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Discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase activated by collagen. We previously reported the functional expression of DDR1 on human monocyte-derived macrophages in vitro; however, information regarding its role in diseases is limited. Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease, and the lesions contain an abundance of collagen. In this study, we examined DDR1 expression on bronchoalveolar lavage fluid (BALF) cells and investigated its functionality using samples obtained from 28 IPF patients, 13 chronic obstructive pulmonary disease patients, and 14 healthy volunteers. The DDR1 expression level in CD14-positive BALF cells was higher in IPF patients than in chronic obstructive pulmonary disease patients or healthy volunteers. The predominant isoform was DDR1b in the IPF group, while DDR1a was predominant in the other two groups. Using immunohistochemical analysis, we also detected DDR1 expression on infiltrating inflammatory cells in the IPF lesion. In IPF patients, DDR1 activation induced the production of MCP-1, IL-8, MIP-1α, and MIP-1β from CD14-positive BALF cells in a p38 MAPK-dependent manner. In contrast, DDR1 activation of CD14-positive BALF cells in the other groups did not induce the production of these chemokines.

IPF is a chronic, usually fatal lung disease characterized by impaired oxygen transfer, alveolar collapse, and interstitial fibrosis (1,2). The alveolar macrophages produce various growth factors and cytokines that attract inflammatory cells such as neutrophils, monocytes, and lymphocytes (3-6). The alveolar macrophages also release chemokines that contribute to the development of IPF and, therefore, we suggest that DDR1 might be associated with the pathogenesis of IPF in the tissue microenvironment. The Journal of Immunology, 2005, 174:6490-6498.

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The basement membrane is a specialized form of the extracellular matrix (ECM) that occupies a substantial portion of the tissue microenvironment and maintains the structural integrity of the alveolar walls. In the development of IPF, disruption of the alveolar basement membrane is associated with inflammation and ECM alterations (8,9). It is also known that the amount of collagen in the alveolar walls is correlated with disease severity (10). The interaction between inflammatory cells and ECM is probably associated with the development of IPF; however, information regarding the molecular mechanisms is limited.

Discoid domain receptor 1 (DDR1) is a receptor tyrosine kinase activated by collagen binding with its ligand, collagen (11,12). DDR1 has a unique extracellular domain that is homologous to discoidin 1 of Dictyostelium discoideum (13). DDR1 is constitutively expressed in normal tissues, such as lung, kidney, colon, and brain, and in tumor cells of epithelial origins such as mammary, ovarian, and lung carcinomas (13). Five DDR1 isoforms (a, b, c, d, and e) can be generated by alternative splicing of the DDR1 gene (13,14). We previously reported that the expression of two DDR1 isoforms, DDR1a and DDR1b, could be induced in vitro in human leukocytes, including neutrophils, monocytes, and lymphocytes. In vivo, studies showed that tissue-infiltrating mononuclear cells, particularly macrophages, were positive for DDR1 mRNA (15). The DDR1a and DDR1b isoforms differ from each other by an in-frame insertion of 111 bp that codes for an additional 37-aa peptide in the proline-rich juxtamembrane region. The 37-aa insertion in DDR1b contains the LXNPXY motif that corresponds to the consensus-binding motif of the Scl phosphotyrosine-binding domain (13). In addition, we recently found that the activation of DDR1 isoforms, most likely DDR1b, up-regulated the production of chemokines in macrophages in a p38 MAPK-dependent manner (16), including MCP-1, which plays an important role in the pathogenesis of IPF (17). Autophosphorylation of DDR1b was highly detectable as...
early as 30 min after DDR1 activation, peaked at 60 min, and returned to basal levels by 120 min (16, 18, 19). In contrast, autophosphorylation of DDR1α was first detected 90 min after DDR1 activation, peaked at 4 h, and became undetectable by 12 h (19). Furthermore, DDR1 is reported to be associated with matrix metalloproteinase-9 (MMP-9) production (20, 21), which plays a pivotal role in the lung remodeling of IPF (22).

The DDR1 ligand, collagen (10), is abundant in IPF, and human monocyte-derived macrophages can express endogenous DDR1 in vitro (15, 19). Therefore, we hypothesized that the alveolar macrophages of IPF patients might express functional DDR1. We investigated DDR1 expression and chemokine production from CD14-positive bronchoalveolar lavage fluid (BALF) cells, which are considered to be alveolar macrophages, by the activation of DDR1. We also examined DDR1 signaling in CD14-positive BALF cells obtained from IPF patients. We found that the CD14-positive BALF cells of IPF patients expressed DDR1, with the DDR1b isoform being the predominant form, and that DDR1 activation induced its autophosphorylation, followed by the recruitment of the DDR1b adaptor protein Shc. DDR1 activation also induced chemokine and MMP-9 production via a p38 MAPK-dependent pathway.

**Materials and Methods**

**Flow cytometry analysis of BALF cells**

This study was reviewed and approved by the Kagoshima University Faculty of Medicine Committee on Human Research. We investigated 28 IPF patients (mean age = 56.4 ± 12.3 years old, male:female = 14:14) and 14 chronic obstructive pulmonary disease (COPD) patients (mean age = 57.2 ± 14.3 years old, male:female = 8:6), and 14 healthy volunteers (mean age = 57.8 ± 17.8 years old, male:female = 8:6) who provided written informed consent. All patients and volunteers provided written informed consent.

The diagnosis of IPF was based on previously published international guidelines for COPD (23).

A bronchofibroscope was introduced into the right B3 segment of the lung to collect BALF cells. BALF fluids were stored at −80°C for analysis. BALF fluids were stored at −80°C for further analysis.

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cultured for 24 h. Following culture, the supernatants were collected, and the concentrations of MCP-1, IL-8, MIP-1β, MMP-2, MMP-9, tissue inhibitor of metalloproteinases (TIMP)-1, and TIMP-2 were measured using ELISA kits (R&D Systems), according to the manufacturer’s protocols. To evaluate the effect of β1 integrin, another collagen receptor, we used β1 integrin neutralizing mAb (DE9, 10μg/ml; Upstate Biotechnology), as previously described (16, 18).

To evaluate whether chemokine and cytokine productions induced by DDR1 activation are dependent on p38 MAPK, we pretreated CD14-positive BALF cells with 10μM SB203580 (Biochem-Novabiochem) for 30 min, followed by stimulation with collagen or DDR1 agonistic Ab. We also measured MCP-1, IL-8, MIP-1β, and GM-CSF concentrations in the BALF from each group.

Cytokine concentrations were determined by linear regression from a standard curve using GraphPad software (Flow Laboratories), as described previously (27).

Gelatin zymography
MMP-2 and MMP-9 activities were analyzed using gelatin zymography. Precast 7.5% polyacrylamide minigels containing 0.3% SDS and gelatin (1 mg/ml) were obtained from the YAGAI Research Center. Fifteen microliters of undiluted culture supernatant was mixed with an equal volume of 50 mM Tris-HCl buffer (pH 6.8) containing 2% SDS, 10% glycerol, and 0.01% bromphenol blue. Samples were loaded and electrophoresed at 10 mA for 20 min, followed by electrophoresis at 20 mA for 80 min, until the dye front reached the bottom of the gel. As a positive control, partially activated MMP-9 and MMP-2 samples were also loaded on the gels. Following electrophoresis, the gels were agitated in 2.5% (v/v) Triton X-100 for 1 h to remove the SDS, followed by washing in 50 mM Tris-HCl buffer (pH 7.5) containing 200 mM NaCl for 1 h to restore the enzymatic activity. The gels were incubated for 24 h at 37°C in 50 mM Tris-HCl buffer (pH 7.5) containing 200 mM NaCl, 5 mM CaCl2, 0.02% (w/v) Brij-35, and 0.01% NaN3 to allow proteolysis of the gelatin substrate. Finally, the gels were stained for 1 h with 0.1% Coomassie brilliant blue G-25 in 30% methanol and 10% acetic acid, followed by destaining for 3 h in 30% methanol and 5% acetic acid. Gelatinolytic activity was identified as clear bands against the blue background.

Western blot analysis
To detect DDR1 isoforms, 1×10⁶ CD14-positive BALF cells, which were selected using magnetic beads (Miltenyi Biotec), were lysed on ice for 20 min in 1 ml of lysis buffer containing 50 mM HEPES, 150 mM NaCl, 1% Triton X-100, 10% glycerol, and a mixture of protease inhibitors (Roche). The lysates were centrifuged, and 20 μl of the supernatant was collected. Subsequently, 20 μl of double-strength sample buffer (20% glycerol, 6% SDS, and 10% 2-ME) was added to the supernatants. The samples were boiled for 10 min. Proteins were analyzed on 8% polyacrylamide gels by SDS-PAGE and transferred electrophoretically to nitrocellulose membranes at 150 mA for 1 h using a semidyed system. The membranes were incubated with rabbit IgGs that specifically recognize DDR1α (16), DDR1β (18), both forms of DDR1 (Santa Cruz), or anti-human actin mouse IgG mAb (Santa Cruz Biotechnology), followed by sheep anti-rabbit or mouse IgG coupled with HRP (Amersham). Peroxidase activity was visualized by

FIGURE 1. FACS analysis for DDR1. A, representative data of the percentage of DDR1-positive cells in the three groups. The percentage of DDR1-positive cells in IPF patients was significantly higher than in the other two groups (A, representative data; B, comparison among the three groups; *, p < 0.01, Bonferroni-Dunn test with one-way factorial ANOVA). C, Western blot analysis for DDR1 expression in 1×10⁶ CD14-positive cells. The amount of total DDR1 was higher in the IPF patient group than in the other groups (*, p < 0.01, Bonferroni-Dunn test with one-way factorial ANOVA). D, DDR1 amount ratio in each group. In IPF patients, DDR1β amount ratio was significantly higher than the DDR1α amount ratio (**, p < 0.01, Bonferroni-Dunn test with one-way factorial ANOVA).
the Enhanced Chemiluminescence Detection System (Amersham). The intensities of DDR1 isoforms and actin were analyzed using the NIH Image Program (National Institutes of Health), and then the relative amount of each DDR1 isoform (DDR1 amount ratio) in each patient was calculated. DDR1 autophosphorylation was analyzed, as previously described (16, 18, 19). First, we evaluated whether DDR1 in fresh CD14-positive BALF cells was activated by lysing \(1 \times 10^7\) freshly isolated CD14-positive BALF cells, as described above. Subsequently, DDR1 in cell lysates was immunoprecipitated using anti-DDR1 Ab (C-20; Santa Cruz) and recombinant protein G-agarose (Invitrogen Life Technologies), as previously reported (16, 18, 19), and tyrosine phosphorylation of DDR1 was analyzed by Western blotting using a mouse monoclonal anti-phosphotyrosine IgG (4G10; Upstate Biotechnology) and a sheep anti-mouse IgG coupled with HRP (Amersham). Peroxidase activity was visualized by the Enhanced Chemiluminescence Detection System (Amersham).

In addition, to evaluate whether DDR1 activation by collagen or DDR1 agonistic Ab induces autophosphorylation of DDR1 and DDR1 signal transduction, \(1 \times 10^7\) CD14-positive BALF cells were plated on dishes, serum starved in RPMI 1640 containing 1% FCS for 10 h, and subsequently activated with 50 \(\mu\)g/ml type I collagen (Sigma-Aldrich) or DDR1 agonistic Ab (S1-DDR1 Ab) (16, 18) and then cultured. Cell lysates were prepared, and DDR1 was immunoprecipitated and analyzed, as described above.

To detect phosphorylation of p38 MAPK, CD14-positive cells were starved, as described above, and then activated with 50 \(\mu\)g/ml type I collagen (Sigma-Aldrich). Twenty microliters of cell lysate was directly presented as the mean ± SD, unless stated otherwise.

Results

BALF analysis in each group

Table I shows the clinical features of the patients investigated in this study. There was no significant difference in sex ratio, age, and body mass index among groups. The COPD patients were classified into four groups. To perform a one-way factorial ANOVA, the Bonferroni-Dunn test with one-way factorial ANOVA was performed. Vital capacity (VC) and DLCO% were significantly lower in IPF patients than in other groups (p = 0.01). BALF MCP-1, IL-8, MIP-1\(\alpha\), and GM-CSF levels in IPF patients were significantly lower than in COPD patients or healthy volunteers (p < 0.01). As shown in Fig. 1, the CD14-positive cells expressed DDR1. The percentage of DDR1-positive cells was significantly higher in IPF patients than in COPD patients or healthy volunteers. Almost all DDR1-positive cells were also CD14-positive. There was no significant difference among the three groups in the percentage of \(\beta_1\) integrin (another collagen receptor)-positive cells, CD14-positive cells, and \(\beta_1\) integrin-double-positive and CD14-positive cells in the total BALF cells (Table I).

CD14-positive BALF cells from IPF patients expressed DDR1b

In all three groups, the majority of CD14-positive cells were identified as macrophages by May-Giemsa staining (IPF patients: macrophages = 95.7 ± 5.4%, neutrophils = 4.6 ± 1.2%; COPD patients: macrophages = 95.8 ± 4.5%, neutrophils = 4.5 ± 1.3%; healthy volunteers: macrophages = 96.8 ± 4.1%, neutrophils = 3.9 ± 1.1%). As shown in Fig. 1, A and B, CD14-positive cells in all three groups express DDR1; however, there was a higher frequency of CD14-positive cells in the BALF from IPF patients (Fig. 1B). The total amount of DDR1 protein was also higher per \(1 \times 10^7\) cells in IPF patients (Fig. 1C), and the proportion of cells expressing the DDR1b isoform was also much higher in the BALF from these patients (Fig. 1D). This experiment was repeated using samples from five different patients, and similar results were observed.

DDR1 autophosphorylation and recruitment of Shc in freshly isolated CD14-positive BALF cells of IPF patients

To evaluate whether DDR1 activation occurs in vivo, we collected freshly isolated BALF CD14-positive cells and examined the phosphorylation levels of DDR1. As shown in Fig. 2, autophosphorylation and recruitment of Shc, the adaptor protein of DDR1b, were observed only in IPF patients and not in the other two groups. This experiment was repeated using samples from five different patients, and similar results were obtained.

Immunohistochemical analysis of DDR1 expression

As shown in Fig. 3, infiltrating inflammatory cells in the IPF lesion stained strongly with DDR1. As shown in Fig. 3A, Bronchial and alveolar epithelial cells were strongly positive for DDR1. Infiltrating inflammatory cells, including large mononuclear cells, were DDR1-positive for CD14 (Fig. 3C). Stromal cells of the subepithelial patients showed similar results. The luciferase reporter system revealed chemokine productions from CD14-positive BALF cells from IPF patients and synergized by the IP-10R of IPF bronchial epithelial cells. Chemokine production was not observed when the IP-10R was depleted (Fig. 3D).

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FIGURE 3. Immunohistochemistry of the biopsied lung of an IPF patient. Inflammatory cells in the IPF lesion showed strong positive staining for DDR1 (A). Bronchial and alveolar epithelial cells showed moderate positive staining for DDR1. Inflammatory cells in the IPF lesion also showed positive staining for CD14 as well (C) (A and B, ×300; C and D, ×500, original magnification; B, negative control for DDR1; D, negative control for CD14).

FIGURE 4. Effect of DDR1 activation on chemokine production in alveolar macrophages. A, DDR1 activation of alveolar macrophages from IPF patients induced MCP-1, IL-8, and MIP-1α production. DDR1 activation had no effect on COPD patients or healthy volunteers (*, p < 0.01, Bonferroni-Dunn test with one-way factorial ANOVA, in comparison with no activation in IPF patients; control IgM, control for DDR1 Ab). B, DDR1 activation showed a synergistic effect on LPS-induced chemokine productions from alveolar macrophages in IPF patients. In the presence of all LPS concentrations including 0 µg/ml, DDR1 activation significantly up-regulated the chemokine production (*, p < 0.01; **, p < 0.001, Bonferroni-Dunn test with one-way factorial ANOVA).
contrast, DDR1 stimulation did not induce nor up-regulate chemokine production from CD14-positive BALF cells from either the control or COPD patients. In preliminary experiments, we cultured CD14-positive cells for various time points (4, 8, 12, 24, 36, and 48 h) and concluded that culture for 24 h is the optimal because the chemokine levels peaked at 24 h and remained elevated in IPF patients (data not shown) and, in the other groups, collagen or DDR1 agonistic Ab stimulation did not up-regulate chemokine production. Furthermore, to evaluate the effect of microbeads, we cultured the isolated CD14-positive cells and cultured freshly obtained BALF cells of each group for various time points (4, 8, 12, 24, 36, and 48 h) without any stimulation. The chemokine concentrations between isolated CD14-positive cells and freshly isolated BALF cells in the culture supernatants were compared. There was no significant difference in the chemokine concentrations between CD14-positive cell supernatants and fresh BALF cell supernatants (data not shown). Taken together, we believe that the effect of microbeads was negligible and, therefore, we concluded that up-regulated chemokine production in IPF patients was induced by DDR1 activation and not by the effect of microbeads used for the CD14-positive selection. DDR1 activation alone also up-regulated LPS-induced chemokine production from CD14-positive cells from IPF patients (Fig. 4B). Our previous study showed that DDR1b, but not DDR1a, could induce or up-regulate chemokine production from human monocyte-derived macrophages (16). In this study, CD14-positive BALF cells from COPD patients and healthy volunteers did not express DDR1b. Thus, the results of this study support the previous reports (16, 19).

**FIGURE 5.** Effect of DDR1 activation on MMP production from alveolar macrophages. A, DDR1 activation of alveolar macrophages obtained from IPF patients induced MMP-9 production without any effect on MMP-2, TIMP-1, or TIMP-2 production (+, p < 0.01, Bonferroni-Dunn test with one-way factorial ANOVA, in comparison with no activation in IPF patients; b1 block Ab, β1 integrin-neutralizing Ab). B, Results of gelatin zymography using culture supernatants from alveolar macrophages obtained from IPF patients (black and white color). DDR1 activation of alveolar macrophages obtained from IPF patients induced active MMP-9 production.

**DDR1 stimulation induced active MMP-9 production in CD14-positive BALF cells from IPF patients**

As shown in Fig. 5A, collagen or DDR1 agonistic Ab stimulation also induced MMP-9 production from IPF patient’s CD14-positive BALF cells. In preliminary experiments, we cultured CD14-positive cells for various time points (4, 8, 12, 24, 36, and 48 h) and decided that culture for 24 h is the optimal time point because the production level of MMP-9 peaked at 24 h and decreased to basal level at 48 h, while the levels of MMP-2 and TIMPs did not change (data not shown). Active MMP-9 was produced from CD14-positive BALF cells (Fig. 5B). This active MMP-9 production was not inhibited by adding an Ab that blocks β1 integrin, another collagen receptor (10 μg/ml; Upstate Biotechnology). Neither collagen nor DDR1 agonistic Ab induced MMP-2, TIMP-1, or TIMP-2 production from CD14-positive BALF cells obtained from COPD patients or healthy volunteers (data not shown).

**Collagen and DDR1 agonistic Ab stimulation induced DDR1 autophosphorylation, recruitment of Shc, and p38 MAPK phosphorylation**

Based on our previous results (16, 18, 19), we predicted that DDR1b signal transduction might occur in the alveolar macrophages of IPF patients, and chose 60 min as the stimulation time. As shown in Fig. 6A, collagen stimulation induced DDR1 autophosphorylation with recruitment of Shc in IPF patient cells, and this was not observed in the other two groups. As shown in Fig. 6B, collagen stimulation induced p38 MAPK phosphorylation in IPF patient cells, but not in the other two groups. The results of
DDR1 agonistic Ab stimulation were the same as those obtained with collagen (data not shown). These experiments were repeated using samples from five different patients, and similar results were obtained.

p38 MAPK inhibitor (SB203580) significantly inhibited chemokine productions induced by DDR1 activation.

To evaluate whether the chemokine and MMP-9 production induced by DDR1 activation is dependent on p38 MAPK, we pretreated CD14-positive BALF cells with a p38 MAPK inhibitor (SB203580) for 30 min and then stimulated the cells with collagen or DDR1 agonistic Ab. As shown in Fig. 7, the p38 MAPK inhibitor significantly attenuated chemokine and MMP-9 production induced by DDR1 activation. Furthermore, the viability of the cells exposed to SB203580 using trypan blue staining confirmed that SB203580 did not affect the viability of the cells (data not shown).

Discussion

The processes observed in IPF are associated with the production, deposition, and proteolysis of the ECM, which may lead to irreversible pulmonary structural remodeling with fibrosis (9). In IPF, the basement membranes, which are a specialized form of the ECM in lung, are thickened, resulting in a dense deposition of collagen (8, 28). The initiating cause is unknown, but alveolar epithelial injury appears to be a critical early event of IPF (29). During this event, alveolar macrophages are the major inflammatory cells recruited into alveolar spaces in patients with IPF (30). During this process, alveolar macrophages have to move into the lesion through ECMs that are composed of collagen, and they also have to encounter dense collagen deposition in the IPF lesion (31). In contrast, in a healthy state, it is difficult for alveolar macrophages to encounter ECMs because ECMs are continuous and closely attached to the basal surface of the bronchial or alveolar epithelial cells in normal lung (31, 32). In this study, CD14-positive BALF cells expressed endogenous DDR1, and the majority of CD14-positive BALF cells were macrophages. Therefore, we believe that DDR1-positive, CD14-positive cells are alveolar macrophages. Taken together, we propose that DDR1 expressed on alveolar macrophages, but not expressed on bronchial and alveolar epithelial cells (32), can easily encounter its ligand, collagen, and transduce signaling events in IPF.

In this study, DDR1 activation of alveolar macrophages of IPF patients induced the secretion of chemokines, such as MCP-1, IL-8, and MIP-1α. These results are compatible with our previous results (16). MCP-1 is a major chemoattractant for monocytes in inflammation and immune responses (33). MCP-1 is detectable in the BALF of IPF patients (34) and has been suggested to be associated with the pathogenesis of IPF (35). Alveolar macrophages and epithelial cells are the main cellular source of MCP-1 production in IPF (36). IL-8 is a potent chemoattractant for neutrophils and plays a pivotal role in acute inflammation by recruiting and activating neutrophils (37). As a result, IL-8 is considered to play a prominent role in the attraction of neutrophils to the lung in IPF (38). In IPF, alveolar macrophages are considered to be the cellular sources of IL-8 (39). MIP-1α is known to regulate the trafficking and activation state of select subgroups of inflammatory cells, including lymphocytes (40). MIP-1α can modulate leukocyte adhesion to the endothelium and contributes to leukocyte recruitment into the lungs (41). In addition, it was reported that BALF MIP-1α levels were elevated in IPF (42). As described above, all chemokines investigated in this study play a pivotal role in the immunological pathogenesis of IPF. The present study also showed that DDR1 activation can dramatically synergize the LPS-induced chemokine production. Taken together, we propose that DDR1 might potentially contribute to the development of IPF in combination with other factors that induce chemokine production.
Our study also showed that DDR1 activation of CD14-positive BALF cells induced the secretion of MMP-9. MMPs are a family of zinc- and calcium-dependent endopeptidases capable of proteolytically degrading many of the components of the ECM (43), and TIMPs are the endogenous inhibitors of MMPs (44). In pulmonary diseases, MMPs are believed to be associated with wound repair of the human respiratory epithelium (45), while TIMPs are believed to be associated with irreversible pulmonary structure remodeling via myofibroblasts (46). The imbalance of these factors is thought to contribute to the development of interstitial lung diseases (47). In IPF, the alveolar macrophage is one of the cellular sources that produces MMP-9 (9) and contributes to lung remodeling in IPF (31). Furthermore, DDR1 was reported to be necessary for MMP-9 production (21). Taken together, we think that DDR1 might be associated with the lung remodeling in IPF via MMP-9 production from alveolar macrophages.

Alveolar macrophages expressed higher levels of DDR1 in IPF patients than in COPD patients or healthy volunteers. The predominant isoform in IPF was DDR1b, while DDR1a was predominant in the other two groups. In our previous reports, we found that GM-CSF could induce DDR1 expression on monocytes and increase the amount of DDR1b (16, 19). In the present study, the GM-CSF concentration in BALF was significantly higher in IPF patients than in other groups. Therefore, we think that the high GM-CSF concentration in BALF might be one of the reasons for the difference in total DDR1 levels and in the DDR1 isoform expression pattern between IPF patients and the other groups. Furthermore, alveolar macrophages of IPF patients are considered to differ functionally and metabolically from alveolar macrophages obtained from normal subjects because previous studies have shown that the spontaneous release of chemotactic factors from inflammatory cells (48, 49). The differences in the expression pattern in alveolar macrophages of IPF patients might be related to the functional differences between IPF patients and healthy individuals.

DDR1 activation plays a unique signaling role in alveolar macrophages. DDR1 activation with collagen up-regulates p38 MAPK in IPF. In conclusion, we showed functional DDR1b expression on alveolar macrophages of IPF patients and proposed a possible association of DDR1 in the pathogenesis of IPF. To date, there have been many reports investigating the inflammatory mediators or molecular interaction between inflammatory mediators and inflammatory cells in IPF; however, there is little information regarding the molecular interaction between the microenvironment, such as ECM, and inflammatory cells. Therefore, further studies addressing this point are necessary to clarify the pathogenesis of IPF.

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Disclosures
The authors have no financial conflict of interest.

References


Letter of Retraction

We wish to retract the article titled “Activation of Discoidin Domain Receptor 1 on CD14-Positive Bronchoalveolar Lavage Fluid Cells Induces Chemokine Production in Idiopathic Pulmonary Fibrosis” by Wataru Matsuyama, Masaki Watanabe, Yuko Shirahama, Ken-ichi Oonakahara, Ikkou Higashimoto, Teizo Yoshimura, Mitsuhiro Osame, and Kimiyoshi Arimura, The Journal of Immunology, 2005, 174: 6490–6498.

This retraction follows an investigation by Kagoshima University into scientific misconduct by Dr. Wataru Matsuyama, the first and corresponding author of the article, which found that the article contains fabricated data. The investigation also found that Dr. Wataru Matsuyama was solely responsible for the scientific misconduct that resulted in the falsified or fabricated data in this paper.

We apologize to the scientific community for the need to retract the article.

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