMID: 12686725 DOI: [10.1254/jphs.91.8](http://dx.doi.org/10.1254/jphs.91.8)]  150 **Kolaczkowska E**, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol* 2013; **13**: 159-175 [PMID: 23435331 DOI: [10.1038/nri3399](http://dx.doi.org/10.1038/nri3399)]  151 **Itagaki K**, Kannan KB, Hauser CJ. Lysophosphatidic acid triggers calcium entry through a non-store-operated pathway in human neutrophils. *J Leukoc Biol* 2005; **77**: 181-189 [PMID: 15522918 DOI: [10.1189/jlb.0704390](http://dx.doi.org/10.1189/jlb.0704390)]  152 **Tou JS**, Gill JS. Lysophosphatidic acid increases phosphatidic acid formation, phospholipase D activity and degranulation by human neutrophils. *Cell Signal* 2005; **17**: 77-82 [PMID: 15451027 DOI: [10.1016/j.cellsig.2004.06.003](http://dx.doi.org/10.1016/j.cellsig.2004.06.003)]  153 **Fischer LG**, Bremer M, Coleman EJ, Conrad B, Krumm B, Gross A, Hollmann MW, Mandell G, Durieux ME. Local anesthetics attenuate lysophosphatidic acid-induced priming in human neutrophils. *Anesth Analg* 2001; **92**: 1041-1047 [PMID: 11273947 DOI: [10.1097/00000539-200104000-00044](http://dx.doi.org/10.1097/00000539-200104000-00044)]  154 **Chettibi S**, Lawrence AJ, Stevenson RD, Young JD. Effect of lysophosphatidic acid on motility, polarisation and metabolic burst of human neutrophils. *FEMS Immunol Med Microbiol* 1994; **8**: 271-281 [PMID: 8004064 DOI: [10.1111/j.1574-695X.1994.tb00452.x](http://dx.doi.org/10.1111/j.1574-695X.1994.tb00452.x)]  155 **Wynn TA**, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. *Nature* 2013; **496**: 445-455 [PMID: 23619691 DOI: [10.1038/nature12034](http://dx.doi.org/10.1038/nature12034)]  156 **Gwyer Findlay E**, Hussell T. Macrophage-mediated inflammation and disease: a focus on the lung. *Mediators Inflamm* 2012; **2012**: 140937 [PMID: 23304058]  157 **Duong CQ**, Bared SM, Abu-Khader A, Buechler C, Schmitz A, Schmitz G. Expression of the lysophospholipid receptor family and investigation of lysophospholipid-mediated responses in human macrophages. *Biochim Biophys Acta* 2004; **1682**: 112-119 [PMID: 15158762]  158 **Hornuss C**, Hammermann R, Fuhrmann M, Juergens UR, Racké K. Human and rat alveolar macrophages express multiple EDG receptors. *Eur J Pharmacol* 2001; **429**: 303-308 [PMID: 11698050 DOI: 10.1016/S0014-2999(01)01329-2]  159 **Lee H**, Liao JJ, Graeler M, Huang MC, Goetzl EJ. Lysophospholipid regulation of mononuclear phagocytes. *Biochim Biophys Acta* 2002; **1582**: 175-177 [PMID: 12069826 DOI: 10.1016/S1388-1981(02)00153-1]  160 **Fueller M**, Wang DA, Tigyi G, Siess W. Activation of human monocytic cells by lysophosphatidic acid and sphingosine-1-phosphate. *Cell Signal* 2003; **15**: 367-375 [PMID: 12618211 DOI: 10.1016/S0898-6568(02)00117-1]  161 **D'Aquilio F**, Procaccini M, Izzi V, Chiurchiu' V, Giambra V, Carotenuto F, Di Nardo P, Baldini PM. Activatory properties of lysophosphatidic acid on human THP-1 cells. *Inflammation* 2005; **29**: 129-140 [PMID: 17089191 DOI: [10.1007/s10753-006-9008-9](http://dx.doi.org/10.1007/s10753-006-9008-9)]  162 **Chang CL**, Hsu HY, Lin HY, Chiang W, Lee H. Lysophosphatidic acid-induced oxidized low-density lipoprotein uptake is class A scavenger receptor-dependent in macrophages. *Prostaglandins Other Lipid Mediat* 2008; **87**: 20-25 [PMID: 18585471 DOI: [10.1016/j.prostaglandins.2008.05.002](http://dx.doi.org/10.1016/j.prostaglandins.2008.05.002)]  163 **Li S**, Xiong C, Zhang J. ATX and LPA receptor 3 are coordinately up-regulated in lipopolysaccharide-stimulated THP-1 cells through PKR and SPK1-mediated pathways. *FEBS Lett* 2012; **586**: 792-797 [PMID: 22314276 DOI: [10.1016/j.febslet.2012.01.044](http://dx.doi.org/10.1016/j.febslet.2012.01.044)]  164 **Li S**, Zhang J. Lipopolysaccharide induces autotaxin expression in human monocytic THP-1 cells. *Biochem Biophys Res Commun* 2009; **378**: 264-268 [PMID: 19027716 DOI: [10.1016/j.bbrc.2008.11.047](http://dx.doi.org/10.1016/j.bbrc.2008.11.047)]  165 **Koh JS**, Lieberthal W, Heydrick S, Levine JS. Lysophosphatidic acid is a major serum noncytokine survival factor for murine macrophages which acts via the phosphatidylinositol 3-kinase signaling pathway. *J Clin Invest* 1998; **102**: 716-727 [PMID: 9710440 DOI: [10.1172/JCI1002](http://dx.doi.org/10.1172/JCI1002)]  166 **McIntyre TM**, Pontsler AV, Silva AR, St Hilaire A, Xu Y, Hinshaw JC, Zimmerman GA, Hama K, Aoki J, Arai H, Prestwich GD. Identification of an intracellular receptor for lysophosphatidic acid (LPA): LPA is a transcellular PPARgamma agonist. *Proc Natl Acad Sci U S A* 2003; **100**: 131-136 [PMID: 12502787 DOI: [10.1073/pnas.0135855100](http://dx.doi.org/10.1073/pnas.0135855100)]  167 **Chang CL**, Lin ME, Hsu HY, Yao CL, Hwang SM, Pan CY, Hsu CY, Lee H. Lysophosphatidic acid-induced interleukin-1 beta expression is mediated through Gi/Rho and the generation of reactive oxygen species in macrophages. *J Biomed Sci* 2008; **15**: 357-363 [PMID: 18038269 DOI: [10.1007/s11373-007-9223-x](http://dx.doi.org/10.1007/s11373-007-9223-x)]  168 **Martino A**, Volpe E, Baldini PM. The influence of lysophosphatidic acid on the immunophenotypic differentiation of human monocytes into dendritic cells. *Haematologica* 2006; **91**: 1273-1274 [PMID: 16956832]  169 **Coutant F**, Perrin-Cocon L, Agaugué S, Delair T, André P, Lotteau V. Mature dendritic cell generation promoted by lysophosphatidylcholine. *J Immunol* 2002; **169**: 1688-1695 [PMID: 12165488]  170 **Lauber K**, Bohn E, Kröber SM, Xiao YJ, Blumenthal SG, Lindemann RK, Marini P, Wiedig C, Zobywalski A, Baksh S, Xu Y, Autenrieth IB, Schulze-Osthoff K, Belka C, Stuhler G, Wesselborg S. Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal. *Cell* 2003; **113**: 717-730 [PMID: 12809603 DOI: 10.1016/S0092-8674(03)00422-7]  171 **Peter C**, Waibel M, Radu CG, Yang LV, Witte ON, Schulze-Osthoff K, Wesselborg S, Lauber K. Migration to apoptotic "find-me" signals is mediated via the phagocyte receptor G2A. *J Biol Chem* 2008; **283**: 5296-5305 [PMID: 18089568 DOI: [10.1074/jbc.M706586200](http://dx.doi.org/10.1074/jbc.M706586200)]  172 **Panther E**, Idzko M, Corinti S, Ferrari D, Herouy Y, Mockenhaupt M, Dichmann S, Gebicke-Haerter P, Di Virgilio F, Girolomoni G, Norgauer J. The influence of lysophosphatidic acid on the functions of human dendritic cells. *J Immunol* 2002; **169**: 4129-4135 [PMID: 12370341]  173 **Chen R**, Roman J, Guo J, West E, McDyer J, Williams MA, Georas SN. Lysophosphatidic acid modulates the activation of human monocyte-derived dendritic cells. *Stem Cells Dev* 2006; **15**: 797-804 [PMID: 17253943 DOI: [10.1089/scd.2006.15.797](http://dx.doi.org/10.1089/scd.2006.15.797)]  174 **Oz-Arslan D**, Rüscher W, Myrtek D, Ziemer M, Jin Y, Damaj BB, Sorichter S, Idzko M, Norgauer J, Maghazachi AA. IL-6 and IL-8 release is mediated via multiple signaling pathways after stimulating dendritic cells with lysophospholipids. *J Leukoc Biol* 2006; **80**: 287-297 [PMID: 16769764 DOI: [10.1189/jlb.1205751](http://dx.doi.org/10.1189/jlb.1205751)]  175 **Chan LC**, Peters W, Xu Y, Chun J, Farese RV, Cases S. LPA3 receptor mediates chemotaxis of immature murine dendritic cells to unsaturated lysophosphatidic acid (LPA). *J Leukoc Biol* 2007; **82**: 1193-1200 [PMID: 17709403 DOI: [10.1189/jlb.0407221](http://dx.doi.org/10.1189/jlb.0407221)]  176 **Goetzl EJ**, Kong Y, Voice JK. Cutting edge: differential constitutive expression of functional receptors for lysophosphatidic acid by human blood lymphocytes. *J Immunol* 2000; **164**: 4996-4999 [PMID: 10799850]  177 **Zheng Y**, Voice JK, Kong Y, Goetzl EJ. Altered expression and functional profile of lysophosphatidic acid receptors in mitogen-activated human blood T lymphocytes. *FASEB J* 2000; **14**: 2387-2389 [PMID: 11024010]  178 **Rubenfeld J**, Guo J, Sookrung N, Chen R, Chaicumpa W, Casolaro V, Zhao Y, Natarajan V, Georas S. Lysophosphatidic acid enhances interleukin-13 gene expression and promoter activity in T cells. *Am J Physiol Lung Cell Mol Physiol* 2006; **290**: L66-L74 [PMID: 16199434 DOI: [10.1152/ajplung.00473.2004](http://dx.doi.org/10.1152/ajplung.00473.2004)]  179 **Kotarsky K**, Boketoft A, Bristulf J, Nilsson NE, Norberg A, Hansson S, Owman C, Sillard R, Leeb-Lundberg LM, Olde B. Lysophosphatidic acid binds to and activates GPR92, a G protein-coupled receptor highly expressed in gastrointestinal lymphocytes. *J Pharmacol Exp Ther* 2006; **318**: 619-628 [PMID: 16651401 DOI: [10.1124/jpet.105.098848](http://dx.doi.org/10.1124/jpet.105.098848)]  180 **Satoh Y**, Ohkawa R, Nakamura K, Higashi K, Kaneko M, Yokota H, Aoki J, Arai H, Yuasa Y, Yatomi Y. Lysophosphatidic acid protection against apoptosis in the human pre-B-cell line Nalm-6. *Eur J Haematol* 2007; **78**: 510-517 [PMID: 17419739 DOI: [10.1111/j.1600-0609.2007.00849.x](http://dx.doi.org/10.1111/j.1600-0609.2007.00849.x)]  181 **Xu Y**, Casey G, Mills GB. Effect of lysophospholipids on signaling in the human Jurkat T cell line. *J Cell Physiol* 1995; **163**: 441-450 [PMID: 7775587 DOI: [10.1002/jcp.1041630303](http://dx.doi.org/10.1002/jcp.1041630303)]  182 **Rosskopf D**, Daelman W, Busch S, Schurks M, Hartung K, Kribben A, Michel MC, Siffert W. Growth factor-like action of lysophosphatidic acid on human B lymphoblasts. *Am J Physiol* 1998; **274**: C1573-C1582 [PMID: 9611122]  183 **Nam JH**, Shin DH, Min JE, Ye SK, Jeon JH, Kim SJ. Ca2+ signaling induced by sphingosine 1-phosphate and lysophosphatidic acid in mouse B cells. *Mol Cells* 2010; **29**: 85-91 [PMID: 20069383 DOI: [10.1007/s10059-010-0020-4](http://dx.doi.org/10.1007/s10059-010-0020-4)]  184 **Zheng Y**, Kong Y, Goetzl EJ. Lysophosphatidic acid receptor-selective effects on Jurkat T cell migration through a Matrigel model basement membrane. *J Immunol* 2001; **166**: 2317-2322 [PMID: 11160288]  185 **Tanikawa T**, Kurohane K, Imai Y. Regulatory effect of lysophosphatidic acid on lymphocyte migration. *Biol Pharm Bull* 2010; **33**: 204-208 [PMID: 20118541 DOI: [10.1248/bpb.33.204](http://dx.doi.org/10.1248/bpb.33.204)]  186 **Rieken S**, Herroeder S, Sassmann A, Wallenwein B, Moers A, Offermanns S, Wettschureck N. Lysophospholipids control integrin-dependent adhesion in splenic B cells through G(i) and G(12)/G(13) family G-proteins but not through G(q)/G(11). *J Biol Chem* 2006; **281**: 36985-36992 [PMID: 17023430 DOI: [10.1074/jbc.M605287200](http://dx.doi.org/10.1074/jbc.M605287200)]  187 **Goetzl EJ**, Kong Y, Mei B. Lysophosphatidic acid and sphingosine 1-phosphate protection of T cells from apoptosis in association with suppression of Bax. *J Immunol* 1999; **162**: 2049-2056 [PMID: 9973477]  188 **Hu X**, Haney N, Kropp D, Kabore AF, Johnston JB, Gibson SB. Lysophosphatidic acid (LPA) protects primary chronic lymphocytic leukemia cells from apoptosis through LPA receptor activation of the anti-apoptotic protein AKT/PKB. *J Biol Chem* 2005; **280**: 9498-9508 [PMID: 15618220 DOI: [10.1074/jbc.M410455200](http://dx.doi.org/10.1074/jbc.M410455200)]  189 **Meng Y**, Graves L, Do TV, So J, Fishman DA. Upregulation of FasL by LPA on ovarian cancer cell surface leads to apoptosis of activated lymphocytes. *Gynecol Oncol* 2004; **95**: 488-495 [PMID: 15581951 DOI: [10.1016/j.ygyno.2004.07.052](http://dx.doi.org/10.1016/j.ygyno.2004.07.052)]  190 **Kang S**, Luo R, Smicun Y, Fishman DA, Meng Y. Selective induction of cyclooxygenase-2 plays a role in lysophosphatidic acid regulated Fas ligand cell surface presentation. *FEBS Lett* 2006; **580**: 443-449 [PMID: 16376882 DOI: [10.1016/j.febslet.2005.12.033](http://dx.doi.org/10.1016/j.febslet.2005.12.033)]  191 **Wang L**, Knudsen E, Jin Y, Gessani S, Maghazachi AA. Lysophospholipids and chemokines activate distinct signal transduction pathways in T helper 1 and T helper 2 cells. *Cell Signal* 2004; **16**: 991-1000 [PMID: 15212760]  192 **Bozza FA**, Shah AM, Weyrich AS, Zimmerman GA. Amicus or adversary: platelets in lung biology, acute injury, and inflammation. *Am J Respir Cell Mol Biol* 2009; **40**: 123-134 [PMID: 18723438 DOI: [10.1165/rcmb.2008-0241TR](http://dx.doi.org/10.1165/rcmb.2008-0241TR)]  193 **Finigan JH**. The coagulation system and pulmonary endothelial function in acute lung injury. *Microvasc Res* 2009; **77**: 35-38 [PMID: 18938186 DOI: [10.1016/j.mvr.2008.09.002](http://dx.doi.org/10.1016/j.mvr.2008.09.002)]  194 **de Boer JD**, Majoor CJ, van 't Veer C, Bel EH, van der Poll T. Asthma and coagulation. *Blood* 2012; **119**: 3236-3244 [PMID: 22262775 DOI: [10.1182/blood-2011-11-391532](http://dx.doi.org/10.1182/blood-2011-11-391532)]  195 **Fulkerson Z**, Wu T, Sunkara M, Kooi CV, Morris AJ, Smyth SS. Binding of autotaxin to integrins localizes lysophosphatidic acid production to platelets and mammalian cells. *J Biol Chem* 2011; **286**: 34654-34663 [PMID: 21832043 DOI: [10.1074/jbc.M111.276725](http://dx.doi.org/10.1074/jbc.M111.276725)]  196 **Hausmann J**, Kamtekar S, Christodoulou E, Day JE, Wu T, Fulkerson Z, Albers HM, van Meeteren LA, Houben AJ, van Zeijl L, Jansen S, Andries M, Hall T, Pegg LE, Benson TE, Kasiem M, Harlos K, Kooi CW, Smyth SS, Ovaa H, Bollen M, Morris AJ, Moolenaar WH, Perrakis A. Structural basis of substrate discrimination and integrin binding by autotaxin. *Nat Struct Mol Biol* 2011; **18**: 198-204 [PMID: 21240271 DOI: [10.1038/nsmb.1980](http://dx.doi.org/10.1038/nsmb.1980)]  197 **Aoki J**, Taira A, Takanezawa Y, Kishi Y, Hama K, Kishimoto T, Mizuno K, Saku K, Taguchi R, Arai H. Serum lysophosphatidic acid is produced through diverse phospholipase pathways. *J Biol Chem* 2002; **277**: 48737-48744 [PMID: 12354767 DOI: [10.1074/jbc.M206812200](http://dx.doi.org/10.1074/jbc.M206812200)]  198 **Voehringer D**. Protective and pathological roles of mast cells and basophils. *Nat Rev Immunol* 2013; **13**: 362-375 [PMID: 23558889 DOI: [10.1038/nri3427](http://dx.doi.org/10.1038/nri3427)]  199 **Bagga S**, Price KS, Lin DA, Friend DS, Austen KF, Boyce JA. Lysophosphatidic acid accelerates the development of human mast cells. *Blood* 2004; **104**: 4080-4087 [PMID: 15319282 DOI: [10.1182/blood-2004-03-1166](http://dx.doi.org/10.1182/blood-2004-03-1166)]  200 **Lin DA**, Boyce JA. IL-4 regulates MEK expression required for lysophosphatidic acid-mediated chemokine generation by human mast cells. *J Immunol* 2005; **175**: 5430-5438 [PMID: 16210650]  201 **Lundequist A**, Boyce JA. LPA5 is abundantly expressed by human mast cells and important for lysophosphatidic acid induced MIP-1β release. *PLoS One* 2011; **6**: e18192 [PMID: 21464938 DOI: [10.1371/journal.pone.0018192](http://dx.doi.org/10.1371/journal.pone.0018192)]  202 **Hashimoto T**, Ohata H, Momose K, Honda K. Lysophosphatidic acid induces histamine release from mast cells and skin fragments. *Pharmacology* 2005; **75**: 13-20 [PMID: 15897679 DOI: [10.1159/000085784](http://dx.doi.org/10.1159/000085784)]  203 **Hashimoto T**, Ohata H, Honda K. Lysophosphatidic acid (LPA) induces plasma exudation and histamine release in mice via LPA receptors. *J Pharmacol Sci* 2006; **100**: 82-87 [PMID: 16404130 DOI: [10.1254/jphs.FPJ05030X](http://dx.doi.org/10.1254/jphs.FPJ05030X)]  204 **Matthay MA**, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest* 2012; **122**: 2731-2740 [PMID: 22850883 DOI: [10.1172/JCI60331](http://dx.doi.org/10.1172/JCI60331)]  205 **Zhao Y**, Gorshkova IA, Berdyshev E, He D, Fu P, Ma W, Su Y, Usatyuk PV, Pendyala S, Oskouian B, Saba JD, Garcia JG, Natarajan V. Protection of LPS-induced murine acute lung injury by sphingosine-1-phosphate lyase suppression. *Am J Respir Cell Mol Biol* 2011; **45**: 426-435 [PMID: 21148740 DOI: [10.1165/rcmb.2010-0422OC](http://dx.doi.org/10.1165/rcmb.2010-0422OC)]  206 **Allen TC**, Kurdowska A. Interleukin 8 and Acute Lung Injury. *Arch Pathol Lab Med* 2013; : [PMID: 23782136 DOI: 10.5858/arpa.2013-0182-RA]  207 **Abraham E**. Neutrophils and acute lung injury. *Crit Care Med* 2003; **31**: S195-S199 [PMID: 12682440 DOI: [10.1097/01.CCM.0000057843.47705.E8](http://dx.doi.org/10.1097/01.CCM.0000057843.47705.E8)]  208 **Lin DA**, Boyce JA. Lysophospholipids as mediators of immunity. *Adv Immunol* 2006; **89**: 141-167 [PMID: 16682274 DOI: 10.1016/S0065-2776(05)89004-2]  209 **He D**, Su Y, Usatyuk PV, Spannhake EW, Kogut P, Solway J, Natarajan V, Zhao Y. Lysophosphatidic acid enhances pulmonary epithelial barrier integrity and protects endotoxin-induced epithelial barrier disruption and lung injury. *J Biol Chem* 2009; **284**: 24123-24132 [PMID: 19586906 DOI: [10.1074/jbc.M109.007393](http://dx.doi.org/10.1074/jbc.M109.007393)]  210 **Pittet JF**, Griffiths MJ, Geiser T, Kaminski N, Dalton SL, Huang X, Brown LA, Gotwals PJ, Koteliansky VE, Matthay MA, Sheppard D. TGF-beta is a critical mediator of acute lung injury. *J Clin Invest* 2001; **107**: 1537-1544 [PMID: 11413161 DOI: [10.1172/JCI11963](http://dx.doi.org/10.1172/JCI11963)]  211 **Jenkins RG**, Su X, Su G, Scotton CJ, Camerer E, Laurent GJ, Davis GE, Chambers RC, Matthay MA, Sheppard D. Ligation of protease-activated receptor 1 enhances alpha(v)beta6 integrin-dependent TGF-beta activation and promotes acute lung injury. *J Clin Invest* 2006; **116**: 1606-1614 [PMID: 16710477 DOI: [10.1172/JCI27183](http://dx.doi.org/10.1172/JCI27183)]  212 **Chambers RC**, Scotton CJ. Coagulation cascade proteinases in lung injury and fibrosis. *Proc Am Thorac Soc* 2012; **9**: 96-101 [PMID: 22802281 DOI: [10.1513/pats.201201-006AW](http://dx.doi.org/10.1513/pats.201201-006AW)]  213 **Raghu G**, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; **183**: 788-824 [PMID: 21471066 DOI: [10.1164/rccm.2009-040GL](http://dx.doi.org/10.1164/rccm.2009-040GL)]  214 **Wynn TA**. Integrating mechanisms of pulmonary fibrosis. *J Exp Med* 2011; **208**: 1339-1350 [PMID: 21727191 DOI: [10.1084/jem.20110551](http://dx.doi.org/10.1084/jem.20110551)]  215 **Moore BB**, Hogaboam CM. Murine models of pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2008; **294**: L152-L160 [PMID: 17993587 DOI: [10.1152/ajplung.00313.2007](http://dx.doi.org/10.1152/ajplung.00313.2007)]  216 **Mouratis MA**, Aidinis V. Modeling pulmonary fibrosis with bleomycin. *Curr Opin Pulm Med* 2011; **17**: 355-361 [PMID: 21832918 DOI: [10.1097/MCP.0b013e328349ac2b](http://dx.doi.org/10.1097/MCP.0b013e328349ac2b)]  217 **Wynn TA**, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. *Nat Med* 2012; **18**: 1028-1040 [PMID: 22772564 DOI: [10.1038/nm.2807](http://dx.doi.org/10.1038/nm.2807)]  218 **Schmidt R**, Ruppert C, Markart P, Lübke N, Ermert L, Weissmann N, Breithecker A, Ermert M, Seeger W, Günther A. Changes in pulmonary surfactant function and composition in bleomycin-induced pneumonitis and fibrosis. *Toxicol Appl Pharmacol* 2004; **195**: 218-231 [PMID: 14998687 DOI: [10.1016/j.taap.2003.11.011](http://dx.doi.org/10.1016/j.taap.2003.11.011)]  219 **Schmidt R**, Meier U, Markart P, Grimminger F, Velcovsky HG, Morr H, Seeger W, Günther A. Altered fatty acid composition of lung surfactant phospholipids in interstitial lung disease. *Am J Physiol Lung Cell Mol Physiol* 2002; **283**: L1079-L1085 [PMID: 12376361]  220 **Günther A**, Schmidt R, Nix F, Yabut-Perez M, Guth C, Rosseau S, Siebert C, Grimminger F, Morr H, Velcovsky HG, Seeger W. Surfactant abnormalities in idiopathic pulmonary fibrosis, hypersensitivity pneumonitis and sarcoidosis. *Eur Respir J* 1999; **14**: 565-573 [PMID: 10543276 DOI: [10.1034/j.1399-3003.1999.14c14.x](http://dx.doi.org/10.1034/j.1399-3003.1999.14c14.x)]  221 **Kuroda K**, Morimoto Y, Ogami A, Oyabu T, Nagatomo H, Hirohashi M, Yamato H, Nagafuchi Y, Tanaka I. Phospholipid concentration in lung lavage fluid as biomarker for pulmonary fibrosis. *Inhal Toxicol* 2006; **18**: 389-393 [PMID: 16513595 DOI: [10.1080/08958370500516200](http://dx.doi.org/10.1080/08958370500516200)]  222 **Oga T**, Matsuoka T, Yao C, Nonomura K, Kitaoka S, Sakata D, Kita Y, Tanizawa K, Taguchi Y, Chin K, Mishima M, Shimizu T, Narumiya S. Prostaglandin F(2alpha) receptor signaling facilitates bleomycin-induced pulmonary fibrosis independently of transforming growth factor-beta. *Nat Med* 2009; **15**: 1426-1430 [PMID: 19966781 DOI: [10.1038/nm.2066](http://dx.doi.org/10.1038/nm.2066)]  223 **Nagase T**, Uozumi N, Ishii S, Kita Y, Yamamoto H, Ohga E, Ouchi Y, Shimizu T. A pivotal role of cytosolic phospholipase A(2) in bleomycin-induced pulmonary fibrosis. *Nat Med* 2002; **8**: 480-484 [PMID: 11984592 DOI: [10.1038/nm0502-480](http://dx.doi.org/10.1038/nm0502-480)]  224 **Hirata H**, Arima M, Fukushima Y, Sugiyama K, Tokuhisa T, Fukuda T. Leukotriene C4 aggravates bleomycin-induced pulmonary fibrosis in mice. *Respirology* 2013; **18**: 674-681 [PMID: 23432979 DOI: [10.1111/resp.12072](http://dx.doi.org/10.1111/resp.12072)]  225 **Kabarowski JH**. G2A and LPC: regulatory functions in immunity. *Prostaglandins Other Lipid Mediat* 2009; **89**: 73-81 [PMID: 19383550 DOI: [10.1016/j.prostaglandins.2009.04.007](http://dx.doi.org/10.1016/j.prostaglandins.2009.04.007)]  226 **Gan L**, Xue JX, Li X, Liu DS, Ge Y, Ni PY, Deng L, Lu Y, Jiang W. Blockade of lysophosphatidic acid receptors LPAR1/3 ameliorates lung fibrosis induced by irradiation. *Biochem Biophys Res Commun* 2011; **409**: 7-13 [PMID: 21545790 DOI: [10.1016/j.bbrc.2011.04.084](http://dx.doi.org/10.1016/j.bbrc.2011.04.084)]  227 **Selman M**, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 2001; **134**: 136-151 [PMID: 11177318 DOI: [10.7326/0003-4819-134-2-200101160-00015](http://dx.doi.org/10.7326/0003-4819-134-2-200101160-00015)]  228 **Hagimoto N**, Kuwano K, Nomoto Y, Kunitake R, Hara N. Apoptosis and expression of Fas/Fas ligand mRNA in bleomycin-induced pulmonary fibrosis in mice. *Am J Respir Cell Mol Biol* 1997; **16**: 91-101 [PMID: 8998084 DOI: [10.1165/ajrcmb.16.1.8998084](http://dx.doi.org/10.1165/ajrcmb.16.1.8998084)]  229 **Kuwano K,** Kunitake R, Maeyama T, Hagimoto N, Kawasaki M, MatsubaT, Yoshimi M, Inoshima I, Yoshid K, Hara N Attenuation of bleomycin-induced pneumopathy in mice by a caspase inhibitor. *Am J Physiol Cell Mol Physio* 2001; 280 L316-L325 [PMID: 11159011]  230 **Oikonomou N,** Harokopos V, Zalevsky J, Valavanis C, Kotanidou A, Szymkowski DE, Kollias G, Aidinis V Soluble TNF Mediates the Transition from Pulmonary Inflammation to Fibrosis. *PLoS ONE* 2006; **1**: e108 [PMID: 17205112 DOI: [10.1371/journal.pone.0000108](http://dx.doi.org/10.1371/journal.pone.0000108)]  231 **Wu JM**, Xu Y, Skill NJ, Sheng H, Zhao Z, Yu M, Saxena R, Maluccio MA. Autotaxin expression and its connection with the TNF-alpha-NF-kappaB axis in human hepatocellular carcinoma. *Mol Cancer* 2010; **9**: 71 [PMID: 20356387 DOI: [10.1186/1476-4598-9-71](http://dx.doi.org/10.1186/1476-4598-9-71)]  232 **Oikonomou N**, Thanasopoulou A, Tzouvelekis A, Harokopos V, Paparountas T, Nikitopoulou I, Witke W, Karameris A, Kotanidou A, Bouros D, Aidinis V. Gelsolin expression is necessary for the development of modelled pulmonary inflammation and fibrosis. *Thorax* 2009; **64**: 467-475 [PMID: 19213772 DOI: [10.1136/thx.2008.107946](http://dx.doi.org/10.1136/thx.2008.107946)]  233 **Shea BS**, Tager AM. Role of the lysophospholipid mediators lysophosphatidic acid and sphingosine 1-phosphate in lung fibrosis. *Proc Am Thorac Soc* 2012; **9**: 102-110 [PMID: 22802282 DOI: [10.1513/pats.201201-005AW](http://dx.doi.org/10.1513/pats.201201-005AW)]  234 **Phan SH**. Genesis of the myofibroblast in lung injury and fibrosis. *Proc Am Thorac Soc* 2012; **9**: 148-152 [PMID: 22802289 DOI: [10.1513/pats.201201-011AW](http://dx.doi.org/10.1513/pats.201201-011AW)]  235 **Fernandez IE**, Eickelberg O. The impact of TGF-β on lung fibrosis: from targeting to biomarkers. *Proc Am Thorac Soc* 2012; **9**: 111-116 [PMID: 22802283 DOI: [10.1513/pats.201203-023AW](http://dx.doi.org/10.1513/pats.201203-023AW)]  236 **Madtes DK**, Rubenfeld G, Klima LD, Milberg JA, Steinberg KP, Martin TR, Raghu G, Hudson LD, Clark JG. Elevated transforming growth factor-alpha levels in bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; **158**: 424-430 [PMID: 9700116 DOI: [10.1164/ajrccm.158.2.9711112](http://dx.doi.org/10.1164/ajrccm.158.2.9711112)]  237 **Liu JY**, Sime PJ, Wu T, Warshamana GS, Pociask D, Tsai SY, Brody AR. Transforming growth factor-beta(1) overexpression in tumor necrosis factor-alpha receptor knockout mice induces fibroproliferative lung disease. *Am J Respir Cell Mol Biol* 2001; **25**: 3-7 [PMID: 11472967 DOI: [10.1165/ajrcmb.25.1.4481](http://dx.doi.org/10.1165/ajrcmb.25.1.4481)]  238 **Sime PJ**, Xing Z, Graham FL, Csaky KG, Gauldie J. Adenovector-mediated gene transfer of active transforming growth factor-beta1 induces prolonged severe fibrosis in rat lung. *J Clin Invest* 1997; **100**: 768-776 [PMID: 9259574 DOI: [10.1172/JCI119590](http://dx.doi.org/10.1172/JCI119590)]  239 **Crestani B**, Marchand-Adam S, Quesnel C, Plantier L, Borensztajn K, Marchal J, Mailleux A, Soler P, Dehoux M. Hepatocyte growth factor and lung fibrosis. *Proc Am Thorac Soc* 2012; **9**: 158-163 [PMID: 22802291 DOI: [10.1513/pats.201202-018AW](http://dx.doi.org/10.1513/pats.201202-018AW)]  240 **Lemanske RF**, Busse WW. Asthma: clinical expression and molecular mechanisms. *J Allergy Clin Immunol* 2010; **125**: S95-102 [PMID: 20176271 DOI: [10.1016/j.jaci.2009.10.047](http://dx.doi.org/10.1016/j.jaci.2009.10.047)]  241 **Holgate ST**. Epithelium dysfunction in asthma. *J Allergy Clin Immunol* 2007; **120**: 1233-144; quiz 1233-144; [PMID: 18073119]  242 **Pepe C**, Foley S, Shannon J, Lemiere C, Olivenstein R, Ernst P, Ludwig MS, Martin JG, Hamid Q. Differences in airway remodeling between subjects with severe and moderate asthma. *J Allergy Clin Immunol* 2005; **116**: 544-549 [PMID: 16159622 DOI: [10.1016/j.jaci.2005.06.011](http://dx.doi.org/10.1016/j.jaci.2005.06.011)]  243 **Pini L**, Hamid Q, Shannon J, Lemelin L, Olivenstein R, Ernst P, Lemière C, Martin JG, Ludwig MS. Differences in proteoglycan deposition in the airways of moderate and severe asthmatics. *Eur Respir J* 2007; **29**: 71-77 [PMID: 17050562 DOI: [10.1183/09031936.00047905](http://dx.doi.org/10.1183/09031936.00047905)]  244 **Park GY**, Lee YG, Berdyshev E, Nyenhuis S, Du J, Fu P, Gorshkova IA, Li Y, Chung S, Karpurapu M, Deng J, Ranjan R, Xiao L, Jaffe HA, Corbridge SJ, Kelly EA, Jarjour NN, Chun J, Prestwich GD, Kaffe E, Ninou I, Aidinis V, Morris AJ, Smyth SS, Ackerman SJ, Natarajan V, Christman JW. Autotaxin production of lysophosphatidic Acid mediates allergic asthmatic inflammation. *Am J Respir Crit Care Med* 2013; **188**: 928-940 [PMID: 24050723 DOI: [10.1164/rccm.201306-1014OC](http://dx.doi.org/10.1164/rccm.201306-1014OC)]  245 **Chung KF**, Barnes PJ. Cytokines in asthma. *Thorax* 1999; **54**: 825-857 [PMID: 10456976 DOI: [10.1136/thx.54.9.825](http://dx.doi.org/10.1136/thx.54.9.825)]  246 **Liu YJ**. Thymic stromal lymphopoietin: master switch for allergic inflammation. *J Exp Med* 2006; **203**: 269-273 [PMID: 16432252 DOI: [10.1084/jem.20051745](http://dx.doi.org/10.1084/jem.20051745)]  247 **Thomas SY**, Banerji A, Medoff BD, Lilly CM, Luster AD. Multiple chemokine receptors, including CCR6 and CXCR3, regulate antigen-induced T cell homing to the human asthmatic airway. *J Immunol* 2007; **179**: 1901-1912 [PMID: 17641057]  248 **Schutyser E**, Struyf S, Van Damme J. The CC chemokine CCL20 and its receptor CCR6. *Cytokine Growth Factor Rev* 2003; **14**: 409-426 [PMID: 12948524 DOI: 10.1016/S1359-6101(03)00049-2]  249 **McMillan SJ**, Xanthou G, Lloyd CM. Manipulation of allergen-induced airway remodeling by treatment with anti-TGF-beta antibody: effect on the Smad signaling pathway. *J Immunol* 2005; **174**: 5774-5780 [PMID: 15843580]  250 **Schnyder-Candrian S**, Togbe D, Couillin I, Mercier I, Brombacher F, Quesniaux V, Fossiez F, Ryffel B, Schnyder B. Interleukin-17 is a negative regulator of established allergic asthma. *J Exp Med* 2006; **203**: 2715-2725 [PMID: 17101734 DOI: [10.1084/jem.20061401](http://dx.doi.org/10.1084/jem.20061401)]  251 **Yang XO**, Chang SH, Park H, Nurieva R, Shah B, Acero L, Wang YH, Schluns KS, Broaddus RR, Zhu Z, Dong C. Regulation of inflammatory responses by IL-17F. *J Exp Med* 2008; **205**: 1063-1075 [PMID: 18411338 DOI: [10.1084/jem.20071978](http://dx.doi.org/10.1084/jem.20071978)]  252 **Veldhoen M**, Uyttenhove C, van Snick J, Helmby H, Westendorf A, Buer J, Martin B, Wilhelm C, Stockinger B. Transforming growth factor-beta 'reprograms' the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset. *Nat Immunol* 2008; **9**: 1341-1346 [PMID: 18931678 DOI: [10.1038/ni.1659](http://dx.doi.org/10.1038/ni.1659)]  253 **Vignola AM**, Paganin F, Capieu L, Scichilone N, Bellia M, Maakel L, Bellia V, Godard P, Bousquet J, Chanez P. Airway remodelling assessed by sputum and high-resolution computed tomography in asthma and COPD. *Eur Respir J* 2004; **24**: 910-917 [PMID: 15572531 DOI: [10.1183/09031936.04.00032603](http://dx.doi.org/10.1183/09031936.04.00032603)]  254 **Meurer R**, Van Riper G, Feeney W, Cunningham P, Hora D, Springer MS, MacIntyre DE, Rosen H. Formation of eosinophilic and monocytic intradermal inflammatory sites in the dog by injection of human RANTES but not human monocyte chemoattractant protein 1, human macrophage inflammatory protein 1 alpha, or human interleukin 8. *J Exp Med* 1993; **178**: 1913-1921 [PMID: 7504053 DOI: [10.1084/jem.178.6.1913](http://dx.doi.org/10.1084/jem.178.6.1913)]  255 **Schall TJ**, Bacon K, Toy KJ, Goeddel DV. Selective attraction of monocytes and T lymphocytes of the memory phenotype by cytokine RANTES. *Nature* 1990; **347**: 669-671 [PMID: 1699135 DOI: [10.1038/347669a0](http://dx.doi.org/10.1038/347669a0)]  256 **Venge J**, Lampinen M, Håkansson L, Rak S, Venge P. Identification of IL-5 and RANTES as the major eosinophil chemoattractants in the asthmatic lung. *J Allergy Clin Immunol* 1996; **97**: 1110-1115 [PMID: 8626989 DOI: 10.1016/S0091-6749(96)70265-8]  257 **Alam R**, York J, Boyars M, Stafford S, Grant JA, Lee J, Forsythe P, Sim T, Ida N. Increased MCP-1, RANTES, and MIP-1alpha in bronchoalveolar lavage fluid of allergic asthmatic patients. *Am J Respir Crit Care Med* 1996; **153**: 1398-1404 [PMID: 8616572 DOI: [10.1164/ajrccm.153.4.8616572](http://dx.doi.org/10.1164/ajrccm.153.4.8616572)]  258 **Fryer AA**, Spiteri MA, Bianco A, Hepple M, Jones PW, Strange RC, Makki R, Tavernier G, Smilie FI, Custovic A, Woodcock AA, Ollier WE, Hajeer AH. The -403 G--& gt; A promoter polymorphism in the RANTES gene is associated with atopy and asthma. *Genes Immun* 2000; **1**: 509-514 [PMID: 11197694 DOI: [10.1038/sj.gene.6363717](http://dx.doi.org/10.1038/sj.gene.6363717)]  259 **Ingram JL**, Kraft M. IL-13 in asthma and allergic disease: asthma phenotypes and targeted therapies. *J Allergy Clin Immunol* 2012; **130**: 829-42; quiz 843-4 [PMID: 22951057 DOI: [10.1016/j.jaci.2012.06.034](http://dx.doi.org/10.1016/j.jaci.2012.06.034)]  260 **Kuperman DA**, Huang X, Koth LL, Chang GH, Dolganov GM, Zhu Z, Elias JA, Sheppard D, Erle DJ. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nat Med* 2002; **8**: 885-889 [PMID: 12091879]  261 **Doe C**, Bafadhel M, Siddiqui S, Desai D, Mistry V, Rugman P, McCormick M, Woods J, May R, Sleeman MA, Anderson IK, Brightling CE. Expression of the T helper 17-associated cytokines IL-17A and IL-17F in asthma and COPD. *Chest* 2010; **138**: 1140-1147 [PMID: 20538817 DOI: [10.1378/chest.09-3058](http://dx.doi.org/10.1378/chest.09-3058)]  262 **Lambrecht BN**, Hammad H. The airway epithelium in asthma. *Nat Med* 2012; **18**: 684-692 [PMID: 22561832 DOI: [10.1038/nm.2737](http://dx.doi.org/10.1038/nm.2737)]  263 **Kicic A**, Sutanto EN, Stevens PT, Knight DA, Stick SM. Intrinsic biochemical and functional differences in bronchial epithelial cells of children with asthma. *Am J Respir Crit Care Med* 2006; **174**: 1110-1118 [PMID: 16908868 DOI: [10.1164/rccm.200603-392OC](http://dx.doi.org/10.1164/rccm.200603-392OC)]  264 **Knight DA**, Holgate ST. The airway epithelium: structural and functional properties in health and disease. *Respirology* 2003; **8**: 432-446 [PMID: 14708552 DOI: [10.1046/j.1440-1843.2003.00493.x](http://dx.doi.org/10.1046/j.1440-1843.2003.00493.x)]  265 **Kaliński P**, Hilkens CM, Snijders A, Snijdewint FG, Kapsenberg ML. IL-12-deficient dendritic cells, generated in the presence of prostaglandin E2, promote type 2 cytokine production in maturing human naive T helper cells. *J Immunol* 1997; **159**: 28-35 [PMID: 9200435]  266 **Kaliński P**, Hilkens CM, Snijders A, Snijdewint FG, Kapsenberg ML. Dendritic cells, obtained from peripheral blood precursors in the presence of PGE2, promote Th2 responses. *Adv Exp Med Biol* 1997; **417**: 363-367 [PMID: 9286387 DOI: [10.1007/978-1-4757-9966-8\_59](http://dx.doi.org/10.1007/978-1-4757-9966-8_59)]  267 **Herbst RS**, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med* 2008; **359**: 1367-1380 [PMID: 18815398 DOI: [10.1056/NEJMra0802714](http://dx.doi.org/10.1056/NEJMra0802714)]  268 **Spira A**, Ettinger DS. Multidisciplinary management of lung cancer. *N Engl J Med* 2004; **350**: 379-392 [PMID: 14736930 DOI: [10.1056/NEJMra035536](http://dx.doi.org/10.1056/NEJMra035536)]  269 **van Zandwijk N**, Mooi WJ, Rodenhuis S. Prognostic factors in NSCLC. Recent experiences. *Lung Cancer* 1995; **12** Suppl 1: S27-S33 [PMID: 7551931 DOI: 10.1016/0169-5002(95)00418-Z]  270 **Schiller JH**. Current standards of care in small-cell and non-small-cell lung cancer. *Oncology* 2001; **61** Suppl 1: 3-13 [PMID: 11598409 DOI: [10.1159/000055386](http://dx.doi.org/10.1159/000055386)]  271 **Travis WD**. Pathology of lung cancer. *Clin Chest Med* 2002; **23**: 65-81, viii [PMID: 11901921 DOI: 10.1016/S0272-5231(03)00061-3]  272 **Zochbauer-Muller S**, Gazdar AF, Minna JD. Molecular pathogenesis of lung cancer. *Annu Rev Physiol* 2002; **64**: 681-708 [PMID: 11826285 DOI: [10.1146/annurev.physiol.64.081501.155828](http://dx.doi.org/10.1146/annurev.physiol.64.081501.155828)]  273 **Hanahan D**, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57-70 [PMID: 10647931 DOI: 10.1016/S0092-8674(00)81683-9]  274 **Stracke ML**, Krutzsch HC, Unsworth EJ, Arestad A, Cioce V, Schiffmann E, Liotta LA. Identification, purification, and partial sequence analysis of autotaxin, a novel motility-stimulating protein. *J Biol Chem* 1992; **267**: 2524-2529 [PMID: 1733949]  275 **Liu S**, Umezu-Goto M, Murph M, Lu Y, Liu W, Zhang F, Yu S, Stephens LC, Cui X, Murrow G, Coombes K, Muller W, Hung MC, Perou CM, Lee AV, Fang X, Mills GB. Expression of autotaxin and lysophosphatidic acid receptors increases mammary tumorigenesis, invasion, and metastases. *Cancer Cell* 2009; **15**: 539-550 [PMID: 19477432 DOI: [10.1016/j.ccr.2009.03.027](http://dx.doi.org/10.1016/j.ccr.2009.03.027)]  276 **Lin S**, Wang D, Iyer S, Ghaleb AM, Shim H, Yang VW, Chun J, Yun CC. The absence of LPA2 attenuates tumor formation in an experimental model of colitis-associated cancer. *Gastroenterology* 2009; **136**: 1711-1720 [PMID: 19328876 DOI: [10.1053/j.gastro.2009.01.002](http://dx.doi.org/10.1053/j.gastro.2009.01.002)]  277 **Lu Y**, Lemon W, Liu PY, Yi Y, Morrison C, Yang P, Sun Z, Szoke J, Gerald WL, Watson M, Govindan R, You M. A gene expression signature predicts survival of patients with stage I non-small cell lung cancer. *PLoS Med* 2006; **3**: e467 [PMID: 17194181 DOI: [10.1371/journal.pmed.0030467](http://dx.doi.org/10.1371/journal.pmed.0030467)]  278 **Oikonomou N,** Thanasopoulou A, Stathopoulos G, Syrigos K, Aidinis V. Decreased Lung Tumorigenesis In Mice With Conditionally Inactivated Enpp2 Gene In CC10 (Clara) Cells. *Am J Respir Crit Care Med* 2010; **181**: A2056  279 **Nikitopoulou I,** Sevastou I, Madan D, Prestwich GD, Aidinis V A bromo-phosphonate analogue of lysophosphatidic acid attenuates the development of collagen induced arthritis. *PLoS One* 2013; in press [DOI: [10.1371/journal.pone.0070941](http://dx.doi.org/10.1371/journal.pone.0070941)]  280 **Jeon ES**, Lee IH, Heo SC, Shin SH, Choi YJ, Park JH, Park do Y, Kim JH. Mesenchymal stem cells stimulate angiogenesis in a murine xenograft model of A549 human adenocarcinoma through an LPA1 receptor-dependent mechanism. *Biochim Biophys Acta* 2010; **1801**: 1205-1213 [PMID: 20708100]  281 **Okabe K**, Hayashi M, Wakabayashi N, Yamawaki Y, Teranishi M, Fukushima N, Tsujiuchi T. Different expressions and DNA methylation patterns of lysophosphatidic acid receptor genes in mouse tumor cells. *Pathobiology* 2010; **77**: 309-314 [PMID: 21266829 DOI: [10.1159/000321898](http://dx.doi.org/10.1159/000321898)]  282 **Müller R**, Berliner C, Leptin J, Pörtner D, Bialecki W, Kleuser B, Schumacher U, Milićević NM. Expression of sphingosine-1-phosphate receptors and lysophosphatidic acid receptors on cultured and xenografted human colon, breast, melanoma, and lung tumor cells. *Tumour Biol* 2010; **31**: 341-349 [PMID: 20480410 DOI: [10.1007/s13277-010-0043-7](http://dx.doi.org/10.1007/s13277-010-0043-7)]  283 **Hayashi M**, Okabe K, Yamawaki Y, Teranishi M, Honoki K, Mori T, Fukushima N, Tsujiuchi T. Loss of lysophosphatidic acid receptor-3 enhances cell migration in rat lung tumor cells. *Biochem Biophys Res Commun* 2011; **405**: 450-454 [PMID: 21255556 DOI: [10.1016/j.bbrc.2011.01.051](http://dx.doi.org/10.1016/j.bbrc.2011.01.051)]  284 **Okabe K**, Hayashi M, Yoshida I, Nishimura K, Fukushima N, Tsujiuchi T. Distinct DNA methylation patterns of lysophosphatidic acid receptor genes during rat hepatocarcinogenesis induced by a choline-deficient L-amino acid-defined diet. *Arch Toxicol* 2011; **85**: 1303-1310 [PMID: 21290119 DOI: [10.1007/s00204-011-0656-7](http://dx.doi.org/10.1007/s00204-011-0656-7)]  285 **Yamada T**, Obo Y, Furukawa M, Hotta M, Yamasaki A, Honoki K, Fukushima N, Tsujiuchi T. Mutations of lysophosphatidic acid receptor-1 gene during progression of lung tumors in rats. *Biochem Biophys Res Commun* 2009; **378**: 424-427 [PMID: 19026987 DOI: [10.1016/j.bbrc.2008.11.044](http://dx.doi.org/10.1016/j.bbrc.2008.11.044)]  286 **Breindel JL**, Haskins JW, Cowell EP, Zhao M, Nguyen DX, Stern DF. EGF receptor activates MET through MAPK to enhance non-small cell lung carcinoma invasion and brain metastasis. *Cancer Res* 2013; **73**: 5053-5065 [PMID: 23794705 DOI: [10.1158/0008-5472.CAN-12-3775](http://dx.doi.org/10.1158/0008-5472.CAN-12-3775)]  287 **Ritter CA**, Arteaga CL. The epidermal growth factor receptor-tyrosine kinase: a promising therapeutic target in solid tumors. *Semin Oncol* 2003; **30**: 3-11 [PMID: 12644979 DOI: [10.1053/sonc.2003.50027](http://dx.doi.org/10.1053/sonc.2003.50027)]  288 **Gschwind A**, Prenzel N, Ullrich A. Lysophosphatidic acid-induced squamous cell carcinoma cell proliferation and motility involves epidermal growth factor receptor signal transactivation. *Cancer Res* 2002; **62**: 6329-6336 [PMID: 12414665]  289 **Jeong KJ**, Cho KH, Panupinthu N, Kim H, Kang J, Park CG, Mills GB, Lee HY. EGFR mediates LPA-induced proteolytic enzyme expression and ovarian cancer invasion: inhibition by resveratrol. *Mol Oncol* 2013; **7**: 121-129 [PMID: 23127547 DOI: [10.1016/j.molonc.2012.10.001](http://dx.doi.org/10.1016/j.molonc.2012.10.001)]  290 **Bektas M**, Payne SG, Liu H, Goparaju S, Milstien S, Spiegel S. A novel acylglycerol kinase that produces lysophosphatidic acid modulates cross talk with EGFR in prostate cancer cells. *J Cell Biol* 2005; **169**: 801-811 [PMID: 15939762 DOI: [10.1083/jcb.200407123](http://dx.doi.org/10.1083/jcb.200407123)]  291 **Shida D**, Kitayama J, Yamaguchi H, Yamashita H, Mori K, Watanabe T, Nagawa H. Lysophosphatidic acid transactivates both c-Met and epidermal growth factor receptor, and induces cyclooxygenase-2 expression in human colon cancer LoVo cells. *World J Gastroenterol* 2005; **11**: 5638-5643 [PMID: 16237757]  292 **Ma PC**, Jagadeeswaran R, Jagadeesh S, Tretiakova MS, Nallasura V, Fox EA, Hansen M, Schaefer E, Naoki K, Lader A, Richards W, Sugarbaker D, Husain AN, Christensen JG, Salgia R. Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. *Cancer Res* 2005; **65**: 1479-1488 [PMID: 15735036 DOI: [10.1158/0008-5472.CAN-04-2650](http://dx.doi.org/10.1158/0008-5472.CAN-04-2650)]  293 **Lin L**, Bivona TG. Mechanisms of Resistance to Epidermal Growth Factor Receptor Inhibitors and Novel Therapeutic Strategies to Overcome Resistance in NSCLC Patients. *Chemother Res Pract* 2012; **2012**: 817297 [PMID: 22970367]  294 **Castoldi R**, Ecker V, Wiehle L, Majety M, Busl-Schuller R, Asmussen M, Nopora A, Jucknischke U, Osl F, Kobold S, Scheuer W, Venturi M, Klein C, Niederfellner G, Sustmann C A novel bispecific EGFR/Met antibody blocks tumor-promoting phenotypic effects induced by resistance to EGFR inhibition and has potent antitumor activity*.* *Oncogene* 2013; In press [PMID: 23812422 DOI: 10.1038/onc.2013.245]  295 **Motohashi K**, Shibata S, Ozaki Y, Yatomi Y, Igarashi Y. Identification of lysophospholipid receptors in human platelets: the relation of two agonists, lysophosphatidic acid and sphingosine 1-phosphate. *FEBS Lett* 2000; **468**: 189-193 [PMID: 10692584 DOI: 10.1016/S0014-5793(00)01222-9]  296 **Amisten S**, Braun OO, Bengtsson A, Erlinge D. Gene expression profiling for the identification of G-protein coupled receptors in human platelets. *Thromb Res* 2008; **122**: 47-57 [PMID: 17920662 DOI: [10.1016/j.thromres.2007.08.014](http://dx.doi.org/10.1016/j.thromres.2007.08.014)]  297 **Pamuklar Z**, Lee JS, Cheng HY, Panchatcharam M, Steinhubl S, Morris AJ, Charnigo R, Smyth SS. Individual heterogeneity in platelet response to lysophosphatidic acid: evidence for a novel inhibitory pathway. *Arterioscler Thromb Vasc Biol* 2008; **28**: 555-561 [PMID: 18202325 DOI: [10.1161/ATVBAHA.107.151837](http://dx.doi.org/10.1161/ATVBAHA.107.151837)]  298 **Badri L**, Lama VN. Lysophosphatidic acid induces migration of human lung-resident mesenchymal stem cells through the β-catenin pathway. *Stem Cells* 2012; **30**: 2010-2019 [PMID: 22782863 DOI: [10.1002/stem.1171](http://dx.doi.org/10.1002/stem.1171)]  299 **Zhao Y**, Zhao J, Mialki RK, Wei J, Spannhake EW, Salgia R, Natarajan V. Lipopolysaccharide-induced phosphorylation of c-Met tyrosine residue 1003 regulates c-Met intracellular trafficking and lung epithelial barrier function. *Am J Physiol Lung Cell Mol Physiol* 2013; **305**: L56-L63 [PMID: 23624790 DOI: [10.1152/ajplung.00417.2012](http://dx.doi.org/10.1152/ajplung.00417.2012)] |

**P-Reviewer:** Lee BS, Shida D, Yun CC **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 Expression of lysophosphatidic acid receptor in pulmonary cell types and leukocytes**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cell type** | **LPAR1** | **LPAR2** | **LPAR3** | **LPAR4** | **LPAR5** | **LPAR6** | **Ref.** |
| NHBEs | +++ | ++ | +++ | - | + | + | [[41](#_ENREF_41)] |
| NHBEs | +++ | ++ | +++ | - | ++ | + | [[59](#_ENREF_59)] |
| NHBEs | ++ | ++ | ++ | - | NA | NA | [[43](#_ENREF_43)] |
| HBE | ++ | ++ | NA | NA | NA | NA | [[56](#_ENREF_56)] |
| HBE (BEAS-2B) | ++ | ++ | ++ | + | ++ | + | [[59](#_ENREF_59)] |
| HBE (HBEpCs) | +++ | + | ++ | + | + | NA | [[209](#_ENREF_209)] |
| HBE (HBEpCs) | ++ | ++ | ++ | NA | NA | NA | [[46](#_ENREF_46)] |
| HBE (HBEpCs) | ++ | ++ | ++ | NA | NA | NA | [[49](#_ENREF_49)] |
| HBE (HBEpCs) | ++ | ++ | ++ | NA | NA | NA | [[68](#_ENREF_68)] |
| Primary mouse tracheal EpCs | ++ | +++ | ++ | ++ | - | NA | [[57](#_ENREF_57)] |
| NHBE cells | ++ | ++ | ++ | - | NA | NA | [[43](#_ENREF_43)] |
| A549 alveolar epithelial carcinoma | ++ | NA | NA | NA | NA | NA | [[40](#_ENREF_40)] |
| A549 alveolar epithelial carcinoma | +++ | + | - | - | NA | NA | [[74](#_ENREF_74)] |
| NCI-H522 lung epithelial carcinoma | - | ++ | + | - | NA | NA | [[74](#_ENREF_74)] |
| RLCNR rat lung adenocarcinoma | NA | NA | - | NA | ++ | NA | [[283](#_ENREF_283)] |
| Primary mouse lung fibroblasts | +++ | + | + | + | ++ | NA | [[31](#_ENREF_31)] |
| human fetal lung fibroblasts MRC5 | +++ | ++ | ++ | + | + | NA | [[226](#_ENREF_226)] |
| Mouse embryonic fibroblasts | +++ | ++ | + | +++ | + | NA | [[101](#_ENREF_101)] |
| NHLFs CCL-151 | +++ | + | ++ | + | + | ++ | [[81](#_ENREF_81)] |
| NHLFs | ++ | ++ | NA | NA | NA | NA | [[42](#_ENREF_42)] |
| Primary mouse lung endothelial | ++ | + | - | +++ | + | NA | [[31](#_ENREF_31)] |
| HPAECs | + | ++ | + | + | + | +++ | [[106](#_ENREF_106)] |
| HMVECs | + | ++ | + | + | + | +++ | [[106](#_ENREF_106)] |
| HEV ECs | NA | NA | NA | ++ | NA | ++ | [[116](#_ENREF_116)] |
| Human eosinophils | + | - | + | NA | NA | NA | [[148](#_ENREF_148)] |
| Primary mouse neutrophils | - | +++ | - | - | + | NA | [[31](#_ENREF_31)] |
| Primary mouse alveolar macrophages | - | + | + | + | + | NA | [[31](#_ENREF_31)] |
| Human alveolar macrophages | + | ++ | ++ | NA | NA | NA | [[158](#_ENREF_158)] |
| Rat alveolar macrophages | ++ | + | - | NA | NA | NA | [[158](#_ENREF_158)] |
| Human monocytes | + | - | - | NA | NA | NA | [[176](#_ENREF_176)] |
| Mouse DCs | ++ | ++ | ++ | NA | NA | NA | [[58](#_ENREF_58)] |
| Human immature DCs | + | + | + | NA | NA | NA | [[172](#_ENREF_172)] |
| Human mature DCs | + | + | + | NA | NA | NA | [[172](#_ENREF_172)] |
| Human immature DCs | - | + | - | NA | NA | NA | [[174](#_ENREF_174)] |
| Human mature DCs | - | + | - | NA | NA | NA | [[174](#_ENREF_174)] |
| Mouse immature DCs | ++ | + | +++ | ++ | +++ | NA | [[175](#_ENREF_175)] |
| Mouse mature DCs | +++ | + | + | ++ | ++ | NA | [[175](#_ENREF_175)] |
| Jurkat T cells | + | +++ | - | NA | NA | NA | [[178](#_ENREF_178)] |
| Jurkat T cells | + | + | + | NA | NA | NA | [[295](#_ENREF_295)] |
| Human CD4 T cells | + | +++ | NA | NA | NA | NA | [[177](#_ENREF_177)] |
| Human CD4 T cells | + | +++ | - | NA | NA | NA | [[176](#_ENREF_176)] |
| Human CD8 T cells | - | - | - | NA | NA | NA | [[176](#_ENREF_176)] |
| Mouse CD4 T cells | + | + | + | + | + | NA | [[31](#_ENREF_31)] |
| Mouse CD8 T cells | + | +++ | + | + | ++ | NA | [[31](#_ENREF_31)] |
| Human B lymphocytes | - | + | + | NA | NA | NA | [[176](#_ENREF_176)] |
| Human platelets | + | NA | + | NA | NA | NA | [[296](#_ENREF_296)] |
| Human platelets | + | + | + | NA | NA | NA | [[295](#_ENREF_295)] |
| Human platelets | + | + | + | + | + | NA | [[297](#_ENREF_297)] |
| Human mast cells | + | + | + | + | NA | NA | [[199](#_ENREF_199)] |
| Human mast cells | + | + | + | - | NA | NA | [[200](#_ENREF_200)] |
| Human mast cells | - | ++ | + | - | +++ | ++ | [[201](#_ENREF_201)] |
| Lung resident mesenchymal stem cells | +++ | + | + | NA | NA | NA | [[298](#_ENREF_298)] |

+++: strong expression; ++: moderate expression; +: low expression; -: no expression; NA: not available; LPAR: lysophosphatidic acid receptor; NHBEs: Normal human bronchial epithelial; HBE: human bronchial epithelial; HBEpCs: human bronchial epithelial cells; NHLFs: Normal human lung fibroblasts; ECs: endothelial cells; HPAECs: Human pulmonary arterial ECs; HMVECs: Human pulmonary microvascular ECs; HMVECs: Human pulmonary microvascular ECs; HEVs: high endothelial venules; DCs: dendritic cells.

**Table 2 lysophosphatidic acid effects on different cell types**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Cell type** | **Primary** | **Species** | **LPA effect** | **Receptor** | **Experiment** | **Carrier** | **Ref** |
| Alveolar and bronchial epithelial | Yes | mouse | Apoptosis | LPAR1 | *In vivo* | Biological fluid | [[41](#_ENREF_41)] |
| Alveolar and bronchial epithelial | Yes | mouse | Apoptosis | LPAR2 | *In vivo* | Biological fluid | [[41](#_ENREF_41),[42](#_ENREF_42)] |
| NHBEs | Yes | human | (anchorage dependent) Apoptosis | LPAR1 | *In vitro* | FAF BSA | [[41](#_ENREF_41)] |
| NHBEs | Yes | human | TSLP, CCL20 induction |  | *In vitro* | no | [[50](#_ENREF_50)] |
| NHBEs | Yes | human | TGF-β activation | LPAR2 | *In vitro* | no | [[43](#_ENREF_43)] |
| NHBEs | Yes | human | Induction of Soluble ST2 expression | LPAR1,3 | *In vitro* | NA | [[61](#_ENREF_61)] |
| Bronchial epithelial (HBEpCs) | Yes | human | EGFR transactivation, IL-8 secretion |  | *In vitro* | BSA;BSA | [[46](#_ENREF_46),[49](#_ENREF_49)] |
| Bronchial epithelial (HBEpCs) | Yes | human | Induction of IL-13Ralpha2 | Gαi linked | *In vitro* | no | [[54](#_ENREF_54)] |
| Bronchial epithelial (HBEpCs) | Yes | human | Epithelial barrier integrity enhancement | LPAR1,3 | *In vitro* | NA;BSA | [[56](#_ENREF_56),[209](#_ENREF_209)] |
| Bronchial epithelial (HBEpCs) | Yes | human | Decrease of EGFR-EGF binding |  | *In vitro* | BSA | [[66](#_ENREF_66)] |
| Bronchial epithelial (HBEpCs) | Yes | human | COX-2 expression, PGE2 secretion | Gαi linked | *In vitro* | no | [[63](#_ENREF_63)] |
| Bronchial epithelial (HBEpCs) | Yes | human | PDGFR-β transactivation |  | *In vitro* | BSA | [[68](#_ENREF_68)] |
| Bronchial epithelial (HBEpCs) | Yes | human | c-Met redistribution on the membrane |  | *In vitro* | no | [[70](#_ENREF_70),[299](#_ENREF_299)] |
| Bronchial epithelial (BEAS-2B) | No | human | EGFR transactivation |  | *In vitro* | BSA | [[66](#_ENREF_66)] |
| Bronchial epithelial (BEAS-2B) | No | human | RANTES inhibition | LPAR1 | *In vitro* | FAF BSA | [[59](#_ENREF_59)] |
| R3/1 Alveolar epithelial | No | rat | Inhibition of attachment |  | *In vitro* | FAF BSA | [[41](#_ENREF_41)] |
| Tracheal epithelial | Yes | mouse | COX-2 expression, PGE2 secretion | LPAR2 | *In vitro/vivo* | no | [[57](#_ENREF_57)] |
| H292 lung cancer epithelial | No | human | Decrease of EGFR-EGF binding |  | *In vitro* | BSA | [[66](#_ENREF_66)] |
| A549 alveolar epithelial carcinoma | No | human | Decrease of EGFR-EGF binding |  | *In vitro* | BSA | [[66](#_ENREF_66)] |
| A549 alveolar epithelial carcinoma | No | human | p53 decrease |  | *In vitro* | FAF BSA | [[73](#_ENREF_73)] |
| A549 alveolar epithelial carcinoma | No | human | Cell migration | LPAR1 | *In vitro* | BSA;BSA | [[40](#_ENREF_40),[74](#_ENREF_74)] |
| NCI-H522 lung epithelial carcinoma | No | human | Cell motility |  | *In vitro* | BSA | [[74](#_ENREF_74)] |
| Fetal lung fibroblasts (HFL1) | No | human | Chemotaxis |  | *In vitro* | Biological fluid | [[31](#_ENREF_31)] |
| NLFs CCL151 | No | human | Proliferation, EGFR ectodomain shedding | Gi/o linked | *In vitro* | no | [[81](#_ENREF_81)] |
| Fetal lung fibroblasts MRC5 | No | human | proliferation | LPAR1,3 | *In vitro* | no | [[226](#_ENREF_226)] |
| Fetal lung fibroblasts IMR-90 | No | human | Chemotaxis | LPAR1 | *In vitro* |  | [[95](#_ENREF_95)] |
| NLFs | Yes | human | Differentiation, TGF-β expression and signaling | LPAR2 | *In vitro* | no | [[42](#_ENREF_42)] |
| Lung fibroblasts | Yes | mouse | Differentiation, TGF-β expression and signaling | LPAR2 | *In vitro* | no | [[42](#_ENREF_42)] |
| Lung fibroblasts | Yes | mouse | Chemotaxis | LPAR1 | *In vitro* | FAF BSA | [[31](#_ENREF_31)] |
| Lung fibroblasts | Yes | mouse | Protection from apoptosis | LPAR1 | *In vitro* | FAF BSA | [[41](#_ENREF_41)] |
| NIH 3T3 fibroblasts | No | mouse | Protection from apoptosis, proliferation | Gi linked | *In vitro* | FAF BSA | [[99](#_ENREF_99)] |
| NIH 3T3 fibroblasts | No | mouse | Migration, protection from apoptosis, proliferation |  | *In vitro* | BSA | [[100](#_ENREF_100)] |
| Rat1/c-Myc fibroblasts | No | rat | Protection from apoptosis |  | *In vitro* | FAF BSA | [[99](#_ENREF_99)] |
| Lung endothelial | Yes | mouse | Vascular leak/extravasation | LPAR1 | *In vivo* | Biological fluid | [[31](#_ENREF_31)] |
| HPAECs pulmonary endothelial | Yes | human | Increase of the endothelial layer permeability | LPAR6 | *In vitro* | FAF BSA | [[106](#_ENREF_106)] |
| BPAE pulmonary artery endothelial | No | bovine | Migration, chemotaxis |  | *In vitro* | FAF BSA | [[127-129](#_ENREF_127)] |
| Smooth muscle cells | Yes | rabbit, cat | Contraction |  | *Ex vivo* | BSA | [[140](#_ENREF_140)] |
| HASM airway smooth muscle cells | Yes | human | Proliferation, stimulation of EGFR signaling |  | *In vitro* | NA; BSA | [[139](#_ENREF_139),[141](#_ENREF_141)] |
| HASM airway smooth muscle cells | Yes | human | Activation of TGF-β |  | *In vitro* | NA | [[143](#_ENREF_143)] |
| Dendritic cells | Yes | mouse | Inhibition of activation | LPAR2 | *In vitro*, *in vivo* | FAF BSA | [[58](#_ENREF_58)] |
| Lung resident mesenchymal stem cells | Yes | human | Migration | LPAR1 | *In vitro* | no | [[298](#_ENREF_298)] |

LPA: lysophosphatidic acid; NHBEs: Normal bronchial epithelial; HBEpCs: human bronchial epithelial cells; BEAS-2B: bronchial epithelial cell line; NLFs: Normal lung fibroblasts; HPAECs: Human pulmonary arterial endothelial cells; LPAR: lysophosphatidic acid receptor; NA: not available; TSLP: thymic stromal lymphopoietin; TGF-β: Transforming growth factor beta; EGFR: epidermal growth factor receptor; BSA: Bovine serum albumin; FAF: Fatty acid free.