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

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Abstract

Angiogenesis is the process of formation of new blood vessels, a physiological process that becomes dysregulated in pathologic 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 explores structural and functional aberrations in Rheumatoid Arthritis synovial vasculature, key pro-angiogenic mediators including vascular endothelial growth factor and angiopoietins, and emerging signaling pathways including Notch and HIF-1α. 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. Through the integration of insights from stromal cell interactions, metabolic reprogramming, and epigenetic regulation, this article underlines the opportunity for disease modification in Rheumatoid Arthritis and broader autoimmune contexts through angiogenesis-targeted interventions. Future directions emphasize precision medicine approaches, including biomarker-driven therapies and combination regimens, to improve remission rates and quality of life.

Keywords: angiogenesis; autoimmunity; rheumatoid arthritis; nanotherapeutics; translational challenges; vascular endothelial growth factor

1.Introduction

A spectrum of autoimmune diseases in which an individual's immune system attacks its own tissues resulting in ongoing inflammation and destruction of tissue. Rheumatoid Arthritis (RA), along with systemic lupus erythematosus (SLE), forms a unique category of autoimmune disease due to the commonality of disease presentation, and its prevalence of 1% of the world's population results in significant morbidity and economic costs associated with the disorder. (1). The characteristics of Rheumatoid Arthritis are forged by an interplay of genetic, environmental and immunologic factors forming a clinical picture of symmetrical polyarthritis, synovial hyperplasia, and progressive joint destruction due to erosive lesions in the bones and cartilage secondary to the pathological state of the synovium (2). An integral part of the pathophysiology of Rheumatoid Arthritis is the inflamed synovium and its hyperplastic tissue, known as pannus tissue, invades both the cartilage and bone causing a self-sustaining cycle of inflammation and degradation of both cartilage and bone (3).

Furthermore, angiogenesis, the formation of new blood vessels from existing vascular networks, plays an important role in embryonic development, the healing of wounds, and the repair of damaged tissues. In addition, angiogenesis promotes the development of tumors, chronic inflammation, and fibrosis during diseased states(4) .Aberrant angiogenesis occurring during autoimmune diseases serves to increase the immune response associated with the inflammatory zones by providing nutrients and oxygen to the area, while also allowing the migration of WBC to the area through the upregulation of adhesion molecules on the endothelial cells (EC)(5). In Rheumatoid Arthritis, synovial angiogenesis occurs very early and is an indication of Rheumatoid Arthritis even before symptoms appear, as it is a key indicator of the degree of RA severity. (6).

This review delves into angiogenesis in autoimmune diseases, with Rheumatoid Arthritis as the focal point, drawing on recent literature from 2023 to 2025. The review delineates the pathological hallmarks of angiogenic vessels in RA synovium, dissect molecular mechanisms involving cytokines, growth factors, and signaling cascades, and appraise therapeutic modalities from biologics to nanotherapeutics. By highlighting underexplored intersections—such as metabolic shifts and epigenetic modulation this review will examine angiogenesis in various autoimmune diseases with a focus on Rheumatoid Arthritis, based on studies published between 2023 and 2025. The key pathological features of angiogenic vessels in Rheumatoid Arthritis will be discussed, along with the associated molecular pathways involved in the production of cytokines, growth factors, and their associated signalling pathways. The review will also provide an overview of the therapeutic agents being investigated from biologics through to nanotherapeutics. This review will highlight some of the lesser-explored areas of research, such as metabolic reprogramming and epigenetic changes in the regulation of angiogenesis and

immune response. This review aims to guide future research toward angiogenesis as a tractable therapeutic axis in RA management.

2. Overview of Angiogenesis

Angiogenesis is an ongoing physiological process of developing new blood vessels from existing ones, which is realised at the molecular level through a complex interplay between proangiogenic and antiangiogenic factors. Under normal conditions, vascular endothelial cells (ECs) exist in a quiescent state and are maintained by pericytes and a basement membrane (7). Specific stimulations such as hypoxia or injury activate ECs through receptor tyrosine kinases (RTKs), allowing them to assume more active roles in developing new blood vessels as "tip" cells and in proliferating as "stalk" cells. Vascular endothelial growth factor-A (VEGF-A) is the prototypical proangiogenic cytokine that initiates EC migration and survival by binding to vascular endothelial growth factor receptor-2 (VEGFR2) on the surface of ECs, resulting in activation of intracellular signaling pathways, including phosphoinositide 3-kinase (PI3K) and mitogen activated protein kinase (MAPK) pathways (8). Additionally, angiopoietins [Ang1 and Ang2] promote the recruitment of pericytes *via* Tie2 receptors on ECs, subsequently stabilizing the mature vessel structure. Also important in the development of mature blood vessels are platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β), which aid in further refining the process (9) Notch signaling is important in regulating branching of developing vessels as the Notch receptors on ECs are activated when DLL4 (a Notch ligand) binds to the notched EC *via* the Tie2 receptor, which in turn induces activation of Notch1 on adjacent stalk-cell ECs, and thus inhibits the expression of VEGFR2, thereby preventing excessive sprouting (6) Hypoxia-inducible factor 1α (HIF-1α), which is upregulated under conditions of decreased oxygen, upregulates transcription factors that regulate expression of VEGF and other key effectors involved in linking the metabolic state of the ECs with growth of the vascular system. 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. As a result, RA patients experience the formation of immature and leaky vessels that are abnormally shaped (e.g., twisted), enlarged, and have gaps between the endothelial cell layer. These abnormalities reduce blood flow and increase hypoxia in the affected tissues (5). Inflammatory cytokines produced by macrophages and fibroblasts increase the production of vascular endothelial growth factor (VEGF), while reactive oxygen species (ROS) resulting from oxidative stress create lipid peroxides that promote angiogenic factors (11). Angiogenesis and immunity intersect within the setting of autoimmune disease: endothelial cells (EC) express intercellular adhesion molecule-1 VCAM-1 (ICAM-1/VCAM-1) and provide sites for leukocyte attachment and infiltration, while chemokines such as CXCL8 (IL-8) help direct these cells to inflamed tissues. While lymphangiogenesis is an understudied area, it serves to

drain antigens from inflamed tissues; however, it is ineffective in the setting of RA, resulting in the accumulation of fluid (e.g., lymph) in these areas (12). Recent studies conducted between 2024 and 2025 revealed that metabolic reprogramming likely underlies these effects: Warburg-like glycolytic pathways observed in synovial ECs represent the continued proliferation of these cells, as the by-products of this process drive the production of fibroblast growth factor-2 (FGF2) through lactate feed-forward loops (13). Additionally, the presence of epigenetic marks such as microRNAs that target VEGF mRNA further regulate these processes and add complexity to our 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 dermal papillary angiogenesis that is maintained by VEGF produced by keratinocytes in response to IL-17/Th17 axis stimulation; anti-VEGF treatments have anecdotally shown some efficacy (16). Mucosal angiogenesis supports chronic colitis in inflammatory bowel disease, and stabilization of HIF-1α 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 illustrates angiogenesis as a pathogenic fulcrum. In contrast to tumour angiogenesis, the vessels in RA are "normalized" periodically by pericytes but remain hyperpermeable, promoting a pro-inflammatory niche. Thus, EPCs mobilized from the bone marrow through SDF-1/CXCR4 home to synovium, differentiating into ECs under CXCL13/CXCR5 guidance.(5). Synovial fibroblasts (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 high levels of PlGF and VCAM-1 and low levels of IL-8, allowing differentiation between active and remitted disease. (3). This signature emphasizes angiogenesis as a biomarker for therapeutic stratification.

4. Pathological Angiogenesis in Rheumatoid Arthritis

RA synovium contains a thick, aberrant microvascular network, with 3- to 5-fold higher microvascular density compared with osteoarthritis (5). The vessels assume linear, tortuous, or mixed configurations with rod-shaped or villous projections into the joint spaces. Early RA is

characterized by intense inflammatory angiogenesis that progresses into a hypertrophic and congested vasculature at chronic stages (19). Immature ECs have fenestrations and discontinuities, with detached α-SMA+ pericytes, leading to hemorrhage and edema. Basement membrane collagen IV degradation by MMP-2/9 further promotes leakiness, enabling plasma extravasation and fibrin deposition, hallmarks of pannus (20). Ultrastructural studies using electron microscopy confirm glycocalyx shedding on ECs, reducing barrier function and promoting immune cell diapedesis (21). 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) (22). 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 (23). Pannus invasion causes erosion of subchondral bone through recruitment of osteoclasts, whereas VEGF enhances expression of RANKL on osteoblasts. Clinically, this presents as tenderness, swelling, and morning stiffness. DAS28 correlates with synovial vascularity as determined by power Doppler ultrasound studies (24). In extra-articular RA, such as ILD, pulmonary angiogenesis drives fibrosis with VEGF-A isoforms promoting fibroblast-to-myofibroblast transition. Periodontal involvement sees gingival neovessels harboring Porphyromonas gingivalis, thus linking oral microbiome to RA flares (25). Longitudinal cohorts (2024–2025) linking baseline angiogenesis indices to radiographic progression: elevated synovial VEGF predicts increase in Sharp score over 2 years (1).

5. Mechanisms of Angiogenesis in RA

The angiogenesis of Rheumatoid Arthritis is predominantly dominated by the VEGF family. VEGF-A secreted by FLS and macrophages binds with VEGFR2 and activates PLCγ/IP3, which in turn mobilizes Ca2+ and forms filopodia (26). Hypoxia stabilizes HIF-1α, which transcribes VEGF alongside glycolytic enzymes.(5). Angiopoietins imbalance: Ang2/Tie2 antagonism destabilizes junctions, synergizing with VEGF for sprouting. FGF-2 from chondrocytes amplifies EC proliferation *via* FGFR1/ERK. HGF from injured epithelium promotes tubulogenesis (27). Inflammatory milieu amplifies: TNF-α/IL-1β upregulate VEGF *via* NF-κB, while IL-6/JAK/STAT3 sustains chronicity. Th17-derived IL-17 induces EC CXCL8, recruiting neutrophils that release MMPs for matrix remodeling (28).

Notch pathway bifurcates Rheumatoid Arthritis angiogenesis: DLL4/Notch1 prunes excess branches but, in inflammation, chronic activation *via* Jagged1 on FLS leads to EC exhaustion and leakiness (6). Crosstalk with HIF-1α: Notch suppresses HIF-1α in normoxia but enhances it under stress, creating a feed-forward loop (6). PI3K/AKT/mTOR promotes metabolic reprogramming: AKT phosphorylates PFKFB3, enhancing glycolysis and lactate export, which acidifies synovium and activates Rho/ROCK to induce loss of contractility in ECs (13). ROS from NOX2/MPO in neutrophils oxidizes lipids into 4-HNE that transactivates VEGF promoter (29). Both MAPK/ERK and JAK2/STAT3 pathway cascades converge on common targets, such as AP-1 and c-Fos transcription factors, integrating cytokine signals. Epigenetics adds layers to

this: for example, miR-126 targets SPRED1, thus enhancing ERK; miR-21 silences PTEN, activating PI3K.(1)

FLS transdifferentiate into myofibroblasts, secreting PDGF-BB for pericyte recruitment-paradoxically stabilizing pathological vessels. Macrophages (CD68+) secrete Ang2/VEGF; Tregs fail to suppress *via* impaired FoxP3 (30). Adipose-derived FABP4 binds VEGF, prolonging half-life; SPARC modulates ECM for EC invasion. ANGPTL4 from the ECs mediates inflammation without affecting lipid metabolism, leading to bone erosion through IL-6/STAT3 (31). New single-cell RNA sequencing reveals heterogeneity in ECs: "tip-like" clusters overexpress VEGFR2, whereas "stalk-like" cells upregulate glycolytic genes, informing targeted perturbations (32,33). Figure 1 depicts the mechanism through which angiogenesis regulates rheumatoid arthritis.

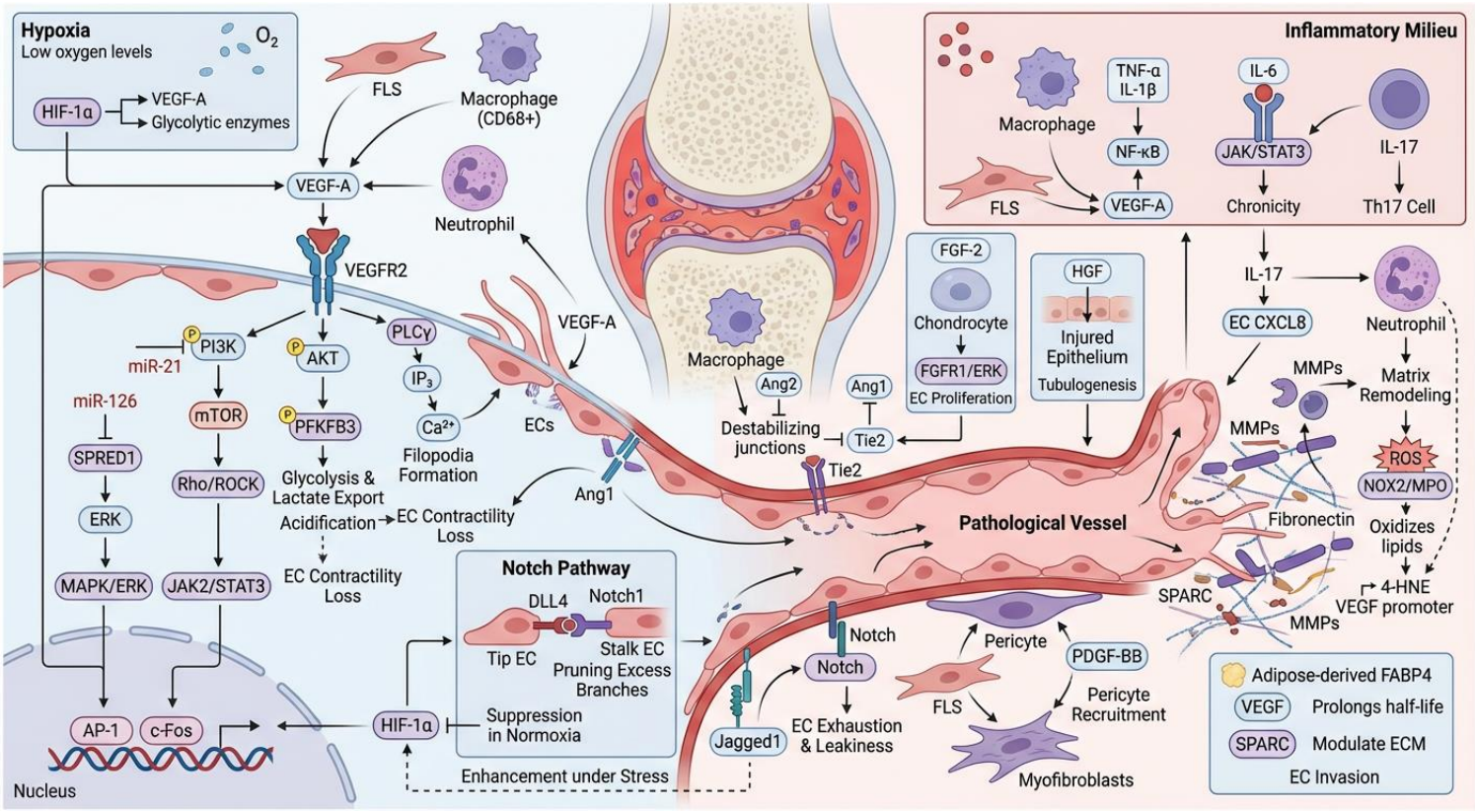

Figure 1. Integrated molecular and cellular mechanisms of angiogenesis in rheumatoid arthritis (RA): Hypoxia-induced HIF-1α drives VEGF-A production from FLS and macrophages, activating VEGFR2 signaling in endothelial cells to promote sprouting. Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-17) amplify angiogenesis via NF-κB 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 (34). Small-molecule TKIs such as sunitinib inhibit VEGFR/FGFR and face resistance *via* Ang2 upregulation (35). JAK inhibitors, such as tofacitinib, indirectly inhibit VEGF by inhibiting STAT3; 2025 data demonstrate superior anti-angiogenic effects over MTX in refractory RA.(36). The 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	(37)
Tyrosine kinase inhibitors	Sunitinib	Inhibits VEGFR, FGFR pathways	Decreases angiogenesis	Resistance via Ang2 upregulation	(38)
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	(39)
Natural compounds	Triptolide	Downregulates HIF-1α/VEGF axis	Reduces disease severity	Toxicity concerns	(31)
Phytotherapeutics	Berberine, Sinomenine	Inhibit NF-κB, ERK pathways	Suppress angiogenesis and cytokines	Limited clinical data	(1)

6.2 Natural Compounds and Phytotherapeutics

Multitargets of resveratrol include the activation of SIRT1, which in turn restores metabolism and inhibits Rho/ROCK, while the upregulation of FOXO suppresses AKT/ERK (13). In CIA

models, Res (50 mg/kg) halves VEGF levels, alleviating paw swelling (40). Triptolide from Tripterygium wilfordii downregulates HIF-1α/VEGF, with clinical trials reporting 40% DAS28 reduction (41). Sinomenine blocks SphK1/S1P, reducing EC migration, while Paeonia lactiflora glucosides inhibit NF-κB/VEGF (42). Berberine inhibits p-ERK/p38, whereas flavonoids (morin) act upon the PPARγ to antagonize Ang/Tie2 (43). In a meta-analysis in 2024, natural medicines have been confirmed to reduce the levels of ESR/CRP by 25–30% due to the inhibition of angiogenesis. (44).

6.3 Cell-Based and Nanotherapeutics

MSCs immunomodulate angiogenesis: paracrine VEGF-B (anti-inflammatory isoform) and thrombospondin-1 promote vessel maturation (45). Phase I/II trials (e.g., NCT05233601) with umbilical MSCs yield 50% ACR20 responses, though homing issues persist—addressed by CXCR4 overexpression (46).

Nanotherapeutics, therefore, represent a revolutionary approach in the management of RA by precisely targeting pathological angiogenesis, which fuels synovial inflammation, pannus invasion, and joint destruction. Traditional anti-angiogenic agents, like bevacizumab, usually bear the disadvantages of poor bioavailability, fast clearance, and off-target effects, leading to suboptimal efficacy with toxicities including hypertension (47). Such limitations are addressed by nanoplatforms, which, due to the enhanced permeability and retention effect or extravasation through leaky vasculature and inflammatory cell-mediated sequestration effects, passively accumulate within inflamed joints (48). 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-1α, besides vessel normalization and reduction of inflammation (49).

Passive targeting involves nanoleaking, immature vasculature in RA synovium, with gaps of up to 200 nm, through which NPs may extravasate and be retained by EPR/ELVIS. 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 (50). Active targeting increases specificity: RGD-modified NPs bind to the αvβ3 integrins that are overexpressed on angiogenic ECs and osteoclasts and promote their 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 (51).

Liposomes are spherical lipid vesicles (25 nm-500nm) that are biocompatible platforms for anti-angiogenic delivery. PEG liposomes ensure extended circulation, evading immune clearance while encapsulating drugs such as Dex, tofacitinib, or berberine (52). In the AIA rat model, PEG

liposomes loaded with Dex reduced the levels of TNF-α and IL-1β, reducing joint swelling by inhibiting inflammatory cascades related to angiogenesis. (53). 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. (50). pH-responsive liposomes induce apoptosis in FLS and macrophages; thereby normalizing vessels by downregulating HIF-1α and ROS, as reported in studies during 2024.(53).

Gold nanoparticles (AuNPs, 1–100 nm) exhibit intrinsic anti-angiogenic properties, particularly at 50 nm, where they inhibit synovial neovascularization in early RA (54). 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 (51). FAGMs (folic acid and guanidine-modified AuNPs) enhance MTX release, minimizing systemic toxicity while targeting folate receptors on angiogenic ECs (50). Similarly, SeNPs–PEG–RGD@Ru (Se@RuNPs) with RGD modification suppress VEGF/VEGFR2 signaling, inhibiting EC proliferation and migration (55).

Chitosan nanoparticles represent an important class of biodegradable and biocompatible dosage forms 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 (56). Their mucoadhesive properties and ease of functionalization further enhance cellular uptake and site-specific delivery. Building on this, sustained release can be achieved through tunable degradation-based systems, particularly using polymeric carriers such as PLGA and chitosan, which allow controlled encapsulation and gradual release of drugs like dexamethasone-palmitate. These formulations improve pharmacokinetics and maintain therapeutic concentrations at the target site while modulating angiogenic pathways such as Ang/Tie2 signaling (57). Sustained release can be provided by Tuneable Degradation by using PLGA and/or chitosan nanoparticle systems to generate an encapsulation system for the controlled delivery of agents such as Dex-Palmitate, which has improved PK properties, and cytoprotective properties *via* the Regulation of the Angiotensin/Tie2 Pathways (50). Chitosan nanoparticle systems for Embelin and Eugenol reduce Cytokines, Synovial Hyperplasia Models induced in the AIA/CIA, *via* ROS Scavenging, with Anti-angiogenic properties (58). Dendrimers are structured like a branched tree, ranging from 1 to 10nm 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(53). Both Chi et al. (2023) and Vaibhav et al. (2024) reported the specific targeting ability of the dendrimer-delivered adalimumab and etanercept-dendrimer combinations for specific delivery.

Further innovation has been brought about by solid lipid nanoparticles (SLNs, 10-1000 nm) and biomimetic NPs. β-Sitosterol-SLNs inhibit NF-κB, downregulating VEGF, while HA-coated prednisolone SLNs reduce joint erosion in CIA mice (59). Biomimetic NPs coated with neutrophil membranes deliver hydroxychloroquine, induce M1 macrophage apoptosis, and vessel normalization in CIA models. (50). Hypoxia-relieving nanomaterials, such as CAT-loaded nanozymes (Pt, MnO_2), produce O_2 in situ and alleviate hypoxia, thereby inhibiting the HIF-1α/VEGF axis. (5). ROS-scavenging NPs, such as Mn_3O_4 and Se NPs, help to repolarize macrophages from M1 to M2 phenotypes, thus reducing Ang2 and promoting anti-angiogenic balance (60).

Innovative platforms include nanofibers and hydrogels. STP peptide + RGD peptide+ Triptolide Metformin **(**STP-RGD@TM) nanofibers self-assemble, blocking VEGFR2 while releasing triptolide/metformin, reducing joint scores by 70% in RA mice with minimal off-targets (5). Injectable hydrogels, temperature-sensitive, deliver Dex or siRNA, enhancing local retention and downregulating MMP-9/PDGF-BB for anti-angiogenic effects (50). Ceria-vesicle hybrids (Ce-MSCNVs) are capable of clearing free radicals and are known to suppress angiogenesis. At this time, Clinical Mitigation remains Limited Based on the Challenges of Biocompatibility, Scale-Up, and Regulatory Requirements Associated with (FDA/EMA) (53) Risks associated with Potential Toxicities include the accumulation of agent within the tissue, Activation of the Immune Response, and Variability in the Manufacturing Process. H-A/T Nanoparticles are capable of Modifying the Structure of VEGF; whereas Rh/SPX-HSA will Generate Oxygen and Suppress HIF-1α. The results of preclinical studies show Promise; e.g., R-M/N-PMs (RGD-MTX-nimesulide) Inhibiting Endothelial Cell Proliferation and Restoring Function in CIA Models was reported by Nakano et al. (5). Nanoplatforms have Revitalized the Platform by which Agents are Delivered; for example, STP-RGD@TM (2025) will Self-assemble into a Nanofiber Platform and provide Normalization of Vessels *Via* VEGFR2 Blockade, while also providing the Controlled Release of Triptolide and Metformin (21). The effects of RA in mice are significantly diminished by 70% and decreased off-targets with kinase inhibitors such as filgotinib acting synergistically as an anti-VEGF (anti-VEGF) agent in combination with anti-TNF on the basis of clinical studies comparing the two drugs (39) with ongoing clinical trials (e.g., NCT06294731) evaluating combined anti-VEGF/JAKi therapy.

In the future, we can expect to see two-dimensional (2D) stimuli-responsive nanoparticles combined with artificial intelligence for designing patient-specific composites; these composites will contain multiple functionalities to facilitate both imaging and treatment (termed theranostics); and so on, CRISPR-based editing of genes from the gene portfolios of multiple patients *via* nanocomposites (e.g., by silencing the expression of the VEGF gene) (53). Combination strategies utilizing phototherapy and/or immunotherapy would potentially eliminate the expressed resistance in one or both therapies, although studies like those authored by Wu et al. will likely be catalysts for the commencement of completed clinical trials with the utilization of functionalized mesoporous silica nanoparticles (5). In conclusion, the use of nanoparticles to

develop new nanotherapeutics represents a major re-engineering of current treatment regimes for rheumatoid arthritis; this change would provide an opportunity for rheumatologists to increase rates of clinical remission as well as improve 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	(52)
PLGA Nanoparticles	Endothelial cells	MTX, Dex-palmitate	Controlled release	Reduced angiogenesis	(51)
SLNs	Macrophages	Prednisolone	Enhanced stability	↓ VEGF	(59)
Dendrimers	FLS, immune cells	Adalimumab	Targeted delivery	↓ VEGF secretion	(53)
Gold NPs	αvβ3 integrins	MTX	Photothermal + anti-angiogenic	↓ neovascularization	(51)
RGD NPs	Endothelial cells	MTX	Integrin targeting	Inhibit EC proliferation	(51)
HA-coated NPs	CD44	Prednisolone	Receptor-mediated uptake	↓ synovial hyperplasia	(50)
Nanofibers	VEGFR2	STP-RGD@TM	Dual drug delivery	↓ joint inflammation	(5)
Hydrogels	Synovial cavity	Dex, siRNA	Sustained release	↓ angiogenesis	(50)
Biomimetic NPs	Immune cells	Hydroxychloroquine	Immune evasion	Vessel normalization	(50)
Nanozymes	Hypoxic tissue	MnO2	O2 generation	↓ HIF-1α	(5)
Exosomes	Endothelial cells	miRNA	Gene regulation	Restore vascular balance	(53)

7. Challenges and Future Directions

Indeed, the translational potential of angiogenesis-based treatment modalities for rheumatoid arthritis (RA) is greatly hindered by the presence of multiple biological, technical, and regulatory factors that impede its implementation even in light of favorable preclinical findings. Biocompatibility is one of the major hurdles since angiogenic targeting nanotherapies must be capable of functioning effectively under conditions of heightened immune response without triggering undesired immune reactions or toxicity. Another issue stems from the potential accumulation of nanoparticles in non-target organs, such as liver or spleen, which may cause

additional health complications due to chronic inflammatory responses in RA patients whose immune systems already tend to work improperly. Variability in physicochemical parameters, such as the size, charge, and surface properties of particles, may have a significant impact on the efficacy of therapy due to changes in biodistribution and pharmacokinetics. Scalability can also become a barrier in cases when particle homogeneity and effective delivery differ 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 industry. Lack of standardization between different agencies, such as the FDA, EMA, or CDSCO, leads to inconsistency in regulations of nanomedicines. Importantly, the majority of current evidence is derived from animal models, and the paucity of large-scale human clinical trials limits definitive conclusions regarding efficacy and long-term safety.

Nonetheless, the prospects of angiogenesis-inhibiting therapies in RA are very bright, especially considering the rapidly evolving field of precision medicine, bioengineering, and computational tools. The paradigm is likely to shift towards more biomarker-based approaches to therapeutic intervention with the help of the detection of angiogenic markers, such as VEGF, PlGF, and adhesion molecules, to name just a few. In addition, the application of artificial intelligence and machine learning techniques may bring about a new era for the development of drugs and individualized 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 promises to open a new window into the monitoring of inflammation and its inhibition by providing imaging capabilities combined 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-1α signaling. Finally, gene-editing systems, such as CRISPR/Cas-based approaches, have the potential to silence pro-angiogenic genes directly. 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 for patients with RA.

8. Conclusion

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. Evidence from 2023 to 2025 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 like Notch, HIF-1α, 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 synoviocytes,

macrophages, and endothelial cells sustains a self-amplifying cycle of inflammation and angiogenesis.

In terms of therapeutics, inhibition of angiogenesis can be considered an exciting strategy for achieving disease modification. Even though anti-VEGF therapies have not been able to produce any significant clinical benefit because of side effects, novel strategies, such as nanotechnology-based drug delivery, natural products like resveratrol and triptolide, and treatment using mesenchymal stem cells, have proved to be more specific and effective. Nonetheless, problems like compensatory mechanisms, scalability, and clinical implementation continue to pose serious obstacles. Strategies in the future will include precision medicine and artificial intelligence.

List of abbreviations

- HIF-1α : Hypoxia-Inducible Factor 1-alpha
- VEGF : Vascular Endothelial Growth Factor
- SLE : Systemic Lupus Erythematosus
- VCAM-1 : Vascular cell adhesion molecule 1
- PlGF : Placental Growth Factor
- CCL20 : C-C motif chemokine ligand 20
- ACPA : Anti-citrullinated protein antibodies
- RANKL : Receptor Activator of Nuclear Factor B Ligand
- PFKFB3 : 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3
- ANGPTL4 : Angiopoietin-like 4
- RA: Rheumatoid Arthritis

Author Contributions:

Abinash Nayak performed Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing—original draft preparation, Visualization. Omprakash Badajena performed Conceptualization, Methodology, Formal analysis, Investigation, Resources, Visualization, Revision of original manuscript and Sudhansu Sekhar Nishank performed Validation of Original manuscript, Supervision and Project administration.. All authors have read and agreed to the published version of the manuscript.

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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 for data generation. The authors take full responsibility for the content of the study.

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