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REVIEW ARTICLE

Angiogenesis in rheumatoid arthritis: epidemiology, pathogenesis, signal transduction pathways, and nano-targeted therapeutic strategies

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ABSTRACT

Angiogenesis is the formation of new blood vessels from existing vessels. In rheumatoid arthritis (RA), new blood vessels maintain a chronic inflammatory state by transporting inflammatory cells to the site of inflammation. Rheumatoid arthritis is a chronic autoimmune disorder that affects approximately 1% of the global population, with a higher prevalence in women. It is characterized by synovial inflammation, hyperplasia, and angiogenesis, leading to joint destruction. Understanding the pathogenesis of RA, particularly the mechanisms driving synovial angiogenesis, is crucial for the development of targeted therapies. Fibroblast-like synoviocytes (FLS) and endothelial cells play key roles in RA pathogenesis by secreting pro-inflammatory cytokines and growth factors, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1β, IL-6, and vascular endothelial growth factor (VEGF). These mediators activate multiple signaling pathways, including VEGF, nuclear factor kappa light chain enhancer of activated B cells (NF-κB), phosphatidylinositol-3 kinase (PI3K)/AKT, mitogen-activated protein kinase (MAPK), wingless-related integration site (Wnt), and the Janus kinase (JAK)/ signal transducer and activator of transcription (STAT), which contribute to synovial angiogenesis, inflammation, and joint damage. A literature search was conducted on PubMed, ScienceDirect, SpringerLink, and Google Scholar databases for sources published in English from 2015 to 2025, using the terms “nanotechnology rheumatoid arthritis,” “angiogenesis,” “synovial inflammation,” “pro-inflammatory cytokines,” “disease-modifying antirheumatic drugs,” and “signal transduction pathways”. Current treatments for RA include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs) (conventional synthetic, biological, and targeted synthetic). An informative overview of anti-angiogenic strategies for treating RA, which may provide new perspectives for developing nanoagents, is opening new horizons in the fight against RA. This review covers RA epidemiology, pathogenesis, and signal transduction, as well as current therapies and their limitations, highlighting the need to develop new treatment strategies that target angiogenesis in RA.

Keywords: Nanotechnology rheumatoid arthritis, angiogenesis, synovial inflammation, pro-inflammatory cytokines; disease-modifying antirheumatic drugs, signal transduction pathways

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic joint inflammation and deformities.[1] This condition is marked by the infiltration of inflammatory cells, an increase in synovial tissue, the formation of pannus, the breakdown of cartilage, and the destruction of bone.[2] This systemic autoimmune disease affects multiple synovial joints, with persistent inflammation leading to joint destruction.[3] Although the disease itself is nonfatal, its complications usually result in disabilities, thus reducing the quality of life of affected individuals.[4] Rheumatoid arthritis affects 1% of the global population[5] and all ethnicities.[5] The disease develops in adults and predominantly affects women.[1,6] Like other chronic diseases, this disease burdens patients and caregivers economically and debilitates work productivity, particularly in industrialized countries.[7] For the most part, there are scarce data on this lifelong disease in developing countries, including Malaysia, unlike in Western countries.

Angiogenesis, the process of new vessel formation, is a key event in the pathogenesis of RA.[8] Disruption of angiogenesis plays a crucial role in the initial development of human RA, which perpetuates chronic inflammation and sustains pannus growth, resulting in joint damage.[9] Recently, it has been discovered that inhibiting synovial angiogenesis has become clinically important to prevent the disease at the initial developmental stage.[8,10] Although managing RA has become more challenging owing to the interplay between RA, aging, and comorbidities,[11] the major drawback of treating this disease is the limitation of available treatments. The use of mainstream therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional disease-modifying antirheumatic drugs (DMARDs) aids in impeding disease progression, but not in treating the disease.[12] Although the introduction of biologic DMARDs to clinically target angiogenesis has significantly improved RA outcomes,[13] treatment response failure is anticipated in some patients.[14] Some biologics, NSAIDs, and conventional DMARDs have also been reported to have contraindications and toxicities.[15] Unfortunately, access to current biologics, particularly among Asian countries, is scarce owing.[7]

No comprehensive reviews have yet examined the progress and fundamental mechanisms of anti-angiogenic nanoagents specifically in RA. Therefore, this review aims to provide a comprehensive review of the pathological mechanisms of angiogenesis in RA, along with the application of anti-angiogenic nanoagents for RA treatment.

METHODS

This review paper involved a thorough literature search on PubMed, ScienceDirect, SpringerLink, and Google Scholar databases to gather relevant English articles published from 2015 to 2025 using the keywords "nanotechnology rheumatoid arthritis," "angiogenesis," "synovial inflammation," "pro-inflammatory cytokines," "disease-modifying antirheumatic drugs," and "signal transduction pathways". Initially, 2,500 articles met the inclusion criteria, but ultimately, 2,342 were excluded due to duplication, access issues, and irrelevant topics, leaving 158 articles for analysis and synthesis (shown in Figure 1). This review included peer-reviewed original research, systematic reviews, meta-analyses, selected narrative reviews, and clinical overviews to comprehensively cover mechanistic and therapeutic aspects of RA, including angiogenesis, signal transduction pathways, and treatment strategies. Non-English articles and case reports were excluded.

Epidemiology of RA

Rheumatoid arthritis is a debilitating disease affecting approximately 1% of the global population.[5] This disease develops in adulthood and is usually observed in young women aged 25-45.[6] In addition, juvenile idiopathic arthritis forms of childhood arthritis (replacing the older term juvenile rheumatoid arthritis), are observed in individuals younger than 16 years at the time of onset, with an estimated occurrence rate of approximately 2–20 cases per 100,000 children.[16] Rheumatoid arthritis affects people of all ethnicities worldwide.[1,5] According to the Rheumatoid Arthritis: Epidemiology Forecast to 2027 report in 2019, by 2027, the global trends of RA in eight key markets, including the United States, France, Germany, Italy, Spain, the United Kingdom, Japan, and Australia, are projected to grow at an annual growth rate (AGR) of 1.09%. Ireland has the highest age-standardized incidence

of RA (ASR), followed by Finland and Kazakhstan.[17] In Malaysia, demographic data have shown that the disease affects major ethnic groups, including Malays (43.3%), Indians (35.4%), and Chinese (20.1%).[18] The Malaysian National Inflammatory Arthritis Registry reports that the occurrence of RA is roughly twice as high in females, with approximately 70% of RA patients being women.[19] However, the exact statistics for RA incidence could have been underestimated owing to the lack of public awareness and limited access to rheumatology care in Malaysia.[20] Although the exact figures remain unknown, the incidence of RA has increased over the past few years.

Pathogenesis of RA

A healthy joint is lined with synovial tissue called the synovium. The synovium comprises a thin intimal lining and a subintimal lining of two to three layers of cells.[21] Synovial tissue contains mainly fibroblast-like synoviocytes (FLS) and macrophages,[22] the former of which are key effector cells of RA.[23] In the inflamed synovium, the healthy layer structure expands (hyperplasia) and transforms into a pannus-like structure, primarily by the over-proliferation of FLS and accumulation of macrophages. The pannus extends into the joint space, invading and degrading the cartilage matrix, thereby promoting joint destruction.[22] The pathophysiology of RA synovium is shown in Figure 2.

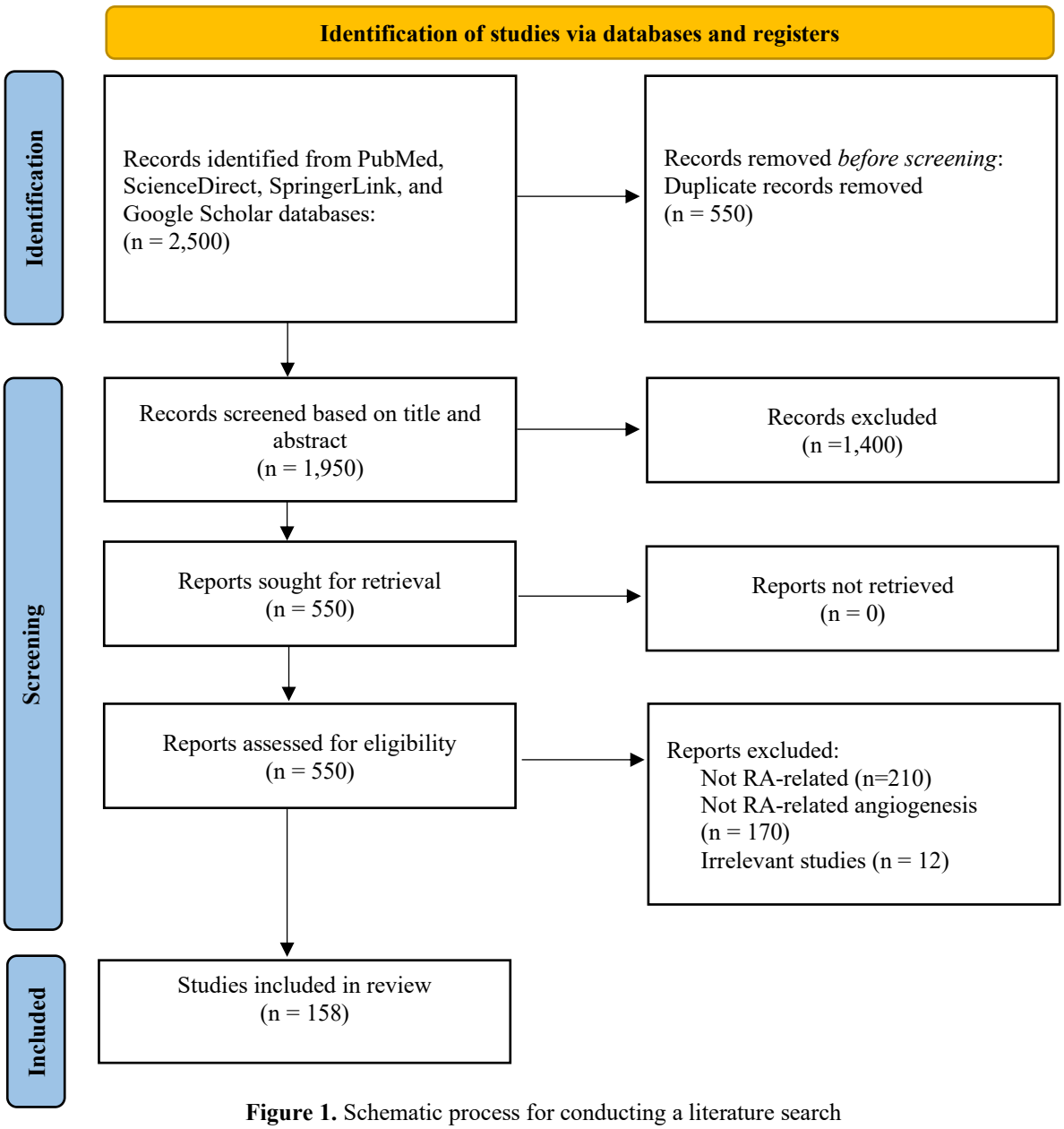

Figure 1. Schematic process for conducting a literature search

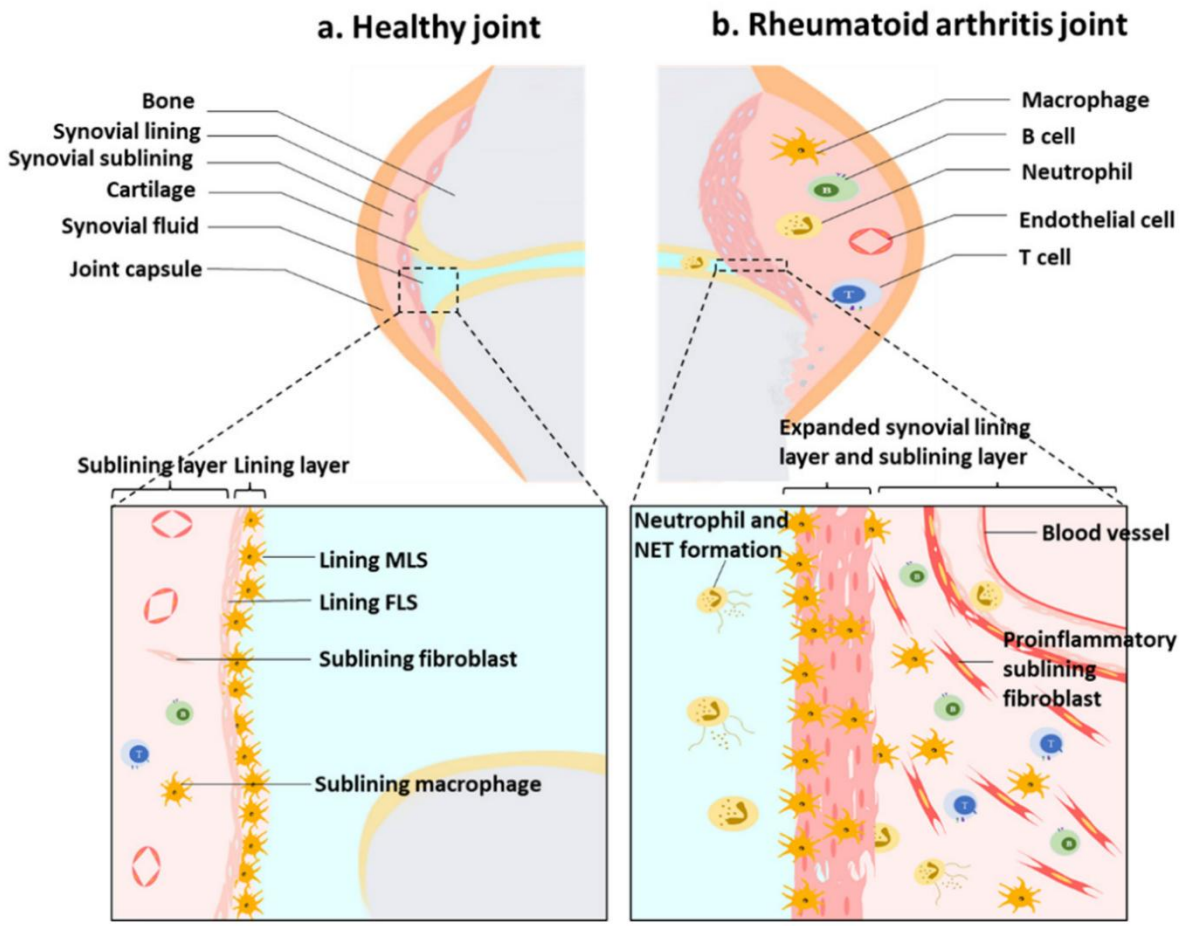

Figure 2. Illustration of (a) healthy synovium and (b) arthritic synovium. In the healthy joint, a thin cell layer of fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS) form a protective barrier, with sublining layers containing fibroblasts, macrophages, and blood vessels. In rheumatoid arthritis, the macrophage barrier is lost, the synovial lining expands abnormally (hyperplasia), and the sublining becomes infiltrated with immune cells and new blood vessels (neovascularization). Reproduced from Wang et al.[24] under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

Synovial tissue inflammation (synovitis) begins with immune cell activation (T and B cells) and leukocyte recruitment within the tissue sublining.[25] Proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β), are released into surrounding tissues by activated T and B cells. FLS and macrophages are stimulated by the release of cytokines within the tissue lining, resulting in the production of growth factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), as well as other proinflammatory mediators (e.g., IL-1, IL-6, and IL-17).[22,26] The sustained release of inflammatory molecules and growth factors within synovial tissue perpetuates synovitis, resulting in hyperplasia.[22,25,27]

The hyperplastic synovium creates reduced oxygen tension (hypoxia) within the inflamed tissues, triggering synovial angiogenesis.[28] Angiogenesis, the outgrowth of new microvessels from pre-existing ones, constitutes the initial phase of RA pathogenesis.[29] Synovial angiogenesis occurs in response to hypoxia-inducible factor (HIF)-1 molecule expressed within the hypoxic synovium. The increase in HIF-1 expression primarily activates the VEGF signaling pathway, which triggers other pro-angiogenic cascades within effector cells.[28, 30] Other proangiogenic mediators, as summarized in Table 1, are among the important players in orchestrating RA angiogenesis.[31,32]

Table 1. Angiogenic elements and mediators in RA

Angiogenic elements	Mediators	Role in RA	References
Growth factor/receptors	VEGF, FGF, PDGF, EGF, TGF-β, HGF VEGFR-2, Ang-1 & 2, Tie2 receptor	Angiogenesis activation via direct effects on EC in synovial tissue	Caliogna L et al.[33] Zhu et al.[34]
Cytokines	TNF-α, IL-1, IL-6, IL-8, IL-15, IL-17, IL-18, G-CSF, GM-CSF, oncostatin M	Enhancing secretion of VEGF by EC and FLS for angiogenesis activation; T and B cell differentiation during synovitis	Tao et al.[35] Narazaki et al.[36]
Chemokines/Receptors	CXCL1, CXCL4, CXCL5, CXCL6, and CXCL8 CXCR2, CXCR4, CXCR5	Leukocyte recruitment into the inflamed synovium	Elemam et al.,[37] Yeo et al.[38]
Hypoxia	HIF-1α	HIF-1α regulates HIF gene transcription in EC for hypoxia-driven angiogenesis in the inflamed synovium	Li et al.[39] Jusman et al.[40]
Matrix metalloproteinases	MMP-2, MMP-9	Proteolytic degradation of extracellular matrix	Bian et al.[41]
Cell adhesion molecules	Integrin, E-selectin, VCAM-1, ICAM-2, PECAM-1	Allow EC migration	Khodadust et al.[42] Mangoni & Zinellu [43]
Others	COX/Prostaglandin E2	COX regulates angiogenesis in RA	Woods et al.[44]

Under aberrant signaling of proangiogenic mediators and their downstream effectors, the synovial endothelium undergoes active cell proliferation, migration, and differentiation, forming immature microvessels within the inflamed synovium.[9,28] These microvessels nourish inflammatory cells within the synovium and allow their infiltration, leading to pannus formation.[45] Pannus is an invasive, highly vascularized structure capable of invading and destroying the cartilage matrix and bone structure.[46] Ideally, these coordinated synovial angiogenesis and joint destruction processes should be therapeutically targetable.[47] The mechanisms underlying synovial angiogenesis in RA are shown in Figure 3.

Fibroblast-like synoviocytes: key effector cells in RA

Fibroblast-like synoviocytes (FLS) are the predominant cell type in the normal synovium.[22,23] As effector cells of RA, FLS initiate and perpetuate RA by secreting proinflammatory cytokines and growth factors, namely TNF-α, IL-1β, IL-6, and VEGF.[49] Cumulative studies have demonstrated that abnormal FLS undergo morphological and behavioral alterations, such as hyperproliferation, invasiveness, and apoptotic resistance.[23,50] Aggressive FLS induce numerous adhesion molecules (e.g., integrins), thus increasing their attachment strength that permeates and plagues the articular cartilage.[51] These FLS also produce matrix-degrading enzymes such as matrix metalloproteinases (MMPs), including MMP-2, MMP-3, and MMP-9, which degrade cartilage matrix.[52] In addition, FLS together with other cytokines, promote the activation of receptor activator of nuclear factor (NF) ligand (RANKL) expressed in osteoclasts, resulting in erosion of the bone.[53] Aggressive FLS activity is controlled by several interrelated pathways and signaling molecules, as reviewed in a later section. The mechanisms and consequences of FLS activation in RA are shown in Figure 4.

In this concept, the loss of proteoglycans from the articular cartilage represents a key initial step. In the context of an as-yet poorly understood immunological sensitization, it directly triggers the activation, increased adhesion, and invasiveness of RA, which ultimately results in tumor-like transformation involving profound epigenetic changes that result in alterations in cell growth, apoptosis, migration, and invasion. These

alterations trigger the homing and survival of immune cells and contribute to increased osteoclastogenesis and angiogenesis as part of the complex pathogenesis of RA.

Angiogenic roles of endothelial cells in RA

In RA, endothelial cells (ECs) lining the blood vessels are an active target for angiogenic activity succeeding angiogenesis.[9] The release of cytokines and the presence of hypoxia firmly regulate EC responses within tissues. The VEGF proteins are the principal activators of EC proliferation, survival, differentiation, and permeability.[55] Upon stimulation by VEGF, resident ECs are loosened at their junctions, causing vasodilation and promoting hyperpermeability of vessels. Accordingly, plasma proteins leak from the bloodstream and disrupt the extracellular matrix scaffold. Activated ECs also produce matrix-degrading enzymes (e.g. MMPs) that dismantle the basement membrane and extracellular matrix.

During proliferation, the endothelial cells migrate distally and directly towards stimuli (e.g., VEGF released by FLS within the synovium) to sustain their continuity from the existing vessels. Sprouting ECs form tubules, which are then stabilized by mural cells (e.g., pericytes and smooth muscle cells) to provide structural support before blood flow.[56] Generally, ECs in RA undergo enhanced proliferation, leading to an increased microvessel density in the inflamed synovium.[9] Ultrasound assessment of synovial tissue also showed an increase in synovial vascularity during the initial stages in patients with RA, which correlated with increased expression of angiogenic factors such as VEGF-A, Ang-2, and Tie2.[57]

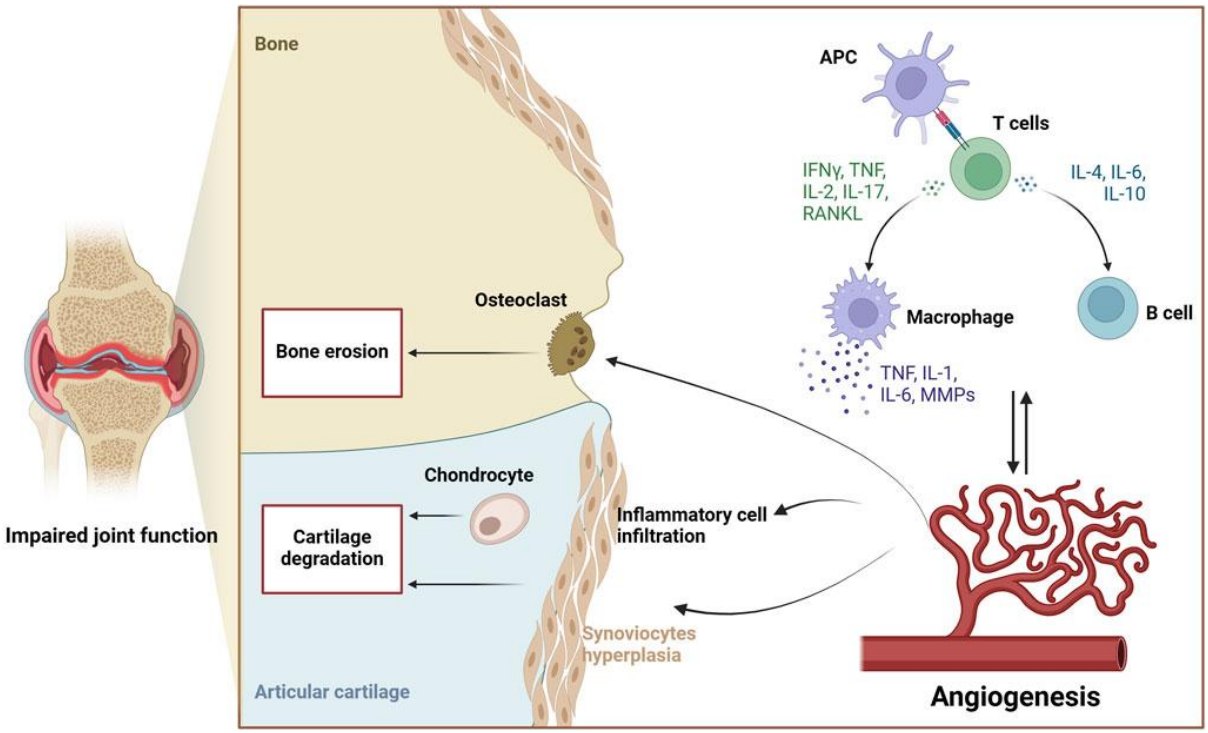

Figure 3. Mechanisms underlying synovial angiogenesis in rheumatoid arthritis. Synovial inflammation begins with the activation of immune cells (T and B cells) that secrete pro-inflammatory cytokines (e.g., TNF-α and interleukins) within the synovial lining, stimulating fibroblast-like synoviocytes (FLS) and macrophages. Activated FLS secrete growth factors (e.g., VEGF), promoting endothelial activation and driving synovial angiogenesis during inflammation, which together with synoviocyte hyperplasia contributes to cartilage damage and bone erosion. Reproduced from Gao et al.[48] under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

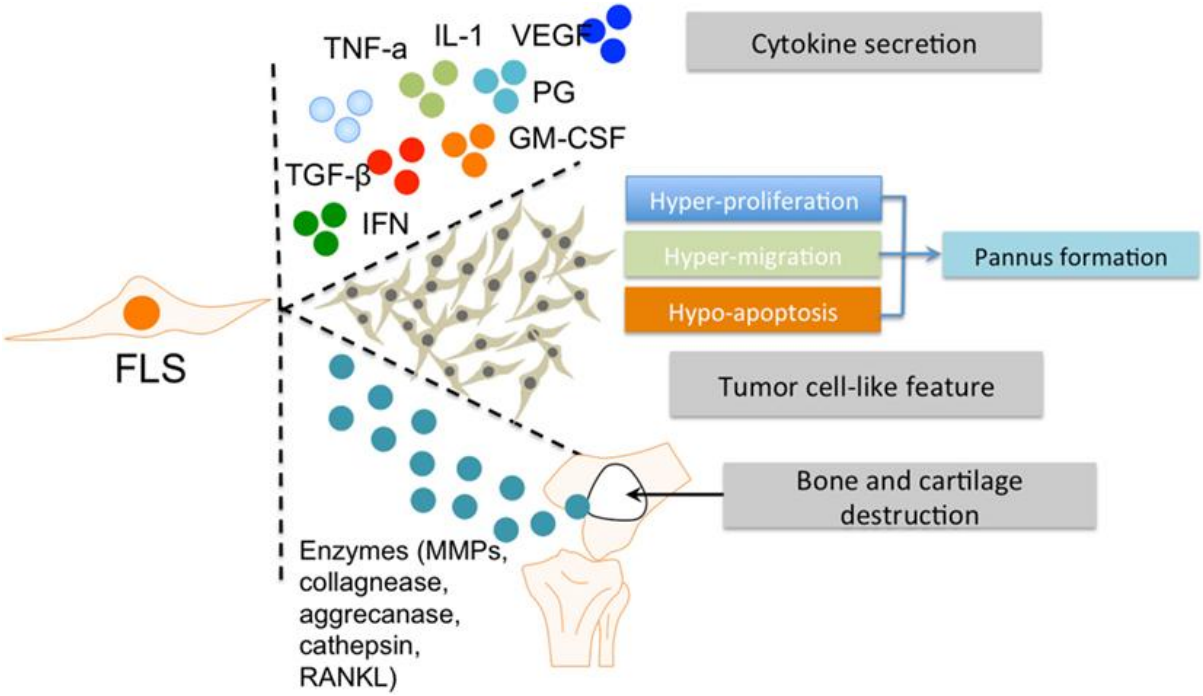

Figure 4. Mechanisms and consequences of FLS activation in RA. FLS are involved in many pathological aspects of RA by promoting synovitis, pannus growth, and cartilage/bone destruction. Reproduced from Tu et al.[54] under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

Signal transduction in RA

Recent studies dissecting signal transduction mechanisms have enhanced our understanding of RA pathogenesis and its potential therapeutic targets.

Vascular endothelial growth factor (VEGF) axis

Vascular endothelial growth factor (VEGF), a growth factor that primarily targets ECs, is well recognized for its role in angiogenesis in RA.[58] The VEGF family consists of five members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PLGF). These VEGF ligands activate intracellular signaling pathways by binding to VEGF receptors on the cell surface. Vascular endothelial growth factor receptors are tyrosine kinase receptors (RTKs) with three isoforms: VEGFR-1, VEGFR-2, and VEGFR-3.[59] Their binding interactions are influenced by proinflammatory cytokines and hypoxia.[60] The binding of VEGF ligands to different VEGF receptors has various functions. For instance, VEGF-A, VEGF-B, and PLGF bind to VEGFR-1 to stimulate monocyte migration and have a proper vasculature organization. Whereas VEGF-C and VEGF-D binding to VEGFR-3 primarily regulates lymphangiogenesis. VEGF-A signaling via VEGFR-2 is essential for the pleiotropic characteristics of ECs during angiogenesis.[61] VEGF-A is activated by hypoxia-inducible factor (HIF)-1α gene transcription during synovial hypoxia in RA.[28] Upon binding of VEGF-A to VEGFR-2, the receptor undergoes autophosphorylation of tyrosine residues, including Y951, Y1175, and Y1214. The phosphorylated tyrosine residues bind and activate intermediate proteins to induce numerous cellular responses.[62] For example, the phosphorylated Y951 (pY951) recruits T-cell-specific adapter protein (Tsad) to activate Src; this process then activates molecules linked to cell adhesion, vascular permeability, and cell survival by engaging the PI3K/AKT pathway. Phosphorylated Y1175 (pY1175) recruits Src Homology-2 domain-containing protein B (SHB), which subsequently triggers the activation of focal adhesion kinase (FAK), facilitating cell attachment and migration. Furthermore, pY1175 activates Ca2+ dependent pathways by engaging PLCγ1, which subsequently governs the transcriptional processes involved in cell proliferation and migration.[61] The dominance of VEGF-A in regulating angiogenesis in RA, as shown in Figure 5, makes it the most critical therapeutic target.[63]

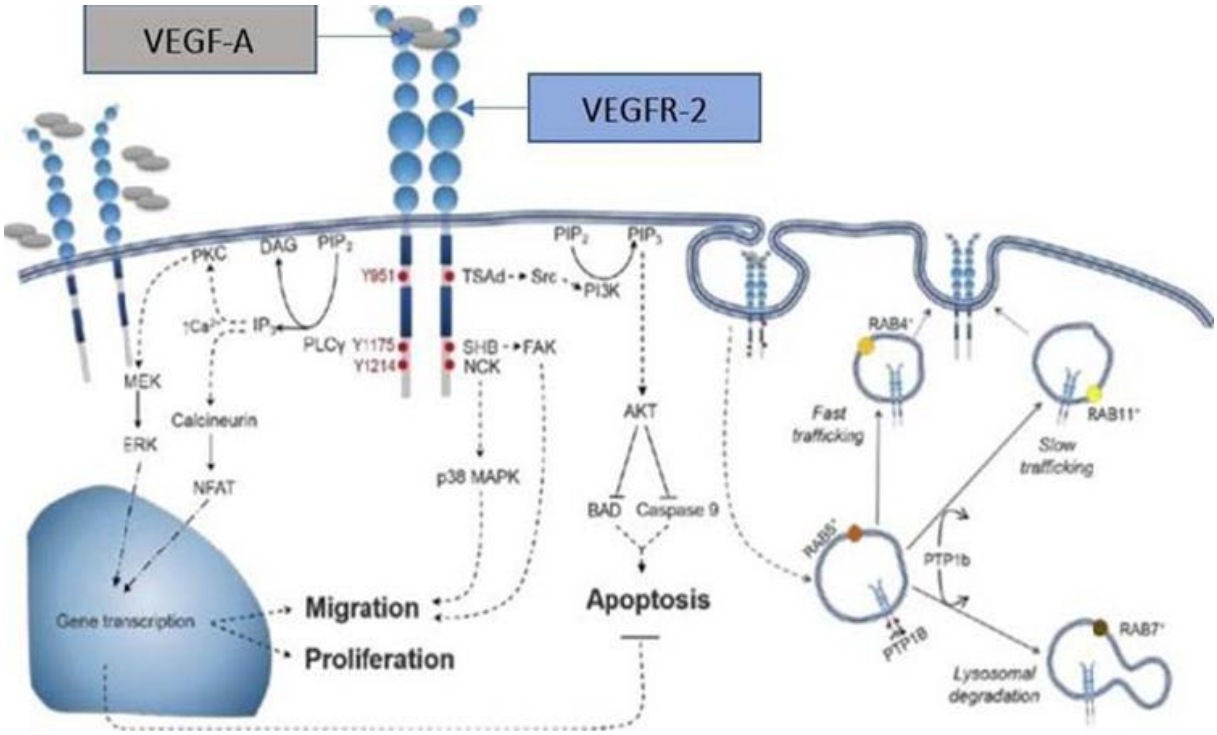

Figure 5. The pathways for VEGFR-2 signal transduction and trafficking are facilitated by VEGF-A (depicted in gray). The dashed lines indicate signaling pathways that include additional components such as other adaptor proteins or indirect signaling routes, which are omitted for brevity. In contrast, the solid lines denote direct signaling pathways. The blue arrows illustrate the paths through which receptors are trafficked for recycling and degradation. Adapted from Peach et al.[61] under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

The diagram shows how signaling pathways function when adaptor proteins are attached to key tyrosine phosphorylation sites. When Y951 is phosphorylated, it attracts TSAd, which binds to and activates Src. Src affects the molecules involved in cell adhesion, blood vessel permeability, and cell survival via the PI3K/AKT pathway. The pY1175 site attracts SHB, which activates FAK, and is important for cell attachment and movement. SHB also activated PI3K/AKT. Additionally, pY1175 attracts PLC, which initiates Ca2+-dependent signaling, leading to the control of cell growth and movement. Cell movement is also controlled by binding of NCK to pY1214, which activates p38MAPK. When VEGFR-2 is activated, it promotes its internalization, and signaling continues inside the endosomes. After entering RAB5+ sorting endosomes, VEGFR-2 can return to the cell surface through RAB4+ endosomes for fast signaling or Rab11+ endosomes for slow signaling limited by PTP1b. Alternatively, VEGFR-2 may have undergone lysosomal degradation in Rab7+ endosomes.

The phosphatidylinositol 3-kinase (PI3K)/ protein kinase (AKT) signaling pathway

The PI3K/AKT pathway, downstream of VEGF-A and VEGFR-2 signal transduction, is a critical regulator of cell proliferation, survival, metabolism, and angiogenesis.[64] Direct binding of PI3K to pY1175 on VEGFR-2 phosphorylates PI3K from phosphatidylinositol bisphosphate (PIP2) to generate phosphatidylinositol triphosphate (PIP3). Phosphorylation of PI3K, together with phosphorylation by 3-phosphoinositide-dependent protein kinase 1 (PDK1), activates AKT, the central sensor of the PI3K pathway.[65] Activated AKT can phosphorylate mTOR to either activate mammalian target of rapamycin complex 1 (mTORC1) directly or indirectly by phosphorylating tuberous sclerosis complex 2 (TSC2) towards the activation of mTORC1.[66] mTOR signaling is the net effector of AKT, resulting in protein synthesis related to the aforementioned cellular processes, as illustrated in Figure 6.[67]

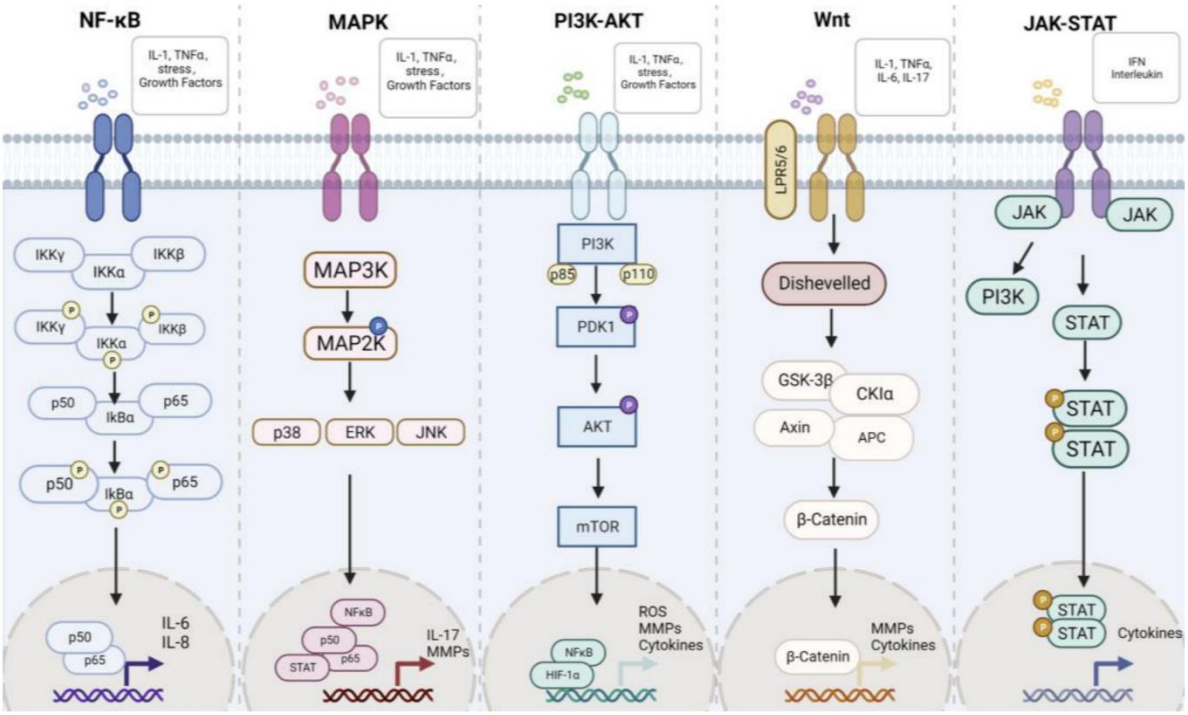

Figure 6. The main signaling pathways in rheumatoid arthritis: NF-κB, MAPK, PI3K/AKT, Wnt, JAK/STAT. Reproduced from Zhu et al.[67] under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)

Active PI3K/AKT signaling is constitutively observed in ECs and FLS during RA pathogenesis.[68] Li et al.[69] demonstrated that HIF-1α regulates the migration and invasion of FLS via the activation of PI3K/AKT signaling. In addition, PI3K/AKT upregulation promotes synovial hyperplasia through increased proliferation and survival of FLS.[68] PI3K/AKT inhibitors such as baicalein have been shown to inhibit cell viability and induce apoptosis in hypoxic RA-FLS.[70] Therefore, inhibition of PI3K/AKT, a critical regulator of angiogenesis, could significantly affect RA pathogenesis.

Nuclear factor-kappa B (NF-κB) pathway

Nuclear factor-kappa B is a transcription factor that is involved in inflammatory arthritis.[71] It exists as either a homo- or heterodimer and comprises NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB, and c-Rel proteins.[72] Nuclear factor-kappa B is activated by multiple stimuli, including cytokines (e.g., TNF-α and IL-1β), microbial components, and environmental stress.[73] The canonical (classical) and noncanonical (alternative) pathways are two distinct pathways that lead to NF-κB activation. The canonical pathway for chronic inflammation in RA is well-established.

In general, inactive NF-κB is sequestered in the cytoplasm by an inhibitor of nuclear factor-kappa B (IκBα) protein. During cell activation, IκBα undergoes degradation mediated by IκB kinases (IKKs), leading to the translocation of NF-κB dimers (p50-p65) into the nucleus to regulate gene transcription [74], as illustrated in Figure 6. Nuclear factor-kappa B, found in rheumatoid synovium, plays a role in controlling the transcription of numerous pro-inflammatory genes. These genes include those encoding cytokines such as TNF-α, IL-1, and IL-6, as well as chemokines, adhesion molecules, and proteins involved in angiogenesis.[75] Blocking the NF-κB pathway suppresses the production of various pro-inflammatory cytokines, such as IL-1, TNF-α, IL6, IL-8, ICAM-1, and VCAM-1, which play a role in synovitis.[76] Moreover, the NF-κB pathway is critical for the proliferation and survival of FLS, as demonstrated in several studies.[74] The central role of NF-κB in regulating gene transcription and survival of FLS in RA has made it an active target for the development of inhibitory agents such as TNF-α and interleukin antagonists.[77]

Mitogen-activated protein kinase (MAPK) pathway

Mitogen-activated protein kinase signaling cascades comprise three groups of protein kinases: extracellular signal-regulated kinase1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38.[78] ERK1/2 in MAPK signaling is activated upon stimulation by tyrosine kinase receptors (RTKs), which primarily regulate cell proliferation and differentiation.[79] ERK1/2 is activated through phosphorylation of mitogen-activated protein kinase (MEK)1/2, an effector of upstream MAPKKK activation (represented by Raf).[80] Upon translocation into the nucleus, activated ERK phosphorylates its downstream substrates to induce gene transcription and cellular function, as illustrated in Figure 6.

In the ERK pathway, Cdk2 regulates cell proliferation, which is also associated with Cyclin E and Cyclin A regulates the cell cycle.[81] The deregulated ERK pathway, which is well established in human cancers,[82] has also been implicated in RA.[83] Research has shown that the activation of ERK and JNK plays a role in the heightened expression of proinflammatory cytokines such as IL-6, IL-1β, and TNF-α in FLS.[84] JNK, which is activated by upstream MAPKKK effectors including MEKK, mixed lineage protein kinase, ASK, TAKI, and Tpl2, regulates cell proliferation and differentiation. The activation of JNK, together with the ERK pathway, can stimulate c-Jun, a crucial component of activator protein-1 (AP-1), through the influence of elevated pro-inflammatory cytokines, such as TNF-α and IL-1. Once activated, c-Jun can increase the production of enzymes, such as MMP-13, which contribute to the degradation of cartilage and joint erosion.[85]

p38 MAPK is the downstream effector of MAPK signaling and consists of four isoforms: p38 MAPKα, -β, -γ, and -δ. TNF-α, IL-1, and IL-6 are major stimuli for p38 MAPK activation.[86] In the cytoplasm, p38 MAPK is activated by MKK3 and MKK6 and occasionally by MKK4 when the upstream MAPKKK is stimulated.[87] Activated p38 MAPK phosphorylates downstream substrates, resulting in gene transcription and cellular responses.[88] In mouse models, joint inflammation has been linked to the activation of p38 MAPK owing to the overexpression of systemic TNF-α.[89] Within synovial microvessels, VEGF leverages the p38 MAPK pathway to transmit growth-promoting signals to endothelial cells, thereby stimulating their proliferation. This function complements VEGF's vital roles in chemoattraction, vasodilation, and angiogenesis amid synovial inflammation.[90] Moreover, p38 MAPK influences NF-κB-driven transcription once it enters the nucleus,[74] thereby contributing to chronic inflammation.[90]

Wingless-related integration site (Wnt) signaling pathway

Wingless-related integration site proteins, encoded by 19 different genes in humans, are a family of highly conserved, cysteine-rich glycoproteins that act as potent angiogenic factors.[91] These Wnt ligands play critical roles in embryonic development and are involved in chronic inflammation, such as cancers and immune disorders.[92] Wnt proteins signal via two pathways: the canonical Wnt/β-catenin-dependent pathway and the noncanonical Wnt/β-catenin-independent pathway, by binding to cell surface co-receptors, such as a complex of Frizzled receptors and low-density lipoprotein receptor-related proteins 5 or 6 (LRP5/6), to activate gene transcription.[67] The Wnt1 class ligands, which include Wnt2, Wnt3, Wnt3a, and Wnt8a, signal through the canonical Wnt pathway,[93] playing a critical role in regulating cell proliferation, survival, and cell fate decisions.[94] In contrast, Wnt5a-type proteins, such as Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, and Wnt11, can initiate noncanonical Wnt signaling,[93] which governs processes such as cell division, polarity, and migration.[94]

Accumulating evidence suggests that the Wnt signaling pathway contributes to FLS activation, bone resorption, and joint damage in RA.[95] In the absence of canonical Wnt ligands, β-catenin levels are kept low in the cytosol by the β-catenin destruction complex, which includes glycogen synthase kinase-3β (GSK-3β), casein kinase Iα (CKIα), adenomatous polyposis coli (APC), and axin.[94] During cell activation, Wnt ligands bind to the co-receptor complex of Frizzled receptors and LRP5/6, and inhibit GSK-3β activity via the disheveled (Dvl) protein. This inhibition prevents β-catenin degradation, allowing it to enter the nucleus and regulate gene transcription (Figure 6).[67,94] β-catenin, a central protein in the canonical Wnt signaling pathway, serves dual roles in cell adhesion and transcription regulation, which may influence cartilage degradation.[96, 97] The canonical Wnt signaling positively influences the proliferation and activation of FLS,[97, 98] making it a potential therapeutic target in RA. In contrast to canonical

Wnt signaling, noncanonical ligands such as Wnt5a can promote an aggressive phenotype of RA FLS (enhanced migration and invasiveness), which occurs through the activation of the RYK receptor and involves the Wnt/$Ca2^{+}$ pathway, Rho/ROCK signaling, and downstream kinases such as p38 and ERK.[99]

JAK/STAT signal transduction pathways

Janus kinase/signal transduction and transcription activation (JAK/STAT) is a signal transduction pathway that integrates external stimuli into the nucleus for gene transcription.[100] Under physiological conditions, the JAK/STAT signaling pathway is strongly regulated by its negative regulators, including suppressor of cytokine signaling (SOCS), protein inhibitor of activated STAT (PIAS), and protein tyrosine phosphatases (PTPs).[101] Various pro-inflammatory cytokines (e.g., IL-4, IL-6, IL-7, IL-12, IL-15, and IL-21), interferon-gamma (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are responsible for regulating the immune response in RA, are dependent on JAK/STAT for biological outcomes such as cellular growth, survival, and differentiation.[102] Deregulated JAK/STAT signaling can lead to elevated levels of these pro-inflammatory cytokines, as commonly observed in rheumatoid synovium.[103]

Janus kinases are tyrosine kinases comprising four members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).[104] Ligation of cytokines, interferons, and growth factors to their respective receptors can activate JAKs.[105] Activated JAKs selectively associate with type I and type II cytokine receptors, leading to the phosphorylation and activation of cytoplasmic STATs. Once phosphorylated, STATs dimerize and translocate to the nucleus to initiate gene transcription (Figure 6).[106] The STAT family comprises seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6.[107] Although multiple ligands can activate a single STAT, certain cytokines can preferentially activate specific STAT molecules. For example, IFN-γ usually activates STAT1, whereas IL-4 is exclusive to STAT6. In contrast, IL-6 and IL-10 appear to favor the activation of STAT3.[108] Incidentally, these preferences create nonredundant biological roles.[109]

While STAT1 and STAT2 predominantly mediate the IFN-initiated JAK/STAT pathway and are closely associated with the immune response to infections,[110] other STATs are active in various cytokine-induced signaling pathways.[109] In contrast, STAT3 and STAT5 are typically associated with hematological disorders, solid organ malignancies, and autoimmune diseases.[111] As hypoxia is also a feature of inflamed synovium,[28] modulation of the JAK/STAT pathway could be another way to block aberrant cytokine signals in the pathophysiology of RA. Tofacitinib (selective JAK1 and JAK3 inhibitor), baricitinib (reversible inhibitor of JAK1 and JAK2), and upadacitinib (selectivity for JAK1) are among the JAK inhibitors approved by the FDA for the treatment of RA.[112-114] Other JAK inhibitors, such as GLPG0634 (JAK1, JAK2, and TYK2 inhibitors) and VX-509 (JAK3 inhibitor), are undergoing phase II clinical trials for the treatment of RA.[109]

Nano-targeted therapeutic strategies

Nanomedicines designed based on two key mechanisms—targeting activated stromal cells and targeting specific removal of pro-angiogenic mediators—hold promise for effectively inhibiting RA-associated angiogenesis at its source.[115] Different treatment approaches for RA are available depending on the disease's advancement and medical history. Although RA has no cure to date, its treatment goals are to reduce and manage pain and delay disease progression.[116] As treatments work efficiently at the onset of this disease, managing early signs is of great importance to benefit from each therapy.[117] In general, RA treatments range from conventional oral drug regimens to invasive procedures such as injections and surgery.

Surgery

Advances in surgical procedures have dramatically improved the clinical outcomes in most RA cases. Patients with advanced RA often require painful orthopedic procedures, including tenosynovectomy, osteotomy, and total joint arthroplasty. Despite improvements in clinical outcomes, these procedures do not spare management issues related to postoperative articular infections and delayed wound healing.[116]

Conventional drug therapies

Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., celecoxib, naproxen, and rofecoxib) are commonly used for early management of chronic pain secondary to inflammation.[118] These anti-inflammatory agents block the production of prostaglandins (PGs) by

inhibiting the cyclooxygenase (COX) pathway.[119] Celecoxib, the first approved selective COX-2 inhibitor for pain management, has improved clinical outcomes in early RA.[120] Despite their clinical effectiveness, NSAIDs are associated with major toxicities and risk of gastrointestinal, renal, and cardiovascular events.[121]

Patients with RA often receive multiple medications to control disease activity. Glucocorticoids (GCs) have been widely used to treat RA since the 1950s. These steroid hormones bind to glucocorticoid receptors and effectively suppress inflammatory mediators such as cytokines, chemokines, growth factors, and their receptors.[122] Synthetic GCs are administered via articular injections for local inflammation. Although GCs are more potent than NSAIDs, they cause greater side effects, including bone thinning, diabetes, and immunosuppression.[116] Although the clinical advantage of GCs is often less significant, these drugs, particularly prednisone, cause drug dependency.[123] Owing to their contraindications, these agents are deemed impractical for long-term treatment of RA.[90]

Therapeutic shift in RA: from conventional DMARDs to biologic, targeted synthetic DMARDs, and emerging nanoagents

The transition from NSAIDs to disease-modifying antirheumatic drugs (DMARDs), along with current biologic, targeted synthetic DMARDs[13], and nano-based therapies, has revolutionized the treatment of RA. DMARDs are immunomodulatory agents classified as conventional synthetic DMARDs (csDMARDs) (e.g., methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine), biologic DMARDs (bDMARDs) (e.g., infliximab, tocilizumab, and abatacept), and more recently targeted synthetic DMARDs (tsDMARDs) (e.g., tofacitinib, baricitinib, and upadacitinib),[112,124] and nano-based agents (e.g., ozoralizumab).[125] csDMARDs were the standard treatment for RA until recently, when bDMARDs, tsDMARDs, and nano-based agents were discovered, which altered the treatment approach to a treat-to-target strategy. The bDMARDs and tsDMARDs are typically chosen when csDMARD therapy fails,[124, 126] whilst emerging nano-based agents may enhance existing treatments.[125, 127-129]

Both bDMARDs and tsDMARDs are highly specific biological agents that target the immune pathways. bDMARDs are monoclonal antibodies targeting tumor necrosis factor (TNF)-α (anti-TNF-α, such as infliximab, adalimumab, and certolizumab) and interleukin (IL)-6 receptor (anti-IL6R, such as tocilizumab).[126,130] At present, bDMARDs are available as subcutaneous or intravenous injections, owing to their size (90,000–150,000 Da). These agents interact by binding to extracellular molecules (e.g., cytokine receptors and co-stimulating molecules) to activate or inhibit intracellular signaling.[13] In contrast, tsDMARDs are orally available small-molecule inhibitors of JAK (i.e., tofacitinib, baricitinib, and upadacitinib) with the ability to inhibit intracellular signaling components because they have a lower molecular weight than bDMARDs.[114,131] Tofacitinib (selectivity for JAK1 and JAK3) was the first tsDMARD approved in the United States (2012) and Europe (2017), followed by baricitinib (selectivity for JAK1 and JAK2) in 2018, and upadacitinib (selectivity for JAK1) in 2019.[112] JAK inhibitors have efficacy and safety profiles comparable to those of bDMARDs.[113, 114]

Although the approval for bDMARDs and tsDMARDs is primarily for monotherapy, in some cases, their combined use with csDMARDs presented better clinical outcomes. In recent years, treatment with either bDMARDs or tsDMARDs in combination with csDMARDs, particularly methotrexate, has significantly improved radiographic progression, thereby affecting clinical remission (low disease activity).[114,132] However, the cost of combined therapy is high, and it is often prescribed only when the patient responds ineffectively to monotherapy.[132]

Recently, nano-based agents have offered new hope for refining the existing biological therapies for RA. Ozoralizumab, a next-generation anti-TNF-α nanoantibody, was the first TNF-α targeting nanoagent to be approved by Japan in September 2022.[125,133] This subcutaneously administered nanoantibody has a structure markedly distinct from traditional therapeutic antibodies, featuring a small molecular size (38 kDa), an albumin-binding domain that extends its plasma half-life for 4-week dosing intervals,[127] and a unique configuration that increases avidity.[133] This trivalent nanoantibody, using a variable heavy-chain format without Fc regions, can bind to multiple targets simultaneously.[125,133] In non-clinical studies, ozoralizumab showed rapid biodistribution into joints,[134] reduced Fcγ receptor-mediated inflammation,[135] and demonstrated high binding affinity to TNF-α.[136]

Findings from early proof-of-concept/dose-finding trials (NCT00959036; NCT01007175; NCT01063803) support its good efficacy and tolerability in patients with RA,[137,138] guiding the way for a long-term extension study on optimal dosing (NCT04077567; JapicCTI-194932).[123,127]

Most other nanotherapies for RA, however, are still in the preclinical or early developmental stages. These include nano-based co-delivery systems (e.g., liposomes, polymeric nanoparticles, and gold nanoparticles),[129] immunomodulatory nano-preparations (e.g., RA-related self-antigens, nucleic acids, immunomodulators or cytokines, and telogenic nanoparticles),[128] and energy-conversion nanoparticles (e.g., light- or ultrasound-activated)[139], which have been demonstrated in animal models and/or laboratory settings. The currently approved bDMARDs, tsDMARDs, and nanoagent therapies for RA are summarized in Table 2.

Table 2. Currently approved bDMARDs, tsDMARDs, and nanoagents and their role in angiogenesis of rheumatoid arthritis

bDMARDs	Mechanism of action	Anti-angiogenic role in RA	References
Infliximab	TNF-α inhibition	Inhibition of serum VEGF levels in RA patients	Selaas et al. [140]
Golimumab	TNF-α inhibition	Inhibition of serum IL-6, TNFRII, MMP-3 level in RA	Doyle et al. [141]
Adalimumab	TNF-α inhibition	Inhibition of serum MMP-3 levels in RA patients	Hattori et al. [142]
Certolizumab	TNF-α inhibition	Suppression on endothelial cell activity by inhibiting TNF-α	Shu et al. [143]
Etanercept	TNF-α inhibition and TNF-β inhibition	Improved endothelial dysfunction in RA patients	Végh et al. [144]
Tocilizumab	IL-6 receptor inhibitor	Inhibition of IL-6 induced expression of TLR2, TNF-α, IL-1β, IL-8, MCP-1, VEGF, VCAM-1, and ICAM-1 in monocytes from RA patients	Ruiz-Limón et al.[145]
Abatacept	Inhibition of T cell activation by blocking CD80/CD86 receptor interaction with CD28	Reduction of proteasome immunosubunit β1i in T cells of patients with RA	Langdon et al.,[146] Ghannam et al. [147]
Anakinra	IL-1 receptor inhibitor	Angiogenesis inhibition in animal models	Cantatore FP et al. [10]
tsDMARDS			
Tofacitinib	Selective JAK1 and JAK3 inhibitor	Reducing hyperplastic intima, inhibiting T cell proliferation, and minimizing IFN-γ, IL-17, and IL-21	Hodge et al. [148]
Baricitinib	Reversible JAK1 and JAK2 inhibitors	Inhibition of IL-6, IL-22, IL-23, IFN-γ, IL-17 (evaluation in an animal model of arthritis and in cell-based assays)	Al-Salama et al. [149]
Upadacitinib	Selective JAK1 inhibitor	Inhibition of JAK1 signaling, and inhibition of IL-6 and IFN-γ mediated inflammatory responses	Duggan and Keam[112] Chaplin [131]
Filgotinib	ATP-competitive, reversible JAK1 preferential inhibitor	Selectively inhibits the activity of JAK1 (> 5-fold higher potency) over JAK2, JAK3 and TYK2	Guo et al. [151]
Nanoagents			
Ozoralizumab	TNF-α inhibition	Inhibition of TNF-α activity	Keam, [125] Ishiwatari-Ogata et al. [136]

Limitations of current therapies

Despite the advancements in current therapies, several shortcomings have emerged. While some patients reported benefiting from the prescribed treatments, others experienced a risk of toxicity and intolerance.[113] Approximately one-third of patients have also been reported to be less responsive to drugs, particularly those prescribed TNF inhibitors, such as etanercept, infliximab, and adalimumab.[14] Indeed, patient responses to these agents are not uniform, with considerable variability in efficacy and toxicity.[151] Undoubtedly, individualized therapy via the concept of pharmacogenomics has better promise for selecting medications and dosages precisely for individual patients. Unfortunately, at present, pharmacogenetic/pharmacogenomic tests are not commonly conducted because of several factors, including the variability of RA, limited understanding of the disease pathogenesis, small sample sizes, and other non-genetic factors (such as demographic, environmental, clinical, or serological markers) that may affect or predict a drug's effectiveness or toxicity in patients with RA.[152] As both bDMARDs and tsDMARDs are immunosuppressants, opportunistic infections are another concern.[153,154] Regarding JAK inhibitors, the most current drugs for RA therapy, the risk of cardiovascular events, thrombosis, and malignancy have been reported.[155,156] Undeniably, prescriptions for these drugs should consider the increasing comorbidities among elderly patients. However, access to DMARDs varies according to demographic factors, socioeconomic status, and geographical location.[124] These limitations have encouraged investigations into innovative future therapeutic methods, especiallyfor patients who do not respond to current therapies. Nano-based technologies may improve existing treatments; however, most research remains primarily in the developmental stages.[128,129,139] Cell-based therapies and gene-editing technologies may offer opportunities for the implementation of personalized medicine in advanced RA treatment.[157]

CONCLUSION

Angiogenesis in RA involves multiple stromal cells and soluble factors. With the yearly increasing RA cases and recent findings indicating that 40% of RA cases can be linked to exposure to potentially modifiable factors, it is appropriate to prevent further disease development by considering the changes.[158] Moreover, owing to the highly varied nature of RA, creating a universally effective treatment plan is challenging, because of the ubiquitous fact that its symptoms and disease progression vary among RA patients. Consequently, developing personalized treatment plans for each patient could enhance the effectiveness and efficiency of medical strategies, thereby reducing the reliance on trial-and-error methods to determine suitable medications for individuals.

Conflict of Interest

On behalf of all the authors, the corresponding author states that there are no conflicts of interest.

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Authors Contributions

JB, MRMR, and RAH searched the literature. JB wrote the manuscript. RAH edited, reviewed, and supervised the study. All the authors have read and approved the final manuscript.

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During the preparation of this work, the author(s) used PAPERPAL to improve language and readability, with caution. After using this tool/service, the author(s) reviewed and edited the content as needed and took full responsibility for the publication's content.

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