REVISTA DE INVESTIGACIÓN CLÍNICA

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Rev Inves Clin. 2015;67:280-6 BRIEF REVIEW

Rheumatoid Arthritis-Associated Interstitial Lung Disease and Idiopathic Pulmonary Fibrosis: Shared Mechanistic and Phenotypic Traits Suggest Overlapping Disease Mechanisms

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ABSTRACT

The prevalence of clinically evident interstitial lung disease in patients with rheumatoid arthritis is approximately 10%. An additional 33% of undiagnosed patients have interstitial lung abnormalities that can be detected with high-resolution computed tomography. Rheumatoid arthritis-interstitial lung disease patients have three times the risk of death compared to those with rheumatoid arthritis occurring in the absence of interstitial lung disease, and the mortality related to interstitial lung disease is rising. Rheumatoid arthritis-interstitial lung disease is most commonly classified as the usual interstitial pneumonia pattern, overlapping mechanistically and phenotypically with idiopathic pulmonary fibrosis, but can occur in a non-usual interstitial pneumonia pattern, mainly nonspecific interstitial pneumonia. Based on this, we propose two possible pathways to explain the coexistence of rheumatoid arthritis and interstitial lung disease: (i) Rheumatoid arthritis-interstitial lung disease with a non-usual interstitial pneumonia pattern may come about when an immune response against citrullinated peptides taking place in another site (e.g. the joints) subsequently affects the lungs; (ii) Rheumatoid arthritis-interstitial lung disease with a usual interstitial pneumonia pattern may represent a disease process in which idiopathic pulmonary fibrosis-like pathology triggers an immune response against citrullinated proteins that promotes articular disease indicative of rheumatoid arthritis. More studies focused on elucidating the basic mechanisms leading to different sub-phenotypes of rheumatoid arthritis-interstitial lung disease and the overlap with idiopathic pulmonary fibrosis are necessary to improve our understanding of the disease process and to define new therapeutic targets. (REV INVES CLIN. 2015;67:280-6)

Key words: Interstitial lung disease. Rheumatoid arthritis. Idiopathic pulmonary fibrosis. Citrullination.

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Received for publication: 16-09-2015
Accepted for publication: 28-09-2015

INTRODUCTION

The prevalence of clinically evident interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) is approximately 10%[1-3]. An additional 33%[4] of undiagnosed patients have ILD that can be detected with high-resolution computed tomography (HRCT) with varying degrees of functional impairment[5]. The mortality related to ILD in this group of patients is rising, second only to cardiovascular disease[1]. Interstitial lung disease is responsible for 7% of all RA-associated deaths[1], and RA-ILD patients have three times the risk of death compared to those with RA occurring in the absence of ILD[6]. Based on lung biopsy and/or CT scan findings, RA-ILD can be classified as either usual interstitial pneumonia (UIP) pattern or non-UIP pattern that is predominantly non-specific interstitial pneumonia (NSIP). Rheumatoid arthritis and interstitial lung disease with UIP is the most common pattern, overlapping mechanistically and phenotypically with idiopathic pulmonary fibrosis (IPF). These observations highlight the scope of the morbidity and mortality associated with ILD in patients with RA and underscore the importance of better understanding the molecular mechanisms that contribute to disease pathogenesis and the putative overlap with IPF. Ultimately, the shared mechanistic and phenotypic traits between RA-ILD and IPF can serve as a basis for the development of therapeutic strategies that improve clinical outcomes in both conditions.

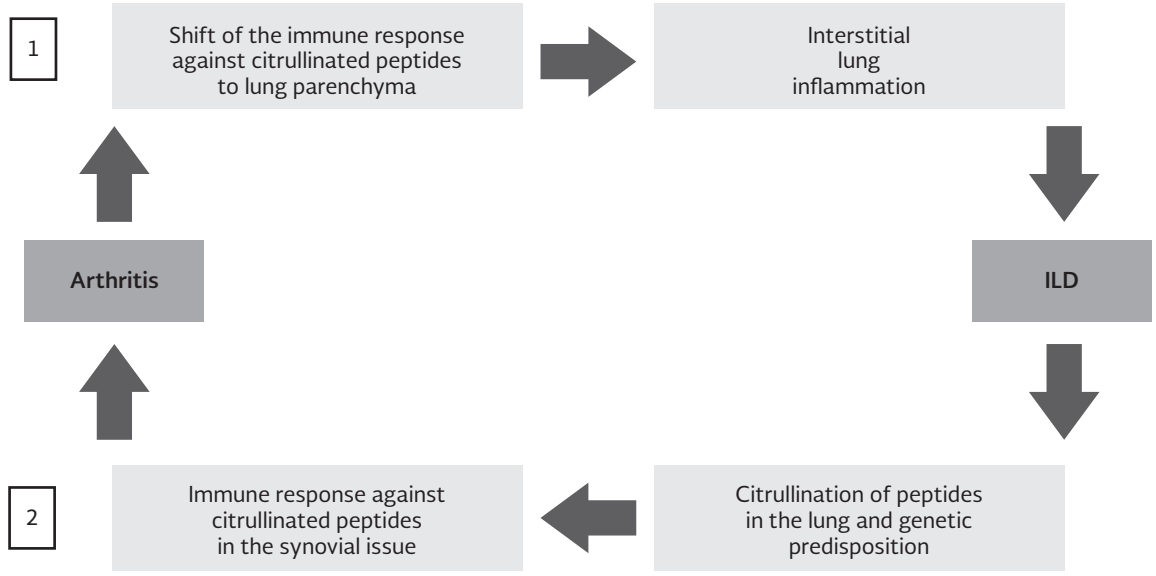
TWO POTENTIAL PATHWAYS EXPLAIN THE COEXISTENCE OF RHEUMATOID ARTHRITIS AND INTERSTITIAL LUNG DISEASE

Citrullination, a post-translational modification marked by the conversion of arginine to citrulline, triggers an immune response that leads to anti-citrullinated protein antibody (ACPA) synthesis[7]. Citrullination is linked to the development of joint damage in RA; although the immune response to citrullinated proteins appears unique to RA, citrullinated proteins are found in the lungs of RA-ILD and IPF subjects[8]. Based on these observations, we propose two potential mechanisms that explain the coexistence of RA and ILD: (i) In the first pathway, an immune response against citrullinated peptides taking place at the joints subsequently shifts to the lungs, resulting in interstitial lung inflammation, most likely a non-UIP pattern; (ii) In the second pathway, individuals with UIP and a genetic susceptibility to RA mount an immune response against citrullinated peptides in the lung, initiating an inflammatory process that secondarily affects the joints. Regardless of whether the immune response begins in the joints or the lungs, poorly defined molecular mechanisms are likely involved in shifting the immune response from one tissue compartment to the other. Plausible explanations for the shared targeting of lung and joints in RA include the formation and deposit of immune complexes (with rheumatoid factor contributing to their deposition by its capacity to bind the Fc portion of IgG)[9], the presence of structural overlap between initiating antigens and subsequent post-translationally modified targets (as reported for citrullinated vimentin present in both lung and synovial tissue in patients with RA)[10], and the immunologic process of epitope spreading (a mechanism that leads to a widening of the immune response spectrum)[11] (Fig. 1).

First pathway: From the joints to the lungs

Given that a significant proportion of RA-ILD patients develop articular manifestations prior to lung involvement[12], it is possible that an inflammatory process primarily taking place in the joints affects the lungs secondarily. Once the inflammatory process has arrived in the lungs, it activates fibroblasts, which in turn differentiate into myofibroblasts capable of directing tissue fibrosis[13]. We hypothesize that, in these cases, the lung histology would likely exhibit a non-UIP pattern due to the inflammatory nature of the initial phenomena[12]. For example, a lung biopsy showing an NSIP pattern would be consistent with this hypothesis since it usually presents with inflammatory infiltrates in the alveolar septa with varying degrees of fibrosis[14]. Moreover, the typical homogeneous distribution of abnormalities along the secondary pulmonary lobule in NSIP[14] is consistent with a process where inflammatory cells and associated mediators reach the lungs through the systemic circulation, a situation which contrasts with the marked involvement of the peripheral zone of the pulmonary lobule in UIP that may result from a variety of sources including mechanical stress[14,15]. After an initial inflammatory phase, the Th1 lymphocyte profile (which plays a key role in the pathogenesis of RA)[7] can turn into a Th2 profile with its well-known potential to activate fibroblasts through the synthesis and

Figure 1. Potential mechanisms linking rheumatoid arthritis and interstitial lung disease. [1] Joints to Lungs: In the first pathway, an immune response against citrullinated peptides taking place at the joints or another site subsequently shifts to the lungs, resulting in rheumatoid arthritis-interstitial lung disease (non-usual interstitial pneumonia pattern). [2] Lungs to Joints: In the second pathway, a patient with interstitial lung disease (usual interstitial pneumonia pattern) and a genetic susceptibility to rheumatoid arthritis mounts an immune response against citrullinated peptides in the lung, initiating an inflammatory process that secondarily affects the joints.



release of interleukins IL-4 and IL-13[16]. Another important T lymphocyte subpopulation that contributes to the pathogenesis of RA and can potentially activate fibroblasts is the Th17 pathway[7]. Together, both Th2- and Th17-associated cytokine cascades may trigger the transition from an inflammatory process to a fibrotic one[13], leading to such pathologic correlates as fibrotic NSIP.

Second pathway: From the lungs to the joints

The coexistence of ILD and RA may also be explained if the presence of ILD and associated immune responses against citrullinated proteins subsequently results in the development of synovial inflammation. In this pathway, the mechanism behind the development of ILD itself is driven by an aberrant epithelial cell and myofibroblast response to alveolar microinjuries[17] conditioned by genetic polymorphisms[18], epigenetic reprogramming[19], and ageing-related changes[20]. The activated fibroblast (myofibroblast) expresses alpha smooth muscle actin (alpha SMA) and is capable of producing large amounts of extracellular matrix, leading to an increase in lung stiffness. This increase in lung stiffness in turn activates the myofibroblast and the epithelial cell, defining a detrimental cycle that leads to a progressive fibrotic remodeling in which inflammation does not play a prominent role[17]. We hypothesize that this mechanism leads to a UIP pattern similar to IPF in which protein citrullination is also seen (but without the immune response characteristic of RA/RA-ILD). Intriguingly, a study that compared the different types of histopathologic patterns in patients with RA and ILD suggests that UIP is the most frequent pattern in patients where the lung is the initial target organ[12].

While the early presence of UIP as a pattern points to a temporal sequence in which primary fibrotic lung disease can lead to subsequent articular involvement, additional evidence supports a paradigm in which the lungs may be a potential site of origin for systemic immune responses[21]. A study comparing HRCT findings in two groups of patients, both without articular symptoms but differing in the presence of ACPAs in serum, showed that those with positive ACPAs had more frequent airway abnormalities, suggesting that these structural alterations could be linked to post-translational modifications such as citrullination[21]. This hypothesis is further supported by the existence of a

cohort of patients with anti-cyclic citrullinated peptide positivity and lung disease in the absence of full blown RA; importantly, 3 out of 33 of these patients developed articular disease within a short follow-up period[22]. This finding strongly suggests that ACPAs detected in patients with lung diseases can predate the development of RA. Moreover, recent work comparing anti-citrullinated heat shock protein 90 (HSP90) antibody profiles in bronchoalveolar lavage fluid and serum derived from RA-ILD patients indicates that the lung microenvironment plays a key role in shaping the repertoire of specific ACPAs[23].

SHARED MECHANISTIC FEATURES OF RHEUMATOID ARTHRITIS-INTERSTITIAL LUNG DISEASE AND IDIOPATHIC PULMONARY FIBROSIS: CITRULLINATION

As previously mentioned, the development of RA/RA-ILD is highly associated with citrullination, a post-translational modification that is catalyzed by an enzyme called peptidyl arginine deiminase (PAD)[24]. The structural/electrostatic changes induced by PAD within these proteins render them immunogenic in a subset of patients who have a genetic predisposition, particularly those possessing the so-called "shared (HLA) epitope"[7,24]. The presence of the shared epitope (HLA-DRB1 alleles) indicates the expression of certain amino acids in positions 70 to 74 of the third hypervariable region of the DRB chains (most of them positively charged), endowing such class II molecules with increased capacity to bind to peptides that have been citrullinated[25]. As a result of this process, citrullinated/post-translationally modified antigens are presented as if they were foreign peptides, subsequently triggering an immune response that leads to ACPA synthesis, which is associated (at least indirectly) with joint damage[7].

In RA-ILD, the presence of lymphoid follicles observed in lung biopsies (most with an underlying UIP pattern) could represent pathologic evidence of an immune response directed against citrullinated peptides. A study comparing the presence of inducible bronchial associated lymphoid tissue (iBALT) in IPF and RA-ILD tissue samples showed that the latter group had more lymphoid follicles, with surrounding expression of the PAD enzyme and citrullinated proteins[26]. This study also demonstrated that patients with higher follicle density had higher titers of ACPAs in both serum and bronchoalveolar lavage (BAL) fluid, suggesting that ACPAs related to an immune response taking place in the lungs could potentially trigger a systemic inflammatory state resulting in joint damage. Moreover, as previously indicated, there is evidence that a specific type of ACPA targeting citrullinated HSP90 is produced in the lung microenvironment, supporting a role for the lung in initiating relevant immune responses and/or spreading the ACPA repertoire[23].

Beyond RA-ILD, citrullination of lung tissue has been reported in IPF. A group of researchers found evidence of citrullination in 46% of 20 samples taken from IPF patients compared with 20% in the control group[8]. There are reasons to consider the epithelial cell as a possible point of origin for citrullination taking place in the lungs of IPF patients. In agreement with an accepted hypothesis regarding IPF pathogenesis, aberrant alveolar epithelial cells subjected to mechanical stress (i.e. respiratory movements) gain the ability to secrete a variety of substances, including growth factors (TGF-B), chemokines (CXCL12), matrix metalloproteinases (MMP-7), pro-coagulants, and vasoactive mediators (FXa, endothelin-1)[17]. In turn, at least some of these substances promote the transition of fibroblasts to myofibroblasts, ultimately favoring the dysregulated deposition of extracellular matrix components and associated tissue fibrosis[17]. Based on these considerations, it is plausible that in select conditions, alveolar epithelial cells gain the ability to citrullinate peptides through the expression of the PAD enzyme, a scenario that could explain the high proportion of IPF lung samples showing citrullination[8].

The rates of protein citrullination in lung tissue of IPF patients (44%) are similar to those found in RA-ILD patients (46%)[8]. Based on this, it seems reasonable to posit that differences in disease expression between these entities (including extra-pulmonary manifestations) reflect immunogenetic factors (e.g., HLA-DR4) predisposing to citrulline-targeted immune responses and potential articular disease. Thus, patients with RA-UIP and IPF could develop ILD through similar molecular mechanisms, with subsequent development of systemic immune responses marked by the emergence of ACPAs occurring more specifically in RA.

Cigarette smoking, the strongest environmental risk factor for the development of chronic lung disease, may represent a common upstream trigger leading to

in situ development of citrullinated proteins, which may play a role in both IPF and RA-ILD. An estimated 94 million U.S. adults who are current or former smokers have an increased risk of developing interstitial lung diseases including IPF[27]. Despite the implementation of aggressive smoking prevention programs throughout the USA, prevalence of smoking ranges from 20 to 40%, with a recent increase in youth, females, and minority ethnic groups[28-30]. Similarly, smoking is a well-known risk factor for RA, conferring both a higher risk of developing the disease as well as a more aggressive course that is proportional to the number of pack-years smoked[31]. This relationship could be partly explained by the effect that cigarette smoking has on the citrullination of peptides in lung tissues. In fact, smokers have more citrullinated peptides in their BAL fluid compared to non-smokers, as well as increased expression of PAD enzyme in bronchoalveolar cells[32]. Collectively, these data suggest that effect of smoking on the development of citrullinated proteins may play a role in both IPF and RA-ILD, either through direct effects or via immune responses (limited to RA-ILD) to citrullinated target antigens.

SHARED PHENOTYPIC TRAITS OF RHEUMATOID ARTHRITIS-INTERSTITIAL LUNG DISEASE AND IDIOPATHIC PULMONARY FIBROSIS

Paralleling this mechanistic overlap between RA-ILD and IPF, RA patients with a UIP pattern are more frequently smokers, male, and of older age[12,33-37] (Table 1). Moreover, the predominance of a UIP pattern (pathognomonic for IPF) in RA-ILD contrasts with other connective tissue disease-associated ILDs where the most common pathologic pattern found in lung biopsies is NSIP[12]. The UIP pattern observed in RA patients is very similar to that seen in IPF[38] and predicts worse survival (3.2 vs. 6.6 years) when compared with a non-UIP pattern of RA-ILD[33]. This situation mirrors IPF prognosis, with a 50% 3-5 year survival in both conditions[33,34]. Of note, although lung biopsies have traditionally been used to define ILD patterns, there is strong evidence supporting the alternative use of HRCT to differentiate ILD subtypes[39,40], particularly when distinguishing between UIP and non-UIP patterns. As shown in patients with IPF, a UIP HRCT pattern strongly correlates with histopathological abnormalities in RA-ILD with excellent specificity (96%) and modest sensitivity (45%)[41].

Further support for the clinical overlap between IPF and RA-ILD comes from molecular profiling analyses of serum proteins, many of which are involved in aberrant epithelial cell activation or a fibrotic processes. For example, in IPF, higher levels of MMP-7 and surfactant protein-D have been associated with reduced survival[42,43]. In RA-ILD, MMP-7 and surfactant protein-D have also been shown to enhance our ability to risk-stratify clinically evident and subclinical disease[44]. In another study, MMP-7 and IP-10 (a chemokine related to Th1 lymphocyte trafficking) have proven their value as pathogenically relevant biomarkers that can contribute to detection of RA-ILD[45].

THERAPEUTICS IN RHEUMATOID ARTHRITIS-INTERSTITIAL LUNG DISEASE AND IDIOPATHIC PULMONARY FIBROSIS

Disease-modifying anti-rheumatic drugs

Many biologic agents have been used successfully to treat the synovial involvement in patients with RA[46]. The anti-TNF group (infliximab, etanercept, adalimumab) is one of the most utilized due to its proven effectiveness in controlling joint inflammation and retarding articular disease progression. Other biologic agents currently used to treat RA are rituximab (anti- CD20 monoclonal antibody), tocilizumab (anti IL-6 monoclonal antibody), and abatacept (fusion molecule of IgG-Fc and cytotoxic T lymphocyte antigen 4 that modulates CD28-mediated T-cell co-stimulation)[46]. Drug-related lung toxicity has been reported with almost all of the biologic agents; however there are some interesting aspects to consider[47]. It is noteworthy that while the anti-TNF agents have been shown in some instances to worsen ILD in patients with RA[48,49], rituximab has been proposed as a therapeutic option for patients with RA-ILD based on limited case series[50]. These observations suggest that anti-TNF drugs may be more effective in blocking the inflammatory process in synovial tissue where the innate response plays a key role[7], but less effective in the lung where the adaptive immune response likely promotes tissue injury/ILD[26].

Intriguingly, it has been demonstrated that methotrexate is more likely to cause ILD when used to treat RA than when used to treat other autoimmune diseases (illustrated by the relative lack of ILD development

Table 1. Comparison of idiopathic pulmonary fibrosis, rheumatoid arthritis-interstitial lung disease/usual interstitial pneumonia pattern, and rheumatoid arthritis-interstitial lung disease/non-usual interstitial pneumonia pattern

	IPF	RA-ILD UIP pattern	RA-ILD Non-UIP pattern
Age[7,12,17] (mean ± SD or median [range])	72 ± 9[12] 66 (55-75)[17]	69 ± 6[12] 61.9 ± 4.9[7]	65 ± 10[12] 58.5 ± 9.8[7]
Male gender[7,15]	62%	65-80%	0-48%
Smoking history[7,12,17]	Majority with history of cigarette smoking, particularly with > 20 pack-years[17] 76% Ever-smokers[12]	20% Current smokers/80% Past smokers[7] 55% Ever-smokers[12]	100% Current smokers[7] 77% Ever-smoker[12]
Exacerbations[11]	Reported	Reported	Not reported
Survival[12]	2.6 years	3.2 years	6.6 years

PF: idiopathic pulmonary fibrosis; RA: rheumatoid arthritis; ILD: interstitial lung disease; UIP: usual interstitial pneumonia.

in psoriatic patients treated with this drug)[51]. Therefore, it is possible that a proportion of cases reported as drug toxicity are in fact due to underlying RA. Future research should investigate if some drug-induced lung toxicity may actually be a result of unmasking underlying ILD rather than direct drug cytotoxicity.

Anti-fibrotics

Given the potential pathophysiological overlap of RA-UIP and IPF, it is also important to consider recent observations in the treatment of IPF and how they may influence the treatment of RA-UIP. For example, a recent multicenter randomized control trial of IPF patients conducted by the Idiopathic Pulmonary Fibrosis Network (IPFNet) found increased rates of death and hospitalization in the group receiving immunosuppression with prednisone, azathioprine, and N-acetylcysteine[52]. Despite some evidence showing that RA-ILD patients with the highest fibrosis scores on HRCT have a similarly worse response to anti-inflammatory therapies[53], clinical trials comparing response to therapy in UIP and non-UIP subsets are lacking in RA patients. Nevertheless, the experience with IPF suggests that we may need to reconsider the common approach to treatment of RA-ILD with prednisone and other immunomodulatory drugs. Because recent findings indicate that IPF is a disease of aberrant alveolar epithelial cell and fibroblast responses to repetitive injury[17], new anti-fibrotic therapeutic options such as pirfenidone and nintedanib have emerged for this disorder[54-56], providing at least some rationale for similar clinical trials in the subset of RA-ILD patients with a UIP pattern.

CONCLUSIONS

We have described two potential pathways that may explain the coexistence of RA and ILD, including the traditional paradigm that joint-initiated inflammation moves to the lungs as well as the more lung-centric model in which IPF-like pathology in the lungs triggers an immune response that promotes articular disease indicative of RA. Citrullination, a key process linked to the development of RA that has been shown in the lungs of both RA-ILD and IPF subjects, may be the mechanistic link between RA-ILD and IPF. This overlap is further supported by the phenotypic and biomolecular similarities between IPF and RA-ILD (mainly the UIP pattern). As such, treatment of both disorders is likely to evolve in parallel, potentially providing the rationale for combination anti-inflammatory and anti-fibrotic therapy that will be required to alter the relentless course of RA-ILD.

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