INTRODUCTION

The diseases of respiratory system are the major cause of death followed by heart diseases, cerebrovascular diseases, and pneumonia [1]. Idiopathic pulmonary fibrosis (IPF) is a progressive chronic disease with a poor prognosis [2]. IPF is characterized by epithelial cell dysfunction caused by various factors, including genetic features, exposure to exogenous agents, or aging [3]. The symptoms of IPF are shortness of breath (dyspnea) and nonproductive cough [4]. The 5-year fatality rate of patients with IPF is 50% to 80% [5] and the median survival time is 3–5 years. The prevalence and incidence of IPF in the United States in 2010 was estimated to be 18.2 and 5.8 new cases per 100,000 person-years, respectively [6], while that in South Korea (hereafter Korea) in 2011 was 30.1 and 13.1 new cases per 100,000 person-years, respectively, which was the higher than that in the United States [7].

Several studies showed that the inflammatory and fibrotic responses induced by polyhexamethylene guanidine phosphate (PHMG-p) were similar to those observed for idiopathic pulmonary fibrosis in South Korea in 2011. "Omic" technologies can be used to understand the mechanisms underlying chemical-induced diseases. Studies to determine the toxicity of chemicals may facilitate understanding of the mechanisms underlying the development of pulmonary fibrosis at a molecular level; thus, such studies may provide information about the toxic characteristics of various substances. In this review, we have outlined the cellular and molecular mechanisms underlying idiopathic pulmonary fibrosis and described pulmonary fibrosis induced by various chemicals, including bleomycin, paraquat, and PHMG-p, based on the results of studies performed to date.

Keywords: pulmonary fibrosis, polyhexamethylene guanidine phosphate (PHMG-p), microRNA, epithelial cell
*in vitro* studies showed that the inflammatory and fibrotic responses induced by PHMG-p were similar to those observed for IPF in 2011 [13,14]. In addition, Lee et al. [15] established a mouse model for pulmonary inflammation and fibrosis by using PHMG-p. Thus, the results of these studies indicate that the IPF occurred in Korea was induced by exposure to the chemicals in HD.

Pulmonary fibrosis is a potential adverse effect of exposure to various drugs such as bleomycin, cyclophosphamide, amiodarone, procainamide, penicillamine, gold, and nitrofurantoin or to certain environmental factors such as gases, asbestos, silica, and pesticides. After infiltrating lungs, these substances damage epithelial cells. Recent studies indicate that pulmonary fibrosis is caused by multiple cycles of epithelial cell injury and activation. In this review, we have outlined the cellular and molecular mechanisms underlying IPF, and we have described pulmonary fibrosis induced by chemicals, including bleomycin, paraquat, and PHMG-p.

**EPITHELIAL-DRIVEN IPF**

To date, chronic inflammation has been thought to play an important role in the development of IPF. According to this hypothesis, the inflammatory process causes epithelial alterations such as loss of type 1 pneumocytes and proliferation of type 2 pneumocytes, which are characteristic of IPF, and the epithelial cells are damaged because of the surrounding inflammatory microenvironment. Recent findings indicate that IPF probably results from multiple cycles of epithelial cell injury and activation that provoke the migration, proliferation, and activation of mesenchymal cells with the formation of active fibroblastic/myofibroblastic foci, which lead to exaggerated accumulation of the extracellular matrix (ECM) and mirror abnormal wound repair [16]. Epithelial cells play an important role in fibrogenesis through three kinds of responses, namely, involvement in the disruption of the epithelial lining, the alteration in the production of mediators, and induction of the epithelial-mesenchymal transition (EMT).

Repeated microscopic injuries cause death of epithelial cell via induction of endoplasmic reticulum (ER) stress and apoptosis [17]. Most studies investigating the role of ER stress in the pathogenesis of IPF have focused on ER stress-induced apoptosis. Epithelial cell apoptosis is a common event and probably an essential feature of IPF. *In vitro* studies have shown that ER stress is accompanied by increased death of epithelial cells [18,19]. Mulugeta et al. [20] showed that increased epithelial death is associated with an increase in caspase activity, specifically through a caspase-4-mediated mechanism. Korfei et al. [21] showed that in the lung tissues in humans, the apoptotic pathway was activated in the areas of fibrosis that prominently expressed markers of ER stress. These results suggest that ER stress may play a role in the pathogenesis of IPF by increasing epithelial injury and death. However, whether these mechanisms of epithelial apoptosis are part of the development of IPF (a secondary process) or are an early and triggering event remains to be clarified. Death of epithelial cells has been noticed in otherwise normal areas of the lung parenchyma, which suggest that it may be an initial event in the pathogenesis of IPF. To date, however, the precise cellular signals that culminate in the initial epithelial dysfunction and death are unknown.

A number of mediators capable of inducing migration and proliferation of epithelial cells have been identified in the lungs of patients with IPF. Injured epithelial cells release diverse growth factors that are potent mitogens, such as hepatocyte growth factor, hepatoma-derived growth factor, epidermal growth factor, and transforming growth factor-α (TGF-α) [22,23]. In addition, they express chemokines that attract resident fibroblasts and bone marrow-derived fibroblasts to the injured sites. Epithelial cells are believed to be the key sources of chemokine ligand 3 (CCL3), and results of a study in an experimental model of bleomycin-induced pulmonary fibrosis showed that anti-CCL3 antibodies significantly reduce the development of fibrosis [24]. Results similar to those reported by Smith et al. [24] were obtained when CCL2 was neutralized, which suggested an involvement of a variety of β-chemokines [25]. Some matrix metalloproteinases (MMPs) may participate in the migration of epithelial cells after injury. In particular, MMP-1 and MMP-7 are highly expressed in bronchiolar and alveolar cells in the lungs of patients with IPF [26]. In addition, the balance between urokinase and plasminogen activator inhibitor-1 (PAI-1) is important in determining the efficiency of epithelial cell migration. Excess of local PAI-1 may worsen scarring by delaying or preventing epithelial migration and restoration [27].

Although fibroblasts/myofibroblasts are known to play a role in the pathogenesis of IPF, the origin and process of activation of fibroblasts/myofibroblasts during fibrotic remodeling remain largely undefined and controversial. EMT may be one of the mechanisms mediating the expansion of fibroblasts/myofibroblasts. EMT is a dynamic cellular process in which polarized epithelial cells lose their epithelial phenotype and gain mesenchymal characteristics. TGF-β is considered to act as a master switch in EMT. TGF-β regulates the transcription of downstream genes responsible for EMT; subsequently, epithelial cells show loss of E-cadherin and claudin-1 and ac-
quision of vimentin and α-smooth muscle actin (α-SMA). Chang et al. [28] reported that more than 40% of fibroblasts were derived from epithelial cells in vivo, which indicated that EMT was a significant contributor to fibroblast expansion in IPF. The myofibroblasts in the foci secrete excessive ECM proteins and stimulate epithelial apoptosis. During these processes, the formation of scar and deregulated secretion of enzymes can induce honeycomb cysts [3,29].

**ROLE OF MiRNA IN IPF**

Micro RNAs (miRNAs) are generated by RNA polymerase as hairpin-shaped primary miRNA and are cleaved by Drosha enzyme to release precursor miRNA. Exportin-5 transports the precursor miRNA to the cytoplasm where it is cleaved by Dicer enzyme, which results in mature miRNA [30]. The miRNAs are short (20–23-nucleotide-long) single-stranded RNAs that regulate the mRNA expression by acting on mRNA 3’-untranslated regions (UTR), followed by impairing the translation of mRNA. One miRNA can regulate hundreds of target genes. In addition, one gene can be simultaneously regulated by diverse miRNAs [31]. Thus, miRNA functions in a broad range of physiological situations. miRNAs fine-tune gene expression or translation by functioning directly before protein synthesis in a wide range of physiological situations [32], and thus, miRNAs have dose- and time-dependent and tissue-specific responses that can reflect the mode of action of the xenobiotics [33].

Recent studies confirm that many miRNAs, including let-7d, miR-26a, miR-1343, miR-375, and miR-200, play a role in IPF by regulating EMT [34]. The expression of let-7d and miR-26a is decreased in patients with IPF, whereas the expression of their target gene, high-mobility group A protein 2 (HMGA2), is upregulated. This leads to a change in the epithelial cell phenotype, deposition of ECM, and development of IPF. Stolzenburg et al. [35] showed that miR-1343 attenuates EMT and fibrogenesis by directly targeting TGF-β receptors. Alternatively, Wang et al. [36] showed that the expression of miR-375 decreases during the trans-differentiation of epithelial cells and ectopic expression of miR-375 inhibits EMT by binding directly to the 3’-UTR of Frizzled 8 and thereby blocking the Wnt/β-catenin pathway. Results of another study showed that the expression of miRNAs belonging to miR-200 family, the overexpression of which inhibits EMT, is downregulated in patients with IPF. Injection of miR-200 prevented pulmonary fibrosis in mice. A recent study by Das et al. [37] showed that the expression of miR-326 is decreased in pulmonary fibrosis, which causes induction of TGF-β1. In contrast, enhanced expression of miR-326 inhibits pulmonary fibrosis by post-transcriptional regulation of the expression of TGF-β1.

Proliferation of fibroblasts and their differentiation into myofibroblasts is important in the development of IPF. Several studies have shown that some miRNAs, including miR-21, miR-26a, and miR-155, can regulate the function of fibroblasts in the lung. Liu et al. [38] showed that miR-21 is upregulated in patients with IPF and only a small amount of miR-21 is expressed in the normal lung tissue of mice. However, after stimulation with bleomycin, the expression of miR-21 was upregulated, which promoted the accumulation of myofibroblasts. Further studies showed that Smad7 is a direct target gene of miR-21. Thus, miR-21 causes the activation of the TGF-β1 pathway and results in the development of IPF by targeting Smad7. A recent study by Li et al. [39] showed that miR-26a inhibits TGF-β1-induced proliferation of fibroblasts, by directly targeting cyclin D2, which regulates the TGF-β receptor I as well as TGF-β2. Inhibition of miR-26a promotes collagen deposition in the lungs of mice. Moreover, overexpression of miR-26a inhibits experimental pulmonary fibrosis in mice. Marshall et al. [40] found that miR-155 participates in pulmonary fibrosis by targeting the Ang-II type 1 receptor, which is located in stromal fibroblasts, and the expression of miR-155 is increased in the lungs of IPF patients and in mice treated with bleomycin. Increase in the expression of miR-155 enhances collagen synthesis in fibroblasts and promotes the development of pulmonary fibrosis.

**PULMONARY FIBROSIS INDUCED BY CHEMICALS**

Bleomycin is one of the most commonly used anticancer drugs for lymphoma and germ cell tumors. Pulmonary toxicity is observed in approximately 10% of patients treated with bleomycin and the condition of 2–3% of the patients progresses to pulmonary fibrosis. Bleomycin forms a complex with Fe³⁺ to form reactive oxygen species (ROS), oxidizes fatty acid followed by destabilization of the membrane, and induces an inflammatory response. Several studies have shown that bleomycin induces apoptosis in epithelial cells through the Fas/FasL pathway [41], Ang-II type 1 receptor [42], and ROS [43]. In addition, bleomycin triggers the production of fibrotic mediators such as growth factors and TGF-β, which mediate pulmonary fibrosis [44]. To date, however, few studies have been performed on induction of EMT by bleomycin. Chen et al. [45] reported that bleomycin induces EMT via the TGF-β/Smad signaling pathway. Several miRNAs associated with EMT have been identified in bleomycin-induced pulmonary fibrosis. Paraquat is the second most commonly used herbicide.
Paraquat induces pulmonary fibrosis by generating excessive ROS, which results in peroxidation of adjacent lipids. Alveolar lipids form a barrier that protect the alveoli, but paraquat alters the amount of lipids, which interferes with the contraction and swelling of the alveoli, thus increasing alveolar damage. In addition, paraquat is oxidized to superoxide, which destroys the structure of the mitochondria, inhibits energy production, and induces cell death not only by DNA damage but also by signal transduction. Type 2 alveolar cells are destroyed by oxidative damage and inflammatory response, followed by accumulation of various mediators that induce early pulmonary fibrosis [46,47]. Furthermore, paraquat promotes EMT by regulating the TGF-β/Smad signaling pathway [48], the Wnt/β-catenin signaling pathway [49], the mitogen-activated protein kinase (MAPK) pathway [50], and the Notch1 pathway [51]. Several studies indicate that miRNA expression is regulated by paraquat. Liu et al. [52] showed that paraquat induces the expression of miR-21, which results in fibrogenesis. In addition, miR-210 contributes to paraquat-induced EMT by targeting RUNX3, which promotes the degradation of HIF-1α [53].

PHMG-p exerts excellent bactericidal effects by inhibiting the dehydrogenase activity and attacking the bacterial membrane. The lungs of animals exposed to PHMG-p showed atrophy/necrosis/hypertrophy of bronchiolar epithelium, inflammatory cell infiltration, mucus plug, and fibrosis. To date, limited information is available about the toxic mechanism of PHMG-p. PHMG-p induces the expression of mRNA and proteins associated with apoptosis, ER stress, and autophagy [54]. Rats exposed to PHMG-p showed an increase in the levels of inflammatory cytokines (interleukin 1β [IL-1β], IL-6, and chemokine (C-X-C motif) ligand 1 [CXCL1]) and a decrease in the level of interferon gamma (IFN-γ). In addition, the expression of fibrotic mediators, including monocyte chemoattractant protein 1 (MCP1), fibronectin, MMP2, MMP12, and TIMP1, was increased. Results of a previous study in a co-culture model of epithelial, macrophage, and mast cells indicate that PHMG-p increases the production of ROS, damages airway barrier, and increases the expression of inflammatory cytokines (increased release of TNF-α, IL-6, IL-8, and TGF-β1) and mediators associated with ECM accumulation (MMP2, MMP9, TIMP1, and TIMP2) [13]. The inflammatory responses induced by PHMG-p are mediated via the TNF-α/NF-κB pathway [55,56]. A recent study showed that PHMG-p induces EMT that increases the expression of α-SMA and decreases the expression of E-cadherin [57]. In addition, it was identified in this study that pulmonary fibrosis-related miRNAs are regulated by PHMG-p. miR-196, miR-454, miR-4286, miR-503, and miR-877-5p were demonstrated to function in apoptosis and/or cell cycle regulation. miR-454, miR-375, miR-503, and miR-27b were engaged with TGF-β signaling. Eight miRNAs regulated by PHMG-p were reported to be involved in the EMT; miR-33b, miR-431-5p, miR-487a, miR-381, miR-375, miR-27b, miR-760, and miR-6126. The expression of none of the miR-
The expression of miR-323a was downregulated in epithelial cells treated with PHMG-p, which was consistent with that observed after treatment with bleomycin. The miRNAs belonging to the miR-323a family play a central role in pulmonary fibrosis by targeting the TGF-α and TGF-β signaling pathways [58]. Figure 1 represents the putative mechanisms of fibrogenesis induced by PHMG-p based on the cellular responses and miRNA microarray analysis.

CONCLUSION

The mRNA and epigenetic profiling can be performed to determine the mechanism underlying the development of IPF. The advanced omics technology, which includes genomics, transcriptomics and proteomics, enables observation of the expression of DNA, mRNA, and proteins. Thus, novel technologies can be used to suggest new hypothesis and understand specific mechanisms underlying the toxic responses of test materials.

The cellular responses of epithelial cells against three chemicals, namely, bleomycin, paraquat, and PHMG-p, were not different in terms of the epithelial function associated with pulmonary fibrosis. To date, however, few studies on pulmonary fibrosis induced by PHMG-p have been conducted using omics technology. Further studies should be performed to determine the genetic networks in the point of cell proliferation, inflammation, and EMT and identify genes and miRNAs that play a central role during lung fibrogenesis. Some miRNAs associated with pulmonary fibrosis induced by PHMG-p were identified in microarray analysis. Understanding the cellular and molecular mechanisms underlying pulmonary fibrosis induced by chemicals may provide insights about the pulmonary diseases at a molecular level. These studies will contribute to the elucidation of the cause-effect relationship and the discovery of a therapeutic target.

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CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

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