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TARGETING COMPLEMENT AND PROTEASOME PATHWAYS IN RHEUMATOID ARTHRITIS: EMERGING THERAPEUTIC STRATEGIES

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Abstract: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovial inflammation, cartilage destruction, and bone erosion, leading to disability and reduced quality of life. Although conventional synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) have improved outcomes, many patients remain refractory or develop adverse effects, necessitating exploration of novel therapeutic strategies. The complement and proteasome pathways play pivotal roles in RA pathogenesis by sustaining immune activation, cytokine amplification, and NF-κB–mediated inflammatory signaling. Pharmacological interventions targeting these pathways, including complement inhibitors (C3, C5, C5aR antagonists) and proteasome inhibitors (Bortezomib, Carfilzomib, Immunoproteasome-selective agents), have demonstrated promising efficacy in preclinical and early clinical studies. Furthermore, combination regimens and dual-targeting approaches provide synergistic effects by simultaneously disrupting extracellular and intracellular inflammatory mechanisms. Advances in immunoproteasome-selective molecules, oral small-molecule inhibitors, nanoparticle-based delivery, and biomarker-driven patient selection are expected to enhance both safety and therapeutic outcomes. Collectively, targeting the complement and proteasome pathways represents an innovative and promising frontier in RA management, particularly for difficult-to-treat and refractory cases.

Keywords: Rheumatoid arthritis, Complement pathway, Proteasome pathway, NF-κB, Synovial inflammation, Immunoproteasome, Cytokines, Targeted therapy, Biologics, Combination therapy

1. Introduction

1.1 Overview of Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a debilitating chronic autoimmune disease primarily characterized by inflammation of the joints, leading to significant damage, reduced quality of life, and substantial morbidity [1]. This systemic inflammation leads to progressive disability, affecting not only the joints but also potentially impacting other organ systems, thus contributing to a decrease in overall well-being and functionality [2]. The disease primarily targets the lining of the synovial joints, causing

progressive deterioration that can lead to premature death and significant socioeconomic burdens on both individuals and healthcare systems [2]. The chronic nature of RA requires continuous management and often results in considerable healthcare costs due to medications, therapies, and supportive care.

RA's multifactorial etiology means it can directly or indirectly affect various organs and systems within the body, complicating its management and requiring a holistic approach to treatment [3]. This complexity arises from the interplay of genetic predispositions, environmental factors, and immune system dysregulation, all of which contribute to the onset and progression of the disease. The systemic nature of RA means that symptoms are not confined to the joints alone, with many patients experiencing fatigue, fever, and other systemic manifestations that impact their daily lives. Given the wide-ranging effects of RA, therapeutic strategies must aim not only to alleviate joint inflammation and prevent joint damage but also to address these broader systemic issues to improve the patient's overall quality of life.

1.2 Current therapeutic options and limitations

Current therapeutic options for RA include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs), but many patients do not respond adequately to these treatments [1]. Despite significant therapeutic advances, a substantial proportion of RA patients do not effectively respond to the current therapies available, highlighting the need for innovative approaches and alternative treatment strategies [2]. Existing drugs often merely alleviate symptoms or slow the progression of the disease without providing a complete cure, leaving patients to cope with residual pain, stiffness, and functional limitations [3]. The goal of achieving complete remission remains elusive for many, underscoring the limitations of current therapeutic interventions. Many current medications can have intolerable side effects, which can lead to disease progression as patients are forced to discontinue or reduce their treatment regimens [4]. These side effects can range from mild discomfort to severe complications, including infections, liver damage, and cardiovascular events, which significantly impact the patient's quality of life and adherence to treatment. The limited efficacy and potential for adverse effects emphasize the importance of exploring new pharmacological targets and developing more targeted and safer therapies to improve outcomes for RA patients. This involves a deeper understanding of the underlying pathological mechanisms of RA and the identification of novel therapeutic targets that can effectively modulate the immune response without causing significant harm.

New pharmacologic targets are needed to increase drug effectiveness and reduce toxicity in the treatment of RA, addressing the limitations of existing medications and improving patient safety [5]. Current RA therapies are often associated with significant side effects, which can limit their use and impact patient quality of life. Identifying new targets that can be modulated with greater specificity and fewer off-target effects is essential for developing safer and more effective treatments for RA. Emerging therapies offer hope for better disease control and potential advantages for future betterment in RA, providing new avenues for therapeutic intervention and improving long-term outcomes for patients [6].

2. Pathophysiology of Rheumatoid Arthritis

2.1 Immune System Dysregulation

2.1.1 Role of T cells, B cells, macrophages, and synovial fibroblasts

The autoimmune response in rheumatoid arthritis (RA) involves a complex interplay between T cells, B cells, macrophages, and synovial fibroblasts driving chronic inflammation and joint destruction. Activated T and B lymphocytes are central to pathogenesis [7]. CD4+ T cells recognize antigens presented by Antigen-Presenting Cells (APCs) via Major Histocompatibility Complex (MHC) class II molecules and release cytokines that amplify inflammation [8,9]. T helper cells, Th1 cells secrete Interferon-gamma (IFN-γ) to activate macrophages, Th2 cells produce interleukin-4 (IL-4) and interleukin-10 (IL-10) to support humoral immunity, and Th17 cells produce interleukin-17 (IL-17), a key pro-inflammatory cytokine. B cells contribute through autoantibody production Rheumatoid

Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPAs), antigen presentation, and cytokine secretion (TNF-α, IL-6), with their importance highlighted by B cell-depleting therapies like rituximab [8,9]. Macrophages, abundant in synovium, release TNF-α, IL-1β, IL-6, and matrix metalloproteinases (MMPs), driving synovitis, cartilage destruction, and bone erosion, while MIF further promotes inflammation, fibroblast proliferation, neutrophil chemotaxis, angiogenesis, and osteoclast differentiation [8,9]. Synovial fibroblasts, activated by cytokines, secrete MMPs, IL-6, IL-8, and express receptor activator of nuclear factor kappa-B ligand (RANKL), facilitating cartilage and bone destruction [10]. These fibroblasts display tumor-like behavior with aggressive proliferation and anti-apoptotic traits. Overall, interactions among these immune cells perpetuate autoimmunity and RA progression [7,8].

2.1.2 Pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, IL-17)

Pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and interleukin-17 (IL-17) are crucial drivers of RA [7,9]. Produced by immune cells such as T cells, B cells, macrophages, and synovial fibroblasts, these cytokines mediate synovitis, cartilage destruction, and bone erosion, making them key therapeutic targets [11].

TNF-α, secreted by macrophages, T cells, and fibroblasts, induces other cytokines, activates immune cells, and stimulates MMP production. It promotes synovitis by enhancing vascular permeability, leukocyte recruitment, and fibroblast proliferation, while contributing to cartilage destruction by inducing MMPs and inhibiting matrix synthesis. TNF-α also stimulates osteoclast differentiation, driving bone erosion, with its role confirmed by the success of TNF-α inhibitors such as Etanercept, Infliximab, Adalimumab, Golimumab, and Certolizumab pegol. IL-6, released by macrophages, T cells, and fibroblasts, contributes to synovitis, osteoclast maturation, and vascular endothelial growth factor (VEGF) induced pannus formation [11]. Beyond joint pathology, IL-6 mediates systemic effects, including anemia through hepcidin, fatigue via the hypothalamic-pituitary-adrenal (HPA) axis, and the acute-phase response. It also promotes B-cell and Th17 differentiation. The therapeutic efficacy of tocilizumab, anti-interleukin-6 receptor (anti-IL-6R) antibody, highlights its importance in RA [11].

IL-1β, mainly from macrophages, enhances vascular permeability, leukocyte infiltration, fibroblast proliferation, and osteoclast differentiation. It induces MMPs, suppresses matrix synthesis, and signals through NF-κB and MAPK pathways, contributing to cartilage and bone destruction. Its pathogenic role is validated by the efficacy of anakinra, an IL-1 receptor antagonist. IL-17, derived from Th17 cells, amplifies RA pathology [12]. It induces TNF-α, IL-6, and IL-1β production by fibroblasts and macrophages, stimulates MMP release leading to cartilage degradation, and promotes RANKL expression, osteoclast activation, and COX-2 induction. Elevated IL-17 levels in synovial fluid correlate with joint inflammation severity. Collectively, TNF-α, IL-6, IL-1β, and IL-17 act synergistically to sustain inflammation and drive joint damage, underscoring their central role in RA pathogenesis and their value as therapeutic targets [7,9,11,12].

2.2 Joint Damage Mechanisms: Chronic Synovitis and Cartilage Destruction with Bone Erosion

Chronic synovitis in rheumatoid arthritis (RA) is defined as persistent inflammation of the synovial membrane (SM) [13]. This process leads to cartilage destruction, bone erosion, and joint dysfunction through the action of immune cells, pro-inflammatory cytokines, and mediators. Persistent synovitis results in the formation of pannus, consisting of synovial fibroblasts (SFs), inflammatory cells, and new blood vessels, which invade and erode cartilage and bone [13]. Tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) drive SF proliferation and migration, while matrix metalloproteinases (MMPs) degrade extracellular matrix. Synovitis and bone marrow edema (BME), detectable by magnetic resonance imaging (MRI), are early predictors of erosions, highlighting the need for early diagnosis [13]. Clinical evaluation (swelling, tenderness, warmth, restricted motion), laboratory tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and imaging by ultrasonography (US) or MRI are essential for assessment [14]. The inflammatory process

is sustained by cytokines, chemokines, and growth factors that recruit immune cells and amplify synovial inflammation [15].

Cartilage destruction and bone erosion are direct consequences of chronic synovitis, contributing to progressive disability in RA [13]. MMPs including MMP-1, MMP-3, MMP-9, and MMP-13, secreted by SFs, chondrocytes, and inflammatory cells, degrade cartilage matrix, with TNF-α and IL-1β stimulating their expression. Aggrecanases also contribute to matrix degradation [8]. Bone resorption is mediated by osteoclasts, multinucleated bone-resorbing cells, activated by receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL is expressed by SFs and T cells and is further induced by TNF-α, IL-1β, and interleukin-17 (IL-17). Activated osteoclasts secrete hydrochloric acid (HCl) and cathepsin K to degrade bone. TNF-like weak inducer of apoptosis (TWEAK), acting through fibroblast growth factor-inducible 14 (Fn14), promotes pro-inflammatory cytokines and MMPs, aggravating tissue damage and impairing repair [16].

2.3 Position of Complement and Proteasome Pathways in RA Pathogenesis

The complement pathway, a key component of innate immunity, contributes to rheumatoid arthritis (RA) by driving inflammation and tissue damage [17]. Activation releases anaphylatoxins (C3a, C5a) that recruit neutrophils, macrophages, and other leukocytes into the synovium, promoting chronic synovitis and pannus formation [18]. Complement further enhances pro-inflammatory cytokine production, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), and the membrane attack complex (MAC) directly damages synovial cells, aggravating joint destruction [19]. Neuropathic conditions like carpal tunnel syndrome (CTS) in RA may also be linked to complement-mediated inflammation, detectable by ultrasound (US) around the median nerve [20]. Synovial fibroblasts (SFs) respond to complement products such as C5a by releasing cytokines and matrix metalloproteinases (MMPs), amplifying joint damage [21].

The proteasome pathway regulates protein degradation and inflammatory mediators in RA [22]. Its inhibition reduces cytokine production and inflammation, as shown by agents like Bortezomib in preclinical studies [23]. A central role involves nuclear factor-kappa B (NF-κB), whose activation depends on proteasome processing; inhibition blocks NF-κB signaling and pro-inflammatory mediator release [22]. The proteasome also degrades intracellular proteins for antigen presentation via MHC molecules, influencing T cell activation [22]. Importantly, complement activation increases cytokine release that stimulates proteasome activity, while the proteasome enhances complement component production, creating a feedback loop that sustains inflammation [22].

3. Complement Pathway in Rheumatoid Arthritis

The complement system, a key part of innate immunity, involves classical, lectin, and alternative pathways that converge to promote inflammation and tissue damage in rheumatoid arthritis (RA) [17].

3.1 Effector Molecules (C3, C5, C3a, C5a)

C3, C5, C3a, and C5a are key effector molecules of the complement system, mediating a variety of pro-inflammatory effects that contribute to RA pathogenesis [22]. These molecules, generated during the complement cascade, play distinct roles in opsonization, inflammation, and target cell lysis. Understanding the specific functions of these effector molecules is crucial for developing targeted therapies that can effectively control complement-mediated inflammation in RA [22].

C3 convertase cleaves C3 into C3a and C3b; C3b mediates opsonization and helps form C5 convertase [17]. C5 convertase cleaves C5 into C5a and C5b, initiating MAC assembly and cell lysis [17]. Anaphylatoxins C3a and C5a recruit and activate immune cells, increasing vascular permeability and cytokine release [22]. C5a strongly recruits neutrophils and macrophages, stimulating cytokines, matrix metalloproteinases (MMPs), and reactive oxygen species, driving cartilage and bone destruction [22].

3.2 Role in RA Pathogenesis: Synovial Inflammation, Leukocyte Recruitment, Tissue Damage

Complement activation in RA promotes synovial inflammation, immune cell influx, cytokine release, and direct tissue damage [22]. C3a and C5a recruit neutrophils and macrophages, leading to hyperplasia, pannus, and matrix destruction [8]. Complement further induces tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), reinforcing inflammation [8]. MAC damages synovial cells, releasing intracellular mediators and perpetuating synovitis [17]. Complement thus amplifies a cycle of chronic inflammation and joint damage [22]. Clinical and experimental data show elevated complement levels in RA serum and synovial fluid [15]. C3a and C5a correlate with disease activity, linking complement activation to severity [15]. Immune complexes (RF, ACPAs) activate the classical pathway, producing anaphylatoxins and MAC [17]. Synovial fibroblasts and macrophages locally produce complement (C3, C5), amplifying joint inflammation [15]. Elevated complement correlates with increased joint damage, confirming its role in RA progression [15].

3.3 Pharmacological Interventions Targeting Complement

C5 inhibitors Eculizumab and Ravulizumab block C5 cleavage, preventing MAC and C5a generation [22]. Eculizumab, a humanized monoclonal antibody with short half-life, requires frequent infusions while Ravulizumab, engineered for longer half-life, allows less frequent dosing [22]. Both reduce inflammation and joint damage, with trials ongoing for RA efficacy [22]. C3 inhibitor AMY-101, a synthetic peptide, blocks C3 cleavage and all three pathways [22]. By preventing C3a, C5a, and C3b generation, it broadly reduces cytokines, leukocyte influx, and tissue damage; preclinical studies show anti-inflammatory effects, with clinical trials in progress [22]. C5a receptor antagonist Avacopan blocks C5a–C5aR1 interaction, reducing leukocyte recruitment and activation [22]. An orally available small molecule, Avacopan has shown efficacy in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and is under trial in RA [22]. Table 1 highlights complement pathway inhibitors that reduce immune-driven inflammation and show therapeutic potential in rheumatoid arthritis.

Table 1. Complement Pathway Inhibitors in Rheumatoid Arthritis

Target	Drug/Compound	Mechanism of Action	Clinical/Preclinical Status
C5	Eculizumab, Ravulizumab	Monoclonal antibodies blocking C5 cleavage → prevent C5a & MAC formation	Approved in PNH, under investigation in autoimmune diseases
C3	Compstatin derivatives (AMY-101)	Binds C3, inhibits activation of all complement pathways	Phase II (C3 glomerulopathy, periodontitis), potential in RA
C5aR1	Avacopan	Small molecule antagonist of C5a receptor → blocks neutrophil recruitment	Phase III in ANCA vasculitis, preclinical in RA

4. Proteasome Pathway in Rheumatoid Arthritis

The proteasome pathway plays a critical role in rheumatoid arthritis (RA) pathogenesis via its function in protein degradation, immune regulation, and signaling pathways such as NF-κB activation.

4.1 Basics of the proteasome system

The proteasome is a large multicatalytic protease complex central to the ubiquitin-proteasome system (UPS), responsible for selective degradation of misfolded, damaged, or regulatory intracellular proteins. This degradation regulates cellular processes including cell cycle, transcription, apoptosis, and immune responses [24]. In the context of immune regulation, the UPS controls degradation of inhibitory kappa B (IκB), the inhibitor of NF-κB; degradation of IκB by the proteasome allows NF-κB translocation to the nucleus and activation of proinflammatory gene expression. Thus, the proteasome modulates inflammatory responses by regulating NF-κB signaling [25].

4.2 Role in RA Pathogenesis

In RA, proteasome activity contributes to enhanced cytokine production, notably tumor necrosis factor alpha (TNF-α), interleukins (IL-1, IL-6), and other pro-inflammatory mediators that drive synovial inflammation [26,27]. TNF-α also stimulates fibroblast-like synoviocytes (FLS), which exhibit tumor-like aggressive behavior, leading to joint destruction via secretion of matrix metalloproteinases (MMPs) and promotion of osteoclast activation [28,29]. The activation of osteoclasts is further enhanced by cytokine signaling pathways such as IL-6 trans-signaling, contributing to bone erosion characteristic of RA [29]. NF-κB activation, regulated by proteasomal degradation of IκB, sustains inflammatory gene expression and synovial hyperplasia, linking inflammation with tissue damage [30].

Studies report increased proteasome activity in cells and tissues from RA patients, correlating with elevated inflammatory responses [31]. Pharmacological inhibition of the proteasome suppresses NF-κB activation, reducing proinflammatory cytokine production and synovial inflammation in preclinical arthritis models. Increased expression of proteasome components and functional evidence of heightened proteasome-mediated protein degradation have been documented in RA synovial tissue and immune cells [32].

4.3 Pharmacological Interventions Targeting Proteasome

Proteasome inhibitors have been explored as a therapeutic strategy in RA, given their capacity to interfere with key inflammatory pathways. First-generation inhibitor Bortezomib is a reversible proteasome inhibitor initially approved for multiple myeloma. It inhibits NF-κB activation by preventing IκB degradation, thus reducing cytokine production and inflammation [24]. Preclinical studies report Bortezomib attenuates arthritis severity and inflammatory responses by inhibiting synovial cell activation [33,34]. Second-generation inhibitors Carfilzomib and Ixazomib are newer proteasome inhibitors with improved specificity and pharmacokinetics. They have been shown to inhibit proteasomal activity effectively and reduce inflammatory and tumor-like activities in synovial fibroblasts [24]. However, clinical data specifically in RA are yet limited, and ongoing research is exploring their potential benefits and safety profiles. Table 2 presents proteasome pathway inhibitors that suppress NF-κB–mediated inflammation and show promise as therapeutic strategies in rheumatoid arthritis.

Table 2. Proteasome Pathway Inhibitors in Rheumatoid Arthritis

Target	Drug/Compound	Mechanism of Action	Clinical/Preclinical Status
26S Proteasome	Bortezomib	Inhibits proteasome → prevents IκB degradation → blocks NF-κB signaling	Approved in multiple myeloma, effective in RA animal models
26S Proteasome	Carfilzomib	Irreversible proteasome inhibitors	Approved in cancers, explored in autoimmune conditions
26S Proteasome	Ixazomib	Oral proteasome inhibitors	Approved in cancers, explored in autoimmune conditions

5. Emerging Pharmacological Strategies

5.1 Combination therapies: Complement inhibitors + DMARDs/biologics

Complement blockade targets a fundamental upstream amplifier of inflammation and therefore offers a mechanistically attractive add-on to conventional DMARDs and biologics. From a pharmacological standpoint, complement inhibitors (targeting C3, C5, or C5aR) reduce generation of anaphylatoxins (C3a/C5a) and downstream membrane attack complex formation, thereby limiting neutrophil and monocyte recruitment, endothelial activation, and immune complex–mediated tissue injury [35,36]. Preclinical arthritis models demonstrate that C5aR antagonism reduces synovial neutrophilia and leukocyte activation and that these effects are additive when complement blockade is combined with agents that target adaptive immunity (for example, methotrexate or B-cell depletion), supporting the combination concept [37,38]. Clinically, evidence is best established outside RA (e.g., avacopan in ANCA-associated vasculitis showed steroid-sparing efficacy and durable remissions), providing

proof-of-principle that C5aR antagonism can be safely combined with background immunosuppression in systemic autoimmunity [39]. Older RA clinical work with terminal pathway blockade (eculizumab) showed biological signal but limited broad efficacy as monotherapy, suggesting that complement inhibition may be most useful in combination regimens or in biomarker-selected subgroups with high complement activation [40,41]. Mechanistic biomarker studies indicate that standard antirheumatic treatments (TNF inhibitors ± MTX) reduce terminal complement activation products in RA patients, implying potential pharmacodynamic overlap and the need for rational sequencing or dose reduction strategies when combining agents to avoid redundant suppression [42]. The principal translational challenges for combination therapy are (a) incremental infection risk (especially to encapsulated organisms) that requires vaccination and prophylactic strategies, (b) cost and route-of-administration considerations for monoclonal complement inhibitors, and (c) the need for biomarker-driven patient selection to identify those with prominent complement-driven disease biology who will derive the greatest net benefit [43,44].

5.2 Proteasome inhibitors with standard therapies

Proteasome inhibition provides an orthogonal intracellular strategy to blunt inflammatory signaling by stabilizing inhibitors of NF-κB (IκB) and decreasing production of TNF-α, IL-6 and other cytokines from immune and stromal cells; this mechanistic action complements extracellular immunomodulation by DMARDs/biologics [45]. In multiple preclinical RA models (collagen-induced arthritis, adjuvant-induced arthritis, collagen antibody-induced arthritis), the prototypic proteasome inhibitor bortezomib produced marked reductions in clinical scores, synovial inflammatory infiltrates, cytokine levels and bone erosion; importantly, several studies reported enhanced efficacy when bortezomib or immunoproteasome-selective inhibitors were combined with methotrexate or TNF blockade, consistent with pharmacologic synergy between suppression of immune cell proliferation and blockade of intracellular cytokine production [46,47,48]. Immunoproteasome-selective inhibitors (ONX-0914/PR-957, KZR-616/zetomipzomib) preferentially target immune-cell proteasomes (LMP7/LMP2) and therefore may spare some constitutive proteasome functions, improving tolerability; ONX-0914 attenuated experimental arthritis more rapidly than anti-TNF in some models, and KZR-616 has progressed into clinical studies in autoimmune diseases, demonstrating pharmacodynamic reduction of pathogenic cytokines in early trials [49,50]. Nevertheless, proteasome inhibitors have class-specific toxicities (peripheral neuropathy, cytopenias, herpesvirus reactivation) and the therapeutic window in chronic inflammatory diseases is narrower than in oncology; thus combination regimens will require lower, intermittent dosing schedules, immunosurveillance and PK/PD-guided dose finding to preserve efficacy while minimizing adverse events [51]. Recent translational work (novel oral proteasome agents and immunoproteasome-selective dosing) and the development of compartmentalized delivery approaches (e.g., synovium-targeted systems) are active areas that could make proteasome combinations safer and more clinically feasible in RA [52].

5.3 Dual targeting (complement + proteasome)

Dual targeting of the complement system and proteasome pathways represents a promising therapeutic strategy for rheumatoid arthritis (RA), an autoimmune disease characterized by chronic inflammation and tissue destruction.The complement system, an ancient component of innate immunity, is crucial for inflammatory responses through opsonization and lytic killing of pathogens but also contributes to RA pathogenesis by mediating immune complex-driven inflammation and tissue damage. Complement activity is not limited to extracellular spaces but also entails intracellular processes influencing cell metabolism and survival, which broadens its role in autoimmune disease mechanisms [53]. Proteasomes are essential for protein homeostasis by degrading misfolded or damaged proteins via the ubiquitin-proteasome system (UPS), regulating inflammatory signaling pathways including NF-κB, which is pivotal in RA inflammation. Proteasome activators such as PA28 are overexpressed in inflammatory conditions and modulate proteolytic activities, affecting antigen processing and cytokine production [54]. Moreover, proteasome inhibitors have been

explored in autoimmune contexts, with some agents like auranofin (also used clinically for RA) inhibiting deubiquitinases, augmenting apoptotic pathways and reducing inflammation, which could be beneficial when combined with other modulators [55]. Integration of complement and proteasome targeting addresses multiple pathological axes of RA, including inhibition of inflammatory cytokine production (e.g., TNF-α, IL-6) and modulation of immune cell activation. NF-κB inhibition is central to this approach, as NF-κB regulates both complement-related inflammatory gene expression and proteasomal degradation of inhibitors controlling immune activation [56].

Recent advances in drug delivery systems, such as nanoparticle-mediated co-delivery, enable simultaneous targeting of complement components and proteasomes, enhancing therapeutic efficacy while reducing toxicity. These strategies allow site-specific, controlled release of combinatorial therapeutics in RA-affected joints [57]. Additionally, PROteolysis TArgeting Chimeras (PROTACs) represent a novel modality using bifunctional molecules to induce proteasomal degradation of disease-relevant proteins, including components involved in complement activation and inflammation, representing a molecularly precise intervention [58].

6. Future Perspectives

Complement and proteasome pathway inhibitors hold promise for both early intervention in RA to prevent irreversible joint damage and as salvage therapy in refractory patients who fail TNF or JAK inhibitors [59.60]. Development of safer and more selective inhibitors, particularly immunoproteasome-specific drugs (e.g., ONX-0914, KZR-616) and next-generation complement blockers (e.g., INF904, factor Bb inhibitors), aims to reduce off-target toxicities while maintaining efficacy [61,62]. The emergence of oral small molecules targeting C5aR1 or the proteasome offers the potential for improved patient compliance compared with intravenous monoclonal antibodies [63]. From a translational perspective, careful evaluation of PK/PD relationships, immunosuppression-related infection risk, and long-term safety will be essential before broad clinical adoption [64,65]. In addition, drug repurposing—such as using oncology-approved proteasome inhibitors (bortezomib, ixazomib) or complement inhibitors developed for rare hematologic diseases—could accelerate availability of these agents for RA through cost- and time-efficient development pipelines [66,67].

7. Conclusion

The complement and proteasome pathways are increasingly recognized as central contributors to the chronic inflammation, immune dysregulation, and tissue destruction that define rheumatoid arthritis. By amplifying cytokine production, recruiting immune cells, and sustaining NF-κB–mediated signaling, these pathways establish a self-perpetuating cycle of synovitis and joint damage. Current therapeutic options, though effective for many patients, remain limited by incomplete remission rates, adverse effects, and resistance in difficult-to-treat RA, making the exploration of novel targets essential. Complement inhibition offers the advantage of intercepting inflammatory cascades at an upstream level, while proteasome blockade interferes with intracellular mechanisms of immune activation, providing mechanistically distinct but synergistic strategies. Dual targeting of both pathways, either sequentially or simultaneously, could enhance efficacy by modulating multiple checkpoints of inflammation.

Importantly, advances in immunoproteasome-selective inhibitors, oral complement blockers, and nanoparticle-based delivery systems are expected to improve tolerability and patient compliance. Biomarker-driven approaches may further enable precision therapy, identifying patient subgroups most likely to benefit from pathway-specific interventions. Nevertheless, challenges such as infection risk, long-term safety concerns, cost, and the need for individualized dosing regimens must be carefully addressed before broad clinical adoption. Looking forward, integrating complement and proteasome modulators into existing treatment frameworks either as add-on strategies or in combination with DMARDs/biologics holds the potential to transform the therapeutic landscape of RA. If successfully translated into clinical practice, these approaches may not only prevent

irreversible joint destruction but also offer new hope for patients with refractory disease, ultimately improving long-term outcomes and quality of life.

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