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Is there a role for specialized pro-resolving mediators in pulmonary fibrosis?

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Abstract

Pulmonary fibrotic diseases are characterized by proliferation of lung fibroblasts and myofibroblasts and excessive deposition of extracellular matrix proteins. Depending on the specific form of lung fibrosis, there can be progressive scarring of the lung, leading in some cases to respiratory failure and/or death. Recent and ongoing research has demonstrated that resolution of inflammation is an active process regulated by families of small bioactive lipid mediators terms “specialized pro-resolving mediators” (SPMs). While there are many reports of beneficial effects of SPMs in animal and cell culture models of acute and chronic inflammatory and immune diseases, there have been fewer reports investigating SPMs and fibrosis, especially pulmonary fibrosis. Here, we will review evidence that resolution pathways are impaired in interstitial lung disease, and that SPMs and other similar bioactive lipid mediators can inhibit fibroblast proliferation, myofibroblast differentiation, and accumulation of excess extracellular matrix in cell culture and animal models of pulmonary fibrosis, and we will consider future therapeutic implications of SPMs in fibrosis.

Keywords

pro-resolving mediators; SPMs; interstitial lung disease; idiopathic pulmonary fibrosis; scleroderma; sarcoidosis; fibroblast

1. Introduction

Pulmonary fibrotic diseases are characterized by proliferation of lung fibroblasts and myofibroblasts and excessive deposition of extracellular matrix proteins. In some forms of fibrosis, including idiopathic pulmonary fibrosis (IFP), progressive scarring of the lung

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Conflicts of interest:

Dr. Sime is a paid consultant for Boehringer Ingelheim, UCB and Three Lakes Foundation. She serves on the board member for the American Thoracic Society, the scientific council of the Parker Francis Foundation, an advisory Board for Galecto and the medical scientific advisory committee for the Pulmonary Fibrosis Foundation. She receives grant funding from the NIH. Dr. Sime holds patents related to fibrosis. The other authors have no financial interests to disclose.

can lead to respiratory failure and even death. Several subtypes of pulmonary fibrosis all classified under the umbrella term “interstitial lung disease” (ILD), that can be caused by various insults to the lung including chemical, immunological, physical and radiological, as well as genetic factors and susceptibilities. IPF is an irreversible, progressive disease with no known cause and is one of the most serious forms of lung fibrosis. Other common ILDs include chronic hypersensitivity pneumonitis (HP) and autoimmune connective tissue (CT)-ILD. Although the FDA has approved pirfenidone and nintedanib for IPF, these drugs only slow the progression of disease in some patients and have significant side effects. The global incidence of IPF is rising, with a mean survival time of 3–5 years after diagnosis that is shorter than that for lung cancer, highlighting an urgent need for more effective therapies (Jeganathan, et al., 2021; Marshall, et al., 2018). The FDA has granted orphan drug status to several upcoming IPF therapies entering clinical trials, but more options are urgently needed.

There is a great deal of attention being paid to the field of *resolution of inflammation*, and the families of bioactive lipids that promote resolution, termed specialized pro-resolving mediators, or SPMs. SPMs have proven to have potent anti-inflammatory and pro-resolving effects in many animal models of disease (reviewed in (Cagnina, et al., 2022; Chiang & Serhan, 2020)). They are exciting candidates for drug development; since they are endogenously produced, they are expected to be well tolerated, and they are easily derivatized to increase their selectivity, potency, and improve their pharmacokinetic properties. SPMs act through G protein coupled receptors (GPCRs), and GPCRs are the largest family of targets for drug development (Park, et al., 2020).

However, it is not immediately obvious if lung fibrosis or other fibrosing diseases should be candidates for SPM therapy. Some of the key effector cells in fibrosis are fibroblasts and myofibroblasts, and the involvement of classical inflammatory or immune processes is less clear. Here, we will review emerging evidence from cell culture, animal models and human patient samples that SPMs have therapeutic potential to treat IPF and other lung fibrosing diseases.

2. Overview of pulmonary fibrosis/interstitial lung disease

Interstitial lung disease (ILD) is a general classification that encompasses a number of diseases that cause scaring or fibrosis of the lungs. ILDs can be chronic and progressive, and can lead to irreversible lung damage and loss of lung function. Depending on the specific disease, therapy can be very challenging (Behr, et al., 2021; Farrand, et al., 2020; Wijsenbeek, et al., 2022). Tissue fibrosis can be understood as an aberrant wound healing process, in which there is epithelial damage, activation of fibroblasts and differentiation of fibroblasts to myofibroblasts. Myofibroblasts are contractile and matrix producing cells with features of both fibroblasts and smooth muscle cells. Fibrosing ILDs are characterized by epithelial injury and repair, proliferation of lung fibroblasts and myofibroblasts, production of excess extracellular matrix proteins including collagens and fibronectin, increased crosslinking of extracellular matrix (ECM), dysregulation of matrix metalloproteinases, and fibroblast resistance to apoptosis. This can lead to increased thickness of alveolar septae, fibrotic destruction of the normal lung architecture, loss of gas exchange, and in severe disease, death due to respiratory failure (Meyer, 2017; Upagupta, et al., 2018) (Figure 1).

Some ILDs have immune or inflammatory involvement. Hypersensitivity pneumonitis (HP), caused by chronic exposure to antigens such as mold or bird dander, can develop into chronic fibrosis and/or chronic inflammatory subtypes. Autoimmune connective tissue (CT) diseases including scleroderma and rheumatoid arthritis can have fibrotic involvement of the lungs. Sarcoidosis is an immune disorder of unknown origin that commonly involves the lungs and is characterized by granulomas and fibrosis. Therapeutic ionizing radiation treatment for breast, esophageal or lung cancer can also cause fibrotic changes in the lung. The risk is proportional to the cumulative radiation dose and the volume irradiated. Radiation-induced fibrosis may be preceded by pneumonitis, but up to 90% of irradiated patients exhibit fibrotic change on CT scans without developing clinically significant pneumonitis (Kalman, et al., 2018). Finally, approximately 10 to 30% of ILDs are diagnosed as idiopathic pulmonary fibrosis (IPF), exhibiting progressive tissue scarring with no known cause (Coultas, et al., 1994; Duchemann, et al., 2017; Hyldgaard, et al., 2014). Two drugs, nintedanib and pifenidone, have been FDA approved to treat IPF, but at best they only slow disease progression in some patients and have significant side effects. The only true cure for IPF at present is lung transplantation, which is not available or appropriate for all patients.

The pathogenesis of IPF is complex and incompletely understood. Evidence suggests that pulmonary fibrosis follows repetitive epithelial injury and aberrant wound healing. Gene defects in familial IPF (encompassing approximately 10–20% of all IPF patients (Borie & Crestani, 2019; Fernandez, et al., 2012; Garcia-Sancho, et al., 2011)) also implicate lung epithelial cell function in IPF, and mouse models of drug-induced or genetically controlled epithelial damage result in fibrogenic pathologies (T. Liu, et al., 2019; Takezaki, et al., 2019; Yasutomo, 2021).

There is strong evidence that the cytokine transforming growth factor-β (TGFβ) is the key pro-fibrotic cytokine. TGFβ promotes activation of fibroblasts and differentiation of fibroblasts to myofibroblasts, and upregulates production and crosslinking of ECM (Biernacka, et al., 2011; Frangogiannis, 2020). TGFβ can be produced by many cell types and is sequestered in the matrix in latent form and can be activated by a variety of stimuli including enzymatic action, mechanical stress, integrins, and low pH (Kottmann, et al., 2012; Munger, et al., 1999; Wipff, et al., 2007). Other pro-fibrotic chemokines include fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF).

Most activated fibroblasts and myofibroblasts in IPF lung tissue are believed to arise from proliferation and differentiation of resident lung fibroblasts (Kendall & Feghali-Bostwick, 2014). However, there is some evidence that some fibroblast-like cells arise via differentiation from epithelial cells in a process called epithelial-mesenchymal transition (EMT), driven by TGFβ (Willis & Borok, 2007; Willis, et al., 2005; L. Yao, et al., 2019). While EMT is described in animal models of lung fibrosis, this process is less well described in human lung. Evidence from rodent models also suggests that some circulating bone marrow-derived cells express fibroblast-like markers (fibrocytes) and can migrate to the site of fibrosis and contribute to disease pathology (Ashley, et al., 2017; Xu, et al., 2009). These processes are well-described in vitro and in rodent models of IPF but their contribution to human disease is uncertain.

Pulmonary fibrosis is also characterized by vascular remodeling, encompassing neovascularization at the boundary between areas of normal and fibrotic lung architecture as well as destruction of the capillary bed in fibrotic foci (Barratt & Millar, 2014). Vascular remodeling in pulmonary fibrosis includes muscularization of vessels, vasoconstriction and perivascular fibrosis, mediated in part by vascular smooth muscle cells. Vascular remodeling including vascular pruning has been demonstrated in experimental models of pulmonary fibrosis (Abdalla, et al., 2015; Santos-Ribeiro, et al., 2023). Pulmonary hypertension due to vascular remodeling occurs in 40% of IPF patients and is associated with increased mortality (Shorr, et al., 2007). Drivers of vascular remodeling in pulmonary fibrosis include TGFβ and CTGF (Tsujino, et al., 2017; T. Wang, et al., 2018; Yanagihara, et al., 2022). The cytokine vascular endothelial growth factor (VEGF) aggravates pulmonary fibrosis in experimental animal models, while blockade of VEGF signaling attenuates experimental fibrosis (Chaudhary, et al., 2007; Farkas, et al., 2009; K. S. Lee, et al., 2008). The FDA approved anti-fibrotic drug nintedanib acts in part by inhibiting the VEGF receptor (Hilberg, et al., 2008).

3. The role of inflammation in pulmonary fibrosis

The question of how much inflammatory or immune mechanisms contribute to the pathogenesis of some forms of pulmonary fibrosis is a contentious debate. There are varying levels of evidence of immune mechanism involvement in the ILD subtypes. There is a strong immune and inflammatory component to CT and HP ILDs, and sarcoid, CT and HP patients can respond to anti-inflammatory and immunotherapies (Boerner, et al., 2020; Morisset, et al., 2017; Vorselaars, et al., 2013), implicating inflammation in the progression of disease. However, nonspecific immunotherapy is harmful for IPF patients. The PANTHER-IPF (Prednisone, Azathioprine, and N-acetylcysteine) clinical trial demonstrated nonspecific immunotherapy offers no clinical benefit and even increases death and hospitalization in IPF patients (Idiopathic Pulmonary Fibrosis Clinical Research, et al., 2012). Histologically, IPF does not exhibit many of the features of classical cellular inflammation. There are signs that non-classical inflammation is present in IPF, but it remains unknown if it is an important driver of fibrosis.

The role of immune cells and soluble mediators in pulmonary fibrosis is reviewed in depth elsewhere (Kolahian, et al., 2016). Briefly, both adaptive and innate immune cells can modulate pro-fibrotic behavior of fibroblasts. Fibroblasts and myofibroblasts are highly responsive to growth factors and cytokines produced by immune cells. There is a complicated and nuanced role for macrophages in fibrosis as they produce multiple cytokines, chemokines, and proteases. In general, classically activated (M1) macrophages are thought to be pro-inflammatory, while alternatively activated macrophages (M2) are believed to promote resolution of inflammation and resolve the wound healing process. However, as M2 macrophages produce TGFβ and PDGF, their presence in IPF tissue is viewed with suspicion (Misharin, et al., 2017; Sennello, et al., 2017; Y. Yao, et al., 2016; Zhang, et al., 2018). T cells can provide both anti- and pro-fibrotic effectors based on subtypes and temporal stage of fibrosis. Th1 cytokines (INF-γ, IL-12) are generally considered antifibrotic (Keane, et al., 2001) while Th2 cytokines (IL-17, IL-13) have reported pro-fibrotic activities (Saito, et al., 2003). Early stage Tregs are pro-fibrotic,

whereas late stage Tregs dampen fibrosis (Boveda-Ruiz, et al., 2013; F. Wang, et al., 2020). The harmful versus beneficial roles of macrophage and T-cell phenotypes remain under investigation.

4. Specialized pro-resolving mediators (SPMs)

In spite of its bad reputation, inflammation is often a beneficial and necessary process. Inflammation serves to mitigate damage from injury, initiate repair processes, and recruit inflammatory and immune cells to clear debris and to orchestrate immune responses to pathogens. “Resolution of inflammation” refers to the return to homeostasis after an inflammatory response, and includes several distinct hallmarks including; class switching of recruited macrophages from pro-inflammatory M1 phenotype to a pro-resolving M2 phenotype; nonphlogistic (non-inflammatory) phagocytosis of pathogens; increased phagocytosis and clearance of apoptotic neutrophils (efferocytosis); and decreased production of pro-inflammatory cytokines and chemokines (reviewed in (Panigrahy, et al., 2021)). It is now well-established that resolution of inflammation is an active process that is mainly controlled by families of “specialized pro-resolving mediators” (SPMs)—bioactive lipids derived from omega-3 and omega-6 polyunsaturated fatty acids through a series of enzymatic reactions (Figure 2) (Chiang & Serhan, 2017; Duvall & Levy, 2016; Serhan, et al., 2015). The first bioactive eicosanoids to be described were the prostaglandins (PGs) and leukotrienes (LTs), which are derived from arachidonic acid via cyclooxygenases and generally have pro-inflammatory effects. The first pro-resolving lipids to be identified were the *lipoxins*, which are derived from arachidonic acid via 5- and 15-lipooxygenase (LO) enzymes (Serhan, et al., 1984). As the field expanded, additional classes of SPMs were identified, termed *resolvins*, *protectins* and *maresins*, derived from docosahexaenoic acid (DHA) and eicosapenatenoic acid (EPA) (Serhan, et al., 2000; Serhan, et al., 2012). Although not formally classified as SPMs, other DHA products have pro-resolving or anti-inflammatory effects. The epoxyeicosatrienoic acids (EETs) are derived from DHA via the action of cytochrome P450 epoxygenases, while hydroxyeicosatetraenoic acids (HETEs) are generated by 12- and 15-LOX. HETEs and EETs have independent pro-resolving activity and can also act as indirect precursors for other SPMs (Spector, et al., 2004; Zeldin, 2001).

The newest class of SPMs are known as *conjugates of tissue regeneration*. It was originally found that maresin-1 can be conjugated to glutathione. Subsequently, the glutathione moiety can be cleaved by gamma-glutamyl transferase to a dipeptide, and further cleaved by dipeptidases to a cysteine monopeptide linked to maresin-1 (Dalli, et al., 2016). It was discovered that these cisteinyl-conjugated SPMs promoted resolution of inflammation but also promoted tissue repair and regeneration, and they were named maresin conjugates of tissue regeneration (MCTR)-1, -2 and -3, respectively. Subsequently, cysteinyl-conjugated forms of D resolvins and protectins were identified and termed resolvin conjugates of tissue regeneration (RCTRs) and protectin conjugates of tissue regeneration (PCTRs) (Dalli, et al., 2015; Jouvene, et al., 2019; Ramon, et al., 2016).

The endogenous sources for SPMs are not well understood. SPMs have been detected in human peripheral blood, immune tissues like spleen and lymph nodes, nervous system tissues including the brain and spinal fluid, in lung tissue, sputum, exhaled breath

condensates and bronchoalveolar lavage fluid, and in many other compartments (Claria, et al., 2013; Colas, et al., 2014; Giera, et al., 2012; Levy, et al., 2007; Mas, et al., 2012). SPMs can be produced by B cells, T cells, macrophages, neutrophils, platelets, epithelial cells, endothelial cells and fibroblasts. However, the exact cellular sources of SPMs in specific tissues or specific disease states are incompletely understood. In animal models, treatment with SPMs have been shown to block inflammation and promote resolution in a wide variety of lung diseases including asthma, emphysema, cystic fibrosis, and multiple infection models (Cagnina, et al., 2022).

SPMs act via a family of GPCRs. Eight SPM receptors have been identified to date, including DRV1/GPR32 (D resolvin receptor 1, binds RvD1, RvD3, and RvD5), DRV2/GPR18 (D resolvin receptor 2, binds RVD2), FPR2/ALX (formyl peptide receptor 2/lipoxin A receptor, binds RvD1, RvD3 and LXA4), ERV1/CMKLR1/ChemR23 (E resolvin receptor 1, binds RvE1), BLT1/LTB4R (leukotriene B4 receptor, binds RvE1 and RvE2), GPR37 (binds protectin D1), LGR6 (binds maresin 1), and GPR101 (binds n-3 D-resolvins) (Figure 3) (Chiang & Serhan, 2020). Some receptors can bind multiple SPMs, and this has important implications for the potential therapeutic uses of SPMs. For example, resolvin D1 (RvD1) and lipoxin A_4 (LXA_4) can both bind either DRV1/GPR32 or FPR2/ALX, and we and others have reported that RvD1 exerts anti-inflammatory and pro-resolving effects via these receptors (Hsiao, et al., 2014). However, FPR2 is also a ligand for serum amyloid A, which provokes pro-inflammatory responses (Tylek, et al., 2021). Similarly, resolvin E1 (RvE1) can bind to either ERV1/ChemR23 or BLT1. As leukotrienes are classical pro-inflammatory mediators, this also highlights the importance of ligand structure and receptor selectivity, as different ligands that bind to the same GPCR can trigger different downstream effects, and understanding ligand structure, binding, and GPCR downstream signaling will be critical to development of SPMs and SPM derivatives as new pharmacotherapeutics (Merlin, et al., 2022; Park, et al., 2020).

Production of SPMs is spatially and temporally regulated, with pro-inflammatory lipids being produced in the initial phases of an inflammatory response, shifting to production of pro-resolving mediators during the resolution phase. This is accomplished by altering expression levels of the key synthetic enzymes in the pro-inflammatory and pro-resolving eicosanoid pathways. Many SPMs can also be degraded into products with significantly reduced biological activity by enzymes including eicosanoid oxidoreductase (EOR, also known as 15-hydroxyprostaglandin dehydrogenase or 15-PGDH) and soluble epoxide hydrolases (sEHs) (Y. P. Sun, et al., 2007; Wagner, et al., 2017). Production of SPM-degrading enzymes is an endogenous part of the temporal regulation of resolution, but inappropriate expression of these enzymes can prolong chronic inflammation by blocking normal resolution responses.

Another important concept in SPM biology is transcellular biosynthesis, in which one cell type produces an SPM intermediate, which is taken up by the target cell and converted to the final bioactive SPM (Capra, et al., 2015). This contributes to the specific spatial and temporal regulation of SPM production. Finally, it is important to note that SPMs are pro-resolving and anti-inflammatory without being immunosuppressive. Classical anti-inflammatory therapies like corticosteroids can suppress immune responses, limiting

inflammation but increasing susceptibility to infection, while SPMs have been shown in multiple animal models to reduce inflammation while improving antibacterial and antiviral immune responses (Basil & Levy, 2016; Bhat, et al., 2021; Codagnone, et al., 2018; Croasdell, et al., 2016; Dalli, et al., 2016; Isopi, et al., 2020; P., et al., 2022; Ramon, et al., 2016; Recchiuti, et al., 2021; Ruiz, et al., 2019).

SPMs are endogenous bioactive lipids that have potent anti-inflammatory and pro-resolving activities against a wide variety of acute and chronic inflammatory and infectious disease models. However, evidence also suggests that SPMs may be able to improve outcomes in pulmonary fibrosis, a group of diseases in which the role of inflammation is much less obvious.

5. The case for SPMs and pulmonary fibrosis

Fibroblasts and myofibroblasts are not classical immune or inflammatory cells, so it is not obvious that SPMs would regulate their function. On the other hand, fibrosis appears to be an aberrant wound healing and repair process, suggesting that SPMs might play a role in promoting resolution and repair in fibrosis. CT and sarcoid ILDs have significant immune system involvement and are amendable to corticosteroid therapy, suggesting that SPMs could promote resolution of these forms of fibrosis via immune cell interactions. However, it remains unclear if we should expect SPMs to have a role in controlling fibrotic diseases that lack a clear underlying immune component.

Data on levels of SPMs in samples from patients with ILDs is extremely limited. A study of 5-LOX derived eicosanoids in bronchoalveolar lavage fluid from scleroderma patients identified elevated levels of LTB_4 and PGE_2 and a decreased ratio of LXA_4:LTB_4 (Kowal-Bielecka, et al., 2005), while LC-MS/MS analysis of eicosanoids in human lung tissue found significantly lower levels of 8,9-EET, 11,12-EET and 14,15-EET in lung tissue from IPF patients compared to control tissue (H. S. Kim, et al., 2021). Untargeted metabolomics analysis of lung tissue from patients undergoing transplantation for end-stage silicosis found upregulated arachidonic acid metabolites including PGE_2 and several D/J series prostaglandins (Pang, et al., 2021). This is a clearly under-studied area, and the availability of LC-MS/MS methods for lipidomics analysis with sensitivities in the picogram range presents significant opportunities for new discoveries in this area.

In the absence of strong patient data, we must rely on cell culture and animal models. Many of the animal models of pulmonary fibrosis have an inflammatory component, making it difficult to determine if the beneficial effects of SPMs on fibrosis are due to direct effects on pro-fibrotic mechanisms, or are an indirect result of reducing the inflammation that precedes fibrosis in these models. This can be overcome to a certain extent by administering the SPM intervention to the animals after the acute inflammatory phase but before the fibrotic phase, and by using in vitro cultures of lung cells to investigate whether SPMs inhibit pro-fibrotic phenotypes and the specific mechanisms involved.

5.1. Data from animal models

The most widely used animal model of pulmonary fibrosis is the bleomycin model. Bleomycin is a chemotherapeutic drug that was found to cause pulmonary fibrosis as a side-effect in cancer patients, that was developed into an animal model of lung fibrosis (T. Liu, et al., 2017). Bleomycin can be instilled directly into the lungs via intranasal aspiration, oropharyngeal aspiration, or intratracheal delivery, or it can be delivered systemically by osmotic minipump or daily subcutaneous injections. Bleomycin is believed to cause fibrosis via DNA damage and oxidative stress to the lung epithelium and lung resident fibroblasts (Walters & Kleeberger, 2008). Bleomycin is also a strong pro-inflammatory stimulus and the single dose lung delivery models are characterized by an inflammatory phase from day 1 to day 7, transitioning to a fibrotic phase, with most investigators harvesting fibrotic endpoints between day 14 and day 35.

Several studies have reported that pre-treating mice with DHA or a fish oil diet prior to administration of bleomycin resulted in reduced fibrosis, reduced collagen content, and preserved lung mechanical function, suggesting that dietary ingestion or lung administration of SPM precursors inhibits the inflammatory and fibrotic responses by changing the spectrum of bioactive mediators produced in response to injury (Galdino de Souza, et al., 2022; Kennedy, et al., 1989; Zhao, et al., 2014). Mice treated with a LXA_4 analog with increased *in vivo* stability exhibited reduced expression of collagen and α-smooth muscle actin (αSMA), a differentiation marker of myofibroblasts, when the analog was given on day 0 or day 4 after bleomycin administration (Martins, et al., 2009). Subsequently, the same group reported that this analog was also effective at reducing fibrosis, improving the survival of alveolar type II (AT-II) epithelial cells, and reducing expression of TGFβ, when given on days 7 and 10 after bleomycin administration, after the acute inflammatory phase. The analog also restored the balance of pro-resolving M2 macrophages in lung tissue (Guilherme, et al., 2013). Two synthetic FPR2/ALX agonists, BML-111 and Quin-C1, attenuated experimental fibrosis in the bleomycin mouse model, with decreased accumulation of collagen, preservation of lung architecture, and decreased expression of TGFβ (He, et al., 2011; Ji, et al., 2018). LXA_4 is also implicated as an anti-fibrotic lipid mediator by a study demonstrating that the pro-inflammatory eicosanoid thromboxane A_2 negatively regulates expression of the LXA_4 receptor FPR2/ALX, preventing LXA_4 signaling. Administration of a thromboxane synthesis inhibitor to mice treated with bleomycin resulted in increased expression of FPR2/ALX and decreased collagen gene expression (Sato, et al., 2004).

A group of related studies examined the effects of MaR1, MCTR1, and protectin DX (PDX) in bleomycin-treated mice. Administration of the SPMs was started late, after the acute inflammatory response. MaR1 was given on days 14–21 with harvest at day 28, while MCTR1 and PDX were given from days 8–21 with harvest on day 21. All three SPMs demonstrated significant anti-fibrotic activity at doses as low as 10 ng/mouse/day, with reductions in expression of ECM proteins including collagen and fibronectin, reduced expression of TGFβ, preserved lung compliance, and improved blood oxygenation. The authors also reported significant preservation of epithelial cell numbers and function (H. Li, et al., 2017; Pan, et al., 2021; Y. Wang, et al., 2015). In another study using late

administration of an SPM, mice received bleomycin by continuous infusion via an implanted osmotic minipump for 7 days, with 17(*R*)-RvD1 administered by i.p. injection on days 21–25 with harvest on day 28. 17(*R*)-RvD1, sometimes referred to as aspirin-trigged (AT)RvD1 (Y. P. Sun, et al., 2007), is an RvD1 stereoisomer with similar bioactivity but greater resistance to degradation by endogenous EOR enzymes. Even with this brief, late treatment, 17(*R*)-RvD1 attenuated fibrosis as determined by Masson's trichrome staining, collagen mRNA, and lung tissue hydroxyproline content, an indirect measure of tissue collagen (Yatomi, et al., 2015). Co-administration of RvD1 with Boc-PLPLP, a peptide antagonist of the RvD1 receptor FPR2/ALX, reversed the effects, demonstrating that the actions of 17(*R*)-RvD1 in this model were receptor-dependent (Yatomi, et al., 2015). A more recent study also investigated 17(*R*)-RvD1 in the bleomycin model. The authors reported that administration of 17(*R*)-RvD1 7 and 10 days after bleomycin treatment significantly reduced inflammation and fibrosis, with reductions in both tissue and brochoalveolar lavage macrophages, neutrophils and inflammatory cytokines, along with reductions in tissue fibrosis, collagen accumulation, and expression of αSMA (Guilherme, et al., 2023). Interestingly, the authors also reported decreased production of extracellular vesicles by macrophages, and inhibition of angiogenesis, suggesting additional routes by which SPMs might inhibit pulmonary fibrosis.

As discussed above, analysis of human lung tissue found significantly lower levels of 8,9-EET, 11,12-EET and 14,15-EET in IPF patients. The EETs are produced from DHA via the action of cytochrome P450 hydrolase enzymes and are metabolized by endogenous soluble epoxide hydrolases (sEH). Soluble epoxide hydrolase inhibitors (sEHIs) have been developed by several pharmaceutical companies as potential therapies for hypertension, inflammation, metabolic syndrome and other indications (Shen & Hammock, 2012). sEHIs raise levels of endogenous EETs by blocking their metabolism, and have shown promise in pre-clinical animal models of lung inflammation (Podolin, et al., 2013; J. Yang, et al., 2015). Kim *et al.* reported that the sEHI 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU) effectively attenuated bleomycin-induced fibrosis when given starting on day 0 (H. S. Kim, et al., 2021), while Tao *et al.* reported that TPPU inhibited bleomycin fibrosis when given starting on day 7, with reductions in lung collagen and αSMA-positive myofibroblasts (J. H. Tao, et al., 2022). This provides strong evidence that endogenous EETs have anti-fibrotic properties that can be enhanced by inhibiting their degradation.

Another group of eicosanoids with potent anti-fibrotic activity *in vitro* are the prostaglandins including PGE_2 and $15dPGJ_2$ (reviewed in (K. Li, et al., 2021). PGE_2 is normally considered a potent pro-inflammatory prostaglandin, but has been shown to inhibit lung fibroblast differentiation to myofibroblasts and production of ECM (Epa, et al., 2015; Kolodsick, et al., 2003; Mukherjee, et al., 2019). In healthy lung, one source for PGE_2 is local production by epithelial cells, which supports the hypothesis that damaged lung epithelium either promotes fibrosis or permits fibrosis to occur via removal of anti-fibrotic checkpoints (Epa, et al., 2015). PGE_2 is metabolized to an inactive form by the enzyme 15-PGDH. Bärnthaler et al. reported that lungs from IPF patients exhibited higher expression of 15-PGDH by immunostaining, and that treating human IPF precision cut lung slices with the 15-PGDH inhibitor SW033291 increased levels of PGE_2 and decreased expression of collagen. SW033291 protected mice from bleomycin-induced fibrosis, with reductions

in lung collagen, reduced apoptosis of AT-II cells, reduced proliferation of fibroblasts, and reduced accumulation of fibrocytes (Barnthaler, et al., 2020). Similar results were obtained in a mouse model of lung fibrosis induced by intravenous, rather than intratracheal, administration of bleomycin. SW033291 reduced fibrosis and collagen accumulation in lung tissue and preserved lung mechanical function (Smith, et al., 2020).

Limited investigations have been carried in out in other mouse models of pulmonary fibrosis. Apolipoprotein A1 (ApoA1) protected mice from an experimental silicosis model, with reductions in fibrotic nodules and TGFβ expression. ApoA1 has anti-inflammatory and anti-oxidative properties and was found to be reduced in lung tissue from IPF patients, but in the silicosis model it appeared to act by increasing LXA_4 (E. Lee, et al., 2013). Mice exposed to a high dose of ionizing radiation delivered to the left lung developed fibrosis at 6 weeks, which was attenuated by daily administration of LXA_4. The effect of LXA_4 was again receptor-dependent, as it could be blocked by an FPR2/ALX antagonist (H. Kim, et al., 2020). Finally, it has been shown that mechanical ventilation can contribute to lung damage, and, when combined with other insults, can sometimes lead to abnormal repair in patients who are placed on mechanical ventilation for acute respiratory distress syndrome (ARDS) and other conditions. Yang et al. reported that using a mouse model of ventilation-induced fibrosis, treatment with RvD1 at 10–1000ng/mouse/day reduced lung fibrosis, lung collagen content, and expression of TGFβ, αSMA and vimentin, and that the effect of RvD1 was dependent on FRP2/ALX (Y. Yang, et al., 2019).

We also highlight here some key results from non-lung disease models that illustrate the therapeutic and translational potential of SPMs in fibrosing diseases. A fish oil diet or treatment with PDX reduced kidney fibrosis in a model of obesity-induced end stage renal disease (Perazza, et al., 2021), while RvD1 mitigated kidney fibrosis induced by unilateral ureteral obstruction (Y. B. Sun, et al., 2013). RvD1 also attenuated right atrial fibrosis in a rat model of pulmonary hypertension, with suppression of collagen and TGFβ expression and increased M2 macrophages (Hiram, et al., 2021). These models are interesting because they exhibit less classical inflammation than the bleomycin mouse model and support the concept that SPMs can promote resolution of fibrosis independent of inflammation.

5.2. SPM effects on fibroblasts and epithelial cells

As mentioned above, most animal models of pulmonary fibrosis exhibit some level of inflammation, and it is difficult to clearly determine whether the anti-fibrotic effects of SPMs are due to direct effects on the mechanisms of fibrosis or are indirect results of decreased inflammation. However, experiments in cultured lung fibroblasts and epithelial cells strongly support that SPMs have direct anti-fibrotic effects.

Several studies have reported that LXA_4 inhibited differentiation of lung fibroblasts to myofibroblasts after stimulation with TGFβ or CTGF. These studies were performed in multiple cell types, including primary human lung fibroblasts from healthy donors and IPF patients, a cloned human lung fibroblast cell line, and the NIH3T3 mouse embryonic fibroblast cell line. LXA_4 is reported to inhibit fibroblast differentiation, proliferation, migration, and activation of the key TGFβ -responsive transcription factor Smad2/3 via its receptor FPR2 (Herrera, et al., 2015; Roach, et al., 2015; Wu, et al., 2006; Zheng, et

al., 2016). Similarly, the FPR2/ALX agonist BML-111 suppressed expression of αSMA in NIH3T3 fibroblasts (Ji, et al., 2018). RvD1 and RvD2 have also been reported to inhibit TGFβ-stimulated fibroblast proliferation and migration via the FPR2/ALX receptor (Herrera, et al., 2015; Zheng, et al., 2016; Zheng, et al., 2018) (Table 1).

In addition to PGE_2 discussed above, prostaglandins in the D/J family, especially $15dPGJ_2$, have potent anti-fibrotic activity in vitro. While PGE_2 acts via the E-prostaglandin receptors (EP1-EP4), $15dPGJ_2$ and other D/J PGs are ligands for the transcription factor peroxisome proliferator-activated receptor (PPAR)γ. There are several reports that PPARγ ligands block TGFβ-stimulated lung myofibroblast differentiation and function (Burgess, et al., 2005; Lacy, et al., 2016; Milam, et al., 2008). Highlighting the importance of bioactive lipids as autocoid factors, activated human lung fibroblasts (HLFs) first produce pro-inflammatory mediators, but undergo a class-switch to produce D/J series PGs that have potent anti-fibrotic activities on bystander HLFs (Lacy, et al., 2016; Lacy, et al., 2019). More recently, it was reported that 11,12-EET and 14,15-EET inhibited expression of αSMA, collagen, proliferation and Smad phosphorylation in mouse lung fibroblasts, also via PPARγ (H. S. Kim, et al., 2021; J. H. Tao, et al., 2022).

As mentioned, epithelial cells are a source of anti-fibrotic factors including PGE_2, and it is hypothesized that epithelial damage can lead to lung fibrosis. The lung epithelium is also subject to epithelial-mesenchymal transition (EMT), in which epithelial cells are differentiated to mesenchymal-like cells that express fibroblast markers, become contractile, and produce excess ECM. This process is well-described in cell culture, although its contribution to fibrosis *in vivo* is contested. LXA_4 and RvD1 were both shown to block EMT and promote proliferation and wound healing in human AT-II cells (Zheng, et al., 2016; Zheng, et al., 2018). RvD1 also inhibited expression of mesenchymal markers in bronchial epithelial cells subjected to cyclic stretching, a model of mechanical ventilation-induced lung fibrosis (Y. Yang, et al., 2019). These effects could be blocked by an FPR2/ALX antagonist, demonstrating the effects were receptor-dependent. Additionally, it was recently reported that MaR1 could inhibit TGFβ-stimulated EMT of the MLE-12 mouse alveolar epithelial cell line, and PDX inhibited EMT in primary rat AT-II cells (H. Li, et al., 2017; Y. Wang, et al., 2015).

Vascular smooth muscle cells (VSMCs) contribute to the pathology of pulmonary fibrosis via vascular remodeling leading to pulmonary hypertension. Although studies of the effect of SPMs on VSMCs have mainly investigated acute vascular injury models, some findings may be extrapolated to suggest that SPMs will have beneficial effects in pulmonary fibrosis that are mediated through VSMCs as well as fibroblasts and epithelial cells. VSMCs can synthesize SPMs including D-series resolvins and protectins and express the FPR2/ALX, DRV1/GPR32 and ERV1/ChemR23 receptors (Chatterjee, et al., 2017; Ho, et al., 2010). EPA, LXA_4, RvD1, RvD2, and RvE1 have each been reported to inhibit VSMC proliferation, migration, and contractility in a receptor-dependent manner (Akagi, et al., 2015; Artiach, et al., 2018; Hiram, et al., 2015; Hiram, et al., 2014; Ho, et al., 2010; Kurahara, et al., 2020; G. Liu, et al., 2018; Miyahara, et al., 2013; Mottola, et al., 2017). MaR1 also inhibited migration and proliferation of rat pulmonary arterial smooth muscle cells in vitro in a receptor (LGR6) dependent manner (H. Li, et al., 2022).

Lastly, we will briefly summarize studies on SPMs in fibroblasts from other organs, as they demonstrate that many of the signaling mechanisms that promote or attenuate fibrotic phenotypes are shared among fibroblasts from different sources. RvD1 inhibited activation and proliferation of kidney and periodontal ligament fibroblasts (Y. B. Sun, et al., 2013; Zarrough, et al., 2022), and also blocked EMT of intestinal epithelial cells in a model of intestinal fibrosis (Zeng, et al., 2022). LXA_4 inhibited EMT in a human kidney epithelial cell line (Wu, et al., 2010). MaR1 reduced activation and expression of TGFβ and the ECM protein fibronectin in glomerular mesangial cells, a type of mesenchymal stromal cell with properties similar to fibroblasts (Tang, et al., 2017). A novel peptide ligand of FPR2/ALX reduced collagen expression in rat hepatic stellate cells (ECM producing cells in the fibroblast lineage) and attenuated liver fibrosis in a rat model of cirrhosis (Jun, et al., 2021). Similar to the relationship between epithelial cells and fibroblasts, natural killer (NK) cells exhibit anti-fibrotic properties in liver fibrosis and inhibit activation of hepatic stellate cells. Inhibition of E-prostanoid 3 receptor (EP3), the PGE_2 receptor, reduced cytotoxic activity of NK cells toward hepatic stellate cells in vitro and aggravated liver fibrosis in a mouse model, strongly supporting an anti-fibrotic role for PGE_2 (X. Tao, et al., 2022).

6. Lessons learned from other chronic lung diseases

The interstitial lung diseases are characterized by parenchymal or interstitial fibrosis, that is, scarring, thickening and ECM accumulation in the interstitial spaces between alveoli, eventually resulting in destruction of the gas exchange surface. Several other lung diseases include fibrosis of the small airways, rather than the parenchyma, resulting in airway narrowing that contributes to disease pathology. Here, we will briefly discuss evidence for the use of SPMs in moderating small airways fibrosis.

The pathologies of chronic obstructive pulmonary disease (COPD) include emphysema (airspace enlargement), chronic bronchitis, and small airway fibrosis (Barnes, 2019). Although there has been considerable research into the use of SPMs to promote resolution of chronic inflammation in COPD (reviewed in (Thatcher, et al., 2019), the most common rodent models of COPD do not develop small airways fibrosis, and thus, studies to date are silent on whether SPMs can prevent or resolve small airways fibrosis in COPD, and a new experimental approach is needed to address the question.

Asthma, although predominantly an immune disorder, also has a component of small airways fibrosis, and SPMs have been extensively studied in multiple asthma models (reviewed in (Cagnina, et al., 2022)). However, little work has directly addressed bioactive lipids and small airways fibrosis. The leukotriene receptor inhibitors pranlukast and montelukast inhibited experimental allergic airway disease in a mouse model of asthma, including reducing expression of αSMA and collagen genes, collagen accumulation in lung tissue, and TGFβ signaling (Hur, et al., 2018; Shin, et al., 2013). A study by Abreu et al. examined the effect of mesenchymal stromal cell therapy on a model of house dust mite-induced asthma in mice. Stromal cells delivered to the lungs after induction of asthma were more effective at reducing asthma phenotypes when they were pretreated with EPA. EPA-treated stromal cells produced RvD1 and reduced lung expression of TGFβ and collagen, and reduced airways fibrosis (Abreu, et al., 2018). In a more recent study, administration

of LXA_4 reduced deposition of collagen and gene expression of collagen and αSMA in the mouse ovalbumin asthma model (Y. Liu, et al., 2021). However, since the LXA_4 was administered before the antigenic challenge, this study demonstrates a preventative effect rather than a pro-resolving or treatment effect. Previous studies have reported that arginase-2 expression in human lung fibroblasts is associated with airway remodeling in asthma. Duggirala et al. reported that EPA and a combination of EPA and DHA reduced expression of arginase-2 in primary lung fibroblasts from asthma patients, but DHA alone or RvD1 did not, providing mixed evidence for the role of SPMs in asthma airway remodeling in human patients (Duggirala, et al., 2022).

Cystic fibrosis (CF) is a genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. The resulting in disruptions in sodium, chloride, and bicarbonate ion transport lead to fluid imbalance in the lung, reduced mucociliary clearance, and chronic pathogen colonization, resulting in chronic epithelial injury and epithelial remodeling. SPMs have been extensively studied in CF in the context of promoting resolution of chronic inflammation and improving bacterial clearance (Briottet, et al., 2020). However, little attention has been paid specifically to airway remodeling. There are reports that lung fibroblasts from CF patients exhibit elevated production of TGFβ, collagen deposition and myofibroblast differentiation, although investigations of SPM effects on CF lung fibroblasts have not been reported (Harris, et al., 2013; Huaux, et al., 2013). It is hypothesized that much of the airway remodeling in CF derives from repeated injury to epithelial cells resulting in EMT (Rout-Pitt, et al., 2018). LXA_4 promoted markers of epithelial repair including ion channel activation, proliferation, migration, and wound repair in CF and non-CF human airway epithelial cells in an FPR2/ALX dependent manner (Buchanan, et al., 2013). LXA_4 also prevented disruption of epithelial tight junctions by *Pseudomonas aeruginosa* in CF and non-CF bronchial epithelial cell lines (Higgins, et al., 2016).

7. Conclusion and future directions.

Interstitial lung diseases represent a chronic wound repair process that has failed to resolve and become pathogenic, leading to accumulation of fibrotic tissue in the lung parenchyma. Although some ILDs including sarcoidosis and CT-ILD have an immune/inflammatory pathology, the role of inflammation in IPF is unclear. SPMs have shown clear anti-fibrotic effects in lung fibroblasts, epithelial cells and mouse models. However, the mouse lung fibrosis models used to date have significant inflammatory components, making it difficult to separate anti-inflammatory from anti-fibrotic effects. One way to address this problem would be to use the bleomycin mouse model but focus on late treatment, beginning on day 7 or later. While this does not completely bypass the inflammatory response, it focuses more on the fibrotic response than treatments begun earlier. Another approach would be to use a less inflammatory based mouse model of IPF. One such model is transient overexpression of TGFβ in lung tissue by a recombinant adenovirus (Sime, et al., 1997; Warshamana, et al., 2002). Administration of a recombinant adenovirus expressing constitutively active TGFβ results in transient inflammation and expression of TGFβ lasting about 7–10 days, with progressive fibrosis developing between days 21–42. SPMs could be administered after day 7, bypassing the immune reaction to the adenovirus particles. Genetic mouse models

of familial IPF that involve inducible epithelial damage may also have less of a classical inflammatory component (Yasutomo, 2021).

On the other hand, perhaps it is not important if we can't separate the anti-inflammatory effects of SPMs from their pro-resolving and pro-repair functions. ILDs have complex pathologies and some of them have a clear inflammatory component, so it may be less important to determine if the exact mechanism of action of SPMs in ILD is primarily anti-inflammatory or primarily anti-fibrotic, as long as they work. When fibrosis is preceded or accompanied by an inflammatory or immune response, treating the inflammation or immune condition with SPMs could be expected to also reduce concomitant fibrosis, even if SPMs do not act directly on fibroblasts or myofibroblasts. This approach might be particularly useful in HP, autoimmune CT-ILDs, and small airway fibrosis in asthma.

There are several distinct approaches to translating SPM research into new clinical therapies. First are the SPMs themselves. As they are endogenous produced, SPM-based therapies are expected to be well-tolerated. SPMs are easily derivatized to improve their pharmacokinetics and increase their target specificity, and they are active in the nanomolar range, which is achievable with typical routes of administration. The second approach involves directly targeting the GPCRs that carry out SPM signaling. GPCRs are the largest target for drug development. GPCRs are highly sensitive to the structures of the ligands that bind them, as illustrated by the ability of FPR2/ALX and BLT1 to have pro-inflammatory or pro-resolving effects depending on the ligand and context (Merlin, et al., 2022). The third approach is illustrated by the development of soluble epoxide hydrolase inhibitors (sEHIs) which block the action of endogenous and pathogen-derived sEHs to metabolize and inactivate anti-inflammatory EETs and HETEs (Guan, et al., 2021). sEHIs have anti-inflammatory effects in several cell culture and animal models, and anti-fibrotic effects in the mouse bleomycin model. There are other endogenous enzymes that metabolize SPMs, including eicosanoid oxidoreductases, and the promise offered by sEHIs suggests that developing inhibitors of eicosanoid oxidoreductase could also be a fruitful approach. Specialized pro-resolving mediators and other bioactive lipids represent a target rich environment for novel anti-fibrotic therapies.

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Abbreviations

15-PGDH	15-hydroxyprostaglandin dehydrogenase, also known as eicosanoid oxidoreductase or EOR
αSMA	α-smooth muscle actin
AT-II	alveolar type II cells
BLT1	leukotriene B4 receptor

CF	cystic fibrosis
COPD	Chronic Obstructive Pulmonary Disease
COX2	cyclooxygenase 2
CT	connective tissue
CTGF	connective tissue growth factor
DHA	docosahexaenoic acid
DRV	D resolvin receptor
ECM	extracellular matrix
EET	epoxyeicosatrienoic acid
EMT	epithelial-mesenchymal transition
EP3	E-prostanoid 3 receptor
EPA	eicosapentaenoic acid
ERV	E resolvin receptor
FGF	fibroblast growth factor
FPR2/ALX	formyl peptide receptor 2/lipoxin A_4 receptor
GPCR	G-protein coupled receptor
HETE	hydroxyeicosatetraenoic acid
HLF	human lung fibroblast
HP	hypersensitivity pneumonitis
IGF	insulin-like growth factor
ILD	interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
LO	lipooxygenase
LPS	lipopolysaccharide
LTB_4	leukotriene B_4
LXA_4	lipoxin A_4
MaR1	maresin 1
MCTR	maresin conjugate of tissue regeneration
NK	natural killer cell

PPARγ	Peroxisome proliferator-activated receptor γ
PCTR	protectin conjugate of tissue regeneration
PD1	protectin D1
PDGF	platelet-derived growth factor
PDX	protectin DX
PG	prostaglandin
PGE_2	prostaglandin E_2
RCTR	resolvin conjugate of tissue regeneration
RvD1	resolvin D1
RvD2	resolvin D2
RvE1	resolvin E1
sEH	soluble epoxide hydrolase
sEHI	soluble epoxide hydrolase inhibitor
SPM	specialized pro-resolving lipid mediator
TGFβ	transforming growth factor-β
VSMC	vascular smooth muscle cell

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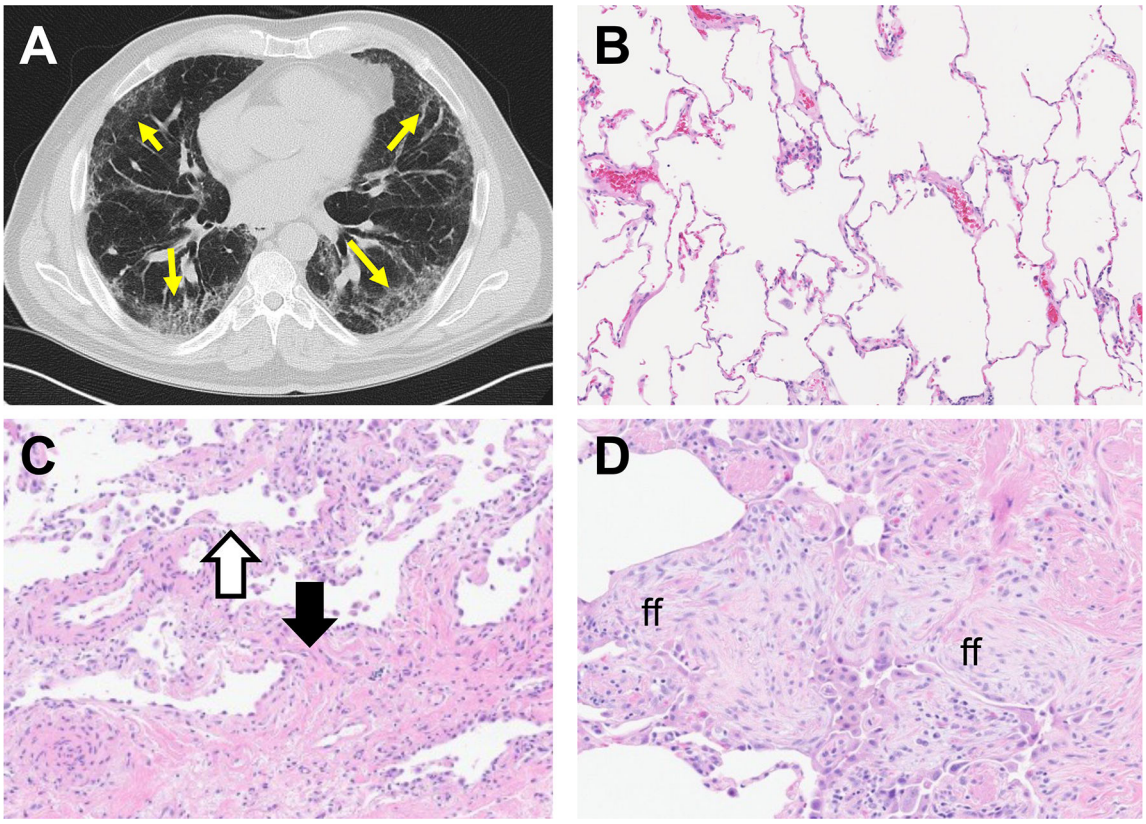

Figure 1. Radiologic and histologic features of Idiopathic Pulmonary Fibrosis (IPF).

A. High resolution CT scan from patient with IPF. Yellow arrows point to honeycombing and fibrotic features. **B-D.** H&E stained sections of normal (B) and IPF (C, D) lung tissue. In C, the black arrow indicates fibrotic tissue while the white area indicates adjacent uninvolved parenchyma. In D, ff indicates fibroblastic foci, a hallmark feature of IPF.

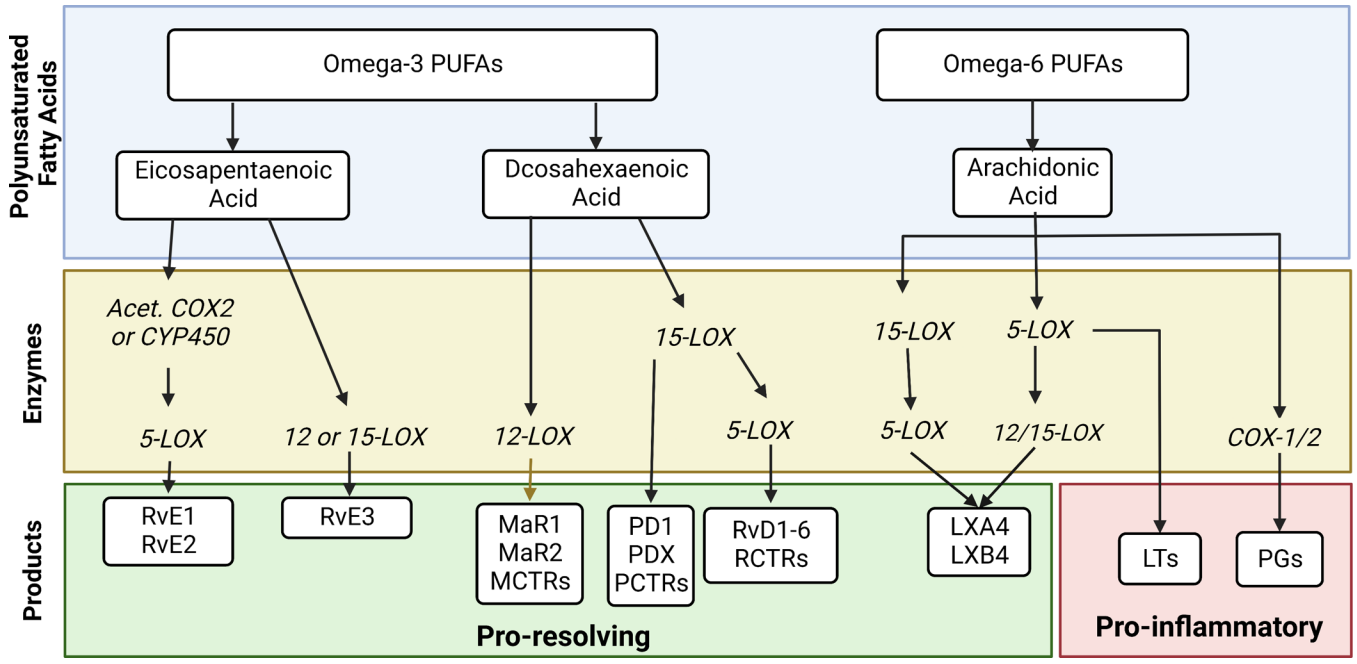

Figure 2. Diagram of synthetic pathways for the major classes of SPMs.

SPMs are derived from Omega-3 and –6 polyunsaturated fatty acids through a series of enzymatic reactions. Pro-resolving mediators consist of Resolvins (Rv-), Maresins (MaR-), Protectins (PD-), and Lipoxins (LX-). Pro-inflammatory mediators Prostaglandins and Leukotrienes are derived from Arachidonic Acid. Abbreviations are defined in the main text and abbreviations table. Created with Biorender.com.

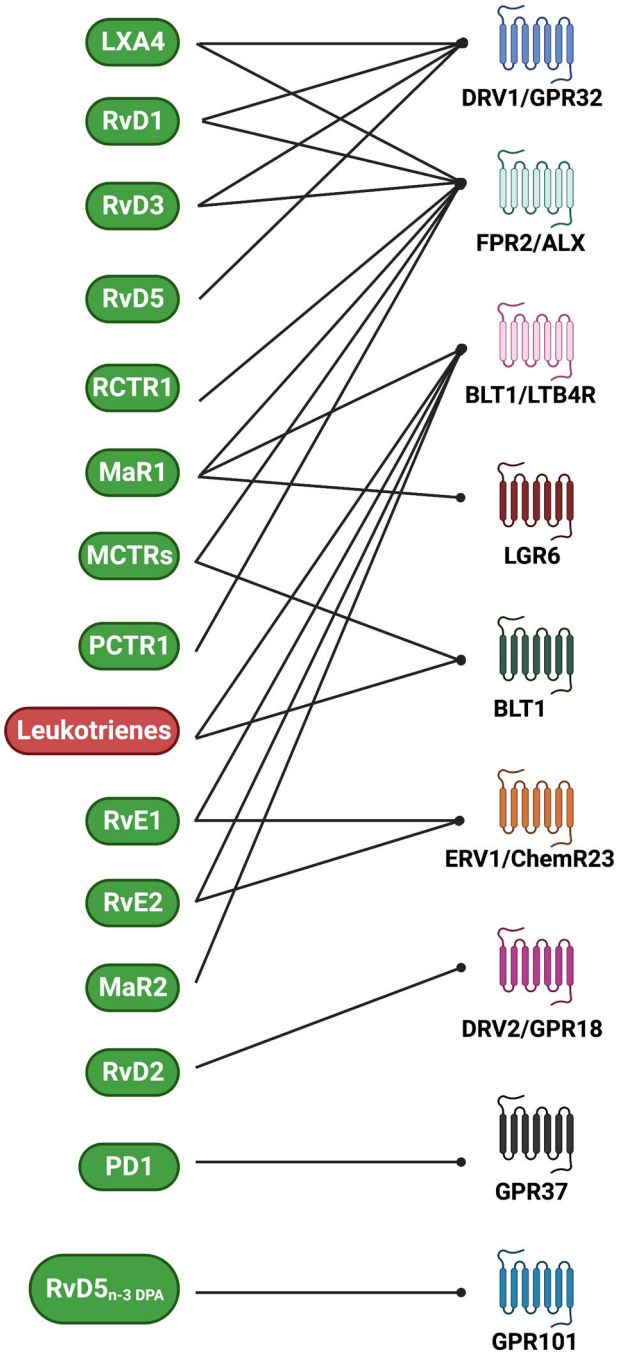

Figure 3. SPM receptor network.

Diagram of the GPCR signaling network for SPMs. Multiple SPMs (left) can bind the same receptors (right). Green indicates pro-resolving mediators, and red indicates pro-inflammatory mediators. Abbreviations are defined in the main text and abbreviations table. Created with Biorender.com.

Table 1.

Anti-fibrotic effects of SPMs and other bioactive lipids *in vitro*.

Treatment (Concentration)	Cell Type	Effects	Reference
Lung fibroblasts			
11,12-EET 1000nM	MRC-5 cell line, primary HLFs from IPF patients	Decreased TGFβ-stimulated differentiation, collagen production and Smad signaling.	(Kim, et al., 2021)
14,15-EET 500–1000nM	Primary murine fibroblasts and NIH3T3 fibroblasts	Inhibited TGFβ-stimulated differentiation, collagen expression, and Smad signaling.	(Tao, et al., 2022)
D/J series PGs NA*	Primary HLFs	Activated HLFs produce D/J series PGs that inhibit myofibroblast differentiation of bystander HLFs.	(Lacy, et al., 2016; Lacy, et al., 2019)
LXA_4 10nM	HLF cell line	Inhibited CTGF-stimulated proliferation via STAT and pI3K pathways.	(Wu, et al., 2006)
LXA_4 1–100nM	Primary HLFs	Reduced TGFβ driven fibroblast proliferation, collagen production, and myofibroblast differentiation. Mediated via FPR2/ALX.	(Zheng, et al., 2016)
LXA_4 1–10nM	Primary HLFs from normal and IPF donors	Inhibited myofibroblast differentiation, collagen expression and stress fiber formation.	(Roach, et al., 2015)
PGE_2 NA*	Primary HLFs	Epithelial cells can inhibit HLF differentiation in co-culture via production of PGE_2	(Epa, et al., 2015)
PGE_2 10–1000nM	Primary HLFs	Inhibited TGFβ-promoted changes in Ca2+, inhibited expression of collagen and αSMA, inhibited stress fiber formation.	(Mukherjee, et al., 2019), (Kolodsick, et al., 2003)
RvD1 10–100nM	Primary HLFs	Inhibited fibroblast proliferation, collagen production, and myofibroblast differentiation	(Zheng, et al., 2018)
Epithelial cells			
LXA_4 1–100nM	Primary Human AT-II cells	Promoted proliferation, inhibited apoptosis, and promoted wound healing.	(Zheng, et al., 2016)
MaR1 0.1–100nM	MLE-12 (immortalized mouse lung epithelial cell line)	Inhibited TGFβ driven EMT	(Wang, et al., 2015)
PDX 1–100nM	Primary rat AT-II	Inhibited TGFβ driven EMT	(Li, et al., 2017)
RvD1 10–100nM	Primary Human AT-II cells	Inhibited EMT in response to TGFβ. Promoted wound repair and proliferation.	(Zheng, et al., 2018)
RvD1 1–100nM	BEAS-2B (immortalized bronchial epithelial cell line)	Reduced markers of EMT in cells exposed to acid and stretch (model of mechanical ventilation-induced fibrosis); dependent on FPR2/ALX.	(Yang, et al., 2019)
Non-lung *in vitro* results			
12-HETE, 15-HETE	Mouse dermal fibroblasts	Inhibited collagen production and MAP kinase activity	(Kronke, et al., 2012)
DHA 0–100μM	Human dermal fibroblasts	Inhibited expression of αSMA and collagen	(Maeshige, et al., 2019)
LXA_4 10–100nM	NIH3T3 fibroblasts	Inhibited TGFβ-stimulated migration but did not alter expression of αSMA or collagen.	(Herrera, et al., 2015)
MaR1 1–100nM	Mouse Glomerular mesangial cells (GMCs)	Reduced activation and expression of TGFβ and fibronectin	(Tang, et al., 2017)
RvD1 1–20nM	HT-29 (immortalized human intestinal epithelial cell line)	Reduced EMT in HT-29 cells. HT-29 cells treated with RvD1 produced anti-fibrotic substances in conditioned medium that	(Zeng, et al., 2022)

Treatment (Concentration)	Cell Type	Effects	Reference
		could inhibit myofibroblast differentiation of fibroblasts.	
RvD2 10–100nM	NIH3T3 fibroblasts	Inhibited TGFβ-stimulated migration but did not alter expression of αSMA or collagen	(Herrera, et al., 2015)
WKYMVm (FPR2 ligand) 1 mM	Immortalized rat hepatic stellate cells	Reduced collagen and αSMA expression in TGFβ treated cells	(Jun, et al., 2021)

*NA, not available.

Abbreviations:

αSMA, α-smooth muscle actin

AT-II, alveolar type II epithelial cells

CTGF, connective tissue growth factor

EET, epoxyeicosatrienoic acid

EMT, epithelial-mesenchymal transformation

FPR2/ALX, formyl peptide receptor 2/lipoxin A_4 receptor

HETE, hydroxyeicosatetraenoic acid

HLF, human lung fibroblast

IPF, idiopathic pulmonary fibrosis

LXA_4, lipoxin A_4

PG, prostaglandin

PG, prostaglandins

PGE_2, prostaglandin E_2

RvD1, resolvin D1

DHA, docosahexaenoic acid