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Review Article

RNAi-Loaded Nanocarriers Targeting the IL-6/JAK-STAT3-NF-κB Cytokine Axis in Rheumatoid Arthritis

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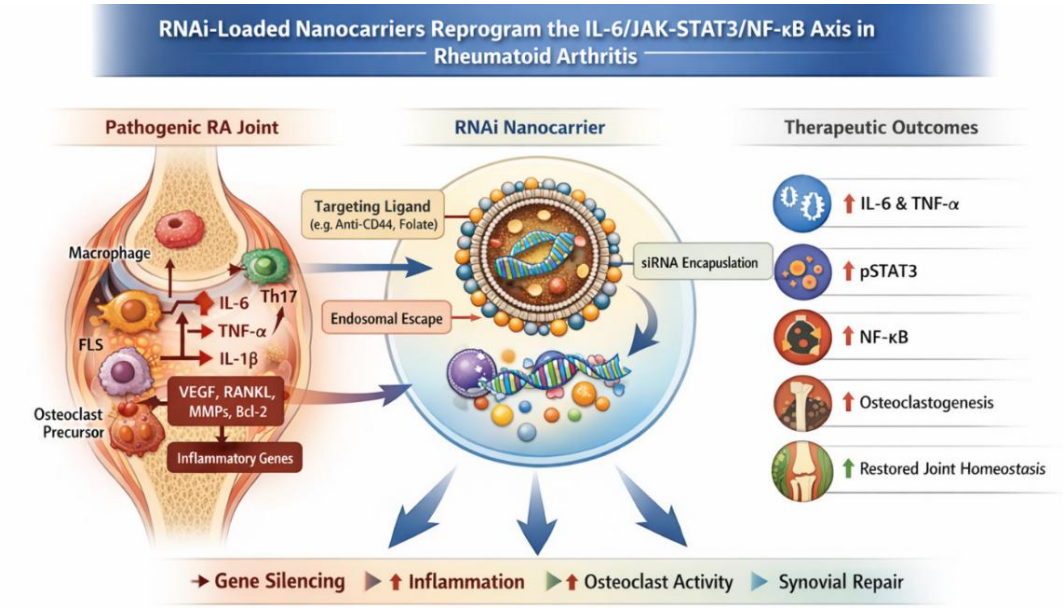
Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent synovial inflammation, progressive cartilage degradation, and bone erosion driven by complex cytokine-mediated signaling networks. Central to its pathogenesis is the dysregulated interplay of the interleukin-6 (IL-6)/Janus kinase (JAK)-signal transducer and activator of transcription-3 (STAT3) and nuclear factor kappa-B (NF-κB) pathways, which coordinate transcription of pro-inflammatory cytokines, angiogenic mediators, and osteoclastogenic factors. Conventional therapeutic strategies, including biologics and small-molecule inhibitors, primarily target extracellular mediators and often fail to adequately suppress intracellular signaling redundancy, leading to incomplete or transient clinical responses. RNA interference (RNAi) has emerged as a promising gene-silencing approach capable of selectively downregulating disease-driving transcripts at the post-transcriptional level. However, the clinical translation of RNAi is limited by instability, poor cellular uptake, and rapid degradation of naked small interfering RNA (siRNA). Nanocarrier-based delivery systems provide a transformative solution by protecting siRNA, enhancing pharmacokinetics, enabling targeted delivery to pathogenic cells, and facilitating cytoplasmic release through stimuli-responsive mechanisms. These RNAi-loaded nanoplatforms can simultaneously modulate multiple inflammatory nodes, reprogram immune-cell behavior, attenuate oxidative stress, and inhibit osteoclast genesis, thereby addressing RA as a systems-level disease. Furthermore, advances in precision targeting and multifunctional nanotechnology highlight the broader applicability of this strategy to other cytokine-driven disorders. Despite existing translational challenges, RNAi nanomedicine represents a paradigm shift toward network-oriented, gene-level therapeutics with the potential to achieve durable immunomodulation and disease modification in rheumatoid arthritis.

Keywords: Inflammation; JAK-STAT3 signaling; nanocarriers; NF-κB; RNA interference; rheumatoid arthritis

Graphical abstract



Highlights

- RNA interference enables sequence-specific silencing of pro-inflammatory genes driving rheumatoid arthritis pathogenesis at the post-transcriptional level.
- The IL-6/JAK-STAT3/NF-κB signaling axis functions as a central regulatory network controlling cytokine amplification, synovial hyperplasia, and osteoclast genesis.
- Nanocarrier-based delivery systems overcome major limitations of naked siRNA, including enzymatic degradation, poor cellular uptake, and rapid systemic clearance.
- Targeted nanoparticles facilitate selective gene silencing in macrophages, fibroblast-like synoviocytes, and osteoclast precursors within inflamed joints.
- Stimuli-responsive nanoplatforms enable microenvironment-triggered release of siRNA, improving therapeutic precision and minimizing off-target effects.
- RNAi nanomedicine provides systems-level immunomodulation by simultaneously regulating inflammatory signaling, immune-cell polarization, and metabolic reprogramming.
- This emerging therapeutic paradigm offers potential for durable disease modification and broader applicability to multiple cytokine-driven inflammatory disorders.

1. Introduction

1.1 Rheumatoid arthritis as a systems-level immune disorder

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation, pannus formation and progressive cartilage and bone erosion. Rather than being driven by a single cytokine or immune cell type, RA represents a systems-level disorder in which innate and adaptive immune responses converge within the synovial microenvironment to sustain chronic inflammation and structural damage.[1,2] Synovial macrophages, fibroblast-like synoviocytes (FLS), Th1/Th17 cells, B cells, dendritic cells, and osteoclast precursors interact through a complex cytokine network dominated by tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and interleukin-17 (IL-17).[1,3] Persistent activation of intracellular signaling cascades including the nuclear factor kappa-B (NF-κB), Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase/Akt (PI3K/Akt) pathways maintains transcriptional programs that promote inflammatory mediator production, angiogenesis, and osteoclast genesis.[2,4] Activation of pattern recognition receptors such as Toll-like receptors (TLRs) and cytokine receptors initiates phosphorylation cascades leading to IκB kinase (IKK) activation, degradation of IκBα, and nuclear translocation of NF-κB p65/p50 heterodimers. This results in transcription of genes encoding TNF-α, IL-6, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and adhesion molecules that perpetuate leukocyte recruitment and synovial hyperplasia.[2,5] Simultaneously, IL-6 binding to membrane-bound or soluble IL-6 receptor complexes triggers gp130-mediated activation of JAK1/JAK2, resulting in STAT3 phosphorylation, dimerization and nuclear translocation. STAT3 directly regulates transcription of vascular endothelial growth factor (VEGF), receptor activator of nuclear factor kappa-B ligand (RANKL), B-cell lymphoma-2 (Bcl-2) and matrix metalloproteinases (MMPs), thereby promoting angiogenesis, resistance to apoptosis, and bone resorption.[3,4] Crosstalk between NF-κB and STAT3 amplifies inflammatory gene expression and stabilizes pathogenic synoviocytes phenotypes, establishing a self-reinforcing cytokine amplification loop.[3] Thus, RA pathogenesis is best understood as a dysregulated transcriptional network rather than a linear inflammatory cascade, emphasizing the need for therapeutic strategies capable of modulating multiple intracellular signaling nodes simultaneously. Figures 1-3 collectively illustrate the immunopathogenic mechanisms and structural consequences of autoimmune joint disease. Figure 1 highlights T-B cell interactions that drive autoantibody production and pro-inflammatory cytokine release, promoting fibroblast and macrophage activation as well as RANKL-RANK-mediated osteoclast activation and bone resorption. Figures 2 and 3 depict the development of synovitis, characterized by inflammation and thickening of the synovial membrane, increased vascularity, and excess synovial fluid accumulation. Together, these processes lead to joint swelling, pain, cartilage degradation, and progressive bone erosion, ultimately resulting in structural joint damage.

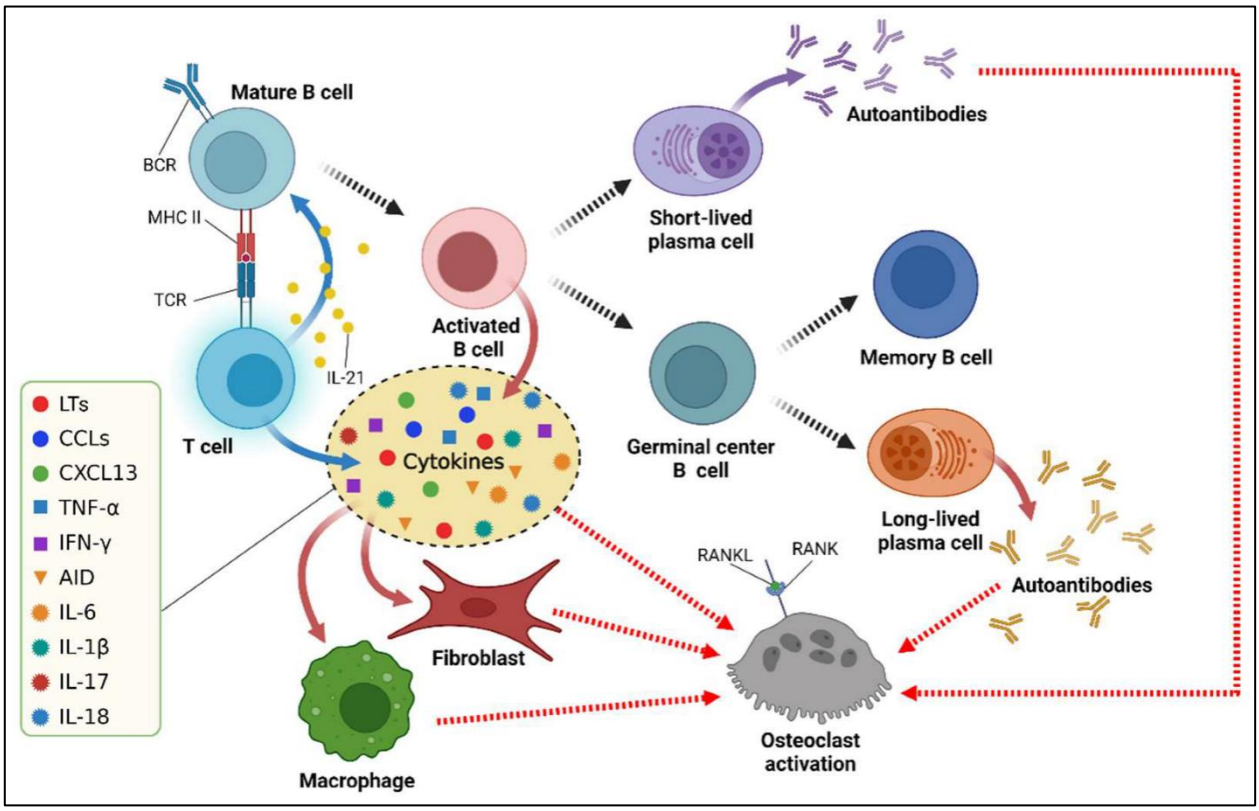


Figure 1: T-B cell interactions, cytokine networks and autoantibody-mediated osteoclast activation in autoimmune inflammation

(This schematic depicts T-B cell interactions driving autoimmune inflammation and bone destruction. Antigen presentation and IL-21 promote B cell activation, germinal center formation, and differentiation into plasma cells and memory B cells, leading to autoantibody production. Activated lymphocytes release pro-inflammatory cytokines that stimulate fibroblasts and macrophages, amplifying inflammation. RANKL-RANK signaling enhances osteoclast activation, resulting in bone resorption)

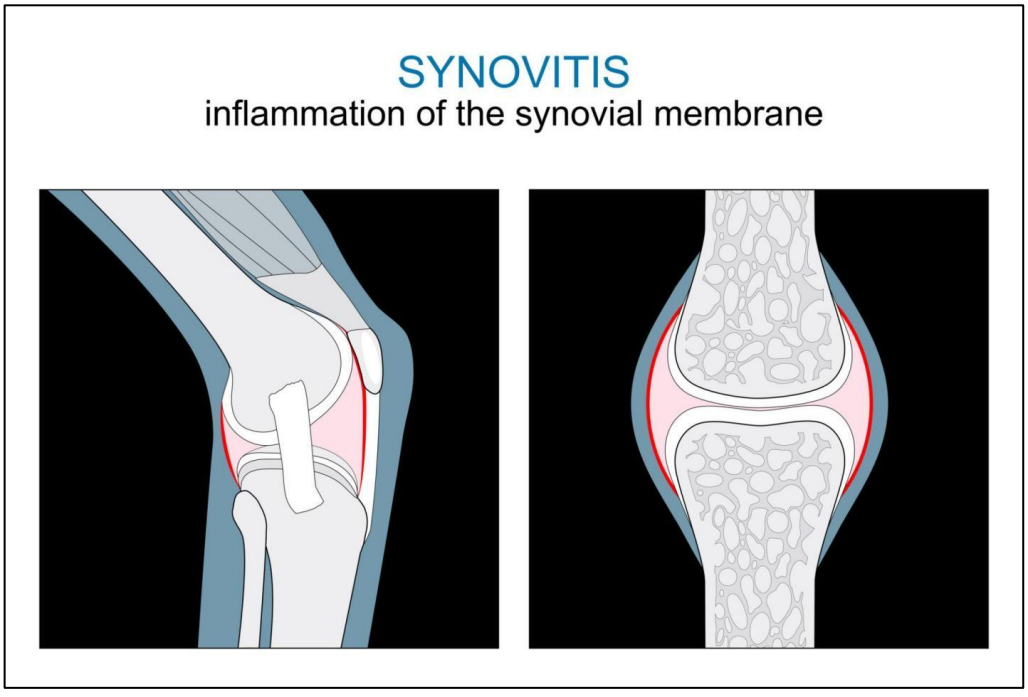


Figure 2: Synovitis: inflammation and thickening of the synovial membrane

(This figure illustrates synovitis, characterized by inflammation of the synovial membrane lining the joint capsule. The red-highlighted areas indicate synovial thickening and inflammatory infiltration surrounding the joint space. Inflammation leads to synovial hyperplasia, increased vascularity and excess synovial fluid production, resulting in joint swelling, pain and stiffness. Persistent synovitis can contribute to cartilage damage and progressive joint destruction)

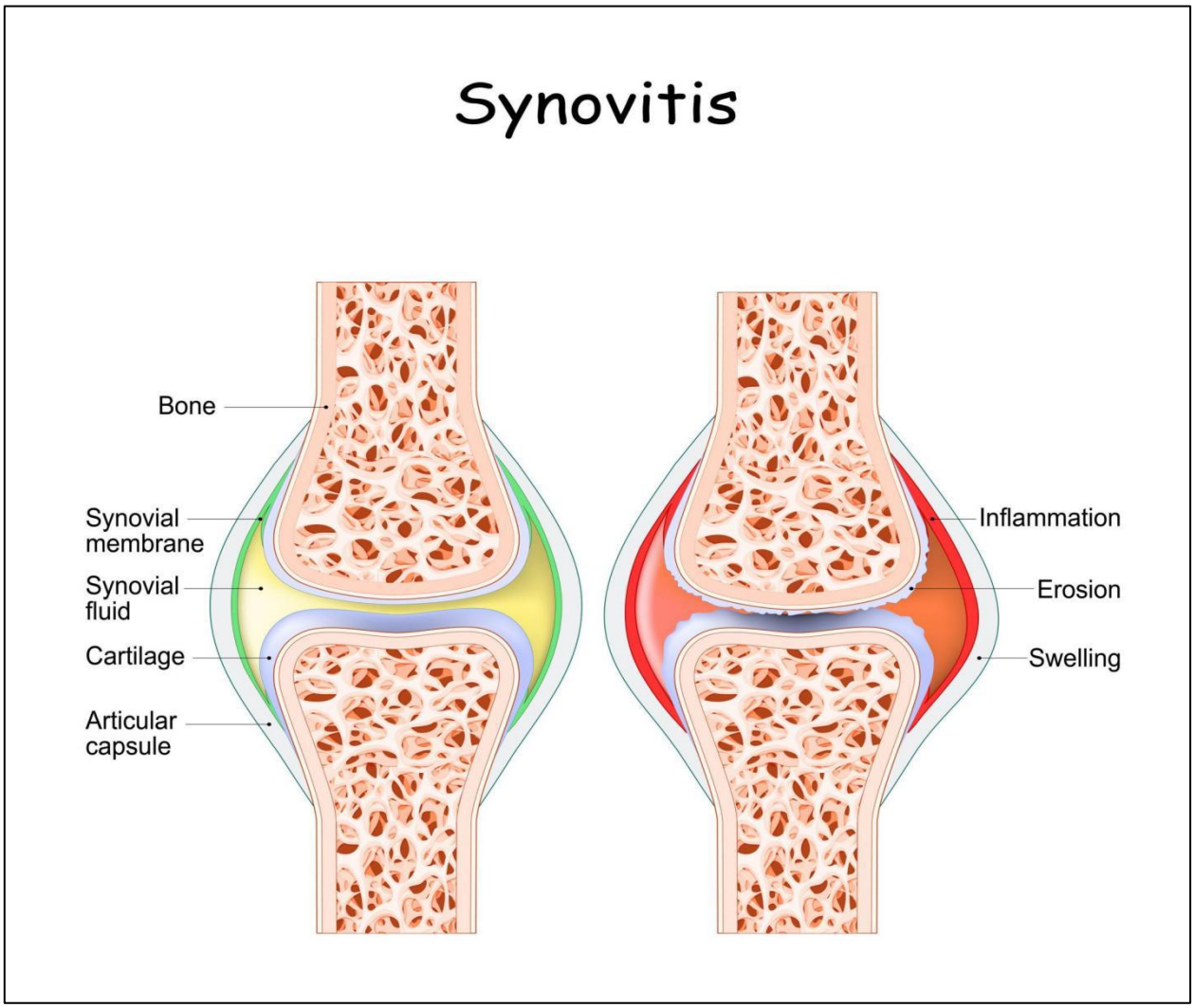


Figure 3: Structural changes in synovitis: from normal joint to inflamed joint

(This figure compares a healthy synovial joint (left) with a joint affected by synovitis (right). The normal joint shows intact bone, cartilage, synovial membrane, synovial fluid, and articular capsule. In synovitis, inflammation of the synovial membrane leads to synovial thickening, increased fluid accumulation (swelling) and progressive cartilage and bone erosion. These pathological changes contribute to joint pain, stiffness and structural damage)

1.2 Limitations of conventional therapies

Current therapeutic strategies for RA include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate, biologic agents targeting TNF-α or IL-6 receptors, and small-molecule JAK inhibitors 1,6. Although these therapies have significantly improved disease management, several limitations remain. First, extracellular cytokine neutralization does not completely suppress upstream intracellular transcriptional regulators, allowing residual inflammatory signaling to persist.[2,6] Second, biologics require chronic systemic administration, increasing the risk of infections and immunosuppression.[1] Third, therapeutic resistance may develop due to compensatory activation of parallel cytokine pathways, particularly involving IL-6/STAT3 and NF-κB signaling 3,6. Blockade of TNF-α alone may reduce NF-κB activation transiently but does not fully inhibit STAT3-mediated transcription or MAPK-dependent inflammatory gene expression.[4] Similarly, JAK inhibitors suppress STAT phosphorylation but may not adequately prevent NF-κB–driven transcriptional activity initiated by TLR or TNF receptor signaling.[5] This pathway redundancy reflects the interconnected architecture of inflammatory signaling networks in RA.Furthermore, systemic exposure to biologics lacks spatial precision, failing to selectively target pathogenic macrophages and FLS within inflamed synovial tissues.[7] Consequently, there is growing interest in gene-level therapeutic strategies that directly modulate intracellular signaling molecules responsible for cytokine production and inflammatory persistence.

1.3 RNA interference as a precision immunomodulatory strategy

RNA interference (RNAi) represents a post-transcriptional gene silencing mechanism mediated by small interfering RNA (siRNA), which guides the RNA-induced silencing complex (RISC) to complementary messenger RNA (mRNA) sequences, resulting in sequence-specific degradation [8]. This mechanism enables selective suppression of genes encoding pro-inflammatory cytokines (e.g., TNF-α, IL-6), signaling kinases (e.g., JAK2), and transcription factors (e.g., STAT3, NF-κB p65) that orchestrate RA pathogenesis[7,8]

At the molecular level, siRNA duplexes are incorporated into Argonaute-containing RISC complexes following cytoplasmic delivery. The antisense strand directs cleavage of target mRNA via endonucleolytic activity, reducing translation of pathogenic proteins.[8] Unlike monoclonal antibodies that neutralize secreted cytokines, RNAi allows upstream suppression of intracellular transcriptional programs, thereby disrupting cytokine amplification loops at their genetic origin[7] Importantly, RNAi offers the potential for multiplex gene targeting, enabling simultaneous modulation of multiple nodes within the IL-6/JAK-STAT3/NF-κB axis. Such combinatorial silencing strategies may overcome pathway redundancy and restore immune homeostasis within the inflamed synovium.[7] However, naked siRNA is rapidly degraded by nucleases and exhibits limited cellular uptake, necessitating the development of advanced nanocarrier systems for effective delivery.[8] Collectively, RNAi-based approaches represent a precision immunomodulatory strategy capable of reprogramming transcriptional networks underlying rheumatoid arthritis, offering a conceptual shift from cytokine neutralization to intracellular pathway engineering.

2. Molecular Pathophysiology of the IL-6/JAK-STAT3/NF-κB Axis in Rheumatoid Arthritis

2.1 Cytokine-Driven Synovial Microenvironment

The rheumatoid synovium represents a highly specialized inflammatory niche in which immune cells and resident stromal cells establish a self-sustaining cytokine network dominated by IL-6, TNF-α, and IL-1β. These mediators are produced primarily by activated macrophages and fibroblast-like synoviocytes (FLS), which acquire an aggressive, tumor-like phenotype characterized by hyperproliferation, resistance to apoptosis, and invasive behavior into cartilage and bone.[9] Persistent cytokine exposure induces epigenetic reprogramming of FLS, including histone acetylation and DNA hypomethylation at promoters of inflammatory genes, thereby stabilizing pathogenic transcriptional responses even in the absence of continuous immune stimulation.[10] This “imprinted” inflammatory memory is a hallmark of chronic RA and underlies disease persistence. At the cellular level, infiltrating Th17 cells further amplify inflammation through secretion of IL-17, which synergizes with TNF-α and IL-6 to enhance production of chemokines such as CCL2, CXCL8, and GM-CSF, promoting recruitment of additional leukocytes into synovial tissue.[9] These cooperative cytokine interactions form a feed-forward loop that continuously activates intracellular signaling pathways.

2.2 IL-6–Mediated JAK-STAT3 Signaling

IL-6 is a pleiotropic cytokine central to RA pathogenesis, acting through both classical signaling (membrane-bound IL-6 receptor) and trans-signaling (soluble IL-6 receptor), the latter greatly expanding the spectrum of responsive cells within the joint microenvironment.[11] Upon IL-6 binding, gp130 receptor homodimerization activates receptor-associated Janus kinases (JAK1/JAK2/TYK2), which phosphorylate tyrosine residues on gp130, creating docking sites for STAT3.STAT3 phosphorylation at Tyr705 leads to dimerization and nuclear translocation, where STAT3 binds γ-activated sequence (GAS) elements to regulate transcription of genes involved in:

- **Cell survival:** Bcl-2, Bcl-xL
- **Angiogenesis:** VEGF, HIF-1α
- **Osteoclasto genesis:** RANKL
- **Matrix degradation:** MMP-1, MMP-3, MMP-9

These gene products collectively drive synovial expansion, neovascularization, and cartilage destruction [11,12.] In addition, STAT3 promotes metabolic reprogramming toward aerobic glycolysis (Warburg-like metabolism) in synoviocytes, ensuring sustained ATP production required for inflammatory biosynthesis.[12]

2.3 NF-κB as a Master Transcriptional Regulator of Chronic Inflammation

NF-κB signaling is persistently activated in RA through stimulation of TNF receptor, IL-1 receptor, and Toll-like receptors by endogenous damage-associated molecular patterns (DAMPs) released from degraded cartilage. Canonical activation involves IκB kinase (IKKβ)–mediated phosphorylation and proteasomal degradation of IκBα, liberating NF-κB p65/p50 dimers to translocate into the nucleus.[13]

Within RA synoviocytes, NF-κB induces transcription of:

- Pro-inflammatory cytokines (TNF-α, IL-6)
- Enzymes mediating prostaglandin synthesis (COX-2)
- Adhesion molecules (ICAM-1, VCAM-1)
- Anti-apoptotic mediators (c-FLIP, XIAP)

This transcriptional program not only sustains inflammation but also confers apoptosis resistance, enabling accumulation of pathogenic FLS within pannus tissue.[13] Moreover, NF-κB signaling enhances expression of RANKL on stromal cells, directly linking inflammation to osteoclast-mediated bone erosion.

2.4 Crosstalk Between STAT3 and NF-κB Signaling

Rather than functioning independently, STAT3 and NF-κB form an integrated signaling module that cooperatively regulates inflammatory gene expression. STAT3 can prolong nuclear retention of NF-κB by promoting acetylation of RelA (p65) through recruitment of p300/CBP acetyltransferases, thereby sustaining transcriptional activity even after initial stimuli decline.[14] Conversely, NF-κB enhances IL-6 transcription, generating a positive feedback loop that continuously reactivates JAK-STAT signaling. This reciprocal reinforcement creates a chronic inflammatory circuit in RA in which IL-6/JAK-STAT3 signaling maintains NF-κB activation, while NF-κB drives further IL-6 production. Such bidirectional coupling explains why inhibition of only one pathway often yields incomplete therapeutic responses. Figures 1-3 depict the integrated molecular and cellular mechanisms

driving inflammation in rheumatoid arthritis (RA). TLR and cytokine receptor activation triggers SYK, NF-κB, and JAK/STAT signaling, leading to nuclear translocation of NF-κB and STAT3 and transcription of pro-inflammatory genes. These pathways amplify cytokine production, including TNF, IL-1, IL-6, IL-17, and IFN-γ. Within the RA joint, activated T cells, B cells, macrophages, and fibroblast-like synoviocytes sustain chronic inflammation, autoantibody formation, angiogenesis and MMP release. RANKL-mediated osteoclast activation promotes bone erosion. The figures also highlight therapeutic targets that interrupt these inflammatory cascades and cellular interactions.

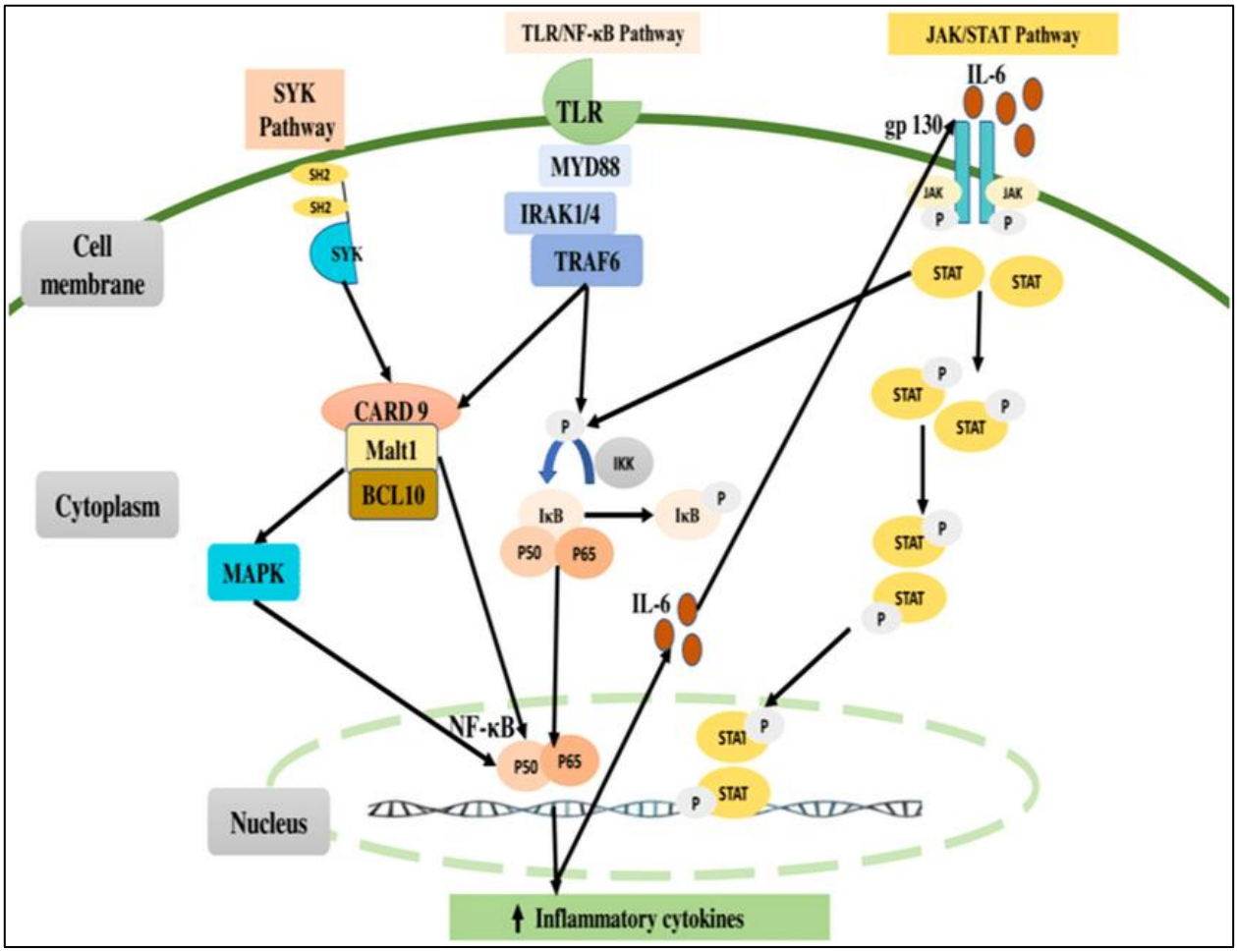


Figure 4: Crosstalk between SYK, TLR/NF-κB, and IL-6/JAK–STAT signaling pathways in the regulation of inflammatory cytokine production

(Schematic representation of SYK, TLR/NF-κB, and IL-6–mediated JAK/STAT signaling pathways and their convergence in promoting inflammatory cytokine expression. TLR activation signals through MYD88, IRAK1/4 and TRAF6 to activate IKK, leading to IκB phosphorylation and NF-κB (p50/p65) nuclear translocation. SYK signaling engages the CARD9-MALT1-BCL10 complex and MAPK to further enhance NF-κB activity. IL-6 activates the gp130/JAK complex, inducing STAT phosphorylation and nuclear translocation. These coordinated pathways culminate in the transcriptional upregulation of inflammatory cytokines)

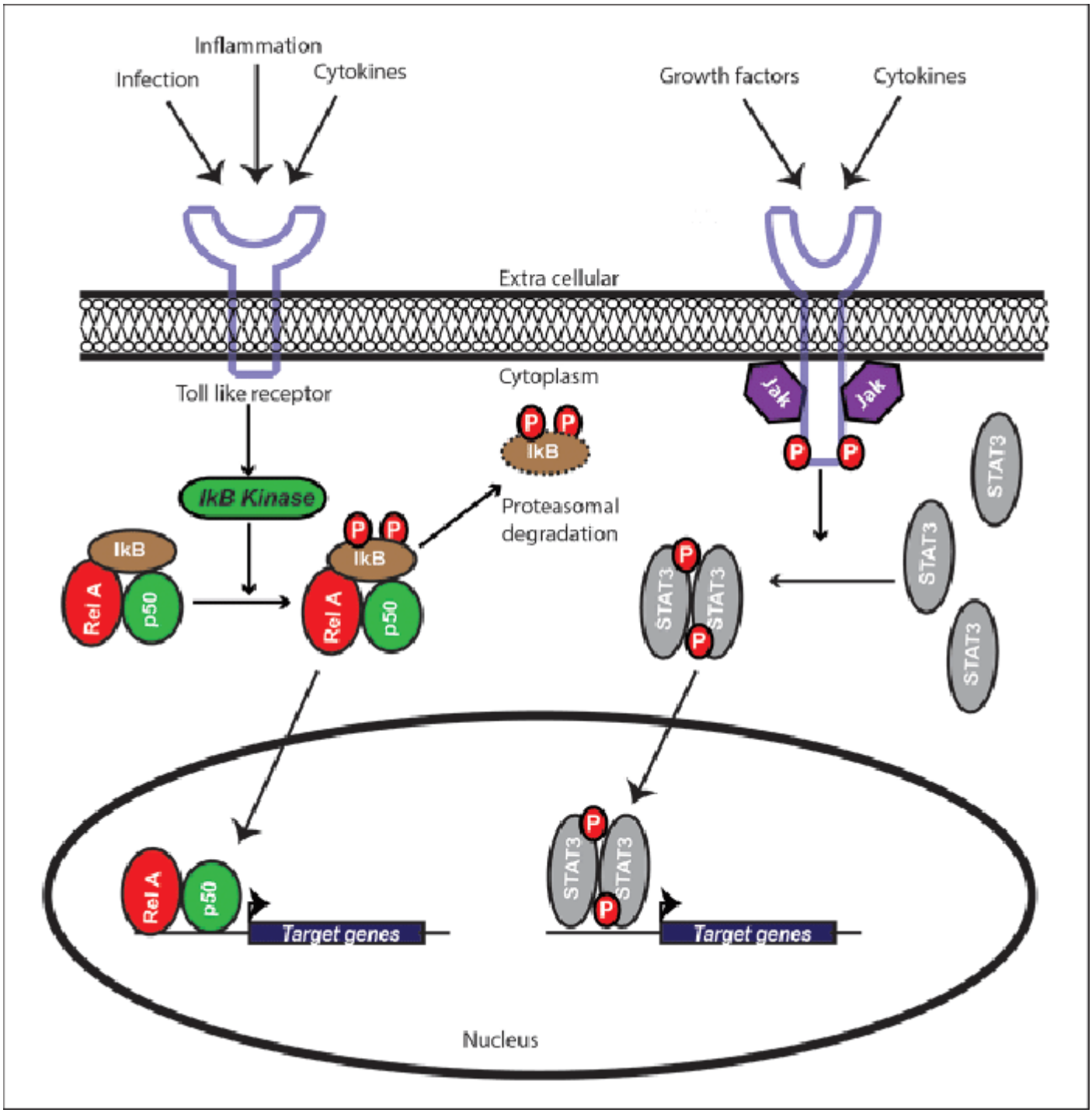


Figure 5: Activation of NF-κB and JAK/STAT3 signaling pathways in inflammatory and growth factor responses

(Diagram illustrating parallel activation of NF-κB and JAK/STAT3 signaling pathways. Toll-like receptor (TLR) engagement by infection or inflammatory cytokines activates IκB kinase (IKK), leading to phosphorylation and proteasomal degradation of IκB, which releases NF-κB (RelA/p50) for nuclear translocation and target gene transcription. In parallel, cytokines and growth factors activate receptor-associated JAK kinases, resulting in STAT3 phosphorylation, dimerization and nuclear translocation to regulate gene expression. Both pathways contribute to transcriptional activation of genes involved in inflammation and cellular responses)

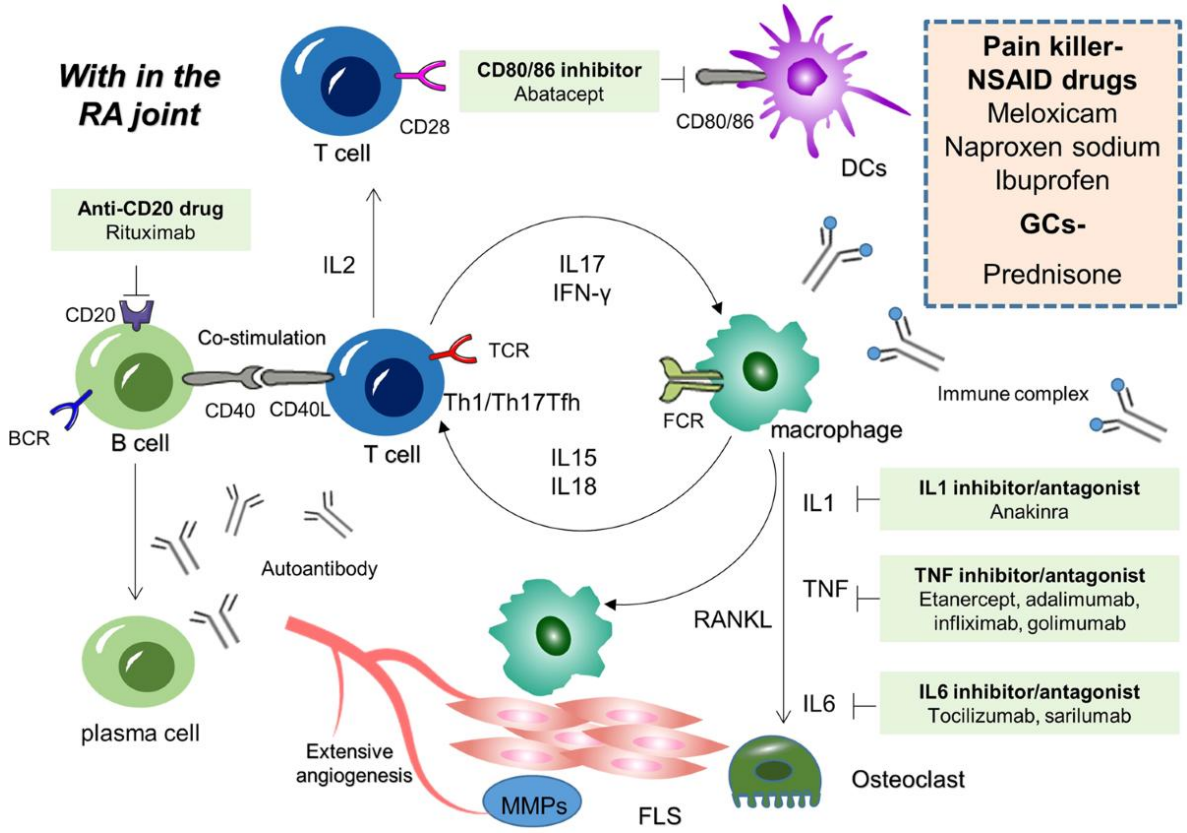


Figure 6: Immunopathogenesis of rheumatoid arthritis and therapeutic targets within the RA joint

(Schematic representation of immune cell interactions and cytokine networks driving inflammation and joint destruction in rheumatoid arthritis (RA). Activated T cells (Th1/Th17/Tfh) stimulate B cells, macrophages, and fibroblast-like synoviocytes (FLS), promoting production of IL-1, TNF, IL-6, IL-17, IFN-γ and autoantibodies. Immune complexes and RANKL-mediated osteoclast activation contribute to bone erosion, while MMPs and angiogenesis drive cartilage and synovial damage. The diagram highlights therapeutic targets, including anti-CD20 (rituximab), CTLA4-Ig (abatacept), IL-1 inhibitors (anakinra), TNF inhibitors (etanercept, adalimumab, infliximab, golimumab), IL-6 inhibitors (tocilizumab, sarilumab), NSAIDs and glucocorticoids)

2.5 MAPK and PI3K/Akt Amplification Pathways

Additional intracellular cascades-including MAPK (ERK, JNK, p38) and PI3K/Akt pathways-act as signal amplifiers downstream of cytokine receptors. Activation of p38 MAPK enhances transcription of MMPs and pro-inflammatory cytokines via AP-1 transcription factors, while PI3K/Akt signaling promotes cell survival and metabolic adaptation of synoviocytes.[10,15] These pathways also intersect with NF-κB signaling through phosphorylation of IKK and modulation of transcriptional co-activators, further stabilizing inflammatory gene expression. Importantly, MAPK-driven phosphorylation of transcription factors increases chromatin accessibility at cytokine promoters, reinforcing sustained inflammatory output.[15]

2.6 Osteoimmunological Consequences: Linking Inflammation to Bone Destruction

The IL-6/JAK-STAT3/NF-κB axis directly connects immune activation to skeletal damage through regulation of osteoclast differentiation. RANKL expression induced by STAT3 and NF-κB binds RANK receptors on osteoclast precursors, activating NFATc1, the master transcription factor of osteoclast genesis.[12] This leads to maturation of bone-resorbing osteoclasts and progressive erosion of subchondral bone, a defining pathological feature of RA. Simultaneously, inflammatory cytokines suppress osteoblast differentiation via inhibition of Wnt signaling, creating an imbalance between bone formation and resorption.[12] Thus, cytokine-driven intracellular signaling not only mediates inflammation but also orchestrates structural joint damage.

2.7 Implications for RNAi-Based Therapeutic Targeting

The central role of transcriptional regulators such as STAT3 and NF-κB makes them attractive yet traditionally inaccessible drug targets. Because these molecules function intracellularly and lack suitable ligand-binding pockets, RNA interference offers a rational strategy to directly silence their gene expression. Targeting multiple nodes within this interconnected signaling axis may disrupt the pathological feedback loops responsible for chronic inflammation and therapeutic resistance.

3. RNAi therapeutics targeting the cytokine axis

3.1 Gene silencing of pro-inflammatory cytokines

RNA interference (RNAi) has emerged as a powerful strategy to selectively suppress expression of genes encoding pro-inflammatory cytokines that drive

rheumatoid arthritis (RA) progression. Small interfering RNA (siRNA) molecules are typically 21-23 nucleotide double-stranded RNAs that, once delivered into the cytoplasm are incorporated into the RNA-induced silencing complex (RISC). The antisense strand guides Argonaute-2 (Ago2) to complementary mRNA transcripts, resulting in sequence-specific endonucleolytic cleavage and degradation, thereby preventing translation of pathogenic proteins.[16] In RA models, silencing of TNF-α, IL-1β and IL-6 transcripts has demonstrated significant attenuation of synovial inflammation, confirming that direct gene-level inhibition can suppress upstream inflammatory triggers rather than neutralizing cytokines after secretion.[17] This distinction is critical because intracellular mRNA degradation interrupts the cytokine production cycle at its source, preventing both autocrine and paracrine signaling amplification. Moreover, RNAi-mediated cytokine suppression reduces downstream activation of NF-κB and MAPK pathways, thereby exerting broader anti-inflammatory effects than single-cytokine biologics.[18] The figure mechanism for post-transcriptional gene silencing. The process is initiated when long double-stranded RNA (dsRNA) or hairpin precursors enter the cytoplasm and are processed by the Dicer-TRBP complex into short small interfering RNA (siRNA) duplexes, typically 19-23 nucleotides in length. These fragments are incorporated into the RNA-induced silencing complex (RISC), where the Argonaute (Ago) protein selects and retains a single guide strand. This guide strand directs the RISC to a complementary target messenger RNA (mRNA) molecule through specific hybridization. Once bound, the complex facilitates mRNA cleavage, decapping, and subsequent degradation, effectively preventing the translation of the transcript into a functional protein and "silencing" the expression of the target gene.

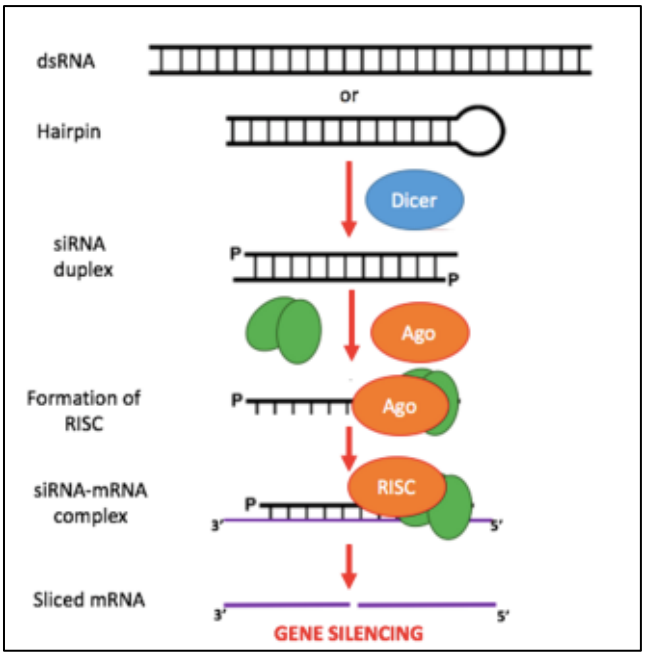


Figure 7: Mechanism of RNA interference (RNAi)-mediated gene silencing

(Schematic illustration of the RNA interference (RNAi) pathway. Double-stranded RNA (dsRNA) or hairpin RNA is processed by Dicer into small interfering RNA (siRNA) duplexes. The siRNA is incorporated into the RNA-induced silencing complex (RISC), where Argonaute (Ago) retains the guide strand. The siRNA-RISC complex binds complementary target mRNA, leading to mRNA cleavage and degradation, ultimately resulting in gene silencing)

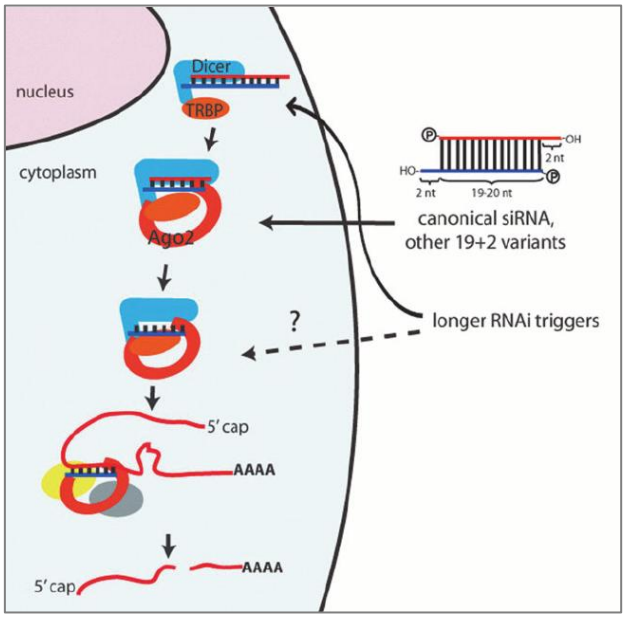


Figure 8: Dicer-TRBP-Ago2-mediated siRNA processing and mRNA cleavage in RNA interference

(Diagram illustrating cytoplasmic processing of canonical siRNA (19+2 nt) by the Dicer-TRBP complex and subsequent loading into Argonaute 2 (Ago2) to form the RNA-induced silencing complex (RISC). The guide strand directs RISC to complementary target mRNA, resulting in cleavage, decapping and degradation of the transcript. The figure also highlights the potential involvement of longer RNAi triggers in RISC loading and gene silencing)

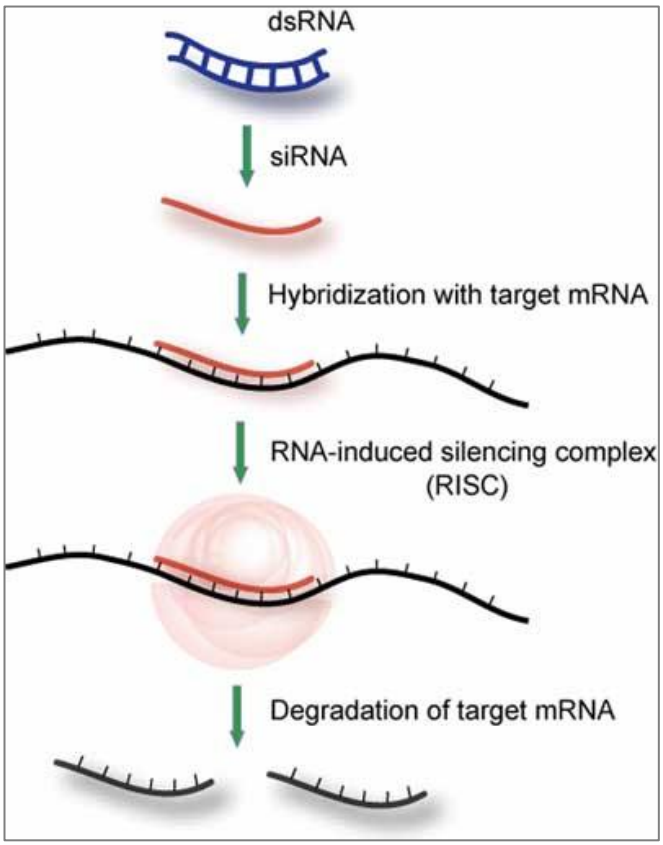


Figure 9: The mechanism of siRNA-mediated gene silencing

(The RNA interference (RNAi) pathway begins when long double-stranded RNA (dsRNA) enters or is produced within a cell and is processed into short small interfering RNA (siRNA) fragments. These siRNA strands then undergo hybridization, specifically binding to a complementary sequence on a target messenger RNA (mRNA) molecule. This binding recruits the RNA-induced silencing complex (RISC), a specialized protein assembly containing the enzyme Argonaute, which facilitates the targeted degradation of the mRNA. By cleaving the mRNA before it can be translated into a protein, the cell effectively "silences" the expression of that specific gene)

3.2 Targeting intracellular signaling molecules previously considered "undruggable"

Unlike monoclonal antibodies and receptor antagonists, RNAi technology enables therapeutic targeting of intracellular transcription factors and kinases lacking conventional ligand-binding domains. Key signaling mediators such as STAT3, IKKβ and JAK2 are particularly suitable RNAi targets because their sustained activation is essential for maintenance of RA pathology 19. Silencing STAT3 mRNA has been shown to downregulate transcription of VEGF, RANKL and anti-apoptotic proteins, thereby reducing angiogenesis and restoring apoptosis sensitivity in fibroblast-like synoviocytes. Similarly, knockdown of IKKβ disrupts phosphorylation of IκBα, preventing NF-κB nuclear translocation and halting transcription of inflammatory mediators.[18,19] These interventions effectively dismantle transcriptional feedback loops that cannot be adequately addressed by extracellular inhibitors.

3.3 Multi-gene silencing and network-level modulation

RA is characterized by redundancy among inflammatory mediators, meaning inhibition of a single cytokine often leads to compensatory activation of alternative pathways. RNAi provides the unique capacity for multiplex targeting through co-delivery of multiple siRNA sequences directed at different nodes within the IL-6/JAK-STAT3/NF-κB axis.[16] This combinatorial gene silencing approach allows simultaneous suppression of cytokines, receptors and transcription factors, thereby collapsing interconnected signaling networks. Experimental systems using dual-target siRNA constructs have demonstrated synergistic reductions in inflammatory mediator production compared with single-gene inhibition, underscoring the importance of pathway-level modulation in chronic autoimmune disease.[20]

3.4 RNAi-induced reprogramming of synovial cell phenotypes

Beyond cytokine suppression, RNAi therapeutics can alter the functional phenotype of key pathogenic cells within the rheumatoid joint. Macrophages exposed to siRNA targeting inflammatory mediators exhibit reduced M1 polarization markers (iNOS, IL-12) and increased expression of M2-associated markers such as arginase-1 and IL-10, indicating a shift toward a pro-resolving phenotype.[21] Similarly, silencing transcriptional regulators in fibroblast-like synoviocytes reduces their invasive capacity and limits secretion of matrix metalloproteinases responsible for cartilage degradation.[17] These findings suggest that RNAi therapy may not only suppress inflammation but also restore tissue homeostasis by reprogramming stromal and immune cell behavior.

3.5 Challenges associated with Naked RNAi therapeutics

Despite its specificity, naked siRNA faces several biological limitations that restrict clinical translation. Rapid degradation by serum nucleases, poor cellular internalization due to negative charge and hydrophilicity and activation of innate immune sensors such as Toll-like receptor-3 (TLR3) can reduce therapeutic efficacy and induce unintended immune responses.[16, 22] Furthermore, efficient RNAi requires cytoplasmic delivery; however, most internalized siRNA becomes trapped within endosomes and undergoes lysosomal degradation. This bottleneck known as the "endosomal escape problem", is one of the major barriers to successful gene silencing *in vivo*.[22] These challenges have driven the development of nanocarrier-based delivery systems designed to stabilize siRNA, facilitate cellular uptake, and ensure controlled intracellular release.

3.6 Rationale for integrating RNAi with nanotechnology

Nanotechnology-enabled delivery platforms provide structural protection against enzymatic degradation, enhance pharmacokinetics, and enable targeted delivery

to inflamed synovial tissue. By engineering nanoparticles capable of receptor-mediated uptake and endosomal escape, RNAi therapeutics can achieve efficient intracellular gene silencing with reduced systemic exposure.[23] Such integration of RNAi with nanocarriers transforms gene silencing into a viable therapeutic modality capable of modulating complex inflammatory networks at the molecular level. Consequently, RNAi nanomedicine is increasingly viewed as a next-generation strategy to overcome the limitations of protein-targeted therapies and enable precision treatment of rheumatoid arthritis.

4. Nanocarriers as enablers of RNAi therapy

4.1 Biological barriers limiting naked SiRNA delivery

The therapeutic translation of RNA interference is fundamentally constrained by biological barriers that hinder the stability and intracellular accessibility of naked siRNA molecules. Systemically administered siRNA is highly susceptible to rapid degradation by circulating RNases, resulting in plasma half-lives often measured in minutes.[24] Additionally, the strong negative charge and hydrophilicity of siRNA prevent passive diffusion across cellular membranes, necessitating active transport mechanisms for cytoplasmic delivery.[24,25] Following endocytosis, a major proportion of internalized siRNA becomes sequestered within endo-lysosomal compartments, where acidic conditions and nucleases promote degradation before engagement with the RNA-induced silencing complex (RISC). This phenomenon, widely known as the "endosomal escape barrier," represents one of the principal determinants of RNAi inefficiency *in vivo*.[25] Moreover, extracellular exposure of siRNA can activate innate immune receptors such as Toll-like receptors (TLR3, TLR7/8), triggering interferon responses that compromise safety and specificity.[26] These intrinsic limitations underscore the necessity of protective delivery vehicles capable of stabilizing siRNA and directing it toward target tissues.

4.2 Design Principles of Nanocarriers for RNAi Delivery

Nanocarrier systems are engineered to overcome pharmacokinetic and cellular barriers through structural encapsulation, electrostatic complexation or chemical conjugation of siRNA. These nanoscale constructs typically range between 20 and 200 nm, allowing them to evade renal clearance while facilitating preferential accumulation in inflamed tissues via enhanced vascular permeability.[27] Cationic lipids and polymers condense siRNA into nano-complexes through electrostatic interactions, shielding nucleic acids from enzymatic degradation and enabling cellular uptake via clathrin-or caveolae-mediated endocytosis. Once internalized, protonatable components within nanocarriers generate osmotic swelling (proton sponge effect), destabilizing endosomal membranes and releasing siRNA into the cytoplasm for gene silencing.[25,28] This controlled intracellular release is essential for efficient loading into RISC and subsequent mRNA cleavage.

4.3 Lipid-Based Nanoparticles: Clinically Advanced RNAi Delivery Platforms

Lipid nanoparticles (LNPs) represent the most clinically validated systems for nucleic acid delivery due to their biocompatibility, scalability, and ability to encapsulate RNA molecules efficiently. Ionizable lipids within LNPs remain neutrally charged at physiological pH but acquire positive charge in acidic endosomes, facilitating membrane fusion and cytoplasmic release of siRNA.[28] This pH-responsive behavior minimizes systemic toxicity while ensuring intracellular bioavailability. In inflammatory environments such as the rheumatoid synovium, LNPs can preferentially accumulate and deliver gene-silencing payloads to macrophages and fibroblast-like synoviocytes, enabling targeted modulation of IL-6/JAK-STAT3/NF-κB signaling pathways.[27]

4.4 Polymeric Nanocarriers and the Proton Sponge Mechanism

Polymeric nanocarriers, including polyethyleneimine (PEI), poly (lactic-co-glycolic acid) (PLGA), and chitosan-based systems, offer structural versatility and tunable degradation kinetics. These carriers often rely on the proton sponge effect, whereby buffering amine groups absorb protons within endosomes, leading to chloride ion influx, osmotic swelling and rupture of the vesicular membrane.[25,29] This mechanism enhances cytoplasmic delivery efficiency and has been shown to significantly increase gene knockdown compared with free siRNA. Furthermore, biodegradable polymers enable sustained release kinetics, allowing prolonged silencing of inflammatory genes within diseased joints.[29] Efficient intracellular delivery of genetic therapeutics requires sophisticated nanocarriers, such as the functionalized lipid nanoparticles (LNPs) detailed in Figure 10, which utilize cationic and helper lipids for stability and targeting. Once internalized into late endosomes (pH 5.0–5.5), these carriers must bypass the endolysosomal barrier to reach cytosolic targets like the RISC complex. As shown in Figure 11 and Figure 12, this escape is achieved through diverse mechanisms including the proton sponge effect (osmotic rupture), physiochemical disintegration via pH-sensitive bond breakage, pore formation, and membrane fusion. By leveraging triggers such as V-type proton pump activity or ion-driven particle swelling, these pathways-further illustrated in Figure 13-ensure the successful translocation of siRNA or pDNA into the cytoplasm.

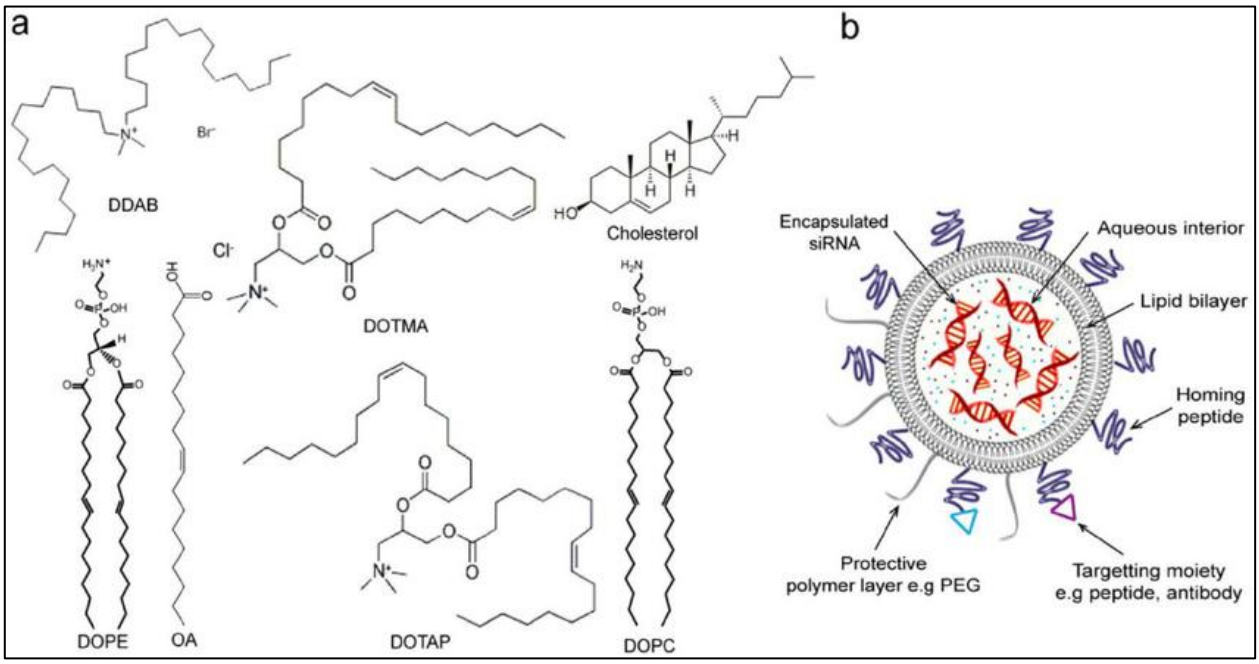


Figure 10: Structural components and architectural design of a functionalized liposomal nanocarrier

(This figure details the chemical and structural composition of a targeted lipid nanoparticle (LNP). Section (a) displays the molecular structures of cationic lipids (DDAB, DOTAP, DOTMA) for nucleic acid binding, neutral helper lipids (DOPE, DOPC) and cholesterol for membrane stability. Section (b) illustrates the final assembly: a multifunctional liposome encapsulating siRNA within an aqueous core, surface-modified with PEG for "stealth" circulation and specific ligands for cell-targeted delivery)

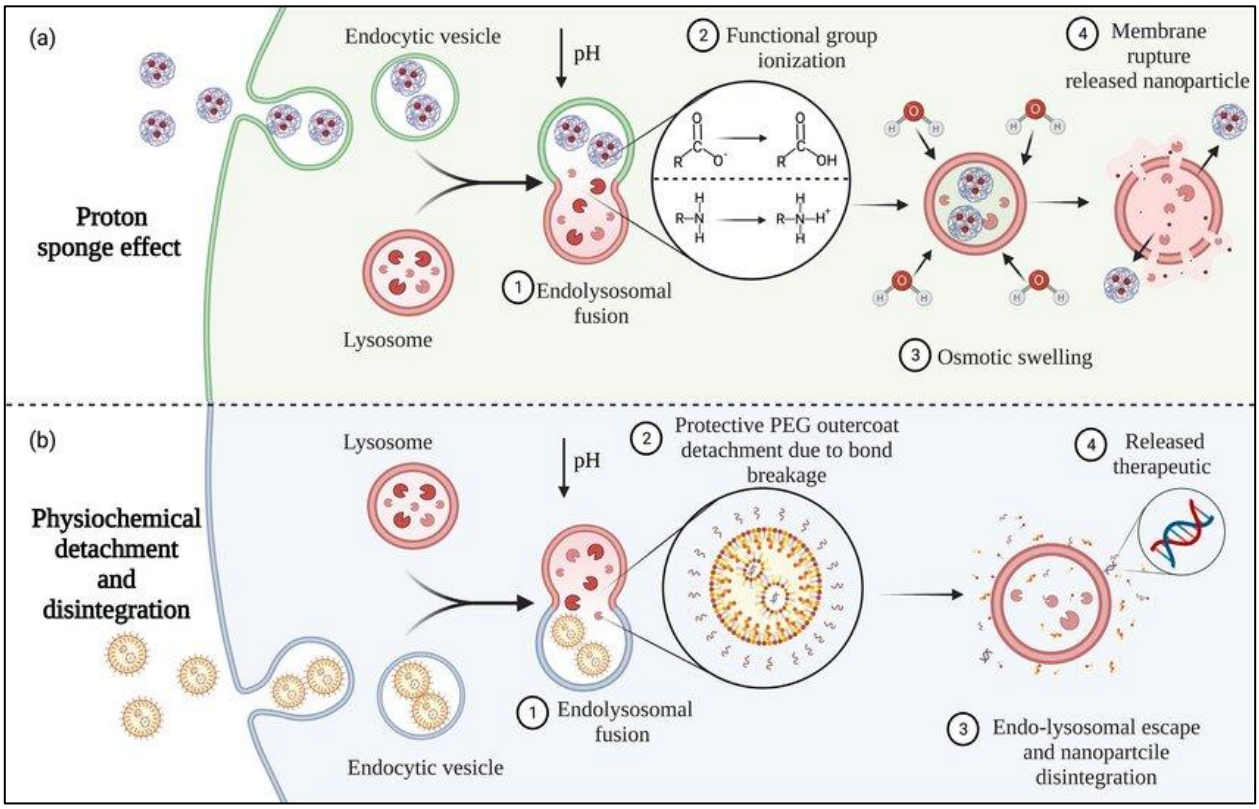


Figure 11: Mechanistic pathways for endosomal escape of nanoparticles

(This figure illustrates two mechanisms for endosomal escape: (a) the proton sponge effect, where polycationic nanoparticles buffer the acidic environment, triggering osmotic swelling and membrane rupture; and (b) physiochemical disintegration, where pH-sensitive bond breakage removes a protective PEG layer to release therapeutics. Both pathways facilitate the bypass of the Endo-lysosomal barrier to ensure successful cytosolic delivery)

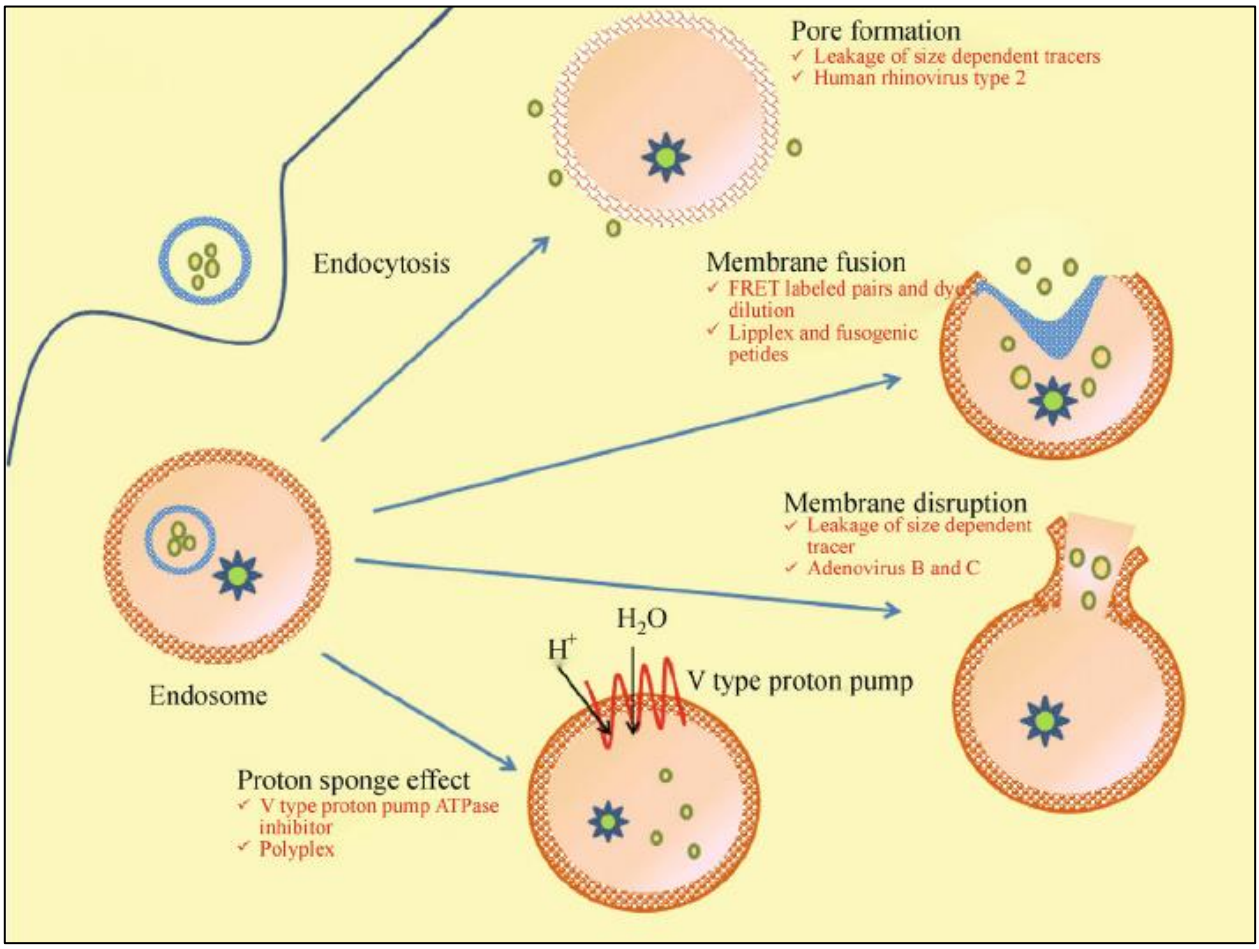


Figure 12: Diverse mechanisms of endosomal escape for intracellular delivery

(Following endocytosis, agents bypass the endosomal barrier through pore formation (e.g., Human rhinovirus type 2) or membrane fusion facilitated by fusogenic peptides. Others utilize membrane disruption, causing extensive physical compromise (e.g., Adenovirus types B and C), or the proton sponge effect, where polyplexes trigger osmotic lysis via V-type proton pump activity. These diverse pathways ensure the successful translocation of therapeutic payloads into the cytosol.)

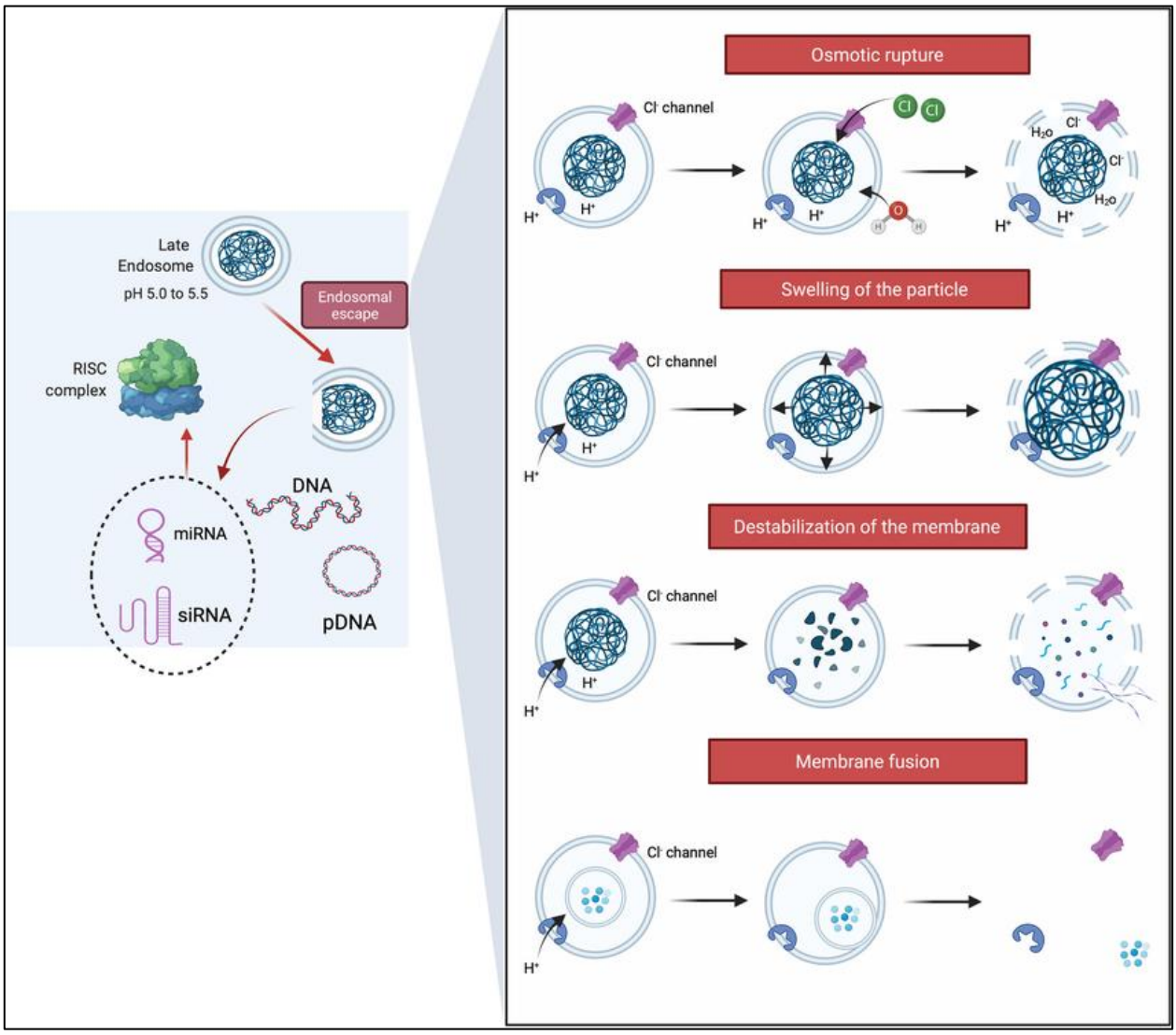


Figure 13: Mechanisms of endosomal escape for the intracellular delivery of genetic cargo

(After internalization into late endosomes (pH 5.0 to 5.5), genetic therapeutics like siRNA or pDNA must reach the cytosol via four primary biophysical pathways. These include osmotic rupture and particle swelling driven by ion influx, as well as direct membrane destabilization or fusion with the endosomal wall. These processes ensure the cargo bypasses the endolysosomal barrier to reach intracellular targets like the RISC complex.)

4.5 Surface Functionalization for Targeted Delivery to Inflamed Synovium

Target specificity is critical for minimizing systemic immunosuppression in RA therapy. Nanocarriers can be functionalized with ligands such as antibodies, peptides, folate or hyaluronic acid to facilitate receptor-mediated uptake by activated macrophages and synoviocytes expressing CD44, scavenger receptors, or integrins.[30] Such active targeting strategies enhance intracellular delivery to disease-driving cells while reducing off-target distribution. Ligand-receptor interactions trigger receptor-mediated endocytosis, improving internalization efficiency and ensuring localized gene silencing within inflamed tissues.[30]

4.6 Stimuli-responsive nanocarriers and microenvironment-triggered release

Advanced nanocarriers incorporate stimuli-responsive elements that exploit pathological features of the rheumatoid joint, including acidic pH, elevated reactive oxygen species (ROS) and over expressed proteolytic enzymes. These systems remain stable during circulation but undergo structural disassembly upon encountering inflammatory microenvironments, resulting in site-specific siRNA release.[31] ROS-responsive linkers, for instance, are cleaved by oxidative stress within activated macrophages, enabling selective activation of therapeutic payloads. This microenvironment-sensitive delivery improves therapeutic precision and reduces systemic exposure, thereby enhancing safety profiles.

4.7 Pharmacokinetic and Immunological Advantages of Nanocarrier-Mediated RNAi

Nanocarrier encapsulation substantially improves pharmacokinetics by prolonging circulation time, reducing renal filtration, and protecting siRNA from enzymatic degradation. Additionally, nanoparticle surfaces can be modified with polyethylene glycol (PEG) to reduce opsonization and clearance by the mononuclear phagocyte system, a process known as "stealth" modification.[27,28.] By ensuring sustained

bioavailability and controlled intracellular release, nanocarriers enable consistent suppression of inflammatory gene expression, allowing durable modulation of cytokine-driven signaling pathways central to RA pathogenesis.

4.8 Integration of Nanotechnology with RNAi for Precision Immunotherapy

The convergence of nanotechnology and RNA interference represents a paradigm shift in inflammatory disease management. Nanocarriers not only function as passive delivery vehicles but also act as programmable platforms capable of co-delivering multiple siRNAs, small molecules or imaging agents, enabling combinatorial therapy and theranostic applications.[31] Such multifunctional systems provide an opportunity to simultaneously inhibit STAT3 and NF-κB signaling, attenuate cytokine production, and monitor therapeutic responses, thereby addressing the complexity and redundancy of RA-associated inflammatory networks.

5. Targeted delivery to pathogenic cells

5.1 Macrophage-directed RNAi nano-therapy

Synovial macrophages are central orchestrators of rheumatoid arthritis (RA) pathology, functioning as dominant producers of TNF-α, IL-6, IL-1β, and granulocyte–macrophage colony-stimulating factor (GM-CSF). These cells sustain chronic inflammation through persistent activation of NF-κB and JAK-STAT3 signaling pathways and serve as amplifiers of cytokine networks within the joint microenvironment.[32] Elevated macrophage density in synovial tissue correlates strongly with disease severity and therapeutic response, underscoring their relevance as a primary cellular target for RNAi nano-therapy.[32,33] Nanocarrier-mediated delivery systems can be engineered to exploit macrophage phagocytic activity and receptor expression profiles. Activated macrophages overexpress scavenger receptors (SR-A, CD36), folate receptor-β, CD44, and mannose receptors, enabling receptor-mediated internalization of ligand-functionalized nanoparticles.[34] Upon uptake, cytoplasmic release of siRNA targeting TNF-α or STAT3 interrupts cytokine transcription at the mRNA level, reducing autocrine activation and attenuating inflammatory amplification loops. Molecularly, STAT3 knockdown in macrophages decreases transcription of IL-6 and VEGF while suppressing metabolic reprogramming toward glycolysis, thereby limiting energy availability for inflammatory mediator synthesis.[35.]

5.2 Fibroblast-like synoviocytes (FLS)-targeted gene silencing

Fibroblast-like synoviocytes (FLS) in RA acquire a pathogenic, tumor-like phenotype characterized by aggressive proliferation, resistance to apoptosis, and invasive cartilage destruction. Persistent NF-κB and STAT3 activation drives expression of matrix metalloproteinases (MMP-1, MMP-3, MMP-9), adhesion molecules, and chemokines that perpetuate tissue damage.[36] Targeted nanocarriers designed to recognize CD44 or integrin receptors overexpressed on activated FLS enable selective intracellular delivery of siRNA constructs. Silencing of IKKβ or p65 in FLS disrupts canonical NF-κB signaling by preventing IκBα phosphorylation and nuclear translocation of NF-κB heterodimers, thereby reducing transcription of pro-inflammatory genes.[37] Concurrently, STAT3 inhibition restores apoptotic sensitivity through downregulation of anti-apoptotic proteins such as Bcl-2 and survivin, limiting synovial hyperplasia. This dual targeting approach addresses both inflammatory mediator production and structural tissue remodeling.

5.3 Dendritic cell and T-Cell modulation

Dendritic cells (DCs) contribute to RA pathogenesis by presenting autoantigens and promoting differentiation of naïve $CD4^+$ T cells into Th1 and Th17 subsets. These effector T cells secrete IFN-γ and IL-17, further activating macrophages and FLS through STAT1 and STAT3 signaling cascades.[38] RNAi-loaded nanoparticles can be engineered to selectively silence co-stimulatory molecules or cytokines within DCs, thereby dampening T-cell activation. For example, silencing IL-6 production in antigen-presenting cells limits Th17 polarization, reducing IL-17-mediated synergistic activation of NF-κB pathways in stromal cells. By intervening at the level of immune priming, RNAi therapy may attenuate systemic autoimmunity while preserving protective immune responses.[38]

5.4 Osteoclast precursor targeting and bone protection

Bone erosion in RA results from excessive differentiation of osteoclast precursors into mature bone-resorbing cells under the influence of RANKL and inflammatory cytokines. NF-κB and STAT3 signaling promote transcription of nuclear factor of activated T cells c1 (NFATc1), the master regulator of osteoclast genesis.[39] Nanocarrier-mediated delivery of siRNA targeting RANKL or NFATc1 transcripts in osteoclast precursors can suppress osteoclast maturation and bone resorption. Molecular inhibition of NF-κB activation prevents transcriptional upregulation of genes essential for osteoclast differentiation, thereby restoring balance between bone formation and resorption.[39] Such targeted gene silencing offers the potential to directly protect structural integrity while simultaneously reducing inflammation.

5.5 Biomimetic and cell-membrane-coated nanocarriers

To enhance cellular specificity and immune compatibility, biomimetic nanocarriers coated with cell membranes derived from macrophages or platelets have emerged as advanced targeting platforms. These systems inherit membrane proteins that facilitate homotypic targeting to inflamed tissues and evade immune clearance.[40.] Macrophage membrane-coated nanoparticles can preferentially accumulate in inflamed synovium through adhesion molecule interactions, delivering siRNA payloads directly into activated macrophages. This strategy improves intracellular gene silencing efficiency while reducing systemic exposure.

Mechanistically, silencing TNF-α or STAT3 within these cells disrupts cytokine-driven NF-κB activation cascades and diminishes paracrine stimulation of surrounding stromal cells.[40]

5.6 Precision Targeting Through Microenvironmental Cues

Inflamed synovial tissue exhibits elevated reactive oxygen species (ROS), acidic pH and upregulated proteases, which can be exploited for precision delivery. ROS-responsive nanocarriers selectively release siRNA in activated macrophages where oxidative stress is abundant. Once released, siRNA-mediated knockdown of key inflammatory mediators reduces mitochondrial ROS production, thereby interrupting oxidative amplification of NF-κB signaling.[41] Such microenvironment-sensitive systems enhance spatial precision and minimize off-target gene silencing, supporting safer long-term administration in chronic autoimmune disease.

5.7 Systems-level impact of cell-specific RNAi targeting

Targeting pathogenic cell populations individually-macrophages, FLS, dendritic cells and osteoclast precursors-allows modular control over distinct pathological processes including cytokine production, antigen presentation, synovial invasion, and bone erosion. By disrupting cell-specific contributions to the IL-6/JAK-STAT3/NF-κB axis, RNAi nano-therapy achieves network-level modulation rather than isolated pathway inhibition.[33,35] This cellular precision reduces compensatory pathway activation and may enable durable remission by restoring immune homeostasis within the joint microenvironment. Figure 14 illustrates a multifunctional nanotherapeutic platform that utilizes ligand functionalization and biomimetic coatings (macrophage/platelet membranes) to bypass immune surveillance and enhance targeting. The platform integrates stimuli-responsive systems (pH, ROS, and nanozymes) for localized drug release within inflammatory microenvironments. Additionally, it incorporates advanced modalities like photodynamic (PDT) and photothermal (PTT) therapies to generate reactive oxygen species ($^1O_2$) and heat for precise therapeutic effects.

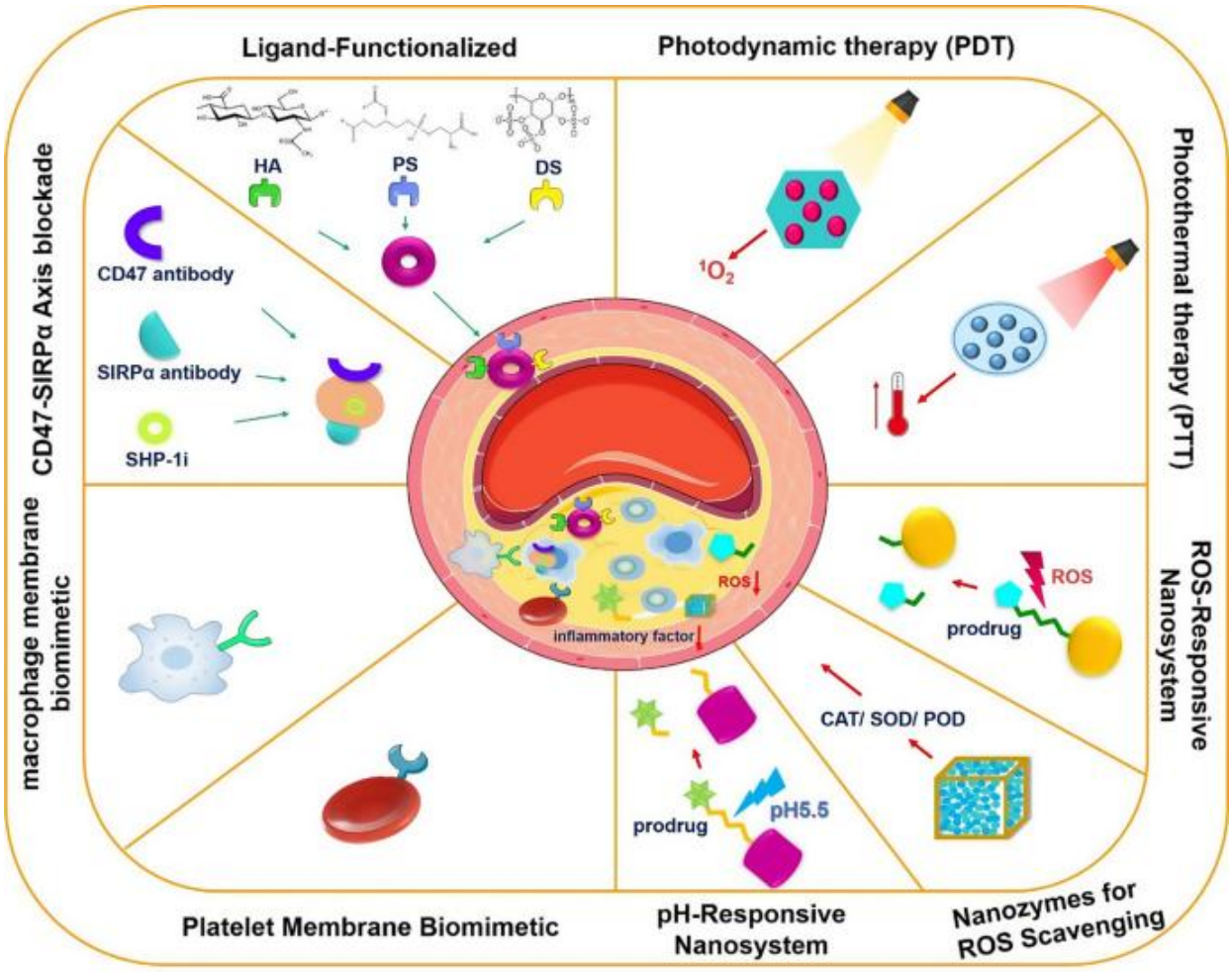


Figure 14: Comprehensive design strategies for multifunctional nanotherapeutic platforms

(This figure illustrates advanced engineering strategies for enhancing nanocarrier efficacy, including surface functionalization with ligands and biomimetic coatings (macrophage/platelet membranes) to bypass immune surveillance. It also highlights stimuli-responsive systems (pH, ROS and nanozymes) that trigger localized therapeutic release within inflammatory microenvironments. Additionally, the integration of photodynamic and photothermal therapies leverages light-activated oxygen species and heat for precise, targeted treatment)

6. Stimuli-responsive and precision-targeted nanocarrier designs

6.1 Rationale for stimuli-responsive RNAi delivery systems

The inflammatory microenvironment of rheumatoid arthritis (RA) presents distinct biochemical and biophysical signatures-including acidic pH, elevated reactive oxygen species (ROS), hypoxia, and overexpression of proteolytic enzymes-that can be exploited to engineer smart nanocarriers capable of site-specific activation. Conventional nanoparticles often release therapeutic cargo passively, which may result in premature siRNA leakage and systemic off-target effects. Stimuli-responsive nanocarriers, in contrast, remain structurally stable during circulation but undergo physicochemical transformation upon encountering disease-specific triggers, thereby enabling controlled intracellular release of RNAi payloads.[42] This approach enhances therapeutic selectivity by confining gene silencing to inflamed synovial tissues while minimizing unintended immunosuppression in healthy organs.

6.2 pH-Responsive Nanocarriers and Endosomal Escape Enhancement

Inflamed synovial tissues exhibit localized extracellular acidosis (pH ~6.4–6.8) due to hypoxia-driven glycolysis and lactate accumulation in activated immune cells. pH-sensitive nanocarriers are designed using ionizable lipids, acid-labile linkers, or protonatable polymers that undergo conformational change under acidic conditions.[43] Upon endocytosis, protonation of these materials destabilizes endosomal membranes, facilitating cytoplasmic release of siRNA through membrane fusion or osmotic rupture mechanisms. This targeted release enhances RISC loading efficiency and improves gene silencing of STAT3 and NF-κB transcripts within pathogenic cells. By synchronizing drug activation with intracellular acidification, pH-responsive systems address one of the major bottlenecks in RNAi therapeutics-inefficient endosomal escape.[43,44]

6.3 ROS-responsive nanoplatforms for inflammation-triggered gene silencing

Reactive oxygen species are markedly elevated in RA joints due to mitochondrial dysfunction and NADPH oxidase activation in macrophages and neutrophils. ROS-responsive nanocarriers incorporate thioketal, boronic ester, or disulfide linkages that are selectively cleaved in oxidative environments.[45] Cleavage of these redox-sensitive bonds induces nanoparticle disassembly and rapid release of encapsulated siRNA specifically within inflamed tissues. Molecularly, suppression of ROS-producing pathways via RNAi targeting of NF-κB or pro-inflammatory cytokines further reduces oxidative stress, creating a feedback mechanism that dampens inflammation and restores redox homeostasis. Such dual functionality-ROS-triggered release and ROS-reducing gene silencing-offers a synergistic therapeutic effect.[45]

6.4 Enzyme-responsive nanocarriers exploiting synovial protease activity

RA synovial fluid is enriched in matrix metalloproteinases (MMPs), cathepsins and hyaluronidases that mediate cartilage degradation. Enzyme-responsive nanocarriers utilize peptide sequences or biodegradable matrices that are selectively cleaved by these enzymes, enabling localized activation of RNAi therapeutics.[46] For example, MMP-sensitive linkers incorporated into nanoparticle shells degrade in protease-rich environments, releasing siRNA targeting inflammatory mediators directly at sites of joint destruction. This spatial precision reduces systemic exposure and aligns therapeutic activity with disease-specific enzymatic signatures.

6.5 Hypoxia-Sensitive Systems and Metabolic Targeting

Hypoxic conditions within the inflamed synovium stabilize hypoxia-inducible factor-1α (HIF-1α), which cooperates with STAT3 to regulate angiogenesis and metabolic adaptation. Hypoxia-responsive nanocarriers containing azobenzene or nitroimidazole moieties undergo structural reduction in low-oxygen environments, triggering payload release.[47] Targeting hypoxia-associated signaling pathways using RNAi can disrupt HIF-1α–mediated VEGF expression and angiogenesis, thereby limiting pannus formation and nutrient supply to invasive synoviocytes. This approach integrates metabolic microenvironment sensing with transcriptional regulation. Figures 15 to 17 detail the clinical transition of "smart" nanocarriers that utilize in vivo (pH, enzymes) and in vitro (magnetic, light, thermal) triggers for precise, localized drug release. This dual-trigger strategy, further optimized through computer-aided design, ensures high nanoparticle specificity and stability while providing critical feedback for personalized therapy. Consequently, these platforms offer significant clinical advantages—including reduced toxicity and enhanced delivery—across a broad spectrum of malignancies.

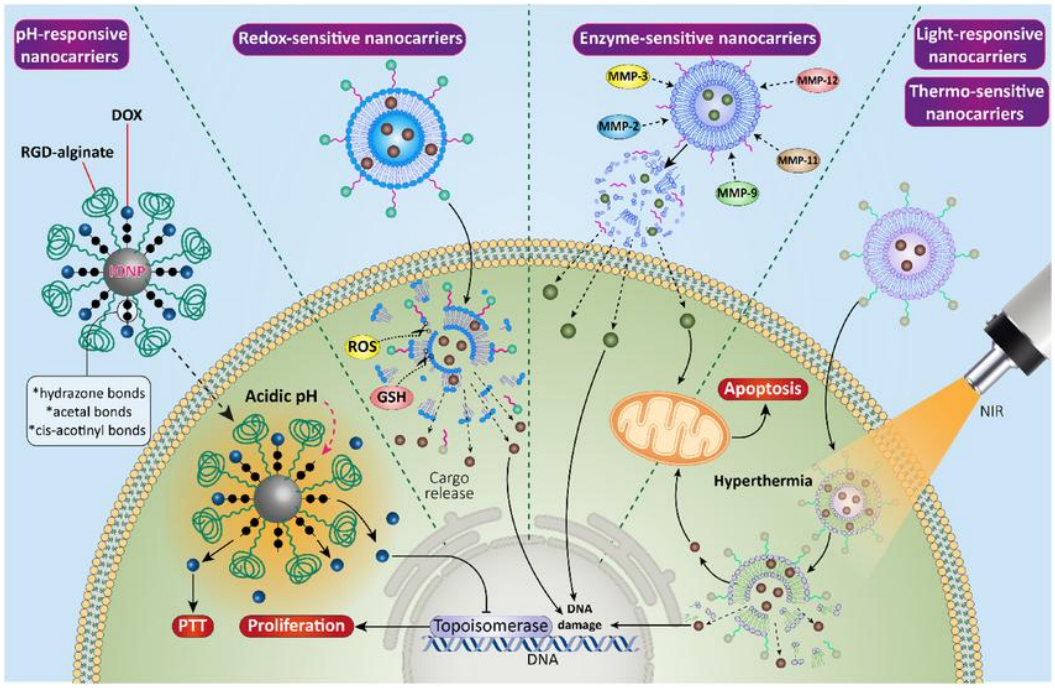


Figure 15: Stimuli-responsive nanocarriers for targeted intracellular drug delivery

("smart" nanocarriers designed to release payloads like DOX or DNA-damaging agents in response to specific triggers. These include pH-responsive and redox-sensitive systems that react to acidic endosomes or intracellular GSH/ROS, and enzyme-sensitive carriers degraded by Matrix Metalloproteinases. Additionally, light/thermo-responsive platforms utilize Near-Infrared (NIR) light to induce hyperthermia and targeted cell death.)

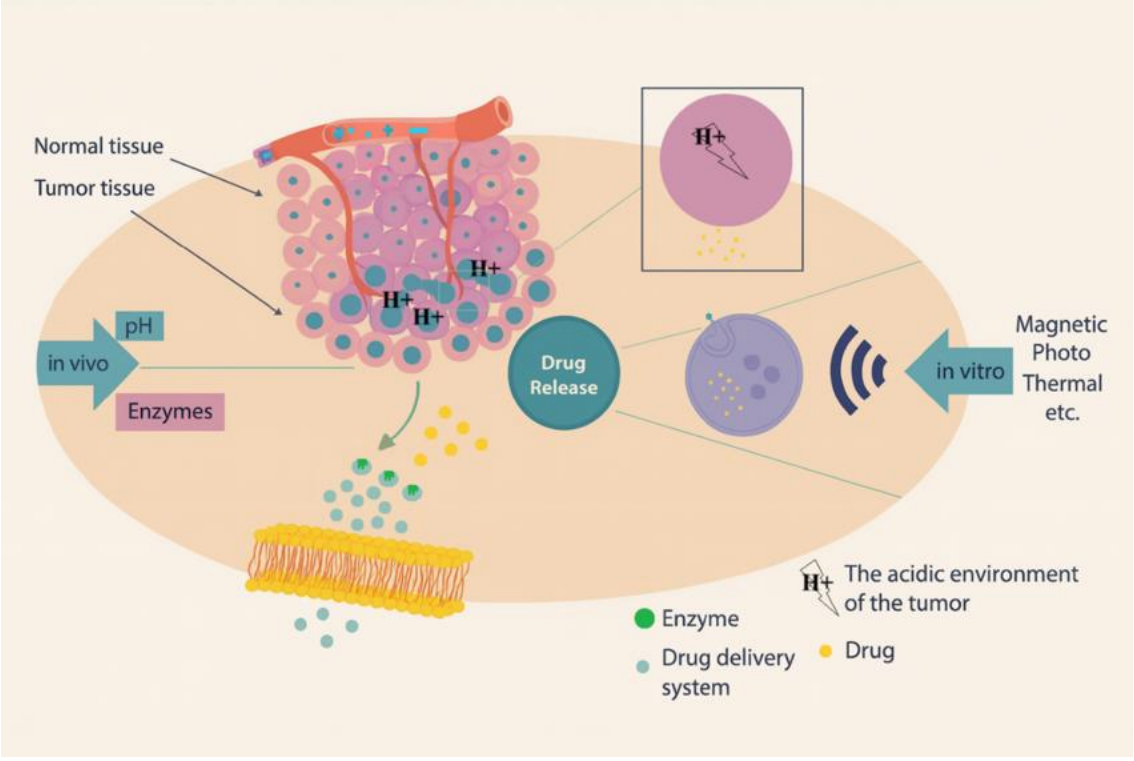


Figure 16: Overview of in vivo and in vitro triggers for controlled drug release in tumor therapy

(Internal and external stimuli to achieve targeted drug release within tumor tissues while sparing normal cells. In vivo triggers exploit the acidic tumor microenvironment (H^+) and overexpressed enzymes for localized activation, while in vitro triggers utilize external magnetic, photo, or thermal energy for remote control. This dual approach ensures precise therapeutic accumulation, significantly enhancing treatment efficacy and minimizing systemic toxicity.)

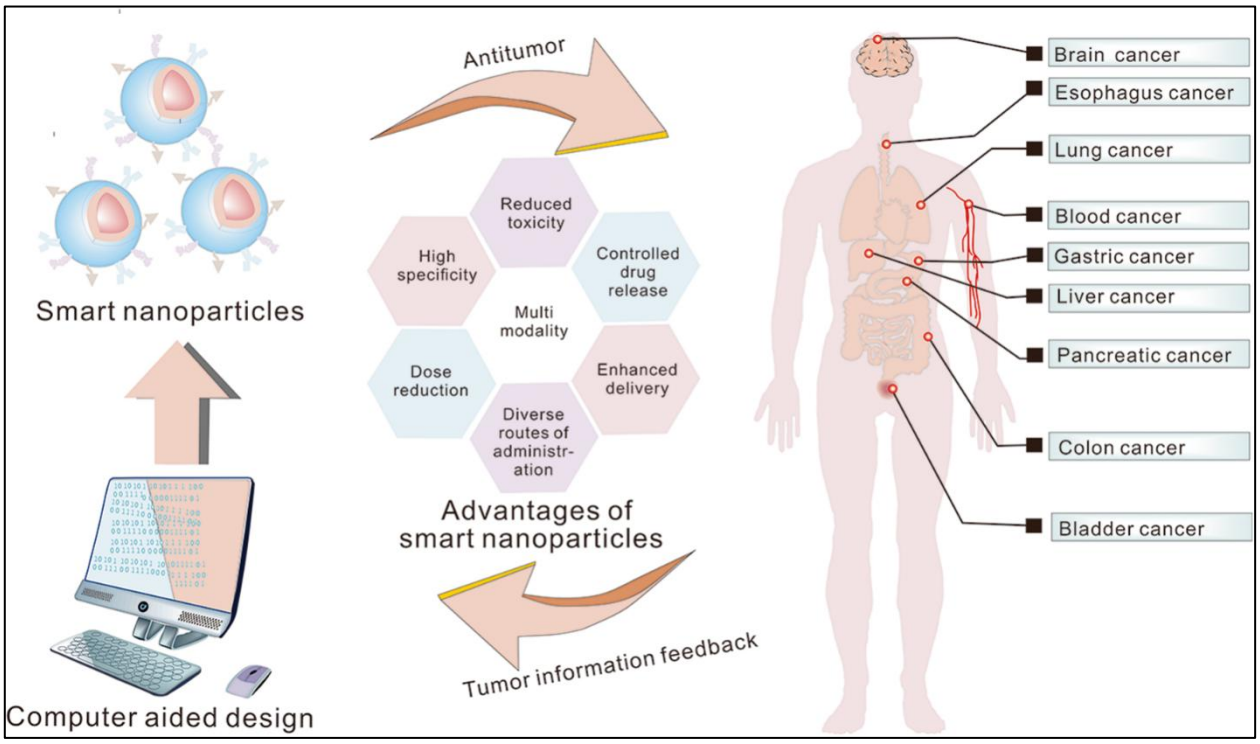


Figure 17: Advantages and clinical applications of computer-aided smart nanoparticles in oncology

(Computer-aided design optimizes smart nanoparticles for high specificity and stability, providing critical feedback for personalized tumor therapy. These platforms offer key clinical advantages, including reduced toxicity, controlled drug release, and enhanced delivery across diverse administration routes. By enabling multimodal treatment and dose reduction, this technology demonstrates broad clinical versatility in treating various malignancies, from brain and lung to gastric and bladder cancers.)

6.6 Ligand-mediated precision targeting to cellular receptors

To enhance cellular specificity, nanocarriers can be functionalized with ligands recognizing receptors overexpressed on activated immune or stromal cells. Examples include hyaluronic acid targeting CD44 on fibroblast-like synoviocytes, folate targeting folate receptor-β on macrophages, and RGD peptides targeting integrins involved in angiogenesis.[48] Ligand-receptor interactions promote receptor-mediated endocytosis, ensuring preferential uptake by pathogenic cells. This molecular recognition strategy enhances intracellular siRNA concentration while minimizing uptake by non-inflamed tissues, thereby improving therapeutic index.

6.7 External stimuli-triggered nanocarriers

In addition to endogenous triggers, externally controlled systems responsive to ultrasound, light, or magnetic fields have been explored to achieve spatiotemporal regulation of RNAi delivery. These platforms enable clinicians to activate therapeutic release at specific anatomical sites and time points, offering unprecedented precision in chronic disease management.[49] For instance, ultrasound-induced cavitation can transiently permeabilize cellular membranes and promote nanoparticle penetration into synovial tissues, enhancing cytoplasmic delivery of siRNA targeting inflammatory signaling molecules.

6.8 Multifunctional and Theranostic Nanocarrier Systems

Modern nanocarriers increasingly integrate therapeutic and diagnostic functionalities within a single platform, enabling simultaneous gene silencing, imaging, and monitoring of therapeutic response. These "theranostic" systems incorporate contrast agents or fluorescent probes alongside siRNA, allowing visualization of nanoparticle biodistribution and inflammation resolution in real time.[42,48] Such multifunctional constructs provide insights into treatment dynamics while enabling adaptive dosing strategies, advancing precision medicine approaches in RA.

6.9 Advantages of stimuli-responsive design in overcoming pathway redundancy

Because RA involves multiple overlapping signaling cascades, stimuli-responsive nanocarriers enhance therapeutic efficacy by ensuring that RNAi payloads are released precisely within pathological niches where IL-6/JAK-STAT3/NF-κB signaling is most active. This targeted activation maximizes gene silencing at disease sites while preserving systemic immune competence, addressing a major limitation of conventional immunosuppressive therapies.[42, 45]

7. Molecular outcomes of RNAi nano-therapy in rheumatoid arthritis

7.1 Suppression of cytokine amplification loops

A principal molecular outcome of RNAi nano-therapy in rheumatoid arthritis (RA) is the disruption of cytokine amplification circuits centered on IL-6/JAK-STAT3 and NF-κB signaling. Sustained production of TNF-α and IL-6

within the synovial microenvironment perpetuates autocrine and paracrine activation of macrophages and fibroblast-like synoviocytes (FLS), maintaining chronic inflammation.[50] RNAi-mediated silencing of TNF-α or IL-6 transcripts reduces upstream cytokine availability, which in turn diminishes receptor-mediated activation of JAK kinases and IκB kinase (IKK) complexes. Decreased TNF-α reduces TNFR1-driven recruitment of TRADD, TRAF2, and RIPK1, thereby attenuating IKKβ phosphorylation and preventing nuclear translocation of NF-κB p65/p50 dimers. Similarly, suppression of IL-6 expression limits gp130-mediated STAT3 phosphorylation and downstream transcription of VEGF and RANKL.[51] This coordinated downregulation collapses positive feedback loops that otherwise sustain inflammatory gene transcription.

7.2 Inhibition of synovial hyperplasia and angiogenesis

RNAi targeting of STAT3 and NF-κB signaling produces marked effects on synovial tissue architecture. STAT3 knockdown reduces transcription of pro-survival genes such as Bcl-2 and Mcl-1, restoring apoptotic sensitivity in hyperproliferative FLS.[52] Reduced expression of VEGF and hypoxia-inducible factor-1α (HIF-1α) limits pathological angiogenesis, thereby decreasing nutrient and oxygen supply required for pannus expansion. Furthermore, NF-κB inhibition diminishes expression of adhesion molecules (ICAM-1, VCAM-1) and chemokines responsible for leukocyte recruitment, curbing inflammatory cell infiltration into synovial tissue.[53] Collectively, these molecular changes translate into reduced synovial thickening and improved structural integrity.

7.3 Attenuation of osteoclast genesis and bone erosion

The IL-6/JAK-STAT3/NF-κB axis directly regulates osteoclast differentiation via induction of RANKL and activation of nuclear factor of activated T cells c1 (NFATc1), the master transcription factor of osteoclast genesis.[54] RNAi-mediated suppression of RANKL or NF-κB components interrupts RANK-RANKL signaling, preventing downstream activation of TRAF6 and inhibition of IκBα degradation in osteoclast precursors. Reduced NFATc1 transcription leads to decreased expression of osteoclast-associated genes including tartrate-resistant acid phosphatase (TRAP) and cathepsin K, thereby limiting bone resorption. By targeting these molecular checkpoints, RNAi nano-therapy directly mitigates structural joint damage in addition to reducing inflammation.[54]

7.4 Modulation of macrophage polarization and metabolic reprogramming

Macrophage phenotype is tightly linked to inflammatory metabolism. Pro-inflammatory M1 macrophages rely predominantly on aerobic glycolysis, driven by NF-κB and STAT3-dependent transcription of glycolytic enzymes and glucose transporters.[55] RNAi targeting of STAT3 disrupts metabolic gene expression, reducing glycolytic flux and lactate production, which are essential for sustained cytokine synthesis. Silencing of inflammatory mediators also decreases inducible nitric oxide synthase (iNOS) expression while promoting arginase-1 and IL-10 production, indicating a shift toward an anti-inflammatory M2 phenotype. This phenotypic reprogramming contributes to resolution of inflammation and restoration of tissue homeostasis.[55]

7.5 Reduction of Oxidative Stress and Mitochondrial Dysfunction

Chronic activation of NF-κB signaling enhances mitochondrial ROS production, further amplifying inflammatory cascades through redox-sensitive transcription factors. RNAi-mediated inhibition of upstream cytokine signaling reduces NADPH oxidase activity and mitochondrial oxidative stress, thereby decreasing activation of redox-sensitive NF-κB pathways.[56] Lower ROS levels not only limit inflammatory gene transcription but also prevent oxidative damage to cartilage matrix components such as collagen II and aggrecan, preserving joint integrity.

7.6 Epigenetic and Transcriptional Reprogramming

Persistent inflammation in RA is associated with stable epigenetic modifications in synoviocytes, including histone acetylation at promoters of cytokine and MMP genes. By reducing upstream cytokine signaling, RNAi therapy indirectly diminishes recruitment of histone acetyltransferases (HATs) to inflammatory gene loci, restoring chromatin balance and reducing transcriptional hyperactivation.[57] This epigenetic normalization may contribute to durable therapeutic effects, as decreased chromatin accessibility limits reactivation of inflammatory genes even after transient stimuli.

7.7 Systems-level restoration of immune homeostasis

Beyond individual molecular targets, RNAi nano-therapy exerts network-wide effects by simultaneously suppressing interconnected signaling nodes. Integrated inhibition of STAT3 and NF-κB disrupts cross-regulatory loops that drive chronic inflammation, leading to coordinated reductions in cytokine production, angiogenesis, and osteoclast differentiation.[50,52] Such systems-level modulation may overcome pathway redundancy that limits conventional therapies, offering the potential for sustained remission and structural disease modification.

8. Extension to Other Cytokine-Driven Disorders

8.1 Shared Inflammatory Signaling Across Autoimmune Diseases

The IL-6/JAK-STAT3/NF-κB signaling axis implicated in rheumatoid arthritis (RA) is not disease-specific but represents a conserved molecular framework underlying multiple chronic inflammatory and autoimmune disorders. Dysregulated activation of these pathways has been documented in conditions such as psoriasis, inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and ankylosing spondylitis, where persistent cytokine signaling drives immune-cell

activation and tissue injury.[58] In these disorders, IL-6-mediated STAT3 activation similarly promotes differentiation of Th17 cells and suppresses regulatory T-cell (Treg) development, shifting immune balance toward sustained inflammation. NF-κB signaling further amplifies transcription of pro-inflammatory mediators and adhesion molecules, reinforcing leukocyte recruitment and chronic tissue damage.[58,59] The mechanistic parallels across these diseases provide a strong rationale for extending RNAi nanotherapeutic strategies beyond RA.

8.2 Psoriasis: targeting keratinocyte-immune crosstalk

Psoriasis is characterized by hyperproliferation of keratinocytes and infiltration of IL-17- and IL-23-producing immune cells, processes heavily dependent on STAT3 and NF-κB activation. Constitutive STAT3 signaling in keratinocytes drives expression of antimicrobial peptides, cytokines, and chemokines that sustain epidermal inflammation 60. RNAi-based suppression of STAT3 or IL-23 signaling pathways has demonstrated the capacity to normalize keratinocyte differentiation and reduce inflammatory plaque formation in experimental models. Because the psoriatic microenvironment shares cytokine redundancy with RA, nanocarrier-mediated siRNA delivery provides a targeted means to modulate intracellular transcriptional programs without systemic immunosuppression.[60,61]

8.3 Inflammatory bowel disease: regulation of mucosal immune homeostasis

In Crohn's disease and ulcerative colitis, excessive activation of NF-κB within intestinal epithelial cells and macrophages leads to sustained secretion of TNF-α, IL-6, and other inflammatory mediators that disrupt epithelial barrier integrity. STAT3 signaling simultaneously regulates epithelial regeneration and inflammatory gene expression, illustrating the dual pathogenic and protective roles of this pathway.[62] RNAi therapeutics targeting NF-κB components or cytokine transcripts can attenuate mucosal inflammation while preserving epithelial repair mechanisms. Nanocarrier systems capable of localized delivery to intestinal tissues are particularly advantageous in minimizing systemic exposure and maintaining immune tolerance within the gut microenvironment.[62]

8.4 Systemic lupus erythematosus: interference with cytokine and interferon networks

Systemic lupus erythematosus involves aberrant activation of both NF-κB and STAT pathways downstream of Toll-like receptor engagement by nucleic acid-containing immune complexes. These signaling cascades drive production of IL-6 and type I interferons, which collectively promote autoreactive B-cell survival and autoantibody production.[63] RNAi-mediated silencing of signaling intermediates offers a strategy to interrupt these transcriptional networks at their origin. By reducing STAT3-dependent survival signaling, RNAi therapies may limit autoreactive lymphocyte expansion and restore immune tolerance, highlighting translational applicability across systemic autoimmune diseases.[63]

8.5 Cancer-associated inflammation and the tumor microenvironment

Chronic activation of IL-6/JAK-STAT3/NF-κB signaling is also a defining feature of many cancers, where inflammatory pathways support tumor cell survival, angiogenesis and immune evasion. STAT3 functions as a central oncogenic transcription factor promoting proliferation and resistance to apoptosis, while NF-κB regulates expression of cytokines that shape the tumor microenvironment.[64] RNAi nanocarriers targeting STAT3 or NF-κB have demonstrated the ability to reprogram tumor-associated macrophages, reduce inflammatory cytokine production, and enhance anti-tumor immunity. These findings reinforce the concept that cytokine-driven diseases share conserved intracellular signaling vulnerabilities amenable to RNAi-based intervention.[64,65]

8.6 Lessons for rheumatoid arthritis therapeutics

The successful application of RNAi nanomedicine in diverse cytokine-mediated disorders underscores the versatility of this strategy in modulating shared inflammatory circuits. Importantly, these cross-disease insights reveal that targeting upstream transcriptional regulators rather than individual cytokines provides broader and more durable therapeutic effects. Such translational convergence suggests that advances in RNAi delivery platforms, safety optimization, and targeting precision achieved in oncology and other inflammatory diseases can inform next-generation therapies for RA and related autoimmune conditions.

9. Systems-level immunomodulation by RNAi nanomedicine

Figure 18 details the complex immune cascade in rheumatoid arthritis, where Myeloid Dendritic Cells drive Th-cell differentiation and B-cell autoantibody production, leading to a massive release of cytokines like IL-1 and TNF that cause irreversible bone and cartilage destruction. To address such pathological protein expression, Figure 19 outlines the RNA interference (RNAi) pathways, showing how endogenous miRNA and exogenous siRNA converge at the RISC complex to induce gene silencing through mRNA degradation or translation repression. Complementing these genetic approaches, Figure 20 highlights the therapeutic potential of Magnolol (MH), which acts as a multi-target inhibitor blocking key signaling pathways (e.g., p38 MAPK, NF-κB) and enzymes to suppress the production of pro-inflammatory mediators and reactive species.

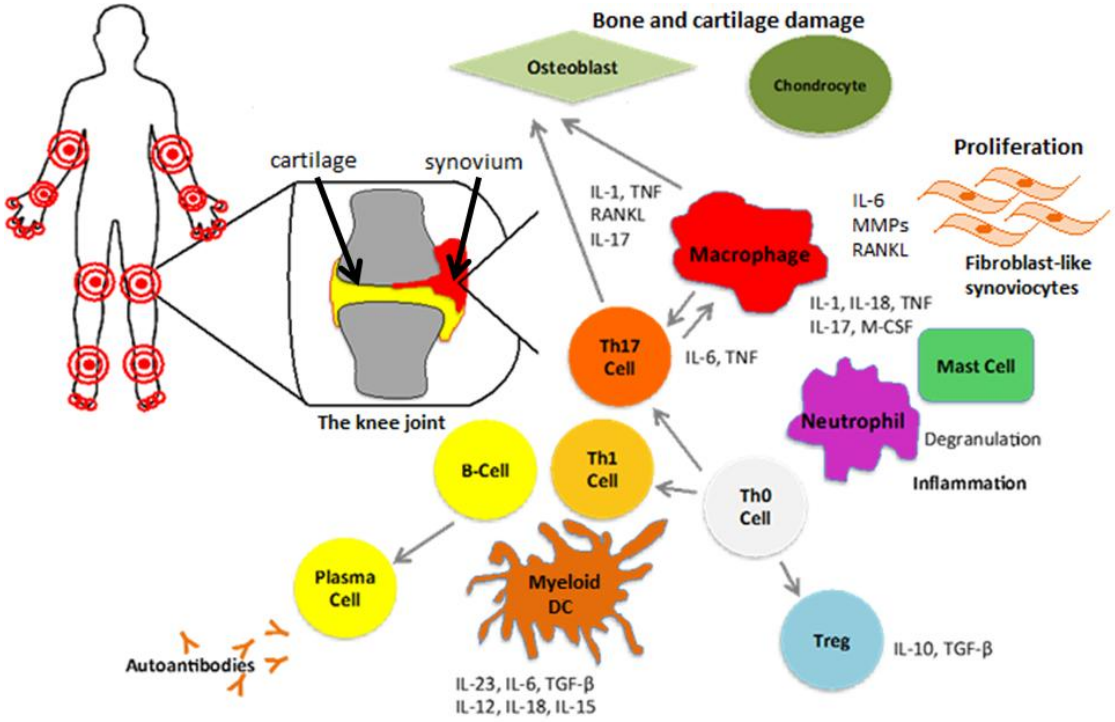


Figure 18: Immunopathological mechanisms of inflammatory joint destruction in rheumatoid arthritis

(The complex immune cascade in rheumatoid arthritis, initiated by Myeloid Dendritic Cells that drive Th-cell differentiation and B-cell autoantibody production. This process recruits' macrophages and neutrophils, triggering a massive release of pro-inflammatory cytokines like IL-1, IL-6, and TNF. Ultimately, these factors stimulate synoviocytes proliferation and activate osteoblasts and chondrocytes, leading to the irreversible destruction of bone and cartilage within the knee joint.)

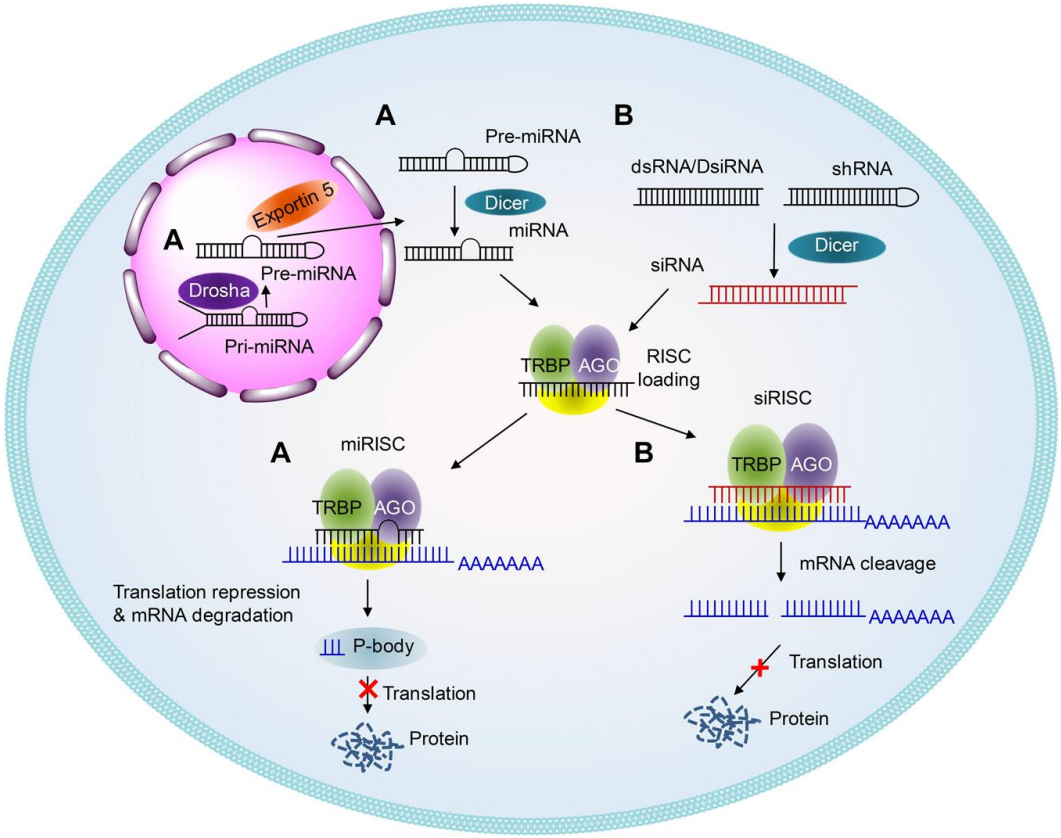


Figure 19: Mechanisms of RNA interference (RNAi) mediated by miRNA and siRNA pathways

(The intracellular processing of RNA for gene silencing via two primary routes: the endogenous miRNA pathway, where pri-miRNA is processed by Drosha and Dicer to induce mRNA degradation in P-bodies, and the exogenous siRNA pathway, which utilizes synthesized dsRNA or shRNA. Both pathways converge at the RISC complex (containing TRBP and AGO), which guides mature miRNA or siRNA to target specific mRNA. This interaction results in either translation repression or direct mRNA cleavage, effectively preventing the synthesis of target proteins.)

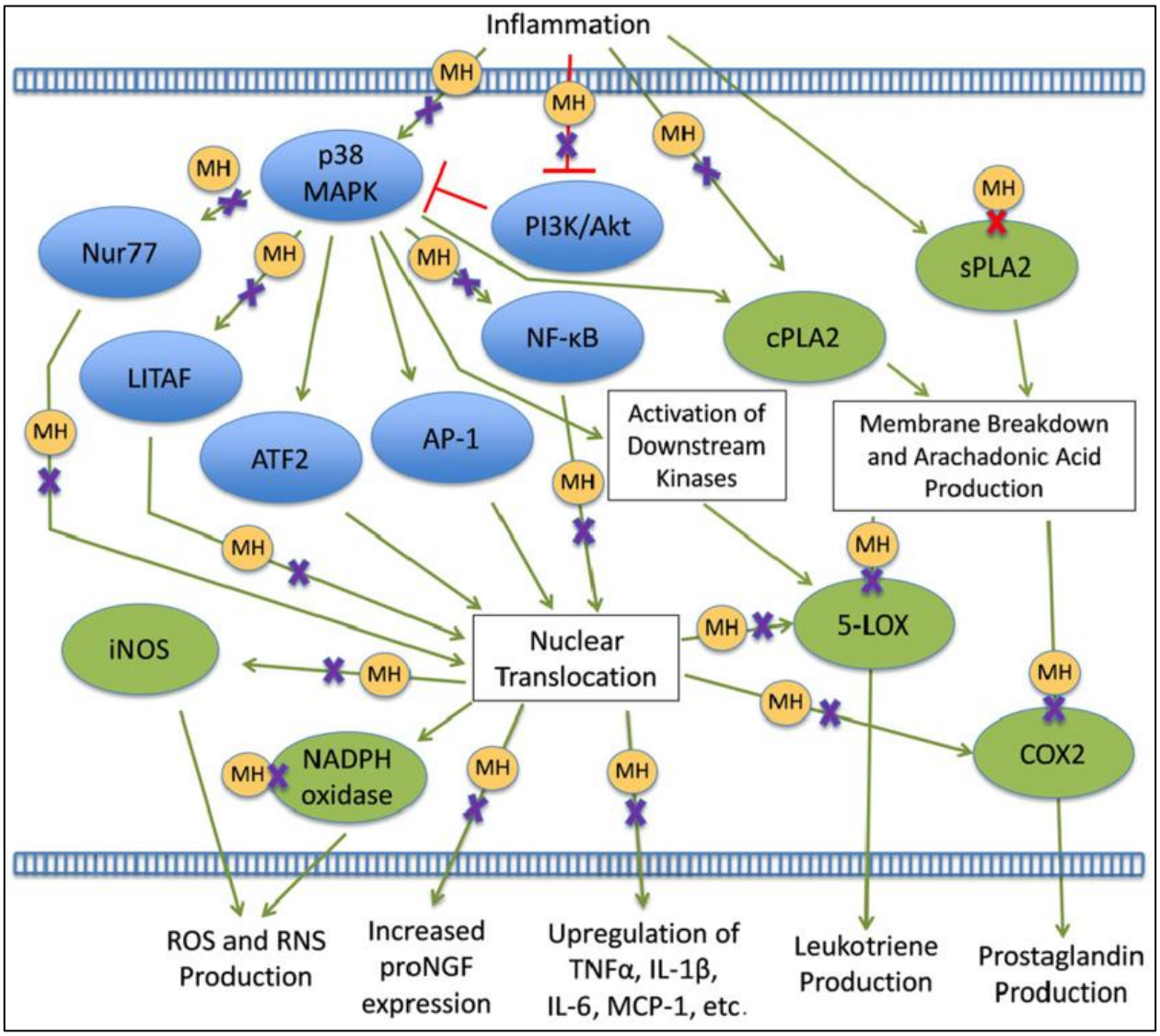


Figure 20: Molecular signaling pathways of inflammation and inhibitory mechanisms of Magnolol (MH)

(Magnolol (MH) acts as a multi-target inhibitor within the inflammatory cascade, blocking the p38 MAPK and PI3K/Akt pathways to prevent the nuclear translocation of transcription factors like NF-κB and AP-1. By suppressing enzymes such as COX2, 5-LOX, and iNOS, MH effectively halts the production of prostaglandins, leukotrienes, and ROS/RNS. This comprehensive blockade results in the significant downregulation of key pro-inflammatory cytokines, including TNFα, IL-1β, and IL-6.)

9.1 Rationale for Network-Oriented Therapeutic Strategies

Rheumatoid arthritis (RA) is increasingly recognized as a systems-level disorder governed by interconnected signaling pathways rather than isolated molecular abnormalities. Traditional pharmacologic interventions that block single cytokines often fail to produce sustained remission because compensatory signaling mechanisms restore inflammatory activity. Systems immunology approaches therefore emphasize simultaneous modulation of multiple regulatory nodes to rebalance immune networks.[66] RNAi nanomedicine uniquely fulfills this requirement by enabling coordinated silencing of genes involved in cytokine production, intracellular signaling, and metabolic adaptation. Through programmable sequence design, siRNA therapeutics can be tailored to target several components of the IL-6/JAK-STAT3/NF-κB axis concurrently, thereby dismantling redundant inflammatory circuits and restoring immune equilibrium.

9.2 Multi-node regulation of cytokine signaling networks

Inflammatory signaling pathways in RA exhibit extensive crosstalk, with STAT3, NF-κB, MAPK, and PI3K/Akt pathways converging to regulate overlapping gene sets. Systems-level suppression using RNAi can reduce expression of upstream cytokines while simultaneously inhibiting transcription factors responsible for downstream amplification.[67] For example, concurrent silencing of IL-6 and STAT3 not only prevents receptor-mediated signaling but also disrupts transcriptional autoregulation loops in which STAT3 promotes further IL-6 production. This multi-node targeting leads to broader suppression of inflammatory mediators compared with single-target inhibition, illustrating the advantages of network-directed therapy.

9.3 Reprogramming Innate-Adaptive Immune Interactions

RNAi nanotherapeutics can modulate communication between innate and adaptive immune compartments, a key determinant of chronic autoimmunity. Silencing cytokine genes in antigen-presenting cells reduces activation of autoreactive T cells and limits differentiation into Th17 subsets, which are central drivers of RA pathology.[68] At the same time, downregulation of inflammatory transcriptional programs promotes expansion of regulatory T cells and anti-inflammatory macrophage phenotypes, facilitating resolution of inflammation. This bidirectional immune reprogramming demonstrates how RNAi-based interventions can shift the overall immune landscape from a pathogenic to a homeostatic state.

9.4 Integration of Immunometabolism and Gene Regulation

Emerging evidence highlights the role of immunometabolism in sustaining inflammatory responses. Activated immune cells undergo metabolic rewiring toward glycolysis and glutaminolysis, processes tightly regulated by STAT3, NF-κB, and HIF-1α signaling.[69] RNAi-mediated inhibition of these transcription factors disrupts metabolic enzyme expression, leading to reduced ATP production and biosynthetic capacity required for cytokine synthesis. By coupling gene silencing with metabolic normalization, RNAi nanomedicine addresses both signaling and energetic drivers of inflammation, offering a comprehensive therapeutic mechanism not achievable with conventional drugs.

9.5 Temporal and Spatial Control of Immune Modulation

Nanocarrier-mediated RNAi delivery allows controlled release kinetics and tissue-specific targeting, enabling precise temporal regulation of immune responses. Sustained yet localized gene silencing within inflamed joints avoids systemic immunosuppression while maintaining long-term suppression of pathogenic signaling pathways.[70] This spatiotemporal precision is particularly important in chronic diseases like RA, where continuous but balanced immune modulation is required to prevent relapse without compromising host defense mechanisms.

9.6 Toward Personalized RNAi Nanomedicine

Advances in transcriptomics and single-cell sequencing have revealed substantial heterogeneity among RA patients, with distinct molecular endotypes defined by differential activation of IL-6/STAT3, TNF/NF-κB, or interferon pathways. RNAi therapeutics can be customized to selectively silence genes most relevant to an individual's inflammatory profile, paving the way for precision medicine approaches.[71] Such adaptability distinguishes RNAi nanomedicine from fixed-target biologics and suggests a future in which therapeutic regimens are guided by molecular diagnostics to achieve optimized disease control.

9.7 Systems-level outcomes and disease modification

By simultaneously modulating cytokine signaling, cellular metabolism, and immune-cell differentiation, RNAi nanomedicine offers the potential to achieve true disease modification rather than symptomatic suppression. Systems-level intervention disrupts the self-sustaining inflammatory circuitry characteristic of RA, promoting restoration of tissue homeostasis and preventing structural damage progression.[66,69] This integrative therapeutic paradigm aligns with the growing recognition that chronic inflammatory diseases must be treated through coordinated regulation of complex biological networks.

10. Translational Barriers and Clinical Challenges

10.1 Delivery Efficiency and Biological Stability

Despite promising preclinical outcomes, the clinical translation of RNAi nanomedicine faces substantial challenges related to delivery efficiency and molecular stability. Systemically administered nanoparticles must navigate complex biological barriers, including serum nuclease degradation, opsonization by plasma proteins, and rapid clearance by the mononuclear phagocyte system (MPS). These processes can significantly reduce the proportion of intact siRNA reaching target tissues.[72] Formation of a protein corona on nanoparticle surfaces alters biodistribution, cellular uptake, and immunological recognition, potentially diminishing targeting specificity. Additionally, heterogeneous vascular permeability within inflamed joints may limit uniform nanoparticle penetration, creating variability in therapeutic response.[73] Overcoming these pharmacokinetic obstacles remains a key requirement for consistent gene silencing in clinical settings.

10.2 Endosomal escape and intracellular trafficking limitations

Even after successful cellular internalization, inefficient endosomal escape remains a major bottleneck in RNAi therapy. A substantial fraction of delivered siRNA is degraded within lysosomes before reaching the cytoplasm, preventing incorporation into the RNA-induced silencing complex (RISC).[74] This intracellular trafficking challenge necessitates advanced carrier designs capable of membrane destabilization or fusion to release siRNA into the cytosol. However, enhancing endosomal escape must be carefully balanced against cytotoxicity, as excessive membrane disruption may induce cellular stress or apoptosis in non-target tissues.

10.3 Off-Target Effects and Immune Activation

RNAi therapeutics may inadvertently silence unintended transcripts due to partial sequence complementarity, leading to off-target gene modulation. Such effects can disrupt physiological pathways and complicate safety assessments.[75] Furthermore, double-stranded RNA molecules may activate innate immune receptors such as TLR3, TLR7, and RIG-I, resulting in interferon responses that mimic viral infection.[75,76] Although chemical modification of siRNA (e.g., 2′-O-methyl or

phosphorothioate substitutions) can reduce immunogenicity, achieving an optimal balance between stability, specificity, and biological activity remains a central design challenge.

10.4 Nanotoxicology and Long-Term Safety Considerations

Long-term safety of nanocarrier systems is a critical concern for chronic diseases like rheumatoid arthritis that require repeated administration. Accumulation of non-biodegradable materials in the liver, spleen, or lymphatic system may provoke unintended inflammatory responses or organ toxicity.[77] Biodegradable polymers and lipid-based nanoparticles have improved safety profiles, yet comprehensive evaluation of their metabolic fate, degradation kinetics, and immunological consequences is essential for regulatory approval. Chronic exposure studies are particularly necessary to assess cumulative toxicity and immune tolerance.

10.5 Manufacturing, scalability, and regulatory complexity

Translation from laboratory-scale synthesis to large-scale manufacturing introduces additional challenges related to reproducibility, quality control, and batch consistency. Nanomedicines often exhibit sensitivity to minor variations in formulation parameters such as particle size, surface charge, and encapsulation efficiency, all of which influence therapeutic performance.[78] Regulatory pathways for RNAi nanotherapeutics are also evolving, as these products combine characteristics of biologics, gene therapies, and drug delivery systems. Establishing standardized evaluation frameworks for pharmacokinetics, biodistribution, and immunogenicity is necessary to facilitate clinical adoption.

10.6 Patient Heterogeneity and Precision Medicine Challenges

Rheumatoid arthritis exhibits substantial molecular heterogeneity among patients, with distinct inflammatory endotypes driven by variable contributions of TNF, IL-6, interferon, or metabolic pathways. This variability complicates the design of universal RNAi therapies and highlights the need for biomarker-guided patient stratification.[79] Integration of transcriptomic profiling and personalized target selection may enhance therapeutic success but also introduces logistical and economic considerations that must be addressed for widespread clinical implementation.

10.7 Clinical Trial Design and Translational Validation

Demonstrating clinical efficacy of RNAi nanomedicine requires carefully designed trials capable of evaluating both molecular and functional outcomes. Unlike conventional drugs, RNAi therapies exert effects at the gene-expression level, necessitating biomarkers that confirm target knockdown alongside clinical improvement.[72] Bridging the gap between preclinical success and clinical validation will depend on standardized assays, robust safety monitoring, and long-term follow-up to establish durable disease modification.

10.8 Future Directions to Overcome Translational Barriers

Emerging solutions include development of biodegradable and biomimetic carriers, improved targeting ligands, and integration of artificial intelligence–guided nanoparticle design to optimize delivery efficiency and minimize toxicity. Advances in genome-wide profiling and precision medicine frameworks are expected to enable individualized RNAi strategies tailored to specific inflammatory signatures.[79] Addressing these translational challenges will be essential to fully realize the therapeutic potential of RNAi nanomedicine as a next-generation treatment paradigm for rheumatoid arthritis.

12. Conclusion

The integration of RNAi-loaded nanocarriers targeting the IL-6/JAK-STAT3-NF-κB axis represents a transformative shift in the management of Rheumatoid Arthritis. By moving beyond the simple neutralization of extracellular cytokines-a method often hindered by signaling redundancy this approach enables the direct reprogramming of the intracellular transcriptional networks that drive chronic inflammation and joint destruction.

List of Abbreviations

Ago2: Argonaute-2

AP-1: Activator Protein-1

ATP: Adenosine Triphosphate

Bcl-2: B-Cell Lymphoma-2

CD: Cluster of Differentiation

COX-2: Cyclooxygenase-2

csDMARDs: Conventional Synthetic Disease-Modifying Antirheumatic Drugs

CXCL: C-X-C Motif Chemokine Ligand

DAMPs: Damage-Associated Molecular Patterns

DCs: Dendritic Cells

DNA: Deoxyribonucleic Acid

FLS: Fibroblast-Like Synoviocytes

GAS: Gamma-Activated Sequence

GM-CSF: Granulocyte–Macrophage Colony-Stimulating Factor

gp130: Glycoprotein 130

HATs: Histone Acetyltransferases

HIF-1α: Hypoxia-Inducible Factor-1 Alpha

ICAM-1: Intercellular Adhesion Molecule-1

IKK: IκB Kinase

IL: Interleukin

IL-6R: Interleukin-6 Receptor

iNOS: Inducible Nitric Oxide Synthase

JAK: Janus Kinase

LNPs: Lipid Nanoparticles

MAPK: Mitogen-Activated Protein Kinase

MCP-1: Monocyte Chemoattractant Protein-1

MMPs: Matrix Metalloproteinases

MPS: Mononuclear Phagocyte System

mRNA: Messenger RNA

NFATc1: Nuclear Factor of Activated T Cells 1

NF-κB: Nuclear Factor Kappa-B

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

PEG: Polyethylene Glycol

PEI: Polyethyleneimine

PI3K: Phosphoinositide 3-Kinase

PLGA: Poly (lactic-co-glycolic acid)

RA: Rheumatoid Arthritis

RANK: Receptor Activator of Nuclear Factor Kappa-B

RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand

RIG-I: Retinoic Acid-Inducible Gene-I

RISC: RNA-Induced Silencing Complex

RNA: Ribonucleic Acid

RNAi: RNA Interference

ROS: Reactive Oxygen Species

siRNA: Small Interfering RNA

SR-A: Scavenger Receptor-A

STAT3: Signal Transducer and Activator of Transcription-3

TLR: Toll-Like Receptor

TNF-α: Tumor Necrosis Factor-Alpha

TRAF6: TNF Receptor-Associated Factor 6

TRAP: Tartrate-Resistant Acid Phosphatase

Treg: Regulatory T Cell

VEGF: Vascular Endothelial Growth Factor

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Shiv Kumar Bhardwaj: Writing-original draft preparation

Abinash Satapathy: Visualization / Schematic representation / Graphical content / Illustration

Abhisek Satapathy: Review and editing

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