



Targeting Angiogenesis in Rheumatoid Arthritis: Mechanistic Insights, Therapeutic Advances and Nanomedicine Perspectives

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Abstract

Angiogenesis is the formation of new blood vessels, a physiological process that can become dysregulated under pathological conditions, including autoimmune diseases. In rheumatoid arthritis, a prototypic autoimmune disorder characterized by chronic synovial inflammation and joint destruction, pathological angiogenesis plays a crucial role in sustaining inflammation, facilitating immune cell infiltration, and promoting pannus formation. This review synthesizes recent advances (2023–2025) in the understanding of the mechanisms driving angiogenesis in autoimmune diseases, with a focused lens on Rheumatoid Arthritis. The review examines the structural and functional abnormalities of the synovial vasculature in Rheumatoid Arthritis, key pro-angiogenic mediators such as vascular endothelial growth factor and angiopoietins, and emerging signaling pathways, including Notch and HIF-1 α . Therapeutic strategies targeting angiogenesis—from conventional anti-VEGF agents to innovative nanomedicines and natural compounds—are reviewed, outlining clinical trial outcomes and challenges such as resistance and off-target effects. By integrating insights into stromal cell interactions, metabolic reprogramming, and epigenetic regulation, this review highlights the potential of angiogenesis-targeted interventions to achieve disease modification in Rheumatoid Arthritis and other autoimmune disorders. Future directions emphasize precision medicine approaches, including biomarker-driven therapies and combination treatment strategies, to improve remission rates and enhance quality of life.

Keywords:

angiogenesis; autoimmunity; rheumatoid arthritis; nanotherapeutics; biomarkers; vascular endothelial growth factor

1. Introduction

Autoimmune diseases comprise a spectrum of disorders in which the immune system mistakenly attacks the body's own tissues, resulting in chronic inflammation and progressive tissue damage. Rheumatoid Arthritis (RA), together with systemic lupus erythematosus (SLE), represents a distinct category of autoimmune diseases characterized by shared clinical features. With a global prevalence of approximately 1%, RA is associated with substantial morbidity and imposes a significant economic burden on healthcare systems and society [1]. The clinical manifestations of Rheumatoid Arthritis arise from a complex interplay of genetic, environmental, and immunological

factors, resulting in symmetrical polyarthritis, synovial hyperplasia, and progressive joint destruction. These pathological features are driven by erosive lesions of the bone and cartilage that develop secondary to synovial inflammation and dysfunction [2]. A central feature of the pathophysiology of Rheumatoid Arthritis is synovial inflammation, in which hyperplastic synovial tissue, known as pannus, invades the cartilage and bone, thereby establishing a self-perpetuating cycle of inflammation and progressive tissue destruction [3].

Furthermore, angiogenesis, the process by which new blood vessels form from pre-existing vascular networks, plays a critical role in embryonic development, wound healing, and tissue repair. However, under patho-

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logical conditions, angiogenesis contributes to tumor progression, chronic inflammation, and fibrosis [4]. Aberrant angiogenesis in autoimmune diseases amplifies the inflammatory response by supplying oxygen and nutrients to affected tissues while facilitating leukocyte recruitment through the upregulation of adhesion molecules on endothelial cells (ECs) [5]. In Rheumatoid Arthritis, synovial angiogenesis occurs early in disease development and may be detected before the onset of clinical symptoms. Furthermore, it serves as an important indicator of disease activity and severity [6].

This review examines the role of angiogenesis in autoimmune diseases, with a particular focus on rheumatoid arthritis (RA), based on studies published between 2023 and 2025. It summarizes the pathological characteristics of angiogenic vasculature in the RA synovium, explores the molecular mechanisms underlying angiogenesis, including the involvement of cytokines, growth factors, and associated signaling pathways, and evaluates emerging therapeutic strategies ranging from biologic agents to nanotherapeutic approaches. In addition, it highlights emerging and comparatively underexplored areas of research, including metabolic reprogramming and epigenetic regulation, and their roles in modulating angiogenesis and immune responses. This review aims to guide future research by highlighting angiogenesis as a promising and therapeutically tractable target for the management of Rheumatoid Arthritis.

2. Overview of Angiogenesis

Angiogenesis is a dynamic physiological process involving the formation of new blood vessels from pre-existing vasculature, regulated at the molecular level by a complex interplay between pro-angiogenic and anti-angiogenic factors. Under normal conditions, vascular endothelial cells (ECs) exist in a quiescent state and are maintained by pericytes and a basement membrane [7]. Specific stimuli, such as hypoxia or tissue injury, activate ECs through receptor tyrosine kinases (RTKs), enabling them to adopt specialized roles during angiogenesis. These roles include functioning as migratory “tip” cells that guide vessel sprouting and proliferative “stalk” cells that support vessel elongation and growth. Vascular endothelial growth factor-A (VEGF-A) is the prototypical proangiogenic cytokine that promotes EC migration, proliferation, and survival through binding to vascular endothelial growth factor receptor-2 (VEGFR2) on the endothelial cell surface. This interaction activates several intracellular signaling cascades, including the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways [8]. Additionally, angiopoietins [Ang1 and Ang2] regulate vessel maturation and remodel-

ing through interactions with Tie2 receptors on ECs, promoting pericyte recruitment and contributing to the stabilization of mature vascular structures. Also important in the development of mature blood vessels are platelet-derived growth factor (PDGF) and transforming growth factor β (TGF- β), which further refine the angiogenic process [9]. Notch signaling plays an important role in regulating vessel branching. Notch signaling is activated when delta-like ligand 4 (DLL4), expressed on endothelial tip cells, interacts with Notch receptors on neighboring stalk cells, thereby regulating tip–stalk cell differentiation. This subsequently inhibits VEGFR2 expression, thereby preventing excessive sprouting [6]. Hypoxia-inducible factor 1 α (HIF-1 α), which is upregulated under conditions of reduced oxygen availability, induces the transcription of factors that regulate VEGF expression and other key effectors involved in linking EC metabolic states with vascular growth. In ECs, the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) promotes the development of filopodia that extend from tip cells [10].

In disease states, the balance of angiogenesis and immune responses leans heavily towards uncontrolled vessel development. Consequently, patients with RA exhibit immature, hyperpermeable vessels with abnormal morphology, including tortuosity, enlargement, and intercellular gaps within the endothelial cell layer. These vascular abnormalities impair blood flow and exacerbate tissue hypoxia [5]. Inflammatory cytokines produced by macrophages and fibroblasts enhance the expression of vascular endothelial growth factor (VEGF), while reactive oxygen species (ROS) generated during oxidative stress induce the formation of lipid peroxides, which further promote the release of angiogenic mediators [11]. Angiogenesis and immunity intersect within the setting of autoimmune disease. ECs express intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), providing sites for leukocyte attachment and infiltration, while chemokines such as CXCL8 (IL-8) help direct these cells to inflamed tissues. Although lymphangiogenesis remains a relatively understudied area, it plays an important role in draining antigens and excess fluid from inflamed tissues. However, lymphatic drainage is often impaired in RA, leading to the accumulation of lymph and other inflammatory fluids within affected tissues [12]. Recent studies suggest that metabolic reprogramming may contribute to these effects. Warburg-like glycolytic pathways observed in synovial ECs support continued cellular proliferation, as the by-products of this process drive fibroblast growth factor-2 (FGF2) production through lactate-mediated feed-forward loops [13]. Additionally, epigenetic mechanisms, including microRNAs that target VEGF mRNA, further regulate

these processes and add complexity to the understanding of this interaction [1].

3. Angiogenesis in Autoimmune Diseases

Autoimmune diseases other than RA, such as systemic lupus erythematosus, psoriasis, and multiple sclerosis, are also characterized by angiogenic dysregulation, although less pronounced [14]. In SLE, renal vasculitis is associated with VEGF-driven glomerular hypervascularity, which correlates with the severity of lupus nephritis [15]. Psoriasis is characterized by angiogenesis within the dermal papillae, a process sustained by VEGF produced by keratinocytes in response to activation of the IL-17/Th17 axis. Notably, limited clinical observations have suggested possible therapeutic benefits of anti-VEGF approaches in selected patients [16]. Mucosal angiogenesis supports chronic colitis in inflammatory bowel disease, and stabilization of HIF-1 α promotes VEGF and angiopoietin-2 production in hypoxic guts. In Sjögren's syndrome, neovascularization of salivary glands accompanies B-cell immigration. Common themes include cytokine storms—for example, the induction of EC permeability by IFN- γ -and stromal-immune crosstalk [17].

RA exemplifies the central role of angiogenesis in disease pathogenesis. Unlike tumor-associated angiogenesis, the vasculature in RA undergoes periodic stabilization through pericyte recruitment; however, the vessels remain hyperpermeable, thereby sustaining a pro-inflammatory microenvironment. Thus, endothelial progenitor cells (EPCs) mobilized from the bone marrow via the SDF-1/CXCR4 axis home to the synovium, where they differentiate into ECs under the guidance of the CXCL13/CXCR5 signaling pathway [5]. Fibroblast-like synoviocytes (FLS) emerge as key orchestrators, secreting VEGF in response to TNF- α , while macrophages polarize to M1 phenotypes, releasing Ang2 to destabilize vessels [6]. Adipokines like FABP4 from perivascular fat exacerbate this, linking metabolic syndrome to autoimmunity [18]. 2025 proteomics data suggest that a serum angiogenic signature in refractory RA is characterized by elevated levels of PlGF and VCAM-1 and reduced levels of IL-8, enabling differentiation between active and remitted disease [3]. This signature emphasizes angiogenesis as a biomarker for therapeutic stratification.

4. Pathological Angiogenesis in Rheumatoid Arthritis

Synovial microvascular density is significantly elevated in RA compared with both healthy and osteoarthritic synovial tissue, correlating with synovitis severity and disease activity [19]. The vessels assume linear, tortuous,

or mixed configurations with rod-shaped or villous projections into the joint spaces. Early RA is characterized by robust inflammatory angiogenesis, which progressively evolves into a hypertrophic and congested vascular network during the chronic stages of the disease [20]. ECs exhibit fenestrations and structural discontinuities and are frequently associated with detached α -SMA⁺ pericytes, resulting in increased vascular permeability, hemorrhage, and edema. Furthermore, degradation of basement membrane collagen IV by Matrix Metalloproteinase-2 (MMP-2) and Matrix Metalloproteinase-9 (MMP-9) exacerbates vascular leakiness, facilitating plasma extravasation and fibrin deposition, which are characteristic features of pannus formation [21]. Ultrastructural studies using electron microscopy have confirmed glycocalyx shedding from ECs, resulting in impaired endothelial barrier function and facilitating immune cell diapedesis [22]. Lymphatic vessels, crucial for resolution, show podoplanin⁺ dilation and reduced contractility due to macrophage/B-cell accumulation, impairing clearance and perpetuating hypoxia (PO₂ < 20 mmHg in synovium) [23]. These vessels maintain inflammation by supplying oxygen/nutrients to hyperplastic synoviocytes and trafficking CCR6⁺ Th17 cells *via* CCL20 gradients. Hyperpermeability allows the entry of autoantibodies (ACPA, RF), further enhancing citrullination and neoantigen formation [24]. Pannus invasion causes erosion of subchondral bone through recruitment of osteoclasts, whereas VEGF enhances expression of RANKL on osteoblasts. Clinically, this manifests as tenderness, swelling, and morning stiffness. Disease Activity Score using 28 joints (DAS28) correlates with synovial vascularity, as assessed by power Doppler ultrasound studies [25]. In extra-articular RA, such as ILD, pulmonary angiogenesis drives fibrosis with VEGF-A isoforms promoting fibroblast-to-myofibroblast transition. Periodontal involvement is characterized by the presence of gingival neovessels that harbor *Porphyromonas gingivalis*, thereby establishing a potential link between the oral microbiome and RA disease flares [26]. Longitudinal cohort studies have suggested associations between baseline angiogenesis indices and radiographic disease progression, with elevated synovial VEGF levels potentially predicting greater increases in Sharp scores over follow-up [1].

5. Mechanisms of Angiogenesis in RA

Angiogenesis in Rheumatoid Arthritis is predominantly driven by members of the VEGF family. VEGF-A, secreted by FLS and macrophages, binds to VEGFR2 and activates the PLC γ /IP3 signaling pathway, leading to Ca²⁺ mobilization and the formation of filopodia [27]. In addition, hypoxia

stabilizes HIF-1 α , which promotes the transcription of VEGF and glycolytic enzymes [5]. An imbalance in angiopoietin signaling contributes to pathological angiogenesis, with Ang2-mediated antagonism of Tie2 destabilizing endothelial junctions and synergizing with VEGF to promote vascular sprouting. Additionally, FGF-2 derived from chondrocytes enhances EC proliferation through activation of the FGFR1/ERK signaling pathway. HGF from injured epithelium promotes tubulogenesis [28]. The inflammatory milieu amplifies angiogenesis, with TNF- α and IL-1 β upregulating VEGF via NF- κ B, while IL-6/JAK/STAT3 signaling sustains chronicity. Th17-derived IL-17 induces EC CXCL8 expression, recruiting neutrophils that release Matrix Metalloproteinase (MMPs) and promote matrix remodeling [29].

The Notch pathway exerts a dual role in Rheumatoid Arthritis angiogenesis, with DLL4/Notch1 signaling limiting excessive vascular branching, whereas under inflammatory conditions, chronic activation via Jagged1 expressed on FLS promotes EC exhaustion and vascular leakiness [6]. Crosstalk with HIF-1 α further modulates angiogenesis, as Notch suppresses HIF-1 α under normoxic conditions but enhances its activity under stress, thereby creating a feed-forward loop [6]. The PI3K/AKT/mTOR pathway promotes metabolic reprogramming, with AKT phosphorylating PFKFB3, thereby enhancing glycolysis and lactate export. This process

acidifies the synovium and activates Rho/ROCK signaling, leading to loss of contractility in ECs [13]. ROS generated by NOX2/MPO in neutrophils oxidizes lipids into 4-HNE, which transactivates the VEGF promoter [30]. Both the MAPK/ERK and JAK2/STAT3 signaling cascades converge on common targets, including AP-1 and c-Fos transcription factors, thereby integrating cytokine signals. Epigenetic mechanisms add further layers of regulation; for example, miR-126 targets SPRED1, thereby enhancing ERK signaling, while miR-21 silences PTEN, leading to PI3K activation [1].

FLS transdifferentiate into myofibroblasts, secreting PDGF-BB to promote pericyte recruitment, which paradoxically stabilizes pathological vessels. Macrophages (CD68+) secrete Ang2 and VEGF, while Tregs fail to exert suppression due to impaired FoxP3 [31]. Adipose-derived FABP4 binds VEGF, prolonging its half-life, while SPARC modulates the extracellular matrix to facilitate EC invasion. ANGPTL4 from the ECs mediates inflammation without affecting lipid metabolism, leading to bone erosion through IL-6/STAT3 [32]. Recent single-cell RNA sequencing studies have revealed heterogeneity among ECs, with “tip-like” clusters exhibiting increased VEGFR2 expression, whereas “stalk-like” cells upregulate glycolytic genes, providing insights for targeted perturbation strategies [33,34]. **Figure 1** depicts the mechanism through which angiogenesis regulates rheumatoid arthritis.

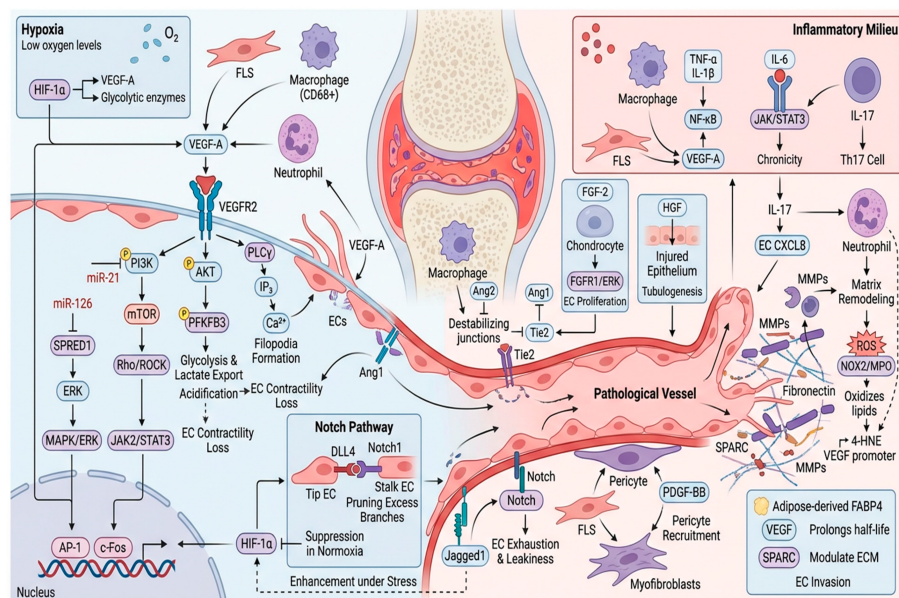


Figure 1: Integrated molecular and cellular mechanisms of angiogenesis in rheumatoid arthritis (RA): Hypoxia-induced HIF-1 α drives VEGF-A production from FLS and macrophages, activating VEGFR2 signaling in endothelial cells to promote sprouting. Pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-17) amplify angiogenesis via NF- κ B and JAK/STAT3 pathways, while neutrophil-derived MMPs and ROS enable matrix remodeling. Angiopoietin imbalance (Ang2/Tie2) destabilizes vessels, and Notch signaling regulates branching and endothelial dysfunction. Metabolic reprogramming (PI3K/AKT/mTOR) and epigenetic factors further enhance pathological vessel formation, with pericyte recruitment and ECM modulators sustaining abnormal vasculature.

6. Therapeutic Strategies Targeting Angiogenesis in RA

6.1. Conventional Anti-Angiogenics

Bevacizumab (anti-VEGF mAb) reduces synovial vascularity in phase II trials but induces hypertension and proteinuria, limiting use [35]. Small-molecule TKIs, such

as sunitinib, inhibit VEGFR/FGFR signaling but may encounter resistance due to Ang2 upregulation [36]. JAK inhibitors, such as tofacitinib, may indirectly inhibit VEGF signaling through STAT3 inhibition, although further clinical evidence is needed to confirm their comparative anti-angiogenic effects against methotrexate in refractory RA [37]. **Table 1** illustrates some conventional and emerging anti-angiogenic therapies in Rheumatoid Arthritis.

Table 1: Conventional and emerging anti-angiogenic therapies in rheumatoid arthritis.

Therapy Type	Agent/Example	Mechanism of Action	Key Effects in RA	Limitations	References
Anti-VEGF monoclonal antibody	Bevacizumab	Neutralizes VEGF, inhibits VEGFR signaling	Reduces synovial vascularity	Hypertension, proteinuria	[38]
Tyrosine kinase inhibitors	Sunitinib	Inhibits VEGFR, FGFR pathways	Decreases angiogenesis	Resistance via Ang2 upregulation	[39]
JAK inhibitors	Tofacitinib	Blocks JAK/STAT → ↓ VEGF expression	Anti-inflammatory + anti-angiogenic	Immunosuppression risks	[5]
Natural compounds	Resveratrol	Activates SIRT1, inhibits AKT/ERK	Reduces VEGF, inflammation	Bioavailability issues	[40]
Natural compounds	Triptolide	Downregulates HIF-1 α /VEGF axis	Reduces disease severity	Toxicity concerns	[32]
Phytotherapeutics	Berberine, Sinomenine	Inhibit NF- κ B, ERK pathways	Suppress angiogenesis and cytokines	Limited clinical data	[1]

6.2. Natural Compounds and Phytotherapeutics

The multitarget effects of resveratrol include activation of SIRT1, which restores metabolic regulation and inhibits Rho/ROCK signaling. Additionally, FOXO upregulation suppresses AKT/ERK signaling [13]. In CIA models, Res (50 mg/kg) halves VEGF levels, alleviating paw swelling [41]. Triptolide from *Tripterygium wilfordii* downregulates HIF-1 α /VEGF, with clinical trials reporting a 40% reduction in DAS28 [42]. Sinomenine blocks SphK1/S1P, reducing EC migration, while *Paeonia lactiflora* glucosides inhibit NF- κ B/VEGF [43]. Berberine inhibits p-ERK/p38, whereas flavonoids (morin) act upon the PPAR γ to antagonize Ang/Tie2 [44]. A recent meta-analysis suggested that natural medicines may reduce ESR and CRP levels, potentially through mechanisms involving angiogenesis inhibition [45].

6.3. Cell-Based and Nanotherapeutics

Mesenchymal stem cells (MSCs) modulate angiogenesis through immunoregulatory mechanisms;

paracrine VEGF-B (anti-inflammatory isoform) and thrombospondin-1 promote vessel maturation [46]. Early-phase trials of umbilical-derived MSCs in RA are still limited and heterogeneous. A pooled analysis of randomized controlled trials reported ACR20 responses in roughly a third of MSC-treated patients (36%, 27/76) versus 14% (5/36) with control treatment, though effect sizes varied across trials and were not sustained beyond 12 months without repeat dosing [47]. Homing to inflamed joints remains a key limitation, which CXCR4-engineered MSC-derived nanovesicles have been shown to overcome, achieving enhanced accumulation in inflamed joints and suppression of synovial inflammation in a collagen-induced arthritis model [48].

Nanotherapeutics represent a promising approach for the management of RA by improving the targeted delivery of agents that modulate pathological angiogenesis, which fuels synovial inflammation, pannus invasion, and joint destruction. Traditional anti-angiogenic agents, such as bevacizumab, are often associated with poor bioavailability, rapid clearance, and off-target effects, resulting in suboptimal efficacy and toxicities, in-

cluding hypertension [49]. Such limitations are addressed by nanoplatforms, which passively accumulate within inflamed joints through the enhanced permeability and retention effect, extravasation through leaky vasculature, and inflammatory cell-mediated sequestration mechanisms [50]. Active targeting further refines delivery *via* ligands such as arginine-glycine-aspartic acid peptides, hyaluronic acid, or folic acid binding integrins, CD44 receptors, or folate receptor- β expressed on ECs, FLS, and macrophages. Accompanying the aforementioned strategies is the inhibition of key pro-angiogenic pathways, including VEGF/VEGFR2, Ang/Tie2, and HIF-1 α signaling, along with vessel normalization and reduction of inflammation [51].

Passive targeting involves nanoleakage through immature vasculature in the RA synovium, which contains gaps of up to 200 nm. Through these gaps, NPs may extravasate and become retained via EPR/ELVIS effects. For example, polymeric micelles (10–100 nm) and liposomes passively accumulate in joints due to vascular permeability and release their payload, such as dexamethasone (Dex) or methotrexate (MTX), in response to a local stimulus, including low pH (~ 6.0), high reactive oxygen species (ROS), or enzymes such as phospholipase A2 [52]. Active targeting increases specificity, as RGD-modified NPs bind to $\alpha_v\beta_3$ integrins that are overexpressed on angiogenic ECs and osteoclasts, promoting endocytosis and intracellular drug release. HA-coated systems target CD44 on activated macrophages and FLSs, while the folic acid-functionalized NPs take advantage of the folate receptor- β for macrophage-selective delivery [53].

Liposomes are spherical lipid vesicles (25 nm–500 nm) that are biocompatible platforms for anti-angiogenic delivery. Poly(ethylene glycol) (PEG) liposomes ensure extended circulation, evading immune clearance while encapsulating drugs such as Dex, tofacitinib, or berberine [54]. In the Adjuvant-Induced Arthritis (AIA) rat model, PEG liposomes loaded with Dex reduced TNF- α and IL-1 β levels, thereby decreasing joint swelling through inhibition of inflammatory cascades associated with angiogenesis [55]. ART-2 peptide-modified liposomes target CD134 on activated T cells to enhance RA relief, while berberine liposomes have mitigated bone erosion *via* activation of miR-23a to indirectly suppress VEGF-driven vessel formation [52]. pH-responsive liposomes induce apoptosis in FLS and macrophages, thereby normalizing vessels through the downregulation of HIF-1 α and ROS, as reported in studies conducted in 2024 [55].

Gold nanoparticles (AuNPs, 1–100 nm) exhibit intrinsic anti-angiogenic properties, particularly at a size of 50 nm, where they inhibit synovial neovascularization in

early RA [56]. cRGD-modified Au/PLGA NPs, loaded with MTX, enable photothermal ablation of neovessels under near-infrared laser, reducing vascular density and inflammation in collagen-induced arthritis (CIA) mice [53]. FAGMs (folic acid and guanidine-modified AuNPs) enhance MTX release, minimizing systemic toxicity while targeting folate receptors on angiogenic ECs [52]. Similarly, SeNPs-PEG-RGD@Ru (Se@RuNPs) with RGD modification suppress VEGF/VEGFR2 signaling, inhibiting EC proliferation and migration [57].

Chitosan nanoparticles represent an important class of biodegradable and biocompatible delivery systems for targeted and sustained drug delivery in Rheumatoid Arthritis (RA). These systems have been widely investigated for encapsulating therapeutic agents such as embelin and eugenol, demonstrating significant anti-inflammatory and anti-angiogenic effects through reactive oxygen species (ROS) scavenging and reduction of synovial hyperplasia in AIA/CIA models [58]. Their mucoadhesive properties and ease of functionalization further enhance cellular uptake and site-specific delivery. These formulations improve pharmacokinetics and maintain therapeutic concentrations at the target site while modulating angiogenic pathways such as Ang/Tie2 signaling [59].

Sustained release can be achieved through tunable degradation using Poly(Lactic-co-Glycolic Acid) (PLGA) and/or chitosan nanoparticle systems, which provide encapsulation platforms for the controlled delivery of agents such as Dex-palmitate. These systems improve pharmacokinetic properties and provide cytoprotective effects through regulation of the Angiotensin/Tie2 pathways [52]. Chitosan nanoparticle systems for Embelin and Eugenol reduce Cytokines, Synovial Hyperplasia Models induced in the AIA/CIA, *via* ROS Scavenging, with Anti-angiogenic properties [60]. Dendrimers are structured like a branched tree, ranging from 1 to 10 nm in size; as a result, they have a unique structural and chemical composition that allows them to encapsulate, deliver, and maintain an even and consistent release of agents (adalimumab/etanercept) as well as modifying the surface of the compounds to provide control over their delivery targets, and reducing the amount of VEGF secreted from FLS [55]. Both Chi et al. (2023) and Rastogi et al. (2024) reported the specific targeting ability of the dendrimer-delivered adalimumab and etanercept-dendrimer combinations for targeted delivery [61,62].

Further innovation has been achieved through the development of solid lipid nanoparticles (SLNs, 10–1000 nm) and biomimetic NPs. β -Sitosterol-SLNs inhibit NF- κ B signaling, thereby downregulating VEGF, while HA-coated prednisolone SLNs reduce joint erosion in CIA mice [63]. Biomimetic NPs coated with neu-

trophil membranes deliver hydroxychloroquine, induce M1 macrophage apoptosis, and induce vessel normalization in CIA models [52]. Hypoxia-relieving nanomaterials, such as CAT-loaded nanozymes (Pt, MnO₂), produce O₂ in situ and alleviate hypoxia, thereby inhibiting the HIF-1 α /VEGF axis [5]. ROS-scavenging NPs, such as Mn₃O₄ and Se NPs, promote macrophage repolarization from the M1 to the M2 phenotype, thereby reducing Ang2 expression and promoting an anti-angiogenic balance [64].

Innovative platforms include nanofibers and hydrogels. STP/RGD peptide-based nanofibers loaded with triptolide and metformin (STP-RGD@TM) can self-assemble, blocking VEGFR2 while enabling the release of triptolide and metformin. This approach reduced joint scores by 70% in RA mice with minimal off-target effects [5]. Injectable hydrogels, temperature-sensitive, deliver Dex or siRNA, enhancing local retention and downregulating MMP-9/PDGF-BB for anti-angiogenic effects [52]. Ceria-vesicle hybrids (Ce-MSCNVs) clear free radicals and suppress angiogenesis in CIA models [65]. At present, clinical translation remains limited due to challenges in biocompatibility, scalability, and regulatory requirements set by agencies such as the FDA and EMA [55]. Potential toxicity risks include tissue accumulation of the agents, activation of immune responses, and variability in the manufacturing process.

H-A/T Nanoparticles are capable of modifying the structure of VEGF, whereas Rh/SPX-HSA generates oxygen and suppresses HIF-1 α . Preclinical studies demonstrate promising results; for example, Wang et al. reported that R-M/N-PMs (RGD-MTX-nimesulide) inhibited endothelial cell proliferation and restored vascular function in CIA models [66]. Nanopatforms have revitalized the strategies for delivering therapeutic agents. For example, STP-RGD@TM (2025) self-assembles into a nanofiber platform that enables vessel normalization

through VEGFR2 blockade while providing controlled release of triptolide and metformin [22]. In mice, RA-associated effects were significantly reduced by 70%, with fewer off-target effects observed when kinase inhibitors such as filgotinib acted synergistically as anti-angiogenic agents in combination with anti-TNF therapy [22]. In head-to-head clinical evaluation (e.g., NCT02889796) against the anti-TNF agent adalimumab, filgotinib demonstrated non-inferior efficacy and a comparable safety profile in patients with an inadequate response to methotrexate [40]. Whether combined anti-VEGF/JAK-inhibitor strategies can further improve outcomes in RA remains an open question and there is still requirement of further research in this field

In the future, two-dimensional (2D) stimuli-responsive nanoparticles combined with artificial intelligence may enable the design of patient-specific composites with multiple functionalities for both imaging and treatment, termed theranostics. Furthermore, CRISPR-based gene editing using nanocomposites may facilitate targeted modulation of gene expression in patient-derived gene portfolios, such as silencing VEGF gene expression [55]. Combination strategies utilizing phototherapy and/or immunotherapy may overcome resistance associated with one or both therapeutic approaches. Studies such as those by Wu et al. are expected to facilitate the advancement toward completed clinical trials involving functionalized mesoporous silica nanoparticles [67]. In conclusion, the application of nanoparticles for developing novel nanotherapeutics represents a major advancement in the re-engineering of current treatment strategies for Rheumatoid Arthritis. These approaches may provide opportunities to improve clinical remission rates and enhance patients' quality of life. A dosage form-oriented overview of angiogenesis-targeted therapies, including delivery systems, molecular targets, and therapeutic agents, is summarized in Table 2.

Table 2: Dosage forms, targets, and therapeutic agents for angiogenesis-targeted therapy in rheumatoid arthritis.

Dosage Form/Delivery System	Target Site/Receptor	Therapeutic Agent(s)	Mechanism of Action	Key Outcome in RA	References
PEGylated Liposomes	Synovial vasculature	Dex, MTX	Passive targeting	↓ inflammation	[54]
PLGA Nanoparticles	Endothelial cells	MTX, Dex-palmitate	Controlled release	Reduced angiogenesis	[53]
SLNs	Macrophages	Prednisolone	Enhanced stability	↓ VEGF	[63]
Dendrimers	FLS, immune cells	Adalimumab	Targeted delivery	↓ VEGF secretion	[62]
Gold NPs	$\alpha v\beta 3$ integrins	MTX	Photothermal + anti-angiogenic	↓ neovascularization	[53]

Table 2: *Cont.*

Dosage Form/Delivery System	Target Site/Receptor	Therapeutic Agent(s)	Mechanism of Action	Key Outcome in RA	References
RGD NPs	Endothelial cells	MTX	Integrin targeting	Inhibit EC proliferation	[53]
HA-coated NPs	CD44	Prednisolone	Receptor-mediated uptake	↓ synovial hyperplasia	[68]
Nanofibers	VEGFR2	STP-RGD@TM	Dual drug delivery	↓ joint inflammation	[22]
Hydrogels	Synovial cavity	Dex, siRNA	Sustained release	↓ angiogenesis	[69]
Biomimetic NPs	Immune cells	Hydroxychloroquine	Immune evasion	Vessel normalization	[70]
Nanozymes	Hypoxic tissue	MnO ₂	O ₂ generation	↓ HIF-1 α	[71]
Exosomes	Endothelial cells	miRNA	Gene regulation	Restore vascular balance	[72]

7. Challenges and Future Directions

Indeed, the translational potential of angiogenesis-based treatment modalities for Rheumatoid Arthritis (RA) is significantly hindered by multiple biological, technical, and regulatory factors that impede clinical implementation despite favorable preclinical findings. Biocompatibility remains one of the major hurdles, as angiogenesis-targeting nanotherapies must function effectively under conditions of heightened immune activation without inducing undesirable immune responses or toxicity. Another challenge arises from the potential accumulation of nanoparticles in non-target organs, such as the liver or spleen, which may lead to additional health complications due to chronic inflammatory responses in RA patients with dysregulated immune systems. Variability in physicochemical parameters, including particle size, charge, and surface properties, may significantly influence therapeutic efficacy by altering biodistribution and pharmacokinetic profiles. Scalability can also present a barrier, as particle homogeneity and effective delivery may vary depending on the manufacturing scale. Moreover, high costs associated with the synthesis and fabrication of nanomaterials pose a significant problem, especially in countries with less developed pharmaceutical industries. The lack of standardization among regulatory agencies, such as the FDA, EMA, and CDSCO, contributes to inconsistencies in the regulation of nanomedicines. Importantly, most current evidence is derived from animal models, and the limited availability of large-scale human clinical trials restricts definitive conclusions regarding therapeutic efficacy and long-term safety.

Nonetheless, the prospects of angiogenesis-inhibiting therapies in RA remain promising, particularly

considering the rapid advancements in precision medicine, bioengineering, and computational tools. The paradigm is likely to shift towards biomarker-based therapeutic approaches, supported by the detection of angiogenic markers such as VEGF, PlGF, and adhesion molecules. In addition, the application of artificial intelligence and machine learning techniques may facilitate advances in drug development and personalized patient care through predictive analytics based on genetic, immunological, and angiogenic markers. Nanotechnology-based approaches in the field are already gaining ground due to their potential to provide highly targeted and responsive treatment methods, including hypoxia-, acidity-, and oxidative stress-responsive mechanisms. Moreover, the development of theranostics may provide new opportunities for monitoring inflammation and its inhibition by integrating imaging capabilities with pharmacotherapy. Finally, hypoxia-driven mechanisms present a completely new target for therapeutic interventions that can disrupt the angiogenic cascade at its metabolic level. This could include targeting HIF-1 α signaling. Finally, gene-editing systems, such as CRISPR/Cas-based approaches, have the potential to directly silence pro-angiogenic genes. Regenerative strategies, including stem cell-derived exosomes and microbiome modulation, are also emerging as innovative approaches to restore vascular homeostasis and immune balance. Collectively, overcoming current limitations through interdisciplinary collaboration and technological innovation will be essential to translate these advances into clinically effective therapies, ultimately improving disease outcomes and quality of life in patients with RA.

8. Conclusions

Rheumatoid arthritis (RA) is a chronic autoimmune disorder in which pathological angiogenesis plays a central role in sustaining synovial inflammation, pannus formation, and progressive joint destruction. Recent evidence highlights that the rheumatoid synovium exhibits structurally abnormal, immature, and hyperpermeable blood vessels that perpetuate hypoxia and immune cell infiltration. Key pro-angiogenic mediators, including VEGF, angiopoietins, and cytokines such as TNF- α and IL-17, interact with signaling pathways such as Notch, HIF-1 α , and PI3K/AKT/mTOR to regulate vascular remodeling. Additionally, metabolic reprogramming and epigenetic mechanisms, particularly microRNAs such as miR-126 and miR-21, further complicate the angiogenic microenvironment. Crosstalk among fibroblast-like synovio-cytes, macrophages, and endothelial cells sustains a self-amplifying cycle of inflammation and angiogenesis.

In terms of therapeutics, inhibition of angiogenesis represents a promising strategy for achieving disease modification. Although anti-VEGF therapies have not demonstrated significant clinical benefits due to limitations such as adverse effects, novel strategies, including nanotechnology-based drug delivery, natural products such as resveratrol and triptolide, and mesenchymal stem cell-based therapies, have shown greater specificity and therapeutic potential. Nonetheless, challenges such as compensatory mechanisms, scalability, and clinical implementation continue to pose significant obstacles. Future strategies will incorporate precision medicine and artificial intelligence approaches.

List of Abbreviations

ACPA	Anti-Citrullinated Protein Antibodies
AIA	Adjuvant-Induced Arthritis
ANGPTL4	Angiopoietin-Like 4
CCL20	C-C Motif Chemokine Ligand 20
CIA	Collagen-Induced Arthritis
DAS28	Disease Activity Score using 28 joints
EPC	Endothelial Progenitor Cells
FLS	Fibroblast-Like Synovio-cytes
HIF-1 α	Hypoxia-Inducible Factor 1-Alpha
MMP	Matrix Metalloproteinase
MSCs	Mesenchymal Stem Cells
PEG	Poly(ethylene glycol)
PFKFB3	6-Phosphofructo-2-Kinase/ Fructose-2,6-Bisphosphatase 3
PLGA	Poly(Lactic-co-Glycolic Acid)
PIGF	Placental Growth Factor
RA	Rheumatoid Arthritis

RANKL	Receptor Activator of Nuclear Factor B Ligand
ROS	Reactive Oxygen Species
SLE	Systemic Lupus Erythematosus
VCAM-1	Vascular Cell Adhesion Molecule 1
VEGF	Vascular Endothelial Growth Factor

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Conceptualization, writing—original draft preparation, and visualization: A.N.; Conceptualization, visualization, and writing—review and editing: O.B.; Validation of the manuscript, supervision, and project administration: S.S.N. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

Grammarly has been used for language editing, as the authors are non-native English speakers. No other AI tools have been used to generate any content of this manuscript. The authors take full responsibility for the content of the study.

References

- [1] Noto, G.; Salvetti, F.; Demaj, A.; Altieri, P.; Chericoni, E.; Ferrigno, E.; Alunno, A.; Puxeddu, I. Pathogenesis of Rheumatoid Arthritis: One Year in Review 2025. *Clin. Exp. Rheumatol.* **2025**, *43*, 1533–1540. [\[CrossRef\]](#)
- [2] Calioglu, L.; Berni, M.; Torriani, C.; Mancuso, M.E.; Di Minno, M.N.D.; Brancato, A.M.; Jannelli, E.; Mosconi, M.; Pasta, G. Pathogenesis of Osteoarthritis, Rheumatoid Arthritis, and Hemophilic Arthropathy: The Role of Angiogenesis. *Haemophilia* **2024**, *30*, 1256–1264. [\[CrossRef\]](#) [\[PubMed\]](#)
- [3] Lesturgie-Talarek, M.; Gonzalez, V.; Combier, A.; Thomas, M.; Boisson, M.; Poiroux, L.; Wanono, S.; Hecquet, S.; Carves, S.; Cauvet, A.; et al. Inflammatory and Angiogenic Serum Profile of Refractory Rheumatoid Arthritis. *Sci. Rep.* **2025**, *15*, 7159. [\[CrossRef\]](#) [\[PubMed\]](#)
- [4] Kretschmer, M.; Rüdiger, D.; Zahler, S. Mechanical Aspects of Angiogenesis. *Cancers* **2021**, *13*, 4987. [\[CrossRef\]](#)

- [5] Zhao, F.; Hu, Z.; Li, G.; Liu, M.; Huang, Q.; Ai, K.; Cai, X. Angiogenesis in Rheumatoid Arthritis: Pathological Characterization, Pathogenic Mechanisms, and Nano-Targeted Therapeutic Strategies. *Bioact. Mater.* **2025**, *50*, 603–639. [[CrossRef](#)] [[PubMed](#)]
- [6] Zhao, F.; He, Y.; Zhao, Z.; He, J.; Huang, H.; Ai, K.; Liu, L.; Cai, X. The Notch Signaling-Regulated Angiogenesis in Rheumatoid Arthritis: Pathogenic Mechanisms and Therapeutic Potentials. *Front. Immunol.* **2023**, *14*, 1272133. [[CrossRef](#)] [[PubMed](#)]
- [7] Cao, Y.; Langer, R.; Ferrara, N. Targeting Angiogenesis in Oncology, Ophthalmology and Beyond. *Nat. Rev. Drug Discov.* **2023**, *22*, 476–495. [[CrossRef](#)] [[PubMed](#)]
- [8] Shaw, P.; Dwivedi, S.K.D.; Bhattacharya, R.; Mukherjee, P.; Rao, G. VEGF Signaling: Role in Angiogenesis and Beyond. *Biochim. Biophys. Acta Rev. Cancer* **2024**, 1879, 189079. [[CrossRef](#)] [[PubMed](#)]
- [9] Ogut, E. Mechanisms and Therapeutic Potential of Ozone Therapy in Enhancing Vasculogenesis and Angiogenesis through Growth Factor Activation and Oxidative Signaling Pathways. *Discov. Med.* **2025**, *2*, 240. [[CrossRef](#)]
- [10] Hu, F.; Yang, C.; Dai, L.; Gao, D.; Luo, H.; Zhong, X.; Chen, P.; Zhu, L.; Xiao, Z.; Zhao, S.; et al. Salvianolic Acid B Promotes Placental and Decidual Angiogenesis by Restoring the Normal Expression of Hypoxia-Inducible Factor-1 α /Vascular Endothelial Growth Factor in Mice with Recurrent Pregnancy Loss. *Am. J. Reprod. Immunol.* **2025**, *94*, e70105. [[CrossRef](#)] [[PubMed](#)]
- [11] Wang, Y.; Yang, C. Enhanced VEGF-A Expression and Mediated Angiogenic Differentiation in Human Gingival Fibroblasts by Stimulating with TNF- α in Vitro. *J. Dent. Sci.* **2022**, *17*, 876–881. [[CrossRef](#)] [[PubMed](#)]
- [12] Rybka, G.; Węglarczyk, K.; Dziedzic, R.; Siedlar, M.; Korkosz, M.; Kosalka-Węgiel, J. Serum Levels of PECAM-1, ICAM-1, and VCAM-1 in Patients with Systemic Lupus Erythematosus: Associations with Disease Activity and Clinical Features from a Single-Center Study. *Rheumatol. Int.* **2025**, *45*, 223. [[CrossRef](#)] [[PubMed](#)]
- [13] Wei, L.; Chen, X.; Liu, M. Global, Regional, and National Burden and Trends of Rheumatoid Arthritis among the Elderly Population: An Analysis Based on the 2021 Global Burden of Disease Study. *Front. Immunol.* **2025**, *16*, 1547763. [[CrossRef](#)] [[PubMed](#)]
- [14] La Mendola, D.; Trincavelli, M.L.; Martini, C. Angiogenesis in Disease. *Int. J. Mol. Sci.* **2022**, *23*, 10962. [[CrossRef](#)] [[PubMed](#)]
- [15] Leone, P.; Prete, M.; Malerba, E.; Bray, A.; Susca, N.; Ingravallo, G.; Racanelli, V. Lupus Vasculitis: An Overview. *Biomedicines* **2021**, *9*, 1626. [[CrossRef](#)] [[PubMed](#)]
- [16] Li, Y.H.; Liu, J.L. Psoriasis Pathogenesis: What's New in Angiogenesis and Angiopoietins. *Int. J. Dermatol. Venereol.* **2024**, *7*, E679–E703. [[CrossRef](#)]
- [17] Tan, Z.; Zhou, J.; Wang, J.; Zhou, Y.; Sun, X.; Wang, L.; Zhou, Z.; Guo, C.; Li, X. OP0143 CXCL10+ Fibroblasts Facilitate Lymphocytic Aggregation in the Salivary Glands of Sjögren's Syndrome by Promoting Angiogenesis and Chemotactic Activity. *Ann. Rheum. Dis.* **2025**, *84*, 123. [[CrossRef](#)]
- [18] Guo, D.; Lin, C.; Lu, Y.; Guan, H.; Qi, W.; Zhang, H.; Shao, Y.; Zeng, C.; Zhang, R.; Zhang, H.; et al. FABP4 Secreted by M1-Polarized Macrophages Promotes Synovitis and Angiogenesis to Exacerbate Rheumatoid Arthritis. *Bone Res.* **2022**, *10*, 45. [[CrossRef](#)] [[PubMed](#)]
- [19] Kennedy, A.; Ng, C.T.; Biniecka, M.; Saber, T.; Taylor, C.; O'Sullivan, J.; Veale, D.J.; Fearon, U. Angiogenesis and Blood Vessel Stability in Inflammatory Arthritis. *Arthritis Rheum.* **2010**, *62*, 711–721. [[CrossRef](#)]
- [20] Khodadust, F.; Ezdoglian, A.; Steinz, M.M.; Van Beijnum, J.R.; Zwezerijnen, G.J.C.; Jansen, G.; Tas, S.W.; van der Laken, C.J. Systematic Review: Targeted Molecular Imaging of Angiogenesis and Its Mediators in Rheumatoid Arthritis. *Int. J. Mol. Sci.* **2022**, *23*, 7071. [[CrossRef](#)] [[PubMed](#)]
- [21] Foster, M.H. Basement Membranes and Autoimmune Diseases. *Matrix Biol.* **2017**, *57–58*, 149–168. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
- [22] Hu, C.; Ma, J.; Chen, X.; Chen, Y.; Song, Y.; Tang, Q.; He, X.; Wang, Y.; Gao, H.; Zhang, J. Microenvironment-Driven Transformable Self-Assembly Nanoplatfrom Enables Spatiotemporal Remodeling for Rheumatoid Arthritis Therapy. *Sci. Adv.* **2025**, *11*, eadu5245. [[CrossRef](#)] [[PubMed](#)]
- [23] Phillippi, J.A. On Vasa Vasorum: A History of Advances in Understanding the Vessels of Vessels. *Sci. Adv.* **2022**, *8*, eabl6364. [[CrossRef](#)] [[PubMed](#)]
- [24] Lönnblom, E.; Agell, M.L.; Sareila, O.; Cheng, L.; Xu, B.; Viljanen, J.; Hafström, I.; Andersson, M.L.E.; Bergström, G.; Ekwall, A.H.; et al. Autoantibodies to Disease-Related Proteins in Joints as Novel Biomarkers for the Diagnosis of Rheumatoid Arthritis. *Arthritis Rheumatol.* **2023**, *75*, 1110–1119. [[CrossRef](#)] [[PubMed](#)]
- [25] Tehsin, F.; Rasheed, A.; Hafeez, U.; Alam, A.; Nawaz, A.U.; Khan, K. Role of Diet in Influencing DAS28 Score in Rheumatoid Arthritis. *J. Health Rehabil. Res.* **2024**, *4*, 1–5. [[CrossRef](#)]
- [26] Dalix, E.; Marotte, H. From a Better Knowledge of Periodontal Disease to Porphyromonas gingivalis Target for Rheumatoid Arthritis Disease Activity. *Jt. Bone Spine* **2025**, *92*, 105822. [[CrossRef](#)] [[PubMed](#)]
- [27] Yuan, M.; Wu, Y.; Zhou, X.; Cai, Y.; Li, H.; Xia, A.; Wang, X.; Wen, J.; Duan, Q.; Xu, C.; et al. Clematichinenside AR Alleviates Rheumatoid Arthritis by Inhibiting Synovial Angiogenesis through the HIF-1 α /VEGFA/ANG2 Axis. *Phytomedicine* **2025**, *139*, 156552. [[CrossRef](#)] [[PubMed](#)]
- [28] Nasef, S.I.; Ellawindy, A.; Askar, A.M.; Hashem, A.A.K.; Omar, H.H. Assessment of Angiopoietin-2 Single Nucleotide Polymorphism in Patients with

- Rheumatoid Arthritis. *Inflammation* **2022**, *46*, 853–860. [[CrossRef](#)] [[PubMed](#)]
- [29] Zhou, Q.; Ren, Q.; Jiao, L.; Huang, J.; Yi, J.; Chen, J.; Lai, J.; Ji, G.; Zheng, T. The Potential Roles of JAK/STAT Signaling in the Progression of Osteoarthritis. *Front. Endocrinol.* **2022**, *13*, 1069057. [[CrossRef](#)] [[PubMed](#)]
- [30] Paclet, M.H.; Laurans, S.; Dupré-Crochet, S. Regulation of Neutrophil NADPH Oxidase, NOX2: A Crucial Effector in Neutrophil Phenotype and Function. *Front. Cell Dev. Biol.* **2022**, *10*, 945749. [[CrossRef](#)] [[PubMed](#)]
- [31] Essler, M.; Kristiansen, G.; Kreppel, B.; Fink, J.; Sanders, C.; Scherping, A.; Hommerding, O.; Marinova, M.; Schmidt-Wolf, I.G.H.; Feldmann, G.; et al. Prognostic Significance of CD68+ Macrophages and FoxP3+ Regulatory T Cells in Neuroendocrine Tumors. *Nuklearmedizin* **2025**, *65*, 39–47. [[CrossRef](#)] [[PubMed](#)]
- [32] Gao, Y.; Zhang, Y.; Liu, X. Rheumatoid Arthritis: Pathogenesis and Therapeutic Advances. *MedComm* **2024**, *5*, e509. [[CrossRef](#)] [[PubMed](#)]
- [33] Blanco, R.; Gerhardt, H. VEGF and Notch in Tip and Stalk Cell Selection. *Cold Spring Harb. Perspect. Med.* **2013**, *3*, a006569. [[CrossRef](#)] [[PubMed](#)]
- [34] Wakabayashi, T.; Naito, H. Cellular Heterogeneity and Stem Cells of Vascular Endothelial Cells in Blood Vessel Formation and Homeostasis: Insights from Single-Cell RNA Sequencing. *Front. Cell Dev. Biol.* **2023**, *11*, 1146399. [[CrossRef](#)] [[PubMed](#)]
- [35] Cantatore, F.P.; Maruotti, N.; Corrado, A.; Ribatti, D. Anti-Angiogenic Effects of Biotechnological Therapies in Rheumatic Diseases. *Biologics* **2017**, *11*, 123. [[CrossRef](#)] [[PubMed](#)]
- [36] Izadpanah, R.; Izadpanah, A.; Alt, E.U. Dual Faces of Angiogenesis: Mechanisms and Therapeutic Applications. *Biochim. Biophys. Acta Rev. Cancer* **2025**, *1880*, 189494. [[CrossRef](#)] [[PubMed](#)]
- [37] Suda, Y.; Ikuta, K.; Hayashi, S.; Wada, K.; Anjiki, K.; Kamenaga, T.; Tsubosaka, M.; Kuroda, Y.; Nakano, N.; Maeda, T.; et al. Comparison of Anti-Inflammatory and Anti-Angiogenic Effects of JAK Inhibitors in IL-6 and TNF α -Stimulated Fibroblast-Like Synoviocytes Derived from Patients with RA. *Sci. Rep.* **2025**, *15*, 9736. [[CrossRef](#)] [[PubMed](#)]
- [38] Bhudia, S.; Raja, S.G. A Narrative Review of Therapeutic Targeting of Angiogenic Signalling Pathways: VEGF and Bevacizumab in Cancer. *AME Med. J.* **2026**, *11*, 5. [[CrossRef](#)]
- [39] Vahabi, M.; Farhadi, E.; Robat-Jazi, B.; Jamshidi, A.; Mahmoudi, M. Vascular Endothelial Growth Factor (VEGF) Biology and Its Proposed Role in Rheumatic Diseases Pathogenesis. *Adv. Rheumatol.* **2026**, *66*, 30. [[CrossRef](#)] [[PubMed](#)]
- [40] Combe, B.; Kivitz, A.; Tanaka, Y.; van der Heijde, D.; Simon, J.A.; Baraf, H.S.B.; Kumar, U.; Matzkies, F.; Bartok, B.; Ye, L.; et al. Filgotinib versus Placebo or Adalimumab in Patients with Rheumatoid Arthritis and Inadequate Response to Methotrexate: A Phase III Randomised Clinical Trial. *Ann. Rheum. Dis.* **2021**, *80*, 848–858. [[CrossRef](#)]
- [41] Xu, Q.; Kong, H.; Ren, S.; Meng, F.; Liu, R.; Jin, H.; Zhang, J. Coix Seed Oil Alleviates Synovial Angiogenesis through Suppressing HIF-1 α /VEGF-A Signaling Pathways via SIRT1 in Collagen-Induced Arthritis Rats. *Chin. Med.* **2023**, *18*, 119. [[CrossRef](#)] [[PubMed](#)]
- [42] Chen, K.; Chen, X.; Huang, S.; Zhou, L.; Zhou, X.; Lu, Y.; Feng, Z. Therapeutic Effects and Mechanisms of Tripterygium wilfordii Extracts in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Preclinical Studies. *Sci. Rep.* **2025**, *15*, 27960. [[CrossRef](#)] [[PubMed](#)]
- [43] Wang, W.; Wang, Z.; Ling, A.; Zhang, C.; Lv, M.; Huang, L.; Niu, Y. Research Progress in Treatment of Rheumatoid Arthritis with Sinomenine and Related Formulations Based on Different Administration Routes. *Front. Pharmacol.* **2025**, *16*, 1613679. [[CrossRef](#)] [[PubMed](#)]
- [44] Xu, H.J.; Su, Y. Potential of Berberine for Rheumatoid Arthritis Prevention and Treatment. *Chin. J. Integr. Med.* **2025**, *31*, 953–959. [[CrossRef](#)] [[PubMed](#)]
- [45] Gao, C.; Di, S.X.; Chen, F.H.; Wei, G.L.; Guo, C.Y. The Protective Effect of Natural Medicines in Rheumatoid Arthritis via Inhibit Angiogenesis. *Front. Pharmacol.* **2024**, *15*, 1380098. [[CrossRef](#)] [[PubMed](#)]
- [46] Gao, Y.F.; Zhao, N.; Hu, C.H. Harnessing Mesenchymal Stem/Stromal Cells-Based Therapies for Rheumatoid Arthritis: Mechanisms, Clinical Applications, and Microenvironmental Interactions. *Stem Cell Res. Ther.* **2025**, *16*, 379. [[CrossRef](#)] [[PubMed](#)]
- [47] Mesa, L.E.; López, J.G.; López Quiceno, L.; Arroyave, F.B.; Halpert, K.; Camacho, J.C. Safety and Efficacy of Mesenchymal Stem Cells Therapy in the Treatment of Rheumatoid Arthritis Disease: A Systematic Review and Meta-Analysis of Clinical Trials. *PLoS ONE* **2023**, *18*, e0284828. [[CrossRef](#)]
- [48] Gan, J.; Zhang, X.; Chen, G.; Hao, X.; Zhao, Y.; Sun, L. CXCR4-Expressing Mesenchymal Stem Cells Derived Nanovesicles for Rheumatoid Arthritis Treatment. *Adv. Healthcare Mater.* **2024**, *13*, e202303300. [[CrossRef](#)]
- [49] Pathade, V.; Nene, S.; Ratnam, S.; Khatri, D.K.; Raghuvanshi, R.S.; Singh, S.B.; Srivastava, S. Emerging Insights of Peptide-Based Nanotherapeutics for Effective Management of Rheumatoid Arthritis. *Life Sci.* **2023**, *312*, 121257. [[CrossRef](#)] [[PubMed](#)]
- [50] Rani, L.; Mathur, P.; Verma, R.; Kumar, V.; Mishra, A.K.; Sahoo, P.K. Translation Research in Therapeutic Approaches from Conventional to Novel Nanotherapeutics for Rheumatoid Arthritis Treatment. *Curr. Rheumatol. Rev.* **2024**, *21*, 37–53. [[CrossRef](#)] [[PubMed](#)]

- [51] Deshmukh, R. Drug Targeting and Nanotherapeutic Advancement in the Treatment of Rheumatoid Arthritis: Recent Progress in Drug Delivery Systems. *Curr. Pharm. Biotechnol.* **2024**, 26, 1459–1481. [[CrossRef](#)] [[PubMed](#)]
- [52] Li, H.; Gou, R.; Liao, J.; Wang, Y.; Qu, R.; Tang, Q.; Gan, J.; Zou, L.Y.; Shi, S. Recent Advances in Nano-Targeting Drug Delivery Systems for Rheumatoid Arthritis Treatment. *Acta Mater. Med.* **2023**, 2, 23–41. [[CrossRef](#)]
- [53] Gupta, N.; Shaik, A.R.; Chettupalli, A.K.; Bukke, S.P.N.; Goruntla, N. Nanomedicine for the Management of Rheumatoid Arthritis: Current Status and Prospective Therapeutic Approaches. *Discov. Med.* **2025**, 2, 111. [[CrossRef](#)]
- [54] Zamanian, M.Y.; Zafari, H.; Osminina, M.K.; Skakodub, A.A.; Al-Aouadi, R.F.A.; Golmohammadi, M.; Nikbakht, N.; Fatemi, I. Improving Dexamethasone Drug Loading and Efficacy in Treating Rheumatoid Arthritis via Liposome: Focusing on Inflammation and Molecular Mechanisms. *Anim. Model Exp. Med.* **2025**, 8, 5–19. [[CrossRef](#)] [[PubMed](#)]
- [55] Zheng, X.; Yang, H.; Zhang, Z.; Liang, X.; Liu, Y.; Wang, C.; Yang, X.; Tang, J.; Mao, J.; Nie, Y.; et al. pH-Responsive Size-Adjustable Liposomes Induce Apoptosis of Fibroblasts and Macrophages for Rheumatoid Arthritis Treatment. *Acta Biomater.* **2024**, 179, 256–271. [[CrossRef](#)]
- [56] Koushki, K.; Shahbaz, S.K.; Keshavarz, M.; Bezonov, E.E.; Sathyapalan, T.; Sahebkar, A. Gold Nanoparticles: Multifaceted Roles in the Management of Autoimmune Disorders. *Biomolecules* **2021**, 11, 1289. [[CrossRef](#)] [[PubMed](#)]
- [57] Bai, X.; Zhou, T.; Wu, X.; Chang, J.; Wu, X. Synthesis and Application of Selenium Nanoparticles for the Modulation of Inflammatory Diseases. *Nano Biomed. Eng.* **2025**, 17, 179. [[CrossRef](#)]
- [58] Mumtaz, Unnithan, D.; Hosseini, H.; Ali, J.; Khan, M.A. Chitosan Nanoparticles for Brain Targeted Nose-to-Brain Drug Delivery in Neurodegenerative Disease: A Comprehensive Exploration of Advances, Limitations and Future Prospects. *Expert Opin. Drug Deliv.* **2026**, 23, 761–779. [[CrossRef](#)] [[PubMed](#)]
- [59] Stefanache, A.; Lungu, I.I.; Anton, N.; Damir, D.; Gutu, C.; Olaru, I.; Plesea Condratovici, A.; Duceac, M.; Constantin, M.; Calin, G.; et al. Chitosan Nanoparticle-Based Drug Delivery Systems: Advances, Challenges, and Future Perspectives. *Polymers* **2025**, 17, 1453. [[CrossRef](#)] [[PubMed](#)]
- [60] Novy, T.C.T.; Joni, I.M.; Lesmana, R.; Biben, V.; Setiawan. Chitosan Nanoparticles as an Alternative Therapeutic Approach for Knee Osteoarthritis Treatment: A Systematic Review. *Int. J. Nanomed.* **2025**, 20, 6187–6203. [[CrossRef](#)] [[PubMed](#)]
- [61] Chi, X.K.; Xu, X.L.; Chen, B.Y.; Su, J.; Du, Y.Z. Combining Nanotechnology with Monoclonal Antibody Drugs for Rheumatoid Arthritis Treatments. *J. Nanobiotechnol.* **2023**, 21, 102. [[CrossRef](#)]
- [62] Rastogi, V.; Yadav, P.; Porwal, M.; Sur, S.; Verma, A. Dendrimer as Nanocarrier for Drug Delivery and Drug Targeting Therapeutics: A Fundamental to Advanced Systematic Review. *Int. J. Polym. Mater. Polym. Biomater.* **2024**, 73, 310–332. [[CrossRef](#)]
- [63] Das, S.S.; Hussain, M.S.; Tambe, S.; Mundhe, S.; Acharya, A.; Bhunia, A.; Mohanto, S.; Ahmed, M.G. Advancement on Nanoparticles-Based Approaches for the Management of Rheumatoid Arthritis (RA): Molecular Mechanism, Toxicity, and Clinical Perspectives. *J. Drug Target.* **2026**, 34, 721–752. [[CrossRef](#)] [[PubMed](#)]
- [64] Taneja, A.; Panda, H.S.; Panda, J.J.; Singh, T.G.; Kour, A. Revolutionizing Precision Medicine: Unveiling Smart Stimuli-Responsive Nanomedicine. *Adv. Ther.* **2025**, 8, e00073. [[CrossRef](#)]
- [65] Koo, S.; Sohn, H.S.; Kim, T.H.; Yang, S.; Jang, S.Y.; Ye, S.; Choi, B.; Kim, S.H.; Park, K.S.; Shin, H.M.; et al. Ceria-Vesicle Nanohybrid Therapeutic for Modulation of Innate and Adaptive Immunity in a Collagen-Induced Arthritis Model. *Nat. Nanotechnol.* **2023**, 18, 1502–1514. [[CrossRef](#)]
- [66] Wang, Y.; Liu, Z.; Li, T.; Chen, L.; Lyu, J.; Li, C.; Lin, Y.; Hao, N.; Zhou, M.; Zhong, Z. Enhanced Therapeutic Effect of RGD-Modified Polymeric Micelles Loaded with Low-Dose Methotrexate and Nimesulide on Rheumatoid Arthritis. *Theranostics* **2019**, 9, 708–720. [[CrossRef](#)]
- [67] Wu, Y.Z.; Chen, W.Y.; Zeng, Y.; Ji, Q.L.; Yang, Y.; Guo, X.L.; Wang, X. Inflammation-Responsive Mesoporous Silica Nanoparticles with Synergistic Anti-Inflammatory and Joint Protection Effects for Rheumatoid Arthritis Treatment. *Pharm. Res.* **2024**, 41, 1493–1505. [[CrossRef](#)]
- [68] Zhou, M.; Hou, J.; Zhong, Z.; Hao, N.; Lin, Y.; Li, C. Targeted Delivery of Hyaluronic Acid-Coated Solid Lipid Nanoparticles for Rheumatoid Arthritis Therapy. *Drug Deliv.* **2018**, 25, 716–722. [[CrossRef](#)]
- [69] Zhao, Y.P.; Han, J.F.; Zhang, F.Y.; Liao, T.T.; Na, R.; Yuan, X.F.; He, G.B.; Ye, W. Flexible Nano-Liposomes-Based Transdermal Hydrogel for Targeted Delivery of Dexamethasone for Rheumatoid Arthritis Therapy. *Drug Deliv.* **2022**, 29, 2269–2279. [[CrossRef](#)]
- [70] Fang, H.; Sha, Y.; Yang, L.; Jiang, J.; Yin, L.; Li, J.; Li, B.; Klumperman, B.; Zhong, Z.; Meng, F. Macrophage-Targeted Hydroxychloroquine Nanotherapeutics for Rheumatoid Arthritis Therapy. *ACS Appl. Mater. Interfaces* **2022**, 14, 8824–8837. [[CrossRef](#)]
- [71] Jia, J.; Liu, M.; Yang, H.; Li, X.F.; Liu, S.; Li, K.; Zhang, J.; Zhao, X. Manganese Dioxide-Based pH-Responsive Multifunctional Nanoparticles Deliver Methotrexate for Targeted Rheumatoid Arthritis Treatment. *Biomater. Res.* **2025**, 29, 0187. [[CrossRef](#)]

[72] Sadeghi, M.; Tavakol Afshari, J.; Fadaee, A.; Dashti, M.; Kheradmand, F.; Dehnavi, S.; Mohammadi, M. Exosomal miRNAs Involvement in Pathogenesis, Di-

agnosis, and Treatment of Rheumatoid Arthritis. *Heliyon* **2025**, *11*, e41983. [[CrossRef](#)]

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