Journal of
Molecular Pathology

MDPI

Review

Rheumatoid Arthritis: What Inflammation Do We Face?

Anastasia V. Poznyak [1,*], Tatyana Vladimirovna Kirichenko [2,3], Dmitry Felixovich Beloyartsev [4], Alexey V. Churov [2,5], Tatiana Ivanovna Kovyanova [1,2], Irina Alexandrovna Starodubtseva [6], Vasily N. Sukhorukov [2,3], Stanislav A. Antonov [2,3] and Alexander N. Orekhov [2,3,*]

1 Institute for Atherosclerosis Research, Osennyaya 4-1-207, 121609 Moscow, Russia; kovyanovat@gmail.com
2 Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, 8 Baltiiskaya Street, 125315 Moscow, Russia; t-gorchakova@mail.ru (T.V.K.); achurou@yandex.ru (A.V.C.); vnsukhorukov@gmail.com (V.N.S.); vamore@inbox.ru (S.A.A.)
3 Petrovsky Russian National Center of Surgery, 2, Abrikosovsky Lane, 119991 Moscow, Russia
4 Vascular Surgery Department, A. V. Vishnevsky National Medical Research Center of Surgery, 27 Bolshaya Serpukhovskaya Street, 117997 Moscow, Russia; beloyar@rambler.ru
5 Institute on Aging Research, Russian Gerontology Clinical Research Centre, Pirogov Russian National Research Medical University, Russian Federation, 16 1st Leonova Street, 129226 Moscow, Russia
6 Department of Polyclinic Therapy, NN Burdenko Voronezh State Medical University, 10 Studencheskaya Street, 394036 Voronezh, Russia; starodubtsevairina1@gmail.com
* Correspondence: tehhy_85@mail.ru (A.V.P.); alexandernikolaevichorekhov@gmail.com (A.N.O.)

Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetrical joint inflammation, cartilage degradation, and bone erosion. This review explores the multifaceted aspects of RA pathogenesis, focusing on the dynamic interplay between innate and adaptive immune responses, genetic predisposition, and environmental triggers. The development of RA involves genetic susceptibility and trigger events such as infections, trauma, smoking, obesity, and microbiome alterations, fostering autoimmune reactions and tissue/organ destruction. The innate immune response, including toll-like receptor activation and synovial fibroblasts' roles, contributes to the acceleration of inflammatory processes in joint tissues. Monocytes and macrophages organize and sustain chronic joint inflammation, leading to tissue damage and bone resorption, while highlighting the significance of CD14 and CD16 subsets in RA pathogenesis. In the adaptive immune response, aberrant activation and proliferation of CD4+ T cells and the role of regulatory T cells in maintaining immune tolerance are discussed. Target cytokines like TNF-α, IL-6, IL-1, IL-17, and BAFF, as well as chemokines such as CCL2, CXCL10, CCL5, and CXCL12, have emerged as critical components in managing chronic inflammation and joint damage in RA. This comprehensive overview provides insights into the pathophysiology of RA and potential therapeutic avenues, emphasizing the importance of understanding these complex immunological and genetic mechanisms for developing more effective treatment strategies.

Keywords: rheumatoid arthritis; inflammation; autoimmune disease; immune response; cytokines; chemokines; pathogenesis; therapeutic targets

Citation: Poznyak, A.V.; Kirichenko, T.V.; Beloyartsev, D.F.; Churov, A.V.; Kovyanova, T.I.; Starodubtseva, I.A.; Sukhorukov, V.N.; Antonov, S.A.; Orekhov, A.N. Rheumatoid Arthritis: What Inflammation Do We Face? *J. Mol. Pathol.* **2024**, *5*, 454–465. https://doi.org/10.3390/jmp5040030

Academic Editor: Giancarlo Troncone

Received: 28 June 2024
Revised: 22 August 2024
Accepted: 29 September 2024
Published: 8 October 2024

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes progressive symmetrical joint inflammation, as well as cartilage destruction and bone erosion.

Clinically, RA symptoms differ significantly between early-stage RA and later stages of the disease, especially without proper treatment [1,2]. In the early stages, the general symptoms of RA may be flu-like, fatigue, or decreased energy, and there is also slight discomfort in the area of some joints. Clinical tests are characterized by elevated levels of C-reactive protein (CRP) and increased erythrocyte sedimentation rate (ESR) [3]. In the later stages, the disease becomes systemic and many subsystems of the body are damaged, leading to pleural effusions, pulmonary nodules and interstitial lung disease, lymphomas,

vasculitis of small and medium-sized arteries, keratoconjunctivitis, atherosclerosis, hematologic disorders (e.g., anemia, leukopenia, neutropenia, eosinophilia, thrombocytopenia or thrombocytosis) and a number of other serious problems [4].

The prevalence of RA ranges from 0.4% to 1.3% of the population, depending on sex and age (women get the disease several times more often than men, and the probability of the disease debut strongly increases after 50 years of age), as well as geography. Thus, the number of RA cases increases from south to north and is higher in urban than in rural areas. RA is one of the most common chronic inflammatory diseases [5].

2. Development of Rheumatoid Arthritis

Although the exact cause of the onset and progression of RA is uncertain, it can be argued that both genetic and environmental factors influence its onset. Two factors are required for the onset of RA: (1) a patient's genetic predisposition to generate autoreactive T and B cells and (2) a triggering event, such as viral and bacterial infections or tissue trauma, that provides activation of antigen-presenting cells (APCs) to activate previously generated autoreactive lymphocytes, leading to a breakdown in tolerance and subsequent tissue/organ destruction [6]. This scenario is characteristic of all or nearly all autoimmune diseases. Importantly, both are equally important: genetic predisposition makes it possible in principle for such immune reactions and biochemical processes to occur, and a trigger event sets in motion a process that was previously only at the level of potentially possible scenarios [7,8]. The influence of genetic factors was established through family history and twin studies, and trigger and environmental factors were established through correlations and statistical studies, some of which were later confirmed by theoretical and empirical studies (see below). Among these trigger events, in addition to infections and trauma, the following range of factors can be identified: smoking, obesity, exposure to ultraviolet rays, sex hormones, medications, changes in the gut, oral and pulmonary microbiome, and periodontal disease [9,10]. In Figure 1, we summarized some major factors of RA development that are discussed in this paper.

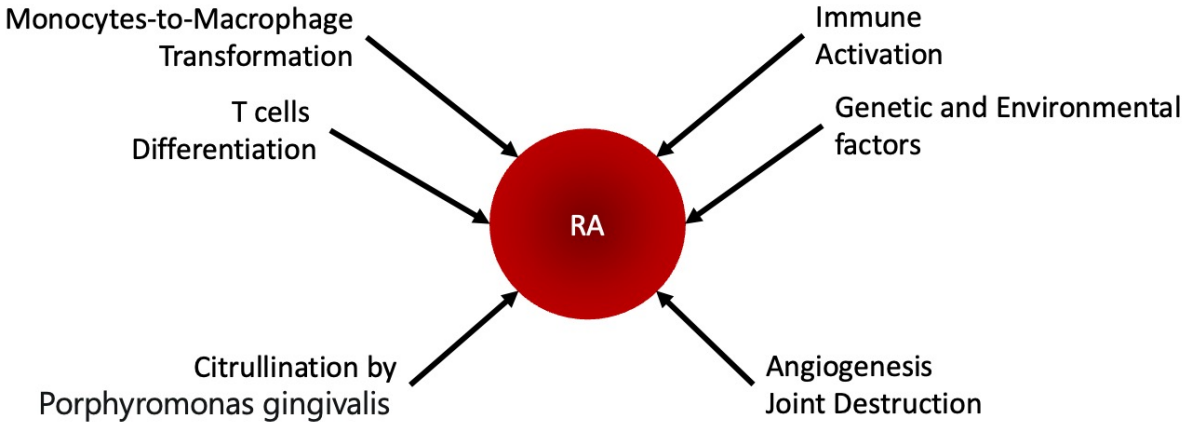

Figure 1. Major factors contributing to development of RA.

Recent studies have identified a link between infections caused by the common periodontal bacterium *Porphyromonas gingivalis* and the induction of autoimmune reactions in RA. This link is largely due to the process of citrullination, during which the enzyme protein-arginine deiminase (PAD) converts positively charged arginine residues in host proteins to neutral citrullinated residues [11,12]. This biochemical transformation results in a net loss of surface charge, making citrullinated proteins more susceptible to degradation and formation of neoepitopes that are mistakenly targeted by the immune system. Disruption of local tolerance to *P. gingivalis*, which expresses PADi4, which promotes this conversion of arginine to citrulline, further stimulates autoimmune responses and leads to the production of anti-citrullinated protein antibodies (ACPA), which is a hallmark of RA [13].

It is also believed that other infections, including those caused by Epstein–Barr virus and bacteria such as Proteus mirabilis and Escherichia coli, can cause RA through molecular mimicry. This occurs when the immune system confuses bacterial or viral proteins with the body's own proteins due to similar amino acid sequences, thereby mistakenly attacking the body's tissues [14,15]. In addition to citrullination, the process of carbamylation, which modifies lysine residues, also plays a role in creating neoepitopes from proteins such as collagen, fibrinogen, and vimentin, which impairs immunologic tolerance [16,17].

Genomic studies using single-nucleotide polymorphisms (SNPs) have identified more than 100 loci associated with the development of RA. These loci are predominantly involved in the regulation and maintenance of the immune response, emphasizing the complex interaction of the disease with the immune system. Notably, specific HLA alleles, in particular HLA-DRB1 variants such as DRB101 and DRB104 (DQ8), contribute significantly to genetic susceptibility, accounting for about half of the genetic risk of developing RA. These HLA alleles share common amino acid sequences in their peptide-binding grooves, which preferentially represent specific peptide epitopes derived from autoantigens in RA. Consequently, these genetic markers are associated not only with an increased risk of developing RA but also with more severe manifestations of the disease, including aggressive bone erosion and higher mortality rates [18].

These findings emphasize the multifactorial nature of RA, including genetic predisposition, immune system dysregulation, and environmental triggers such as infections. They point to potential avenues for therapeutic intervention, such as targeting PAD enzymes or modulating immune responses to prevent the breakdown of tolerance to self-proteins. Understanding these mechanisms is crucial for developing strategies for prognosis, prevention and more effective treatment of RA, taking into account both genetic and environmental aspects [19].

3. Innate Immune Response

Cells and soluble mediators of the innate immune system are crucial for nonspecific pathogen recognition and serve as the first line of defense against microbes. Recent studies suggest that dysregulation of this system may contribute to the development and acceleration of inflammatory processes in joint tissues in RA. Innate immune cells can be activated by numerous specialized receptors, including toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns expressed by microbial pathogens and damage-associated molecular patterns [20]. Pathologically altered TLR-mediated responses are thought to play a key role in the pathogenesis of RA. Increased expression levels of TLR1, TLR4, and TLR8 have been found in seropositive RA patients, indicating their significant involvement in the inflammatory response. Factors such as endoplasmic reticulum (ER) stress and its regulator, X-box binding protein-1 (XBP-1), may interact with TLRs to stimulate inflammation [21,22].

3.1. Contributions of Mast Cells and Neutrophils

In addition to monocytes and macrophages, mast cells and neutrophils also contribute significantly to joint inflammation in RA. Mast cells, present in the synovial tissue, release pro-inflammatory mediators such as histamine and cytokines that amplify inflammation. Neutrophils, as the first responders to infection or injury, accumulate in inflamed joints and produce reactive oxygen species and proteolytic enzymes, further exacerbating tissue damage and inflammatory responses.

3.2. Role of Chemokines in Immune Cell Recruitment

Chemokines play a central role in directing the recruitment and activation of immune cells in RA. For example, C-C motif ligand 2 (CCL2), also known as monocyte chemoattractant protein-1 (MCP-1), is produced by various cell types, including synovial fibroblasts and macrophages. It binds to the CCR2 receptor on monocytes, facilitating their migration into

the synovium where they differentiate into macrophages, perpetuating the inflammatory cycle [23]. Elevated levels of CCL2 have been correlated with disease activity in RA.

CCL5 (RANTES) also attracts various immune cells, including T cells, monocytes, and eosinophils, contributing to inflammatory cell infiltration in the joints [24]. Additionally, CXCL10 (IP-10) promotes the recruitment of Th1 cells through its interaction with the CXCR3 receptor, enhancing cytokine production and sustaining the immune response in RA [25].

3.3. Synovial Fibroblasts and Inflammation

Synovial fibroblasts (SFs) residing in synovial tissue are key players in RA pathogenesis. Activated SFs promote inflammation and joint destruction by invading articular cartilage and secreting various mediators, including cytokines, chemokines, and matrix metalloproteinases (MMPs), ultimately leading to remodeling of the extracellular matrix and cartilage [26]. In vitro experiments showed that the chemokine CCL11, secreted by neutrophils after TNF-α stimulation, binds to its receptor CCR3 on SFs, enhancing its autocrine production and CCR3 expression. This self-reinforcement mechanism of CCL11 via CCR3 may enhance inflammation and profibrotic effects of SFs. Furthermore, TNF-α promotes interactions between these structural cells and B cells by enhancing the expression of vascular cell adhesion molecule-1 (VCAM-1) in SFs through the production of B-cell activation factor (BAFF) and JNK activation [27].

3.4. Pro-Angiogenic Mechanisms in RA

Pro-angiogenic mechanisms also play an important role in RA inflammation and remodeling. The expression of pro-inflammatory cytokines such as IL-17A, IL-6, and TNF-α, as well as pro-angiogenic mediators VEGF and HIF-1α, is significantly increased by IL-34 stimulation in SFs [28,29]. METTL3 can induce neutrophil activation and inflammatory responses by triggering the NF-κB signaling pathway. Recent reports have emphasized the role of MCP-1 in stimulating SF proliferation and migration while suppressing apoptosis in collagen-induced arthritis models [30].

These data highlight the complex interplay between the innate immune system, chemokines, and synovial fibroblasts in RA, revealing multiple pathways that may be targeted for therapeutic action. A better understanding of these mechanisms may lead to the development of more effective therapies aimed at reducing inflammation, preventing joint damage, and improving the quality of life of patients with RA [31].

3.5. Monocyte Differentiation and Inflammation

Monocytes play a crucial role in organizing joint inflammation in RA through various mechanisms that stimulate the inflammatory process and promote tissue damage. These immune cells enter the inflamed joint from the bloodstream in response to chemotactic signals such as MCP-1, directing them to foci of inflammation. Once infiltrating synovial tissue, monocytes differentiate into macrophages and dendritic cells, which play a key role in maintaining the chronic inflammation characteristic of RA [32,33].

3.6. Macrophage Activation and Cytokine Production

Macrophages in synovial tissue are activated and secrete multiple pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. These cytokines enhance the inflammatory response by promoting the activation and proliferation of other immune cells, such as T cells and B cells, and by increasing the production of additional inflammatory mediators [34,35]. TNF-α stimulates synovial fibroblasts to produce more cytokines and chemokines and increases adhesion molecule expression on endothelial cells, promoting immune cell recruitment to the joint [36].

3.7. Inflammatory Environment and Synovial Fibroblasts

The inflammatory environment created by these cytokines leads to the activation of synovial fibroblasts. Activated SFs proliferate and secrete MMPs, degrading the extracellular matrix and resulting in cartilage breakdown and joint damage. Additionally, activated SFs produce chemokines that attract more monocytes and immune cells, maintaining the cycle of inflammation and tissue degradation [37].

3.8. Cell–Cell Interactions in the Synovium

Monocytes and their differentiated forms also engage in direct cell–cell interactions with other immune cells in the synovium. They present antigens to T cells, promoting their activation and production of pro-inflammatory cytokines such as IFN-γ, supporting the inflammatory response and contributing to the autoimmunity seen in RA [38,39].

3.9. Osteoclast Formation and Bone Erosion

In addition to their inflammatory role, monocytes and macrophages contribute to the formation of osteoclasts, cells responsible for bone resorption. Under the influence of cytokines such as RANKL, produced by activated T cells and SFs, monocytes differentiate into osteoclasts that destroy bone tissue, resulting in bone erosion commonly seen in RA [40].

The interaction between monocytes, their differentiated forms, and other immune cells creates a self-sustaining cycle of inflammation and tissue destruction in RA. Targeting pathways involved in monocyte recruitment, activation, and differentiation represents a strategic approach to developing therapies aimed at mitigating joint inflammation and preventing progressive damage. Understanding these mechanisms emphasizes the complexity of RA and the critical role of monocytes in the disease process [41].

3.10. Surface Markers in Monocyte Function

Importantly, CD14 and CD16 are surface markers that play a crucial role in monocyte and macrophage function in RA. Monocytes are categorized based on these markers, and they are differentially involved in the inflammatory processes observed in RA [42,43].

CD14 is a co-receptor for recognizing bacterial lipopolysaccharide (LPS) and works with TLR4 to induce an inflammatory response. CD14++ monocytes are particularly efficient at producing pro-inflammatory cytokines such as TNF-α and IL-6. In RA, CD14++ monocytes are recruited to the inflamed synovium, where they differentiate into macrophages and contribute to inflammation [44,45].

CD16 defines a subset of monocytes known as non-classical or patrolling monocytes. These cells are involved in blood vessel control, tissue repair, and resolution of inflammation. However, in chronic inflammatory diseases such as RA, CD14+ CD16++ monocytes may adopt a pro-inflammatory phenotype, producing cytokines like TNF-α and IL-1β and participating in antibody-dependent cellular cytotoxicity [46].

The balance and function of these monocyte subsets are impaired in RA, with both CD14++ and CD14+ CD16++ monocytes found in increased numbers in patients. These cells migrate to the joint, contributing to chronic inflammation and tissue destruction. Understanding the roles of CD14 and CD16 in monocyte function may aid in developing targeted therapies to alleviate inflammation and prevent joint damage in RA [47].

4. Adaptive Immune Response

The adaptive immune response in rheumatoid arthritis (RA) plays a crucial role in the chronic inflammation and joint destruction that characterize the disease. This response is primarily mediated by T cells and B cells, which become activated and produce a range of cytokines that perpetuate the inflammatory environment within the joints.

4.1. T-Cell Subtypes and Their Roles

One of the central aspects of the adaptive immune response in RA is the aberrant activation and proliferation of CD4+ T cells [48]. These T cells differentiate into various subsets, including Th1, Th17, and Tfh cells, each contributing differently to the disease process. Th1 cells produce interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which are potent pro-inflammatory cytokines. TNF-α is a key driver of inflammation in RA, promoting the activation of synovial fibroblasts, macrophages, and endothelial cells, leading to the production of other inflammatory mediators and the recruitment of additional immune cells to the synovium [49,50]. Furthermore, CD6 expression on T effector cells enhances their activation and proliferation, linking T-cell signaling to ongoing inflammatory processes.

4.2. Th17 Cells and Their Contributions

Th17 cells produce interleukin-17 (IL-17), which amplifies the inflammatory response by inducing the production of cytokines such as interleukin-6 (IL-6) and chemokines like CXCL10. Elevated levels of IL-6 are found in the synovial fluid and blood of RA patients, correlating with disease activity and severity [51]. CXCL10, also known as interferon gamma-induced protein 10 (IP-10), recruits T cells and monocytes to inflamed joints, thereby contributing to chronic inflammation [25,52].

4.3. Th2 Cells and Their Contribution

In addition to Th1 and Th17 cells, Th2 cells also play an important immunomodulatory role in rheumatoid arthritis. While Th2 cells are often associated with anti-inflammatory responses, they can influence the disease context in RA. Th2 cells produce cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), which can promote B-cell differentiation and the production of antibodies, including autoantibodies. Elevated levels of IL-4 and IL-13 have been observed in the joints of RA patients, suggesting that Th2 polarization may contribute to a more chronic inflammatory environment. Additionally, Th2 cytokines can interact with other immune cells, modulating the overall immune response and possibly promoting tissue repair processes. However, the persistent activation of Th2 responses in the context of chronic inflammation can also exacerbate joint damage by sustaining immune dysregulation, highlighting the complex role of Th2 cells in RA pathogenesis [53,54].

4.4. The Role of Regulatory T Cells (Tregs)

Regulatory T cells (Tregs) play a critical role in maintaining immune tolerance and preventing excessive inflammation. However, in RA, the function and number of Tregs are often impaired, leading to uncontrolled immune activation and autoimmunity. Tregs typically produce anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which help to dampen immune responses [55,56].

CTLA-4 is a key molecule expressed by Tregs that downregulates immune responses by inhibiting co-stimulatory signals necessary for T-cell activation. It is critical for the immune checkpoint that prevents autoimmunity. Additionally, FoxP3 is a transcription factor essential for the development and function of Tregs, and its expression is decreased in RA Tregs, contributing to their dysfunction [57].

4.5. Regulatory Checkpoints and Treg Function

The interplay between Tregs and effector T cells is also regulated by various checkpoints, reinforcing the balance between tolerance and autoimmunity. Disruption of these regulatory mechanisms may lead to exacerbated T effector function and inflammation in RA.

4.6. B Cells and Their Roles

B cells significantly contribute to the adaptive immune response in RA. They produce autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), which form immune complexes that deposit in the joints and activate complement pathways, leading to further inflammation and tissue damage. B cells also act as antigen-presenting cells, presenting antigens to T cells and producing cytokines like IL-6 and TNF-α, enhancing the inflammatory milieu [58,59].

B regulatory cells (Bregs) are a subset of B-cells that contribute to immune regulation, producing anti-inflammatory cytokines such as IL-35. In RA, Bregs can help restore balance by inhibiting excessive T-cell activation and cytokine production. The presence of BAFF (B-cell activating factor) is crucial for B-cell survival and maturation, and elevated levels of BAFF have been implicated in the pathogenesis of RA as they promote the expansion of autoreactive B-cells [60,61].

4.7. MicroRNA and Inflammatory Responses

MicroRNA-132 (miR-132) is a small non-coding RNA molecule that regulates gene expression by binding to the 3′ untranslated regions (UTRs) of target mRNAs, potentially limiting excessive inflammation. Dysregulation of miR-132 in RA can contribute to the persistence of inflammatory signals and influence processes critical in the disease's pathogenesis [62].

4.8. Cytokine Profile in RA

The cytokine profile in RA is characterized by elevated levels of TNF-α, IL-6, IL-17, IL-2, and CXCL10. IL-2, produced by activated T cells, is essential for T cell proliferation and survival, further supporting the expansion of autoreactive T cells. This persistent production of cytokines creates an environment that promotes the recruitment and activation of various immune cells, leading to the chronic inflammation and joint destruction seen in RA [35].

5. Treatment of RA

Rheumatoid arthritis (RA) treatment has evolved significantly, with a focus on both conventional and biologic therapies that target key pathways involved in inflammation and joint damage. While biologic agents have gained attention, it is important to highlight that methotrexate remains the anchor drug and first-line therapy for RA. It is well established for its ability to suppress IL-6 and modulate the cytokine network effectively. In Table 1, we summarize the existing therapies for RA.

Table 1. Therapeutic strategies for RA.

Target	Mechanism	Therapeutic Agents	Effects	References
DHFR	Folate antagonist; modulates immune response and suppresses inflammation.	Methotrexate	Reduces disease activity, improves function, and is the cornerstone of RA therapy.	[63]
TNF-α	Pro-inflammatory cytokine that promotes inflammation and joint destruction.	Infliximab, Adalimumab, Etanercept, Certolizumab, Golimumab	Reduces symptoms, improves function, slows disease progression.	[64,65]
IL-6	Promotes inflammation and B-cell differentiation; elevated in the synovial fluid.	Tocilizumab, Sarilumab	Alleviates symptoms, reduces inflammation, prevents joint damage.	[63,66,67]

Table 1. *Cont.*

Target	Mechanism	Therapeutic Agents	Effects	References
IL-1	Contributes to inflammation and cartilage degradation; produced by activated macrophages.	Anakinra	Effective in patients unresponsive to other treatments; reduces inflammation.	[68]
IL-17	Induces production of pro-inflammatory cytokines and matrix metalloproteinases.	Secukinumab, Ixekizumab	Reduces inflammation by neutralizing IL-17 activity.	[69]
BAFF	Promotes B-cell survival and function; elevated levels contribute to autoantibody production.	Belimumab	Reduces B-cell activity and autoantibody levels; therapeutic benefits.	[70]
CCL2 (MCP-1)	Facilitates recruitment of monocytes to inflamed joints.	CCL2 inhibitors	Reduces monocyte infiltration, diminishing local inflammation.	[23,71]
CXCL10	Promotes T-cell migration to inflamed tissues; involved in Th1 recruitment.	CXCL10 inhibitors	Decreases T-cell influx into the synovium, alleviating inflammation.	[25,72]
CCL5 (RANTES)	Attracts various immune cells, contributing to inflammatory infiltrate.	CCL5 inhibitors	Reduces recruitment of inflammatory cells to joints.	[24,73]
CXCL12	Involved in retention and migration of various immune cells; promotes chronicity.	CXCL12 inhibitors	Reduces retention of inflammatory cells in the joints.	[74,75]
CCL20 (MIP-3α)	Critical in recruiting Th17 cells, which promote joint destruction.	CCL20 inhibitors	Decreases migration of Th17 cells, reducing IL-17-mediated inflammation.	[76]
JAK Kinase	Inhibits multiple cytokine signaling pathways involved in inflammation	Tofacitinib, Baricitinib, Upadacitinib	Improves symptoms, reduces inflammation, and provides clinical benefits for patients with moderate-to-severe RA; approved for RA	[77,78]

Targeting cytokines has reshaped the treatment of rheumatoid arthritis, offering tailored therapies aimed at specific pathways driving the disease. Methotrexate is widely recognized as the cornerstone of RA treatment and is essential in the management of early and established disease.

Biologic agents targeting tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) remain crucial, especially for patients who fail to respond to methotrexate. Additionally, interest in Janus kinase (JAK) inhibitors has grown due to their ability to inhibit multiple cytokines, which has demonstrated success in RA therapy.

While therapies targeting IL-17 and BAFF are currently approved for other autoimmune diseases, they are not yet approved for RA treatment. Chemokine targets such as CCL2 and CXCL10 play vital roles in recruiting inflammatory cells and facilitating sustained inflammation in the synovium. Inhibitors targeting these chemokines are still considered experimental for RA treatment. Overall, a deeper understanding of the immunological mechanisms underlying RA fosters the continuous development of more effective and targeted therapies for managing this chronic disease.

6. Conclusions

Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by chronic inflammation and joint damage, impacting the physical and psychological well-being of affected individuals. The understanding of RA pathogenesis has evolved, emphasizing the intertwined role of genetic predisposition, dysregulated immune responses, and en-

vironmental triggers in disease onset and progression. The innate and adaptive immune responses orchestrate a cascade of cellular and biochemical events, contributing to the perpetuation of inflammation, tissue destruction, and bone erosion in the joints.

Significant progress has been made in therapeutic strategies targeting specific pro-inflammatory cytokines and chemokines, leading to improved outcomes for many RA patients. The advent of biologic therapies and small-molecule inhibitors has revolutionized RA management, offering more targeted approaches to modulate the immune response and minimize joint damage. However, challenges remain in tailoring treatments to individual patients based on their unique immunological and genetic profiles.

Moving forward, a personalized medicine approach that integrates genetic, immunological, and environmental factors holds promise for optimizing RA management. The identification of novel therapeutic targets, including specific immune cell subpopulations and molecular pathways, presents exciting opportunities for the development of more effective and tailored interventions. Advancements in precision medicine, immunotherapy, and genetic research may pave the way for transformative breakthroughs in RA treatment, aiming to achieve sustained remission, restore joint function, and enhance the quality of life for individuals living with RA.

In summary, this comprehensive review underscores the intricate and multifaceted nature of RA pathogenesis, highlighting the critical role of immune dysregulation and genetic susceptibility. By leveraging this deeper understanding, the ongoing pursuit of innovative therapeutic strategies offers hope for a future where RA can be effectively managed, and its impact on patients' lives can be minimized.

Author Contributions: Writing—original draft preparation, A.V.P.; writing—review and editing, V.N.S., T.V.K., T.I.K., I.A.S., D.F.B., A.N.O., A.V.C. and S.A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Russian Science Foundation, grant number 24-15-00217.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Lin, Y.J.; Anzaghe, M.; Schülke, S. Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. *Cells* **2020**, *9*, 880. [CrossRef]
2. Jahid, M.; Khan, K.U.; Rehan-Ul-Haq; Ahmed, R.S. Overview of Rheumatoid Arthritis and Scientific Understanding of the Disease. *Mediterr. J. Rheumatol.* **2023**, *34*, 284–291. [CrossRef] [PubMed]
3. Grätzel, P. Rheuma-Verdacht: Welche Patienten müssen zum Spezialisten? Das entscheidet der Hausarzt [Suspected rheumatoid arthritis: Which patient must be referred to a specialist? The family physician decides]. *MMW Fortschritte Med.* **2014**, *156*, 20. [CrossRef]
4. Feragalli, B.; Mantini, C.; Sperandeo, M.; Galluzzo, M.; Belcaro, G.; Tartaro, A.; Cotroneo, A.R. The lung in systemic vasculitis: Radiological patterns and differential diagnosis. *Br. J. Radiol.* **2016**, *89*, 20150992. [CrossRef] [PubMed]
5. Nilsson, J.; Andersson, M.L.E.; Hafström, I.; Svensson, B.; Forslind, K.; Ajeganova, S.; Leu Agelii, M.; Gjertsson, I. Influence of Age and Sex on Disease Course and Treatment in Rheumatoid Arthritis. *Open Access Rheumatol. Res. Rev.* **2021**, *13*, 123–138. [CrossRef] [PubMed]
6. Romão, V.C.; Fonseca, J.E. Etiology and Risk Factors for Rheumatoid Arthritis: A State-of-the-Art Review. *Front. Med.* **2021**, *8*, 689698. [CrossRef]
7. Pankratov, V.; Yunusbaeva, M.; Ryakhovsky, S.; Zarodniuk, M.; Estonian Biobank Research Team; Yunusbayev, B. Prioritizing autoimmunity risk variants for functional analyses by fine-mapping mutations under natural selection. *Nat. Commun.* **2022**, *13*, 7069. [CrossRef]
8. Pisetsky, D.S. Pathogenesis of autoimmune disease. *Nat. Rev. Nephrol.* **2023**, *19*, 509–524. [CrossRef]
9. Haworth, C.M.; Dale, P.; Plomin, R. A Twin Study into the Genetic and Environmental Influences on Academic Performance in Science in nine-year-old Boys and Girls. *Int. J. Sci. Educ.* **2008**, *30*, 1003–1025. [CrossRef] [PubMed]
10. Reiss, D.; Leve, L.D.; Neiderhiser, J.M. How genes and the social environment moderate each other. *Am. J. Public Health* **2013**, *103* (Suppl. S1), S111–S121. [CrossRef]
11. Koziel, J.; Mydel, P.; Potempa, J. The link between periodontal disease and rheumatoid arthritis: An updated review. *Curr. Rheumatol. Rep.* **2014**, *16*, 408. [CrossRef] [PubMed]

12. Chow, Y.C.; Yam, H.C.; Gunasekaran, B.; Lai, W.Y.; Wo, W.Y.; Agarwal, T.; Ong, Y.Y.; Cheong, S.L.; Tan, S.A. Implications of *Porphyromonas gingivalis* peptidyl arginine deiminase and gingipain R in human health and diseases. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 987683. [CrossRef] [PubMed]
13. Ciesielski, O.; Biesiekierska, M.; Panthu, B.; Soszyński, M.; Pirola, L.; Balcerczyk, A. Citrullination in the pathology of inflammatory and autoimmune disorders: Recent advances and future perspectives. *Cell. Mol. Life Sci. CMLS* **2022**, *79*, 94. [CrossRef]
14. Maoz-Segal, R.; Andrade, P. Molecular Mimicry and Autoimmunity. In *Infection and Autoimmunity*; Academic Press: Cambridge, MA, USA, 2015; pp. 27–44. [CrossRef]
15. Neamțu, M.; Bild, V.; Vasincu, A.; Arcan, O.D.; Bulea, D.; Ababei, D.C.; Rusu, R.N.; Macadan, I.; Sciucă, A.M.; Neamțu, A. Inflammasome Molecular Insights in Autoimmune Diseases. *Curr. Issues Mol. Biol.* **2024**, *46*, 3502–3532. [CrossRef] [PubMed]
16. Pruijn, G.J. Citrullination and carbamylation in the pathophysiology of rheumatoid arthritis. *Front. Immunol.* **2015**, *6*, 192. [CrossRef]
17. Haro, I.; Sanmartí, R.; Gómara, M.J. Implications of Post-Translational Modifications in Autoimmunity with Emphasis on Citrullination, Homocitrullination and Acetylation for the Pathogenesis, Diagnosis and Prognosis of Rheumatoid Arthritis. *Int. J. Mol. Sci.* **2022**, *23*, 15803. [CrossRef]
18. Daghestani, M.; Othman, N.; Omair, M.A.; Alenzi, F.; Omair, M.A.; Alqurtas, E.; Amin, S.; Warsy, A. Single Nucleotide Polymorphisms Associated with Rheumatoid Arthritis in Saudi Patients. *J. Clin. Med.* **2023**, *12*, 4944. [CrossRef]
19. Alghamdi, M.; Alasmari, D.; Assiri, A.; Mattar, E.; Aljaddawi, A.A.; Alattas, S.G.; Redwan, E.M. An Overview of the Intrinsic Role of Citrullination in Autoimmune Disorders. *J. Immunol. Res.* **2019**, *2019*, 7592851. [CrossRef]
20. Andrés, C.M.C.; Pérez de la Lastra, J.M.; Juan, C.A.; Plou, F.J.; Pérez-Lebeña, E. The Role of Reactive Species on Innate Immunity. *Vaccines* **2022**, *10*, 1735. [CrossRef]
21. Unterberger, S.; Davies, K.A.; Rambhatla, S.B.; Sacre, S. Contribution of Toll-Like Receptors and the NLRP3 Inflammasome in Rheumatoid Arthritis Pathophysiology. *ImmunoTargets Ther.* **2021**, *10*, 285–298. [CrossRef]
22. Huang, Q.Q.; Pope, R.M. The role of toll-like receptors in rheumatoid arthritis. *Curr. Rheumatol. Rep.* **2009**, *11*, 357–364. [CrossRef] [PubMed]
23. Singh, S.; Anshita, D.; Ravichandiran, V. MCP-1: Function, regulation, and involvement in disease. *Int. Immunopharmacol.* **2021**, *101 Pt B*, 107598. [CrossRef]
24. Zeng, Z.; Lan, T.; Wei, Y.; Wei, X. CCL5/CCR5 axis in human diseases and related treatments. *Genes Dis.* **2022**, *9*, 12–27. [CrossRef]
25. Liu, M.; Guo, S.; Hibbert, J.M.; Jain, V.; Singh, N.; Wilson, N.O.; Stiles, J.K. CXCL10/IP-10 in infectious diseases pathogenesis and potential therapeutic implications. *Cytokine Growth Factor Rev.* **2011**, *22*, 121–130. [CrossRef]
26. Lefèvre, S.; Knedla, A.; Tennie, C.; Kampmann, A.; Wunrau, C.; Dinser, R.; Korb, A.; Schnäker, E.M.; Tarner, I.H.; Robbins, P.D.; et al. Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. *Nat. Med.* **2009**, *15*, 1414–1420. [CrossRef]
27. Matsukura, S.; Odaka, M.; Kurokawa, M.; Kuga, H.; Homma, T.; Takeuchi, H.; Notomi, K.; Kokubu, F.; Kawaguchi, M.; Schleimer, R.P.; et al. Transforming growth factor-β stimulates the expression of eotaxin/CC chemokine ligand 11 and its promoter activity through binding site for nuclear factor-κβ in airway smooth muscle cells. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* **2010**, *40*, 763–771. [CrossRef] [PubMed]
28. Lee, Y.E.; Lee, S.H.; Kim, W.U. Cytokines, Vascular Endothelial Growth Factors, and PlGF in Autoimmunity: Insights from Rheumatoid Arthritis to Multiple Sclerosis. *Immune Netw.* **2024**, *24*, e10. [CrossRef]
29. Le, T.H.V.; Kwon, S.M. Vascular Endothelial Growth Factor Biology and Its Potential as a Therapeutic Target in Rheumatic Diseases. *Int. J. Mol. Sci.* **2021**, *22*, 5387. [CrossRef]
30. Tang, H.; Huang, L.; Hu, J. Inhibition of the m6A Methyltransferase METTL3 Attenuates the Inflammatory Response in Fusarium solani-Induced Keratitis via the NF-κB Signaling Pathway. *Investig. Ophthalmol. Vis. Sci.* **2022**, *63*, 2. [CrossRef]
31. Edilova, M.I.; Akram, A.; Abdul-Sater, A.A. Innate immunity drives pathogenesis of rheumatoid arthritis. *Biomed. J.* **2021**, *44*, 172–182. [CrossRef]
32. Cecchinato, V.; D'Agostino, G.; Raeli, L.; Nerviani, A.; Schiraldi, M.; Danelon, G.; Manzo, A.; Thelen, M.; Ciurea, A.; Bianchi, M.E.; et al. Redox-Mediated Mechanisms Fuel Monocyte Responses to CXCL12/HMGB1 in Active Rheumatoid Arthritis. *Front. Immunol.* **2018**, *9*, 2118. [CrossRef] [PubMed]
33. Wu, C.Y.; Yang, H.Y.; Huang, J.L.; Lai, J.H. Signals and Mechanisms Regulating Monocyte and Macrophage Activation in the Pathogenesis of Juvenile Idiopathic Arthritis. *Int. J. Mol. Sci.* **2021**, *22*, 7960. [CrossRef] [PubMed]
34. Zhao, K.; Ruan, J.; Nie, L.; Ye, X.; Li, J. Effects of synovial macrophages in osteoarthritis. *Front. Immunol.* **2023**, *14*, 1164137. [CrossRef] [PubMed]
35. Kondo, N.; Kuroda, T.; Kobayashi, D. Cytokine Networks in the Pathogenesis of Rheumatoid Arthritis. *Int. J. Mol. Sci.* **2021**, *22*, 10922. [CrossRef] [PubMed]
36. Koedderitzsch, K.; Zezina, E.; Li, L.; Herrmann, M.; Biesemann, N. TNF induces glycolytic shift in fibroblast like synoviocytes via GLUT1 and HIF1A. *Sci. Rep.* **2021**, *11*, 19385. [CrossRef]
37. Mukherjee, A.; Das, B. The role of inflammatory mediators and matrix metalloproteinases (MMPs) in the progression of osteoarthritis. *Biomater. Biosyst.* **2024**, *13*, 100090. [CrossRef]
38. Roberts, C.A.; Dickinson, A.K.; Taams, L.S. The Interplay Between Monocytes/Macrophages and CD4(+) T Cell Subsets in Rheumatoid Arthritis. *Front. Immunol.* **2015**, *6*, 571. [CrossRef] [PubMed]

39. Tran, C.N.; Lundy, S.K.; Fox, D.A. Synovial biology and T cells in rheumatoid arthritis. *Pathophysiol. Off. J. Int. Soc. Pathophysiol.* **2005**, *12*, 183–189. [CrossRef]
40. Gu, Q.; Yang, H.; Shi, Q. Macrophages and bone inflammation. *J. Orthop. Transl.* **2017**, *10*, 86–93. [CrossRef]
41. Cutolo, M.; Campitiello, R.; Gotelli, E.; Soldano, S. The Role of M1/M2 Macrophage Polarization in Rheumatoid Arthritis Synovitis. *Front. Immunol.* **2022**, *13*, 867260. [CrossRef]
42. Salnikova, D.I.; Nikiforov, N.G.; Postnov, A.Y.; Orekhov, A.N. Target Role of Monocytes as Key Cells of Innate Immunity in Rheumatoid Arthritis. *Diseases* **2024**, *12*, 81. [CrossRef] [PubMed]
43. Williams, H.; Mack, C.; Baraz, R.; Marimuthu, R.; Naralashetty, S.; Li, S.; Medbury, H. Monocyte Differentiation and Heterogeneity: Inter-Subset and Interindividual Differences. *Int. J. Mol. Sci.* **2023**, *24*, 8757. [CrossRef] [PubMed]
44. He, Z.; Riva, M.; Björk, P.; Swärd, K.; Mörgelin, M.; Leanderson, T.; Ivars, F. CD14 Is a Co-Receptor for TLR4 in the S100A9-Induced Pro-Inflammatory Response in Monocytes. *PLoS ONE* **2016**, *11*, e0156377. [CrossRef]
45. Tsukamoto, H.; Takeuchi, S.; Kubota, K.; Kobayashi, Y.; Kozakai, S.; Ukai, I.; Shichiku, A.; Okubo, M.; Numasaki, M.; Kanemitsu, Y.; et al. Lipopolysaccharide (LPS)-binding protein stimulates CD14-dependent Toll-like receptor 4 internalization and LPS-induced TBK1-IKKε-IRF3 axis activation. *J. Biol. Chem.* **2018**, *293*, 10186–10201. [CrossRef] [PubMed]
46. Ruder, A.V.; Wetzels, S.M.W.; Temmerman, L.; Biessen, E.A.L.; Goossens, P. Monocyte heterogeneity in cardiovascular disease. *Cardiovasc. Res.* **2023**, *119*, 2033–2045. [CrossRef]
47. Kinne, R.W.; Bräuer, R.; Stuhlmüller, B.; Palombo-Kinne, E.; Burmester, G.R. Macrophages in rheumatoid arthritis. *Arthritis Res.* **2000**, *2*, 189–202. [CrossRef]
48. Jang, S.; Kwon, E.J.; Lee, J.J. Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells. *Int. J. Mol. Sci.* **2022**, *23*, 905. [CrossRef]
49. Wang, W.; Sung, N.; Gilman-Sachs, A.; Kwak-Kim, J. T Helper (Th) Cell Profiles in Pregnancy and Recurrent Pregnancy Losses: Th1/Th2/Th9/Th17/Th22/Tfh Cells. *Front. Immunol.* **2020**, *11*, 2025. [CrossRef]
50. Ren, J.; Crowley, S.D. Role of T-cell activation in salt-sensitive hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *316*, H1345–H1353. [CrossRef]
51. Brevi, A.; Cogrossi, L.L.; Grazia, G.; Masciovecchio, D.; Impellizzieri, D.; Lacanfora, L.; Grioni, M.; Bellone, M. Much More Than IL-17A: Cytokines of the IL-17 Family Between Microbiota and Cancer. *Front. Immunol.* **2020**, *11*, 565470. [CrossRef]
52. Elemam, N.M.; Talaat, I.M.; Maghazachi, A.A. CXCL10 Chemokine: A Critical Player in RNA and DNA Viral Infections. *Viruses* **2022**, *14*, 2445. [CrossRef] [PubMed]
53. Luo, P.; Wang, P.; Xu, J.; Hou, W.; Xu, P.; Xu, K.; Liu, L. Immunomodulatory role of T helper cells in rheumatoid arthritis: A comprehensive research review. *Bone Jt. Res.* **2022**, *11*, 426–438. [CrossRef]
54. Chen, Z.; Bozec, A.; Ramming, A.; Schett, G. Anti-inflammatory and immune-regulatory cytokines in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **2019**, *15*, 9–17. [CrossRef]
55. Oparaugo, N.C.; Ouyang, K.; Nguyen, N.P.N.; Nelson, A.M.; Agak, G.W. Human Regulatory T Cells: Understanding the Role of Tregs in Select Autoimmune Skin Diseases and Post-Transplant Nonmelanoma Skin Cancers. *Int. J. Mol. Sci.* **2023**, *24*, 1527. [CrossRef] [PubMed]
56. Zhang, J.; Liu, H.; Chen, Y.; Liu, H.; Zhang, S.; Yin, G.; Xie, Q. Augmenting regulatory T cells: New therapeutic strategy for rheumatoid arthritis. *Front. Immunol.* **2024**, *15*, 1312919. [CrossRef]
57. Ranasinghe, R.; Eri, R. Pleiotropic Immune Functions of Chemokine Receptor 6 in Health and Disease. *Medicines* **2018**, *5*, 69. [CrossRef] [PubMed]
58. Volkov, M.; van Schie, K.A.; van der Woude, D. Autoantibodies and B Cells: The ABC of rheumatoid arthritis pathophysiology. *Immunol. Rev.* **2020**, *294*, 148–163. [CrossRef] [PubMed]
59. Fang, Q.; Ou, J.; Nandakumar, K.S. Autoantibodies as Diagnostic Markers and Mediator of Joint Inflammation in Arthritis. *Mediat. Inflamm.* **2019**, *2019*, 6363086. [CrossRef]
60. Walgrave, H.; Penning, A.; Tosoni, G.; Snoeck, S.; Davie, K.; Davis, E.; Wolfs, L.; Sierksma, A.; Mars, M.; Bu, T.; et al. microRNA-132 regulates gene expression programs involved in microglial homeostasis. *iScience* **2023**, *26*, 106829. [CrossRef]
61. Cui, J.; Zheng, W.; Sun, Y.; Xu, T. Inducible MicroRNA-132 Inhibits the Production of Inflammatory Cytokines by Targeting TRAF6, TAK1, and TAB1 in Teleost Fish. *Infect. Immun.* **2022**, *90*, e0012022. [CrossRef]
62. Das, K.; Rao, L.V.M. The Role of microRNAs in Inflammation. *Int. J. Mol. Sci.* **2022**, *23*, 15479. [CrossRef] [PubMed]
63. Boyapati, A.; Schwartzman, S.; Msihid, J.; Choy, E.; Genovese, M.C.; Burmester, G.R.; Lam, G.; Kimura, T.; Sadeh, J.; Weinreich, D.M.; et al. Association of High Serum Interleukin-6 Levels with Severe Progression of Rheumatoid Arthritis and Increased Treatment Response Differentiating Sarilumab from Adalimumab or Methotrexate in a Post Hoc Analysis. *Arthritis Rheumatol.* **2020**, *72*, 1456–1466. [CrossRef]
64. Mueller, A.L.; Payandeh, Z.; Mohammadkhani, N.; Mubarak, S.M.H.; Zakeri, A.; Alagheband Bahrami, A.; Brockmueller, A.; Shakibaei, M. Recent Advances in Understanding the Pathogenesis of Rheumatoid Arthritis: New Treatment Strategies. *Cells* **2021**, *10*, 3017. [CrossRef]
65. Peyrin-Biroulet, L.; Sandborn, W.J.; Panaccione, R.; Domènech, E.; Pouillon, L.; Siegmund, B.; Danese, S.; Ghosh, S. Tumour necrosis factor inhibitors in inflammatory bowel disease: The story continues. *Ther. Adv. Gastroenterol.* **2021**, *14*, 17562848211059954. [CrossRef]

66. Srirangan, S.; Choy, E.H. The role of interleukin 6 in the pathophysiology of rheumatoid arthritis. *Ther. Adv. Musculoskelet. Dis.* **2010**, *2*, 247–256. [CrossRef] [PubMed]
67. Yip, R.M.L.; Yim, C.W. Role of Interleukin 6 Inhibitors in the Management of Rheumatoid Arthritis. *J. Clin. Rheumatol. Pract. Rep. Rheum. Musculoskelet. Dis.* **2021**, *27*, e516–e524. [CrossRef]
68. Magyari, L.; Varszegi, D.; Kovesdi, E.; Sarlos, P.; Farago, B.; Javorhazy, A.; Sumegi, K.; Banfai, Z.; Melegh, B. Interleukins and interleukin receptors in rheumatoid arthritis: Research, diagnostics and clinical implications. *World J. Orthop.* **2014**, *5*, 516–536. [CrossRef] [PubMed]
69. Chyuan, I.T.; Chen, J.Y. Role of Interleukin- (IL-) 17 in the Pathogenesis and Targeted Therapies in Spondyloarthropathies. *Mediat. Inflamm.* **2018**, *2018*, 2403935. [CrossRef]
70. Nakayamada, S.; Tanaka, Y. BAFF- and APRIL-targeted therapy in systemic autoimmune diseases. *Inflamm. Regen.* **2016**, *36*, 6. [CrossRef]
71. Yap, H.Y.; Tee, S.Z.; Wong, M.M.; Chow, S.K.; Peh, S.C.; Teow, S.Y. Pathogenic Role of Immune Cells in Rheumatoid Arthritis: Implications in Clinical Treatment and Biomarker Development. *Cells* **2018**, *7*, 161. [CrossRef]
72. Murayama, M.A.; Shimizu, J.; Miyabe, C.; Yudo, K.; Miyabe, Y. Chemokines and chemokine receptors as promising targets in rheumatoid arthritis. *Front. Immunol.* **2023**, *14*, 1100869. [CrossRef] [PubMed]
73. Elemam, N.M.; Hannawi, S.; Maghazachi, A.A. Role of Chemokines and Chemokine Receptors in Rheumatoid Arthritis. *ImmunoTargets Ther.* **2020**, *9*, 43–56. [CrossRef] [PubMed]
74. Hascoët, E.; Blanchard, F.; Blin-Wakkach, C.; Guicheux, J.; Lesclous, P.; Cloitre, A. New insights into inflammatory osteoclast precursors as therapeutic targets for rheumatoid arthritis and periodontitis. *Bone Res.* **2023**, *11*, 26. [CrossRef] [PubMed]
75. Vacinova, G.; Vejražkova, D.; Rusina, R.; Holmerová, I.; Vaňková, H.; Jarolímová, E.; Včelák, J.; Bendlová, B.; Vaňková, M. Regulated upon activation, normal T cell expressed and secreted (RANTES) levels in the peripheral blood of patients with Alzheimer's disease. *Neural Regen. Res.* **2021**, *16*, 796–800. [CrossRef] [PubMed]
76. Filer, A.; Raza, K.; Salmon, M.; Buckley, C.D. The role of chemokines in leucocyte-stromal interactions in rheumatoid arthritis. *Front. Biosci. J. Virtual Libr.* **2008**, *13*, 2674–2685. [CrossRef]
77. Bradfield, P.F.; Amft, N.; Vernon-Wilson, E.; Exley, A.E.; Parsonage, G.; Rainger, G.E.; Nash, G.B.; Thomas, A.M.; Simmons, D.L.; Salmon, M.; et al. Rheumatoid fibroblast-like synoviocytes overexpress the chemokine stromal cell-derived factor 1 (CXCL12), which supports distinct patterns and rates of CD4+ and CD8+ T cell migration within synovial tissue. *Arthritis Rheum.* **2003**, *48*, 2472–2482. [CrossRef]
78. Gómez-Melero, S.; Caballero-Villarraso, J. CCR6 as a Potential Target for Therapeutic Antibodies for the Treatment of Inflammatory Diseases. *Antibodies* **2023**, *12*, 30. [CrossRef]