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Review Article

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Synovial Fluid as a Crucial Component of the Joint Microenvironment in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disease closely associated with synovial tissue proliferation, pannus formation in small joints such as the hands, wrists, and feet, cartilage destruction, and systemic complications such as pulmonary, cardiovascular, neurological, and skeletal muscle lesions, glucocorticoid-induced osteoporosis and infections. The importance of confirming the diagnosis and determining local activity is given to the study of synovial fluid. A deep understanding of the pathological process in the joint in RA, characterized by changes in autoreactive CD4+ T cells, B cells, macrophages, inflammatory cytokines, chemokines, and autoantibodies, has now been achieved, although much remains to be explored. This article provides an updated overview of the pathogenesis of RA, revealing even more therapeutic targets for the intra-articular pathological process.

Keywords: Rheumatoid arthritis; Synovial fluid; T-cells; B-lymphocytes; Innate immunity; Structural damage

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by invading hematopoietic and non-hematopoietic cells in the synovial tissue able to secrete several mediators, which induce chronic joint inflammation and severe bone damage (1-5). Therefore, the synovial fluid (SF) harbors a complex population of immune and non-immune cells whose function has long been restricted to a simplistic inflammation context. Recent evidence supports the idea that RA synovial fluid (RASF) rules a much more complex task in the autoimmunity of this pathology. The autoimmune etiology of RA has been investigated for many years, and is yet currently inquiring, about biomedical research about its complex immune pathogenesis (6). Global epidemiology of RA, according to the Global Burden of Diseases, reported a survey where the US has the highest age-standardized prevalence of RA (0.38%, 95% confidence interval [CI], 0.36–0.40), followed by Western Europe (0.35%, 95%

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Conflict of Interest

The authors declare no potential conflicts of interest.

Abbreviations

ADSC, adipose-tissue derived stem cell; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCR, B cell membrane receptor; CI, confidence interval; CIA, collagen-induced arthritis; DC, dendritic cell; ICAM, intercellular adhesion molecule; LYVE1, lymphatic vessel endothelial hyaluronan receptor 1; MC, mast cell; MerTK, Mer tyrosine kinase; MMP, matrix metalloproteinase; MRP, myeloid-related protein; mtDNA, mitochondrial DNA; NETosis, NET formation; NLRP3, NOD-like receptor family pyrin domain containing 3; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-kappa B ligand; SF, synovial fluid; SM, synovial macrophage; TF, tissue factor; TREM2, triggering receptor expressed on myeloid cells 2.

Author Contributions

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CI, 0.31–0.38) (7). Therefore, RA still raises a huge interest in human health sciences, as its impact on social life could be particularly concerning (8).

For many years it has been acknowledged that joints are the targeted anatomy of RA, although extra-articular manifestations of RA were recently reported (9,10). It is well known that joints are complex anatomical structures that warrant the ability to move several contiguous skeletal segments and, taken together, allow a movement harmony of the body. Joints can be classified into synovial and non-synovial ones. A typical synovial joint consists of 2 contiguous bony heads covered by hyaline cartilage, a capsulation circumscribing the joint cavity, ligaments representing stabilizing articulation elements, and by nerve endings.

SF is a complex immune micro-environment, which represents a challenging issue for fully elucidating RA pathogenesis and its successful treatment.

Animal models, such as collagen-induced arthritis (CIA) mice or K/BxN mice, should allow shedding light on the immunopathogenesis of RA by focusing on the immune microenvironment of SF. These models are characterized by the strong dependence on autoantibodies against type II collagen or glucose-6-phosphate isomerase, and animals can transfer RA from an arthritic mouse to a healthy recipient animal (11-13). Other models, such as the SKG mouse, allow researchers to investigate the role of highly reactive Th $CD4^+$ cells rather than autoantibodies, as synovial inflammation in these mice models is mediated by Th cells (14). The SKG mouse model, a fundamental tool to dissect the extreme complexity of RA pathogenesis, is caused by a spontaneous mutation in the ZAP-70 gene (known to encode proteins highly crucial in T-cell development and immune function) in BALB/c mice. The mutation W163C ZAP-70 strongly impacts T-cell-driven RA in these animals (15).

A fundamental role in RA is exerted by Th17 cells (see below) (16,17).

During RA, the immunological role of SF is completely altered (1). However, the first consideration is that SF is not simply an inflamed microenvironment with deleterious consequences on joints and neighboring tissues but a signaling context that modulates immunity and the rejuvenation role of other anatomical compartments, such as the adipose tissue. The pro-inflammatory hallmark of RASF has a role in maintaining the proliferative ability of adipose-tissue derived stem cells (ADSCs) by upregulating the expression of indoleamine 1,2 dioxygenase, cyclooxygenase 2, intercellular adhesion molecule 1 (ICAM-1), TNF-stimulated gene 6, IL-6 and PD-L1, which are all factors ruling a fundamental task in ADSCs-mediated immunomodulation (18). RASF also induces CD4+Foxp3+CD25 high Tregs to dampen the expression of pro-inflammatory markers in macrophages, such as CD40 and CD80 (18).

In this context, the role of RASF may be much more intriguing than expected.

Suppose the RASF immune microenvironment modulates the interplay between musculoskeletal joints and other neighboring tissues or anatomical districts. In that case, RASF may be used as a model to investigate how the organism addresses autoimmunity and which is its real origin. For example, a link with mitochondria functional impairments has been highlighted (19). Defects in mitophagy may be paramount in driving autoimmune disorders, for example. The autophagy genes IRGM, ATG5, and ATG7 are implicated in autoimmune diseases (19), and failure in mitochondria-autophagic mechanisms may lead to autoimmune events due to the mitochondrial DNA (mtDNA) triggering of type I IFN (19).

RA has numerous pathogenetic links with mitochondrial abnormalities (20,21). Therefore, it is important to investigate how RASF changes its immune, cellular, and molecular microenvironment during the RA pathogenesis and chronicity to investigate how autoimmunity evolves in this complex context.

A GLANCE AT THE IMMUNE MICROENVIRONMENT OF RASF

To focus on the causative nature of RASF, i.e., how RASF is formed and evolved, we should take into account the different interplays between immunity and tissue plastic regulation, as RASF is the microenvironment where these 2 fundamental contexts usually cross-talk each other. T cells infiltrate the synovium in RA, activating macrophages and synovial fibroblasts, turning them into tissue-destroying effector cells. T cells have a pro-inflammatory subset of Th-17 cells defined by their production of IL-17. Although many T cells exist in the synovial environment, their functional role remains unknown (22,23). Both individual susceptibilities to genetic interactions and environmental components may promote a loss in the immune tolerance to those citrullinated self-proteins, which the organism generates post-translationally (24,25). A co-stimulation interplay between dendritic cells (DCs), T cells, and B cells may generate an auto-immune response to these self-proteins (23). The inflammatory event involves primarily the lymph node and then the joint with RASF. A complex mechanism driven to address wound healing in the damaged (inflamed) tissue and tissue remodeling recruits humoral factors and cells to the SF, where interactive loops occurring among synovial fibroblasts, natural immune cells, chondrocytes, and osteoclasts drive the microenvironment to the pathological milieu characterizing RA pathogenesis. To date, RA is not simply considered a Th1-mediated disease but a dysregulation immune pathology where Th17 cells play a paramount role (17,25).

The first consideration is that Th17 cells are highly expressed in RASF (26). The number of Th17 cells in RASF closely correlates with other pathological biomarkers, such as C-reactive protein and Abs against citrullinated proteins, besides the RA activity score (27). The increase in the level of Th17 cells in RASF is associated with plasma increase in IL-21 and IL-23, as it is widely known that Th17 cells are implicated in the expression of various cytokines, such as Il-17A, IL-17F, IL-22 (17). These cytokines trigger fibroblasts in synovia and macrophages to produce pro-inflammatory cytokines, i.e., IL-1, IL-6, and TNF-α, besides PGE_2, exacerbating the joint's inflammatory landscape (28,29).

The role of Th17 cells in RA merits further elucidation.

A first hallmark of Th17 cells is their extremely wide plasticity, which enables these lymphocytes to exert effector actions differentiating into Th1 or Treg cells (30,31). These cells are usually identified by defined surface and functional markers, as they produce IL-17 and IL-22, many chemokine receptors such as CCR4, CCR6, and CD161, and are RORγt and STAT3 positive (17). These cells contribute to the RA inflammatory milieu by secreting IL-17, which triggers synovial fibroblasts and macrophages to produce pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, exacerbating joint inflammation. Despite the pivotal role of IL-17 in RA pathogenesis, clinical trials targeting IL-17 have not yielded successful outcomes, suggesting that other T cell subsets might also be involved (6). Recent studies have highlighted the role of Tph cells in RA pathogenesis. Tph cells, characterized

by the expression of CXCL13, PD-1, and inducible costimulatory molecule, are involved in promoting B cell responses, particularly within inflamed tissues like the RA synovium. These cells are distinct from the traditional T follicular helper cells and have been shown to contribute to the formation of ectopic lymphoid structures within the joints, thereby sustaining chronic inflammation. The failure of IL-17 inhibitors suggests that targeting Tph cells might offer a new therapeutic avenue, as these cells play a crucial role in perpetuating the immune response in RA (6).

In SKG models of mice, the arthritic pathogenesis may be initiated by self-reactive CD4+ T cells (called arthritogenic cells), which differentiate into effector Th17 cells, then migrate into the affected joints. CD4+ cells are initially activated by peripheral antigen-presenting cells via the stimulation of CD80/CD86 through CD40/CD40L, which then produce IL-6, IL-23, and IL-1, so activating the naïve CD4+ cells into Th17 arthritogenic cells, thanks also to the tissue-released TGF-β (1). Migration of these cells into the synovial microenvironment occurs under the modulation of the CCR6/CCL20 axis (32). This model is considered to explain how RA emerges and how RASF is formed.

Specific cytokines and growth factors probably maintain inflammation in the RASF. For example, it is widely known that GM-CSF exacerbates chronic inflammation in RASF (33,34). Moreover, chondrocytes, upon IL-1β stimulation, release a consistent number of metalloproteinases such as matrix metalloproteinase (MMP)-1 and MMP-13, alongside the release of IFN-γ, VEGF-A, IL-6, IL-33, IL-18 and GM-CSF (35).

Selectins, integrins, and chemokines play an essential role in the invasion of blood cells into the synovial tissue and, consequently, in the intensity of the inflammatory response at this stage (23). For example, adhesion molecules αvβ3 and α5β1 are considered fundamental glycoproteins in the etiology of RA (36). Other cytokines, such as IL-3, may have modulatory roles, such as promoting the Treg commitment from Th17 in an IL-2-dependent way (37).

RASF microenvironment represents an interchangeable compartment where the auto-immune disorder leading to RA pathogenesis tries to achieve an immune tolerance via inflammasome regulation (38). While inflammasomes are a group of molecules deputed to elicit a pro-inflammatory response to fight invading microbes, their dysregulation was associated with chronic pathologies and autoimmunity (38).

Inflammasomes regulate the differentiation and functions of various immune effector cells, modulating self-tolerance and the onset of autoimmunity (38).

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, a multimeric protein complex involved in the alarming sensing of pathogens and damage warning molecules, is a promising target in the therapy of autoimmune disorders, as NLRP3 promotes the secretion of IL-18 and IL-1β, besides pyroptosis in innate immune cells via caspase-3 (39).

NLRP3 is fundamental in elucidating RASF because its activity is closely intertwined with the role of mitochondria in autoimmunity and, therefore, in RA pathogenesis (20,21). Upon mitochondria stress, mtDNA escapes from organelles' pores made up of voltage-dependent anion channels, behaving as a molecular trigger of autoimmune diseases such as lupus (40).

RASF has been reported in the presence of extracellular mtDNA and oxidatively damaged mtDNA (41). Patients with RA showed the presence of mtDNA and the metabolite 8-hydroxy-2'-deoxyguanosine in SF, a biomarker correlated with the presence of rheumatoid factor (41). Noteworthy, patients with RA suffer from mitochondria dysfunction (42). But furthermore, RA may be associated with genetic variability in the mtDNA (43). A recent contribution evaluated 382 single nucleotide mtDNA variants, 23.82% occurring in the hypervariable region and 76.18% in some coding regions, present in RA patients and healthy controls. A variant (513 GCA < ACA), having G in HVR-III (which controls the translational activity of mitochondria), was significantly present in RA patients (43).

The pathogenesis of RA is influenced by a complex interplay of immune cells, cytokines, and genetic factors. Th17 cells, known for their plasticity, produce pro-inflammatory cytokines like IL-17, but their targeting in clinical trials has been less successful comparing to Tph cells. The SKG mouse model provides insights into how self-reactive CD4+ T cells differentiate into Th17 cells and migrate to affected joints, exacerbate inflammation through interactions with synovial fibroblasts and macrophages. Inflammasomes, particularly the NLRP3 inflammasome, highlight the importance of innate immune mechanisms in RA. Mitochondrial dysfunction, oxidative stress, and extracellular mtDNA further underscore the link between cellular stress and autoimmunity in RA. The identification of specific mtDNA variants in RA patients suggests a potential genetic predisposition contributing to disease susceptibility and progression.

IMMUNITY OF RASF: THE INNATE IMMUNE CELL POPULATION

Innate immune cells are particularly represented in RASF. For example, the role of synovial macrophages (SMs) in RA has been recently reviewed (44). The M1/M2 skewing in RASF SMs is not so different from other compartments, as M1 has a pro-inflammatory role, and M2 is the contrary. SMs with M1 phenotype account for mediators such as NF-κB, tissue factor (TF) leading the pathway mediated by STAT1, IRF5, and SOCS1and released mediators such as IL-1β, IL-12, IL-23, TNF-α, CCL5, CXCL9, CXCL10, CXCL11. For instance, recent research has highlighted the presence of specific regulatory macrophages in the synovium of RA patients, characterized by the expression of markers such as Mer tyrosine kinase (MerTK), triggering receptor expressed on myeloid cells 2 (TREM2), and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1). These macrophages are argued to play a role in modulating the inflammatory response and promoting tissue repair. MerTK is a receptor that facilitates the clearance of apoptotic cells, thereby preventing the release of potentially inflammatory cellular contents. TREM2 is involved in the phagocytosis of debris and the resolution of inflammation. LYVE1 is associated with lymphangiogenesis and the clearance of excess fluids from inflamed tissues. The presence of these regulatory macrophages suggests a complex role in the synovial environment, where they may act to counterbalance the pro-inflammatory macrophages that contribute to RA pathogenesis. This dual role of macrophages—both as drivers of inflammation and as regulators of tissue homeostasis—adds an additional layer of complexity to our understanding of RA and opens up new potential therapeutic targets.

SMs with phenotype M2 account for TF leading the pathway mediated by STAT6, IRF4, SOCS3, Klf4, c-myc, and released mediators such as IL-4, IL-10, CCL17, and CCL22 (44).

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A normal healthy joint synovium can be considered a thin tissue region containing few layers of cells. In contrast, RA can be described as a hyperplastic synovium, usually made of 2 thick layers, a lining, and a sub-lining layer, both highly represented by SMs. Usually, the number of SMs correlated with the severity of RA and articular destruction (45). These macrophages comprise 2 different populations of innate immune cells: resident SMs and macrophages from other sites (45). Tissue-resident macrophages share many features with other macrophages, such as the Clec4f+ Kupffer cells of the liver (46). Circulating macrophages from external sites and infiltrating the synovium are usually Ms4a3^{+} macrophages of utmost importance in RA pathogenesis (47).

The functionality of these SMs is particularly burdensome in RASF (48,49). Some cell biomarkers, such as CD14 and myeloid-related proteins (MRPs) 8 and 14 (MRP8 and MRP14), are considered for circulating SMs, whereas resident SMs are usually CD68 and CD163 positive, aside from some controversial opinions (42,50). Biomarkers only sometimes allow easy recognition of different SM populations' origin and function (44). The issue is particularly complicated by the recent discovery of other SM biomarkers, for example, the Z39Ig, which is the complement receptor for C3b and iC3b, and expansion of Z23Ig^{+}CD11^{+} cells is a diagnostic marker of RA (51). In rat models, resident SMs in RASF is positive for CD68, CD163, Z39Ig, F4/80, MerTK, ED2/3, and 25F9, whereas bone marrow-derived SM are positive for CD16, CD14, CD11b, MPO, CCR2, MMR, Ly6C, ED1 and lysozyme (44).

As with granulocytes are concerned, RASF affects the respiratory burst of most represented granulocytes, such as neutrophils, significantly (52).

Neutrophils play a paramount role in RA, and their presence in RASF is crucial to elucidate RA pathogenesis (53). In 2004, Brinkmann et al. (54) reported that neutrophils use a neutrophil extracellular trap (NET) to kill microbes and exert an inflammatory response, where histones and DNA fiber mainly form NET to catch and trap pathogens and eradicate them. Neutrophils' NET formation (NETosis) appears to be involved in the citrullination of proteins in RA, despite controversial opinions also existing (55). For example, according to other evidence, protein citrullination in RA may come from leukotoxic hyper-citrullination or even defects in mitophagy occurring in neutrophils (56). Undoubtedly, neutrophils yet represent a fundamental causative pathogenetic factor in RA (57,58). This should explicate why neutrophils are probably the most abundant innate immune cell population in RASF (59). The evidence should encourage research to deepen their role in RA pathogenesis. In RA, neutrophils are primed for the oxidative burst (60); moreover, both anti-citrullinated protein Abs and the rheumatoid factor can trigger neutrophil degranulation via the FcγR (61).

Dysregulation in neutrophil function leads to autoimmune diseases like lupus and RA (62). For example, dysregulation in neutrophil apoptosis is a typical hallmark of RA in RASF (63,64) (**Fig. 1**).

Circulating neutrophils in RA patients highly express MCL1 and express higher levels of activated NF-κB and lower levels of caspase-9, compared to non-RA healthy patients (63), causing delayed apoptosis, which is concurrently elicited by other components such as adenosine and lactoferrin (65,66). This neutrophils' apoptosis is delayed, because of the existence in RASF of IFNs and inflammatory mediators, such as GM-CSF, TNF-α, and IL-1β (67). Furthermore, the hypoxic microenvironment contributes to this scenario (68).

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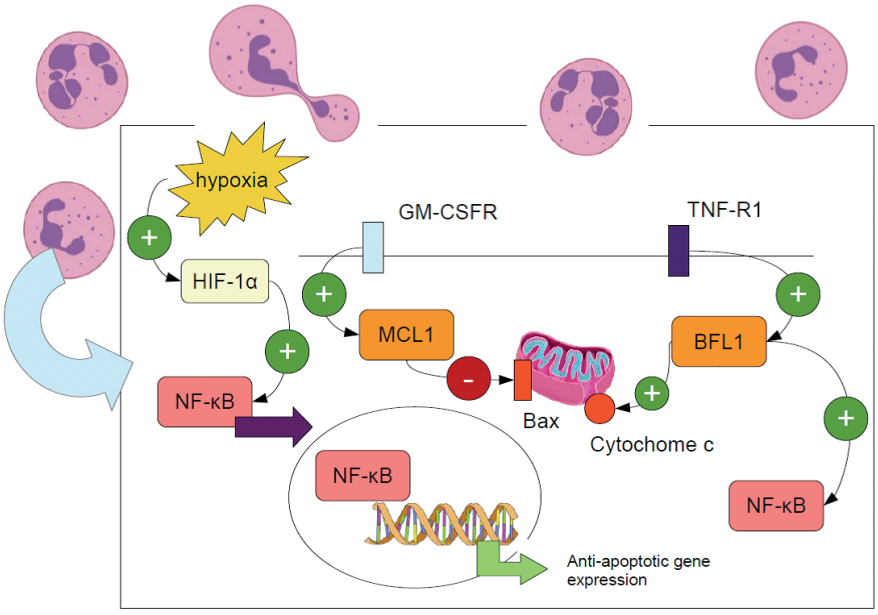

Figure 1. Apoptosis delay in RASF neutrophils. In RA, anti-apoptotic factors, such as cytokines and hypoxia, activate NF-κB and prevent mitochondrial cytochrome c driven apoptosis through activation of BFL1 and stabilization of MCL1. This prevents BAX:BAK pore formation, cytochrome c leakage, and apoptosome formation. Green circles: activation and promotion; Red circles: inhibition.
HIF-1, hypoxia-inducible factor-1; GM-CSFR, granulocyte macrophage-colony stimulating factor receptor; TNF-R1, tumor necrosis factor receptor 1.

The intricate interplay between SMs and neutrophils in RA highlights the complexity of the disease's pathogenesis. SMs exhibit a dual role, with M1 macrophages driving inflammation and M2 macrophages promoting tissue repair. Recent discoveries of regulatory macrophages expressing markers such as MerTK, TREM2, and LYVE1 further complicate our understanding, suggesting that these cells may act to counterbalance the destructive inflammation seen in RA. Neutrophils, on the other hand, are not only abundant in the RASF but also play a crucial role in perpetuating the inflammatory response through mechanisms such as NETosis and delayed apoptosis. The dysregulation of these innate immune cells contributes significantly to the chronic inflammation and tissue damage characteristic of RA. Subsequently, Neutrophils and macrophages are leading innate immune cells in RA pathogenesis. Understanding the nuanced roles of these cells and their interactions within the RA microenvironment could open new avenues for therapeutic interventions aimed at restoring immune balance and mitigating disease progression.

IMMUNITY OF RASF: THE ADAPTIVE IMMUNE CELL POPULATION AND B CELLS

It is well known that B cells are an important component of human adaptive immunity, but in the case of RA, they also serve as one of the main causes of the disease. Autoreactive B cells recognize host antigens and destroy those cells or tissues (69). Two checkpoints (the B cell membrane receptor [BCR] signal and the costimulatory signal) of autoreactive B cells are usually eliminated. Both checkpoints are generally defective in RA, resulting in a large production of autoreactive mature naive B cells.

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The combination of antigen and BCR provides the first signal for B cell activation, and the co-stimulatory signal is required for B cells to overcome inhibitory checkpoints. TLR and CD40 on B cells are primarily responsible for delivering costimulatory signals (70). BCR signaling is involved in developing autoreactive B cells in RA (71). This can be understood by the mutation of non-receptor type 22 protein tyrosine phosphatase in BCR signaling. This peripheral checkpoint signaling pathway dysfunction leads to defects in the resistance of T cells and B cells to suppression and apoptosis (72,73). In RA patients, B-cell activating factor (BAFF) and proliferation-inducing ligand A (APRIL) are constitutively expressed by various cells (including neutrophils, follicular DCs, macrophages, and fibroblast-like synoviocytes), and their expression is significantly higher in an inflammatory environment (74). BAFF can activate and differentiate B cells along the NF-κB pathway, producing autoantibodies and inflammatory cytokines and ultimately causing bone erosion and destruction in RA patients (75). There is evidence that inhibition of BAFF and APRIL receptors reduces anti-collagen IgG levels in mice with CIA, ultimately reducing joint inflammation (76).

Moreover, local synthesis of cytokines such as TNF-α, IL-6, IL-12, and IL-21 also influences inflammation and damage to bone cartilage. IL-6 is produced by B cells and macrophages in the RASF patients (77). Because IL-6 stimulates osteoclast formation, it will be associated with joint damage in RA patients. Therefore, an elevated serum IL-6 concentration has been associated with RA (78). Blocking the cytokine IL-6 with tocilizumab significantly improved clinical symptoms in RA patients by inhibiting memory B cells (CD19+CD27+) (79). Cytokine IL-21 provides a pro-inflammatory response by promoting the activation and reproduction of B cells. Therefore, blocking IL-21 will reduce T-cell-induced proliferation and differentiation of B cells, so reduced inflammation can be observed.

The consideration here is that B cells play an important role in the development and progression of RA by producing autoantibodies and pro-inflammatory cytokines and presenting antigens to T cells. In RA, TNF-α, IL-1, and RANKL promote osteoclast activation and osteolysis (80). Moreover, TNF-α stimulates the release of IL-1 by synovial fibroblasts and macrophages. Targeting B cells is an effective treatment approach to reduce inflammation, pain, and joint damage in people with RA. Ongoing research into B cell biology and the role of autoantibodies in RA may lead to the development of more effective and targeted treatments for this devastating disease (70). **Fig. 2** details this evidence.

IMMUNITY OF RASF: HOW IMMUNE CELLS DAMAGE THE JOINT

The synovium contains many innate effector cells, including macrophages, mast cells (MCs), neutrophils, and natural killer cells. Elevated levels of these parts of the innate immune system suggest that they are directly involved in joint inflammation and the destruction of articular cartilage and bone (81).

As detailed before, macrophages are found in synovial tissue. The abundance and activation of macrophages in the inflamed synovium are highly correlated with the severity of RA (82). Macrophages are critical in RA because they produce cytokines that promote inflammation and promote cartilage and bone destruction. Although macrophages are unlikely to be the "initiators" of RA, they have widespread pro-inflammatory, destructive, and remodeling abilities that may contribute significantly to the acute and chronic phases of the disease

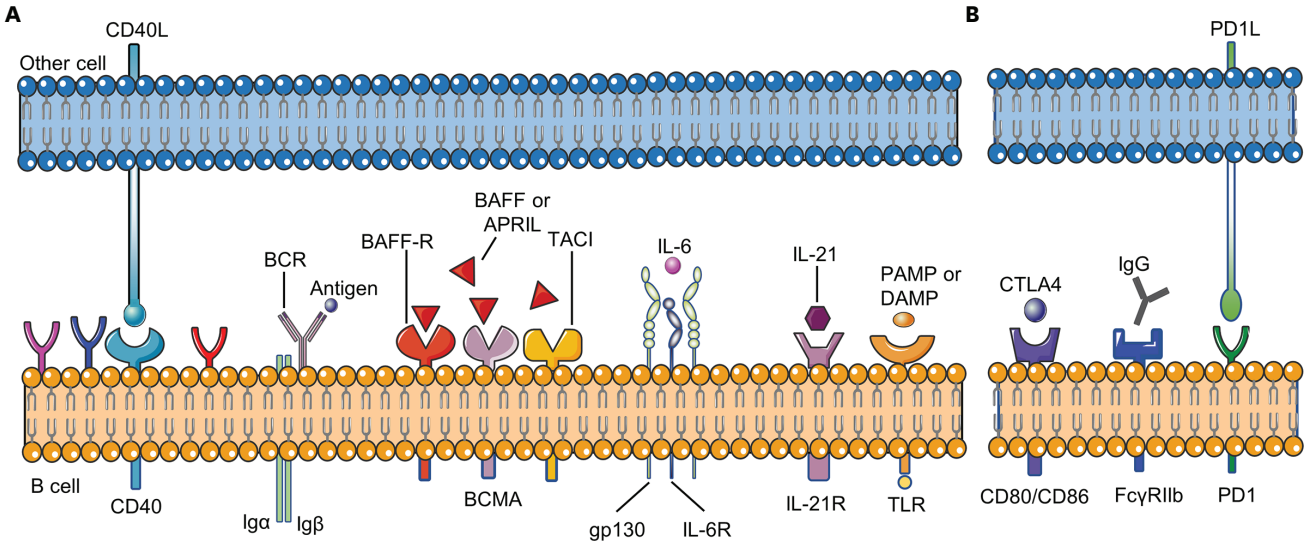

Figure 2. B cell checkpoints and signals associated with survival, development, and differentiation. B cell checkpoint signals serve various functions for survival, development, differentiation, inhibition, and other physiological processes. (A) Stimulatory checkpoint. (B) Inhibitory checkpoint. Permitted from Wu F, Gao J, Kang J, Wang X, Niu Q, Liu J, Zhang L. B cells in rheumatoid arthritis: pathogenic mechanisms and treatment prospects. *Front Immunol* 2021;12:750753 (73).

(48). In patients with joint inflammation, the number of macrophages will increase as they regulate the secretion of pro-inflammatory cytokines, including GM-GSF, IL-1, TNF-α, IL-12, IL-15, and IL-18 (82). Macrophage activation results from the ligation of TLR-2 and TLR-4 (83). In RA patients, macrophages interact with other signaling inflammatory cells to induce synovitis. Because inflammatory macrophage functions can be stimulated by paraformaldehyde-fixed T cells, this leads to an interaction with T cells, and this interaction causes monocytes to produce metalloproteinases, IL-1α and IL-1β.

Moreover, there are cases where, in the absence of costimulatory cytokines, peripheral CD4+ T cells could activate monocytes to produce IL-1 but not resting CD4+ T cells (84).

Therefore, the interaction of T cells with inflammatory macrophages will lead to synovitis. There are other interactions of macrophages with fibroblasts, and this interaction is of interest in connection with the resulting inflammation and tissue damage. This interaction will produce IL-6, GM-CSF, and IL-8. Some studies show that this interaction between fibroblasts and macrophages results in cartilage degradation *in vitro* (85). By producing pro-inflammatory mediators and enzymes, macrophages contribute to chronic inflammation and joint damage. The role of macrophages in RA is multifaceted, and researchers continue to explore new ways to target these cells to reduce inflammation and promote recovery in patients with the disease.

MCs, immune cells that infiltrate the synovium, are also involved in the pathogenesis of RA. Their presence in the synovium of patients with early RA has been associated with systemic inflammation, disease activity, and the presence of autoantibodies. Synovial MCs have previously been investigated as a potential biomarker for RA. However, results have been inconclusive, and the exact mechanism of MCs in RA remains unknown (86). However, some recent studies show that activated MCs secrete mediators, stimulate other immune cells and synoviocytes in the RA synovium, and recruit circulating inflammatory cells. A research team is currently looking into ways to target MCs to reduce inflammation and joint damage in patients with RA. One approach is to use drugs that block MC receptors responsible for their activation.

Another method is to target enzymes that MCs use to produce inflammatory molecules (87). Thus, the role of MCs in RA is complex and needs to be fully understood. However, targeting these cells may be a promising strategy to reduce inflammation and joint damage in RA.

In addition, NK cells can damage normal cells or cause autoimmune diseases such as RA through interactions with other cells such as DCs, macrophages, and T cells. This is manifested by a decrease in perforin production and a reduction of lytic function. NK cells isolated from the joints of RA patients suggest that they may play a role in the disease (88). By directly targeting osteoclasts, these cytotoxic NK cells can control their pathogenic bone absorptive function (90).

Finally, DCs have been found in the synovial membrane and joint fluid in RA, often at the center of T-cell clumps. They activate and proliferate autoreactive pro-inflammatory effector T cells (89). MHC II, costimulatory molecules CD40, CD80, and CD86, ICAMs such as DC-SIGN, and chemokine receptors such as CCR7 are expressed by DCs (90). Therefore, blocking some of the functions of DCs can be used as a treatment for RA.

In RA, the main factor in cartilage damage is synovial hyperplasia. In RA patients, extensive synovial fibroblast production (ESFP) in RASF produces hyperplastic synovium that aggressively destroys the underlying cartilage (91). Thus, ESFP has been identified as one of RA's most important mediators of cartilage destruction (91). In addition, fibroblast-like synovial cells and MMP synthesis degrade the type II collagen network, so biomechanical damage to cartilage may contribute to bone matrix degradation, as shown in some studies (92,93), cartilage is progressively devoid of chondrocytes that undergo apoptosis, with the participation of synovial cytokines (especially interleukin-1 and 17A) and reactive nitrogen forms (94).

In the first year of RA, bone erosion occurs due to prolonged inflammation (95,96). In RA patients, TNF-α and IL-1,6 activate receptor activator of nuclear factor-kappa B ligand (RANKL), leading to osteoclast differentiation and activation. Although blocking RANKL will have a small beneficial effect, it will only affect bone damage, and blocking will not impact inflammation or cartilage degradation (97). RANKL, on the other hand, also regulates the interaction of T cells with DCs. In an experimental model of arthritis, local T cell activation is associated with RANKL expression leading to joint destruction (98). In RA, there are also mechanical factors that lead to bone damage. These are not random sites of bone erosion in RA. Bone erosion can be seen in some mechanically vulnerable areas of human joints. The radial surfaces of the fingers are more susceptible to RA, while the ulnar side is affected less frequently (99).

Moreover, the second and third metacarpals are prone to erosive changes (100). Structural damage is a serious complication of RA that can significantly affect a person's quality of life. Early diagnosis and treatment of disease-modifying antirheumatic drugs and biologics, as well as lifestyle changes, can help slow or halt the progression of joint damage and improve outcomes for people with this chronic immune-inflammatory disease.

CONCLUSIONS

In the modern world, the number of autoimmune diseases is increasing. Among them, RA is one of the widespread autoimmune diseases. RA is a chronic inflammatory disease that affects the joints and can harm various body systems, including the skin, eyes, lungs,

heart, and blood vessels. The exact pathogenetic mechanism of RA is still unknown and is being studied. However, T cells are believed to play a key role in the development of the disease. In RA, T cells become activated and migrate to the joints, releasing cytokines and other inflammatory molecules contributing to joint damage. We need to understand the factors that cause loss of tolerance and localization of joint inflammation. Also, we should not overlook other immune cells, including B-lymphocytes, DCs, and MCs, which play an important role in the progression of the disease. By understanding the role of various immune cells in the disease, researchers and clinicians can develop new therapies that target immune cells that reduce inflammation and joint damage in patients with RA.

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