Review

Pathogenesis of rheumatoid arthritis: one year in review 2026

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by joint destruction and extra-articular manifestations. It is well known that underlying the pathogenesis of the disease a complex interplay of genetic susceptibility, epigenetic modifications, and immune dysregulation takes place. Over the past year, basic and clinical research studies in the field of RA have been conducted, shedding further light on certain pathogenetic mechanisms not yet fully clarified. In particular, advances have been made in understanding the interaction between cells of the innate immune system, such as neutrophils and macrophages, and structural cells, such as fibroblast-like synoviocytes (FLS). Furthermore, due to recent findings obtained at cellular and molecular levels, it has been possible to better define the interactions between the innate and adaptive immune systems and to better explain how RA-specific antibodies can exert a regulatory effect on the innate immune system. Identifying new elements regulating the mechanisms underlying RA pathogenesis is crucial for designing new therapeutic strategies and utilising biomarkers useful for the diagnosis and managements of the disease.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease mainly due to abnormal responses of the immune system against self-components, with consequent tissue damage and organs disfunction. It is well known that underlying RA pathogenesis a complex interplay of genetic susceptibility, epigenetic modifications, and immune dysregulation takes place. The specific elements that regulate different mechanisms involved in these intricate processes are not yet clear and every year data obtained from research activity allow us to add another piece to the complex world of RA pathogenesis (1). Improving the current knowledge on gene regulation and different molecular and cellular components of the innate as well as adaptive immune systems allows us to improve our knowledge on the mechanisms responsible for the development and progression of the disease, enabling the identification of genetic and/or molecular targets for the development of personalised therapies.

In this review article we summarised the results of a Medline search of original research articles in English published in the PubMed database from January 1 to December 31, 2025.

Genetic and epigenetic advances

Current data on RA pathogenesis support the contribution of genetic variants in disease susceptibility, progression of inflammatory processes and, in some cases, long-term disability. In the last year, results of Genome-Wide Association Studies (GWAS) support the role of some genetic variants in cytokine signalling amplification, antigen presentation and T-cell activation, all aspects of immune system dysregulation relevant for the development of RA. Several recent evidences reveal that the probability of developing RA is associated at about 60% with genetic factors, specifically with human leukocyte antigen (HLA) polymorphisms, including HLA-DR and HLA-DQ (2). It is well known that the HLA locus is present on the short arm of chromosome 6, which encodes the major histocompatibility complex (MHC), and it is defined as an important cell-surface protein essential for antigen presentation. The

current classification of HLA identifies HLA class I, including HLA-A, HLA-B and HLA-C, which presents intracellular antigens to $CD8^+$ cytotoxic T cells, and HLA class II, including HLA-DR, HLA-DP and HLA-DQ, presenting extracellular antigens to $CD4^+$ helper T cells. Among the HLA class II, the HLA-DRB1 gene, especially the HLA-DRB1*04 and HLA-DRB1*01 alleles, seems to be associated with a higher risk of developing RA among females, while men have a higher risk of developing extra-articular manifestations. In addition, these alleles may favour the production of anti-citrullinated antibodies, resulting from the loss of central immune tolerance (2). The shared epitope (SE), an amino acid sequence located in certain HLA-DRB1 alleles within the antigen-binding region, is recognised to be one of the most important factors in RA pathogenesis, resulting in a higher susceptibility to develop the disease. This has recently been confirmed by a recent large study conducted in three hundred Greek patients in which smoking and the presence of SE alleles increased the risk of developing anti-citrullinated protein antibodies (ACPA)-positive RA (3). However, the isolated involved alleles are not sufficient for promoting disease development and an interaction between HLA alleles and the immune system is required for disease progression and organ damage. Although the role of HLA alleles in RA development has been extensively studied, particular attention has been recently given to the role of epigenetic modifications in the mechanisms underlying RA pathogenesis. Specifically, DNA methylation, histone modifications, and non-coding RNA-associated regulation, key mechanisms that control gene expression without altering the underlying DNA sequence, are able to influence the activity of structural cells resident in the joints of RA patients. This is the case of FLS, key cells required for the development and maintenance of synovia inflammation. In this setting, recent findings highlight how epigenetic remodelling drives ferroptosis, an iron-dependent, inflammatory cell death, occurring in FLS from RA patients (4). Specifically, overactive histone demethylase enzymes seem to alter chromatin structure of the joint tissue of RA patients, triggering the over-expression of the regulatory microRNA miR-128-3p. This microRNA is responsible for targeting and downregulating the Solute Carrier Family 7 Member 11 (SLC7A11) gene, silencing a core component of the cell's antioxidant defense system. Exposed of these protective mechanisms, the FLS as well as other synovial cells, might experience severe oxidative stress, toxic iron accumulation, and lipid damage, resulting in ferroptosis (4). Beyond these chromatin-levels alterations, epitranscriptomic mechanisms might further contribute to dysregulation of the synovial tissue. N6-methyladenosine (m6A) is the most prevalent chemical modification in mRNA, and it is mainly involved in the post-transcriptional gene regulation. A recent study proved that insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3)-mediated m6A modification is associated with increased FLS proliferation, invasion and cytokine production in RA patients, amplifying inflammation with consequent joint injury (5). Targeted inhibition of IGF2BP3 has therefore been proposed as a potential therapeutic strategy for RA. By reducing cell proliferation and inflammatory activation, this approach might limit disease progression and the consequent potential joint damage. Given the key role of FLS in RA pathogenesis, recent studies are focused on the potential modulation of these cells to limit disease progression. This is the case of Alpha-Ketoglutarate-Dependent Homolog 5 (ALKBH5), a member of the AlkB family of Fe(II)/α-KG-dependent dioxygenases that functions as RNA demethylase removing m6A. The ability of ALKBH5 to regulate FLS apoptosis takes place through m6A-dependent modifications of miRNA maturation, in particular resulting in a higher expression of miR-181b-5p. Therefore, over-expression of ALKBH5 promotes apoptosis and inhibits proliferation in RA-FLS by demethylating m6A on pre-miR-181b-1, thereby enhancing miR-181b-5p maturation (6). Modulating ALKBH5 to limit RA progression could also be useful in light of its effect on macrophage polarisation in the joints of RA by epitranscriptomic regulation.

In the last year, particular attention has been given to the possible epigenetic regulation of macrophages as a strategic therapeutic approach in RA. In fact, recent data have identified piENOX2, a PIWI-interacting RNA over-expressed in synovial macrophages, as a key epigenetic driver of pro-inflammatory M1 polarisation, while a piENOX2 inhibitor seems to facilitate the differentiation into M2 (7). By using methylated RNA immunoprecipitation sequencing and methylated RNA immunoprecipitation together with quantitative PCR, it was possible to demostrate the regolatory role of piENOX2 on ALKBH5-mediated m6A modification of integrin subunit alpha 4 (ITGA4) mRNA, thereby influencing macrophage polarisation through the PI3K-AKT signalling pathway (7). In parallel, m6A-related gene RNA binding motif protein 15 (RBM15), reduced in patients with RA, was recently investigated in humans as well as in mouse model of collagen-induced arthritis (CIA), focusing on its impact on NLR family pyrin domain containing 3 (NLRP3) inflammasome activation. Combining the results obtained in both human and animal models made it possible to identify this gene as a potential protective factor against the development of RA. In fact, RBM15 over-expression reversed *in vitro* the increased macrophages activity and reduced RA symptoms, pathological damage, and inflammatory responses in CIA model (8). Therefore, by modulating epigenetic mechanisms that promote the pro-inflammatory phenotype of macrophage, it is possible to downregulate some pro-inflammatory processes relevant in the development of RA. Through a deeper understanding of the mechanisms regulating genetic aspects of RA pathogenesis, it is possible to identify susceptible patients and support them toward personalised therapies.

Take home messages

- Smoking and the presence of SE alleles increased the risk of developing ACPA-positive RA in Greek population (3).
- Over-expression of ALKBH5 promotes apoptosis and inhibits prolifer-

ation in FLS derived by RA patients by demethylating m6A on pre-miR-181b-1 (6).
- Targeting the downregulation of PI-ENOX2 in macrophages promotes macrophage differentiation toward the M2 phenotype, resulting in an anti-inflammatory effect in RA (7).
- RBM15 overexpression reduced RA symptoms, pathological damage, and inflammatory responses in CIA model (8).

New insights in environmental aspects

Dietary habits play a key role in the setting of environmental factors influencing the immune system and therefore, potentially involved in RA pathogenesis. Some eating patterns are rather standardised, such as the Mediterranean diet, whereas others may broadly differ across cohorts as gluten-free diets, sharing the feature of avoiding food containing gluten, but the rest of the food intake is variable. Therefore, when appraising the results of different studies it is advisable to focus also on nutrients or combinations of nutrients rather than on the overall dietary pattern only. In line with this and based on previous evidences on cardiovascular diseases and cancer, different dietary scores are often used in the rheumatology setting to account for the effects of different combinations of nutrients.

The registry-based nested case control study by Bäcklund *et al*. observed that higher intake of red/processed meat was associated with a higher risk of seropositive RA, whereas vegetables and fruits were associated with a lower risk of RA (9). Likewise, two studies reported that higher dietary fibre intake was associated with lower RA prevalence (10, 11), whereas Wang *and al*. identified a negative genetic causal relationship between cereal intake and oily fish intake (12). The intake of one-carbon metabolism nutrients such as vitamin B9 (folate), vitamin B12 (cobalamin), and vitamin B2 (riboflavin) (13), and a low-carbohydrate diet (14) were also linked to reduced risk to develop RA. On the contrary, higher consumption of ultra-processed food that contain high amounts of saturated fats, salt and sugar was linker to higher likelihood of RA (15).

Wholegrain products, fibres, fruits, vegetables and oily fish are in fact key components of the Mediterranean diet that should be regularly consumed whereas red meat, saturated fats and sugar seat at the top of the Mediterranean diet pyramid as their consumption should be minimised. From a basic research point of view, adherence to the Mediterranean diet was also linked to a peculiar metabolic signature, including for example a higher n-3 fatty acids to total fatty acids ratio, that may attenuate genetic predisposition to RA (16).

In line with this, high values of the dietary inflammatory index, a score weighting nutrients according to their anti-inflammatory effect, were significantly associated with increased RA prevalence (17). Furthermore, higher dietary antioxidants intake was correlated with a lower RA incidence (18). A study applying a broader perspective, namely observing healthy eating patterns, as measured by the healthy eating index-2015 and healthy lifestyle demonstrated that the adherence to a greater variety of healthy lifestyle behaviours was negatively associated with the occurrence of RA (19). The widespread use of various dietary regimens makes it possible to conduct association analyses between diet and the development of autoimmune diseases. In particular, it has been possible to identify which dietary patterns may play a protective role against the development of autoimmune diseases. This is the case of the gluten-free diet that has been proven to protect from RA onset by modulating, at least in part, specific immune cell subpopulations such as $CD14^+$ $CD16^+$ monocytes and CD20 on IgD^+ CD38^dim B cells (20).

However, we have to take into account that exclusion diets such as gluten-free, vegetarian, and dairy-free diets in patients with RA remain a subject of debate and are not always recommended by various guidelines.

Another important aspect of the environmental scenario is the microbiome, whose diversity in patients with RA compared to normal individuals has been extensively assessed.

An interesting study conducted in two independent cohorts of monozygotic twins discordant for RA showed that although faecal microbiome diversity and composition did not differ between twins, a significant decrease in short-chain fatty acid-producing bacteria (*e.g*. *Blautia faecis*, *Gemmiger formicilis* and *Faecalicatena fissicatena*) was observed (21). In addition, α-diversity of the oral microbiome was negatively correlated with RA, namely the lower the variety of bacteria, the higher the likelihood of having RA in a large nationwide study (22). Based on recent data, environmental factors can either promote the development of RA or play a protective role. However, accurate interpretation requires an assessment of genetic aspects of the population analysed and potential epigenetic modifications that may occur.

Take home messages

- High intake of cereals, oily fish, fruit, vegetables, fibre and one-carbon metabolism nutrients (*e.g*. B9 and B12 vitamins) may reduce the likelihood of developing RA (13).
- High intake of red meat and higher consumption of ultra-processed food that contain high amounts of saturated fats, salt and sugar were linked to higher likelihood of RA (15).
- More than oral and fecal microbiome diversity it is the decreased presence of short-chain fatty acid-producing bacteria that may modulate the risk of developing RA (21, 22).

Novelties in the innate immune response

The innate immune system, with its cellular and soluble components, plays a fundamental role in organ and tissue homeostasis. In RA, as in other autoimmune diseases, the innate immune system can actively contribute to the development of autoimmunity through close interaction with cells of the adaptive immune system, including T and B lymphocytes. Furthermore, cells of the innate immune system, including structural cells actively contribute to promoting and amplifying the inflammatory and remodelling processes in the joints, with consequent cartilage

and bones damage. It is well known that one of the main pathophysiological features of RA is the inflammation of synovial membranes and formation of a hyperplastic pannus where structural cells such as FLS play a key role. In the joints of RA patients, the pro-inflammatory activity of FLS can be regulated by soluble mediators such as cytokines, chemokines, and growth factors as well as by RA-pathognomonic antibodies, such as ACPA. Recently, by using *in vitro* approaches, it has been shown that ACPA are able to increase receptor activator of nuclear factor-kappaB ligand (RANKL) and pro-inflammatory cytokines in FLS derived by RA patients. Furthermore, these activated FLS are able to promote osteoclastogenesis, process down-regulated by acting mainly on CD64 and peptidylarginine-deiminase (PAD)-2 pathways (23).

The mechanisms regulating FLS activity in RA is quite complex and not been fully elucidated. Recent analysis of miRNAs in RA-FLS demonstrated that hsa-miR-21-5p promotes cells proliferation and consequent exacerbation and perpetuation of synovia inflammation (24). Furthermore, the demonstration that IL-6, key cytokine in the pathogenesis of RA, is able to increase the expression of this miRNA, supports the role of the pro-inflammatory environment in amplifying inflammation and tissue remodelling in the joints (24).

In the complex scenario of synovial inflammation, the infiltration of inflammatory cells and the proliferation and activation of FLS are particularly relevant. Specifically, neutrophils and macrophages tightly interact with FLS amplifying and perpetuating local inflammatory processes as well as exerting systemic effects. Neutrophils are the first immune cells recruited in the inflamed tissue, including the joints, and their action mainly involves the formation of neutrophil extracellular traps (NETs), web-like structures made of DNA, histones, and cytotoxic proteins. Periodontal, pumonary and intestinal mucosa are main triggering site of citrullination and in RA NETs are enriched in citrullinated autoantigens, thereby promoting anti-citrullinated protein antibody production and contributing to structural damage in the joints. Therefore, the production of IL-1 family cytokines, inflammasome activation, and NETs formation in RA appear to be closely linked. In fact, the NLRP3 inflammasome has been recently proposed as a pivotal upstream regulator of gasdermin D (GSDMD)-dependent NETosis in RA, and a possible target for new therapeutic approaches to control the disease. In fact, by inhibiting NLRP3 or GSDMD is possibile to reduce NETs formation and to exert a down-regulation of local inflammation (25). Although the mechanisms regulating NETs in RA has not yet been elucidated, recent studies demonstrated the ability of NETs to increase glycoprotein Ib (GPIba) expression, thereby promoting proliferation of FLS, IL-6 production and differentiation of T follicular helper lymphocytes (26, 27).

The direct interaction between the innate and adaptive immune systems in RA has been further confirmed by recent studies demonstrating how ACPA in CIA animal model are able to induce the priming and activation of the NLRP3 inflammasome by the release of ATP and the efflux of K^+ (28). In fact, an increased levels of IL-1β in the peripheral blood and more pronounced pyroptosis and caspase-1 (p20) expression in the synovial tissue have been detected in ACPA-induced CIA compared to mice induced with common collagen, supporting the direct role of ACPA in regulating local inflammation.

In the complex landscape of cells of the immune system, parallel to neutrophils, macrophages play key roles in some of the mechanisms involved in RA pathogenesis. They are activated in the tissue mainly through Toll-like receptors (TLR) and by opsonisation. After their recruitment in inflamed synovial tissue, they are the main source of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, leading to amplify inflammation and to promote joint damage. However, we have to take in account that not all macrophages perform the same function. In fact, two different phenotypes of macrophages have been identified and characterised, based on their polarisation: M1 macrophages, which promote inflammation through phagocytosis, and M2 macrophages, which promote tissue repair and remodelling. In RA, it has been shown that this polarisation is shifted toward the pro-inflammatory M1 and this is mainly due to exosomal circ-CBLB secreted from RA-FLS (29), supporting the pivotal role of the cross-talk between macrophages and FLS in the RA pathogenesis.

How macrophages maintain their pro-inflammatory profile (M1 phenotype) it has not yet been clarified. Recently, it has been demonstrated that GM-CSF supports the maintenance of the pro-inflammatory nature of RA monocyte-derived macrophages, driving CCL22-mediated T cell responses, promoting $CD4^+$ T cell migration and differentiation toward Th1 and Th17 subsets, but not regulatory T cells (30).

Therefore, identifying new components of the innate immune system relevant for the regulation of the mechanisms underlying RA pathogenesis is crucial for designing new therapeutic strategies and utilising biomarkers useful for diagnosis and disease monitoring.

Take home messages

- ACPA are able to trigger both the priming and activation of the NLRP3 inflammasome in innate immune cells, identifying a possible bridge between the innate and adaptive immune systems (28).
- In RA, macrophage polarisation is shifted toward the pro-inflammatory M1 macrophages and this is mainly due to exosomal circ-CBLB secreted from RA-FLSs (29).
- GM-CSF supports the maintenance of the pro-inflammatory nature of RA monocyte- derived macrophages, driving CCL22-mediated T cell responses, promoting $CD4^+$ T cell migration and differentiation toward Th1 and Th17 subsets (30).

Novelties in the adaptative immune system

While the innate immune system is fundamental to inflammatory and remodelling processes, the adaptive immune system is crucial for the development of autoimmune processes, leading to the formation of autoantibodies. Different cells from the adaptative im-

mune system are involved in initiating and sustaining the development of RA. Among these, follicular helper T (Tfh) cells are a heterogeneous $CD4^+$ T cell subset able to trigger B-lymphocyte response namely leading to their activation, proliferation and differentiation into antibody producing cells. A recent study exploring different Tfh subpopulations in patients with RA revealed that circulating (c) Tfh cells display a robust B helper-associated function, potentially linked to the CXCL13-CXCR5 axis and enhancing glycolysis (31). Of interest, by inhibiting glycolysis in an experimental model, a reduction of B helper-related molecules was observed in parallel with a clinical and histological improvement of the disease. Regarding regulatory T (Treg) cells, the T cell population aimed at counteracting autoimmune responses and some recent studies unmasked novel pathogenic mechanisms. For example, it is well established that the expression of immune checkpoint receptors such as PD-1 is associated with survival, proliferation, and enhanced effector functions of several immune cells in different autoimmune diseases. However, the PD-1 pathway also plays a critical role in Treg-mediated suppression of inflammatory T cells and studies on experimental models of RA revealed that an impairment of the PD-1 pathway reduced the suppressive activity of Treg cells within the inflamed synovial tissue (32). On the same line, Emerson *et al.* demonstrated that IL-6 and TNF, key cytokines in RA, are able to increase the expression of PD-1 and other immune checkpoint receptors on $CD4^+$ lymphocytes *in vitro* (33), suggesting that in the synovial microenvironment, the engagement of PD-1 on effector $CD4^+$ cells rather than on Treg cells may be predominant. In this scenario, it seems to be relevant the immunosenescence since $CD4^+PD\text{-}1^+$ T cells in RA patients exhibited hallmark senescence features, and transfering these cells in mice with experimental arthritis significantly accelerated disease progression (34).

In the inflammatory environment of RA where pro-inflammatory mediators often play synergistic roles, TNF is recognised as a potent inducer of endotoxin tolerance-associated molecules, such as interleukin-1 receptor-associated kinase 3 (IRAK3) whose pathogenic role in RA via Treg cells has been recently suggested. In fact, by inducing experimental RA in $IRAK^{-/-}$ mice the disease progression was significantly accelerated compared to the wild-type counterpart. Of interest, the $IRAK^{-/-}$ mice displayed reduced proportions of Treg cells already before the disease onset and also during the disease course, unlike the Th1 and Th17 cell subsets (35). In the last year, particular attention has been paid to the regulatory processes of Treg cells in RA. In fact, Bahabayi *et al.* revealed that human and murine Treg cells lacking CD55 exert a more suppressive activity than those with normal expression of this surface molecule, adding another piece to the current understanding of Treg cell regulation (36).

Parallel to T cells, particular attention has been given to the regulation of B lymphocytes, often extensively studied in both humans and animal models of RA. Understanding B-cell regulation in the phases preceding disease development is crucial for designing early interventions. With this aim, de Vries *et al.* explored B cells phenotype in individuals at risk of developing RA and observed that unswitched and switched memory B-cell frequencies were similar in in the cohort at risk of developing RA and in the normal subjects, but not in those of patients with overt RA. In addition, individuals at risk that eventually progressed to RA showed an early activation profile of naive B cells in the pre-clinical phase and RA progressors had a significantly greater expansion of CD27-negative IgG+ B cells compared to individuals that did not developed RA (37). All these recent results demonstrate marked B-cell heterogeneity across the different stages of the disease and the need to evaluate morphological and functional differences of B cells during the preclinical stages of the disease.

Take home messages

- Follicular T helper cells play a role in RA pathogenesis by triggering B lymphocytes via chemokine-receptor interaction among other mechanism (31).
- The expression and engagement of surface molecules such as PD-1 and CD55 can affect the suppressive activity of regulatory T cells in RA (36).
- Patients at risk of developing RA display B cell abnormalities since the preclinical phases of the disease (37).

Conclusions

The mechanisms underlying RA pathogenesis are quite complex and several cells and mediators contribute to the development of different features of the disease. Research activities in humans as wells as in animal models of RA involving genetic, epigenetic and molecular biology lead to identify and better characterise new mechanisms involved in RA pathogenesis. Recent discoveries in the field of RA pathogenesis have made it possible to identify potential therapeutic targets and biological components suitable for use as biomarkers for the diagnosis and follow-up of patients with RA.

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