Biomarkers for interstitial lung disease and acute-onset diffuse interstitial lung disease in rheumatoid arthritis

Hiroshi Furukawa, Shomi Oka, Takashi Higuchi, Kota Shimada, Atsushi Hashimoto, Toshihiro Matsui and Shigeto Tohma

Abstract: Interstitial lung disease (ILD) is frequently a complication of rheumatoid arthritis (RA) as an extra-articular manifestation which has a poor prognosis. Acute-onset diffuse ILD (AoDILD) occasionally occurs in RA and includes acute exacerbation of ILD, drug-induced ILD, and Pneumocystis pneumonia. AoDILD also confers a poor prognosis in RA. Previously-established biomarkers for ILD include Krebs von den lungen-6 and surfactant protein-D originally defined in patients with idiopathic pulmonary fibrosis; the sensitivity of these markers for RA-associated ILD (RA-ILD) is low. Although many studies on ILD markers have been performed in idiopathic pulmonary fibrosis, only a few validation studies in RA-ILD or AoDILD have been reported. Biomarkers for RA-ILD and AoDILD are thus still required. Recently, genomic, cytokine, antibody, and metabolomic profiles of RA-ILD or AoDILD have been investigated with the aim of improving biomarkers. In this review, we summarize current preliminary data on these potential biomarkers for RA-ILD or AoDILD. The development of biomarkers on RA-ILD has only just begun. When validated, such candidate biomarkers will provide valuable information on pathogenesis, prognosis, and drug responses in RA-ILD in future.

Keywords: biomarker, rheumatoid arthritis, interstitial lung disease, acute-onset diffuse interstitial lung disease

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown etiology with a prevalence of 0.5–1.0%. Genetic, environmental, and stochastic factors are thought to be involved in its pathogenesis. The synovial joints are destroyed in RA but extra-articular manifestations are also frequent complications, namely, serositis, Felty’s syndrome, rheumatoid vasculitis, lymphoproliferative disease, and interstitial lung disease (ILD). The last is characterized by interstitial inflammation of the lung as a complication in 10–70% of RA patients. Such RA-associated ILD (RA-ILD) confers a poor prognosis in RA. Previously-established biomarkers for ILD include Krebs von den lungen-6 and surfactant protein-D originally defined in patients with idiopathic pulmonary fibrosis; the sensitivity of these markers for RA-associated ILD (RA-ILD) is low. Although many studies on ILD markers have been performed in idiopathic pulmonary fibrosis, only a few validation studies in RA-ILD or AoDILD have been reported. Biomarkers for RA-ILD and AoDILD are thus still required. Recently, genomic, cytokine, antibody, and metabolomic profiles of RA-ILD or AoDILD have been investigated with the aim of improving biomarkers. In this review, we summarize current preliminary data on these potential biomarkers for RA-ILD or AoDILD. The development of biomarkers on RA-ILD has only just begun. When validated, such candidate biomarkers will provide valuable information on pathogenesis, prognosis, and drug responses in RA-ILD in future.
The pathogenesis of AoDILD is believed to involve “immune reconstitution inflammatory syndrome” caused by infection by pathogens including *Pneumocystis jirovecii*.21 Patients with collagen disease treated with immunosuppressive drugs may be affected by immune reconstitution inflammatory syndrome.22,23 It was reported that AoDILD occurring in RA patients confers a poor prognosis.11,12

Krebs von den lungen-6 (KL-6) and surfactant protein-D (SP-D) are currently used as biomarkers for ILD. The cutoff levels for KL-6 and SP-D were set to distinguish both idiopathic pulmonary fibrosis (IPF) and collagen vascular disease-associated ILD from healthy controls and patients with bacterial pneumonia.24,25 These markers have been validated in RA patients with ILD or AoDILD but their sensitivity is not acceptable.26,27 KL-6 levels fluctuate during RA treatments with methotrexate or biological disease-modifying anti-rheumatic drugs under no clinical events.28,29 Serum KL-6 levels were normal in about 30% of the RA patients with biological disease-modifying anti-rheumatic drug-induced ILD.30,31 However, the efficacy of KL-6 for diagnosis of ILD in RA has been investigated.32–35 Risk factors for ILD in RA are age, male sex, and smoking status.10,36,37 Risk factors for AoDILD in RA are age at diagnosis of ILD, methotrexate use, and UIP pattern,38 whereas risk factors for drug-induced ILD in RA are older age, disease-modifying anti-rheumatic drug use, existing ILD, hypoalbuminemia, and diabetes.16 Prognostic factors for RA-ILD are age, male sex, forced vital capacity, history of AoDILD, and UIP pattern.39–43 Although KL-6 could be a prognostic marker for RA-ILD, it was not better than other factors.44 KL-6 might be a predictive biomarker for AoDILD in RA patients.45 KL-6 levels in RA-ILD patients were reported to be reduced by baricitinib therapy.46 Many studies of ILD markers were performed in IPF, but only a few validation studies on RA-ILD or AoDILD were reported. Thus, biomarkers for RA-ILD and AoDILD are required (Table 1).

Antibody biomarkers for RA-ILD or AoDILD

Rheumatoid factors (RFs) are autoantibodies against denatured Fc fragments of immunoglobulin (Ig) G which are present in the sera of 80% of RA patients. Most RF are IgM antibodies, high levels of which are associated with ILD in RA patients.10,11,47 IgA RFs were also reported to be associated with ILD in RA patients.48,49 Anti-citrullinated protein antibodies (ACPAs) are specific for proteins in which the arginine residues have been modified by peptidylarginine deiminases; they are detected in the sera of 70–80% of RA patients. It is known that the specificity of ACPAs for RA is higher than RFs. High levels of ACPAs in RA are also associated with ILD.47,49,50 It was reported that IPF is associated with the production of IgA-ACPAs,48,51 although this was not associated with ILD as a complication of RA. It was also reported that circulating secretory IgA-ACPAs were associated with RA with ILD.52 ACPAs were detected in the sera of ILD patients without RA who were former or current smokers.53,54 Citrullinated peptides found in the lung of RA-ILD patients could be generated by smoking55 and thus contribute to the pathogenesis of RA.56 Anti-carbamylated protein antibodies are auto-antibodies against homocitrullinated proteins (in which lysine residues are modified by a non-enzymatic post-translational mechanism); these are also increased in RA with ILD.57 Anti-citrullinated alpha-enolase peptide-1 antibodies are included in the ACPA grouping and are also associated with RA with ILD.58,59 It was also reported that other autoantibodies, including anti-citrullinated heat shock protein 90 antibodies or anti-malondialdehyde-acetaldehyde antibodies, can be detected in sera from RA patients with ILD.60,61

It has also been reported that anti-melanoma differentiation-associated gene 5 (MDA5)-specific antibodies are found in the sera of clinically amyopathic dermatomyositis patients and are biomarkers for AoDILD in Japanese dermatomyositis patients.62 Anti-aminocetyl-tRNA synthetase antibodies are also frequently detected in polymyositis/dermatomyositis patients with ILD.63 Anti-MDA5 antibodies or anti-aminocetyl-tRNA synthetase antibodies are usually absent in RA patient sera.64,65 Acute respiratory distress syndrome associated with blood transfusion, designated “transfusion-related acute lung injury” is caused by anti-human leukocyte antigen (HLA) antibodies or anti-granulocyte antibodies in transfused blood.66,67 Thus, some autoantibodies are biomarkers for collagen vascular disease-associated ILD or AoDILD. Similarly, anti-major histocompatibility complex class I chain-related gene A antibodies in RA are associated with ILD.68 We ourselves have also extensively investigated autoantibody profiles of ILD and AoDILD in RA patients using a protein array method, Protoarray (Thermo Fisher Scientific Inc., Waltham, MA, USA; unpublished results). This protein array allows for screening autoantibodies in sera from RA patients with ILD or without
| Table 1. Candidate biomarkers for RA-ILD or AoDILD. |
|--------------------------------------------------|
| **RA-ILD** | **AoDILD** | **References** |
|--------------------------------------------------|-------------|----------------|
| **Antibody biomarkers** | | |
| Rheumatoid factors | Oka et al.,10 Kakutani et al.,11 and Mori et al.47 | |
| IgA rheumatoid factors | Bernstein et al.48 and Joshua et al.49 | |
| Anti-citrullinated protein antibodies | Mori et al.,47 Joshua et al.,49 and Zhu et al.50 | |
| Circulating secretory IgA anti-citrullinated protein antibodies | Roos Ljungberg et al.52 | |
| Anti-carbamylated protein antibodies | Castellanos-Moreira et al.57 | |
| Anti-citrullinated alpha-enolase peptide-1 antibodies | Alunno et al.58 and Liu et al.59 | |
| Anti-citrullinated heat shock protein 90 antibodies | Harlow et al.60 | |
| Anti-malondialdehyde-acetaldehyde antibodies | England et al.61 | |
| Anti-major histocompatibility complex class I chain-related gene A antibodies | Furukawa et al.68 | |
| **Genetic biomarkers** | | |
| rs35705950 in MUC5B gene | Juge et al.72 | |
| rs12702634 in the RPA3-UMAD1 gene | Shirai et al.76 | |
| Rare variants in the genes responsible for IPF | Juge et al.72 | |
| Rare variants of the MUC5B gene | Wang et al.78 | |
| Rare variants in the genes upregulated in acute exacerbation of IPF | Furukawa et al.80 | |
| HLA DR2 alleles | Furukawa et al.,4 Oka et al.,10 Mori et al.,47 and Migita et al.87 | |
| Shared epitope alleles (protective) | Furukawa et al.,4 Mori et al.,47 Migita et al.,87 and Turesson et al.88 | |
| HLA-A*31:01 | Furukawa et al.90 | |
| hsa-miR-214-5p and hsa-miR-7-5p | Oka et al.97 | |
| Long non-coding RNAs | Zhou et al.98 | |
| Krebs von den lungen-6 | Ohnishi et al.24 and Nakajima et al.25 | |
| Surfactant protein-D | Ohnishi et al.24 | |
| Protein biomarkers | | |
| Matrix metalloproteinase7, C-C motif chemokine ligand 18 | Doyle et al.105 | |

(continued)
chronic lung diseases; our data suggested KIAA0174, RPS19, PCDHA4, and ANKR D45 as four candidate target autoantigens in this case. In contrast, this approach suggested six candidate autoantigens, FGF12, MGC21881, MTHFD2, RBM22, PPIL2, and XAGE1D, when screening sera from RA patients before and after an AoDILD episode. Additionally, anti-MDA5 antibodies were detected in one RA patient with AoDILD. It was attempted to validate these candidate antigens by the Protoplex method (Thermo Fisher Scientific Inc.), a multiplex flow-cytometric microsphere-based immunoassay, but the results could not be confirmed. These candidate antigens were also analyzed by glutathione S-transferase-capture enzyme-linked immuno-sorbent assay for validation of the results of protein arrays, but again the results could not be confirmed. Thus, comprehensive exploration of auto-antibody biomarkers for RA-ILD has been conducted, but with inconclusive results. Thus, the exploration of antibody biomarkers for RA-ILD or AoDILD has been conducted.

### Genetic biomarkers for RA-ILD or AoDILD

Although genetic risk factors for RA or IPF have been sought, only a few reports on genetic associations with ILD in RA have been published. A single nucleotide variant (SNV) rs35705950 in the promoter region of the MUC5B gene was found to be associated with familial and sporadic IPF70,71 and an association between RA-ILD and this SNV was confirmed,72 although rs35705950 was not associated with ILD in systemic sclerosis (SSc) patients.73 This risk allele increases the expression of the MUC5B gene,74 which encodes a secretory mucin expressed on submucosal gland cells in the lung. An excess of MUC5B could impair alveolar repair. However, this risk allele was paradoxically associated with better survival of IPF patients,75 suggesting its importance in mild IPF. Genome-wide association studies (GWASs) have been conducted to determine the role of common variants on disease predisposition; a Japanese GWAS was performed for ILD in RA with the result that a significant association with SNV rs12702634 in the RPA3-UMAD1

| RA-ILD | AoDILD | References |
|--------|--------|------------|
| Matrix metalloproteinase, C-X-C motif chemokine ligand 10 | Chen et al.,106 |
| Interleukin-18 | Matsuo et al.,107 |
| Interleukin-13 | Hussein et al.,109 |
| Soluble programmed death-ligand 1 | Wu et al.,108 |
| Matrix metalloproteinase-1, tissue inhibitors of metalloproteinases-1, osteopontin, soluble interleukin-2 receptor α, and interleukin-1 receptor antagonist | Oka et al.,13 |
| Mannosamine, alliin, kynurenine, and 2-hydroxybutyric acid | Furukawa et al.,27 |
| Platelet/lymphocyte ratio | Chen et al.,119 |

AoDILD, acute-onset diffuse interstitial lung disease; HLA, human leukocyte antigen; IPF, idiopathic pulmonary fibrosis; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease.
gene was found. Deleterious rare variants including loss of function variants and deleterious missense variants are causative in some diseases. A role for rare variants in the genes responsible for IPF was reported in European RA patients with ILD. A role for rare variants of the MUCSB gene was also reported in Chinese RA patients with ILD. Genes upregulated in acute exacerbation of IPF have been reported as well and the frequency of rare deleterious alleles of these candidate genes was increased in AoDILD.

HLA molecules present antigens to T-cell receptors, and for this reason HLA alleles are associated with many diseases. Thus, HLA-B*15, B*40, HLA-DR2 (DRB1*15 and DRB1*16), and MICA*001 are associated with IPF. HLA-DRB1*04:01, *04:04, *04:05, *01:01, and *10:01 are associated with RA. Because these RA risk alleles share amino acid sequences at positions 70–74 of the HLA-DRβ protein (QKRAA, RRRAA, or QRRRAA), they are designated “shared epitope” (SE) alleles. DR2 alleles were reported to predispose to ILD in RA, whereas SE alleles were protective against ILD in RA. Although SE alleles were strongly associated with ACPA-positive RA, frequencies of these alleles are relatively lower in RA patients with ILD. An association of HLA-A*31:01 with methotrexate-induced ILD in RA patients was reported. A GWAS was conducted on methotrexate-induced ILD, but no significant associations were detected.

Micro RNAs (miRNAs) are small non-coding RNAs of approximately 22 nucleotides in length. They modulate the expression of protein-coding genes at the post-transcriptional level. Circulating miRNAs can be used as disease biomarkers. Some circulating miRNAs are also dysregulated in RA and IPF. Plasma levels of miRNAs were also investigated in RA with ILD and hsa-miR-214-5p and hsa-miR-7-5p were reported to be increased. Long non-coding RNAs are transcripts >200 nucleotides in length which are not translated into protein. The levels of some of these long non-coding RNAs were also reported to be increased in peripheral blood mononuclear cells from RA-ILD patients. Thus, genetic biomarkers for RA-ILD or AoDILD have been investigated.

 Protein biomarkers for RA-ILD or AoDILD

Cytokines, chemokines, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) are involved in the pathogenesis of IPF. MMP7 was frequently reported to be increased in IPF. The role of these proteins in RA-ILD was also investigated in several studies. Increased levels of MMP7, C-X-C motif chemokine ligand 10, C-C motif chemokine ligand 18, soluble programmed death-ligand 1, interleukin (IL)-18, and IL-13 have all been detected in sera from RA-ILD patients. Disparate results on serum cytokine levels have been obtained in different cohorts, suggesting heterogeneity of RA-ILD. Increased levels of MMP7 were also detected in idiopathic inflammatory myopathy and in systemic sclerosis patients with ILD. Cytokine, chemokine, MMP, and TIMP profiles have all been investigated in AoDILD. Serum MMP-1, TIMP-1, osteopontin, soluble IL-2 receptor α, and IL-1 receptor antagonist levels are increased, but MMP-3, TIMP-2, and eotaxin 2 are decreased in AoDILD. Serum MMP-1, MMP-3, MMP-8, MMP-9, TIMP-2, TIMP-3, osteopontin, and soluble IL-2 receptor α levels could be prognostic biomarkers in AoDILD. Thus, protein biomarkers for RA-ILD or AoDILD have been extensively analyzed.

Other biomarkers for RA-ILD or AoDILD

Low molecular weight metabolites are determined in order to elucidate altered metabolic states under pathological conditions, and to identify biomarkers. Some metabolomic analyses have been conducted separately for RA or IPF. Plasma amino acid levels were analyzed in RA patients with ILD or without chronic lung diseases. A complex biomarker constellation was assembled from amino acid profiles, but did not perform better than KL-6. Serum metabolomic profiles of ILD in RA have been systematically analyzed. Serum levels of decanoic acid and morpholine were decreased in RA with ILD, and glycerol was increased. Serum levels of these metabolites in RA with UIP or RA with NSIP were similarly changed. The partial least squares-discriminant analysis (PLS-DA) model using these three metabolites could distinguish ILD in RA. Serum metabolomic profiles of AoDILD in RA were also investigated. PLS-DA was conducted to create a complex biomarker cluster with four metabolites (mannosamine, alliin, kynurenine, and 2-hydroxybutyric acid); this was able to distinguish between AoDILD and stable states. It was also reported that the platelet/lymphocyte ratio was increased in RA-ILD. Thus, other biomarkers for ILD in RA have also been investigated in recent studies.
Conclusions
Several candidate biomarkers for RA-ILD have been reported over the last few years and the number of studies on these biomarkers is increasing. The development of biomarkers on RA-ILD has only just begun and the utility for diagnosis and the prediction efficacy of severity and prognosis were not well validated for almost all of the biomarkers reported. Additionally, sensitivity and specificity of these markers were not compared. The treatment of RA-ILD was not established, but some new drugs have been developed. Thus, the important roles of these new biomarkers for decision of appropriate therapies would be validated in future. Although these serological and genetic biomarkers seem promising, validation needs to be undertaken in comparing RA-ILD with IPF, RA-ILD with RA patients having emphysema or airway diseases, RA-ILD with pulmonary tuberculosis, RA-ILD with non-tuberculous mycobacterial pulmonary disease, and, finally, RA-ILD with healthy controls. Longitudinal studies of these markers should be conducted for the assessment of correlations with clinical course. ILD in RA is of NSIP and UIP type, and is pathogenically heterogeneous. Predictive markers to distinguish NSIP from UIP would be a useful application of these biomarkers. Stratified analyses for biomarkers may reveal differences in the pathogenesis of disease subtypes and might provide an explanation for the pathogenic heterogeneity of RA-ILD. Glucocorticoid or other immunosuppressive agents are used for RA with the NSIP pattern whereas anti-fibrotic agents would be used for RA-ILD in the near future. Treatment response needs to be predicted with sufficient improved accuracy by recently-identified biomarker candidates for RA-ILD. Because the prognosis of RA patients with the complication of ILD is worse,7–9 new biomarkers for ILD in RA may predict the prognosis. AoDILD is an acute hypersensitivity pneumonitis conferring a poor prognosis in RA11,12; novel biomarkers would facilitate early detection and treatment of AoDILD and improve the prognosis. Thus, extensive recent studies have aimed to establish robust new specific biomarkers for RA-ILD and to develop many applications. The future prospects of the biomarkers for RA-ILD would be splendid.

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Author contributions
HF and ST conceived and designed the experiments. HF, SO, and TH performed the experiments. HF analyzed the data. HF, KS, AH, TM, and ST contributed reagents/materials/analysis tools. HF, KS, AH, TM, and ST wrote the manuscript.

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Data availability statement
All datasets presented in this study are included in the article.

Ethics statement and informed consent
This study protocol was reviewed and approved by the NHO central Institutional Review Board. Written informed consents were obtained from all the participants. The study was performed in accordance with the principles expressed in the Declaration of Helsinki.

ORCID iD
Hiroshi Furukawa https://orcid.org/0000-0003-1353-8056

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