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REVIEW

Rheumatoid Arthritis Therapy Based on B Cells

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent synovial inflammation, joint destruction, and progressive disability. While current therapeutic approaches—including corticosteroids, disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and biologic agents—provide symptomatic relief, their clinical utility remains constrained by substantial limitations such as systemic toxicity, drug resistance, and cumulative adverse effects. These challenges underscore the critical need for novel therapeutic strategies with improved safety and efficacy profiles. The pathogenesis of RA involves multifaceted immune dysregulation, with emerging evidence highlighting the central role of B lymphocytes in both disease initiation and progression. Although B cell-targeted therapies like rituximab demonstrate clinical efficacy, unanswered questions persist regarding the precise immune functions of B cell subpopulations in RA pathogenesis and their potential as translatable therapeutic targets. This comprehensive review examines the clinical burden of RA, limitations of conventional therapies, and the evolving understanding of B cell pathophysiology. We critically evaluate established B cell-directed interventions—including B cell depletion, B cell functional modulation, and regulatory B cell (Breg) promotion—while exploring innovative nanofabrication technologies that may overcome current therapeutic barriers. By synthesizing recent advances in immunomodulatory research, this analysis aims to inform future directions for targeted RA management.

Keywords: RA, B cells, targeted therapy, immune regulation, antigen presentation

Introduction

Characterization of RA

RA is a chronic autoimmune disorder characterized by synovial inflammation. It predominantly affects women, with a female-to-male ratio ranging from 2:1 to 4:1, and typically presents between the ages of 35 and 50 years. RA is associated with substantial morbidity, a chronic progression, multisystem complications, and elevated rates of disability and mortality. While the precise etiology remains unclear, emerging evidence suggests that genetic, environmental, infectious, immune, and endocrine factors contribute to disease development (Figure 1).[1]

RA presents with heterogeneous clinical manifestations, typically developing insidious with symmetrical inflammatory polyarthritis, predilection for the hands, wrists, and feet. Patients often experience morning stiffness, fatigue, low-grade pyrexia, myalgia, and weight loss. Although rare, fulminant disease onset with rapid joint destruction may occur.[2] Once joint damage is established, it is largely irreversible. Without appropriate treatment, RA results in a 70% cumulative disability incidence within three years, with functional limitations progressively worsening over time. Beyond the joints, RA can involve pathogenesis of multiple organ systems such as pericarditis, lung-related complications, renal complications, Sjögren's syndrome, hematological abnormalities, neurological issues, and other systemic complications.

RA remains incurable, with current management emphasizing early standardized treatment and continuous monitoring. The therapeutic paradigm prioritizes achieving clinical remission or sustaining low disease activity to attenuate disability progression and enhance quality of life. Contemporary interventions comprise pharmacological therapies

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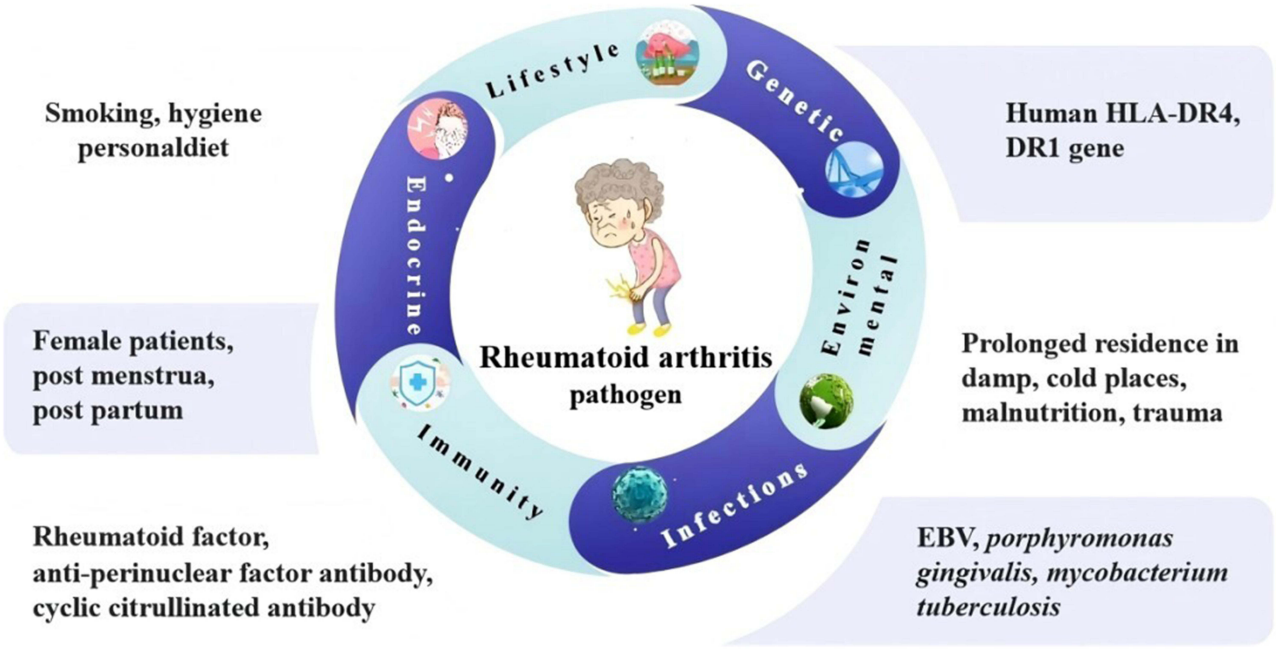

Figure 1 Pathogenic factors of RA. The pathogenesis of RA involves a multifactorial interplay of genetic susceptibility, environmental triggers, immune dysregulation, hormonal fluctuations, aging processes, and lifestyle influences, with immune system aberrations constituting the central pathogenic driver.

(central to disease control) and surgical options (Table 1). DMARDs, including methotrexate, leflunomide, and sulfasalazine, constitute first-line therapy to retard disease progression. Combination DMARD regimens are advocated for treatment-refractory cases. Common adverse effects encompass bone marrow suppression, gastrointestinal intolerance, and hepatobiliary toxicity. NSAIDs (eg, ibuprofen, celecoxib) offer symptomatic analgesia but lack disease-modifying properties. Their gastrointestinal ulcerogenic potential and cardiovascular thrombotic risks necessitate cautious drug selection. Glucocorticoids (eg, triamcinolone) serve as short-term anti-inflammatory agents but carry risks of metabolic disturbances and osteoporosis. Phytotherapeutic compounds such as tripterygium glycosides demonstrate therapeutic

Table 1 General Clinical Treatments and Methods for RA

Type	Name	Indications	Side Effects	Ref.
NSAIDS	Dindimeacin, Ibuprofen, Piroxicam, Celecoxib	Active arthritis	Nausea, vomiting, gastrointestinal ulcer bleeding, renal function impairment	[3]
Glucocorticoid	Triamcinolone, Betamethasone	Medium/high mobility joints	Metabolism disorders, severe infection, osteoporosis	[4]
DMARDs	Methotrexate, Leflunomide, Sulfasalazine Alamod	Active arthritis	Leukocyte reduction, pulpulp suppression, gastrointestinal reaction, liver function damage	[5]
Biologics	Infliximab Tocilizumab	Moderate/severe active RA Refractory arthritis	Nausea, vomiting, infection Infusion reaction, cytopenia, cholesterol increased, infection	[6,7]
Targeted synthesis	Tofacipcrib	Moderate/severe active RA Refractory arthritis	Cardiovascular events, malignancies, thrombosis	[8]
Plant agents	Penidine, Curcumin, Ginger	Active arthritis	Liver function damage, kidney function damage, anaphylaxis	[9]
Surgery	Joint replacement Synovectomy	Loss of joint deformity Refractory arthritis, monoarthritis, major arthritis	Infection, deep venous embolization, recidivation Synovial hyperplasia	[10,11]

efficacy yet require rigorous toxicity monitoring. TNF-α inhibitors (eg, infliximab, adalimumab) demonstrate efficacy in DMARD-refractory disease, while CD20-targeted biologics (eg, rituximab) underscore the therapeutic value of B cell-depleting strategies.

In summary, while the precise etiopathogenesis of RA remains incompletely elucidated, B cell-directed therapies have emerged as a promising therapeutic paradigm. Current disease-modifying agents lack curative potential, requiring lifelong administration with significant adverse effect profiles. Biologic agents, particularly B cell-depleting modalities, demonstrate enhanced clinical efficacy, highlighting the therapeutic promise of mechanism-driven immunomodulatory strategies in this chronic immune-mediated disorder.

Role and Mechanism of B Cells in RA Development

B lymphocytes, central cellular components of adaptive immunity, fulfill critical immunological roles including high-affinity immunoglobulin production immune memory establishment, antigen presentation capacity, pleiotropic cytokine secretion (IL-6, IFN-γ, TNF-α, GM-CSF, IL-10, TGF-β1, IL-35). Memory B cell subsets and long-lived plasma cells mediate pathogenic antibody synthesis (IgG/IgM/IgE). In the pathogenesis of RA, B cells not only initiate immune responses but also directly contribute to disease progression and joint damage. They perform multifaceted roles, including autoantibody production, secretion of proinflammatory cytokines, and interactions with other immune cells (eg, T cells, dendritic cells) (Figure 2). Auto-antibody generation (rheumatoid factor [RF]/anti-citrullinated protein antibodies [ACPA]) serving as diagnostic/prognostic biomarkers while directly contributing to synovitis.[12] T cell activation (MHC-II/TLR-dependent and cytokine-driven pathways) sustaining inflammatory cascades.[13,14] Immune complex deposition and proinflammatory cytokine networks. Functional impairment of regulatory lymphocytes (Treg/Breg suppression).[15] Thus, understanding the complex interplay between dysregulated B cell function and RA pathogenesis not only enhances our comprehension of disease mechanisms but also paves the way for the development of novel therapeutic strategies targeting B cells for RA management.

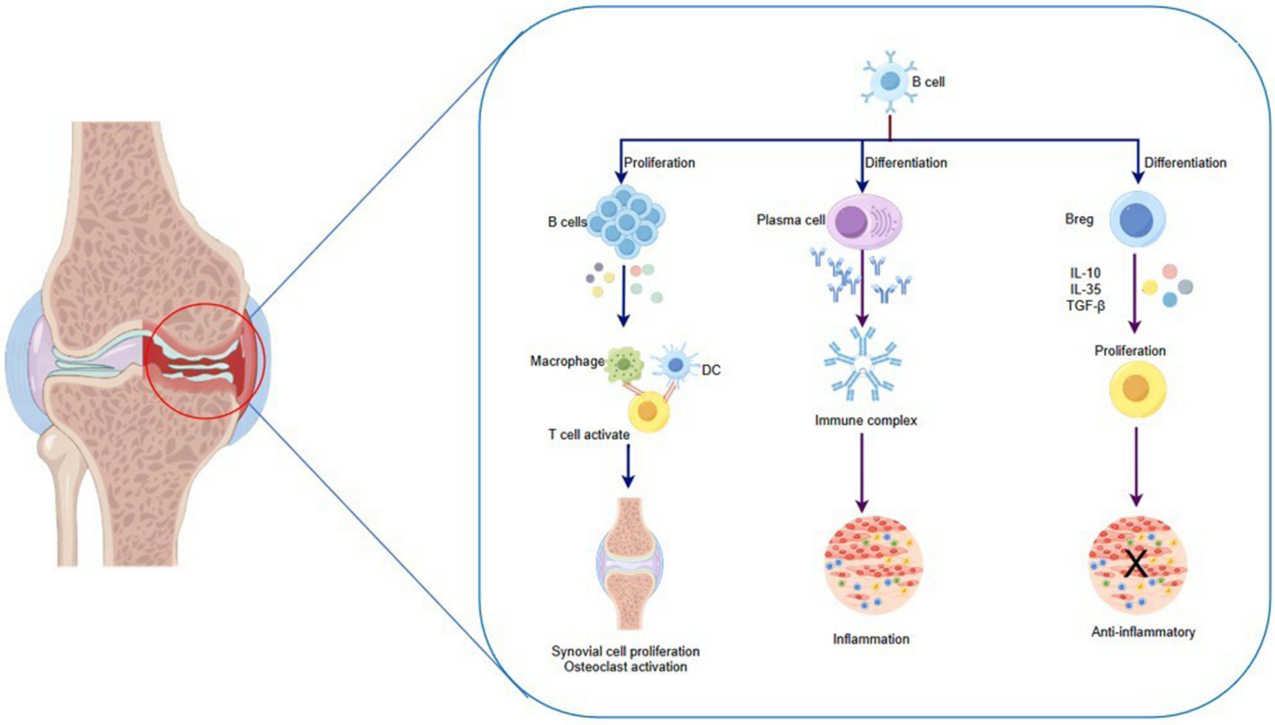

Figure 2 Role of B cells in RA. In RA pathogenesis, B lymphocytes orchestrate inflammatory cascades through antigen presentation, immune cell activation, and direct cytokine secretion. Pathologically hyperactivated autoreactive B cells drive excessive autoantibody production, concomitant with Breg depletion, collectively propelling RA initiation and progression.

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Abnormalities of B Cell Function Exacerbated RA

Dysregulated B cell activation constitutes a central pathogenic mechanism in RA initiation and progression. Physiologically, B cell responses are tightly controlled through foreign antigen-specific immune surveillance. In RA, breakdown of self-tolerance drives autoantigen-directed immune responses through: aberrant self-antigen recognition, dysfunctional costimulatory signaling, BCR hyperactivation, pathogenic immune complex formation, Proinflammatory cytokine milieu disruption. Genome-wide association studies implicate HLA-DRβ1 shared epitope alleles in enhanced antigen-presenting cell (APC) function, facilitating citrullinated antigen presentation to autoreactive B cells.[16] Complete B cell activation requires both BCR engagement and costimulatory signals. RA synovium exhibits upregulated CD40/CD80-CD86 expression, enhancing B-T cell crosstalk via CD40-CD40L interactions and CD28-mediated costimulation. These signaling axes drive autoreactive B cell expansion, ACPA/RF overproduction, and feed-forward inflammatory loops characterizing RA's chronic destructive arthritis.[17]

The development of lymphoid follicle-like architectures within RA synovium pathognomonically reflects sustained immune system overactivation, B lymphocyte clustering, and proinflammatory cytokine dysregulation. These ectopic tertiary lymphoid structures (TLS) mimic secondary lymphoid organ organization, establishing specialized microenvironments that drive pathogenic B cell activation/differentiation while sustaining autoimmune amplification loops.[18] Molecular profiling reveals marked upregulation of NF-κB-inducing kinase (NIK) and non-canonical NF-κB pathway components in TLS-positive synovium versus TLS-negative tissue.[19] NIK-mediated signaling and high endothelial venule (HEV) neogenesis—induced through lymphotoxin-β (LTβ) secretion from infiltrating immune cells—constitute pivotal mechanisms in TLS ontogeny. Proinflammatory cytokines (TNF-α/IL-6 dominant) orchestrate disease-driving immune responses by stimulating B cell maturation, clonal expansion, and autoantibody secretion.[20] Activated B cells undergo terminal differentiation into long-lived plasma cells, perpetuating synovial inflammation through sustained autoantibody production and osteoclastogenic cytokine release.[21]

Interaction of B Cells with Other Immune Cells in RA

The immunopathogenesis of RA involves multifactorial mechanisms where B lymphocytes orchestrate disease progression through autonomous activation, autoantibody production, and bidirectional crosstalk with T cells, dendritic cells (DCs), macrophages, and natural killer (NK) cells (Figure 3). Antigen-presenting B cells engage $CD4^+$ T cells via MHC-II/antigen complexes, sustaining autoimmune activation through co-stimulatory molecule interactions (CD80/CD86-CD28) and proinflammatory cytokine secretion (IL-6/TNF-α) amplifying chronic synovitis.[22] DCs potentiate humoral immunity by enhancing B cell maturation and immunoglobulin class-switching, exacerbating articular immune injury. B cell-macrophage interactions via TNF-α/IL-6 signaling establish feed-forward inflammatory cycles, while Fcγ receptor-bound immune complexes trigger macrophage-mediated B cell hyperactivation.[23–25] NK cell cytotoxicity, primed by B cell-derived IL-15, synergizes with IFN-γ-mediated immunomodulation to augment autoimmune responses.[26] RA synovial fibroblasts (RA-FLS) exhibit CD40/BAFF-driven MMP secretion when stimulated by B cell contact, directing cartilage/bone matrix degradation.[27]

Paradoxically, regulatory B cells (Bregs) counterbalance inflammation via IL-10-mediated Treg expansion.[22]

Molecular Mechanism of Abnormal Activation of B Cells in RA

B cell dysregulation in RA involves complex signaling cascades that drive clonal expansion, plasmablast differentiation, and autoantibody overproduction via SYK/PI3K/MAPK/NF-κB pathway activation, perpetuating chronic immune-inflammatory pathology. Targeting these pathways represents novel therapeutic strategies for disease modification.

Bruton's tyrosine kinase (BTK), essential for BCR signaling, emerges as a key therapeutic target with BTK inhibitors demonstrating significant anti-inflammatory efficacy.[28] TLR-MyD88 signaling amplifies autoimmune memory through IFN-α/CpG ODN-mediated B cell activation.[29] BAFF/BLyS axis hyperactivation sustains pathogenic B cell survival and complement-mediated inflammation.[30] IL-6 trans-signaling via JAK/STAT3 phosphorylation promotes synovial damage, while PI3K-AKT pathway orchestrates B cell proliferative responses.[31,32] AKT inhibitors (eg, perifosine) attenuate immune cell activation through AKT-mTOR blockade.[33] MAPK/NF-κB cascades coordinate

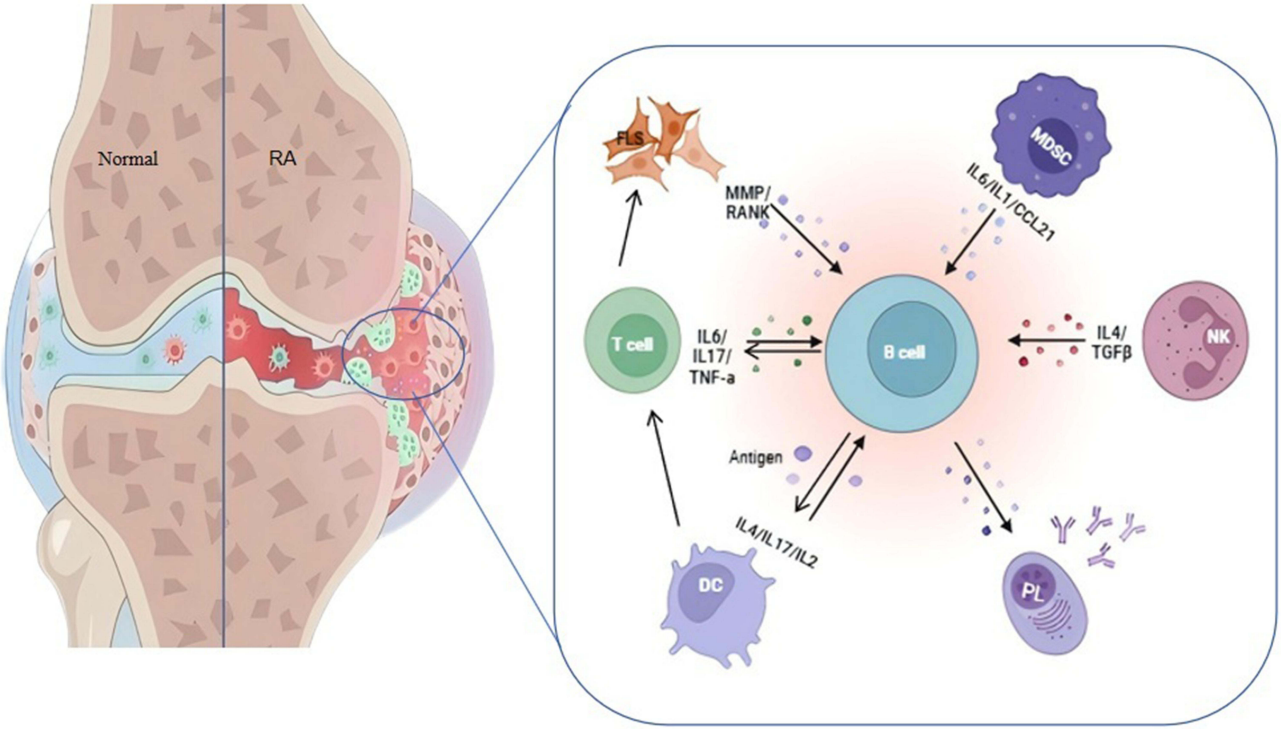

Figure 3 Role and immune imbalance between B cells and other immune cells in RA. B lymphocytes exert multifaceted roles in RA pathogenesis, not only generating pathogenic autoantibodies including RF and ACPA directly implicated in immune dysregulation, but also engaging in dynamic crosstalk with T lymphocytes, dendritic cells, macrophages, and other immune effectors. These cellular interactions perpetuate inflammatory cascades, sustaining chronic inflammation while paradoxically disrupting immune homeostasis when inflammatory regulation becomes impaired.

inflammatory gene expression via ERK/p38/IκB kinase activation.[34,35] JAK-STAT4 axis modulates B cell differentiation, whereas FcγRIIb-CD19 co-targeting (eg, obexelimab) restores immune tolerance by dual inhibition of B cell activation (Figure 4).[36,37]

In summary, the role of B cells in RA is multifaceted. This intricate signaling network positions B cells as both pathogenic mediators and promising therapeutic targets in RA.

Recent Progress of RA Therapy Based on B Cells

Recent advances in RA therapeutics have yielded refined pharmacological agents with enhanced clinical efficacy and improved safety profiles. Research prioritization has shifted toward B cell-directed strategies, given their multimodal pathogenic contributions—autoantibody production, proinflammatory cytokine secretion, and antigen presentation—collectively driving chronic synovial inflammation. Immunomodulation of B cell effector functions demonstrates therapeutic potential through dampening pathogenic inflammation and ameliorating autoimmunity, thereby mitigating RA symptomatology.

Emerging B cell-targeted therapies are elucidated through three mechanistic categories (Table 2): 1) Surface antigen-directed biologics: CD19/CD20/CD22—key immunoregulatory checkpoints—monoclonal antibodies mediate B cell depletion or functional blockade, suppressing autoantibody titers and synovitis; 2) Pathway-specific inhibitors: BCR-mediated signaling (SYK/BTK), TLR-MyD88 axis, BAFF/APRIL system, IL-6 trans-signaling, PI3K-AKT-mTOR cascade, MAPK/NF-κB pathways, and JAK-STAT network—small-molecule inhibitors modulate cytokine/receptor crosstalk to attenuate B cell hyperactivity; 3) Advanced biotechnological interventions: B cell vaccines, CAR-T (Chimeric Antigen Receptor T-Cell Immunotherapy), mesenchymal stem cell infusions, and Breg augmentation strategically recalibrate B cell homeostasis, ameliorating clinical outcomes.

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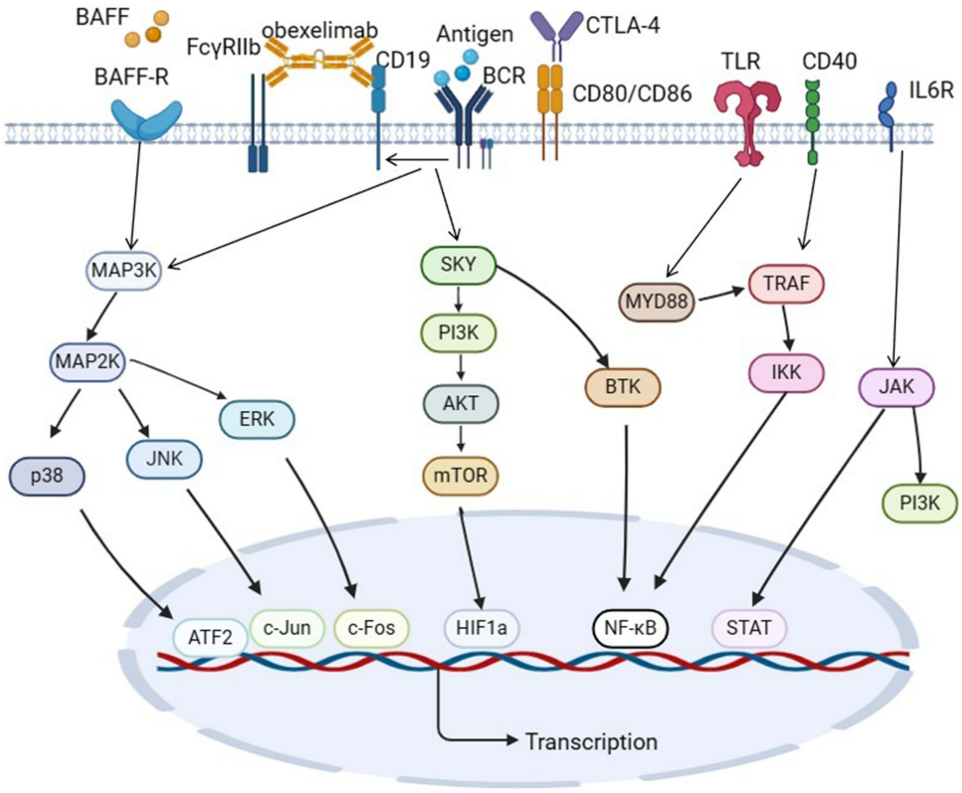

Figure 4 Signaling pathways and targets of B cells involved in RA. B lymphocytes orchestrate rheumatoid arthritis pathogenesis through a multi-pathway network involving BTK, TLR-MyD88, BAFF/BLyS, IL-6/IL-6R, PI3K-AKT, MAPK, NF-κB, and FcγR signaling axes.

These therapeutic interventions stratify into three B cell-centric categories: B cell-depleting modalities, B cell-modulating approaches, and Breg-potentiating strategies, based on their immunomodulatory mechanisms. This chapter delineates these paradigms, with particular emphasis on their mechanistic divergences within B cell-targeted pathways.

Table 2 Regulates the Types and Effects of Drugs and Therapies of B Cells for RA

Type		Name	Function	Advantage	Limitation	Ref.
CD molecule monoclonal antibody	CD19	Belingozumab	Targeting specific B cell surface antigens to effectively regulate B cell function	High specificity, targeted, availability	Tolerance, infection, high costs, limited drugs	[38]
	CD20	Rituximab Obinutuzumab				[39,40]
	CD22	Eppacizumab Shucilizumab				[41]
Immune suppression drugs	BAFF inhibitor	Belimumab Atacicept BAFF-Trap	Binding to BAFF-R, TACI, and BCMA to promote B cell growth	Targeted Multi-target High safety	Limited efficacy, immunodepression, diarrhoea	[42]
Immune suppression drugs	CTLA-4 inhibitor	Abasip	Boosting T cell activation to indirectly affect B cell response.	Enhancing the immune response, long-lasting immune memory	Immune-related adverse effects, individual differences	[43,44]
	JAK inhibitor	Balitinib Ruxolitinib	Inhibiting Janus kinase to regulate cytokine signaling and B cell function.	Multi-target, convenient, efficient anti-inflammatory	Infection, injection site reaction, abnormality	[45,46]
	TNF-α inhibitor	Adalimumab Infliximab	Blocking TNF-α binding to its receptor reduces B cell activation by cytokines.			[47,48]

(*Continued*)

Table 2 (Continued).

Type		Name	Function	Advantage	Limitation	Ref.
Immune suppression drugs	IL-6 inhibitor	Tocilizumab Sacuzumab	Inhibition of IL-6-mediated signaling and regulates B cell function	Targeted, efficient anti-inflammatory	Infection, injection site reaction	[47,49]
	IL-17 inhibitor	Secukinumab Ixekizumab	Reducing cytokines reduces B cell activation and autoantibodies.			[50,51]
Cell therapy	Vaccine	CIT-Ag	Targeting B cell function to regulate immune response.	Long-term efficacy, high safety	High cost, complex operation	[52]
	Adoptive cell therapy	MSCs	Inhibiting the proliferation and activation of B cells			[53]
		Bregs	Supplementing Breg			[54]
		CAR-T	Cytokine Release Syndrome Immune Effector Cell-Associated Neurotoxicity Syndrome Infection Cytopenias			[55]

Therapy Through B Cell Depletion

In RA pathogenesis, B cell hyperactivation, autoantibody generation, and immune homeostasis disruption constitute central pathogenic drivers. Pharmacological targeting of B cell surface antigens (functional modulation/clonal depletion) represents a cornerstone therapeutic approach. Rituximab, a chimeric anti-CD20 monoclonal antibody, remains the first FDA-approved B cell-depleting agent, mediating selective B cell depletion and demonstrating clinical efficacy in refractory RA management. Emerging agents targeting CD19, BAFF, and BR3 are under active investigation.

Cluster of differentiation (CD) molecules—surface markers dynamically expressed during leukocyte differentiation/activation—serve as critical therapeutic targets. Monoclonal antibodies (mAbs) targeting CD antigens (CD19/CD20/CD22) enable precision B cell modulation in RA through depleting pathogenic B cell clones and disrupting co-receptor signaling. Rituximab (anti-CD20 mAb) remains the clinical cornerstone, while novel CD19-targeted agents demonstrate promise. Georg et al[38] developed blinatumomab (CD19×CD3 bispecific T cell engager), inducing T cell-mediated B cell cytotoxicity. In multidrug-refractory RA, low-dose blinatumomab reduced peripheral B cell counts (Figure 5A), reconfigured B cell subsets (Figure 5B and C), lowered autoantibody titers, and ameliorated synovitis (Figure 5D and E). CD22, a BCR co-inhibitory receptor, regulates NF-κB-mediated survival signals. SM03 (recombinant anti-CD22 IgG1) blocks CD22 homotypic interactions, suppressing B cell proliferation via NF-κB inhibition[41,56] (Figure 5F).

CAR-T therapy—a personalized cellular immunotherapy—engineers T cells to express chimeric antigen receptors (CARs), enabling specific recognition and lysis of antigen-expressing cells. Preclinical studies demonstrate CRISPR-Cas9-edited allogeneic CD19-targeting CAR-T cells overcome host immunity with favorable safety/efficacy profiles in refractory autoimmune diseases.[57] In RA, pathogenically skewed B cells are eliminated via CD19/CD20/BAFF-R-targeted CAR-T constructs depleting autoreactive B cell clones and mitigation of autoantibody-driven pathology and inflammatory cascades.[55] Notably, BAFF-R-specific CAR-T cells achieve dual therapeutic effects by Eradicating BAFF-R B cells and disrupting BAFF/BAFF-R survival signaling. CD19-directed CAR-T therapy—the most clinically advanced approach—clears circulating/tissue-resident B cells, reduces autoantibody/cytokine burden, and attenuates osteoarticular destruction. Szabo et al[58] reported a refractory RA case treated with B cell-targeted CAR-T therapy. Diagnosed in 2011, the patient exhibited persistent synovitis despite conventional DMARD/biologic regimens (Figure 6A). Longitudinal analysis demonstrated: declined DAS28-CRP scores, and reduced anti-vimentin/anti-dsDNA autoantibody titers (Figure 6B and C). Following 2023 DLBCL diagnosis, CAR-T therapy (post-chemotherapy failure) yielded: rapid RF decline (48 IU/mL at 3 weeks), sustained serologic remission (13 IU/mL at 1 year), clinical symptom resolution (Figure 6D). This dual therapeutic efficacy highlights CAR-T's potential beyond hematologic malignancies into immune-mediated disorders.

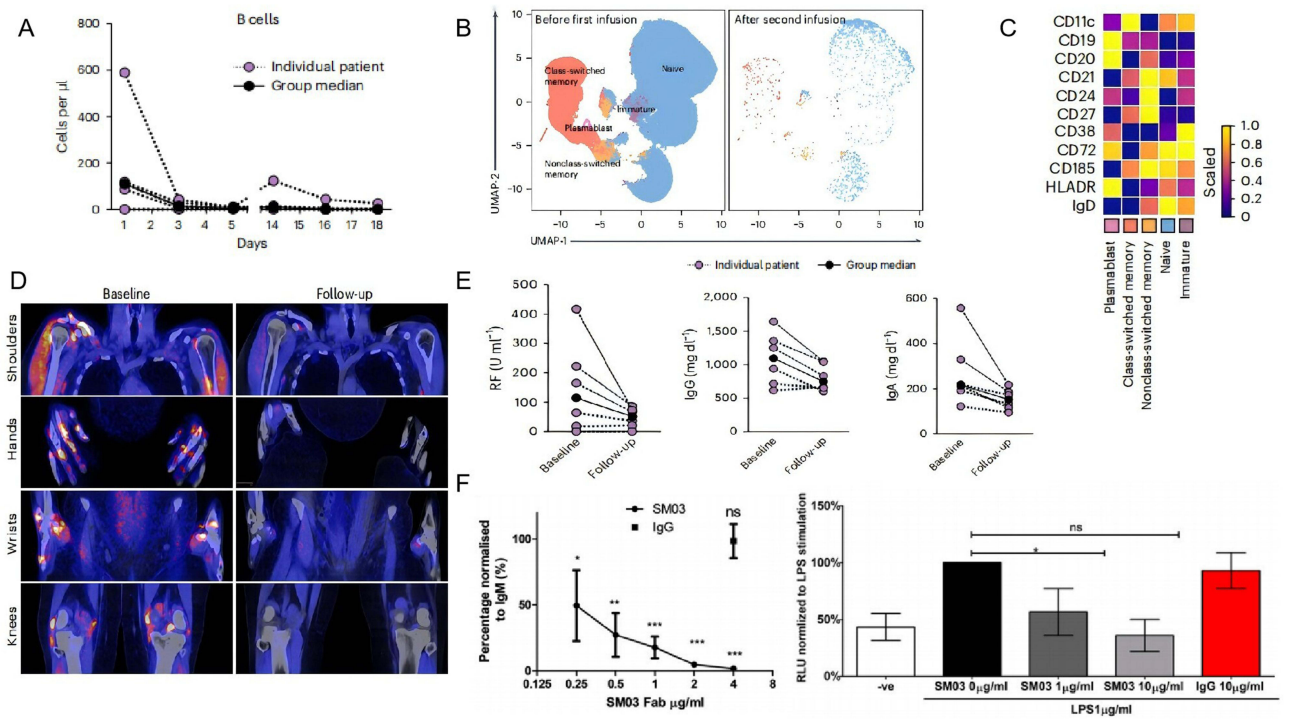

Figure 5 Targeted CD molecules for treating RA. (**A**) Temporal dynamics of B cell counts following mAb infusion (18-day observation). (**B** and **C**) Comparative analysis of B cell subpopulations pre- vs post-mAb administration. (**D**) Systemic disease activity quantification pre- and post-intervention. (**E**) Longitudinal profiles of RF and autoantibody titers. (**F**) Nano-Glo® luciferase assay (Promega) evaluation of viral transduction efficiency. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Reproduced from Bucci L, Hagen M, Rothe T et al. Bispecific T cell engager therapy for refractory RA. Nat Med. 2024;30(6):1593–1601. *Copyright © 2024, The Author(s), under exclusive licence to Springer Nature America, Inc.*[38]

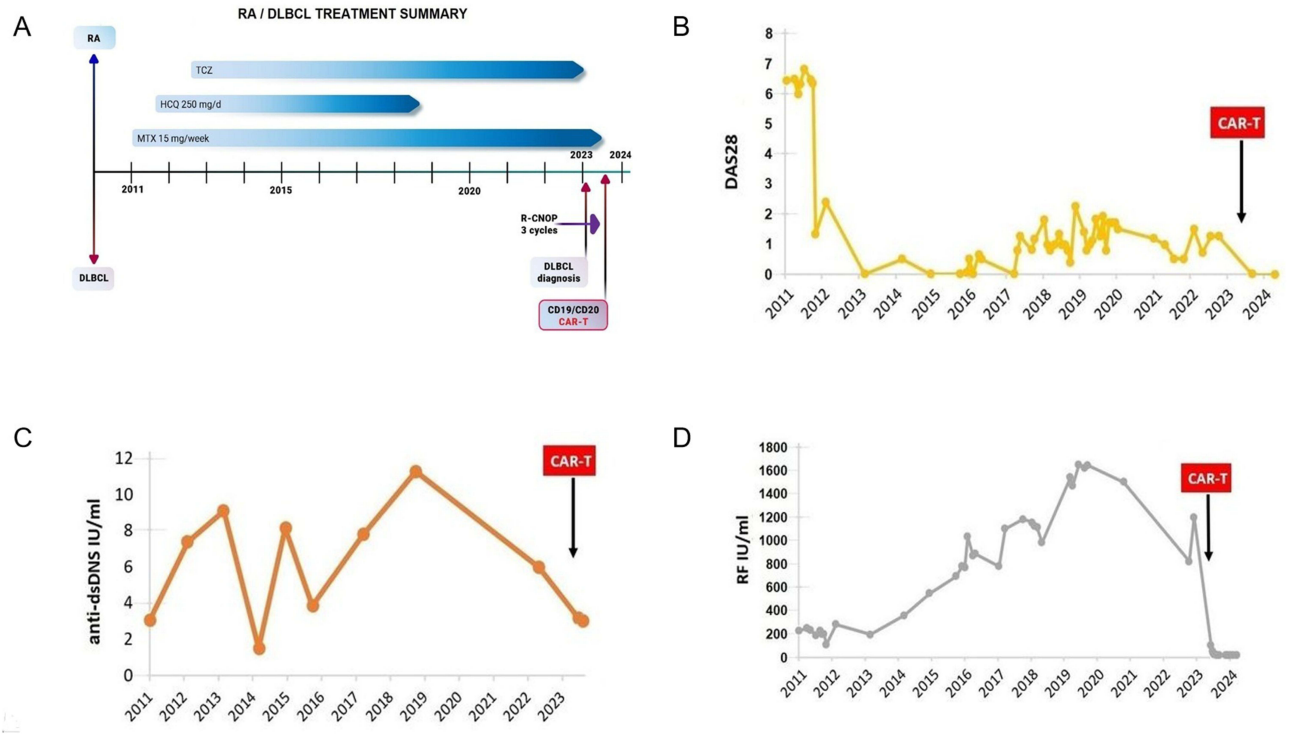

Figure 6 CAR-T treatment for refractory RA. (**A**) Longitudinal treatment history of the RA patient (2011–2024). (**B**) Temporal evolution of disease activity scores (DAS28), (**C**) anti-vimentin/anti-dsDNA antibody titers, and (**D**) RF levels during therapeutic intervention. Reproduced from Szabo D, Balogh A, Gopcsa L et al. Sustained drug-free remission in RA associated with diffuse large B-cell lymphoma following tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy using zamtocabtagene autoleucel. RMD Open. 2024;10(4): e004727. Copyright © Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ.[58]

Therapy via Regulating B Cell Function

B lymphocytes orchestrate pivotal pathogenic roles in RA, driving recent research focus on functional reprogramming strategies. Traditional DMARDs exert B cell regulatory effects through pharmacodynamic optimization, while emerging immune checkpoint inhibitors (CTLA-4/BAFFR-targeted) and intracellular signaling antagonists (PI3K/SYK/JAK-STAT /MAPK/BTK) attenuate inflammatory cascades via: Immune cell activity suppression and Synovio-protective effects. B cell-activating factor (BAFF)—a TNF superfamily cytokine predominantly expressed by monocytes, dendritic cells, and T cells —mediates B cell homeostasis through three receptors: BAFFR: Sustains mature B cell survival/response, TACI: Modulates B-T cell crosstalk, BCMA: Regulates humoral immunity. BAFF inhibitors achieve therapeutic efficacy by: competitively binding soluble BAFF, disrupting BAFF-receptor interactions, and normalizing peripheral B cell pools. Sun et al[42] engineered BAFF-Trap, a high-affinity BAFF antagonist, demonstrating potent neutralization of soluble BAFF. In collagen-induced arthritis (CIA) models, intraperitoneal BAFF-Trap administration reduced serum BAFF levels (Figure 7A), expanded Breg populations (joint microenvironment modulation) (Figure 7B), suppressed pathogenic autoantibody titers (Figure 7C), and attenuated both CIA and adjuvant-induced arthritis progression. Bruton's tyrosine kinase (BTK)—a key BCR downstream effector—mediates autoimmune pathogenesis. BTK inhibitors significantly impair: B cell activation thresholds, co-stimulatory molecule upregulation, clonal proliferation (Figure 7D).[59] Currie et al[60] identified CGI1746, a selective BTK inhibitor blocking enzymatic activation via dual inhibition of autophosphorylation/transphosphorylation. CIA trials revealed reduced autoantibody burden, validating its RA therapeutic potential.

While immune signaling inhibitors demonstrate therapeutic precision in RA through targeted immunomodulation and joint preservation, their clinical application is constrained by mechanism-driven adverse effects including immune-related adverse events (irAEs), infection susceptibility from immunosuppression, treatment refractoriness, and acquired drug resistance. These limitations necessitate risk-stratified patient selection, therapeutic drug monitoring, and

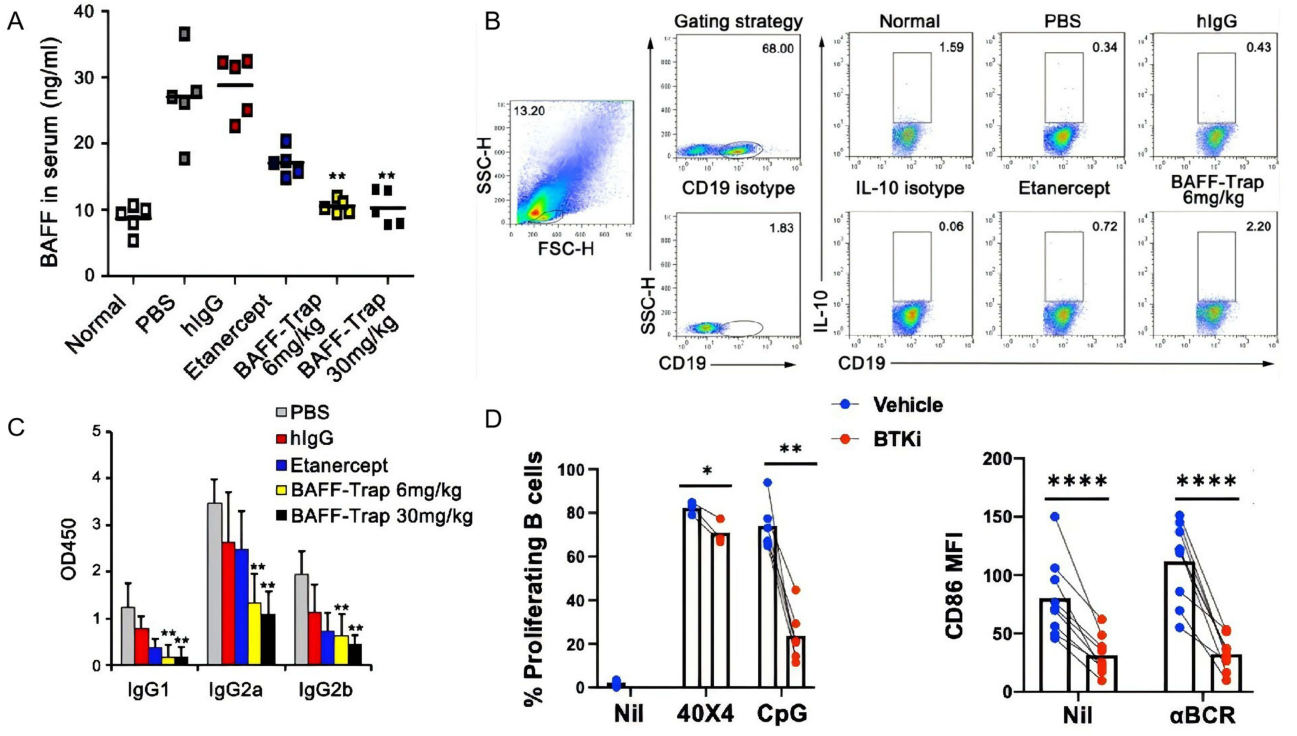

Figure 7 BAFF-Trap and BTi modulate the proliferation and differentiation of B cells. (**A**) BAFF expression profiles in B lymphocytes following BAFF-Trap administration. (**B** and **C**) BAFF-Trap-modulated B cell regulation of IL-10 secretion and antibody titers. (**D**) BTK inhibitor (BTKi) impact on B cell proliferative capacity, activation thresholds, and co-stimulatory molecule upregulation. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$. Zhou B, Zhang H, Su X et al. Therapeutic effects of a novel BAFF blocker on arthritis. Signal Transduct Target Ther. 2019;4:19. © The Author(s) 2019. Creative Commons Attribution 4.0 International License.[42] Reproduced from Li R, Tang H, Burns JC, Hopkins BT, Le Coz C, Zhang B, de Barcelos IP, Romberg N, Goldstein AC, Banwell BL, Luning Prak ET, Mingueneau M, Bar-Or A. BTK inhibition limits B-cell-T-cell interaction through modulation of B-cell metabolism: implications for multiple sclerosis therapy. Acta Neuropathol. 2022 ;143(4):505–521. © The Author(s) 2022. Creative Commons Attribution 4.0 International License.[59]

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personalized therapeutic regimens. Despite these challenges, pathway-specific inhibitors remain a viable therapeutic paradigm when strategically integrated into precision medicine frameworks to optimize risk-benefit profiles.

Therapy with Enhanced Bregs

Bregs serve as critical immunomodulators in RA pathogenesis, suppressing inflammatory cascades and reinstating immune homeostasis through IL-10 secretion and cellular crosstalk with effector lymphocytes. Therapeutic potentiation of Breg functionality represents a promising immunoregulatory strategy; however, translational challenges persist regarding their phenotypic stability, mechanistic elucidation of suppressive networks, and safe clinical translation. Further investigations into Breg plasticity and targeted delivery systems are imperative to harness their full therapeutic potential.

The modulation of B cell populations—either by depleting pathogenic subsets or augmenting immunosuppressive Bregs—holds therapeutic potential to attenuate inflammatory and autoimmune processes in RA, particularly among treatment-refractory patients. RA pathogenesis involves compromised Breg quantity/function, impairing regulatory control over effector B and T lymphocytes, which perpetuates aberrant immune activation. Ex vivo Breg expansion followed by adoptive transfer presents a promising strategy, entailing peripheral blood isolation, in vitro activation/proliferation, and autologous reinfusion to amplify immunoregulatory capacity—an approach demonstrating efficacy in other autoimmune conditions.[61] However, clinical translation of Breg-based therapies remains constrained by technical challenges including limited cell yields and suboptimal post-transfer persistence. Korneev et al[54] investigated B cell activation strategies to induce immunoregulatory phenotypes, demonstrating that combinatorial stimulation with CD40L, CpG, and IL-21 generates Bregs exhibiting robust immunosuppressive potential (Figure 8A). Notably, combinatorial-treated B cells demonstrated enhanced Treg expansion (Figure 8E) and elevated IL-10 production without concomitant TNF upregulation (Figure 8B and C–F), indicating optimal in vitro differentiation of functionally active Bregs. However,

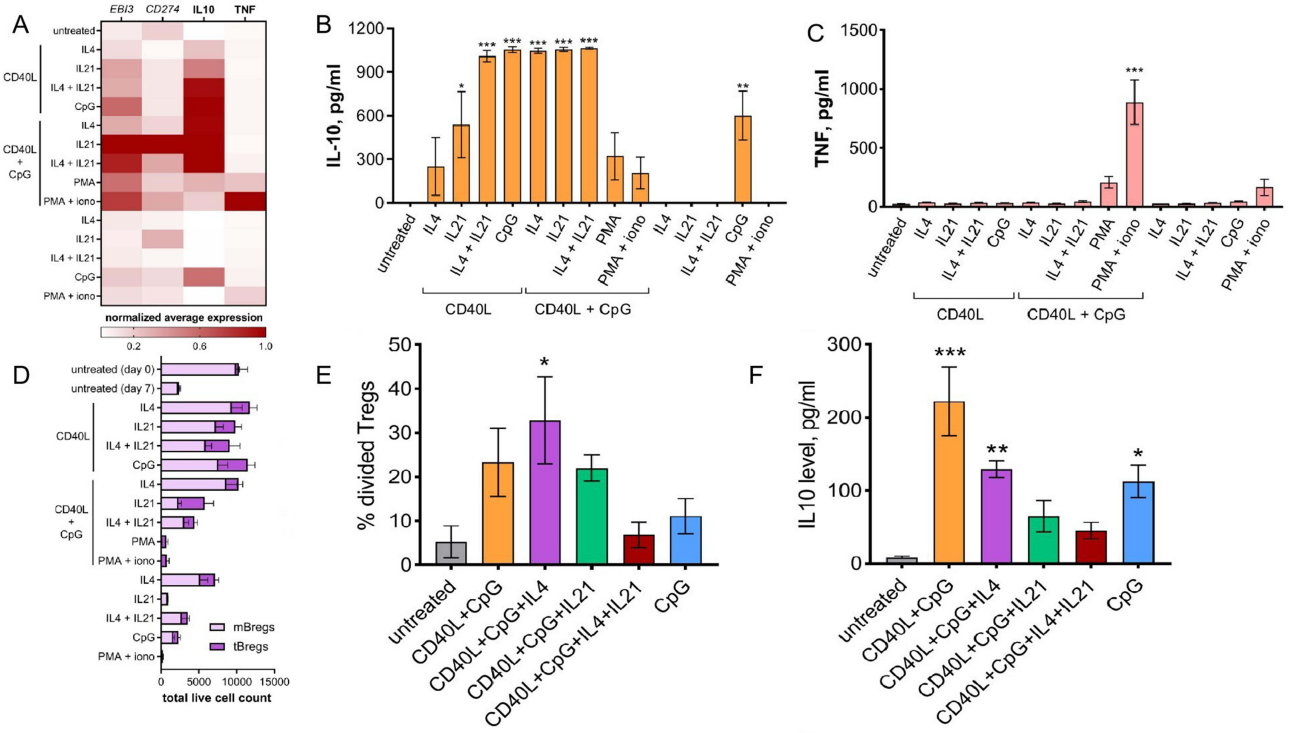

Figure 8 Therapy with In vitro expanded Bregs. (**A**) Heatmap depicting expression profiles of EBI3, CD274, IL-10, and TNF in differentially activated B cell subsets. (**B**) IL-10 and (**C**) TNF concentrations, with (**D**) Breg viability rates under therapeutic interventions. (**E**) Proliferation kinetics of Tregs, activated B cells, and CD4+ T lymphocytes. (**F**) ELISA quantification of IL-10 in CD4+ T cell co-culture supernatants. *p < 0.05, **p < 0.01, ***p < 0.001. Reproduced from Zheremyan EA, Ustiugova AS, Uvarova AN et al. Differentially activated B cells develop regulatory phenotype and show varying immunosuppressive features: a comparative study. Front Immunol. 2023;14:1178445. Copyright © 2023 Zheremyan, Ustiugova, Uvarova, Karamushka, Stasevich, Gogoleva, Bogolyubova, Mitkin, Kuprash and Korneev.[54]

IL-21 inclusion correlated with diminished cellular viability (Figure 8D), highlighting a critical translational barrier requiring protocol refinement.

Short-chain fatty acids (SCFAs)—volatile saturated fatty acids with ≤6 carbons (eg, acetate, propionate, butyrate)—are gut microbiota-derived metabolites from dietary fiber fermentation that modulate Breg function. Valerate enhances Breg immunosuppressive capacity by upregulating IL-10 secretion. Our data demonstrate SCFA-induced Breg expansion under diverse stimuli, including LPS and CD40-activated splenic B cells (Figure 9A), primarily mediated through histone deacetylase (HDAC) inhibition (Figure 9B and C). Butyrate and other HDAC inhibitors further promote B10 cell generation via MAPK pathway activation (Figure 9D). Mauri et al[62] identified butyrate-driven elevation of 5-hydroxyindole-3-acetic acid (5-HIAA), a serotonin metabolite that activates aryl hydrocarbon receptor (AhR) signaling to foster Breg differentiation while suppressing germinal center B cells and plasmablasts, ameliorating RA pathology.

Emerging Nanotherapeutics

Recent advances in nanomedicine offer targeted drug delivery with minimized off-target effects and enhanced therapeutic precision.[63] Emerging nanotherapeutic platforms demonstrate clinical potential in RA management through composite nanosystems,[64] mRNA/siRNA-based delivery vectors, spleen-targeted mRNA nanoparticles,[65] and innovative B cell immunomodulatory strategies.[66] B cell-targeted nanotherapies represent a paradigm shift in RA precision medicine. Wang et al[40] engineered PEG density- and zeta potential-optimized nanocarriers for in vivo B cell targeting, achieving targeted B cell depletion via CRISPR-Cas9/gBAFFR system delivery—a novel approach for RA intervention. Wang et al[67] engineered cationic lipid-assisted PEG-b-PLGA nanoparticles encapsulating BTK-targeting siRNA, effectively suppressing BTK expression in B cells/macrophages while modulating immune cell functionality and alleviating RA symptoms, circumventing high-dose BTK inhibitor toxicity. Yang et al[68] developed an exosome-silk fibroin hydrogel composite via in situ photopolymerization, demonstrating potent suppression of T follicular helper (Tfh) cell responses and germinal center B cell-plasma cell differentiation, thereby attenuating synovitis and osteocartilaginous destruction.

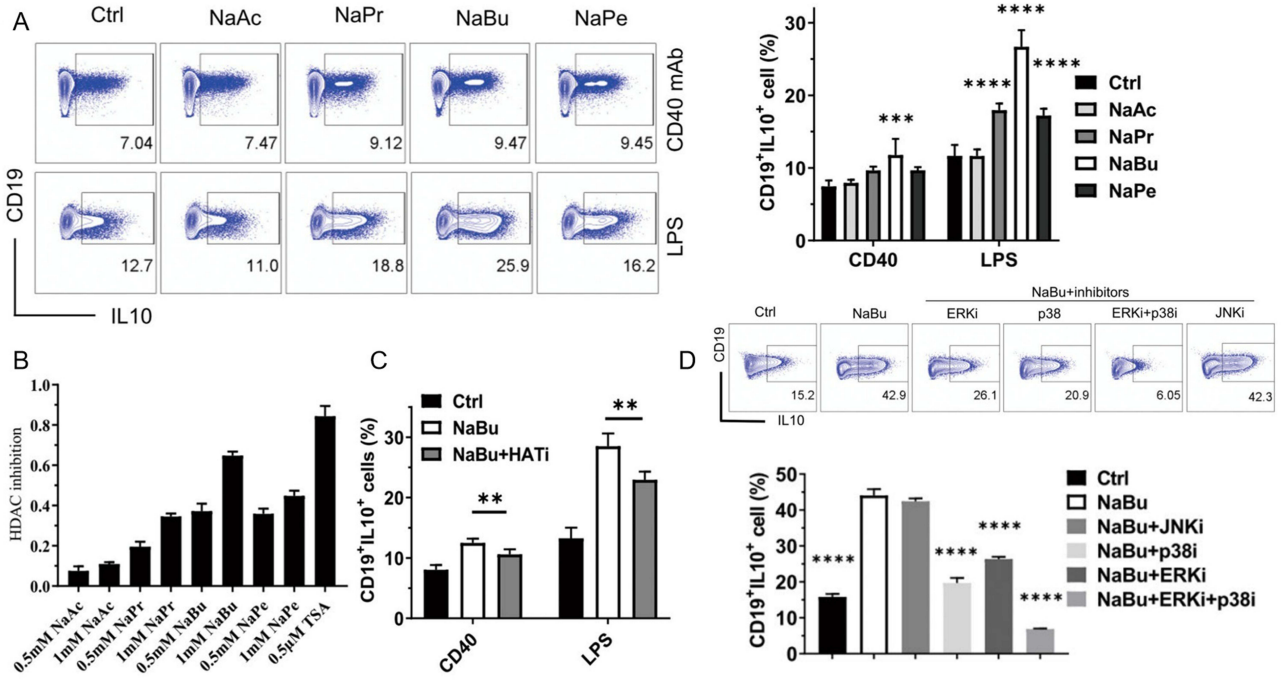

Figure 9 SCFAs promote the generation of B10. (**A**) Flow cytometric analysis assessing IL-10 modulation by LPS/CD40 stimulants. (**B**) Sodium butyrate-mediated IL-10 regulation with/without signaling pathway inhibitors. (**C**) Pharmacologic HDAC inhibition impacts IL-10 induction across stimulation conditions. (**D**) Sodium butyrate's IL-10 modulation under kinase inhibitor cotreatment. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. Reproduced from Zou F, Qiu Y, Huang Y et al. Effects of short-chain fatty acids in inhibiting HDAC and activating p38 MAPK are critical for promoting B10 cell generation and function. Cell Death Dis. 2021;12(6):582. Creative Commons Attribution 4.0 International License.[61]

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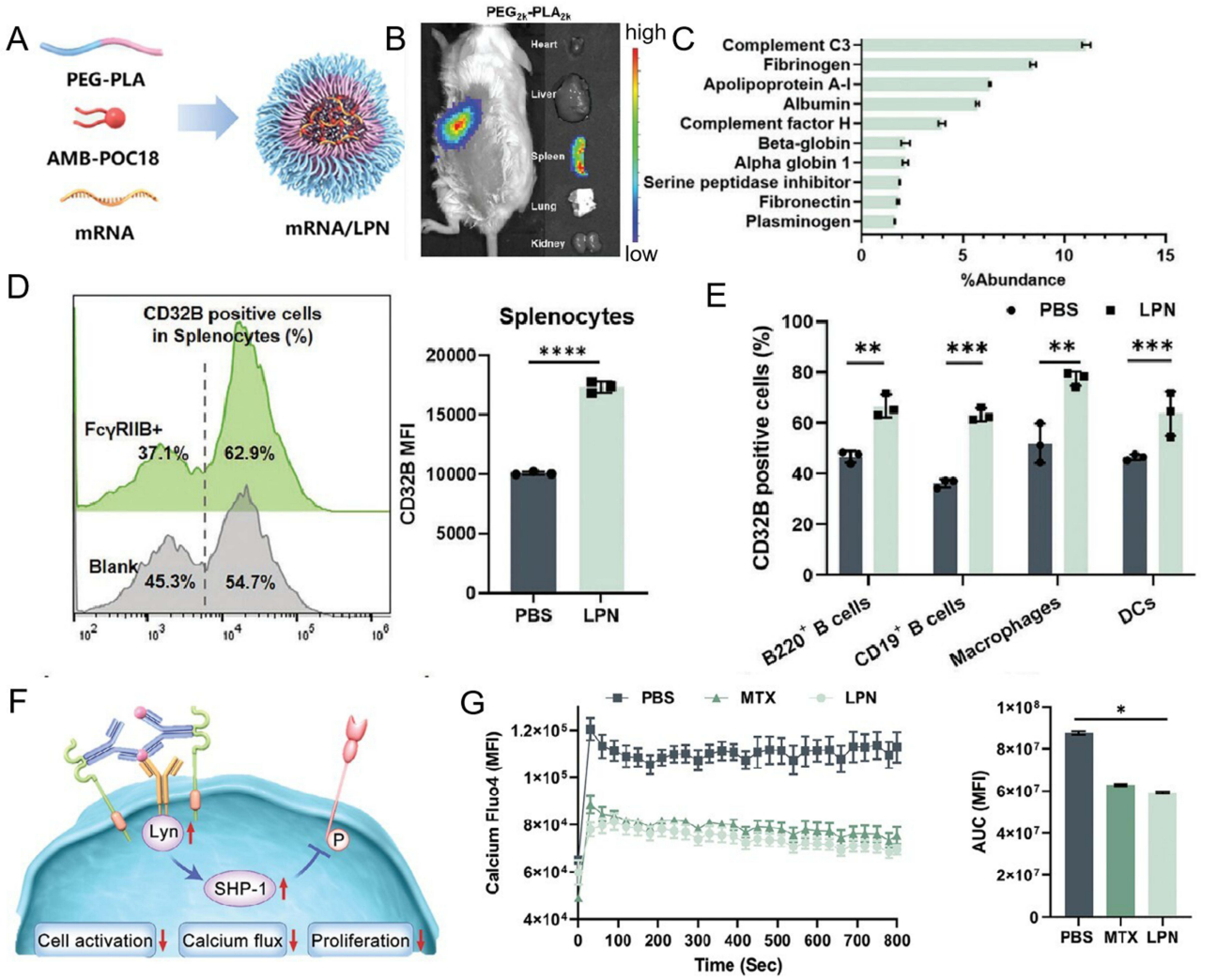

Figure 10 Effect and mechanism diagram of LPN on mouse spleen B cells. (**A**) PEG-PLA polymer formulations with varied molecular weights optimized for LPN-mediated mRNA delivery. (**B**) Protein Corona composition profiling identifies the top 10 plasma proteins adsorbed onto LPN surfaces. (**C**) In vivo fluorescence imaging of fluorescein-labeled mRNA/LPN biodistribution following tail vein administration. (**D**) Splenic transfection efficiency quantification of mFcγRIIB/LPNs. (**E**) FACS analysis of splenocyte subpopulations post mRNA transfection. (**F**) Mechanistic schema illustrating FcγRIIB overexpression-mediated BCR signaling suppression via Lyn/SHP-1 cascade. (**G**) Intracellular Ca^{2+} flux dynamics in activated B cells. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Reproduced from Yanpeng Liu RZ, Qiu N, Wang S, et al, Spleen-Targeted mRNA Nanoparticles for Modulating B Cell Hyperactivation in RA Therapy. Advanced Function Materials, 2024: 101:1–12. Copyright 2024, Jhon Wiley and Sons.[69]

FcγRIIB, an inhibitory B cell receptor, suppresses B cell activation via BCR interaction-mediated immunoregulation. Shen et al[69] engineered mRNA/LPNs using AMB-POC18 and PEG2k-PLGA2k polymers complexed with mRNA (Figure 10A). Intravenous mRNA/LPNs selectively adsorbed complement C3 within the protein corona, enabling spleen-specific targeting in murine models (Figure 10B and C). mFcγRIIB/LPNs elevated FcγRIIB expression in splenocytes from 54.7% to 62.9%, with >20% increases in B cells and macrophages (Figure 10D and E). Compared to PBS/MTX controls, mFcγRIIB/LPN-treated mice exhibited upregulated FcγRIIB/Lyn/SHP-1 signaling alongside reduced CD19 phosphorylation (Figure 10F), mechanistically inhibiting BCR activation through FcγRIIB-mediated pathways. Furthermore, mFcγRIIB/LPNs attenuated intracellular Ca^{2+} flux in B cells, effectively curbing pathological hyperactivation and demonstrating therapeutic efficacy in RA (Figure 10G).

Discussion and Perspective

RA is a chronic systemic autoimmune disorder characterized by complex pathophysiological mechanisms. Current therapeutic paradigms prioritize achieving clinical remission or maintaining low disease activity through early

standardized interventions to mitigate disability progression and enhance quality of life. However, RA management persists with unmet clinical challenges, including incomplete understanding of its multifactorial etiopathogenesis involving dynamic genetic-environmental-immunoendocrine interactions, which complicates precision therapeutic development. Marked interpatient heterogeneity in clinical manifestations and irreversible cumulative joint damage necessitate timely intervention to prevent high disability risks. Conventional pharmacotherapies predominantly provide symptomatic palliation without modifying disease progression, while long-term use carries treatment-related comorbidities. Biologic agents (eg, TNF-α inhibitors, CD20-targeted mAbs) have revolutionized RA management, with emerging evidence supporting obinutuzumab—a glycoengineered anti-CD20 mAb exhibiting augmented antibody-dependent cellular cytotoxicity (ADCC)—originally developed for B cell malignancies. Preliminary trials indicate superior B cell depletion efficacy versus rituximab, suggesting therapeutic potential for refractory RA. However, the safety profile and therapeutic durability of obinutuzumab in RA necessitate further investigation.[70] Ruxolitinib, a selective JAK1/2 inhibitor blocking IL-6/IFN-γ signaling, demonstrates clinical potential in RA but warrants additional validation.[71] Persistent challenges include primary non-response or acquired resistance to biologics, compounded by economic constraints limiting accessibility. While CD20 antigen loss—a recognized resistance mechanism in B-cell malignancies—is uncommon in RA due to preserved CD20 expression on synovial B cells, alternative pathways contribute to therapeutic refractoriness: chronic B cell activation within RA-specific immune niches, incomplete depletion of synovial tissue-resident B cell reservoirs perpetuating inflammation through anatomical sanctuary effects, and compensatory upregulation of BAFF/APRIL axis signaling post-depletion sustaining residual B cell survival and autoantibody secretion. Prolonged B cell depletion may paradoxically disrupt immunoregulatory balance through Breg attrition, potentially exacerbating inflammatory cascades.

A comprehensive understanding of RA pathogenesis is pivotal for developing targeted therapeutic strategies. The hallmark production of pathogenic autoantibodies—notably RF and ACPA—establishes B lymphocytes as central mediators of RA pathophysiology. B cells perpetuate synovial inflammation and articular destruction through three principal mechanisms: (1) autoantibody synthesis, (2) pro-inflammatory cytokine secretion (IL-6/TNF-α), and (3) antigen presentation-driven T cell activation. This pathogenic triad stems from dysregulated B cell signaling via SYK-PI3K-MAPK-NF-κB axis hyperactivation, creating self-perpetuating immune dyshomeostasis. Therapeutic interventions combining B cell proliferation inhibition with Breg expansion therefore represent promising approaches to restore immunologic equilibrium in RA.

Recent advancements in B cell-targeted therapies have significantly advanced RA management. B cell-depleting modalities, including anti-CD20 monoclonal antibodies (eg, rituximab) and bispecific CD19/CD3 antibodies engaging T cell-mediated cytotoxicity, effectively reduce pathogenic B cell burden. Emerging CAR-T cell therapies targeting B cell surface antigens (eg, CD19/CD20) demonstrate potential in ablating autoreactive B cell populations, though large-scale clinical validation of their safety and efficacy remains imperative. Pharmacologic modulation of B cell activity through BAFF/BTK pathway inhibition attenuates pathogenic B cell survival and signaling, while adjunctive IL-6/TNF-α inhibitors provide complementary immunomodulation. However, therapeutic optimization requires addressing challenges in efficacy durability, adverse event mitigation, and resistance mechanisms.

Enhancement of Breg populations via ex vivo expansion or pharmacologic potentiation represents an emerging immunoregulatory strategy, albeit requiring rigorous clinical validation. Concurrently, nanotherapeutic platforms leveraging targeted delivery systems show promise in enhancing therapeutic precision while minimizing systemic toxicity. Integrative application of single-cell multi-omics, epigenetic profiling, and metabolomics is elucidating B cell heterogeneity and dysregulation in RA, paving the way for personalized therapeutic regimens with optimized safety-efficacy profiles. These multidisciplinary advances hold transformative potential for achieving sustained remission and improved long-term outcomes in RA.

Consent for Publication

Agree to publish any image information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no competing interests.

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