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MOLECULAR MECHANISMS OF CYTOKINE-INDUCED CARTILAGE DESTRUCTION IN RHEUMATOID ARTHRITIS

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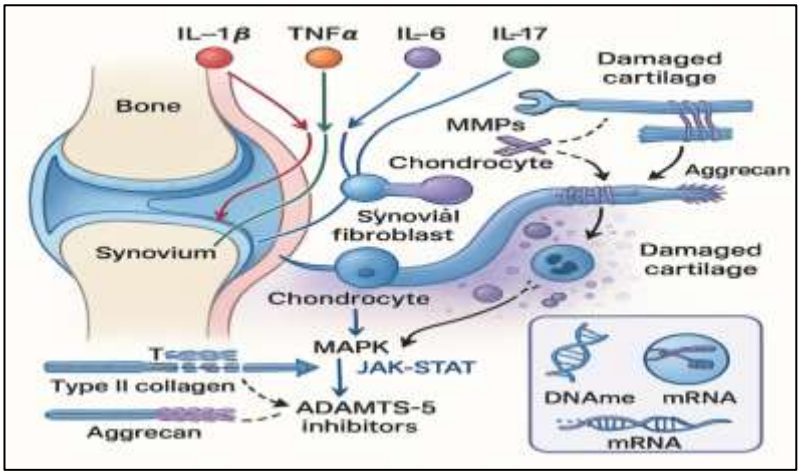
ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes long-term destruction of cartilage and leads to irreversible arthritis. Pro-inflammatory messengers such as interleukin-1 beta (IL-1 beta), tumour necrosis factor-alpha (TNF alpha), interleukin-6 (IL-6), and interleukin-17 (IL-17)—drive this destructive process by targeting cells in joint tissue. Once released, these signals activate known pathways within chondrocytes and synovial fibroblasts, like NF-kappa B, MAPKs, and JAK-STAT, prompting these cells to produce destructive enzymes such as matrix metalloproteinases (MMPs) and aggrecans (ADAMTS). Because the production of these enzymes exceeds tissue repair, the cartilage structure—a mesh of type II collagen and aggrecan—begins to break down, leading to pain and disability. Additionally, cytokine-mediated chondrocyte apoptosis and phenotypic changes contribute to impaired cartilage repair and ongoing inflammation. Epigenetic modifications, including DNA methylation (DNAme) and microRNA (miRNA)-mediated regulation, influence cytokine functions in chondrocytes and may serve as therapeutic targets. Current RA treatments include TNF inhibitors, IL-6 receptor blockers, and JAK inhibitors that aim to block cytokine signalling pathways to slow disease progression. In addition, the development of targeted therapies, such as selective inhibitors of ADAMTS-5 and epigenetic regulators, offers hope for improved cartilage protection in RA. Understanding this complex network of cytokines, signalling pathways, and effector enzymes involved in cartilage destruction is essential for developing new disease-modifying strategies for RA.

GRAPHICAL ABSTRACT:



KEYWORDS: Rheumatoid arthritis, Cartilage degradation, Interleukin-1β, Autoimmune disease, Cytokines, Matrix metalloproteinases

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that primarily affects synovial joints and leads to progressive destruction of articular cartilage and bone.1 Affecting approximately 0.5–1% of the global population, RA remains a significant cause of disability, reduced quality of life, and increased mortality worldwide.2 While advances in early diagnosis and biologic therapies have improved patient outcomes, irreversible joint damage continues to occur in a substantial proportion of individuals, highlighting a critical need to understand the molecular basis of tissue destruction.3 Cartilage degradation in RA is a hallmark of disease progression and a major determinant of long-term functional impairment.4 Unlike osteoarthritis, where cartilage damage results from mechanical wear, RA-related cartilage loss is driven by immune-mediated inflammatory responses originating in the synovium.5 The formation of an invasive pannus—comprising hyperplastic synovial fibroblasts, immune cells, and neo-vasculature—establishes a destructive microenvironment that promotes degradation of the cartilage extracellular matrix (ECM).6

Among the most prominent mediators of joint damage in RA are pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17).7 These cytokines act synergistically to stimulate the production of cartilage-degrading enzymes, modulate intracellular signalling pathways (including NF-κB, MAPKs, and JAK-STAT), and alter chondrocyte phenotype and survival.8 Moreover, emerging evidence suggests that epigenetic changes, including DNA methylation and non-coding RNA regulation, further exacerbate cytokine-driven joint destruction.9

Despite significant therapeutic advances, the molecular intricacies underlying cytokine-induced cartilage breakdown remain incompletely understood.10 There is increasing interest in targeting not only upstream cytokines but also the downstream signalling molecules and effector enzymes—such as matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS)—that mediate ECM degradation.11 Understanding the integrated signalling networks and feedback loops that drive cartilage pathology is essential to inform the development of more effective, disease-modifying strategies.12

This review aims to comprehensively examine the molecular mechanisms through which pro-inflammatory cytokines mediate cartilage destruction in RA. We begin by discussing the role of individual cytokines and their downstream signalling pathways, then by exploring the proteolytic enzymes responsible for ECM degradation. We also examine the role of chondrocyte apoptosis and epigenetic regulation in cartilage pathology and conclude with an overview of current and emerging therapeutic approaches. By synthesising recent discoveries and identifying critical gaps in the literature, we aim to provide a timely and clinically relevant resource for researchers and clinicians in the field of rheumatology and molecular pharmacology. Figure 1 illustrates the complex cellular interactions and cytokine networks involved in RA pathogenesis.

2. Role of cytokines in rheumatoid arthritis:

Cytokines are crucial to the development and progression of rheumatoid arthritis (RA), which is characterised by long-lasting autoimmune inflammation. These local proteins act as mediators in numerous important biological functions such as inflammation, immunity, cell growth, and differentiation.13 In RA, pro-inflammatory cytokines such as tumour necrosis factor (TNFα), interleukin 1 (IL-1), and interleukin 6 (IL-6) are overexpressed, leading to synovial inflammation, destruction of cartilage tissues, and erosion of bones.14 These cytokines activate synovial fibroblasts along with other cells like chondrocytes and osteoclasts, which trigger the production of matrix-degrading enzymes and other inflammatory mediators.15 Additionally, interferon-gamma (IFNγ) and interleukin 2 (IL-2) cytokines help to stimulate T-cell activation along with their proliferation, contributing towards the autoimmune reaction.16 Grasping the intricate relationship between various cytokines in RA has made it possible to develop biologic treatments such as TNF-α inhibitors, which have improved management strategies for patients, along with their outcomes.17

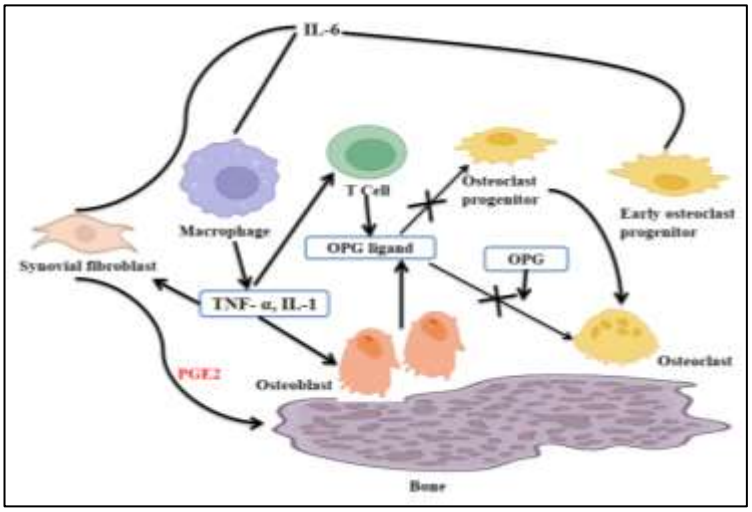


Figure 1: Cellular crosstalk and cytokine networks in the pathogenesis of rheumatoid arthritis. [Summarises the cellular interactions believed to be of importance in the pathogenesis of RA and describes the interaction among macrophages, T cells, B cells, and non-hematopoietic cells (fibroblasts, connective tissue cells, and bone) 12. These interactions are facilitated by the actions of cytokines released from the activated cells that then, through both autocrine (feedback on the

same cell) and paracrine (via other cell types) mechanisms, induce the production of other pro-inflammatory cytokines, which together contribute to the pathogenesis of this disease.]

2.1. Proinflammatory Cytokines in Cartilage Destruction

Rheumatoid arthritis (RA) is driven by an excess of proinflammatory cytokines that promote cartilage matrix breakdown.18 Key cytokines include interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), IL-6, and IL-17, which are produced by activated macrophages, synovial fibroblasts, and T cells in the inflamed joint.19 These cytokines bind receptors on chondrocytes and synovium to trigger signalling cascades that upregulate degradative enzymes and inflammatory mediators, creating a vicious feedback loop of tissue damage.20 For example, IL-1β potently induces synovial cells to secrete matrix metalloproteinases (MMPs) and aggrecanases, and stimulates chondrocytes to release nitric oxide (NO) and prostaglandin E_2 (PGE_2), inhibiting matrix synthesis.21 TNF-α likewise activates NF-κB and MAPKs to increase MMP and ADAMTS aggrecanase production, and stimulates chondrocytes to release IL-6 and IL-8.22 IL-6 contributes by activating JAK/STAT3 signalling in cartilage and synovium, promoting MMP expression and chondrocyte apoptosis.23 IL-17, mainly from Th17 cells in RA synovium, synergises with IL-1 and TNF to amplify MMP production and inflammation; IL-17–stimulated chondrocytes show elevated catabolic mediators leading to rapid proteoglycan loss.24 Together, these cytokines orchestrate ECM degradation and chondrocyte dysfunction (Table 1). 24,25

The inflamed synovial environment in RA involves macrophage-like (MLS) and fibroblast-like (FLS) synoviocytes interacting with T and B cells. 26 Activated synoviocytes secrete IL-1β, TNF-α, and IL-6, driving chondrocytes to produce matrix-degrading enzymes (MMPs, ADAMTS) that cause cartilage breakdown and bone erosion.27 Immune cells (Th1, Th17) produce IFN-γ, IL-17, and other factors that further amplify this destructive cycle. Synovial hyperplasia and pannus formation also contribute to cartilage invasion. 28

2.2 Interleukin 1β (IL-1β)

IL-1β is a master regulator of cartilage catabolism in RA. Produced by macrophages and synoviocytes via inflammasome activation, IL-1β binds to IL-1R1, triggering NF-κB and MAPK pathways in chondrocytes and fibroblasts. This causes robust upregulation of MMPs (especially collagenases) and aggrecanases, leading to collagen and proteoglycan breakdown.29 IL-1β also induces chondrocytes to generate NO and PGE_2, which suppress collagen II and aggrecan synthesis. 30 In addition, IL-1β amplifies inflammation by promoting the expression of TNF-α, IL-6, and IL-17 in the joint. Blocking IL-1 signalling (e.g., with anakinra) has shown moderate benefits in slowing erosion, highlighting IL-1β's role in structural damage. 31

2.2 Tumour Necrosis Factor α (TNF-α)

TNF-α is a central effector in RA that synergises with IL-1β. Secreted mainly by macrophages and fibroblasts, TNF-α engages TNFR1 on chondrocytes to activate NF-κB and JNK/p38 MAPK pathways. This drives production of MMP-1, MMP-3, and ADAMTS enzymes, as well as IL-6 and chemokines 32. TNF-α can also induce chondrocyte apoptosis at high levels and inhibit chondrogenic differentiation via p38 signalling 33. Clinically, TNF inhibitors (etanercept, infliximab, adalimumab) dramatically reduce joint erosion and MMP levels in RA patients 34. Mechanistically, anti-TNF treatment decreases synovial MMP/ADAMTS production, preserving cartilage integrity 34.

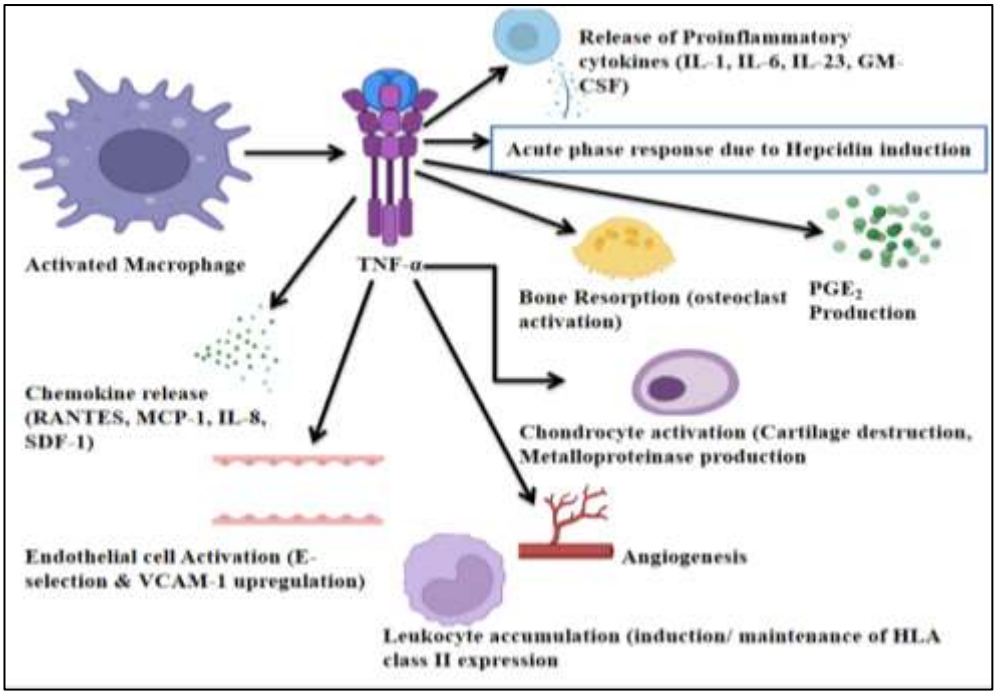


Figure 2: Pleiotropic Inflammatory Effects of TNF-α Released from Activated Macrophages

The presentation of major inflammatory responses mediated by TNF-alpha, which is a major cytokine secreted by macrophages after activation, is well demonstrated in the diagram. When macrophages are activated, TNF-alpha activates various downstream effects, including the production of proinflammatory cytokines (IL-1, IL-6, IL-23 and GM-CSF), which then initiate various effects, including activation of the acute phase response by hepcidin. It seizes bone resorption through the stimulation of osteoclasts, triggers the production of PGE2, which leads to pain and inflammation, and stimulates chondrocytes, which, after that, cannot resist cartilage degradation with the help of metalloproteinases. Furthermore, TNF-alpha helps to release more chemokines such as RANTES, MCP-1, IL-8 and SDF-1, which help attract more immune cells toward the inflamed site. It activates adhesion molecules (e-selectin and VCAM-1) of the endothelial cells to amplify migration of leukocytes, and it causes leukocyte accumulation and activation by increasing HLA-class II levels. Moreover, TNF-α promotes angiogenesis that delivers nutrients and immune cells to the affected tissue. In general, the diagram is a well-founded explanation of the multidimensional role of TNF-alpha in the mechanisms of inflammation and immune modulation in the pathological processes, especially chronic inflammatory diseases.

2.3 Interleukin 6 (IL-6)

IL-6, produced by synoviocytes and infiltrating cells, signals through gp130/JAK/STAT3 in chondrocytes and synovium. IL-6 stimulates expression of MMPs and catabolic factors in cartilage and promotes osteoclastogenesis via RANKL induction. In vitro, IL-6 increases chondrocyte MMP secretion and apoptosis 35. IL-6 also drives Th17 differentiation, indirectly boosting IL-17 levels.36 Clinically, IL-6 receptor blockade (tocilizumab, sarilumab) slows cartilage loss and reduces bone erosion, underscoring IL-6's destructive role.37 Figure 2 illustrates the pleiotropic inflammatory effects of TNF-α released from activated macrophages.

2.4 Interleukin 17 (IL-17)

IL-17A from Th17 cells is abundant in RA joints and intensifies cartilage damage. IL-17R signalling activates NF-κB and MAPKs in chondrocytes, upregulating IL-6, IL-8, and MMPs (e.g. MMP-13)38. IL-17 synergises with TNF-α and IL-1β to amplify catabolic gene expression in synovium and cartilage39. Though IL-17 inhibitors are more effective in spondylarthritis, IL-17 contributes to RA cartilage destruction by driving inflammatory mediator release and ECM degradation 40.

Table 1. Key proinflammatory cytokines and their effects on RA cartilage. Major roles are compiled from recent studies 41-45.

Cytokine	Source Cells	Cartilage Effects	References
IL-1β	Macrophages, synovial fibroblasts	↑ MMPs/ADAMTS, ↑ NO/PGE_2 (↓ matrix synthesis), ↑ TNF/IL-6/IL-17	[41], [42]
TNF-α	Macrophages, fibroblasts	↑ MMPs/ADAMTS, ↑ IL-6/IL-8 from chondrocytes, chondrocyte apoptosis	[43], [44]
IL-6	Synoviocytes, macrophages, and T cells	JAK/STAT3 activation → MMP expression, RANKL induction, chondrocyte apoptosis	[45]
IL-17A	Th17 cells, others	↑ MMPs (esp. MMP-13), ↑ chemokines, synergise with TNF/IL-1 for cartilage erosion	[43], [42]

3. Intracellular Signalling Pathways

Cytokine receptors on synovial and chondrocyte surfaces trigger classical intracellular cascades that mediate inflammation and catabolism. Three major pathways are NF-κB, MAPK (p38, JNK, ERK), and JAK/STAT.46-48

3.1 NF-κB Pathway

The NF-κB pathway is a master regulator of inflammatory gene transcription in RA. Stimulation by TNF-α, IL-1β, or TLR ligands leads to IKK complex activation, degradation of IκBα, and nuclear translocation of NF-κB (p65/p50)49. In the nucleus, NF-κB upregulates numerous proinflammatory genes, including TNF-α, IL-1β, IL-6, COX2, and MMPs 50. Pathological NF-κB activation in RA synovium and cartilage perpetuates cytokine production and MMP expression, driving cartilage breakdown51. Excessive NF-κB signalling also promotes chondrocyte apoptosis and synovial hyperplasia. Inhibiting NF-κB (via IKK inhibitors or cytokine blockade) reduces MMP-1, -3, -9, and -13, and cartilage degradation52.

3.3 JAK/STAT Signalling

The JAK/STAT pathway transduces signals from cytokines like IL-6, IL-2, IL-15, and interferons. In RA, IL-6 binding IL-6R/gp130 activates JAK1/JAK2 to phosphorylate STAT356. Phospho-STAT3 dimerises and induces transcription of target genes involved in survival, proliferation, and inflammation (e.g., SOCS3, RANKL). Dysregulated JAK/STAT signalling is strongly associated with RA synovitis and cartilage destruction57. In chondrocytes, JAK/STAT3 can upregulate MMPs and promote apoptosis under cytokine exposure. The clinical success of JAK inhibitors (tofacitinib, baricitinib) in reducing synovitis and bone erosion underscores the pathway's importance in RA pathology 58. Table 2 summarises these major pathways, their activators, and downstream effects.

Table 2. Major signalling pathways in RA chondrocytes, activators, and downstream effects. Key outcomes are summarised from recent studies 59-61.

Pathway	Activated by	Downstream Effects	References
NF-κB	TNF-α, IL-1β, TLR ligands	↑ Proinflammatory cytokines (TNF, IL-1, IL-6) and MMPs; chronic inflammation	[59]
MAPK	TNF-α, IL-1β, IL-17	Activation of AP-1; ↑ MMPs (e.g., MMP-1, MMP-13), cytokines, and chondrocyte apoptosis	[60]
JAK/STAT	IL-6, IL-2 family, GM-CSF	STAT3 activation; ↑ inflammatory gene expression (e.g., RANKL, IL6); synovial hyperplasia	[61]

3.2 MAPK Cascades

MAPK pathways (p38, JNK, ERK) are activated by cytokines and stress in RA chondrocytes. IL-1β and TNF-α strongly activate p38 and JNK, leading to phosphorylation of AP-1 transcription factors (c-Jun/c-Fos)53. AP-1 then drives expression of MMPs and inflammatory cytokines in cartilage. For example, IL-1β–induced MMP-13 in chondrocytes is MAPK-dependent54. ERK signalling (often via TNF-α) can also regulate both anabolic and catabolic genes through EGR-1 and other transcription factors 55. Overall, MAPKs amplify cytokine signals to boost degradative enzyme production and block cartilage repair.

4. Extracellular Matrix Degrading Enzymes

4.1 Matrix Metalloproteinases (MMPs)

MMPs are zinc-dependent proteases that cleave collagen and other ECM proteins. In RA, chondrocytes and synovial fibroblasts overexpress MMP-1, -3, -13, and others under cytokine stimulation 62,63. MMP-13 (collagenase-3) is especially potent against type II collagen in cartilage. Pro-inflammatory signals (IL-1, TNF, IL-17) upregulate MMP gene transcription via NF-κB/AP-1. Active MMPs degrade the collagen II network, leading to irreversible cartilage erosion. Clinical studies show elevated MMP levels correlate with joint damage in RA. Inhibition of MMPs (e.g., by TIMPs or synthetic inhibitors) can partly protect cartilage in vitro, highlighting their central role.

4.2 ADAMTS Aggrecanases

ADAMTS-4 and ADAMTS-5 are the main aggrecanases that degrade aggrecan, the cartilage proteoglycan. IL-1β and TNF-α strongly induce ADAMTS expression in chondrocytes and fibroblasts64. ADAMTS-mediated aggrecan cleavage yields aggrecan fragments that elicit further inflammation 65. Loss of aggrecan renders cartilage susceptible to collagen breakdown by MMPs. In RA joints, elevated ADAMTS activity is evident and contributes to cartilage thinning. Selective ADAMTS inhibitors are under investigation, as broad MMP inhibitors proved too toxic. Combined, MMPs and ADAMTS drive the bulk of cytokine-induced ECM destruction in RA cartilage 66.

5. Chondrocyte Fate and Phenotypic Alterations

5.1 Apoptosis

Unlike synovial cells, RA chondrocytes often undergo apoptosis. TNF-α, IL-1β and IL-17 can directly trigger death pathways in chondrocytes via caspase-8 and mitochondrial routes. For example, TNF-α (with IFN-γ) reduces chondrocyte viability67. Elevated chondrocyte apoptosis is observed in human RA cartilage and animal models68. Inflammatory mediators (FasL, nitric oxide) also sensitise chondrocytes to apoptosis. Loss of chondrocytes leads to insufficient matrix maintenance and repair. Conversely, some studies note resistance to apoptosis in synovial fibroblasts in RA, highlighting a paradox of hyperplasia in the joint lining versus chondrocyte death in cartilage 69.

5.2 Molecular Reprogramming

RA chondrocytes acquire a pro-inflammatory, catabolic phenotype. Under cytokine exposure, they not only release MMPs and ADAMTS, but also produce cytokines and chemokines themselves 70. For instance, IL-1β activation of chondrocytes induces IL-6 and IL-8 production via IKK/NF-κB pathways. Synovial signals upregulate IKKβ and inflammatory genes in chondrocytes 71. This “reprogramming” means chondrocytes become active participants in joint inflammation, contributing to a self-amplifying loop of cartilage damage. At the molecular level, chronic inflammation triggers epigenetic changes (below) and alters transcription factor profiles in chondrocytes, shifting the balance from anabolic to catabolic gene expression. Thus, chondrocytes in RA emerge as effector cells that perpetuate matrix degradation 72.

6. Epigenetic and Post-transcriptional Regulation

Epigenetic mechanisms modulate cytokine-driven pathways in RA. Aberrant DNA methylation patterns have been reported in RA, affecting the expression of cytokines and degradative enzymes 73. For example, hypomethylation of inflammatory gene promoters can sustain their overexpression. Non-coding RNAs, especially microRNAs, also regulate cartilage catabolism. Specific miRNAs are dysregulated in RA chondrocytes: miR-23a normally suppresses IL-17–induced inflammation (by targeting IKKα), and is downregulated in RA, leading to heightened NF-κB signalling 74. miR-26a is decreased in RA cartilage; its restoration reduces chondrocyte apoptosis and inflammation (pmc.ncbi.nlm.nih.gov). miR-27b-3p levels drop in RA, and overexpressing it suppresses pro-apoptotic factors in chondrocytes 75. Other miRNAs (e.g., miR-146a, miR-155) influence the cytokine signalling systemically 76. These epigenetic and post-transcriptional changes fine-tune chondrocyte responses to cytokines and are potential therapeutic targets.

7. Therapeutic Implications

Blocking cytokine pathways can protect cartilage in RA. Biologic DMARDs that target TNF-α (etanercept, infliximab, adalimumab) or IL-6R (tocilizumab, sarilumab) dramatically slow radiographic progression 77,78. TNF inhibitors reduce synovial MMP and ADAMTS production, preserving cartilage 79,80. IL-1 blockade with anakinra has only modest effects, likely because redundant cytokines compensate 81 (Table 3 summarises major approved agents.) JAK inhibitors (tofacitinib, baricitinib, upadacitinib) interrupt the signalling of IL-6 and other cytokines and are effective in reducing erosion and inflammation. MMP/ADAMTS inhibitors have been explored: broad-spectrum MMP inhibitors failed clinically due to toxicity, but selective ADAMTS-5 inhibitors are under development. Other novel approaches include GM-CSF inhibitors (mavrilimumab) and strategies to modulate epigenetic regulators. Overall, targeting these molecular pathways can greatly mitigate cartilage destruction in RA82.

Table 3. Therapeutic interventions targeting cytokine-mediated joint damage. Clinical agents and their molecular targets are listed (examples and key effects on cartilage).

Therapy	Target	Examples	Effect on Cartilage	References
TNF inhibitors	TNF-α	Etanercept, Infliximab, Adalimumab	↓ MMP/ADAMTS release; halt erosions	[83], [84]
IL-6R inhibitors	IL-6 receptor	Tocilizumab, Sarilumab	↓ inflammation and osteoclastogenesis; slow erosion	[84]
IL-1R inhibitors	IL-1 receptor	Anakinra, Canakinumab	Moderate reduction in inflammation; modest bone/cartilage protection	[85]
JAK inhibitors	JAK1/2/3	Tofacitinib, Baricitinib, Upadacitinib	↓ STAT3-mediated catabolism; improve cartilage markers	[84]
MMP/ADAMTS inhibitors	MMPs / ADAMTS-5	– (none approved)	Preclinical ADAMTS-5 inhibitors aim to prevent aggrecan loss	[84]
Emerging/Future	Various (e.g., GM-CSF)	Mavrilimumab (anti–GM–CSF), others	Under study: potential to reduce cytokine cascades and tissue damage	[84]

Future Perspectives: Understanding of cytokine cross-talk and intracellular networks continues to grow. Novel approaches such as dual cytokine blockade, cell-based therapies, and targeting miRNAs or epigenetic enzymes are in development. The ultimate goal is to precisely interrupt the molecular switches of cartilage destruction to achieve remission of RA without structural damage.

Declaration:

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Authors' contributions:

- Subhendu Dey- Conceptualisation, Writing—original draft preparation
- Chayanika Goswami- Technical support with literature search/figure preparation
- Tanmay Mohanta- Review and editing
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- Subham Roy-Review and editing
- Didhiti De- Writing, review, and editing, Visualisation
- Subhasish Saha- Supervision

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Table 4: List of Abbreviations

Abbreviation	Full form / Description

ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin motifs (aggrecanases / ADAMTS family)
ADAMTS-4	A Disintegrin and Metalloproteinase with Thrombospondin motifs 4
ADAMTS-5	A Disintegrin and Metalloproteinase with Thrombospondin motifs 5
AP-1	Activator protein-1 (transcription factor)
c-Fos	Component of AP-1 transcription factor
c-Jun	Component of AP-1 transcription factor
caspase-8	Initiator caspase involved in apoptosis
COX2	Cyclooxygenase-2
DMARDs	Disease-modifying antirheumatic drugs
DNAme	DNA methylation
ECM	Extracellular matrix
ERK	Extracellular signal-regulated kinase (a MAPK)
FasL	Fas ligand (apoptosis mediator)
FLS	Fibroblast-like synoviocytes
GM-CSF	Granulocyte–macrophage colony-stimulating factor
gp130	Glycoprotein 130 (IL-6 signal transducer)
IFN-γ	Interferon-gamma
IKK	IκB kinase complex (activates NF-κB)
IL-1	Interleukin-1 (general form)
IL-17	Interleukin-17
IL-17R	Interleukin-17 receptor
IL-1R1	Interleukin-1 receptor type 1
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2
IL-6	Interleukin-6
IκBα	Inhibitor of κB alpha (NF-κB inhibitor)
JAK-STAT	Janus kinase — signal transducer and activator of transcription (signalling pathway)
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JNK	c-Jun N-terminal kinase (a MAPK)
MAPKs	Mitogen-activated protein kinases
miR-146a	microRNA-146a
miR-155	microRNA-155
miR-23a	microRNA-23a
miR-26a	microRNA-26a
miR-27b-3p	microRNA-27b-3p
miRNA	MicroRNA (post-transcriptional regulators)
MLS	Macrophage-like synoviocytes
MMP-1	Matrix metalloproteinase-1
MMP-13	Matrix metalloproteinase-13 (collagenase-3)
MMP-3	Matrix metalloproteinase-3
MMPs	Matrix metalloproteinases (ECM-degrading enzymes)
NF-κB	Nuclear factor-kappa B (inflammatory transcription factor)
NO	Nitric oxide
p38	p38 MAP kinase (a MAPK)
p50	NF-κB p50 subunit
p65	NF-κB p65 (RelA) subunit
PGE_2	Prostaglandin E_2
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor-κB ligand (osteoclastogenic factor)
SOCS3	Suppressor of cytokine signaling 3
STAT3	Signal transducer and activator of transcription 3
Th17	T helper 17 cells (IL-17-producing T cell subset)
TIMPs	Tissue inhibitors of metalloproteinases
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor-alpha
TNFR1	Tumor necrosis factor receptor 1
TNFα	Tumor necrosis factor-alpha (alternate notation)

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