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REVIEW

Overview on the Link Between the Complement System and Auto-Immune Articular and Pulmonary Disease

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Abstract: Complement system (CS) dysregulation is a key factor in the pathogenesis of different autoimmune diseases playing a central role in many immune innate and adaptive processes. Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by ta breach of self-tolerance leading to a synovitis and extra-articular manifestations. The CS is activated in RA and seems not only to mediate direct tissue damage but also play a role in the initiation of RA pathogenetic mechanisms through interactions with citrullinated proteins. Interstitial lung disease (ILD) represents the most common extra-articular manifestation that can lead to progressive fibrosis. In this review, we focused on the evidence of CS dysregulation in RA and in ILD, and highlighted the role of the CS in both the innate and adaptive immune responses in the development of diseases, by using idiopathic pulmonary fibrosis as a model of lung disease. As a proof of concept, we dissected the evidence that several treatments used to treat RA and ILD such as glucocorticoids, pirfenidone, disease modifying antirheumatic drugs, targeted biologics such as tumor necrosis factor (TNF)-inhibitors, rituximab, tocilizumab, and nintedanib may act indirectly on the CS, suggesting that the CS might represent a potential therapeutic target in these complex diseases.

Keywords: complement system, rheumatoid arthritis, interstitial lung disease, target therapies

Introduction

The complement system (CS) is a component of the innate immune system and consists of several proteins that play a pivotal role in many protective immune processes.[1] The primary aim of the CS is to protect the host against microbes, repair injuries, and contribute to the elimination of cellular debris or immune complexes (IC). Moreover, it has been described that CS components have immunoregulatory functions too through the modulation of both adaptive and innate immune responses.[2] The detection of C3 receptors on lymphocytes provides the first evidence of CS participation in adaptive immunity.[3] In the following years, it was documented that the CS is also crucial for the regulation of autoreactive B cells as well as for the development of T cell immunity and natural antibodies.[4] Three different pathways which share a common terminal pathway activate the CS (Figure 1). C1q, C1r and C1s components are part of the classical pathway (CP) of the complement, while the lectin pathway (LP) includes complement components mannan-binding lectin (MBL), ficolins (FCNs) and collectins (CLs), along with three MBL-associated serum proteases (MASPs). The C3 convertase, made up of C2 and C4 components, is shared by both CP and LP. The alternative pathway (AP) includes C3, factor B (FB), factor D (FD) and Properdin (P). The C5 and the complex C5b-C9, also known as the membrane attack complex (MAC), represent the terminal pathway.[5] Among CS components, C3a, C4a and C5a also known as anaphylatoxins have pro-inflammatory functions even at a very low concentration.[1] They also drive other processes such as immune cell modulation and chemotaxis, cell survival, tissue repair and regeneration, vasodilatation, and smooth muscle contraction. The formation of IC represents the principal way of activating the CP of the CS.

CS dysfunctions in terms of upregulation, downregulation, or dysregulation can create an imbalance of both host defence and inflammatory response leading to autoimmunity.[6,7] As well described by evidence from the literature, the CS

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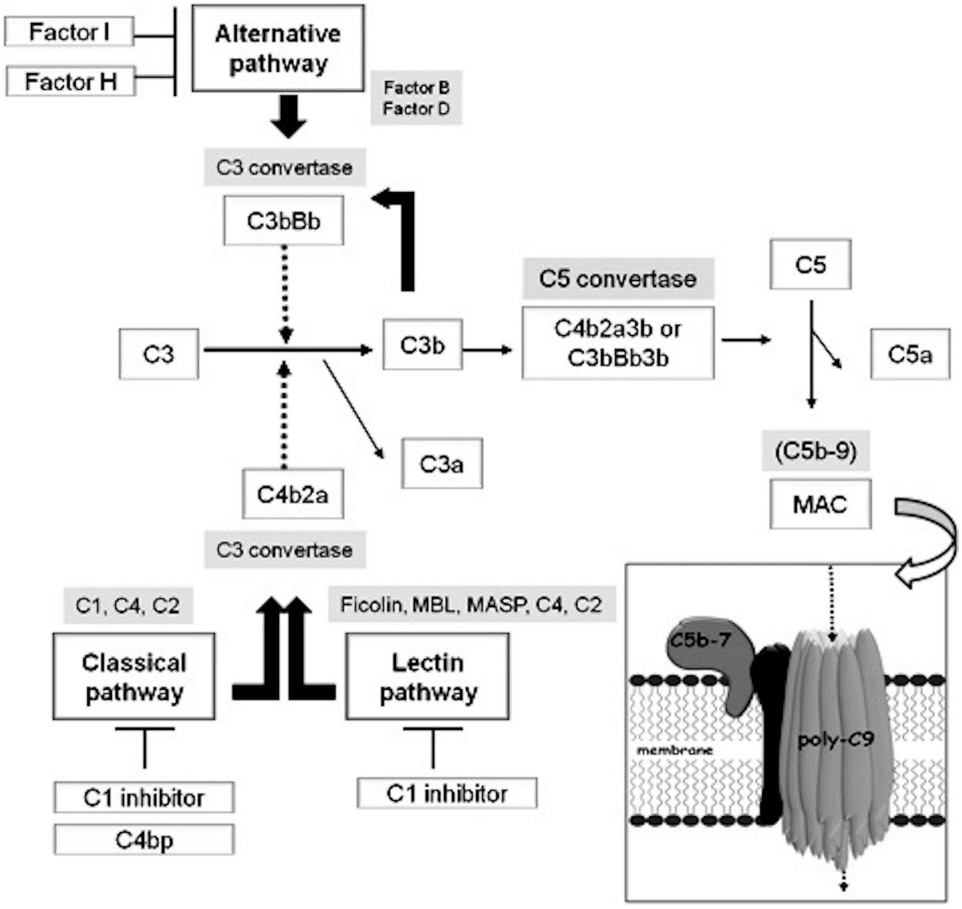

Figure 1 Activation of the complement system. Activation of the complement system (CS) occurs through three possible pathways: the classical, the alternative and the lectin pathway. All the pathways converge at the activation of C3 and C5 and lead to the formation of the membrane attack complex (MAC). Activation of the cascades is controlled by several regulatory proteins. C1 inhibitor, C4 binding protein, Factor I and Factor H represent the most important regulators and act at different points of the pathways.

dramatically acts in the pathogenesis of several systemic autoimmune diseases including rheumatoid arthritis (RA).[1] In this review, we aimed at focusing on the role of the CS in the pathogenesis of different autoimmune diseases with a particular focus on a specific extra-articular manifestation of RA, the RA-associated interstitial lung disease (ILD). With this purpose, we reviewed the main points of the CS-mediated mechanisms in the pathogenesis of autoimmune diseases such as Systemic Lupus Erythematosus (SLE), Anti-phospholipid Syndrome (APS), Systemic Sclerosis (SSc), Sjögren's Syndrome (SjS), vasculitides, and Psoriatic Arthritis (PsA). We focused on the pathogenic role of CS dysregulation in parenchymal lung disorders of both known and unknown causes that can be classified into ILD and, thus, the interplay between CS, inflammation, and autoimmunity in ILD. Therefore, the intriguing challenge of modulating CS as a treatment strategy for ILD has been discussed.

What is so special about complement in RA-ILD? What about other innate pathways? Is there evidence of immune complex deposition in the lung to suggest what activates complement?

CS Dysregulation in Autoimmune Diseases and RA

As is well documented, the abnormal CS activity has a pathogenic role in several autoimmune diseases, mainly including RA and SLE, APS, SSc, SjS, vasculitides and PsA.[4] The best "model" of the pathogenetic role of the CS in autoimmune diseases is in SLE where it seems to exert both a protective and a pathogenetic role. Indeed, the deficiency of early components C1q, C1r, C1s, C4, and C2 results in severe forms of SLE with an early onset.[7] Moreover, anti-C1q autoantibodies can be found in 30–60% of SLE patients and their presence correlates with renal involvement and with the

severity of lupus nephritis.[8–10] In patients with APS, increasing data indicate that the CS is highly activated and acts as a cofactor in the pathogenesis of clinical manifestations promoting coagulation and mediating pregnancy morbidity. For instance, catastrophic APS seems to be associated with mutations in CS regulatory genes serving as a second hit in the pathogenesis.[11,12] In SSc, the CS is locally activated in the skin of patients at immunohistochemistry level where complement C5b-9 and C5aR could be detected in involved skin samples from SSc patients, with a perivascular localization.[13] Complement deposition has also been detected in renal biopsies from SSc patients with a peritubular capillary deposition of C4d and C1q and glomerular deposits of C3b.[14–16] Another disease where hypocomplementemia has been observed is the SjS ranging between 2−25% for C3, 10–39.5% for C4 and 14–15% for CH50.[17] Heterozygous C2 deficiency in combination with a low copy number of C4a substantially increases the risk of primary SjS and this genetic combination is associated with low age at diagnosis.[18] The apparent interaction between C4a copy number and heterozygous C2 deficiency further strengthens the pivotal role of the classical complement pathway in the pathogenesis of SjS.[18] In small-medium-vessel vasculitides, the role of the CS can be different in accordance with the specific diseases. In general, the pathogenesis of vasculitides is related to the presence of leukocytes in the vessels and the formation of IC with their local deposition; therefore, CS is activated and mediates directly the damage of vessel structures.[2]

Differently from autoimmune diseases, serum C3 and C4 levels have been reported to be higher in PsA patients compared with healthy controls.[19] Likewise, complement activation has been detected at joint level where C3 levels in the synovial fluid from PsA patients were found to be higher compared with those from RA patients and osteoarthritis.[20]

The CS seems to play a role both in the initiation and evolution of RA, in particular in tissue damage in RA through interactions with citrullinated proteins from synovial neutrophils.[1,21] Authors have shown that antibodies against citrullinated proteins (ACPA) activate the CS in vitro via both the classical (CP) and the alternative (AP) but not through the lectin pathway (LP): ACPA from all enrolled subjects activated the CS suggesting that complement activation could play a key role in ACPA-positive RA patients.[22]

Autoantibodies in RA patients target antigens in cartilage and the synovium, contributing to the formation of different types of circulating ICs (Circulating immune complexes (CICs), small, intermediate and large).[23] Intermediate CICs typically cause the most damage as they get trapped in the tissues or in the joints.[1] Crucially, these CICs can activate complement, which give rise to chronic destruction of the joint, via the initiation of innate as well as adaptive immune responses.[23]

The possible participation of C1s in cartilage remodelling is supported by a few studies, one of them demonstrating that C1s is intensely immunostained in the hypertrophic chondrocytes, but not in normal articular chondrocytes.[24] The authors described the evidence for a negative C1 staining in normal articular cartilage biopsies together with its positivity in all degenerating cartilage biopsies from analyzed RA samples.[25] Furthermore, IgM rheumatoid factor (RF) and IgA RF amplify the CS activation mediated by ACPA-containing IC.[26] ACPA-IC, incorporating IgM or IgA RF may participate in the triggering of the inflammation promoting activation of complement cascades in RA joints. Both ACPA and RF have been shown to have a role in systemic bone loss in early RA patients due to the presence of citrullinated antigens on the surface of osteoclastic cells, making these cells the main targets of circulating ACPA leading to the induction of osteoclastogenesis.[27,28]

Although increased CS activation is potentially related to the occurrence and/or exacerbation of inflammation in RA, a status of complement deficiency may predispose to RA. The association between CS defects and RA has been reported for deficiencies of several complement components, including C1r and C1s, C1q, C4, C7, C9 and factor I.[29–31] Association between CS activation and disease activity in RA has been documented in the literature. According to Wouters et al, a correlation between plasma levels of C1q-C4 complexes and disease activity score was shown in RA patients.[32] Makinde et al, have shown that the ratios C3d/C3 and C4d/C4 may provide a sensitive assessment of disease activity in RA.[33] Doherty et al reported raised synovial C3d levels in active compared with inactive RA.[34] Moreover, Nguyen et al demonstrated that antirheumatic therapy is associated with reduced complement activation in RA.[35]

However, other potential triggers for CS activation in RA should be considered such as C-reactive protein (CRP).[36–38] In 2001, Moleenar et al demonstrated that plasma levels of activated CS components and CRP–complement complexes are increased in most patients with RA and correlated with disease activity, pointing to the role of CRP-mediated complement activation in RA pathogenesis.[39]

Lung Involvement in RA

Pulmonary nodules, pleural effusion, bronchiectasis, and ILD are the most common extra-articular manifestations of respiratory disorders that are RA-correlated.[40,41] ILD is the most common among these, representing the second reason of mortality in RA patients due to progressive fibrosis of the lung parenchyma.[42] Moreover, RA patients can develop lung complications due to immunosuppressive therapy, such as drug toxicity and/or infections.[43,44]

The epidemiology of lung involvement in RA has been difficult to define over time in terms of morbidity and symptoms: according to some authors, radiological evidence of the disease has been observed from 19–67% of RA patients, clinical prevalence is estimated to be 3–5% while some studies report an elevated post mortem incidence of RA-ILD.[45,46]

Recent evidence defines RA-ILD as the second leading cause of death in RA patients, overcoming the risk of death from malignancy.[47] Though RA is itself a known risk factor for ILD, only a subset of patients develops the lung disease.[42,48] Sex and/or age, environmental agents, serological variables, clinical features, genetic background, and drug-related pathways have been reported as potential risk factors by several authors[49–51] but an international consensus has not yet been reached.[52] According to radiological data in conventional chest radiography studies, the prevalence of ILD in RA patients (RA-ILD) varies from 1–6%, while from 5–67.3% in high-resolution computed tomography (HRCT) studies.[53,54]

HRCT has emerged as an important tool for the detection of ILD in RA patients[55,56]: the most common HRCT pattern in RA-ILD is the Usual Interstitial Pneumonia (UIP) while Nonspecific Interstitial Pneumonia (NSIP) is described less frequently.[57,58] RA-associated UIP (RA-UIP) is difficult to differ from the idiopathic one (e.g. idiopathic pulmonary fibrosis [IPF]) on HRCT scans. The crucial features include the peripheral- and basal-predominant reticulation and the honeycombing with or without bronchiectasis. In a recent study, investigators found that HRCT-UIP significantly correlates with histological-UIP in patients with RA-ILD, potentially obviating the need for a lung biopsy in individuals showing specific HRCT finding.[59] Limited data suggest the prognostic utility of the HRCT in RA-ILD: the HRCT-UIP appears to predict a worse survival compared with the other ILD patterns including NSIP in RA patients.[60,61] In addition, the occurrence of traction bronchiectasis and honeycombing, documented by HRCT, seems to confer additional survival information in RA-patients.[57] In accordance with the most recent American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) guidelines, three defined HRCT patterns of fibrosing lung disease can be described in the setting of an IPF: definite UIP, possible UIP, and inconsistent with UIP. Definite UIP and possible UIP differ for the presence of honeycombing.[62] However, studies from selected IPF patients have documented no significant difference in survival according to the type of HRCT findings.[63–65] Broader studies on idiopathic interstitial pneumonias (IIPs) reported that a definite UIP on HRCT scans is able to predict a worse survival with the respect to an indeterminate UIP.[66] Nevertheless, the prognostic value of HRCT-UIP classifications has not been definitely analysed in RA-ILD patients. As described in the literature, the impairment in respiratory functions and/or the worsening in general respiratory functions over time have been proposed as poor prognostic factors in connective tissue disease (CTD)-ILD. In addition, patients showing an UIP pattern on HRCT were also suggested to have a worse prognosis than those with a different HRCT pattern regardless of the specific disease diagnosis.[60,67,68]

CS Dysregulation in ILD

As described, ILD comprises several types of parenchymal lung disorders that can be categorized into four subtypes: ILDs with a known association (e.g., treatments, CTD), granulomatous (e.g., sarcoidosis), idiopathic interstitial pneumonias (IIPs) and rare ILDs.[69] Despite the different aetiologies, some ILDs share common pathophysiological aspects: the proliferation of fibroblasts and myofibroblasts, the accumulation in the extracellular matrix, and the consequent interstitial fibrosis.[70] The CS may act with a functional duality at the lung level, in host defence and lung injury.[71,72] As known, the CS plays a key role in the innate immune response to pathogens at the lung level.[73] Pathogens can escape the complement-mediated eradication by inhibiting CP or AP genes.[74] Interestingly, recent evidence documents a localized production of complement components in peripheral tissues and mucosal sides including the lung.[75–77] Recently, authors documented that complement-related genes might contribute to the pro-fibrotic inflammatory lung responses in the

setting of autoimmune arthritis and could be both targeted and predictive for disease burden (Figure 2).[78] Data described C3 in mesothelial cells and fibroblasts in both murine and human lungs as well as in goblet, mucous and alveolar epithelial type (AT)2 cells in humans; the component C5 was mainly documented in AT2 cells.[71] In addition, human Properdin (CFP) expression has been reported in epithelial cells and alveolar macrophages.[73,79] The constitutive expression of C5 has been described to affect the functions of immunoregulation and repair of AT2 cells during infection and lung injury.[80]

Gu et al have shown that patients with IPF showed greater levels of local and systemic C3a and C5a.[81] C3aR is expressed ubiquitously, including in the lung.[82] Interestingly, mechanisms of cellular damage mediated by C3a and C5a have been observed in acute lung injury and the highly fatal acute respiratory distress syndrome.[72,83–85] Among the CS components, C1q can interact with fibronectin and lead the fibroblasts' adhesion to IC with resulting collagen synthesis.[86] A potential role of the CS in lung fibrosis was previously suggested by the bleomycin-induced fibrosis in mice without the specific identification of individual proteins involved in the establishment of fibrosis.[87] Authors indicated a crucial role for C5 which was related with the expression of TGF-β1 and matrix metalloproteinase-3, key profibrotic mediators in murine models.[88] C5-deficient mice showed elevated inflammatory markers compared with C5-sufficient mice during acute bleomycin-induced lung injury suggesting the anti-inflammatory role for C5; in contrast, during chronic stages of bleomycin-induced injury, C5 had a potential profibrotic role.[88] Studies described in both the sera and the bronchoalveolar fluid from IPF patients increased levels of IC as well as CS fragments supporting a relevant activation of CS pathways and its potential association with pulmonary fibrosis in IPF.[81,89–91] An impaired clearance of apoptotic debris might promote an inflammatory status: the epithelial injuries are able to trigger and enhance the mesenchymal activation and, thus, might affect the alveolar epithelial mechanisms of repair.[92] In the past years, authors reported that IC could activate the CS in IPF.[89] However, more recent evidence described the presence of CS components in patients with IPF and documented that products by the AP were clinically significant as indicators of disease severity. An increased risk of lung diseases has been associated with low serum levels of mannose- binding lectin (MBL).[93] MBL deficiency is also

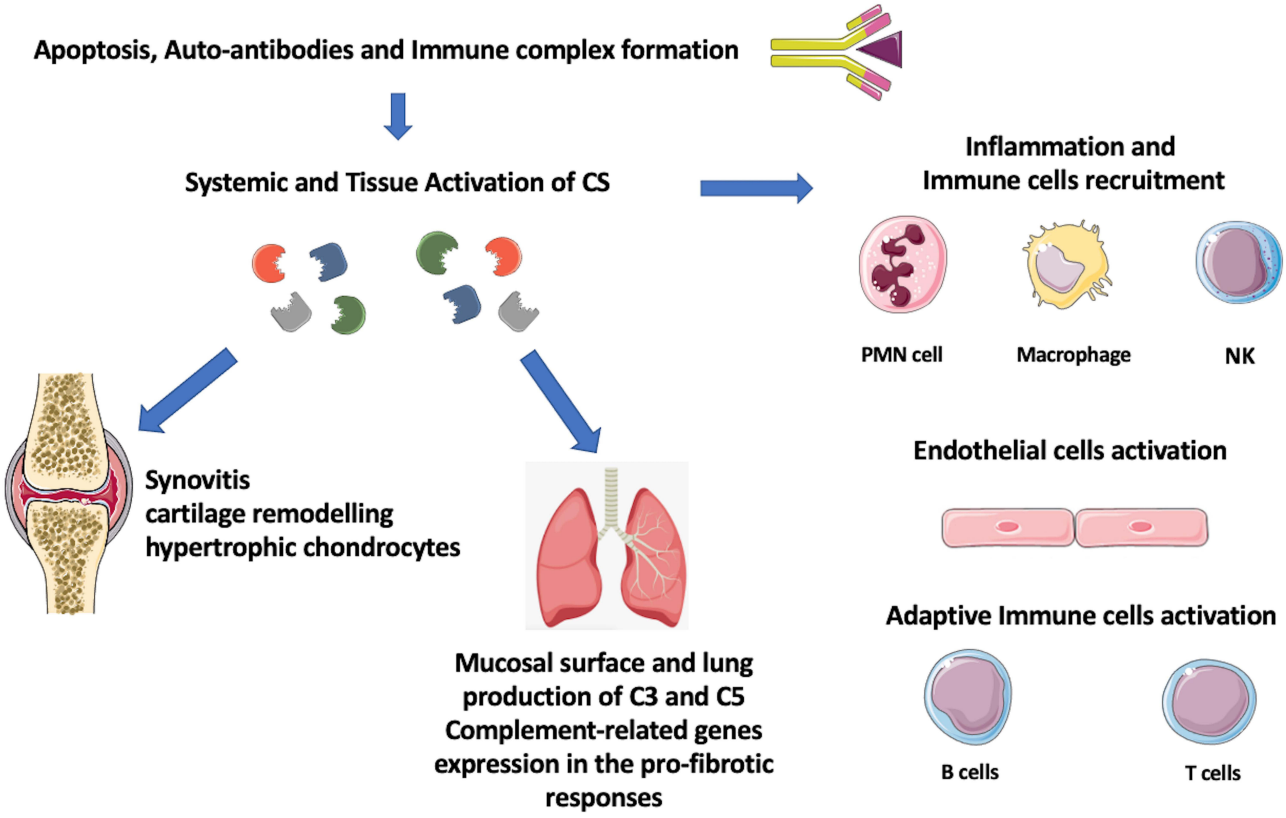

Figure 2 Link between autoimmunity, inflammation and tissue injury and complement system (CS) activation in rheumatoid arthritis and interstitial lung disease.

associated with CTDs (SLE, cystic fibrosis, and primary immunodeficiencies).[94] In addition, a case control study described the occurrence of MBL deficiency in early onset IPF and familial cases.[95] The possible involvement of the LP in the pathogenesis of ILD has been suggested by evidence reporting the significantly higher level of CS products in the bronchoalveolar lavage fluid (BALF) in a cohort of patients with ILD compared with controls.[96] Authors hypothesized that, in SSc-ILD, the recurrent injuries, which recognized a lectin-mediated ischemic-reperfusion mechanism, might cause an endothelial dysfunction potentially leading to endothelial and epithelial apoptosis and the fibrotic response in the lung.[97] In a recent study from Pellicano et al the total complement activity was associated with ILD, assessed by both diffusing capacity for carbon monoxide (DLco) and HRCT, suggesting its pathogenetic role in ILD.[98] The potential link between innate immune response, including CS, and ILD has been thus proposed and documented. In this context, the CS appears to accelerate the pathogenesis of IPF.[99,100]

May the CS be a Treatment Target in RA?

Genome-wide studies in RA patients have shown the occurrence of specific CS polymorphisms, including C5 and C3 gene polymorphisms that resulted in an efficient cleavage into the proinflammatory anaphylatoxins.[101,102] Recently, a positive correlation between disease activity [by disease activity score (DAS)-28] and specific complement mRNA expression levels was demonstrated in the synovium from patients with early RA.[103] Elevated levels of CS activation fragments have been detected in blood, synovial fluid, and tissue from RA patients supporting the possible inadequate control of CS activation in disease pathogenesis.[1,104–107] Murine models of arthritis such as collagen-induced arthritis demonstrated that a compromised CS may be associated with a less severe disease.[108,109] Likewise, in K/BxN mouse model of arthritis, mediated by T-cell dependent autoantibody response to glucose-6-phosphate isomerase (GPI), GPI deposits localized in the joints with IgG and C3 complement.[110,111] Circulating C3 is necessary and sufficient for the induction of arthritis in this model.[111] A trigger of complement activation in humans could be autoantibodies such as RF and ACPA that interact locally in the joint with antigens, resulting in IC that triggers classical local CS activation.[107] ACPA were demonstrated to activate complement in a dose-dependent manner via the CP and also the AP.[112] Moreover, RA patients have been reported to have higher concentrations of terminal complement complex (TCC) in the blood than negative controls.[5,113] Indeed, synovial tissue seems a complement factor rich environment, since different cells such as synovial fibroblasts, macrophages, and endothelial cells produce complement factors locally in the joints.[104,114,115] Recent findings highlight that, in inflammatory tissues, synovial fibroblasts express high amounts of C3 and C3a receptor which drive metabolic reprogramming of fibroblasts, and shift to a pro-inflammatory state.[116] In arthritis, tissue priming may provide an explanation for relapses and for the evolution from self-limited arthritis to chronic inflammation. Furthermore, complement C3 and C5 and its receptors are produced intracellularly in T cells and in turn activate the cells in an autocrine manner.[117–120]

Upregulation of complement synovial tissue and tendons has also been previously associated with exacerbation of arthritis caused by mechanical stress.[121,122] The increased observed plasma levels of C3 and C4 in active RA patients may reflect increased hepatic synthesis induced by interleukin (IL)-6, as for other acute phase reactants.[32] Indeed, local complement activation within affected joints could be triggered by extracellular DNA, dead cells and CRP.[112] Several conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological (b)DMARDs that are used in RA treatment have been demonstrated to affect CS. Few studies suggested direct effects of methotrexate (MTX) on CS.[123] The MTX, via its metabolite adenosine, exerts an inhibitory effect on production of Tumor necrosis factor (TNF) and promotes the IL-6 production, thus potentially attenuating the complement cascade.[124] MTX exposure has been associated with an elevated expression of complement genes, and increased C3 and C5 in liver of patients with inflammatory arthritis.[125] The effects of MTX and TNF inhibitors (TNFi), such as adalimumab, etanercept or infliximab, on CS activation have been assessed recently using soluble TCC levels in RA.[35] Patients with active RA had elevated baseline TCC levels, indicating an increased complement activation and TCC decreased quickly with MTX, while a sustained reduction was observed with combination treatment of adalimumab, etanercept or infliximab plus MTX during a 6-month follow-up period. Other studies previously showed an effect of adalimumab and etanercept on CS with a significant reduction of C3 and C4 levels during treatment while complement activity correlated with RF in a cohort of RA patients.[126–128] Higher levels of complement C3 were associated with a worse EULAR response and normalization of

C3 complement levels was associated with improvement of disease activity in RA patients treated with adalimumab or etanercept.[126] Similar results were obtained in PsA patients treated with TNFi agents suggesting that elevated C3 and C4 levels could be considered a negative predictive factor of response influencing the outcome of TNFi therapy in treated patients.[19,129] Elevated complement C3 levels may reflect the presence of the inflammatory process contributing to the acute phase response. High plasma amounts of component C3 could be due to spill over from the joints or to an abnormal production. The mechanisms underlining complement activation in response to TNFi may have several explanations: complement components are produced by hepatocytes, and hepatic synthesis may be upregulated in response to TNF.[130,131] TNFi might revert the increased soluble complement products. Second, antirheumatic therapy can reduce CRP levels which is able to interact with CS with subsequent activation of the classical complement cascade.[39,132] Third, most antirheumatic therapies exert their effect partly by inhibition of IL-6, which in turn causes a downregulation of CRP synthesis by hepatocytes and subsequently reduced activation of the CP.[133] Of note, also tocilizumab (TCZ), an anti-IL6 receptor monoclonal antibody, has been described to be able to reduce levels of CRP, C3 and C4 as early as 4 weeks after the first treatment in a cohort of RA patients.[134] This effect has been demonstrated with other biological disease-modifying anti-rheumatic drug (**bDMARD**) such as rituximab (RTX), an anti-CD20 monoclonal antibody used to treat RA: RTX was found to affect complement C3 levels in RA patients reinforcing the concept to represent a potential useful serological marker of disease activity and response to treatment.[135] However, evidence on potential effects of both TCZ and RTX via CS describe mainly indirect mechanisms.[134,135]

A direct proof of efficacy of specific complement-targeted therapy in human arthritis is still lacking.[1,112] In animal models, the inhibition of C5, administered systemically or at intra-articular level, was associated with good results.[112,136] The C5a-C5aR axis may be a relevant target for treatment of arthritis.[137] However, both the inhibitory anti-C5 antibody eculizumab and the oral C5aR inhibitor PMX-53 resulted unsuccessful in clinical trials for RA treatment.[138,139] Eculizumab, the first approved CS antagonist, is an IgG-kappa humanized monoclonal antibody, that binds C5 protein inhibiting its cleavage, thus preventing the generation of active C5a and C5b, and the C5b-C9. It has been developed to treat RA and SLE and obtained approval for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).[140] Of note, both the eculizumab and the oral C5aR inhibitor act downstream of C3 cleavage rather than targeting intracellular autocrine C3 function. Treatment with PMX-53 did not result in a reduction of synovial inflammation nor in a clinical improvement in RA patients.[138] Therefore, an intriguing strategy might be to target C3- or C3a preventing flares due to its effect on tissue priming rather than to decrease inflammatory response interfering with cytokines and anaphylatoxins.

May the CS be a Treatment Target in ILD?

The current knowledge on the role of CS dysregulation in the pathogenesis of ILD remains not completely defined. Furthermore, direct evidence of its role in the pathogenesis of RA-ILD is missing. However, different treatments for patients with ILD, including RA-ILD, might indirectly act on CS-mediated inflammation (Table 1).[112]

Glucocorticoids (GCs) are anti-inflammatory agents used to treat ILD. The mechanism of their action is complex and includes the regulation of gene expression, from signal transduction to post-translational variations.[160,161] GCs induce genes of anti-inflammatory factors thus raising innate immunity actions.[162] GCs are powerful inhibitors of key pro-inflammatory genes including ILs and chemokines as well as granulocyte/macrophage colony stimulating factor (GM-CSF) and TNF-α.[141] As documented, neutrophils have a crucial role in the acute phase of inflammation: however, aggregated neutrophils could promote fibrosis in lung damage.[142] GCs inhibit complement-induced granulocyte aggregation.[143] However, the potential prognostic value of the neutrophilic inflammation in IPF lungs remains unclear. C5a is a chemoattractant for neutrophils, and the link C5a-C5aR/CD88 activates neutrophils;[149] in addition, the feedback mechanism between activation of neutrophils and the CS participates in the progress of tissue damage in autoimmune and IC diseases characterized “as having” pulmonary involvement.[163]

In 2014, pirfenidone (PFD) and nintedanib were approved by the US Food and Drug Administration and recommended for the treatment of IPF, for their effectiveness in reducing disease progression.[164] PFD is a non-peptide synthetic chemical that inhibits the production of cytokines including TGF-β1, TNF-α, and platelet-derived growth factor (PDGF).[144,145] It thus can slow or inhibit the progressive fibrosis.[165] Nintedanib inhibits in vitro a distinctive spectrum of kinases at pharmacologically significant concentrations that comprises the vascular endothelial growth factor

Table 1 Effect of Therapeutic Agents in Rheumatoid Arthritis and Interstitial Lung Disease

Compound	Mechanism of Action/ Targets	Effects on ILD	Effects on CS	References
GCs	Anti-inflammatory	Inhibits GM-CSF and fibrosis induced by neutrophils.	Inhibits CS-induced granulocyte aggregation.	[141–143]
Pirfenidone	TGF-β and PDGF	Acts altering the TGF-β pathway reducing fibroblast proliferation.	Indirectly acts on CS-mediated inflammation	[144–146]
Nintedanib	PDGFR, FGFR and VEGFR	Interferes with processes active in fibrosis.	Indirectly acts on CS-mediated inflammation	[146–148]
Eculizumab	C5	Inhibits C5a, a powerful chemoattractant for neutrophils.	Prevents the generation of C5a by inhibiting C5 cleavage.	[107,149]
Rituximab	Anti-CD20	Acts on lymphocytes CD20+ pulmonary infiltrates.	Reduces C3 levels	[135,150]
Tocilizumab	Interleukin-6 receptor (IL-6R)	Reduce the expression of profibrotic M2 macrophage-associated genes.	Reduces C3/C4 levels	[134,151,152]
GSH	OX-REDOX	Acts by S-glutathionylation, inflammation and cell death, involved in lung fibrosis.	Inhibits the CS-mediated damage.	[153–157]
Pentraxin	Clearance of injured tissue components and regulates related inflammation.	Inhibits differentiation of monocytes into macrophages and fibrocytes with pro-inflammatory and pro-fibrotic properties.	Inhibits C3b to prevent excessive damage.	[158,159]

Abbreviations: ILD, interstitial lung disease; CS, complement system; GCs, glucocorticoids; GM-CSF, granulocyte-macrophage colony-stimulating factor; TGF-β, transforming growth factor beta; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; C5a, Complement 5 anaphylatoxin; IL-6R, Interleukin-6 receptor; M2, macrophages 2; GSH, Glutathione; OX-REDOX, oxidation-reduction.

receptor (VEGFR) subtypes, the fibroblast growth factor receptor (FGFR) types 1, 2 and 3, and PDGF receptors (R)-α and -β with a key antifibrotic effect.[147,148] Evidence of a direct CS regulation by PFD is not yet described as well as for nintedanib. However, as documented, PDGFs activate CS through both the CP and AP and, through CS, increase the levels of several mediators, trigger polarization of macrophages, thereby promoting mechanisms of pathological neovascularization and their functions of tissue-regeneration together with anti-/pro-fibrotic effects.[146] PDGFs are, thus, involved in the advancement of inflammation and increase the migration of mononuclear cells in tissue damage.[166] It can be hypothesized that by modulating PDGFs, both PFD and nintedanib can be able to indirectly act on CS-mediated inflammatory pathways. In addition, nintedanib inhibits profibrotic mechanisms also acting on VEGFR subtypes.[148,167] The interaction between the CS and VEGF is suggested by its role in neovascular age-related macular degeneration (nAMD) mainly relying on the evidence of both the uncontrolled activation of CS and the upregulation of VEGF in nAMD.[168] However, recent findings suggest an association between polymorphisms in genes related to the CS with the severity of macular lesions as well as with the response to antiangiogenic therapy in patients with nAMD.[169] In IPF, pulmonary endothelial cells might be the source of pulmonary fibroblasts through endothelial mesenchymal transition (EndoMT), which participates in pulmonary fibrosis.[170] Interestingly, both in vivo and in vitro studies documented that nintedanib inhibits EndoMT, probably by modulating the VEGF signaling pathway.[170]

In autoimmune associated-ILD, as reported by data from the literature, the lung progression during treatment with Conventional synthetic (cs)DMARDs represents the most frequent rationale for starting targeted therapies: RTX seems to be the most available option together with nintedanib and TCZ, and the combination therapy represents the most frequent therapeutic scheme for nintedanib and RTX.[171] In addition, RTX therapy appears to be effective in stabilising lung function deterioration and ILD involvement in RA patients with UIP.[172] In patients with CTD-NSIP, the reasons for RTX use rely on the evidence of immunoglobulins, complement depots, and lymphocytes CD20+ infiltrates in the pulmonary

capillaries in patients with NSIP.[150] The antitumor molecular mechanisms of anti-CD20 antibodies include a potent complement activation: nevertheless, complement depletion significantly reduced the antitumor activity of RTX.[173] However, RTX activates the CS in vitro, and there is an ongoing debate on the exact role of this mechanism of action in vivo.[174] Results of randomized controlled and clinical studies also support the use of TCZ for SSc-ILD.[171] Specifically, TCZ is able to reduce C3 and C4 serum levels during treatment by inhibiting IL-6-mediated signal transduction.[134] As reported, IL-6 dysregulated expression is implicated in the pathogenesis of interstitial pneumonias and IPF.[175,176] In addition, decreased complement levels have been associated with the TCZ treatment longevity without specific adverse outcomes.[151]

Khanna et al in a phase 3 trial, have shown that TCZ is able to preserve lung function through the reduction in expression of genes associated to profibrotic M2 macrophages, thus supporting its antifibrotic effects.[152] Furthermore, ongoing studies are designed to compare efficacy and safety of TCZ versus regular treatments, in patients with severe rapidly progressive-ILD secondary to systemic diseases.[177] As described, IL-6 activates the JAK/STAT signalling pathway, initiating the cellular changes observed in ILDs.[178] The JAK/STAT axis is also activated by growth factors such as TGF-β1, FGF, PDGF, and VEGF: in this context, TCZ by acting on IL-6/JAK/STAT signalling could also represent an indirect JAK/STAT inhibitor.[179]

To date, several trials are ongoing on different treatment strategies in IPF. Abnormalities in redox homeostasis have been described in both patients with IPF and animal models of fibrosis.[180] A complex network includes redox-dependent processes including S-glutathionylation, inflammation, and cell death, all mechanisms involved in lung fibrosis.[154] Among novel strategies under investigation in IPF, antioxidant agents have been proposed: they may act on the CS because of the known effects of CS on intracellular glutathione (GSH) and its disulphide forms leading to oxidative damage.[164] Authors documented that GSH can inhibit the CS and suggested the possibility for designing additional therapeutic interventions modulating GSH metabolism in order to inhibit CS-mediated damage in autoimmune diseases.[155,156]

Pentraxins are soluble receptors of innate immunity and include sensing danger molecules, protect against infections, regulate inflammation and the clearance of injured tissue components.[158,181] They have a dual link with the CS. Initially, the pentraxins activate CS by binding C1q. Therefore, pentraxins inhibit the CS at the C3b stage to avoid excessive damage. However, the emerging inflammation needs to be limited to the target area.[158,159] A completed phase 2 trial has recently shown a significant reduction in modifications of respiratory volumes and 6-min walk distance from baseline in patients with ILD.[182]

Animal models described potential beneficial effects of CS inhibition in bleomycin-induced lung fibrosis: the blockade of C3aR and C5aR resulted in the reduction of the progression of fibrosis by alleviating the local CS activation and suggested an encouraging treatment strategy for IPF.[100] However, recent evidence did not confirm the role of eculizumab in lung fibrosis induced by bleomycin.[183] Case reports describe efficacy of eculizumab in rapidly inducing remission in aggressive patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) with respiratory syndromes.[184]

More recently, authors interestingly provided evidence supporting a therapeutic strategy by targeting the CS in lung damage in an acute setting.

Conclusion

Overall, the activation of the CS is critical in different autoimmune-mediated diseases such as RA where it can amplify tissue injury directly or indirectly. Its dysregulation can create an imbalance of both host defence and inflammatory response inducing the development of autoimmunity. Autoantibodies such as RF and ACPA activate the CS in vitro via both the CP and the AP, contributing to the formation of IC. Autoantibodies may have a detrimental effect not only at joint levels but also in systemic manifestations, such as lung involvement. RA-ILD is typically associated with the presence of ACPA and the CS and may act at this level with a role in favouring lung injury. Local and systemic activation of CS has been demonstrated in IPF with increased levels of IC in BALF and sera of patients. Murine models of lung fibrosis explored the role of CS and C5 has been associated with profibrotic mediators. Current therapeutic strategies in RA and ILD take advantage of the molecular mechanisms implicated in the inflammatory process as highlighted by the advent of biological treatments that can slow down the progression of the diseases. To date, there is no direct evidence strongly supporting that any of the current treatments for RA-ILD act via the CS pathway but indirect mechanisms link CS and several therapeutic options of both conditions. Nevertheless, therapeutic agents for ILD, such as nintedanib and

pirfenidone, mainly show direct mechanisms of action that are independent of their effect on the CS but they both might indirectly act on CS-mediated inflammation: the idea of potential interplay between anti-fibrotic pathways and CS certainly needs further investigations.

RA is a complex disease with different tissues being the target of inflammation and damage. Key molecules such as those in the CS bridging innate and adaptive immune responses might be future therapeutic targets in those conditions where local activation at tissue site, IC deposition, and anaphylatoxins exert pro-inflammatory activities.

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