Air Pollution and Pulmonary Fibrosis: A Mechanistic Perspective

Deep Chanda • Mukta Barman • Samik Bindu*

Abstract Fibrosis is a major global problem accounting to ≈45% of deaths in the developed countries. Fibrosis-associated extensive tissue remodeling, organ failure and consequent mortality is evident in diverse diseases including liver cirrhosis, systemic sclerosis, cardiovascular fibrosis, nephritis and most notably pulmonary fibrosis (PF). PF is characterized by thickening and scarring of lung tissue with reduced vital capacity which interferes with the ability to breathe. According to the World Health Organization, deaths due to lung diseases in India were on the rise accounting for 11% of the total deaths, thereby ranking India 1st in lung disease-associated deaths. PF comprises 15% of the pulmonary physician’s practice and interestingly, the Indian Council of Medical Research has estimated the incidence of Chronic Obstructive Pulmonary Disease as 5% in Indian men. In fact, PF is among the most severe complications of interstitial lung disease (ILD), which are heterogeneous admixture of acute to chronic inflammatory and fibrotic lung pathologies characterized by proliferated and thickened pulmonary interstitium. With the advancement in the understanding of PF pathogenesis, it is becoming further clear that air pollution (AP) is a major etiological contributor. A recent report projects AP to be the third highest cause of deaths in India. The problem is more significant in developed/developing cities where industrial and automobile exhausts largely contribute to the deteriorating environmental health. The present review precisely discusses the role of AP in the development of PF along with comments on the future perspectives in PF-research as well as regulatory strategies to control AP.

Keywords Air pollution, pulmonary fibrosis, myofibroblasts, TGF-β1, cigarette smoke, particulate matter

INTRODUCTION

Fibrosis is a severe clinical complication characterized by scarring and hardening of the affected tissue due to exaggerated deposition of extracellular matrix (ECM) components including collagen and fibronectin (Wynn 2008). The process initiates as a normal wound healing response where fibroblasts participate to repair the injury by producing ECM. But owing to the loss of control in the repair process, due to unregulated fibroblast activation under the...
influence of various proinflammatory cytokines and chemokines (predominantly transforming growth factor-β1, TGF-β1), the parenchyma hardens resulting in organ damage. Fibrosis is progressive, irreversible and debilitating. It affects multiple organs including liver, heart, kidney, lungs, skin and intestine. Multiple causes including genetic and epigenetic factors contribute to the pathogenesis. Chronic inflammatory conditions often end up with fibrotic organ failure. Pulmonary fibrosis (PF) is a very common complication where the lungs stiffen resulting in breathing trouble in patients. The histological appearance (upon surgical lung biopsies) largely resembles typical features of usual interstitial pneumonia (UIP). In the lungs, type I alveolar epithelial cells (AECs I) predominate the alveolar surface mediating gaseous exchange besides controlling AEC-II-dependent surfactant secretion for lubrication. In response to pulmonary injuries, AECs-I die and AECs-II initially grows in order to cover the injured surfaces. These hyperplastic AECs-II later die after the wound is repaired and the remaining cells differentiate into AEC-I. However, chronic cycles of injury-repair accompanied by faulty restoration process and alveolar epithelial-mesenchymal crosstalk defects result in pre-mature death of even AECs-II along with accumulation of resident fibroblasts in these foci leading to fibrogenesis (Hosseinzadeh et al. 2018). Diverse molecular pathways activate pro-fibrotic signaling. Wingless/Int (WNT)-β-catenin pathway, TGF-β1-SMAD pathway and recently YAP/TAZ-Hippo pathway have been extensively explored in regards to establishing anti-fibrotic targets. Most of these pathways converge at some points and signaling cross-talks occur for maintaining myoFB phenotype and nuclear translocation of transcriptional up regulators for profibrotic gene expression (Piersma et al. 2015). Fibrosis initiates as a typical inflammatory process with complex interplay of T_cytotoxic and T_helper cells. Th1-derived cytokines initiate the proinflammatory signaling in response to injury which later shifts towards the Th2 arm to allow a chronic inflammatory and fibrogenic state (Wick et al. 2010). Among T_helper cells, Th2-derived cytokines (including IL-4, IL-5, IL-10 and IL-13) have been found to especially contribute to fibroblast activation and matrix development (Keane 2008). Of the various pro-inflammatory cytokines (including IFN-γ, IL-12, IL-18, TNF-α, IL-1β, IL-4, IL-5 and IL-10) and chemokines (including CXCL2 and CXCL3), that have been evidently linked with fibrosis, TGF-β1 is the foremost critical mediator of fibroblast activation that triggers their transformation into myofibroblasts (myoFBs), which attain hyper contractile properties owing to the over expression of specialized proteins including α-smooth muscle actin (α-SMA) (Kolahian et al. 2016). In the lungs, TGF-β1 is produced by alveolar macrophages, activated AECs, neutrophils, platelets, fibroblasts and myoFBs. In fact α-SMA-induced contractile force generated from the activated myoFBs has been found to activate latent TGF-β1 from the ECM which in turn triggers more fibroblast trans-differentiation to myoFBs in a perpetuating positive feedback loop (Zhao et al. 2018). Moreover, α-
SMA is also directly implicated in wound contraction by ECM remodelling and has been documented in stress fibers (Shinde et al. 2017). These myoFBs are highly efficient in ECM deposition and maintain a dynamic relation with their microenvironment during tissue repair, with reciprocal actions leading to cell differentiation, angiogenesis, proliferation, quiescence, and apoptosis. During normal wound healing, α-SMA-dependent myoFB contraction plays crucial role in maintaining tissue architecture and wound closure via contraction of the granulation tissue. After sufficient collagen deposition and resolution of wound, the activated fibroblasts die. However, the reciprocal interaction between myoFBs and various cellular/acellular components in their microenvironment gets altered during chronic inflammation, fibrosis and aging (Darby et al. 2014) and the myoFBs become resistant to apoptosis. A detailed discussion on fibrosis-associated changes in myoFB life span and metabolism has been extensively explained (Kis et al. 2011). This results in the loss of metabolic homeostasis and persistence of hyper-contractile myoFBs in the pulmonary interstitium, at the cost of epithelial cells, causing detrimental ECM remodelling (Yazdani et al. 2017), parenchymal retraction and alveolar collapse which ultimately ends up into typical honeycombing of the pulmonary parenchyma, which is a signature of PF (Aburto et al. 2018). Environmental and occupational exposure to pulmonary irritants, smoking, gastroesophageal reflux disease, certain drugs (chemotherapeutic drugs like bleomycin, methotrexate and cyclophosphamide, cardioprotective drugs like amiodarone, antibiotics like nitrofurantoin and ethambutol and anti-inflammatory drugs like rituximab and sulfasalazine), infectious agents, metabolic diseases including diabetes mellitus, systemic lupus erythematosus, sarcoidosis, pulmonary hypertension, lung cancer, radiation therapies and even inherent genetic factors are some of the established risk factors of PF. MyoFB accumulation may be traced back to 4 independent sources including activation and trans-differentiation of the resident fibroblasts in response to lung injuries (Phan 2002), transition of the pulmonary AECs into mesenchymal state by EMT (Kim et al. 2006), origination from pericytes of the pulmonary interstitium and finally differentiation of the bone marrow-derived circulating mesenchymal fibrocytes into fibroblasts (Moeller et al. 2009). In addition to aforesaid determined factors that facilitate fibrogenesis, PF has been often diagnosed with no conclusive underlying cause. These cases with unknown etiological factors are referred to as idiopathic pulmonary fibrosis (IPF) that mostly affects middle-aged and older adults (mostly above 50 years of age) with no cure (Pardo and Selman 2016). In fact, IPF is clinically most challenging among pulmonary complications owing to the dart of non-invasive therapeutic options, progressive nature, complex molecular etiology and an average median lifespan of ≤ 3 year in patients post diagnosis (Vancheri et al. 2010). IPF is diagnosed by physical examination, clinical data and high resolution CT images of the chest and histopathological examination of lung biopsies (Lynch et al. 2018). Cigarette
smoking (Baumgartner et al. 1997), air pollutants, microbes (Han et al. 2014; Lawson et al. 2008; Molyneaux et al. 2013; Stewart et al. 1999; Tang et al. 2003), gastroesophageal reflux (Lee et al. 2011; Tobin et al. 1998), genetic predisposition (Allen et al. 2017; Noth et al. 2013) due to mutations (Armanios et al. 2007; Kropski et al. 2015; Stuart et al. 2015; Thomas et al. 2002; van Moorsel et al. 2010) and telomere dysfunction (Alder et al. 2008; Naikawadi et al. 2016; Stuart et al. 2015) are potential risk factors for IPF. Lung transplantation seems the only option in the end stage respiratory anomalies. Hence precise understanding of underlying factors triggering the pathogenesis is essential. Owing to the alarming and concerted increase of air pollution (AP) and pulmonary complications, the present review highlights the unequivocal association of AP and PF along with emphasis on environmental contribution and occupational risk factors, contributing to the pathogenesis. It also highlights some clinical case reports and therapeutic research for identifying potential anti-fibrotic compounds/drugs. Finally, a future perspective in anti-fibrotic research is presented along with suggestion on designing rational preventive measures as an effort to fight this seemingly un-opposable progressive fatal disease.

AIR POLLUTION AND LUNG FIBROSIS

The relation of “bad air” and human ailments stemmed out much earlier (much of 19th century and some quarters of 20th century) when the physicians extravagantly condemned polluted air as the causative factor for seemingly all kinds of diseases. According to the “miasmatic theory”, several diseases like cholera, Chlamydia and plague were caused by “miasma” (μίασμα, ancient Greek: "pollution"), which referred to “pollution” or “bad air” (Halliday 2001). Although this is an obsolete medical theory displaced by the discovery of germs in 19th century, still a number of epidemiological data have correlated AP with the occurrence of IPF, chronic obstructive pulmonary disease (COPD), asthma and even lung cancer. AP is an established risk factor behind multiple respiratory complications with polluted air initiating, accelerating and exacerbating various forms of ILDs through pulmonary and systemic inflammation (Johannson et al. 2015). Occupational and environmental exposure to aluminium, silicon, carbon black, silicon oxide, titanium dioxide, asbestos, ozone [O₃] and nitrogen dioxide cause epithelial cell damage, inflammatory response and oxidative stress which further triggers fibrogenesis characterized by elevated expression of fibrotic markers including hydroxyproline, TGF-β1, MMP-9, TIMP and consequent deposition of collagen fibers in the lung tissue. The influence of polluted air on the natural history of the incidence of PF (Sese et al. 2018b) and functional decline especially in IPF has been extensively studied (Winterbottom et al., 2018). The United States Environmental Protection Agency has classified 6 air pollutants as nitrogen dioxide [NO₂], particulate matter [PM], sulphur dioxide, O₃, carbon monoxide and lead; of which PM, NO₂ and ground-level O₃ are most prominently implicated in respiratory pathologies (Johannson et al.
The quality of ambient PM is a strong determinant of the associated ILD in the people living in that particular area. PM is a heterogeneous admixture comprising of solid particles, liquid droplets and gaseous components from diverse geological sources, metals and end products of fossil fuel combustion like carbon and diesel exhaust-particles. Studies have revealed a significant association of exposure to PM with an aerodynamic diameter ≤ 10 µm (PM$_{10}$) and IPF progression although little or no link was found with PM$_{2.5}$; although prolonged exposure to air with PM$_{2.5}$ demanded greater oxygen consumption in 6 min. walk-test (Sese et al. 2018a). In fact, pollutants like O$_3$ and NO$_2$ synergistically contributes to PM toxicity. The potential of air quality as a determinant of ILDs and specifically IPF stems from the fact that PM directly deposits in the respiratory tract epithelia upon long term exposure thereby causing oxidative stress and inflammation along with telomeric distortions in the air way cells (Grahame and Schlesinger 2012). The pro-inflammatory stimuli initiated in the lungs further spread systemically to potentiate the damage. The major contributors of reactive oxygen species (ROS)-induced pulmonary damage are superoxide anions and hydroxide radicals. Endogenous glutathiones counteract these cyto-damaging entities; however, overwhelming accumulation due to acute and persistent pollution overpowers the inherent ability of the lungs to cope up with the insult leading to IPF (Grahame and Schlesinger 2012). The loss of lung function is prominently evident from reduced forced vital capacity (FVC) as monitored by spirometry. These responses eventually turn into systemic complications owing to the development of a perpetual inflammatory state that worsens the prognosis (Sese et al. 2018a). Cigarette smoke (CM) is a significant contributor of AP and risk factor of IPF (Baumgartner et al. 1997; Ye et al. 2014) and smokers are at 60% higher risk of developing and/or exacerbating ILDs (Baumgartner et al. 1997). CM essentially subjects the lungs to encounter volatile organic compounds and PMs of various sizes which often results in aberrant, hyper activated immune response leading to persistent inflammation, airway epithelial injury and consequent fibrosis as a gradual response. In addition to CM, another prominent domestic risk factor significantly contributing to IPF exacerbations is incense smoke. In Asian countries, including India, incense sticks are regularly burned as a religious practice. Interestingly, incense smoke contains most of the characterized air pollutants including toxic gases, volatile organic compounds and PM and that too more compared to CM thereby qualifying as an even worse risk factor for various pulmonary diseases including neoplasms (Lin et al. 2008). Daily exposure to incense fumes is strikingly associated with compromised lung functions as evident from a study in adolescent students (Chen et al. 2017). Prolonged exposure to toxic gases like O$_3$ and NO$_2$ also inherently increases the risk of IPF exacerbations. The most significant, but controllable, sources of NO$_2$ and O$_3$ in the industrialized portions of the world are emissions from the motor-driven vehicles. Tropospheric O$_3$ (formed as a result of
Figure 1. Air pollutants, pulmonary injury and fibrosis. Exposure of bronchiolar and alveolar epithelial cells to different pollutants result in the activation and transformation of fibroblast to myofibroblast under the direct influence of cytokines secreted from damaged epithelial cells and/or resident as well as infiltrated leucocytes. The process primarily starts as a normal wound healing response. Persistent insult disrupts the immunoregulatory homeostasis leading to progression of fibrosis under the major influence of TGF-β1 through overwhelming deposition of extracellular matrix components that ultimately causes pulmonary thickening, hardening, scarring and functional failure.
miscellaneous chemical reactions between NO$_2$, volatile organic compounds in presence of sunlight) triggers inflammation-associated hyper-reactions, elevated mucus secretion and altered expression of various immunoregulatory proteins in the airway epithelia (Alexis et al. 2010; Larsen et al. 2010). In addition to IPF, while O$_3$ is mostly associated with exacerbation-risks of asthma and cystic fibrosis, NO$_2$ has been implicated in COPD, asthma, traffic-associated pollution exposure and consequent increased risk of post lung transplant bronchiolitis obliterans syndrome (Johannson et al. 2014). A direct association of O$_3$ exposure and irreversible elevation in interstitial collagen deposition (Reiser et al. 1987) as well as epithelial lesions is also documented (Adamson et al. 1999). NO$_2$ and other nitrogen oxides often combine with NH$_3$ and moisture to form pulmonary penetrable end products which initiate pronounced bronchial inflammatory response associated with altered distribution of leukocytes in circulation as well as bronchoalveolar fluid (Ayyagari et al. 2004). Notably, in regard to occupational and environmental risk factors of IPF, it has been found that there is a pronounced male predominance of the disease owing to the skewed sex distribution in professions involving exposure to metal and wood-dust in industries. Although there is an appreciable diversity of pollutants contributing to respiratory symptoms in IPF, oxidative stress plays the major role in triggering as well as perpetuating the detrimental immunomodulatory and tissue remodeling responses with TGF-β1 acting as the central player in most fibrogenic signaling cascades. Telomere shortening and elevated expression of epithelial to mesenchymal (EMT) transition proteins have been largely documented in IPF associated with hyper-activated TGF-β1 signaling (Armand et al. 2013; Chen et al. 2013). Hence the relationship of AP and PF stands undoubtedly clear and warrants for serious consideration from the research as well as regulatory perspectives.

**CLINICAL CASE REPORTS**

Although the cause of IPF is unknown, several reports suggest a role of polluted environment and occupational exposure in the etiology especially as “risk factors” rather than direct “cause” (Garantziotis and Schwartz 2006; Miyake et al. 2005; Taskar and Coultas 2006). Metallic dust exposure is very hazardous and found to be associated with PF (Koo et al. 2017). Occupational and environmental exposure of metals like arsenic, copper, cadmium, nickel, molybdenum, uranium, tungsten, cobalt, vanadium (Assad et al. 2018) and aerosol containing Indium tin oxide (InSnO) (Homma et al. 2005) are also positively correlated with PF. Workers in the aluminium, asbestos, silica industries, coal mines and those exposed to organic dusts, wood dusts and PM are particularly susceptible.

Aluminium in different forms is used in cosmetics, ceramics, boat-construction industries and fireworks factories. The first case of PF in aluminium-industry worker was reported from Great Britain (Mitchell 1959). Recently, a study on geographically diverse, large population revealed pulmonary deposition of aluminium trihydroxide and silicon in IPF patients.
Bauxite produces dust and fumes when processed at high temperature. An autopsy-based study revealed that workers exposed to these dusts and fumes and other aluminium oxides were at high risk of PF (Bellot et al. 1984; Jederlinic et al. 1990).

In addition to aluminium, workers from asbestos industry are also at risk of PF. The first case of death due to PF on account of extensive asbestos exposure was reported in 1899 which is now known as the “Montague Murray Case” after British physician Dr. Montague Murray. Radiographic screening of workers below 70 years of age and at least with 1 year of working experience in asbestos industry showed consistent interstitial PF (Koskinen et al. 1998).

Several radiological studies relating PF to asbestos-exposed industry workers (Kang et al. 2018; Kim, 2009; Koskinen et al. 1996) along with smoking history have identified a positive correlation of smoking and asbestosis in PF (Lilis et al. 1986; Roggli et al. 1986) although certain instances of cigarette smoking-independent PF was also evident (Johansson et al. 2014). In fact asbestos-exposed workers show characteristics of IPF which is classified as “atypical” asbestosis (Attanoos et al. 2016).

It is worth mentioning that owing to the similar histological and radiographic manifestations, it is difficult to differentiate IPF from asbestos/silica exposure based on CT scan images in spite of differences in coarseness of fibrosis (Gotway et al. 2007; Wells et al. 2003), bronchiolar obstruction (Akira et al. 2003), opacity, emphysema and traction bronchiectasis (Arakawa et al. 2007). Several other industrial pollutants have been implicated in PF pathogenesis. In metallurgical industries, quartz (crystalline silica) is heated above the boiling point to produce vapors of amorphous silica which is then cooled and condensed to fine powder. Quartz is widely correlated with the pathogenesis of PF (Martin et al. 1972); even chronic exposure to amorphous chemically inert silica with diameter < 1 µm and regular surface appears to cause nodular PF (Vitums et al. 1977). Risk factors of IPF also involve lead, brass, steel (Hubbard et al. 1996), fabricated metal products (Pinheiro et al. 2008). In fact male workers (in chemical, petrochemical industries, carpentry, those exposed to wood dusts and wood preservatives) and female workers (involved in farming, bird raising and those with occupational exposure to dusts, pesticides, animal feeds) are at increased risk of occupational IPF (Awadalla et al. 2012; Taskar and Coultas 2006). A recent study in southern Europe showed higher incidence of IPF among farmers, veterinarians, gardeners, metallurgical and steel industry workers (Paolocci et al. 2018) wherein metal dust, fumes and organic dust were found to be the major risk factors positively associated with the extent of occupational exposure.

In addition to the aforesaid pollutants, CM demands especial mention as potential risk factor for IPF. Both familial and sporadic IPF have been linked with smoking (Steele et al. 2005; Taskar and Coultas 2006).

CM has been found to induce changes in the methylation pattern of genes, including WNT7A, involved in IPF pathogenesis (Tennis et al. 2012). Reports also exist about differential survival extents of smoker vs.
Table 1: *In vitro* Studies on Pulmonary Fibrosis due to Air Pollution

<table>
<thead>
<tr>
<th>Nature of pollutant/s</th>
<th>Source of pollutant/s</th>
<th>Affected cells</th>
<th>Cellular effect/s</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Vanadium pentoxide</td>
<td>Fumes from oil burning furnaces which use V_{2}O_{5}-containing fuels</td>
<td>Lung fibroblasts</td>
<td>Increased proliferation and elevated collagen deposition through stimulation of other pulmonary cells</td>
<td>(Cooper, 2007; Fortoul et al., 2014; Hoppe et al., 1991)</td>
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<td></td>
<td></td>
<td>Macrophage</td>
<td>Enhanced IL-1β release and activation of PDGF-α receptor in rat lung myoFBs</td>
<td>(Bonner et al., 1998a)</td>
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<td></td>
<td></td>
<td>Lung fibroblasts and bronchial epithelial cells</td>
<td>HB-EGF and CTGF expression</td>
<td>(Ingram et al., 2007; Ingram et al., 2003; Zhang et al., 2001)</td>
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<td></td>
<td></td>
<td>Rat myoFBs</td>
<td>Elevated ERK-MAPK activation</td>
<td>(Wang and Bonner, 2000)</td>
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<tr>
<td>Uranium</td>
<td>Nuclear industrial effluents and military munitions industries</td>
<td>NR8383 macrophages</td>
<td>TNF-α secretion through JNK and p38 MAPK activation</td>
<td>(Gazin et al., 2004)</td>
</tr>
<tr>
<td>Chrysotile asbestos, residual oil fly ash and titanium dioxide</td>
<td>Contaminated air and industrial effluents</td>
<td>Lung fibroblasts</td>
<td>Upregulation of PDGF receptor-α and IL-1α expression</td>
<td>(Lindroos et al., 1997)</td>
</tr>
<tr>
<td>SiO₂, Al₂O₃, Fe₂O₃, and TiO₂</td>
<td>Asian dust particles containing PM₁₀</td>
<td>Bronchial cells</td>
<td>Upregulation of TGF-β and fibronectin along with ROS production</td>
<td>(Kyung et al., 2012)</td>
</tr>
<tr>
<td>PM₁₀</td>
<td>Dust from southern, northern and central Mexico Urban commercial and industrial zone</td>
<td>Human airway epithelial cells</td>
<td>Up regulation of PDGF receptor expression</td>
<td>(Bonner et al., 1998b)</td>
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<td></td>
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<td>Enhanced MMP-2 and MMP-9 expression</td>
<td>(Morales-Barcenas et al., 2015)</td>
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### Table 1: *In vitro* Studies on Pulmonary Fibrosis due to Air Pollution (continued)

<table>
<thead>
<tr>
<th>Nature of pollutant/s</th>
<th>Source of pollutant/s</th>
<th>Affected cells</th>
<th>Cellular effect/s</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td><strong>PM$_{2.5}$</strong></td>
<td>Polluted air</td>
<td>Bronchial epithelial cells, pulmonary fibroblast and macrophage</td>
<td>Epithelial to mesenchymal transition Fibroblast activation and TGF-β/Smad dependent-macrophage activation</td>
<td>(Xu et al., 2019)</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>Air from cache valley (Northern Utah)</td>
<td>Bronchial epithelial cell</td>
<td>Elevation of IL-1, IL-6 and STAT 3 and IL-6/GP130/STAT3-associated fibrotic signaling</td>
<td>(Watterson et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>Polluted air, motor vehicle exhaust</td>
<td>Human Airway Epithelial Cells</td>
<td>HMGB1-RAGE-dependent fibrotic signaling through elevated TGF-β1, PDGF-AB, and PDGF-BB expression</td>
<td>(Zou et al., 2018)</td>
</tr>
<tr>
<td>Crystalline silica, zinc and iron salts, 1-nitropyrene and lipopolysaccharide</td>
<td>PM containing dust</td>
<td>Human bronchial epithelial cells</td>
<td>CXCL8 elevation in a TACE/TGF-α/EGFR-regulated pathway</td>
<td>(Keane et al., 1997; Ovrevik et al., 2009; Ovrevik et al., 2011)</td>
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<tr>
<td><strong>PM$_{2.5}$</strong></td>
<td>Diesel exhaust</td>
<td>A549 and NCI-H292 cells</td>
<td>Increased MMP-1 expression via ERK 1/2 pathway mediated by NOX4</td>
<td>(Amara et al., 2007; Kagawa, 2002)</td>
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<td>Ligands of aryl hydrocarbon receptor (AhR) like benzopyrene, nitrated polyanromatic hydrocarbon and polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin</td>
<td>Urban polluted air</td>
<td>NCI-H441 cells</td>
<td>Elevated MMPs, IL-1β and TNF-α expression</td>
<td>(Wong et al., 2010)</td>
</tr>
<tr>
<td>Single walled and multi walled carbon nano tubes</td>
<td>Polluted air borne of carbon nano tube manufacturing industries</td>
<td>Fibroblasts and macrophages</td>
<td>Elevated TGF-β1 and PDGF production to induce fibroblast to myoFB transformation</td>
<td>(Azad et al., 2013; Chen et al., 1977; He et al., 2011; Wang et al., 2010)</td>
</tr>
<tr>
<td>Nature of pollutant/s</td>
<td>Source of pollutant/s</td>
<td>Affected species and route of administration</td>
<td>Cellular effect/s</td>
<td>Reference</td>
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<tr>
<td>Copper oxide nano particles</td>
<td>Effluent of electronic industries</td>
<td>Mice (intranasal delivery)</td>
<td>Pulmonary inflammation and myoFB activation via α-SMA expression</td>
<td>(Lai et al., 2018)</td>
</tr>
<tr>
<td>Titanium dioxide (TiO₂)</td>
<td>Nano particles in air</td>
<td>Rats (intra-tracheal instillation) and human lung fibroblasts</td>
<td>Transient inflammation. Fibrogenic effect through MMP-1 induction via IL-1β-dependent pathways</td>
<td>(Armand et al., 2013; Oyabu et al., 2013; Yoshiura et al., 2015)</td>
</tr>
<tr>
<td>Nickel Dioxide (NiO₂) and Nickel (II) oxide (NiO)</td>
<td>Nano particles in air</td>
<td>Rats (intra-tracheal instillation and inhalation)</td>
<td>Increased expression of pro-inflammatory cytokines; response is specific to pollutant nature. Highly toxic in intravenous treatment and at higher dose</td>
<td>(Halappanavar et al., 2015; Morimoto et al., 2011; Rahman et al., 2017; Xu et al., 2013)</td>
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<td>Indium oxide (In₂O₃), sintered indium tin oxide (SITO), indium oxide (IO) and indium tin oxide (ITO)</td>
<td>Ventilation dust and aerosol</td>
<td>Rats and mice (inhalation)</td>
<td>Pulmonary fibrosis</td>
<td>(Badding et al., 2016)</td>
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Table 2: In vivo Studies on Pulmonary Fibrosis due to Air Pollution (continued)

<table>
<thead>
<tr>
<th>Nature of pollutant/s</th>
<th>Source of pollutant/s</th>
<th>Affected species and route of administration</th>
<th>Cellular effect/s</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Pure alpha-alumina</td>
<td>Foundry dust</td>
<td>Rats (intra-tracheal instillation)</td>
<td>Increased collagen, elastase fibre deposition. MMP2 and MMP9 elevation in lungs, irritation and inflammation in lungs</td>
<td>(Halatek et al., 2005)</td>
</tr>
<tr>
<td>V$_2$O$_5$ and Uranium</td>
<td>Polluted air from industries</td>
<td>Rats and mice (intra-tracheal instillation or inhalation)</td>
<td>Non neoplastic lesions, increased collagen deposition, inflammation and oxidative stress leading to PF progression</td>
<td>(Bonner et al., 2000; Monleau et al., 2006; Ress et al., 2003; Walters et al., 2014)</td>
</tr>
<tr>
<td>Diesel exhaust</td>
<td>Polluted air</td>
<td>Mice (Bleomycin pre-treated mice exposed to diesel exhaust)</td>
<td>NF-E2-related factor 2 (Nrf2)-regulated lung fibrosis</td>
<td>(Li et al., 2017)</td>
</tr>
<tr>
<td>PM$_5$, titanium, iron, silicon, calcium, aluminium, magnesium</td>
<td>Iraq dust</td>
<td>Army men samples, A549 cell line treatment and exposure of mice to dust challenges</td>
<td>IL-2 upregulation and depletion of T$_{reg}$ cells to induce PF</td>
<td>(Harrington et al., 2017; Szema et al., 2014)</td>
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non-smoker IPF patients (Antoniou et al. 2008). Ambient AP is another crucial risk factor of IPF wherein NO$_2$, O$_3$ and PM were differentially implicated in the development and exacerbation of IPF as evident from the diverse reports (Conti et al. 2018; Johannson et al. 2014; Johannson et al. 1987; Sese et al. 2018b; Winterbottom et al. 2018).

A recent study performed in a slum area in New Delhi, India showed that both ambient and household AP affects lung function among adult women (Arora et al. 2018). Although there is much debate regarding the specific contribution of different toxic gases and particulate components, due to differences in region and context-specific observations, the involvement of AP in the pathogenesis of PF is unambiguous and alarming. Recently a number of in vitro and in vivo studies have established the association of air pollutants with the occurrence of IPF. A detailed mention about
these findings is presented in table 1 and table 2.

**THERAPEUTIC RESEARCH**

PF is progressive and fatal with limited therapeutic options and that too mostly depending on anti-inflammatory agents and immunosuppressive agents that only prevent disease progression (Rafii et al. 2013; Woodcock and Maher 2014). Lung transplantation is the last resort (Gross and Hunninghake 2001; Macagno et al. 2017). Corticosteroids have proven slightly helpful owing to their immunosuppressive action that can deter persistent inflammation and pulmonary scarring (Rafii et al. 2013). Nintedanib (receptor tyrosine kinase inhibitor in the form of humanized monoclonal antibody) and pirfenidone (a drug that down regulates growth factor and pro-collagen production) are the two currently used FDA–approved (King et al. 2014; Noble et al. 2011; Richeldi et al. 2011; Richeldi et al. 2014) drugs against PF. In addition, Lebrikizumab, STX and doxycycline have proven highly promising and are under clinical trials (Mishra et al. 2011; Woodcock and Maher 2014). However, due to the various side effects of the available drugs and poor efficacy in completely subduing the disease (Hughes et al. 2016; Zeskind 2011), alternative strategies for identifying potential anti-fibrotic remedies (mostly relying on herbal medicines) are always in demand. Traditional medicinal plant-based research for IPF treatment has shown marked increase in recent times owing to the reduced toxicity of the herbal formulations. Owing to the constraint in scope and space, these studies are not discussed in the current review. However, extensive information about herbal extracts and their efficacy in combating PF may be found in the literature (Bahri et al. 2017; Hosseini et al. 2018; Mojiri-Forushani et al. 2017).

**CONCLUSION AND FUTURE PERSPECTIVE**

The role of AP in causing pulmonary damage, especially IPF, is unambiguous. Although definitive evidences regarding the role of air pollutants as initiators of injury or exacerbators of existing pulmonary complications (leading to fibrosis) stand elusive, longitudinal epidemiological and translational studies clearly warrant the need for reframing the regulatory guidelines for monitoring as well as controlling AP with an aim to counter ILDs. Clearly defining the “exposome” in the air-pollution-associated pulmonary complications will help to design rational monitoring and regulatory strategies catering to public health. Identifying potential environmental contributors to IPF, either directly or through posing epigenetic regulation by gene-environment crosstalk, will help in better understanding of the complex molecular etiology. Existing studies have already characterized certain biomarkers of exposure to air pollutants (Berhane et al. 2014; Fry et al. 2014; Neophytou et al. 2013). Further explorative studies to identify novel non-invasive biomarkers predicting early stages of PF in pollutant-exposed population from highly industrialized area are essentially required. In this regard, profiling of respiratory tract microbiome as biomarker of pollution might prove instrumental in characterizing stage-
specific changes in the microflora as a potential indicator of respiratory microenvironmental alteration. Moreover plausible changes in BAL fluid pH might also help to address the changing physicochemical parameters in the respiratory tract. These studies will be challenging due to the difficulties in precisely defining the exposome in PF patients (compared to normal individuals) owing to the requirement for repeated measurements of the diverse biomarkers of exposure and that too in a longitudinal manner in sufficiently large cohorts; however, the end result will be highly rewarding. Government bodies should strictly monitor the quality of ambient air in the cities with stern measures to reduce pollution. At a personalized level, awareness and avoidance of exposure to potential household pollutants like incense smoke, CM and occupational as well as traffic-associated pollutants are highly desired in order to invite a better tomorrow with a pollution free atmosphere and people with healthy lungs.

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