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Reinterpreting Evidence of Rheumatoid Arthritis-Associated Interstitial Lung Disease to Understand Etiology

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Abstract

Interstitial lung disease (ILD) is a well-known complication ofrheumatoid arthritis (RA) which often results in significant morbidity and mortality. It is often diagnosed late in the disease process via descriptive criteria. Multiple subtypes ofRA-ILD exist as defined by chest CT and histopathology [1]. In the absence of formal natural history studies and definitive diagnostics, a conventional dogma has emerged that there are two major subtypes ofRA-ILD (nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP)). These subtypes are based on clinical experience and correlation studies [2–4]. However, recent animal model data are incongruous with established paradigms ofRA- ILD and beg reassessment of the clinical evidence in order to better understand etiology, pathogenesis, prognosis, and response to therapy. To this

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CONFLICT OF INTEREST

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end, here we: 1) review the literature on epidemiology, radiology, histopathology and clinical outcomes of the various RA-ILD subtypes, existing animal models, and current theories on RA-ILD pathogenesis; 2) highlight the major gaps in our knowledge; and 3) propose future research to test an emerging theory of RA-ILD that posits initial rheumatic lung inflammation in the form of NSIP-like pathology transforms mesenchymal cells to derive chimeric disease, and subsequently develops into frank UIP-like fibrosis in some RA patients. Elucidation of the pathogenesis ofRA-ILD is critical for the development of effective interventions for RA-ILD.

Keywords

Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD); Nonspecific Interstitial Pneumonia (NSIP); Usual Interstitial Pneumonia (UIP); Computed Tomography (CT); Histology; Inflammation; Fibrosis; Animal Models

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease estimated to affect 0.5–1% of the world's population [5, 6]. Significantly, RA is commonly associated with symmetric immune infiltration into diarthrodial joints [7] leading to synovitis [8], and progressive erosion of bone and cartilage [9]. This pathology ultimately leads to deformity of multiple joints, decreases in quality of life, and constitution of a high economic burden [6, 10].

While joints are known to be the primary targets of RA, there are several extra-articular manifestations of the disease which become the main causes of mortality in RA patients [11] and ultimately contribute to the lower overall survival rate of RA patients [11–13]. These non-arthritic pathologies include nodule formation, cardiovascular disease, ocular inflammation, and pulmonary disease; of these, cardiovascular disease and respiratory related mortality were found to be disproportionately associated with RA [14].

Interstitial lung disease (ILD) is one of the primary extra-articular manifestations of RA, causing significant mortality [15, 16]. Moreover, rheumatoid arthritis-associated ILD (RA-ILD) is heterogeneous, with tissue pathology showing a highly variable mix of both fibrotic and inflammatory changes. High-resolution computed tomography (HRCT) is currently the most utilized clinical method to diagnose RA-ILD. While there have been a number of studies evaluating the implications of radiographic characterization schemes with regard to prognosis, pathogenesis, and treatment, the resulting data is conflicting and often inconsistent. Multiple attempts at defining the differences between certain subsets of RA-ILD have served to highlight the overlaps in radiographic patterns, as well as similar risk factors, and hypothesized etiologies for various ILD subtypes. Moreover, defining RA-ILD subtype based on HRCT results is further complicated by literature correlating HRCT imaging with corresponding histopathology in the context of RA-ILD, as the strength of the correlations between the tests are variable depending on the study [17, 18]. Finally, the enigma of RAILD subtypes posits that there must be distinct etiologies, which remain elusive. Thus, to the end of establishing an evidence-based understanding of RA-ILD and its subtypes, here we address the current estimates of disease prevalence, mortality, theories on

pathogenesis, and histopathological effects of conventional therapies. Furthermore, we review the most recent research correlating radiographic imaging to histologic patterns in RA-ILD cases and interpret these data to summarize critical gaps in our knowledge. Finally, we briefly discuss experimental evidence from pre-clinical models of RA-ILD, which are being used to formally elucidate the pathogenesis of lung disease in RA.

2. Epidemiology

The prevalence of RA-ILD within the RA patient cohort has been reported to be between 3.6–58% [15, 16, 19–23]. The large degree of variability in these numbers is related to the differences in sensitivity between methods and thresholds of detection used in each separate study. Methods of diagnosis ranged from clinical data and spirometry-based pulmonary function tests to HRCT and X-ray imaging results, bronchoalveolar lavage, and biopsy studies. In a study by Bongartz et al looking specifically at RA-ILD, RA patients were estimated to have an approximate 10% lifetime risk of being diagnosed with ILD [15]. Compared to the non-RA population, this results in a hazard ratio of 8.96 (95% CI 4.02–19.94) [15], suggesting that patients with RA are almost nine times more likely to be diagnosed with ILD than the non-RA group.

In patients diagnosed with RA-ILD, Kaplan-Meier analyses revealed a significantly increased mortality rate compared to those with no pulmonary disease, with a median survival expectancy of 2.6 years post-diagnosis [15], and a 10-year survival rate of 20–40% [15, 24]. Other RA-ILD studies have described similar trends [25], with median survival expectancies ranging from 3–8.27 years [26–29]. To attain a more accurate and specific prognosis, RA-ILD can be broken down into multiple subtypes based on pulmonary histopathology and radiologic patterns. The most prevalent patterns of RA-ILD are usual interstitial pneumonia (UIP), which is predominantly fibrotic, and nonspecific interstitial pneumonia (NSIP), which can be further broken down into inflammatory and fibrotic subtypes [30]. The implications of these different pathologic patterns with regards to diagnostic and prognostic capabilities have been an intense area of research interest. Multiple studies have shown that patients with UIP have more severe progressive lung pathology [31–34], yet there is conflicting data on the prognostic utility of radiographic assessments. In a recent study of RA-ILD mortality, Solomon et al found that UIP patterns on CT had greater rates of pulmonary function decline, with higher rates of death (44%), compared to the NSIP cohort (24%). Median survival time was also found to be worse in the UIP cohort as compared to the NSIP subjects (10.18 vs. 13.62 years, respectively) [31]. While median survival times were markedly shorter, Kim et al also found definitive UIP to be significantly worse than ILD without this pattern (median survival 3.2 vs. 6.6 years), and of similar severity as idiopathic pulmonary fibrosis [35]. However, no significant correlations have been found between radiographic subtypes and mortality once adjusted for confounding variables (including age, sex, smoking history, baseline FVC%, and change in FVC%) [31], suggesting that it is the degree of lung function, independent of radiographic pattern, that correlates best with prognosis. While HRCT pattern was not a significant predictor in these models, it was noted that changes in pulmonary function (FVC% and DLCO% over time) were found to be accelerated in UIP.

There have also been studies on ILD that failed to identify significant differences in mortality based on disease subtype. Nurmi et al compared disease progression based on different radiographic patterns, and they reported similar median survival times between UIP (92 months, 95% CI 62.8–121.2) and non-UIP (137 months, 95% CI 31.0–243.0) patterns [32]. Interestingly, Zamora-Legoff et al found that while UIP had a definite correlation to more progressive disease compared to NSIP [33], there was no difference in 5-year survival rates (UIP 55.2%, 95% CI 43.7–69.8, vs NSIP 65.0%, 95% CI 53.6–78.8) [29]. This apparent discrepancy in survival rates between UIP and non-UIP patterns may be explained by a recent study, done by Yunt et al, where it was demonstrated that nuances in the radiographic classification criteria affect the ability of an accurate prognosis. In classifying radiographic data into 3 distinct groups of “definite UIP”, “possible UIP”, and “definite NSIP”, no statistical differences were found in survival between the groups. However, when combined into a single group, “definite or possible UIP” had worse survival compared to “definite NSIP”. It was therefore concluded that any sign of UIP is sufficient for an accurate prognosis [28]. Taken together, these clinical studies highlight the need for better radiographic phenotyping of ILD, which could permit for more objective diagnoses, and more definitive prognoses between subtypes.

Another important demographic factor, for which there is also a lack of consensus, is sexual dimorphism. As it is known that the prevalence of RA and mortality rates of RA patients are significantly higher in females [1, 2], many investigators have attempted to apply this parameter to studies on extra-articular symptoms. Conflicting evidence exists from a variety of studies regarding sexual dimorphism in RA-ILD. Historically, it has been suggested that men who develop RA have worse disease and increased mortality. However, more recent data purports that the confounding factors of smoking and cardiovascular disease, both higher in men than in women, may have resulted in increased mortality risk in men with RA. Olson et al found that there is a higher prevalence and age-adjusted mortality rate in women compared to men in RA patient populations [16]. The majority of other studies, however, have found that RAILD is a predominantly male-skewed pathology [15, 25, 34,36]. Some papers have found a trend towards males with regards to disease progression, although no statistical significance was achieved [31, 33]. This finding supported previously published data by Bongartz et al, which found males to be the predominant population of RA-ILD patients (58.7%), with a calculated hazard ratio for males of 4.37 (95% CI 2.43–7.88) [15]. The same conclusions were found by Wang et al, in which the distribution of male:female RA-ILD patients was significantly higher to that of RA patients in general [36]. Notably, few papers have attempted to define sexual dimorphism in the context of pulmonary radiographic subtypes. When categorizing their RA-ILD cohort by subtype, Lee et al found that while UIP was predominately male dominated (M:F, 8:2), NSIP was found to be more female populated (M:F, 0:6) [30]. Thus, there are likely differences between men and women who develop RA-ILD, but further studies in both pre-clinical and clinical settings are needed to clarify the existence and significance of sexual dimorphism in this disease.

3. Radiologic Imaging Patterns in RA-ILD

The current standard of care for RA-ILD diagnosis is high-resolution computed tomography (HRCT) imaging [37, 38]. While chest radiographs and pulmonary function testing are also

commonly used to evaluate lung disease and function, HRCT has been shown to detect more subtle structural abnormalities in the pulmonary tissue at earlier stages of disease [39]. This method of diagnosis has replaced lung biopsy based on the presumption that imaging correlates with histopathologic changes, despite the fact that this is often not the case. Many argue that this begs reassessment of the NSIP vs. UIP system for general characterization of RA-ILD. Clinically, NSIP and UIP pathologies mimic each other very closely, and there is much debate about the two being truly distinct clinical entities, although there is consensus on the differences found in prognosis between them [40, 41]. Similarly, discordance between radiographic and histologic findings is not uncommon, with an HRCT diagnosis of NSIP lacking the sensitivity to exclude a UIP finding on biopsy [17, 41]. Other studies have found that multiple interstitial pneumonia patterns can be found in the same lung, leading many to believe that the distinction between NSIP and UIP is not dichotomous [42–45].

When evaluating RA-ILD, much of the literature describes it in the context of pulmonary pathology seen in multiple connective tissue diseases (CTD) [46]. Earlier studies of CTD-ILDs emphasized involvement in the context of scleroderma, dermatomyositis-polymyositis, and Sjogren's syndrome. In these cases, the predominant radiographic pattern was found to be NSIP [1, 47–50]. In RA-ILD specifically, the predominant radiographic pattern was UIP, followed by NSIP [30, 46], making RA cases unique among CTD-ILDs.

Multiple clinical studies have found UIP to be the predominant pattern in RA-ILD, consisting of 19.6–65% of enrolled RA-ILD cases [15, 26, 29–32, 34, 35, 51, 52]. The UIP pattern shared by many ILD pathologies is characterized by wide-spread bilateral fibrotic changes in the pulmonary interstitium. Radiographic hallmarks on CT include heterogenous honeycombing at the bases and periphery of the lungs, subpleural reticular opacities, and architectural distortions indicative of fibrotic scarring [53] (Fig. 1B, Table 1). The correlating histology findings for UIP include temporally spaced fibrotic lesions, fibroblastic foci, interstitial fibrosis, and honeycomb changes with dilated airspaces and thickened interstitial walls [53, 54] (Table 1).

In the context of RA-ILD, NSIP was found to be the second most predominant pattern, making up 2.2–43.75% of RA-ILD cases [15, 26, 30–32, 34, 51, 52]. NSIP is traditionally more inflammatory and less fibrotic in nature. Radiographic findings for NSIP include bilateral ground-glass opacities with subpleural sparing, some reticular opacities, and a loss of lower lung volume, with advancement to consolidation and possible honeycombing [53] (Fig. 1A, Table 1). More specifically, NSIP can be further subcategorized into fibrotic and cellular types. In fibrotic NSIP, the prognosis is similar to UIP, with a mixture of both fibrotic interstitial thickening and inflammatory changes. Notably, analysis of the bronchoalveolar lavage fluid (BALF) composition of UIP and fibrotic NSIP lungs found no significant differences in composition with regards to both absolute and differential cell counts [30, 55]. This suggests that fibrotic NSIP may be a variant of UIP, but there is no literature to date that focuses on NSIP variants. Cellular NSIP, on the other hand, is characterized as having an inflammatory cellular infiltration, leading to interstitial disease. While both fibrotic and cellular NSIP types are found to have ground-glass opacities and airspace consolidation on CT, a study by MacDonald et al [56] found that cellular NSIP had "finer patterns of reticular abnormalities" with greater subpleural sparing compared to

fibrotic NSIP [53] (Table 1). Between the two subtypes, cellular NSIP was also found to have a better prognosis with a 90% 5-year survival rate compared to 45–90% 5-year survival rate in fibrotic NSIP [57, 58]. This becomes important with regard to the implications of clinically classifying ILD subtypes, especially because the data correlating HRCT patterns and prognosis is variable across different studies [58–60]. Interestingly, in a study by Akira et al, a series of CT scans was used to evaluate 29 patients with suspected pulmonary pathology to correlate specific imaging findings (ex. reticulation, consolidation) with prognosis, resulting in significant prognostic ability for RA-ILD [61]. It was found that reticulation and/or honeycombing (the two most consistent with UIP) were the greatest prognostic indicators for progressive and terminal disease. Other studies have similarly agreed, specifically in RA-ILD, that a UIP diagnosis leads to a marginally worse survival prognosis as compared to NSIP [62].

It should be noted that while the patterns found in non-RA related ILD have been well documented, there have been few studies that focus specifically on the clinical presentation of RA-related cases. In non-RA ILD, there is extensive data which correlate radiographic patterns to specific histologic patterns (although, as mentioned before, the patterns are not as exclusive as to make them truly distinct in all cases). On the other hand, there is sparse literature that confirms the histologic and radiographic correlates in RA-ILD. As previously mentioned, clinical RA-ILD studies were predominantly imaging-based [28, 34, 35, 61, 63, 64]. More recently, attempts have been made to address this question, and potentially shed some light on the relationship between imaging and histopathology in RAILD. In a study done by Lee et al, the histopathologic patterns for 18 RA-ILD cases were analyzed and found to be well correlated to the associated findings on CT for the predicted ILD subtype [30]. Of those 18 cases, 10 were found to be UIP, 6 were found to be NSIP, and 2 others were classified as organizing pneumonia based on histopathologic diagnosis. Only one case of histologic UIP was found to conflict with the CT findings of ground-glass and reticular opacities. A study done by Tanaka et al was similarly focused on CT evaluation of pathology [64]. Of the 63 patients assessed for the study, 17 of them also underwent biopsy. Histopathologic analysis was found to correlate closely with CT patterns, with the exception of 4 patients, 2 of whom were initially characterized as having UIP on CT and recategorized as NSIP on histologic evaluation. However, Tanaka et al did note the overlap of UIP and NSIP CT patterns, a feature that was expounded on by the Yunt et al study described earlier relating CT patterns to mortality rates [28]. Notably, the Kim et al study failed to find differences between the indeterminate group and the other 2 groups, although the criteria which were used for classifying the CT scans was slightly different between the studies [28,35].

There are also studies that found conflicting evidence connecting CT and histology. Kim et al assessed 18 ILD patients that had histopathologic data available [35]. They observed that 2 had been defined as “definite UIP”, 9 as “likely NSIP”, and 7 as “indeterminate” via HRCT image analysis. However, of the 9 “likely NSIP”s, only 2 were confirmed by histopathology to be NSIP, with 5 defined as UIP, 1 as organizing pneumonia (with little evidence of an underlying ILD), and 1 as indeterminate. Furthermore, neither of the “definite UIP” HRCT patterns were found to be UIP upon histologic examination, with 1 indeterminate and 1 necrotizing pneumonia pattern. Interestingly, the “indeterminate” HRCT

patterns were mostly found to be UIP (n=5), with the remaining 2 being defined as NSIP and diffuse alveolar damage. The authors determined that in cases of non-UIP HRCT patterns, histopathology data was not as easily predicted as would be believed from the previously cited studies. The small number of “definite UIP” patients (n=2) did not allow for a comprehensive evaluation between HRCT and histopathology, yet suggests further need for correlative data between the two. It should be noted that the authors attributed these results to a certain amount of selection bias based on how the samples were collected.

Another study by Assayag et al aimed to determine the accuracy of CT analysis in identifying UIP histopathology, specifically in the context of RA-ILD [51]. A total of 69 patients were independently evaluated via radiology and lung histopathology. CT patterns were defined as either “definite UIP”, “possible UIP”, or “inconsistent with UIP”. “Definite UIP” was defined as a subpleural and basal predominance of reticular abnormalities, with honeycombing, and without extensive ground-glass opacities, nodules, cysts, air trapping, or segmented consolidation. While 61% of patients were found to have a histopathologic UIP pattern, only 29% had a “definite UIP” pattern on CT. This makes for a 96% specificity of CT UIP patterns, with 45% sensitivity [51]. A similar study on RAILD NSIP found that those diagnosed with NSIP histopathology could be found to lack honey-combing on radiography, along with a predominance of ground-glass opacities [52]. Based on the above data, it appears that use of CT imaging in diagnosing RA-ILD may be informative to some degree, but it may not necessarily correlate with the underlying histopathology. It may therefore be necessary to use more invasive procedures, including lung biopsy, to more accurately diagnose RA-ILD subtype. The use of lung biopsy, however, should be weighed against its risks, including potential exacerbation of lung disease.

4. Efficacy of Standard of Care RA Therapies on ILD Histopathology

One of the most challenging aspects of RA-ILD has been the effects of the therapeutic management of arthritis on the lung disease. Specifically, the use of disease modifying anti-rheumatic drugs (DMARDs) and biologic therapeutics has not consistently shown amelioration of lung inflammation. Given that one of the theories on pathogenesis of lung disease in the setting of chronic joint inflammation has been that tumor necrosis factor (TNF) plays a primary pathogenic role, the expectation would be that anti-TNF therapies would improve lung disease. On the contrary, multiple studies have suggested that conventional DMARDs such as methotrexate, and biologics such as anti-TNF therapy, may exacerbate lung disease [65–69], while some have suggested no effect of RA treatment on lung disease [35, 70]. Immunosuppressive therapies such as cyclophosphamide and mycophenolate mofetil are used in other connective tissue disease associated ILD [71–73]; however, these medications are not standard of care in RA, and therefore are not discussed in detail here. Other therapies for RA-ILD aside from the aforementioned immune suppressive medications include high dose (ie “pulse”) steroid therapy [74] and conventional synthetic DMARDs [75]. However, there are no publications to date describing histological changes using these therapies in patients with RA-ILD. Lastly, in the differential of lung inflammation in RA, there should be a high suspicion of infectious etiologies, including bacterial, fungal, and mycobacterial [76–78], as most immune modulating therapies can

predispose to infectious pneumonia, thus making the diagnosis of RA-ILD more challenging.

In general, there have been few reports describing lung histology in the setting of treatment therapy. However, we can gain some information from studies focusing on drug-induced lung disease. One of the largest cohorts for such a study was collected in the late 1990s, which assessed histopathologic features of lung parenchyma in the setting of methotrexate injury in RA patients [79]. Pathologists reviewed lung tissue of 29 patients treated with methotrexate. They classified tissue as ILD when there was “dense fibrosis and honeycombed architecture… and lymphoid infiltrates.” versus methotrexate injury as “type II pneumocyte hyperplasia and fibroblastic proliferation.”. There was no characterization of the subtypes of ILD. Based on their criteria, 27 of the 29 tissue specimens were definite methotrexate lung injury, and two were probable. They noted that it was very difficult at times to differentiate between ILD and methotrexate induced lung injury, as the histological criteria for ILD was not well-established. Unfortunately, there has been no follow up study in the two decades since publication, and the issue of drug induced lung injury versus disease induced injury remains an open question. Overall, it is unclear whether there is a definitive worsening of ILD in RA patients [70, 80] when treated with methotrexate so use of this therapy should be judicious.

Histopathological data in the setting of biological therapies is likewise not well reported in the literature, in part due to the reliance on imaging via HRCT for diagnosis of RA-ILD. One of the more recent retrospective studies examined 122 cases of either ILD onset or exacerbation after biological therapy was initiated [67]. Only 20 cases described histology categorized by ILD subtype, with the most predominant being UIP (7 cases) or NSIP (7 cases). No further histological description was given, and it was unclear whether any of the 20 cases diagnosed as ILD were present prior to biological therapy onset. Additionally, some of the cases likely included concomitant use of DMARDs including methotrexate, but this was not identified. Likewise, rituximab, a second-line RA biologic targeting B cells, has been used as a disease modulator in RA-ILD [81]. A recent study by Yusof et al described overall improvement or stabilization of ILD in patients with RA post-rituximab therapy (68% of 44 patients studied retrospectively) [82]. However, this conclusion was based on PFT data and HRCT imaging and no patients had biopsies to evaluate what type of histological change was brought about with B cell targeting therapy. There have been some limited studies on other biologics including abatacept, a selective T-cell costimulation blocker, showing possible response in patients with RA-ILD [83, 84]. To date, there is no literature on whether or how the use of DMARDs or biological agents may alter the histopathology of ILD in RA. More specifically, it remains unknown as to whether or not standard of care RA therapy alters underlying lung inflammation. Interestingly, however, in systemic juvenile idiopathic arthritis, a recent retrospective evaluation of patients treated with IL-1 blockade has suggested a possible increase in ILD and pulmonary hypertension [85].

5. Animal Models of RA-ILD

There are multiple animal models of RA that have been generated to replicate joint pathology [86], but very few have demonstrated pulmonary pathology as an extra-articular manifestation of disease. As of now, there are three main arthritic models which contain lung pathology for the study of RA-ILD; the SKG model, the adjuvant arthritis (AA) model, and the TNF-transgenic (TNF-Tg) model.

The first arthritis model found to manifest lung pathology was the SKG murine model, which contains a point-mutation in the ZAP70 gene, causing a deficiency in thymic selection [87]. This mutation ultimately leads to the production of autoreactive $CD4^+$ T cells, resulting in a chronic autoimmune arthritis similar to RA [87, 88]. In 2012, Keith et al described a mixed cellular and fibrotic pulmonary pathology in the SKG model [89]. SKG-ILD is highly capricious and heterogeneous in nature, demonstrating a large range of disease severity between animals and unpredictable inflammatory and fibrotic pathology. The inflammatory pathology is described as localized to the pleura and perivascular spaces, composed of macrophages, neutrophils, and lymphocytes. Further characterization found these cells to be Th17 cells, $CD4^+$GM-CSF^+ T cells, and $CD11b^+Gr1^+$ cells, with GM-CSF mediating a significant amount of disease burden through immune cell infiltration and induced cytokine production [90]. Further studies defined the CD11b+$Gr1^{dim}$ cells as immature tolerogenic dendritic-like cells, which act to suppress T cell proliferation and inhibit ILD progression [91]. Fibrotic change was also present, as confirmed by decreased static compliance and elevated hydroxyproline levels [89, 90]. Based on histopathologic analysis, the SKG-ILD most closely resembles an NSIP pattern of pathology.

The AA is an inducible T-cell mediated autoimmune arthritis model, in which rats are intradermally injected in either the tail vein or paw with complete Freud's adjuvant (CFA) and mycobacterium antigen, or with a synthetic adjuvant propanediamine (N,N-dioctyldecyl-N', N-bis(2-hydroxy-ethyl)) [92]. These injections result in both chronic and acute manifestations of arthritis, with polyarticular inflammation, bone loss, cartilage destruction, and periosteal bone growth over the course of 10–15 days [93]. Since only certain strains are susceptible to AA induction, this model has been utilized for determining genetic predisposition towards autoimmune arthritis [94]. However, Song et al described fibrotic and inflammatory pulmonary pathology in the AA model [95]. At 21 days post-CFA injection, they noted significant infiltration into alveolar spaces, composed of granulocytes, lymphocytes, and macrophages, although no formal characterization analysis was done on the infiltrating cells. Alveolar wall thickening and collagen deposition were also noted at days 21 and 28. It should be noted that dysregulation of regulatory T cells (Treg) has previously been connected to reduced pulmonary function in AA rats, although formal pathologic evaluation was not done on the lung [96, 97]. Thus, AA also appears to induce NSIP, although further characterization of the AA-ILD lung is still required to formally determine the histopathologic subtype pattern in this model. One point to note is that a similar, less reliable, pulmonary inflammation was noted in the collagen-induced arthritis model in which mice are immunized with collagen II in CFA. It was found that the pulmonary pathology of this model was completely dependent on the CFA component of the immunization, while the lack of collagen II decreased the efficiency of arthritis induction in

these mice, suggesting a mechanism dependent on a generalized inflammation for pulmonary pathogenesis [98].

A third animal model of RA that demonstrates a RA-ILD-like disease state are TNF transgenic (Tg) mice, which systemically overexpress chronically low levels of TNF-α over the life of the animal [99]. This model exists as several distinct genetic lines, each containing variable amounts of the human TNF-α gene (hTNF). RA-ILD-like pathology was specifically found in the 3647 line [100], which presents with an inflammatory-erosive arthritis at 2 months of age [101], initially in the ankle, and then proceeds to the wrists and larger joints [102]. Disease continuously progresses, eventually resulting in symmetric polyarthritis with synovial hyperplasia, inflammatory synovial infiltrate, pannus formation, articular cartilage destruction, subchondral bone erosion, and dislocation of the metacarpal and tibia-talus joints [99]. Of note, Shelef et al found autoantibodies against native and citrullinated antigens in this model, with the loss of peptidylarginine deiminase 4 (PAD4) leading to a decrease in total serum IgG levels and reduced inflammation [103]. While lung pathology had been previously observed in the surfactant protein-C/TNF-transgenic mouse [104, 105], Shelef and colleagues have shown that systemic TNFTg mice also develop ILD, presenting with a perivascular and interstitial inflammatory infiltration, and subsequent destructive vasculitis [100]. Thus, it is noteworthy that while further characterization of lung histopathology is warranted, it appears that all known models of RA-ILD closely resemble cellular NSIP with limited evidence of fibrosis.

6. Current Theories of RA-ILD Pathogenesis and Reconciling NSIP and UIP

A plethora of evidence exists that supports the idea of both environmental and genetic factors playing crucial roles in the induction and persistence of RA pathology [106]. Many studies have correlated specific high-risk genes (e.g. human leukocyte antigen (HLA)-DRB1, MUC5B) and environmental insults (e.g. smoking) to the diagnosis of RA, along with several comorbidities [8, 59, 107, 108]. These observations support the idea that both genetic and environmental factors collaborate to establish RA.

Individually, both components have been noted to play a role in the pathogenesis of RA through extensive research. The most widely known genetic contributor to RA, HLADRB1, has long been cited as an independent risk factor for RA [109], and more recently as a factor associated with fibrotic RA-ILD [110, 111]. Together as a synergistic effect between environmental and genetic factors, it has also been known that for ACPA-positive RA, smoking and HLA-DR genes interact to create a 21-fold increased risk for RA development [112]. More specifically for RA-ILD, many researchers have noted the similarities between the UIP RAILD cases and isolated pulmonary fibrosis. Researchers have hypothesized, given the similarities in disease, that RA-ILD and idiopathic pulmonary fibrosis (IPF) share risk factors leading to similar pathogeneses between the two diseases.

Juge, et al have found a remarkable association between the UIP pattern of RA-ILD and the gain-of-function promoter, MUC5B. MUC5B, known to be the strongest genetic risk factor for the development of IPF, encodes mucin 5B and has been estimated to account for ~30%

of risk for developing IPF [113–121]. In a retrospective study, Juge et al found that patients with RA-UIP had a significantly higher odds ratio associating MUC5B expression with overall RA-ILD as opposed to RA patients with no lung pathology (OR 6.1, 95% CI 2.9–13.1), and more specifically with the UIP pattern as opposed to the non-UIP phenotype of lung disease (OR 2.9, 95% CI 1.7–4.8). Notably, there was no correlation found between smoking status and the MUC5B promoter [108]. Researchers have also found other genetic markers which similarly correlate with predisposition to these two diseases [122].

The epidemiologic association between pulmonary pathology and RA has strong implications, especially when taken into context with regards to the total incidences of RA and ILD individually, as ILD disproportionately affects RA patients compared to the general population [14, 15]. Together, this correlation suggests that while the pathogenesis of RA-ILD remains poorly defined, there appears to be a connection between the pulmonary and articular pathologies.

One of the more intriguing theories in the field postulates that the lung, as an active immune site protecting against environmental exacerbations, acts as the initial site of injury in RA [123]. Smoking, as a quintessential respiratory insult, is thought to facilitate this pathogenic process, as it has been implicated in the citrullination of proteins in a process of pulmonary insult independent of RA status or development [124, 125].

Based on the current knowledge of the effects of smoking on pulmonary issue, it is thought that an external insult delivered via the respiratory system catalyzes the citrullination of proteins in the lung, leading to the production of anti-citrullinated protein antibodies (ACPAs), and subsequent systemic inflammation leading to the articular manifestations of RA [112, 126]. Given that ACPAs are present in the majority of RA patients [127], it is believed that citrullination of endogenous proteins in both the lung [128, 129] and synovial tissue [130, 131] is a key factor that initiates the breakdown of autoimmune tolerance in RA. This theory is supported by the vast body of literature correlating both smoking history [26, 29, 31, 33, 34, 132] and seropositivity [29, 31, 34, 132] as predictive risk factors for RA-ILD morbidity and mortality, and the known interaction between cigarette smoke and genetic factors [133]. This argument is further strengthened by the body of work directly connecting smoking to ACPA production in genetically predisposed individuals with early RA [129, 134–139]. It should be noted that smoking has also been correlated to the diagnosis of RA [112, 140–143] independent of ILD, which implicates an important role of lung tissue-specific immune tolerance breakdown. A role for primary immunological alterations in the lung during RAILD pathogenesis is further supported by studies demonstrating the preferential development of ACPAs in bronchoalveolar lavage fluid (BALF) compared to serum, with the presence of BALF ACPAs that are qualitatively different from ACPAs in serum [144].

An alternative theory of RA-ILD is that the condition exists as distinct pulmonary and articular pathologies. This idea has been supported by data acquired from recent animal models. In contrast to the conventional theory of pulmonary inflammation and citrullination leading to autoantibody production and arthritis, evidence from multiple studies shows that localized lung injury via TNF-α fails to induce arthritic pathology [100, 104, 105]. These

studies, which utilized a TNF-α transgene under a surfactant promoter to induce lung disease, failed to find arthritic pathology. These findings also corroborate data from SKG mouse studies, which similarly failed to induce arthritic change with localized pulmonary injury [89]. While overexpression of TNF-α in lung tissue alone failed to induce arthritis, it should be noted that a direct comparison between lung pathologies in the systemic TNF-α and localized TNF-α models has yet to be made. Additionally, these mice models do not replicate all clinical cases, as some patients present with pulmonary disease and/or ACPA positivity prior to onset of articular disease. While the manifestation of lung-dominant CTD is a noted clinical phenomenon, the interpretation of autoantibody screenings in idiopathic lung disease is still under debate [145].

Based on the confounding results from clinical studies, and the new information provided from the murine models, we propose an alternative theory to explain the development and progression of RA-ILD (Fig. 2). Given that localized pulmonary injury does not induce arthritic pathology, while models of chronic inflammatory arthritis have ILD, we propose a two-step process, in which chronic inflammation (either systemic or local in nature) directly initiates lung injury. In this model, inflammatory cytokines, such as interferon-gamma (IFN-γ) and TNF-α, affect the lung and induce an upregulation of adhesion molecules (e.g. P-selectin, E-selectin, and ICAM-1), on pulmonary vascular endothelial cells. These inflammatory signals, in turn, lead to the recruitment and extravasation of circulating monocytes/macrophages, while the cytokines themselves directly activate tissue-resident macrophages and other local immune populations. Macrophages would continue induction of inflammatory molecules and upregulation of complement activation. This activation and recruitment would then lead to cellular accumulation and follicle formation resembling cellular NSIP. At this point, while the system is primed with an abundance of inflammatory cells, external environmental component(s) can trigger antigen (i.e. citrullinated peptides) presentation by macrophages and dendritic cells, leading to the activation of the secondary (adaptive) immune response. This response would not only involve the continuous activation of accumulated macrophages, but also the activation of both T cell and B cell populations. Given the damage done to pulmonary tissue, the production of ACPAs would follow. The second wave of inflammation would also trigger a release of factors such as TGF-β, which in turn would activate fibroblasts, leading to collagen deposition and subsequent fibrosis in the lung. It is at this point that the lung transitions to an irreversible fibrotic lung disease, such as UIP. In this theory, we therefore suggest that an inflammatory state is a necessary precursor towards the development of later fibrotic pathology, and that aggressive-early treatment of “NSIP-like” pathology could prevent development of the more irreversible fibrotic-predominant disease.

This idea of lung pathology evolution from NSIP to UIP has been discussed extensively through the pulmonology community for many years, and is still a point of controversy. While inflammation is certainly a component to the development and persistence of fibrotic disease, there are cases of inflammatory disease which do not progress to fibrosis, and likewise cases of fibrosis in which a preceding inflammatory component was not identified. This combined with the non-exclusivity of histologic patterns within the same lung [45] makes this chicken-and-egg conundrum a challenge to resolve.

7. CONCLUSION

In conclusion, we find that the extensive literature on RA-ILD is conflicted about the nature of NSIP and UIP, based on inconsistencies and variabilities in clinical radiology and histopathology studies. Moreover, the absence of natural history studies and effective interventions for RAILD limits our knowledge of its etiology and ability to treat its severe morbidity and mortality. As critical information is challenging to obtain from clinical studies, the field is focusing on animal models, which appear to be leading to a new understanding of ILD pathology secondary to chronic-systemic inflammation. However, as these models have inconsistencies with RA-ILD, most notably the absence of fibrosis and UIP features, future studies should be directed on assessing parallels with NSIP, and determining whether UIP is a continuum of NSIP, which may go largely undetected in the early stages of RA-ILD.

REFERENCES

1. Kim EJ, Collard HR, and King TE Jr., Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest, 2009 136(5): p. 1397–405. [PubMed: 19892679]
2. O'Dwyer DN, et al., Rheumatoid Arthritis (RA) associated interstitial lung disease (ILD). Eur J Intern Med, 2013 24(7): p. 597–603. [PubMed: 23916467]
3. Aubart F, et al., High levels of anti-cyclic citrullinated peptide autoantibodies are associated with co-occurrence of pulmonary diseases with rheumatoid arthritis. J Rheumatol, 2011 38(6): p. 979–82. [PubMed: 21362759]
4. Luukkainen R, et al., Relationship of rheumatoid factor to lung diffusion capacity in smoking and non-smoking patients with rheumatoid arthritis. Scand J Rheumatol, 1995 24(2): p. 119–20. [PubMed: 7747143]
5. Gibofsky A, Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care, 2012 18(13 Suppl): p. S295–302. [PubMed: 23327517]
6. Helmick CG, et al., Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum, 2008 58(1): p. 15–25. [PubMed: 18163481]
7. Haringman JJ, et al., Synovial tissue macrophages: a sensitive biomarker for response to treatment in patients with rheumatoid arthritis. Ann Rheum Dis, 2005 64(6): p. 834–8. [PubMed: 15576415]
8. McInnes IB and Schett G, The pathogenesis of rheumatoid arthritis. N Engl J Med, 2011 365(23): p. 2205–19. [PubMed: 22150039]
9. Firestein GS, Evolving concepts of rheumatoid arthritis. Nature, 2003 423(6937): p. 356–61. [PubMed: 12748655]
10. Lajas C, et al., Costs and predictors of costs in rheumatoid arthritis: a prevalence-based study. Arthritis Rheum, 2003 49(1): p. 64–70. [PubMed: 12579595]
11. Gabriel SE, et al., Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum, 2003 48(1): p. 54–8. [PubMed: 12528103]
12. Minaur NJ, et al., Outcome after 40 years with rheumatoid arthritis: a prospective study of function, disease activity, and mortality. J Rheumatol Suppl, 2004 69: p. 3–8. [PubMed: 15053445]
13. Kuo CF, et al., Rheumatoid arthritis prevalence, incidence, and mortality rates: a nationwide population study in Taiwan. Rheumatol Int, 2013 33(2): p. 355–60. [PubMed: 22451027]
14. Sparks JA, et al., Rheumatoid Arthritis and Mortality Among Women During 36 Years of Prospective Follow-Up: Results From the Nurses' Health Study. Arthritis Care Res (Hoboken), 2016 68(6): p. 753–62. [PubMed: 26473946]
15. Bongartz T, et al., Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum, 2010 62(6): p. 1583–91. [PubMed: 20155830]

16. Olson AL, et al., Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med, 2011 183(3): p. 372–8. [PubMed: 20851924]
17. Schmidt SL, Sundaram B, and Flaherty KR, Diagnosing fibrotic lung disease: when is high-resolution computed tomography sufficient to make a diagnosis of idiopathic pulmonary fibrosis? Respirology, 2009 14(7): p. 934–9. [PubMed: 19740255]
18. Aalokken TM, et al., Diagnostic accuracy of computed tomography and histopathology in the diagnosis of usual interstitial pneumonia. Acta Radiol, 2012 53(3): p. 296–302. [PubMed: 22334869]
19. Doyle JJ, et al., Prevalence of pulmonary disorders in patients with newly diagnosed rheumatoid arthritis. Clin Rheumatol, 2000 19(3): p. 217–21. [PubMed: 10870658]
20. Richman NC, et al., Extraarticular manifestations of rheumatoid arthritis in a multiethnic cohort of predominantly Hispanic and Asian patients. Medicine (Baltimore), 2013 92(2): p. 92–7. [PubMed: 23429352]
21. Carmona L, et al., Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis, 2003 62(9): p. 897–900. [PubMed: 12922967]
22. Gabbay E, et al., Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med, 1997 156(2 Pt 1): p. 528–35. [PubMed: 9279235]
23. Mori S, et al., Comparison of pulmonary abnormalities on high-resolution computed tomography in patients with early versus longstanding rheumatoid arthritis. J Rheumatol, 2008 35(8): p. 1513–21. [PubMed: 18597412]
24. Hyldgaard C, et al., A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis, 2017 76(10): p. 1700–1706. [PubMed: 28611082]
25. Kim D, et al., Impact of interstitial lung disease on mortality of patients with rheumatoid arthritis. Rheumatol Int, 2017.
26. Solomon JJ, et al., Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RAILD). Respir Med, 2013 107(8): p. 1247–52. [PubMed: 23791462]
27. Koduri G, et al., Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford), 2010 49(8): p. 1483–9. [PubMed: 20223814]
28. Yunt ZX, et al., High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: Relationship to survival. Respir Med, 2017 126: p. 100–104. [PubMed: 28427540]
29. Zamora-Legoff JA, et al., Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology (Oxford), 2017 56(3): p. 344–350. [PubMed: 27940586]
30. Lee HK, et al., Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest, 2005 127(6): p. 2019–27. [PubMed: 15947315]
31. Solomon JJ, et al., Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J, 2016 47(2): p. 588–96. [PubMed: 26585429]
32. Nurmi HM, et al., Variable course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes. BMC Pulm Med, 2016 16(1): p. 107. [PubMed: 27461264]
33. Zamora-Legoff JA, et al., Progressive Decline of Lung Function in Rheumatoid Arthritis-Associated Interstitial Lung Disease. Arthritis Rheumatol, 2017 69(3): p. 542–549. [PubMed: 27788297]
34. Kelly CA, et al., Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics-- a large multicentre UK study. Rheumatology (Oxford), 2014 53(9): p. 1676–82. [PubMed: 24758887]
35. Kim EJ, et al., Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J, 2010 35(6): p. 1322–8. [PubMed: 19996193]
36. Wang JX and Du CG, A retrospective study of clinical characteristics of interstitial lung disease associated with rheumatoid arthritis in Chinese patients. Med Sci Monit, 2015 21: p. 708–15. [PubMed: 25746669]

37. Fujii M, et al., Interstitial lung disease in rheumatoid arthritis: assessment with high-resolution computed tomography. J Thorac Imaging, 1993 8(1): p. 54–62. [PubMed: 8418318]
38. Cortet B, et al., Use of high resolution computed tomography of the lungs in patients with rheumatoid arthritis. Ann Rheum Dis, 1995 54(10): p. 815–9. [PubMed: 7492220]
39. Franquet T, High-resolution CT of lung disease related to collagen vascular disease. Radiol Clin North Am, 2001 39(6): p. 1171–87. [PubMed: 11699667]
40. du Bois R and King TE Jr., Challenges in pulmonary fibrosis x 5: the NSIP/UIP debate. Thorax, 2007 62(11): p. 1008–12. [PubMed: 17965079]
41. Flaherty KR, et al., Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax, 2003 58(2): p. 143–8. [PubMed: 12554898]
42. Flaherty KR, et al., Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med, 2001 164(9): p. 1722–7. [PubMed: 11719316]
43. Li XR, Peng SC, and Wei LQ, Nonspecific interstitial pneumonia overlaps organizing pneumonia in lung-dominant connective tissue disease. Int J Clin Exp Pathol, 2015 8(9): p. 11230–5. [PubMed: 26617847]
44. Makela K, et al., Analysis of the Histologic Features Associated With Interobserver Variation in Idiopathic Pulmonary Fibrosis. Am J Surg Pathol, 2018 42(5): p. 672–678. [PubMed: 29438171]
45. Katzenstein AL, et al., Usual interstitial pneumonia: histologic study of biopsy and explant specimens. Am J Surg Pathol, 2002 26(12): p. 1567–77. [PubMed: 12459623]
46. Doyle TJ and Dellaripa PF, Lung Manifestations in the Rheumatic Diseases. Chest, 2017.
47. Bouros D, et al., Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med, 2002 165(12): p. 1581–6. [PubMed: 12070056]
48. Douglas WW, et al., Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med, 2001 164(7): p. 1182–5. [PubMed: 11673206]
49. Kim DS, et al., The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis, 2002 19(2): p. 121–7. [PubMed: 12108451]
50. Ito I, et al., Pulmonary manifestations of primary Sjogren's syndrome: a clinical, radiologic, and pathologic study. Am J Respir Crit Care Med, 2005 171(6): p. 632–8. [PubMed: 15579729]
51. Assayag D, et al., Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology, 2014 270(2): p. 583–8. [PubMed: 24126367]
52. Yoshinouchi T, et al., Nonspecific interstitial pneumonia pattern as pulmonary involvement of rheumatoid arthritis. Rheumatol Int, 2005 26(2): p. 121–5. [PubMed: 15580351]
53. Travis WD, et al., An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med, 2013 188(6): p. 733–48. [PubMed: 24032382]
54. Katzenstein AL, Mukhopadhyay S, and Myers JL, Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. Hum Pathol, 2008 39(9): p. 1275–94. [PubMed: 18706349]
55. Veeraraghavan S, et al., BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J, 2003 22(2): p. 239–44. [PubMed: 12952254]
56. MacDonald SL, et al., Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. Radiology, 2001 221(3): p. 600–5. [PubMed: 11719652]
57. Kligerman SJ, et al., Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations. Radiographics, 2009 29(1): p. 73–87. [PubMed: 19168837]
58. Travis WD, et al., Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol, 2000 24(1): p. 19–33. [PubMed: 10632484]
59. Johnson C, Recent advances in the pathogenesis, prediction, and management of rheumatoid arthritis-associated interstitial lung disease. Curr Opin Rheumatol, 2017 29(3): p. 254–259. [PubMed: 28207496]

60. Nicholson AG, et al., The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med, 2000 162(6): p. 2213–7. [PubMed: 11112140]
61. Akira M, Sakatani M, and Hara H, Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses. J Comput Assist Tomogr, 1999 23(6): p. 941–8. [PubMed: 10589572]
62. Assayag D, et al., Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology, 2014 19(4): p. 493–500. [PubMed: 24372981]
63. Remy-Jardin M, et al., Lung changes in rheumatoid arthritis: CT findings. Radiology, 1994 193(2): p. 375–82. [PubMed: 7972746]
64. Tanaka N, et al., Rheumatoid arthritis-related lung diseases: CT findings. Radiology, 2004 232(1): p. 81–91. [PubMed: 15166329]
65. Mori S, Management of Rheumatoid Arthritis Patients with Interstitial Lung Disease: Safety of Biological Antirheumatic Drugs and Assessment of Pulmonary Fibrosis. Clinical Medicine Insights-Circulatory Respiratory and Pulmonary Medicine, 2015 9: p. 41–49.
66. Roubille C and Haraoui B, Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: A systematic literature review. Seminars in Arthritis and Rheumatism, 2014 43(5): p. 613–626. [PubMed: 24231065]
67. Perez-Alvarez R, et al., Interstitial Lung Disease Induced or Exacerbated by TNF-Targeted Therapies: Analysis of 122 Cases. Seminars in Arthritis and Rheumatism, 2011 41(2): p. 256–264. [PubMed: 21277618]
68. Koo BS, et al., Mortality in patients with rheumatoid arthritis-associated interstitial lung disease treated with an anti-tumor necrosis factor agent. Korean Journal of Internal Medicine, 2015 30(1): p. 104–109. [PubMed: 25589842]
69. Conway R, et al., Methotrexate and interstitial lung disease in rheumatoid arthritis-a systematic literature review and meta-analysis. Irish Journal of Medical Science, 2013 182: p. S94–S94.
70. Dawson JK, et al., Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests. Rheumatology, 2002 41(3): p. 262–267. [PubMed: 11934961]
71. Khanna D, et al., Mycophenolate Mofetil Versus Oral Cyclophosphamide in Scleroderma-Related Interstitial Lung Disease: Scleroderma Lung Study Ii. Annals of the Rheumatic Diseases, 2016 75: p. 531–531.
72. Hayashi M, Kikuchi T, and Takada T, Mycophenolate mofetil for the patients with interstitial lung diseases in amyopathic dermatomyositis with anti-MDA-5 antibodies. Clinical Rheumatology, 2017 36(1): p. 239–240. [PubMed: 27718019]
73. Tashkin DP, et al., Cyclophosphamide versus placebo in scleroderma lung disease. New England Journal of Medicine, 2006 354(25): p. 2655–2666. [PubMed: 16790698]
74. Suda T, Up-to-Date Information on Rheumatoid Arthritis-Associated Interstitial Lung Disease. Clin Med Insights Circ Respir Pulm Med, 2015 9(Suppl 1): p. 155–62. [PubMed: 27279757]
75. Picchianti Diamanti A, et al., Therapeutic management of patients with rheumatoid arthritis and associated interstitial lung disease: case report and literature review. Ther Adv Respir Dis, 2017 11(1): p. 64–72. [PubMed: 27733490]
76. Wolfe F, Caplan L, and Michaud K, Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum, 2006 54(2): p. 628–34. [PubMed: 16447241]
77. Gomez-Reino JJ, et al., Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum, 2003 48(8): p. 2122–7. [PubMed: 12905464]
78. British Thoracic Society Standards of Care, C., BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. Thorax, 2005 60(10): p. 800–5. [PubMed: 16055611]

79. Kremer JM, et al., Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis - A multicenter study with literature review. Arthritis and Rheumatism, 1997 40(10): p. 1829–1837. [PubMed: 9336418]
80. Conway R, et al., Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheumatol, 2014 66(4): p. 803–12. [PubMed: 24757133]
81. Yusof MYM, et al., Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology, 2017 56(8): p. 1348–1357. [PubMed: 28444364]
82. Md Yusof MY, et al., Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford), 2017 56(8): p. 1348–1357. [PubMed: 28444364]
83. Mera-Varela A and Perez-Pampin E, Abatacept therapy in rheumatoid arthritis with interstitial lung disease. J Clin Rheumatol, 2014 20(8): p. 445–6. [PubMed: 25417684]
84. Fernandez-Diaz C, et al., Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. Semin Arthritis Rheum, 2018.
85. Kimura Y, et al., Pulmonary hypertension and other potentially fatal pulmonary complications in systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken), 2013 65(5): p. 745–52. [PubMed: 23139240]
86. Asquith DL, et al., Animal models of rheumatoid arthritis. Eur J Immunol, 2009 39(8): p. 2040–4. [PubMed: 19672892]
87. Sakaguchi N, et al., Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. Nature, 2003 426(6965): p. 454–60. [PubMed: 14647385]
88. Sakaguchi S, et al., SKG mice, a new genetic model of rheumatoid arthritis. Arthritis Res Ther, 2003 5(Suppl 3): p. S4.
89. Keith RC, et al., A novel model of rheumatoid arthritis-associated interstitial lung disease in SKG mice. Exp Lung Res, 2012 38(2): p. 55–66. [PubMed: 22185348]
90. Shiomi A, et al., GM-CSF but not IL-17 is critical for the development of severe interstitial lung disease in SKG mice. J Immunol, 2014 193(2): p. 849–59. [PubMed: 24951817]
91. Sendo S, et al., CD11b+ Gr1dim Tolerogenic Dendritic Cell-like Cells are Expanded in Interstitial Lung Disease in SKG Mice. Arthritis Rheumatol, 2017.
92. van Eden W, Wagenaar-Hilbers JP, and Wauben MH, Adjuvant arthritis in the rat. Curr Protoc Immunol, 2001 Chapter 15: p. Unit 15 4. [PubMed: 18432732]
93. Bendele A, Animal models of rheumatoid arthritis. J Musculoskelet Neuronal Interact, 2001 1(4): p. 377–85. [PubMed: 15758488]
94. Kim EY and Moudgil KD, The determinants of susceptibility/resistance to adjuvant arthritis in rats. Arthritis Res Ther, 2009 11(4): p. 239. [PubMed: 19678912]
95. Song LN, et al., Establishment of a Rat Adjuvant Arthritis-Interstitial Lung Disease Model. Biomed Res Int, 2016 2016: p. 2970783. [PubMed: 26881215]
96. Liu J, et al., [The correlative study on pulmonary function changes and Th1/Th2 cells & regulatory T cells in adjuvant arthritis rats]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi, 2011 27(1): p. 56–60. [PubMed: 21208566]
97. Wan L, et al., [The reduced pulmonary function is related to the decreased expression of Treg and Foxp3 in adjuvant-induced arthritis rats]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi, 2013 29(3): p. 251–5. [PubMed: 23643080]
98. Schurgers E, et al., Pulmonary inflammation in mice with collagen-induced arthritis is conditioned by complete Freund's adjuvant and regulated by endogenous IFN-gamma. Eur J Immunol, 2012 42(12): p. 3223–34. [PubMed: 22930199]
99. Keffer J, et al., Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. EMBO J, 1991 10(13): p. 4025–31. [PubMed: 1721867]
100. Bawadekar M, et al., Tumor necrosis factor alpha, citrullination, and peptidylarginine deiminase 4 in lung and joint inflammation. Arthritis Res Ther, 2016 18(1): p. 173. [PubMed: 27450561]
101. Douni E, et al., Transgenic and knockout analyses of the role of TNF in immune regulation and disease pathogenesis. J Inflamm, 1995 47(1–2): p. 27–38. [PubMed: 8913927]

102. Li P and Schwarz EM, The TNF-alpha transgenic mouse model of inflammatory arthritis. Springer Semin Immunopathol, 2003 25(1): p. 19–33. [PubMed: 12904889]
103. Shelef MA, et al., Peptidylarginine deiminase 4 contributes to tumor necrosis factor alpha-induced inflammatory arthritis. Arthritis Rheumatol, 2014 66(6): p. 1482–91. [PubMed: 24497204]
104. Miyazaki Y, et al., Expression of a tumor necrosis factor-alpha transgene in murine lung causes lymphocytic and fibrosing alveolitis. A mouse model of progressive pulmonary fibrosis. J Clin Invest, 1995 96(1): p. 250–9. [PubMed: 7542280]
105. Lundblad LK, et al., Tumor necrosis factor-alpha overexpression in lung disease: a single cause behind a complex phenotype. Am J Respir Crit Care Med, 2005 171(12): p. 1363–70. [PubMed: 15805183]
106. Klareskog L, et al., Genes, environment and immunity in the development of rheumatoid arthritis. Curr Opin Immunol, 2006 18(6): p. 650–5. [PubMed: 17010589]
107. Klareskog L, et al., Mechanisms of disease: Genetic susceptibility and environmental triggers in the development of rheumatoid arthritis. Nat Clin Pract Rheumatol, 2006 2(8): p. 425–33. [PubMed: 16932734]
108. Juge PA, et al., MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease. N Engl J Med, 2018.
109. Jawaheer D, et al., Dissecting the genetic complexity of the association between human leukocyte antigens and rheumatoid arthritis. Am J Hum Genet, 2002 71(3): p. 585–94. [PubMed: 12181776]
110. Migita K, et al., HLA-DRB1 alleles and rheumatoid arthritis-related pulmonary fibrosis. J Rheumatol, 2010 37(1): p. 205–7. [PubMed: 20040645]
111. Ennis H, et al., HLA-DRB1 associations with rheumatoid arthritis-related pulmonary fibrosis. Scand J Rheumatol, 2014 43(1): p. 75–6. [PubMed: 24295149]
112. Klareskog L, et al., A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum, 2006 54(1): p. 38–46. [PubMed: 16385494]
113. Seibold MA, et al., A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med, 2011 364(16): p. 1503–12. [PubMed: 21506741]
114. Zhang GY, Liao T, and Gao WY, MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med, 2011 365(2): p. 178; author reply 178–9.
115. Zhang Y, et al., A variant in the promoter of MUC5B and idiopathic pulmonary fibrosis. N Engl J Med, 2011 364(16): p. 1576–7. [PubMed: 21506748]
116. Fingerlin TE, et al., Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nat Genet, 2013 45(6): p. 613–20. [PubMed: 23583980]
117. Noth I, et al., Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. Lancet Respir Med, 2013 1(4): p. 309–317. [PubMed: 24429156]
118. Borie R, et al., The MUC5B variant is associated with idiopathic pulmonary fibrosis but not with systemic sclerosis interstitial lung disease in the European Caucasian population. PLoS One, 2013 8(8): p. e70621. [PubMed: 23940607]
119. Horimasu Y, et al., MUC5B promoter polymorphism in Japanese patients with idiopathic pulmonary fibrosis. Respirology, 2015 20(3): p. 439–44. [PubMed: 25581455]
120. Lee MG and Lee YH, A meta-analysis examining the association between the MUC5B rs35705950 T/G polymorphism and susceptibility to idiopathic pulmonary fibrosis. Inflamm Res, 2015 64(6): p. 463–70. [PubMed: 25926289]
121. van der Vis JJ, et al., Effect of Muc5b promoter polymorphism on disease predisposition and survival in idiopathic interstitial pneumonias. Respirology, 2016 21(4): p. 712–7. [PubMed: 26699835]
122. Juge PA, et al., Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J, 2017 49(5).
123. Shaw M, et al., Rheumatoid arthritis-associated lung disease. Eur Respir Rev, 2015 24(135): p. 1–16. [PubMed: 25726549]

124. Kilsgard O, et al., Peptidylarginine deiminases present in the airways during tobacco smoking and inflammation can citrullinate the host defense peptide LL-37, resulting in altered activities. Am J Respir Cell Mol Biol, 2012 46(2): p. 240–8. [PubMed: 21960546]
125. Makrygiannakis D, et al., Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis, 2008 67(10): p. 1488–92. [PubMed: 18413445]
126. Perry E, et al., The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? Rheumatology (Oxford), 2014 53(11): p. 1940–50. [PubMed: 24831057]
127. Nishimura K, et al., Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med, 2007 146(11): p. 797–808. [PubMed: 17548411]
128. Bongartz T, et al., Citrullination in extra-articular manifestations of rheumatoid arthritis. Rheumatology (Oxford), 2007 46(1): p. 70–5. [PubMed: 16782731]
129. Samara KD, et al., Upregulation of citrullination pathway: From Autoimmune to Idiopathic Lung Fibrosis. Respir Res, 2017 18(1): p. 218. [PubMed: 29287593]
130. Chang X, et al., Localization of peptidylarginine deiminase 4 (PADI4) and citrullinated protein in synovial tissue of rheumatoid arthritis. Rheumatology (Oxford), 2005 44(1): p. 40–50. [PubMed: 15466895]
131. Baeten D, et al., Specific presence of intracellular citrullinated proteins in rheumatoid arthritis synovium: relevance to antifilaggrin autoantibodies. Arthritis Rheum, 2001 44(10): p. 2255–62. [PubMed: 11665966]
132. Zhang Y, et al., Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol, 2017 36(4): p. 817–823. [PubMed: 28191607]
133. Vassallo R, et al., Cellular and humoral immunity in arthritis are profoundly influenced by the interaction between cigarette smoke effects and host HLA-DR and DQ genes. Clin Immunol, 2014 152(1–2): p. 25–35. [PubMed: 24631425]
134. Svard A, et al., Associations with smoking and shared epitope differ between IgA- and IgG-class antibodies to cyclic citrullinated peptides in early rheumatoid arthritis. Arthritis Rheumatol, 2015 67(8): p. 2032–7. [PubMed: 25916813]
135. Kokkonen H, et al., Associations of antibodies against citrullinated peptides with human leukocyte antigen-shared epitope and smoking prior to the development of rheumatoid arthritis. Arthritis Res Ther, 2015 17: p.125. [PubMed: 25990747]
136. Lee YH, Bae SC, and Song GG, Gene-environmental interaction between smoking and shared epitope on the development of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis: a meta-analysis. Int J Rheum Dis, 2014 17(5): p. 528–35. [PubMed: 24618101]
137. Lugli EB, et al., Expression of citrulline and homocitrulline residues in the lungs of non-smokers and smokers: implications for autoimmunity in rheumatoid arthritis. Arthritis Res Ther, 2015 17: p. 9. [PubMed: 25600626]
138. Terao C, et al., Effects of smoking and shared epitope on the production of anti-citrullinated peptide antibody in a Japanese adult population. Arthritis Care Res (Hoboken), 2014 66(12): p. 1818–27. [PubMed: 24942650]
139. Terao C, et al., An association between amino acid position 74 of HLA-DRB1 and anti-citrullinated protein antibody levels in Japanese patients with anti-citrullinated protein antibody-positive rheumatoid arthritis. Arthritis Rheumatol, 2015 67(8): p. 2038–45. [PubMed: 25832994]
140. Chang K, et al., Smoking and rheumatoid arthritis. Int J Mol Sci, 2014 15(12): p. 22279–95. [PubMed: 25479074]
141. Sparks JA, et al., Smoking Behavior Changes in the Early Rheumatoid Arthritis Period and Risk of Mortality During Thirty-Six Years of Prospective Followup. Arthritis Care Res (Hoboken), 2018 70(1): p. 19–29. [PubMed: 28464477]
142. Sparks JA, et al., Associations of Smoking and Age With Inflammatory Joint Signs Among Unaffected First-Degree Relatives of Rheumatoid Arthritis Patients: Results From Studies of the Etiology of Rheumatoid Arthritis. Arthritis Rheumatol, 2016 68(8): p. 1828–38. [PubMed: 26866831]

143. Kallberg H, et al., Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis, 2011 70(3): p. 508–11. [PubMed: 21149499]

144. Reynisdottir G, et al., Structural changes and antibody enrichment in the lungs are early features of anti-citrullinated protein antibody-positive rheumatoid arthritis. Arthritis Rheumatol, 2014 66(1): p. 31–9. [PubMed: 24449573]

145. Pereira DA, Kawassaki Ade M, and Baldi BG, Interpretation of autoantibody positivity in interstitial lung disease and lung-dominant connective tissue disease. J Bras Pneumol, 2013 39(6): p. 728–41. [PubMed: 24473767]

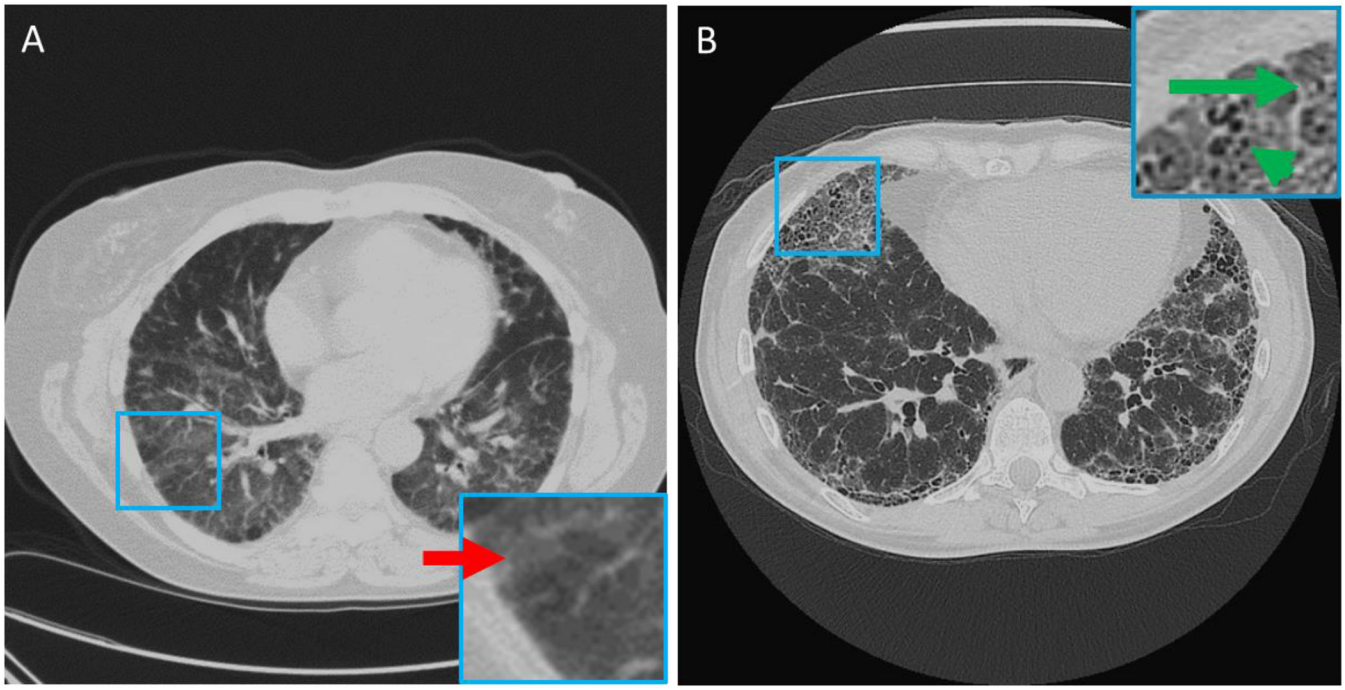

Figure 1:

Representative high-resolution CT images of rheumatoid arthritis (RA) associated interstitial lung disease. A: Nonspecific usual interstitial pneumonia (NSIP) with ground glass opacities (red arrow in A). This patient was diagnosed with RA three years prior to the CT image. B: Usual interstitial pneumonia (UIP), characterized by reticular opacities (green long arrow) and honeycombing (green short arrow). This patient was diagnosed with RA 10 years prior to the CT image.

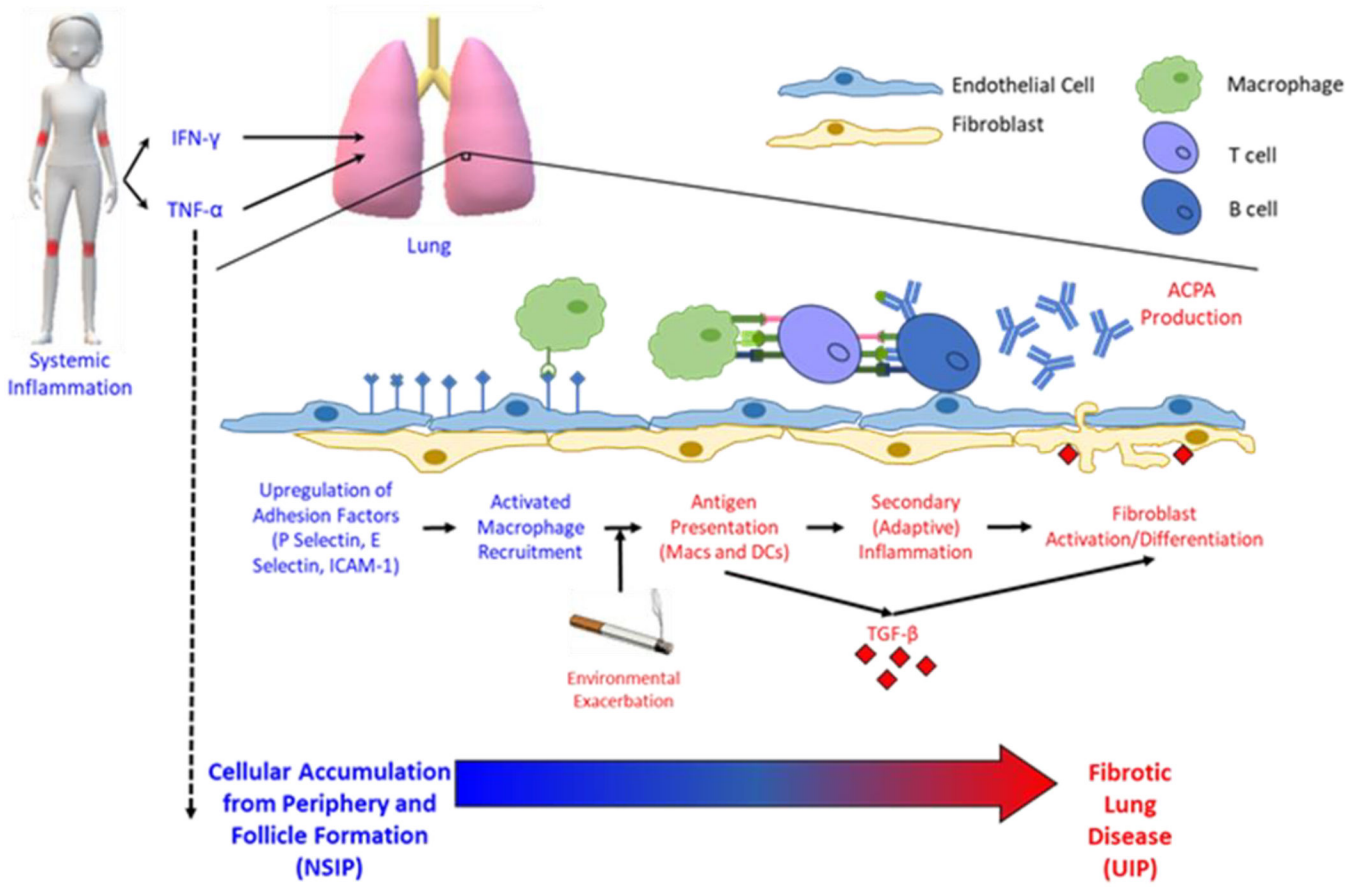

Figure 2: Theory of progressive ILD development.

Systemic inflammation leads to the production of inflammatory cytokines, such as TNF-α and INF-γ. These factors circulate and act on the lung, where they induce the upregulation of several adhesion factors, such as P and E selectin, and ICAM-1. These ultimately lead to the recruitment and extravasation of circulating monocytes/macrophages, while the cytokines continue to activate tissue-resident inflammatory cells such as alveolar macrophages. With the activation of the local environment, the tissue is primed for exacerbation by an external antigen, such as cigarette smoke. Once there is antigen presentation, a secondary immune response is activated, leading to the recruitment and activation of T and B cells, thereby resulting in ACPA production. Antigen-presentation and activation of the macrophage and DC populations can also induce the expression of TGF-β, which activates local fibroblasts and leads to collagen deposition, resulting in fibrosis.

Table 1-

Characteristics of non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia(UIP) patternsofRA-ILD

	NSIP	UIP
HRCT Findings *	Ground Glass Opacities Fine Reticulations Consolidation Possible architectural distortion	Honeycombing Course Reticular Opacities Traction Bronchiectasis Architectural distortion
Pathologic Distribution *	Basilar Subpleural sparing Symmetric	Basilar Subpleural Hetergenous Distribution
Histologic Findings *	Cellular Infiltrate Chronic interstitial Inflammation Type II Pneumocyte Hyperplasia Mild/Moderate Uniform Fibrosis	Dense, Patchy Fibrosis Fibroblastic foci with scar formation Interstitial fibrosis Patchy lung involvement
Lung Function [30,31]	Slower decline over time	Accelerated decline over time
ACPA + [28,31]	Some evidence for lower titers	Some evidence for higher titers
Smoking [30,31,64]	Some association with smoking	Greatly associated with smoking
Efficacy of Treatment [65–69]	Response to anti-inflammatory treatment Variable treatment efficacy	Poor response to any treatment
Median Survival [28,30, 31,35,41,58,60,61,62]	Longerthan UIP	Shorter than NSIP

* Consensus over ssveral studies, as dictated by the American Thoracic Society, 2013 Update [53]