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Biological mechanisms of pulmonary inflammation and its association with seropositive rheumatoid arthritis

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Although the pathogenesis of seropositive rheumatoid arthritis (RA) remains unclear, studies suggest that pulmonary inflammation-related biological mechanisms play a significant role in its development. This review thoroughly explores the mechanisms underlying early pulmonary lesions in seropositive RA, focusing on the mucosal barrier hypothesis, neutrophil extracellular traps, pathogenic microbial infections like COVID-19, Vitamin D, the microbiome and gut-lung axis, inhalation exposures and chronic pulmonary diseases. This study seeks to provide novel insights and theoretical foundations for the prevention and treatment of seropositive rheumatoid arthritis.

KEYWORDS

rheumatoid arthritis, pulmonary inflammation, anti-citrullinated protein antibodies, COVID-19, gut-lung axis

1 Introduction

Rheumatoid Arthritis (RA) is a systemic autoimmune disease manifesting as chronic inflammatory polyarthritis, which can ultimately lead to joint deformity and loss of workforce productivity (1). Abnormal protein citrullination and the formation of anti-citrullinated protein antibodies (ACPA) are critical pathogenic mechanisms in RA and are associated with severe joint lesions and extra-articular organ damage (2–4). Rheumatoid factor (RF) is an autoantibody that primarily targets the Fc fragment of IgG antibodies (5). Seropositive RA refers to rheumatoid arthritis where patients exhibit the presence of RF or ACPA, often involving early damage to lung tissue (6). Inflammation-related mechanisms in the lungs are crucial in the onset and progression of seropositive RA, involving the mucosal barrier hypothesis, neutrophil extracellular traps, pathogenic infections like COVID-19, Vitamin D, the microbiome and gut-lung axis, inhalation exposures and chronic pulmonary diseases (7–10).

Therefore, exploring the role of pulmonary inflammation-related biological mechanisms in the pathogenesis of seropositive RA holds significant clinical implications. This review explores how pulmonary inflammation influences the onset and progression of seropositive RA, offering insights and theoretical foundations for its early detection, diagnosis, and treatment.

2 Seropositive rheumatoid arthritis

The global prevalence of RA has remained approximately 0.46% over the last 40 years (11). RA is an autoimmune disease mainly characterized by synovitis, with pulmonary involvement frequently examined as an extra-articular manifestation (12). RA is categorized into seropositive and seronegative types based on the presence of RF and ACPA, showing notable differences in risk factors, clinical features, and prognosis (13). The diagnosis of seropositive RA relies on the detection of key biomarkers, such as RF and ACPA (14, 15).

However, many studies have shown that seropositive RA patients may exhibit RA-specific biomarkers in the blood for years without meeting the clinical or histological criteria for joint pathology (16–18). The occurrence of ACPA or RF serological markers prior to joint pathology suggests that joint involvement may not be the initial site of disease manifestation in seropositive RA patients. Although this hypothesis is yet to be systematically validated or supported by sufficient evidence, the possibility of pulmonary inflammatory lesions serving as the initial autoimmune site in seropositive RA is gaining increasing attention (19). Therefore, this study provides a comprehensive review of the potential link between pulmonary inflammation-related biological mechanisms and seropositive RA.

3 Biological mechanisms of pulmonary inflammation and seropositive rheumatoid arthritis

3.1 Mucosal barrier hypothesis

The large mucosal surface area of the lungs is exposed to the external environment, coming into direct contact with antigens, pollutants, and microorganisms, thereby maintaining a relatively active immune response over time (20). Recurrent lung inflammation can persistently activate mucosal immunity, potentially resulting in abnormal protein and autoantibody production, which may progress to affect the synovial tissue. In studies on the preclinical stage of seropositive RA, serum samples from high-risk individuals show elevated inflammatory factors, altered T-cell phenotypes, and expanded autoantibody profiles (7, 21–28). Additionally, the serum biomarker patterns in high-risk individuals were consistent with those found in retrospective studies of RA patients (7). Therefore, studying the origin of these biomarkers in high-risk populations for seropositive RA is of great significance, as pulmonary mucosal inflammation may be one of the causes of immune abnormalities in these individuals. Research on mucosal immunity indicates that IgA-ACPA and RF emerge long before the onset of joint symptoms in seropositive RA. The production of IgA isotypes ACPA and RF is common in mucosal tissues and has been shown to be associated with local mucosal inflammation (29–31). Through sequencing and characterization of plasmablasts in high-risk individuals, control subjects, and early seropositive RA patients, IgA and IgG antibodies have been

phylogenetically shown to have a close relationship (32–34). The compromised mucosal barrier integrity can lead to antibodies entering the systemic circulation (35). This indicates that in seropositive RA, a persistent immune response linked to mucosal antigens might occur, with mucosal barrier dysfunction and systemic spread of IgG autoantibodies potentially being crucial early events in preclinical development.

3.2 Neutrophil extracellular traps

Neutrophil extracellular traps (NETs) are web-like structures composed of DNA and neutrophil-derived proteins that can rapidly control infections and exert immune functions, inducing local inflammation and tissue damage (36). The persistent activation of neutrophils and the formation and scaffolding role of NETs are closely associated with the local production of IgA ACPA in the lungs (37). During pulmonary infections, inflammatory mediators released at the infection site, together with locally produced ACPA, can trigger the formation of NETs through a process known as NETosis. Notably, in patients with RA-associated pulmonary inflammation, neutrophils demonstrate a markedly increased ability to form NETs (38). Growing evidence indicates that chronic airway inflammation contributes to the onset of seropositive RA by promoting NETosis, which leads to the breakdown of immune tolerance (39). Furthermore, the citrullination of various proteins within NETs has been identified as a critical factor driving ACPA production during the progression of RA (40). This process further amplifies NETosis by activating inflammasomes in macrophages, thereby promoting an immunogenic and pro-inflammatory microenvironment (41). The generation of ACPA and the persistence of inflammatory conditions are key mechanisms that drive the onset and progression of seropositive RA. During NET formation or apoptosis, elevated intracellular calcium concentrations lead to Ca^{2+} binding to the Ca^{2+} -binding sites of peptidylarginine deiminases (PADs), resulting in their conformational activation (42). Activation of PADs enhances ACPA production, thereby contributing to the autoimmune pathogenesis of seropositive RA. The link between PAD activity and inflammatory states has been experimentally validated, with both factors working synergistically to drive the formation of NETs (43). Through these mechanisms, immune tolerance is compromised, establishing a self-perpetuating inflammatory state. The systemic spread of seropositive RA-associated immune cells, autoantibodies (particularly ACPA), and inflammatory mediators via the bloodstream constitutes a crucial pathway that drives both the onset of immune dysregulation and the ongoing inflammation characteristic of seropositive RA. Disruption of this process can exacerbate inflammation and tissue damage, creating a vicious cycle, and the notable inhibitory effects of specific PAD4 inhibitors on protein citrullination and NET formation provide supporting evidence for this hypothesis (43, 44).

The body has mechanisms to limit this vicious cycle. Myeloid inhibitory C-type lectin-like receptor (MILR) is predominantly found on myeloid cell surfaces, functioning as an inhibitory receptor. It regulates local immune responses, particularly the

inflammatory response during cell death (45–47). The study by Malamud et al. demonstrated that MICL can recognize DNA within NETs and regulate NET formation by inhibiting neutrophil activation. Deficiency or inhibition of MICL triggers excessive NET formation via the ROS-PAD4 pathway, establishing a pathogenic autoinflammatory feedback loop in seropositive RA. They also confirmed a significant increase in anti-MICL autoantibody titers in the early stages of seropositive RA, with a correlation between anti-MICL antibody levels and ACPA levels (48). Therefore, anti-MICL antibodies produced in seropositive RA patients may be one of the factors that promote disease onset. When NETs are released, the resulting citrullinated neopeptides promote the production of ACPA. Loss or inhibition of MICL function increases NET formation, leading to the development of a positive feedback loop in autoimmunity (49).

Furthermore, abnormal expression of the protein tyrosine phosphatase, non-receptor type 22 (PTPN22) gene leading to hypercitrullination of proteins can increase the propensity for NET formation, which is not uncommon in seropositive RA patients (50, 51). PTPN22 is a phosphatase involved in regulating immune responses and can also inhibit the process of histone citrullination (52). In peripheral CD4⁺ T cells, dysfunction of the PTPN22 gene may lead to abnormal protein citrullination, elevated Th17 cytokines, and decreased Th2 cytokines (52). This indicates that CD4⁺ T cells with dysfunctional PTPN22 are more prone to inflammation, aligning with mucosal inflammation and potentially linked to ACPA production.

3.3 Pathogenic microbial infections and COVID-19

The lungs are a common site for pathogenic microbial infections that cause tissue damage and trigger inflammation. During the inflammatory process, the pattern recognition receptor NOD-like receptor protein 3 (NLRP3) can detect and respond to pathogenic stimuli, assembling the NLRP3 inflammasome and activating caspase-1, which induces pyroptosis and promotes the maturation of interleukin-1 (IL-1 β) and IL-18, thereby triggering an inflammatory response (53). This mechanism is particularly relevant in infections with certain serotypes of *Streptococcus pneumoniae* (54). Excessive activation of NLRP3 may be associated with the pathogenesis of seropositive RA. IL-1 β is a key pro-inflammatory factor that facilitates inflammation by recruiting leukocytes, promoting systemic inflammation, inducing IL-12 to boost interferon- γ (IFN- γ) production, driving Th17 or Th9 cell differentiation, stimulating naive CD8⁺ T cell proliferation, differentiation, and migration, and promoting the proliferation of B cells and the synthesis of antibodies (55–62). IL-18 can direct Th1 responses and induce the production of IFN- γ and IL-8 (63–67). IL-18 originating from epithelial cells can also modulate the differentiation of Th17 cells and the functionality of regulatory T cells (Tregs). Moreover, a dysregulation in the Th17/Treg balance has been implicated in the pathogenesis of seropositive RA (66, 67). ACPA found in seropositive RA patients can enhance the expression of NLRP3 and IL-1 β . This aberrant activation may

establish a deleterious feedback loop in the lungs of seropositive RA patients, aggravating the disease condition (Figure 1) (68).

In addition, cytokines can play a significant role in the pathogenesis and progression of seropositive RA through other pathways. IL-1 β can activate C/EBP β , which, either alone or in synergy with NF- κ B, upregulates the expression of factors such as tumor necrosis factor α (TNF- α), IL-1 β , and IL-6, thereby exacerbating the inflammatory response in seropositive RA (69). IL-6 is widely involved in immune regulation and inflammatory responses and is a key factor in cytokine storms. Overproduction and unregulated receptor signaling may contribute to inflammatory diseases (70). IL-6 can influence the autoimmune response in seropositive RA by promoting Th17/Treg imbalance and can synergize with IL-21 to mediate antibody production, further exacerbating autoantibody production in seropositive RA (71, 72).

The massive release of cytokines triggered by pathogenic microbes may also cause immune dysregulation in other ways, inducing the onset of seropositive RA autoimmunity. Jonsson et al. (73) identified a novel population of CD8⁺ T cells with reduced cytotoxicity that can be rapidly activated by cytokines and produce high concentrations of IFN- γ and TNF- α , playing a key role in driving inflammation. These cells exhibit clonal expansion in inflamed tissues and can be activated both by cytokines such as IL-12 and in an antigen-specific manner, potentially linked to NLRP3 inflammasome-mediated inflammatory responses. This population is present in the blood, can migrate between tissues without changing phenotype, and shows higher enrichment in inflamed tissues. The characteristics of this novel CD8⁺ T cell population suggest that it may be one of the mechanisms by which pulmonary inflammation contributes to seropositive RA.

Cytokines may also play a crucial role in the pathogenesis of seropositive RA through the action of macrophages. Simmons et al. (74) demonstrated that signaling lymphocytic activation molecule family member 7 (SLAMF7) a receptor associated with macrophage hyperactivation in RA, and confirmed the presence of a SLAMF7 hyperactivated macrophage population in the synovial fluid of seropositive RA patients and in the lung tissue of COVID-19 patients. IFN- γ is a key regulator of SLAMF7 expression, driving robust expression of SLAMF7-mediated inflammatory factors and inducing a TNF- α autocrine signaling loop that amplifies inflammation. The novel CD8⁺ T cell population may contribute to the activation of this pathway by secreting large amounts of IFN- γ . This finding suggests a significant impact of COVID-19 on RA, though the relationship between the two requires further elucidation. Previous research indicates that TNF- α , a pro-inflammatory factor, contributes to the development of seropositive RA. However, it can also induce the expression of IL-7R on monocytes in the blood of seropositive RA patients, conferring anti-inflammatory properties on these monocytes (75). The imbalance between macrophage-mediated inflammatory and anti-inflammatory responses in RA patients may be one of the factors contributing to the disease's onset and progression.

The COVID-19 pandemic has profoundly affected human health. During the COVID-19 pandemic, the overall incidence of RA increased significantly, particularly for seropositive RA (IRR = 1.60), suggesting an association between COVID-19 and seropositive RA

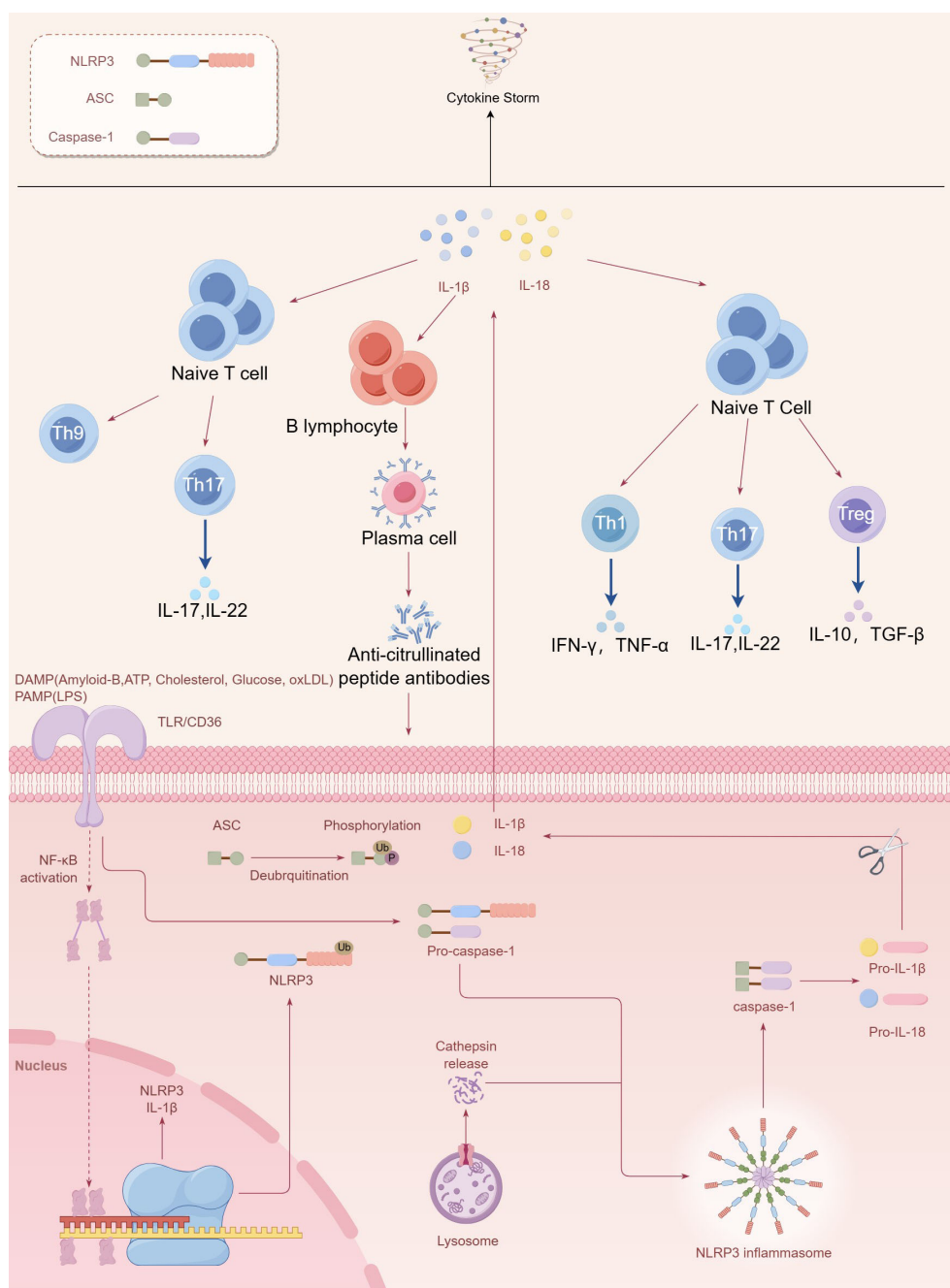


FIGURE 1

The vicious cycle in the lungs of seropositive rheumatoid arthritis patients. Inflammation triggers the NF- κ B signaling pathway via pathogen-associated molecular pattern (PAMP) or damage-associated molecular pattern (DAMP) receptors, leading to the expression of NLRP3 and IL-1 β . NLRP3 proteins assemble into the NLRP3 inflammasome complex, activating caspase-1 to trigger pyroptosis and facilitate the maturation of IL-1 β and IL-18, thereby initiating downstream immune responses. The NLRP3-mediated inflammatory response can ultimately promote B cell proliferation and antibody production as well as T cell proliferation, differentiation, and cytokine release. ACPA enhances the expression of NLRP3 and IL-1 β . This abnormal activation may create a vicious cycle in the lungs of seropositive RA patients and potentially lead to a cytokine storm.

(76). SARS-CoV-2, the virus responsible for COVID-19, can trigger autoimmune responses via inflammation and immune reactions, utilizing mechanisms like epitope spreading, molecular mimicry, and bystander activation (77). During the immune response to viral infection, interferon (IFN) is a key cytokine in antiviral immunity. Autoantibodies against IFN were detected in 13.7% of severe COVID-19 patients, indicating immune dysregulation in the context

of SARS-CoV-2 infection (78). SARS-CoV-2 infection can also induce the generation of various autoantibodies. The acute phase is characterized by a severe inflammatory response, while the persistent inflammatory response observed during the recovery phase is associated with multiple autoimmune diseases (79).

COVID-19 primarily affects the lungs and can trigger excessive immune responses and cytokine storms, leading to severe pneumonia

(80). Overproduction of factors like IL-6, IL-1 β , and TNF mirrors the inflammatory response observed in RA. COVID-19 and seropositive RA both involve abnormal immune cell activation, resulting in tissue damage and inflammatory cell infiltration (81). SARS-CoV-2 infection can induce excessive inflammatory responses in seropositive RA patients by activating the NLRP3/CASP1 pyroptosis pathway and may enhance autoantibody production through similar mechanisms (82). In addition to the inflammatory response induced by innate immunity, an alternative and extrafollicular immune response to SARS-CoV-2 occurs in pulmonary tissues, which alters humoral immunity and memory T cell responses (83). This ultimately leads to breakdown of immune tolerance and generation of seropositive RA-associated autoantibodies. Studies have confirmed that the spike glycoprotein of SARS-CoV-2 shares 13 of 24 pentapeptides with pulmonary surfactant protein, which may contribute to specific immune responses and cross-reactivity following SARS-CoV-2 infection, potentially triggering seropositive RA (84). Moreover, studies demonstrate that impaired NET degradation in severe COVID-19 establishes a vicious cycle of NETosis and ACPA production, perpetuating a pro-inflammatory milieu in seropositive RA patients (85). Prolonged immune activation from COVID-19 may result in persistent autoantibodies, potentially causing seropositive RA. Additionally, SARS-CoV-2 infection may ultimately lead to pulmonary fibrosis, sharing similar mechanisms with RA-associated interstitial lung disease (RA-ILD), which will be discussed further (86).

3.4 Vitamin D

Vitamin D is crucial for infection resistance, inflammation reduction, and immune balance regulation (87). Vitamin D deficiency may exacerbate the burden of autoimmune diseases, a concern that is particularly pronounced during the COVID-19 pandemic (88). Vitamin D requires activation within the body to exert its physiological functions, and various immune cells can express vitamin D receptors and activating enzymes (89). 1,25-Dihydroxyvitamin D, the active form of vitamin D, promotes Th2 differentiation and the secretion of anti-inflammatory cytokines while reducing Th1 differentiation and the secretion of pro-inflammatory cytokines (such as IL-2, IFN- γ , and TNF- α). It also regulates the Th17/Treg balance and can inhibit the differentiation or maturation of naive B cells, indicating its potential to downregulate the activity of seropositive RA (90–92). Research on early RA patients indicates that vitamin D deficiency correlates with disease activity and serves as a predictive biomarker for disability progression within a year (93). Therefore, vitamin D potentially regulates pulmonary inflammation and may slow the progression of seropositive RA.

3.5 Microbiome and the gut-lung axis

The human microbiome, comprising all microorganisms residing in body cavities and on surfaces, impacts the host's immune system via microbial antigens and metabolic products

(94, 95). It is crucial for sustaining homeostasis and supporting immune function (96). Previously considered sterile, the lungs are the largest organ directly interacting with the environment (10, 97). Recent studies have identified the presence of bacteria in human lungs, noting their alterations in lung diseases and their links to alveolar immunity and disease outcomes (98, 99). The lung microbiome's composition is mainly shaped by three factors: (i) the microbiota from the oral cavity, stomach, and air; (ii) mucociliary escalator and cough reflex clearance mechanisms; (iii) the local physicochemical conditions within the lungs (100). When lung inflammation occurs, the balance of these three factors may shift, potentially leading to alterations in the microbiome.

Pulmonary microbiota typically develops in areas of bronchial alteration, with a composition similar to that of the oropharynx but with a lower bacterial load (101). The pulmonary microbiota may be influenced by various regulators, impacting lung health. Vitamin D deficiency is linked to alterations in microbial populations and is associated with bronchiectasis and bacterial colonization (102). Alterations in the lung microbiota could significantly influence the progression of seropositive RA. Research indicates that seropositive RA patients exhibit significantly reduced microbial diversity and population imbalances in bronchoalveolar lavage samples compared to healthy individuals. Additionally, the disease activity of seropositive RA is significantly positively correlated with *Micrococcus* and *Renibacterium* (103). Therefore, alterations in the pulmonary microbiota are associated with seropositive RA; however, further research is needed to establish a causal relationship between the two.

The gut and lungs share a degree of homology in tissue embryology, resulting in certain similarities in their mucosal structure and function (104). The potential anatomical connections between the gut and lungs, along with the complex microbiota-related pathways involved, further support the existence of the gut-lung axis (105). Research indicates that changes in gut microbiota can influence lung immune responses via mechanisms involving Treg cells, toll-like receptors (TLRs), and inflammatory factors (106). Therefore, disruption of the gut microbiota is associated with various pulmonary diseases, including chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, and interstitial lung disease (ILD) (100, 105, 107). These diseases may have an important impact on the development and progression of seropositive RA, which will be discussed in the following section. RA. Structural changes in the gut microbiota, through direct or indirect effects, can impact the onset of seropositive RA by decreasing anti-inflammatory microbes and increasing pro-inflammatory microbes (108). Studies have confirmed that the number of short-chain fatty acid-producing bacteria is significantly reduced in RA patients, while oral colonizing bacteria are increased. This transition results in decreased short-chain fatty acid-related metabolites and elevated amino acid and carbohydrate metabolites. These alterations show a positive correlation with pro-inflammatory cytokines like IL-6 and a negative correlation with anti-inflammatory cytokines such as IL-12, potentially affecting pulmonary inflammation via the gut-lung axis (109).

Pulmonary infections or chronic inflammation may alter the microbiota in both the lungs and gut, impacting local mucosal immune responses through multiple pathways and ultimately influencing joints via systemic inflammation (110). In seropositive RA patients, changes in the microbiota may affect the severity of joint symptoms, thereby influencing the assessment of seropositive RA activity. Animal studies on RA often use a collagen-induced arthritis model. During the preparation of this model, arthritic mice exhibit dysbiosis of the gut microbiota, and transplanting fecal matter from these arthritic mice to germ-free mice accelerates the development of arthritis (111). Another experiment demonstrated that using broad-spectrum antibiotics to modulate the microbiota prior to arthritis induction can reduce disease severity, while administering antibiotics in the late stages of arthritis induction can almost completely suppress the arthritis (112). This suggests that the role of the microbiome in the preclinical and clinical development of RA is multifaceted, potentially influencing various stages of the autoimmune initiation process, thereby impacting the activity of RA.

Mucosal dysbiosis can also trigger persistent mucosal inflammation, activate local innate immunity, and drive the disruption of the mucosal barrier, leading to the translocation of bacterial DNA, endotoxins, and other substances into circulation, which subsequently induces the production of systemic IgG autoantibodies (113, 114). The alleviation of mucosal inflammation in the lungs, intestines, and other sites is associated with substances such as resolvins (115, 116). Resolvins and protectins belong to the bioactive mediators synthesized from omega-3 polyunsaturated fatty acids (n-3 PUFAs). They are capable of reducing cellular activation and inflammation mediated by immune complexes (117). Chronic mucosal inflammation can lead to significant depletion of n-3 PUFAs, causing reduced circulating levels in RA patients (118). In patients with RA, persistent mucosal inflammation can deplete n-3 PUFAs, resulting in lower circulating levels (119, 120). This suggests a potentially close association between local mucosal inflammation, autoantibody production, and n-3 PUFA levels. Excessive mucosal inflammation and n-3 PUFA deficiency may both be essential factors for the persistent progression of RA.

Moreover, the mucosal microbiome may influence the development of seropositive RA through additional mechanisms. Alterations in mucosal surface microorganisms can lead to the occurrence of cross-reactivity, partially supporting a causal relationship between mucosal exposure, dysbiosis, and the progression of high-risk individuals to active RA (121). In seropositive RA patients, antigens carried by certain organisms can cross-react with ACPA (122), which may represent a key mechanism driving and influencing disease progression. It is currently known that seropositive RA is strongly linked to periodontitis resulting from *Porphyromonas gingivalis* infection, with underlying mechanisms involving molecular mimicry and specific antibody formation (123, 124). The periodontal pathogen *Porphyromonas gingivalis* encodes a PAD enzyme that citrullinates both bacterial and host proteins (125). Furthermore, periodontal abscesses can trigger the release of NETs, which, along with the

forementioned factors, contribute to the detection of ACPA in the gingival crevicular fluid. These findings support the association between periodontal disease and increased citrullination within the inflammatory environment, which in turn impacts systemic ACPA levels (126–128). Previous studies have also demonstrated a link between oral bacteremia and RA flare-ups (129). Silva et al. (130, 131) confirmed a positive correlation between the severity of periodontitis and RA disease activity, showing that treatment of periodontal disease in RA patients was associated with a decrease in ACPA levels. They further noted that this reduction in ACPA was observed only in patients with baseline IgG ACPA levels below 150 AU ($P = 0.006$). These results support the hypothesis that ACPA responses are triggered and sustained within the gingival mucosa, and given the anatomical and microbiological similarities between the lung and oropharyngeal mucosa, this process may also influence the development of pulmonary mucosal responses.

In addition to the influence of the oral microbiota, the gut microbiota may also drive the development of seropositive RA through its interference with the immune system. Research by Pianta et al. (132) indicates a significant association between *Prevotella* species and the onset of RA. *Prevotella* can induce Th1-type immune responses, promote the production of ACPA-associated IgA antibodies and *Prevotella* DNA-associated IgG antibodies, and facilitate systemic dissemination of *Prevotella* DNA through phagocyte-mediated mechanisms. In addition to phagocytes, lymphocyte subsets in the mucosa can also migrate to other sites via circulation (133). Therefore, the interactions between immune cells and the microbiome may not only manifest locally but also influence immune and autoimmune responses in other tissues. This could be a critical step in the immunological dysregulation of T cells and B cells, wherein their activation occurs locally, such as in the lungs or intestinal mucosa, subsequently triggering systemic immune responses.

The composition of the pulmonary mucosal microbiome remains under investigation and is of significant importance to the onset and progression of seropositive RA. The relationship between the mucosa, its associated microbiome, and seropositive RA warrants further exploration.

3.6 Inhalation exposure and chronic pulmonary diseases

Inhalation exposure's potential contribution to RA development has been widely researched (134). Inflammatory responses induced by the inhalation of toxic substances can promote the accumulation and activation of pulmonary antigen-presenting cells, induce the expression and activation of PAD, and enhance protein citrullination in the lungs, ultimately leading to the production of ACPA (135). Smoking has been established as a significant risk factor for seropositive RA, playing a pivotal role in the initial formation of RF and ACPA (136). In addition, air pollution factors such as silica, biomass burning, and PM2.5 are associated with higher rates of ACPA positivity (137–139). Studies have shown that the relationship between air pollution and RA-

associated autoimmunity differs between high-risk individuals and seropositive RA patients (140). It is possible that air pollution may contribute to the progression of RA by facilitating the transition of RA-associated autoantibodies from pulmonary inflammation to synovitis. Aspiration of gastric contents due to gastroesophageal reflux disease, alongside environmental factors, is a risk factor for seropositive RA (141).

Inhalation exposures, including smoking, are risk factors for seropositive RA and contribute to chronic inflammatory lung diseases (142, 143). This may be one of the reasons for the close relationship between RA and chronic inflammatory pulmonary diseases. Inhalation exposure-induced pulmonary injury causes chronic inflammation in the lungs, which sustains the immune system in a state of prolonged high stress, potentially triggering and advancing seropositive RA via mechanisms like reactive oxygen species-induced tissue damage, airway remodeling-induced chronic hypoxia, molecular mimicry-driven autoimmunity, and chronic infections that enhance joint-specific susceptibility (144). Clinical evidence supports the involvement of airway processes in seropositive RA, showing the frequent coexistence of persistent airway inflammation and ACPA positivity both before and during disease onset (19). This likely reflects a key mechanism underlying the breakdown of immune tolerance and the persistence of inflammation in patients with seropositive RA. Related diseases include ILD, COPD, bronchiectasis, asthma, and others.

Epidemiological studies have found a significantly increased prevalence of pulmonary diseases during the preclinical phase of seropositive RA, supporting the notion that pulmonary diseases may be a risk factor for the development of seropositive RA (145). During the diagnosis of seropositive RA, ACPA demonstrate high specificity. However, ACPA can also be detected in some patients with chronic pulmonary diseases who have not yet been diagnosed with RA. This group has a significantly increased likelihood of developing seropositive RA in the future (146). The detection of ACPA prior to the clinical diagnosis of RA may be related to mucosal immune responses triggered by pulmonary inflammation. Research by Kelmenson et al. (147) indicates that during the period surrounding the clinical diagnosis of seropositive RA, the positivity rate of IgA-ACPA significantly increases, while the positivity rate of IgG-ACPA remains stable. This phenomenon suggests that IgA-dominated mucosal immunity may drive the onset of seropositive RA. Studies on lung biopsies and bronchoalveolar lavage fluid from early seropositive RA cases have shown that ACPA produced in the lungs shares some similar characteristics with ACPA produced in the joints (148). Moreover, structural abnormalities and inflammatory manifestations in the lungs may be associated with this process (149). The induction of bronchus-associated lymphoid tissue is a common structural abnormality in chronic pulmonary inflammation and is frequently detected in patients with seropositive RA (148). This structure has been shown to be associated with the local production of RF and ACPA (150).

ILD is often discussed as a consequence of the progression of seropositive RA. However, research indicates that abnormal protein modifications and immune responses triggered by smoking or other lung injuries can lead to ILD, which may subsequently induce

secondary joint diseases, including seropositive RA (151). This indicates that the lungs might be the first location for immune tolerance disruption, with ILD possibly being the initial irregularity in seropositive RA development. However, ILD does not necessarily progress to RA. Multiple lines of evidence indicate distinct inflammatory components in the progression of RA-ILD compared to non-RA-related ILD. For instance, the influx of CXCR3-positive lymphocytes suggests a high local concentration of IFN- γ and the activation of Th1-type immune responses (152). Unlike non-RA-related ILD, the development of RA-ILD involves factors closely related to RA itself, such as abnormal activity of PAD, which is strongly associated with the production of autoantibodies, including ACPA (153). Research by Brink et al. (154) has demonstrated that ACPA is an independent risk factor for RA-ILD, with 11 types of ACPA targeting different antigens being associated with the development of pulmonary fibrosis.

COPD patients show increased pulmonary citrullination and a greater likelihood of producing diverse autoantibodies compared to those without airway diseases. This may increase susceptibility to seropositive RA (155, 156). Previous studies have indicated a significant association between seropositive RA and an increased risk of subsequently developing COPD (157). Therefore, small airway disease preceding the clinical diagnosis of COPD may be a contributing factor to the onset of seropositive RA. Evaluations performed on patients with similar small airway changes identified through high-resolution CT, using induced sputum collection, have detected RA-related IgA and IgG autoantibodies in the lungs, even when serum ACPA or RF is undetectable (31). These autoantibodies have been demonstrated to originate locally (30). Therefore, COPD may play a facilitating role in the development of seropositive RA, although further research is required to substantiate this relationship.

Chronic bacterial infections in seropositive RA patients with bronchiectasis may elevate autoantibody levels, indicating bronchiectasis could contribute to seropositive RA progression (158). However, although bronchiectasis may precede the joint manifestations of RA, it is often regarded as a late complication due to the immunosuppressive state of seropositive RA patients, which predisposes them to recurrent infections (159). A study involving seropositive RA patients without a clinical diagnosis of arthritis provided evidence supporting the possibility that chronic pulmonary inflammation triggers immune dysregulation in seropositive RA. In this study, 14% of the patients had bronchiectasis, and 76% exhibited pulmonary abnormalities (160). These findings suggest that the lungs, under chronic inflammatory conditions, may serve as the initial site for the production of autoantibodies in seropositive RA. However, the precise correlation and underlying mechanisms require further investigation to be fully elucidated.

The impact of asthma on the development of RA has been a subject of debate (161–164). However, a recent study indicates a correlation between asthma and an increased risk of seropositive RA, particularly over an extended period preceding its onset (> 0–10 years) (165). The specific mechanisms by which asthma influences the onset and progression of seropositive RA remain to be further investigated.

3.7 Anti-citrullinated protein antibodies

Extensive research has demonstrated that seropositive RA is closely associated with abnormal protein citrullination (166–168). Studies have found that ACPAs are present in the sputum of seropositive ACPA individuals without arthritis and are enriched in the bronchoalveolar lavage fluid of early ACPA-positive RA patients (31, 169). These phenomena suggest that pulmonary inflammation may play a role in the early stages of seropositive RA development. Repeated pulmonary inflammation leads to cellular damage and apoptosis, resulting in the release of large amounts of calcium ions, which activate PAD (170). PAD catalyzes the conversion of arginine residues in proteins to citrulline residues, leading to the deposition of citrullinated proteins in lung tissue. This disruption of immune tolerance leads to the presentation of citrullinated proteins as antigens by antigen-presenting cells, which triggers a specific immune response and the production of ACPAs (Figure 2) (171–174). The pulmonary inflammation-related biological mechanisms mentioned above may influence the onset of seropositive RA by triggering the extensive formation of ACPAs. Persistent pulmonary inflammation impacts mucosal immune responses through various pathways. In the progression from localized mucosal immune dysregulation to systemic seropositive RA, characterized predominantly by arthritis, several factors may play pivotal roles.

These factors encompass shared antigenic targets between the lungs and joints, epitope spreading to joint-specific antigens, and the deposition of immune complexes within the joints (175).

4 The relationship between immune responses and seropositive rheumatoid arthritis inflammation

RA is a chronic, systemic autoimmune inflammatory disorder driven by complex, multifactorial interactions that involve dysregulation at various levels of the immune system (176). Specifically, the innate and adaptive immune systems form a coordinated yet dysregulated network that collectively drives both the onset and progression of RA-associated inflammation (177).

4.1 Innate immunity

Accumulating evidence highlights the role of innate immunity as both the initiator and perpetuator in the pathogenesis of seropositive RA. Innate immune components not only trigger the initial breach of self-tolerance but also actively sustain inflammatory cascades throughout disease progression (178).

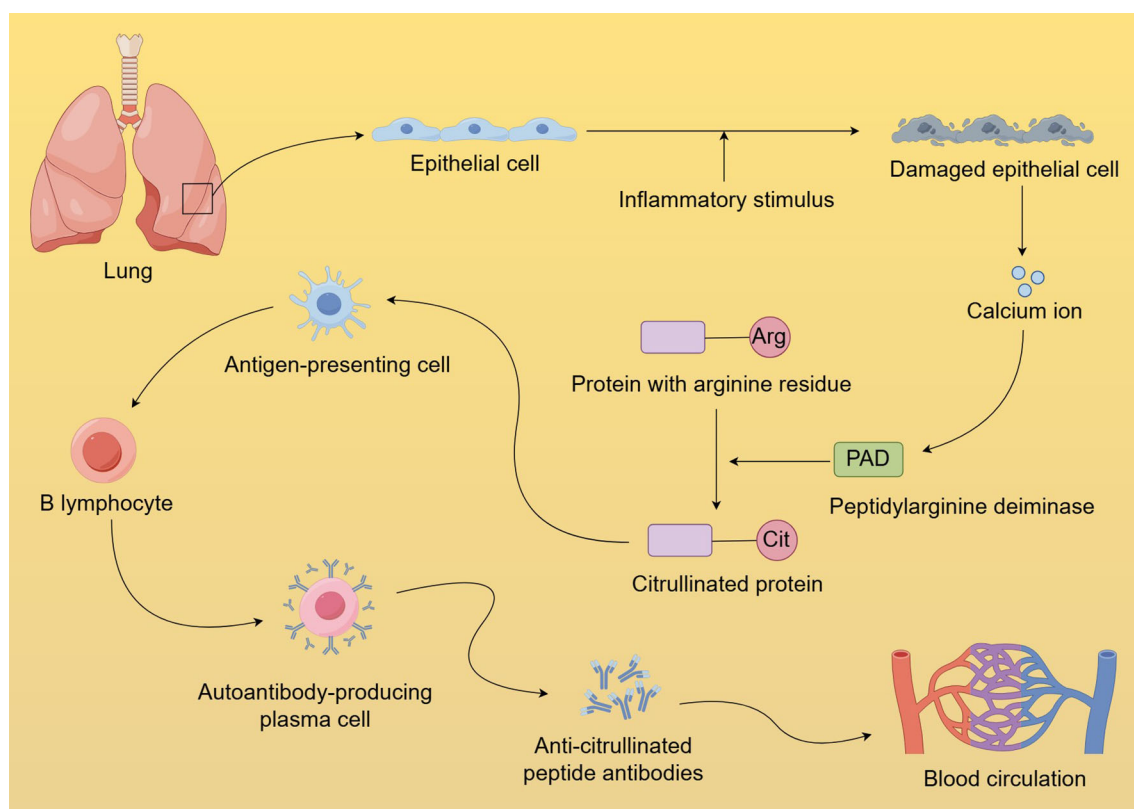


FIGURE 2

Formation and dissemination of anti-citrullinated protein antibodies in the lungs. Chronic pulmonary inflammation causes cellular damage and apoptosis, releasing significant calcium ions that activate PAD. PAD facilitates the transformation of protein arginine residues into citrulline, which disrupts immune tolerance, and triggers a specific immune response, resulting in ACPA production. The loss of mucosal barrier integrity caused by pulmonary inflammation further facilitates the leakage of abnormally produced ACPA into systemic circulation.

In addition to neutrophils and NETosis, the innate immune landscape in seropositive RA prominently involves monocytes, macrophages, and dendritic cells (DCs), which play critical roles in disease initiation and perpetuation through processes such as phagocytosis, antigen presentation, and cytokine production (179, 180).

Under homeostatic conditions, the maintenance of peripheral immune tolerance relies critically on immature dendritic cells (imDCs), which continuously sample and present self-antigens derived from tissue and blood (181, 182). Experimental evidence shows that depletion of imDCs leads to spontaneous autoimmunity, characterized by autoantibody production, inflammatory cell infiltration in peripheral organs, and a systemic wasting syndrome (183). The maturation of DCs is tightly regulated by TLR activation and influenced by various factors, including cytokines, hormones, vitamins, and environmental stimuli (178). During maturation, DCs undergo phenotypic reprogramming, marked by a downregulation of antigen uptake capacity and an upregulation of migration markers, which enables their trafficking to secondary lymphoid organs where they prime naïve T cells (184–186). Clinically, the induction of tolerogenic DCs in RA patients reduces activated T cell populations while increasing the Treg/effector T cell ratio, highlighting the important role of DCs in the pathogenesis of seropositive RA (187).

Research has shown that DCs in seropositive RA patients overproduce a wide range of immune mediators, including pro-inflammatory cytokines (such as IL-1, IL-6, IL-12, TNF, and IFN), differentiation factors (such as macrophage colony-stimulating factor and fibroblast growth factor), and chemokines (188–190). These DC-derived factors play key roles in sustaining synovial inflammation and are directly involved in several immunological processes that underpin RA pathogenesis (191). Activated by these inflammatory mediators, monocytes and macrophages not only amplify their own inflammatory responses but also become major producers of pathogenic cytokines, thereby driving a self-perpetuating cycle of inflammation and tissue destruction, which is central to RA pathogenesis and correlates with disease activity (192–196).

Innate lymphoid cells (ILCs) and natural killer (NK) cells play significant roles as regulators of inflammatory responses, contributing to the pathogenesis of autoimmunity in a dual manner (197). Studies have identified an altered ILC balance in RA patients, characterized by reduced frequencies of ILC2s in peripheral blood and synovial tissue, alongside an expansion of ILC3s. ILC2s exert protective effects through IL-9-mediated enhancement of Treg function, and their depletion is associated with increased arthritis severity (198–200). In contrast, ILC3s secrete IL-17 and other cytokines, which are now recognized as key mediators linking airway inflammation to RA pathogenesis (201–203). However, the precise role of NK cells in RA remains incompletely understood (204). Current evidence points to a compartmentalized dysregulation: activated NK cells accumulate in the synovium but are reduced in peripheral blood (205, 206). Synovial fluid analyses suggest that NK cells may exacerbate RA progression through two mechanisms: (i) secreting

pro-inflammatory cytokines such as TNF- α and IFN- γ , and (ii) promoting osteoclastogenesis through cellular crosstalk (206, 207).

Collectively, pro-inflammatory cytokines (such as TNF- α and IFN- γ) released by activated innate immune cells drive the maturation of DCs, creating a self-amplifying loop that exacerbates innate immune activation and bridges to adaptive immunity, ultimately orchestrating the initiation and progression of seropositive RA.

4.2 Adaptive immunity

The breakdown of immune tolerance and the development of adaptive immunity-driven autoantibodies are hallmark features of seropositive RA. T lymphocytes and B lymphocytes, as key mediators of adaptive immunity, work synergistically with DCs to form a crucial link between innate and adaptive immune responses (208).

B cells play a central role in the pathogenesis of seropositive RA. Upon activation, they differentiate into autoantibody-producing plasma cells that generate RF and ACPAs, which are hallmarks of seropositive RA. In addition to their antibody-producing capacity, B cells contribute to disease progression through cytokine-mediated mechanisms, secreting pro-inflammatory factors including IL-1, IL-6, IL-8, IL-12, and TNF- α . These cytokines not only amplify immune dysregulation but also help establish and maintain a chronic inflammatory microenvironment that perpetuates disease activity (209, 210). B cell-derived cytokines also influence innate immune responses. For instance, TNF- α and IL-6 can activate synovial fibroblasts, while IL-8 promotes neutrophil infiltration—both mechanisms are closely associated with joint destruction in RA (211, 212). Additionally, IFN- γ produced during innate immune reactions can induce a significant increase in CXCR3⁺RANKL⁺ B cells in RA patients. These cells may further recruit IFN- γ -producing Th1 cells and additional CXCR3⁺RANKL⁺ B cells to the joint, establishing a pathogenic feedback loop that amplifies joint inflammation in RA (213, 214).

T cells play a significant role in the adaptive immune dysregulation of seropositive RA, particularly CD4⁺ T cells, which drive inflammation and support antibody production by B cells (215). The antigen-presenting function of innate immune cells, such as DCs and macrophages, along with B cells, is crucial for T cell activation (216). Upon activation, CD4⁺ T cells secrete pro-inflammatory cytokines, including IL-17, IL-21, granulocyte-macrophage colony-stimulating factor, TNF- α , IFN- γ , and CXCL13, which are essential for B cell recruitment and helper functions. These cytokines also modulate innate immune responses, representing a key mechanism in the initiation and perpetuation of seropositive RA (217–221). The precise role of CD8⁺ T cells in RA pathogenesis is still not fully understood. However, studies have shown that CD8⁺ T cells in RA patients exhibit significantly elevated IFN- γ production and are crucial for the formation of ectopic lymphoid neogenesis within the synovium, correlating with higher titers of RF and ACPAs (222–225).

Beyond the direct pro-inflammatory effects of adaptive immunity in RA, antibodies can also exert innate immune

effector functions through their antigen-binding domains. These mechanisms include antibody-dependent cellular cytotoxicity, complement activation, and Fcγ receptor-mediated cell activation, all of which amplify inflammatory responses and contribute to joint damage (178).

As outlined above, innate and adaptive immunity do not function independently but rather work synergistically, creating a self-reinforcing autoimmune feedback loop. Pathogenic factors, both endogenous and exogenous, activate innate immune cells, triggering the release of inflammatory mediators that, in turn, activate the adaptive immune system. In response, activated adaptive immune cells exacerbate innate immune responses through cytokine production, further amplifying the inflammatory cascade and breaking immune tolerance. Simultaneously, the cytokines and other mediators produced by innate immunity actively regulate adaptive immune responses, likely contributing to the dysregulation of adaptive immunity and the destruction of adaptive immune cells. Collectively, the intra- and extra-articular inflammation characteristic of seropositive RA results from aberrant, mutually reinforcing activation of both immune arms. Understanding their interconnected regulatory mechanisms will not only reveal novel therapeutic targets but also provide a conceptual framework for future immune-modulatory strategies in seropositive RA.

5 Conclusions

In patients with seropositive RA, recurrent or chronic pulmonary inflammation may be associated with the disease's onset through various biological mechanisms, underscoring the close relationship between pulmonary inflammatory factors and RA development. While seropositive RA is primarily characterized by joint symptoms, its systemic and multi-organ involvement requires greater emphasis. Among the extrajoint complications associated with seropositive RA, pulmonary diseases are relatively common and represent a significant cause of mortality in these patients. In certain cases, the progression of seropositive RA may originate from autoimmune processes in the lungs, manifest predominantly as joint symptoms, and culminate in severe pulmonary involvement during the disease's terminal stages. The role of pulmonary immune dysregulation in the course of RA remains incompletely understood. The large volume and compensatory capacity of the lungs may obscure histological changes that precede joint symptoms, posing challenges for research into the mechanisms underlying seropositive RA. Inflammatory responses triggered by various pulmonary diseases need to be classified and studied in greater detail based on their specific immune characteristics to clarify their role in systemic immune dysregulation, thereby offering new avenues for the prevention and treatment of autoimmune diseases such as seropositive RA.

Studies have shown that the incidence of seropositive RA has been increasing. Early identification of seropositive RA is critical for reducing the disability associated with disease progression. Autoantibodies such as ACPA and RF can be detected prior to the clinical onset of seropositive RA, making them valuable for early

diagnosis. As the close relationship between ACPA and pulmonary diseases becomes increasingly evident, screening and monitoring ACPA in individuals with long-standing pulmonary inflammation or seropositive RA patients without overt lung disease is of great significance. This may provide new hope for improving patients' quality of life and extending their life expectancy. Additionally, further exploration of related biomarkers and their implications for systemic immunity is essential for advancing our understanding of seropositive RA progression and prognosis.

Thus, the prevention and early treatment of pulmonary inflammation should receive greater attention in the context of seropositive RA management. From the perspective of mitigating inflammation, maintaining a healthy microbiome, and supplementing n-3 PUFAs and vitamin D may serve as adjunctive measures for RA prevention and treatment. Recent studies have provided new directions for controlling inflammation in seropositive RA, including the suppression of inflammatory responses and the induction or enhancement of anti-inflammatory mechanisms. These strategies are particularly important for breaking the vicious cycles associated with seropositive RA pathogenesis. However, because these pathways are not unique to seropositive RA, they may present challenges in the development of targeted therapies. Further elucidation of the specific mechanisms underlying RA pathogenesis is needed to minimize potential adverse effects associated with new therapies.

Author contributions

PY: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. YS: Conceptualization, Writing – review & editing. ML: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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