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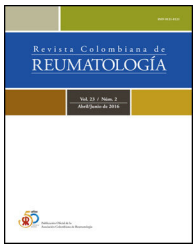

Review Article

The lung as a target and as an initiator of rheumatoid arthritis-associated immunity: Implications for interstitial lung disease

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ABSTRACT

Interstitial lung disease (ILD) is a serious extra-articular co-morbidity in rheumatoid arthritis (RA) patients and accounts for a substantial part of the increased mortality in RA. In this review, we describe how environmental and lifestyle factors interact with genetic variants in the HLA genetic locus in triggering RA-specific antibodies against post-translationally modified, mainly citrullinated proteins (ACPA), which are associated with an increased risk of ILD. The same environmental risk factors, i.e. exposure to noxious agents such as smoke to the lungs contribute additionally to the emergence of RA ILD as does long-lasting high disease activity and an additional ILD-specific genetic risk variant related to mucus formation (MUC5B). Options for prevention and therapy of RA ILD resulting from this so far incomplete knowledge of its pathophysiology are expanding. The most obvious option is to address modifiable environmental risk factors, such as smoking and exposure to other noxious agents affecting the lungs. The second option is to reduce the inflammatory activity of RA; here different anti-rheumatic therapies appear to have differential effects on ILD development. The third and novel option is to use anti-fibrotic therapy which may reduce the development of RA ILD but has not yet been shown to revert existing fibrosis. The main conclusion concerning the clinical handling of RA ILD is therefore an early awareness of the risk for RA ILD combined with active measures to reduce modifiable environmental/lifestyle factors and use optimal anti-rheumatic therapies for early and sustained reduction of disease activity. These actions should be combined with a preparedness to use anti-fibrotic therapy for patients at high risk for ILD despite previous risk reduction efforts.

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El pulmón como diana y como iniciador de la inmunidad asociada a la artritis reumatoide; implicaciones para la enfermedad pulmonar intersticial

Palabras clave:
Artritis reumatoide
Enfermedad pulmonar intersticial
Fibrosis pulmonar intersticial
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RESUMEN

La enfermedad pulmonar intersticial (EPI) es una comorbilidad extraarticular grave en pacientes con artritis reumatoide y representa una parte sustancial del aumento de la mortalidad en esta última. En esta revisión describimos cómo los factores ambientales y de estilo de vida interactúan con variantes genéticas en el locus genético HLA para desencadenar anticuerpos específicos de AR contra proteínas, principalmente citrulinadas, modificadas de forma postraduccional (Ac anti-PCC), que están asociadas con un mayor riesgo de EPI. Los mismos factores de riesgo ambientales, es decir, la exposición a agentes nocivos como el humo en los pulmones, contribuyen adicionalmente a la aparición de EPI con AR, al igual que la alta actividad prolongada de la enfermedad y una variante de riesgo genético adicional específica de la EPI relacionada con la formación de mucoso (MUC5B). Las opciones para la prevención y el tratamiento de la EPI con AR resultantes de este conocimiento hasta ahora incompleto de su fisiopatología se están ampliando: la opción más obvia es abordar los factores de riesgo ambientales modificables, como el tabaquismo y la exposición a otros agentes nocivos que afectan los pulmones. La segunda opción es reducir la actividad inflamatoria de la AR; aquí las diferentes terapias antirreumáticas parecen tener efectos diferenciales en el desarrollo de la EPI. La tercera y novedosa opción es utilizar una terapia antifibrótica que puede reducir el desarrollo de EPI con AR, pero aún no se ha demostrado que revierta la fibrosis existente. La conclusión principal sobre el manejo clínico de la EPI con AR es, en consecuencia, una conciencia temprana del riesgo de EPI con AR, combinada con medidas activas para reducir los factores ambientales y de estilo de vida modificables y utilizar terapias antirreumáticas óptimas para una reducción temprana y sostenida de la actividad de la enfermedad. Estas acciones deben combinarse con una preparación para usar la terapia antifibrótica en pacientes con alto riesgo de EPI, a pesar de los esfuerzos previos de reducción del riesgo.

Introduction

Lungs are essential immune organs where immune defense against the many hostile agents in the environment are handled, i.e. microbes as well as many hazardous environmental agents. Lungs are also the place in the body where environment meets immune system without other protective layers or environments such as the epidermis in the skin or the acidity in the stomach. The lungs are therefore vulnerable for many types of immune-dependent events, both concerning too limited immunity resulting in bacterial or viral airway infections or concerning too vigorous immune responses resulting in autoimmune disease. Research over recent years has demonstrated that the lungs are not only organs where immunity may result in local pulmonary inflammation and subsequent fibrosis but may also be sites where immunity is triggered that results in autoimmune disease elsewhere. A prime example of this is rheumatoid arthritis[1,2] which will be further discussed in this review, but similar relationships have been demonstrated for multiple sclerosis[3] and certain variants of myositis.[4]

In order to understand, prevent, and treat pulmonary inflammation as potential trigger of systemic inflammatory disease and pulmonary fibrosis as a co-morbidity to other inflammatory diseases such as RA, there is thus a need to understand the functional relationships between immunity in the lungs and immune-mediated disease affecting other organs such as the joints. This will be the perspective in this review.

Lung-associated morbidity and mortality in RA: take-homes from epidemiology

Lung complications, i.e. mainly interstitial pulmonary fibrosis resulting from chronic inflammation in lungs, are major reasons for increased mortality and long-term morbidity in RA, and in contrast to other co-morbidities such as infections and cardiovascular disease, the frequency of pulmonary complications have remained high in RA.[5,6] Similar to other extra-articular manifestations of RA, lung complications and interstitial pulmonary fibrosis are most common in RA patients who are positive for antibodies to citrullinated protein antigens (ACPA) and/or rheumatoid factors (RF).[7,8] These observations indicate that we should search at least part of the explanation to the occurrence of long-term lung inflammation and interstitial pulmonary fibrosis in factors that trigger

the production of these antibodies and are involved in their effector mechanisms.

Epidemiological studies on risk factors for development of RA have demonstrated that exposure of airways to noxious agents such as smoke, silica dust, and several other occupational airways are the major environmental risk factors for RA, and that these risk factors are mainly restricted to the ACPA and/or RF positive subset of disease.[9–13] Major gene–environment interactions were also demonstrated between these airway exposures and presence of the major genetic risk factors for RA, i.e. certain alleles within the MHC class II.[1,11,13] Taken together, these data suggested that lungs might be sites where these immune reactions are triggered in a MHC class II restricted way.[14,15]

The lung as a site for triggering of RA-associated immunity

Several molecular and cellular studies have further supported that immunity to citrullinated antigens might be triggered in the lungs and that such triggering may occur before onset of clinically defined arthritis. Such evidence comes from the demonstration of higher levels of ACPA in BAL fluids as compared to serum suggesting local production of the antibodies.[16] Similar results have come from sputum analysis if taken already before onset of arthritis.[17] A recent addition to these data, giving further evidence for the contribution of T cell-driven antibody production was the finding of ACPA-producing B cells/plasma cells obtained from bronchoalveolar lavage obtained both at early stages of RA and from ACPA-positive individuals at high risk for RA.[18] Notably, the Ig genes coding for these antibodies and derived from single ACPA-producing B cells/plasma cells were highly somatically mutated indicating local T cell help.[18] These and other cellular and molecular studies have substantiated the concept of a mucosal origin of at least part of the RA-associated autoantibodies and most probably also of the seropositive RA itself[1,2,14,15]; the concept has sometimes been denoted the "mucosal hypothesis" for an origin of seropositive RA.[2]

Inflammation in lungs as a consequence of RA-associated immunity

An obvious question is whether the lung immune systems is not only involved in triggering of RA-associated immunity but whether the same immunity is also involved in effector functions, i.e. contributing to pulmonary inflammation and subsequent fibrosis. Some evidence supports such a scenario: one is observations from HRCT investigations of lungs at early diagnosis of RA, where signs of inflammation were observed in the ACPA/RF positive subset of the disease as compared to control and ACPA/RF negative RA.[16] Additional studies have demonstrated the presence of certain lung abnormalities in ACPA and/or RF positive individuals already before onset of clinically diagnosed RA.[19] It is still not clear, however, how ACPA and RF and associated T cell immunity can activate pro-inflammatory events. Thus, some in vitro studies have demonstrated that ACPA may be involved both in activation of macrophages in a Fc receptor and often immune complex mediated way.[20] Pro-inflammatory in vitro effects of ACPA have also been demonstrated in neutrophil assays where some ACPA may recognized activated neutrophils and contribute to pro-inflammatory effects of NET-osis.[21] To which extent such immune-mediated effects from ACPA/RF contribute to the long- term inflammation and fibrosis is so far less known.

Long-term effects of lung inflammation in RA: development of interstitial lung disease

As stated in the introduction, chronic inflammation and subsequent fibrosis constitute major reasons for long-term morbidity and also mortality in RA, and lung involvement can be found in as many as 70% of RA patients, where RA interstitial lung disease (ILD) is the most common finding.[22] Approximately 2–10% of RA patients will develop symptomatic RA ILD during the course of the disease as seen in cohort-based studies and as many as 20% will develop asymptomatic disease.[23–27] The median survival in patients with RA ILD ranges between 3 and 10 years in historic cohorts.[25,28,29] RA ILD is strongly related to the presence of relatively well characterized risk factors. Such risk factors contributing to interstitial lung fibrosis in RA are presence of ACPA and/or RF, and exposure to noxious airways agent, and inflammatory activity over time.[23] The genetic risk factor most distinctly related to the fibrotic phenotype in RA ILD is an allelic form of the mucoprotein MUC5B.[30] This protein is secreted by submucosal mucinous gland cells and is involved in mucosal ciliary function and may also be involved in the regulation of local immune responses and alveolar regeneration following injury.[23] Genetics, in particular the RA-associated MHC class II alleles also contribute, mainly related to presence of ACPA.[1,31] Additional risk factors are long-standing disease and long-term inflammatory load as well as age and male gender.[32]

The subtype of ILD most common in RA is the "Usual Interstitial Pneumonia" (UIP).[32] The histopathological and radiological pattern of UIP is similar to findings in idiopathic pulmonary fibrosis (IPF) which is characterized by a progressive fibrosis of the lungs and is also associated with the highest mortality as compared to other ILD subtypes.[32,33] On imaging, typical features of UIP include basal predominant reticular opacities, traction bronchiectasis, and honeycombing. Non-specific interstitial pneumonia (NSIP) is the second most common HRCT pattern characterized by ground glass opacities without honeycombing.[34] The distinct disease phenotypes of RA ILD impact differently on clinical outcomes. When comparing patients with IPF to patients with RA ILD, Kim et al.[35] described a median survival of 3.2 years in RA ILD with UIP pattern, which was similar to those with IPF and significantly shorter than the median survival of 6.6 years in patients without UIP pattern (Fig. 1).

Mechanisms that are involved in the mediation of lung fibrosis from the presence of the described risk factors, are not yet well understood. Descriptive studies have shown increase of macrophage and fibroblast activation as well as increased presence of B and T cells at sites of chronic pulmonary

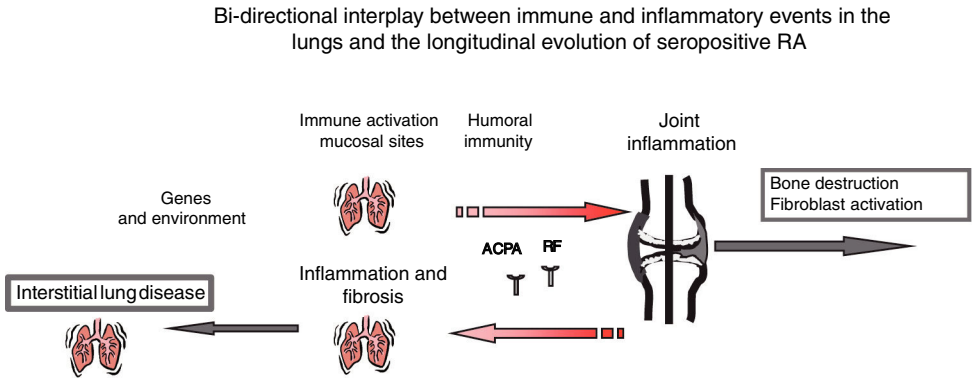

Fig. 1 – The figure illustrates the bi-directional interplay between immune and inflammatory events in the lungs and the longitudinal evolution of seropositive RA. Immunity triggered in the lungs is assumed to contribute to the development of seropositive RA and inflammation in RA is assumed to contribute to inflammation and fibrosis in the lungs.

inflammation and fibrosis in RA as compared to ILD in individuals without RA,[23] and it appears that fibrosis development occurs as a result of inflammation that may involve all these cells.[35] Notably, noxious agents like smoking being risk factors for RA as well as RA-ILD are able to cause increased production and activation of enzymes, peptidyl-arginine deiminases (PADs) that cause citrullination.[36] Citrullinated molecules in the lungs may then be involved both in triggering autoimmunity towards these post-translationally modified molecules in the context of certain genotypes[36–38] but may also directly be involved in activation of macrophages[20] and neutrophils via binding to pattern recognition molecules such as toll-like receptors,[21] often in immune-complex-dependent contexts – thereby potentially explaining an additive role of rheumatoid factors in addition to the ACPAs. Whether presence of ACPA and/or RF have independent effects on fibrosis development in addition to having effects on inflammation and macrophage activation is presently now known. It is feasible, however, that specific interactions may occur between T cells and fibroblasts in the lung tissue similar to what has recently been described for these cells in the synovial tissue in RA.[39] It is also possible that ACPA and ACPA-containing immune complexes are involved in the activation of neutrophils and subsequent NETosis, which may also be directly involved in activation and proliferation of fibroblasts and subsequent fibrosis.[40] The overall conclusion from what is specifically known about inflammation and fibrosis in the lung of RA patients, suggest that largely similar risk factors and mechanism as for seropositive RA are involved in the pathogenesis of RA ILD. Nevertheless, the relationship between development of RA-ILD and inflammation in RA is far from linear, and thus additional lung-specific mechanisms should therefore be possible to identify. Pathways associated with mutations in MUC5B represent one such option to follow.[30] Investigations of the lung microbiome, which is different in RA patients as compared to otherwise healthy individuals[41] indicate that that better understanding of the interplay between lung microbiome and lung inflammation and fibrosis may be another way forward.

Options for prevention and treatment of pulmonary morbidity in RA

As the major known risk factors and pathways involved in the development of RA-ILD are the same as those involved in the development and perpetuation of seropositive RA, the same options for prevention and treatment that exists for RA should be used to prevent and treat RA ILD. As extensively reviewed and discussed elsewhere,[42] such options involve very early diagnosis, rapid reduction of inflammation with appropriate pharmaceuticals as well as targeting of modifiable lifestyle and environmental factors, in particular those that include airway noxious substances.[10] The most important of these options remain smoking cessation, which has been shown to reduce risk for RA, reduce inflammation in ongoing RA and improve effects of anti-rheumatic treatments.[43,44]

The importance of detecting RA ILD in an early stage cannot be stressed enough due to its large impact on mortality and morbidity. A clinical obstacle is that most patients are asymptomatic and the prevalence of RA ILD is relatively low compared to ILD in other connective tissue diseases such as systemic sclerosis (SSc). HRCT is the preferred imaging technique for the diagnosis of ILD and in all patients with SSc, HRCT is used as the screening method according to guidelines for SSc ILD. In RA it is not justifiable to screen all patients with HRCT since most patients will show no signs of ILD. International guidelines for screening and monitoring RA ILD are lacking.[27] One group has recently suggested a screening algorithm that involves lung auscultation, history of respiratory symptoms and assessment of risk factors for ILD. They have also suggested a risk score to better identify the patients that benefit from HRCT.[45] Another group has suggested a slightly different algorithm for screening for RA ILD.[22] Further clinical studies are needed and ongoing for justification of these and other algorithms and risk scores. Ideally, the management of RA ILD should involve multidisciplinary collaboration, including rheumatologists, pulmonologists, radiologists, and pathologists.[25,33]

Prevention of RA-ILD should be considered already from the diagnosis of RA and involve careful monitoring of risk factors for RA ILD and efforts to reduce modifiable risk factors.

RA disease activity has been associated with an increased risk of developing RA-ILD[25,29,46] and therapies targeting RA can thus potentially reduce the risk to develop RA ILD. Post hoc analyses of existing trials and observational studies have demonstrated mixed results. Rituximab was associated with improved lung function[47] and better survival in RA ILD patients than other DMARDs.[48,49] Promising results have also been shown for Abatacept with respect to improvement of lung function in RA ILD,[50] but a large registry study could only demonstrate stabilization of lung function.[51] Tocilizumab showed no progression of ILD in three-fourth of the RA ILD cases in a small retrospective study but demonstrated a good safety profile.[52] TNF-inhibitors may even have a negative effect on RA ILD, however, this is still a matter of debate.[53] Evidence from randomized controlled trials targeting RA ILD is still lacking.

Recent progress in reducing fibrosis development in individuals with existing ILD has provided a completely novel way to reduced morbidity in ILD,[54,55] and this is described elsewhere in this theme issue of inflammatory diseases and ILD. The INBUILD study included patients with progressive fibrosing ILD and compared tyrosine kinase inhibitor nintedanib with placebo. In a subgroup analysis of 170 patients with connective tissue disease, 89 patients had RA ILD. There was a reduction in the rate of decline in FVC over 52 weeks by 60% in the RA ILD subgroup which were similar results as seen in the overall population. There was no difference in the RA ILD subgroup in patients who were or were not taking DMARDs or glucocorticoids in the nintedanib or placebo group.[56] In an animal model of RA ILD, nintedanib was demonstrated to reduce pulmonary collagen levels while reducing arthritis.[57] Another possible mechanism of action is the suppression of M2 macrophage polarization and hyperplasia of Type 2 alveolar epithelial cells.[58] One notable progress of large importance for everyday clinical practice in RA treatment is that methotrexate, the anchor drug in RA treatment is not associated with increased risk or worse prognosis of ILD, contrary to some earlier assumptions.[59–61] In fact, use of methotrexate was associated with improved survival in patients with acute exacerbation of RA ILD.[62] Thus, methotrexate remains the anchor drug for reduction of inflammation also in individuals at increased risk of ILD.

Options for the future are plentiful and involve both improved and earlier use of therapies used for RA today and more specific options, for example inhibition of PAD enzyme activity that has shown promise in experimental animal models.[63] Also enhanced B cell depletion, for example with CAR T cell therapy that has shown remarkable effects also on pulmonary symptoms in case reports of myositis with severe ILD[64,65] may be an option for patients with severe and treatment-resistant RA-ILD already today.

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Conflict of interest

None.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2023.09.006.

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