Expert Reviews in Molecular Medicine

www.cambridge.org/erm

Unveiling the Therapeutic Potential: Targeting Fibroblast-like Synoviocytes in Rheumatoid Arthritis

Siran Yue[1,2], Junyu Fan[1,2,3], Duoli Xie[1,2], Chunhao Cao[1,2], Zhuqian Wang[1,2], Jie Huang[1,2], Fang Qiu[1,2], Xu Yang[4], Dongyi He[3], Aiping Lu[2,5,6] and Chao Liang[1,2,7]

[1]Department of Systems Biology, School of Life Sciences, Southern University of Science and Technology, Shenzhen, China; [2]Institute of Integrated Bioinfomedicine and Translational Science (IBTS), School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China; [3]Department of Rheumatology, Guanghua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China; [4]Department of Computational Biology, St. Jude Children's Research Hospital, Memphis, TN, USA; [5]Guangdong-Hong Kong-Macau Joint Lab on Chinese Medicine and Immune Disease Research, Guangzhou, China; [6]Shanghai University of Traditional Chinese Medicine, Shanghai, China and [7]State Key Laboratory of Proteomics, National Center for Protein Sciences (Beijing), Beijing Institute of Lifeomics, Beijing, China

Review

Cite this article: Yue S, Fan J, Xie D, Cao C, Wang Z, Huang J, Qiu F, Yang X, He D, Lu A and Liang C (2025). Unveiling the Therapeutic Potential: Targeting Fibroblast-like Synoviocytes in Rheumatoid Arthritis. *Expert Reviews in Molecular Medicine*, **27**, e18, 1–13
https://doi.org/10.1017/erm.2025.11

Received: 10 October 2023
Revised: 06 May 2024
Accepted: 02 April 2025

Keywords:
fibroblast-like synoviocytes; pannus; rheumatoid arthritis; synovium; targeted therapy

Corresponding authors:
Dongyi He, Aiping Lu and Chao Liang;
Emails: hedongyi1967@shutcm.edu.cn; aipinglu@hkbu.edu.hk; liangc@sustech.edu.cn

S.Y., J.F. and D.X. authors contributed equally to this review.

Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the synovial membrane, leading to cartilage destruction and bone erosion. Due to the complex pathogenesis of RA and the limitations of current therapies, increasing research attention has been directed towards novel strategies targeting fibroblast-like synoviocytes (FLS), which are key cellular components of the hyperplastic pannus. Recent studies have highlighted the pivotal role of FLS in the initiation and progression of RA, driven by their tumour-like transformation and the secretion of pro-inflammatory mediators, including cytokines, chemokines and matrix metalloproteinases. The aggressive phenotype of RA-FLS is marked by excessive proliferation, resistance to apoptosis, and enhanced migratory and invasive capacities. Consequently, FLS-targeted therapies represent a promising avenue for the development of next-generation RA treatments. The efficacy of such strategies – particularly those aimed at modulating FLS signalling pathways – has been demonstrated in both preclinical and clinical settings, underscoring their therapeutic potential. This review provides an updated overview of the pathogenic mechanisms and functional roles of FLS in RA, with a focus on critical signalling pathways under investigation, including Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), Notch and interleukin-1 receptor-associated kinase 4 (IRAK4). In addition, we discuss the emerging understanding of FLS-subset-specific contributions to immunometabolism and explore how computational biology is shaping novel targeted therapeutic strategies. A deeper understanding of the molecular and functional heterogeneity of FLS may pave the way for more effective and precise therapeutic interventions in RA.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic joint inflammation, hyperplastic synovial pannus formation, and joint and bone destruction (Ref. 1). Globally, RA impacts about 0.5% of the population, exhibiting a higher incidence in women than in men (Ref. 2). Although targeted therapies like disease-modifying anti-rheumatic drugs, biologics, steroids and anti-inflammatory drugs have improved outcomes in RA patients, a considerable population of patients still exhibit persistent nonresponse (Refs. 3, 4, 5, 6, 7, 8). The variation in treatment responses indicates that RA involves diverse underlying mechanisms, despite the similarity in clinical symptoms among patients. This highlights the importance of identifying novel therapeutic targets. Recent studies have emphasized the critical role of mesenchymal-cell-derived cells, particularly fibroblast-like synoviocytes (FLS), in both initiating and perpetuating the complex processes in RA. Thus, developing strategies that specifically target FLS can offer new perspectives and significantly improve the treatment of RA (Refs. 9, 10, 11, 12, 13, 14).

The composition of synovial tissue in RA primarily consists of cells, including macrophage-like cells (MLCs), T lymphocytes, myeloid cells and FLS (Refs. 15, 16). FLS are crucial cell types lining articular joints, reflecting the inflammatory state and joint destruction in RA (Ref. 17). The pathogenesis of RA begins with the abnormal activation of FLS, which proliferate excessively and resist apoptosis, leading to the formation of a hyperplastic synovial pannus. The pannus invades and erodes adjacent cartilage and bone, causing the characteristic joint damage observed in

RA. FLS in RA also secrete pro-inflammatory cytokines, chemokines and matrix metalloproteinases (MMPs), which further exacerbate joint inflammation and degradation (Refs. 18, 19, 20). Consequently, various aspects of the life cycle and activation of RA-FLS can be targeted, including their generation and proliferation, migration, direct destructive functions, and interactions with leukocytes (Ref. 21). Advances in molecular biology, immunology and computational biology have improved our understanding of the heterogeneous nature of FLS and their interactions with immune cells within the synovial environment of the joint. In this review, we highlight the role of FLS in promoting pannus formation and investigate the molecular mechanisms that regulate the balance between resident FLS and joint pathogenesis. We also emphasize the potential of targeting FLS and their signalling pathways, such as Janus kinase /signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), Notch and interleukin-1 receptor-associated kinase 4 (IRAK4), as therapeutic strategies. These approaches hold promise for developing more effective treatments that could potentially halt or reverse the progression of RA. Moreover, we consider the fields of immunometabolism and computational biology, discussing their potential for therapeutic interventions targeting FLS. These insights may open up new avenues for developing FLS-targeted strategies for treating RA patients.

The physiological role of FLS

A healthy diarthrodial joint is lined by the synovium, a thin membrane composed of soft tissue. This structure typically consists of a few cell layers and includes type A synoviocytes (macrophage-like synoviocytes) and type B synoviocytes (FLS). FLS, as specialized mesenchymal cells, are essential in maintaining the structure of the synovium, featuring a substantial amount of rough endoplasmic reticulum. The synovium forms a protective membrane at the edges of joints, providing lubrication and nourishment to the cartilage through the production of synovial fluid (Ref. 22), which is crucial for maintaining joint integrity (Ref. 10). Additionally, FLS are instrumental in regulating the synovial fluid and the extracellular matrix (ECM) of the joint lining, critical for maintaining the structural and functional integrity of diarthrodial joints. They actively produce various matrix components such as collagen, tenascin, laminin and proteoglycans, as well as enzymes that regulate ECM degradation, including MMPs, cathepsins and proteases (Ref. 5).

FLS also serve as vigilant immune sentinels that are capable of producing cytokines, small-molecule mediators and proteases, thereby forming the synovial intima (Ref. 17). The observation that inflammation is suppressed in mice lacking the FLS scaffold further highlights their immunomodulatory effects (Ref. 11). Beyond their role in producing pro-inflammatory mediators, FLS contribute to a synovial matrix that encompasses macrophages and other leukocytes, thus facilitating the activation of these cells.

The pathological transformations of FLS in RA

In RA, the infiltrating synovium primarily consists of FLS, comparable to tumour cells (Refs. 10, 14). Studies indicated that an increase in FLS contributes to inflammation, hyperplasia and aggressiveness in the synovial lining, triggered by exposure to platelet-derived growth factor (PDGF), tumour necrosis factor (TNF) or interleukin (IL)-1. This leads to the formation of a destructive tissue known as pannus (Refs. 23, 24), which damages the cartilage and non-osseous structural elements of the joint microenvironment in RA (Refs. 25, 26, 27) (see Figure 1). Targeting FLS was considered a critical therapeutic approach in managing

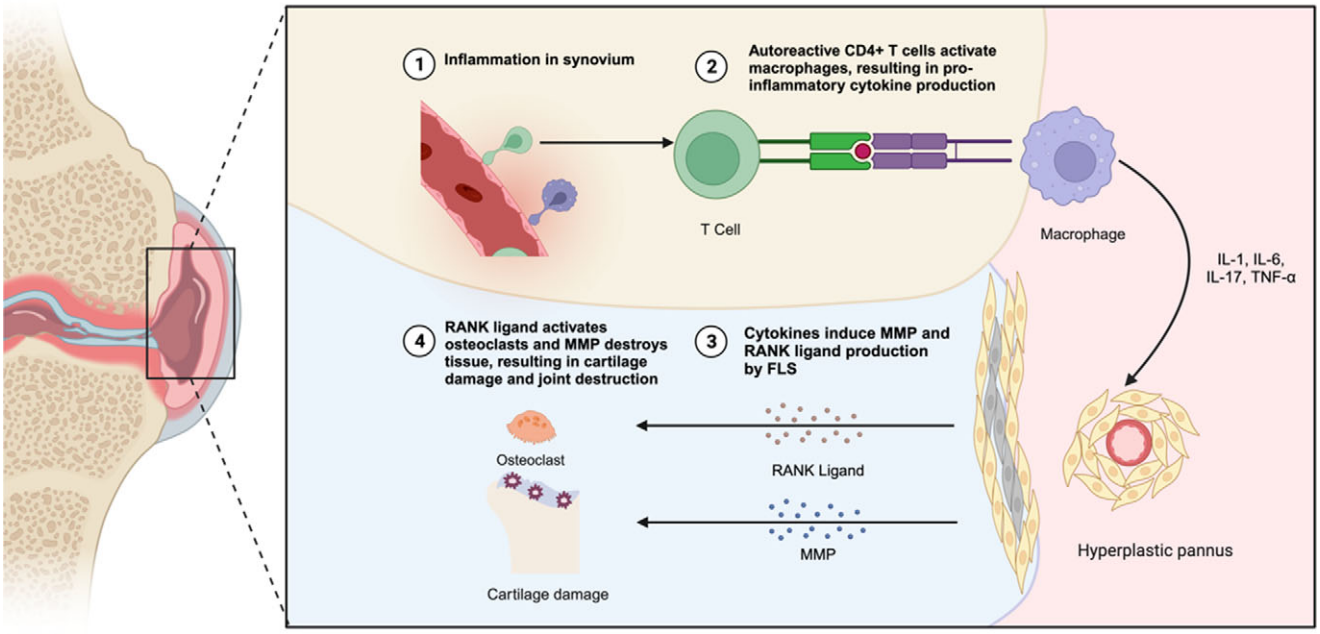

Figure 1. The pathological changes in the RA synovial joint. In RA, the synovial lining undergoes hyperplasia, forming an invasive pannus that contributes to joint destruction. FLS play a central role in this process by producing pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and chemokines that drive chronic inflammation and cartilage degradation. Additionally, FLS interact with immune cells such as macrophages, which secrete TNF-α and IL-1β, further amplifying inflammatory signalling, and T cells, which activate FLS via IL-17 and other cytokines. This crosstalk promotes the recruitment and activation of osteoclast precursors, enhancing bone erosion while simultaneously inhibiting osteoblast-mediated bone repair. The combined effects of these pathological interactions lead to irreversible joint damage and progressive disability in RA patients.

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

RA, focussing on reducing inflammation and halting disease progression (Refs. 11, 28).

The impact of FLS proliferation and pannus formation in RA

FLS proliferation significantly contributes to RA pathogenesis through excessive proliferation in the synovial lining and sublining. Several factors drive their proliferation, including resistance to apoptosis, enhanced autophagy, growth factors, inflammatory cytokines and stress responses with the endoplasmic reticulum stress (ERS) (Refs. 29, 30, 31, 32, 33). Additionally, the differentiation and migration of mesenchymal stem cells into the synovium further promote FLS accumulation, enhancing synovial tissue thickening (hyperplasia) (Refs. 34, 35). Recent studies have identified pre-inflammatory mesenchymal (PRIME) cells, which infiltrate the synovium during RA flare-ups. These PRIME cells interact with endothelial cells, subsequently differentiating into sublining FLS subsets, thus contributing to synovial expansion and disease progression (Refs. 36, 37). The proliferation and invasive characteristics of FLS also drive the formation of pannus, an aggressive fibrovascular tissue that contributes directly to joint damage in RA. Within pannus tissue, FLS exhibit tumour-like properties, including increased invasiveness, migration and resistance to normal growth inhibition, enabling their spread and infiltration into joint structures (Refs. 1, 29) These pannus-resident FLS, influenced by inflammatory mediators such as galectin-3, produce large amounts of matrix-degrading enzymes, cytokines and chemokines, accelerating immune cell infiltration, cartilage destruction and joint erosion (Refs. 38, 39).

Within the synovium, FLS exhibit marked heterogeneity, which can be classified based on their functional roles and anatomical localization (see Table 1). Beyond surface marker expression, single-cell RNA sequencing (scRNA-seq) has offered deeper insight into the dynamic phenotypes of FLS subsets in RA. ScRNA-seq studies from both human RA patients and murine models have revealed a conserved landscape of FLS subsets implicated in disease pathogenesis. In mice, distinct fibroblast populations localize to the synovial lining and sublining regions, with inflammatory and matrix-remodelling subsets expanding during arthritis progression (Ref. 18). Likewise, human RA synovium harbours transcriptionally analogous populations, including immunofibroblasts expressing human leukocyte antigen-DR alpha (HLA-DRA), IL-6, and destructive fibroblasts marked by MMP-3, MMP-9 and FAP (Ref. 15). Cross-species comparisons confirm the conservation of these pathogenic phenotypes, indicating that murine models effectively recapitulate human FLS heterogeneity. Notably, therapeutic targeting of specific subsets – such as FAP^+ fibroblasts – in mice reduces inflammation and joint damage, emphasizing the translational potential of subset-specific strategies in human RA (Ref. 47). Overall, identifying these functional and locational markers provides valuable insights into RA pathogenesis and supports targeted therapeutic strategies aimed at reducing inflammation and preserving joint integrity.

Table 1. The key markers expressed by FLS

Type	Markers	Characteristics
Locational markers	CD55	A classic marker of lining layer FLS (SC-F4), which are involved in maintaining the synovial barrier and are more stable in phenotype. CD55+ FLS also show activity in oxidative stress regulation and endothelial interactions (Ref. 18).
	THY1 (CD90)	Marks sublining FLS, which are typically more inflammatory and invasive. Loss of CD90 expression during FLS migration may reflect a phenotypic transition from matrix remodelling to more destructive behaviours (Ref. 18).
	CD248 (endosialin)	Localized to sublining regions, indicating its role in the deeper synovial layer involved in vascular and immune interactions (Refs. 15, 40, 41, 42).
	PDPN (podoplanin)	Primarily expressed in the lining layer, where it marks a subset involved in cartilage invasion and tissue remodelling (Refs. 18, 43).
Functional markers	Cadherin11 (CDH11)	A cell adhesion molecule highly expressed in RA-FLS. Genetic deletion of CDH11 in animal models significantly reduces synovial hyperplasia, inflammation and joint erosion, underscoring its central role in disease progression (Ref. 44).
	Fibroblast activation protein-α (FAPα)	A protease associated with tissue remodelling. FAP+ FLS subsets play dual roles: FAP^+CD90^+ cells are linked to inflammation via cytokine and chemokine production, while FAP^+CD90^- cells drive cartilage and bone destruction (Ref. 18).
	VCAM–1 (CD106)	An adhesion molecule upregulated in response to TNF-α and IL–1β. It mediates the interaction between FLS and immune cells, contributing to leukocyte recruitment and chronic synovial inflammation (Refs. 45, 46).

The role of macrophages and FLS interactions in RA

Under normal conditions, macrophages are key cellular components of the synovium. Using scRNA-seq and immunometabolism analyses, various subpopulations of macrophages with distinct homoeostatic, regulatory and inflammatory functions have been identified within the synovium (Ref. 25). In RA, the interaction between FLS and macrophages plays a critical role in both the initiation of synovial inflammation and subsequent joint destruction.

CX3CR1+ macrophages, which form a protective barrier layer alongside fibroblasts in the synovial tissue, comprise 40% of the macrophage population under resting conditions. Their removal in experimental arthritis models in mice leads to the infiltration of cells derived from monocytes and neutrophils, damaging the synovial barrier. These findings highlight the critical role of CX3CR1+ macrophages as a primary immune-regulatory checkpoint in controlling synovial inflammation. Dysfunction of this checkpoint results in chronic joint inflammation. When CX3CR1 + macrophages are removed from the synovium in mice with experimental arthritis, an influx of neutrophils and monocyte-derived cells into the synovium occurs, causing damage to the synovial barrier (Ref. 48). Recently, Alivernini et al. observed that compared to patients with active RA, healthy synovium and patients in remission from RA had higher numbers of MERTK+ $TREM2^{high}$ and LYVE1+ macrophages. Synovial tissues with a

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

lower number of these cellular subgroups were more prone to flare-ups (Ref. 25). MERTK+ macrophages are known to produce pro-resolving lipids and promote FLS repair, while MERTK− macrophages proliferate and release high levels of TNF-α and IL-6 during the active phase, leading to pathogenic FLS activation (Ref. 25). Thus, MERTK+ macrophages act as a crucial inhibitory mechanism to counteract pro-inflammatory FLS behaviours. In the absence of this checkpoint, pathogenic FLS subsets may develop with sustained activation.

FLS release chemokines such as CCL2, CCL5, CCL8, CXCL5 and CXCL10 in response to inflammatory stimuli, which lead to the recruitment of macrophages and monocytes (Ref. 14). RA is driven by cytokine networks at the sites of inflammation (Refs. 49, 50, 51). TNF-induced soluble factors from RA-FLS inhibit the expression of type I interferon-regulated genes in macrophages by downregulating JAK/STAT signalling (Ref. 52). Alongside pro-inflammatory factors, prostaglandins produced by RA-FLS induce macrophages into a state characterized by an increased production of pro-heparin-binding EGF-like growth factor (HBEGF) and pro-inflammatory genes (Ref. 53). It is widely recognized that macrophages are the primary source of IL-1β and TNF, while FLS in the intimal lining are the main producers of IL-6 (Ref. 54). Additionally, FLS in the intimal lining secrete colony-stimulating factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage-colony stimulating factor (M-CSF) (Ref. 55). IL-1β/TNF-stimulated FLS upregulate GM-CSF production, further facilitating the recruitment and activation of macrophages. Therapies targeting CXCL10 and GM-CSF receptors have shown promising results in RA treatment (Refs. 56, 57).

Another aspect of the complex interaction between macrophages and FLS is the differentiation of macrophages into osteoclasts, specialized cells that absorb bone. Multinucleated osteoclasts perform extensive bone resorption at the apex of the pannus (Ref. 58). A key factor in the differentiation of macrophages into osteoclasts is receptor activator of nuclear factor kappa B ligand (RANKL) (Refs. 59, 60). Upon activation, FLS can produce a significant amount of RANKL and M-CSF (Ref. 61). Clinical trials involving anti-RANKL antibodies have shown significant efficacy in reducing bone loss associated with RA (Ref. 62). Moreover, RA-FLS inhibit the activation of osteoblasts by secreting Dickkopf-1, a regulator of the Wnt signalling pathway, thereby impeding the repair processes of bone erosions (Ref. 63).

The epigenic modification in RA-FLS

Emerging evidence underscores the significance of epigenetic modifications, including DNA methylation, SUMOylation, histone modifications and non-coding RNA (ncRNA) expression, in the pathogenesis of RA (Refs. 64, 65, 66). These epigenetic changes critically influence FLS behaviour, promoting inflammation, invasion and joint damage. Additionally, genetic mutations in TP53 (Ref. 67) contribute further to apoptosis resistance, enhanced survival and invasiveness of RA-FLS. Furthermore, mitochondrial dysfunction induced by inflammatory signalling exacerbates oxidative stress and inflammation in the synovium (Refs. 68, 69).

DNA methylation, a crucial epigenetic modification regulating gene expression, is increasingly recognized as a key driver of the aggressive and invasive behaviour of FLS in RA. RA-FLS display distinct genome-wide DNA methylation patterns compared to healthy synovial fibroblasts, characterized by widespread hypomethylation, particularly in promoter regions of genes involved in inflammation, matrix degradation and cellular adhesion. This altered methylation landscape facilitates aberrant gene expression, promoting synovial hyperplasia and joint destruction (Refs. 64, 66). This aberrant methylation pattern leads to the overexpression of pro-inflammatory cytokines and MMPs, thereby enhancing synovial inflammation and tissue invasion. One key target gene, phosphatase and tensin homolog (PTEN), known for its anti-inflammatory and anti-proliferative effects, is epigenetically silenced in RA-FLS through promoter hypermethylation. This modification is induced by pro-inflammatory stimuli such as TNF-α and contributes to the increased production of cytokines and chemokines, as well as enhanced FLS proliferation and migration (Refs. 70, 71). Additionally, the upregulation of DNA methyltransferases (DNMTs), particularly DNMT1, further contributes to maintaining this aberrant methylation landscape (Ref. 71). Integrative epigenomic and transcriptomic analyses have identified numerous hypomethylated, overexpressed genes in RA-FLS, including Huntingtin-interacting protein 1 (HIP1) and other regulators of cytoskeletal remodelling and cell migration, providing mechanistic insights into FLS invasiveness (Refs. 70, 71, 72). Collectively, these findings highlight DNA methylation as a dynamic and functional contributor to the pathological activation of RA-FLS. Targeting specific epigenetic alterations, particularly those regulating key genes like PTEN and HIP1, may offer novel therapeutic strategies to limit joint damage and inflammation in RA.

Epigenetic modifications such as SUMOylation and histone modifications play integral roles in the pathological activation and invasive phenotype of FLS in RA. SUMOylation, a post-translational process involving the covalent attachment of small ubiquitin-like modifier (SUMO) proteins to lysine residues of target proteins, regulates their stability, localization and interactions (Ref. 73). In RA-FLS, components of the SUMOylation pathway, including the SUMO-activating enzyme SAE1/UBA2 and the conjugating enzyme UBC9, are significantly upregulated (Refs. 74, 75, 76, 77). This enhanced SUMOylation promotes glycolytic reprogramming via modification of pyruvate kinase M2 (PKM2) and increases the secretion of inflammatory mediators such as vascular endothelial growth factor (VEGF)-A, MMP-3 and MMP-9, thereby driving FLS proliferation, migration and joint invasion. Importantly, SUMOylation and histone modifications are tightly linked processes; SUMOylation can directly modify histones or modulate histone-modifying enzymes, thereby influencing chromatin structure and gene expression (Ref. 78). A key regulatory axis in this system is the balance between SUMO ligases and deSUMOylating enzymes like SENP1. In RA-FLS, SENP1 is downregulated, contributing to excessive SUMOylation of transcription factors (TFs) and histones (Ref. 79). Notably, SUMOylation enhances histone H4 acetylation at the MMP-1 promoter, promoting its transcription and contributing to cartilage degradation. Restoration of SENP1 reverses these effects by reducing histone acetylation and MMP-1 expression (Ref. 80). Inflammatory cytokines such as TNF-α further amplify this epigenetic dysregulation by increasing histone deacetylase (HDAC) activity, which modifies chromatin structure and sustains pro-inflammatory gene expression (Ref. 81). This interplay creates a feedback loop that reinforces transcriptional programmes associated with inflammation and tissue invasion. Moreover, dysregulated SUMOylation intersects with key signalling pathways such as Wnt, further driving FLS proliferation and invasiveness (Ref. 82). A notable example is the overexpression of the histone methyltransferase enhancer of zeste homolog 2 (EZH2), which catalyses H3K27 trimethylation and represses secreted frizzled-related protein 1 (SFRP1) – an endogenous inhibitor of the Wnt pathway (Ref. 83). Suppression of SFRP1

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

by EZH2 promotes unchecked Wnt signalling, exacerbating RA synovial pathology. Collectively, these findings highlight how SUMOylation acts in concert with histone modifications – particularly acetylation and methylation – to reprogramme RA-FLS towards an aggressive, tissue-destructive phenotype. Targeting components of these pathways, such as SAE1/UBA2, UBC9, SENP1, HDACs and EZH2, offers promising therapeutic potential to reduce synovial inflammation and joint damage in RA.

ncRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), also regulate RA-FLS behaviour by modulating gene expression at transcriptional and post-transcriptional levels (Refs. 84, 85). miRNAs typically suppress target gene expression by binding to messenger RNAs (mRNAs), causing mRNA degradation or inhibiting translation. Researchers found that miR-221 levels were increased in the serum and synovial tissues of RA patients compared to healthy controls (Ref. 86). When miR-221 was downregulated in FLS stimulated with lipopolysaccharide (LPS), there was a significant decrease in the expression of pro-inflammatory cytokines and chemokines. Additionally, the downregulation of miR-221 inhibited FLS migration and invasion, which was associated with the reduced expression of VEGF, MMP-3 and MMP-9. These findings suggest that miR-221 contributes to RA pathogenesis by promoting inflammation and joint destruction through the upregulation of MMPs and other pro-inflammatory mediators (Refs. 86, 87). Conversely, lncRNAs regulate gene expression primarily via chromatin remodelling or recruiting transcriptional regulators. Homoeobox antisense intergenic RNA (HOTAIR), a lncRNA overexpressed in RA-FLS, can modulate the expression of specific MMPs such as MMP-2 and MMP-13 through epigenetic mechanisms. While increased HOTAIR typically suppresses certain MMPs, in various pathological contexts it paradoxically enhances cell invasiveness, illustrating context-dependent regulatory roles of lncRNAs (Refs. 88, 89).

Collectively, epigenetic modifications – DNA methylation, SUMOylation, histone acetylation and methylation, and ncRNA regulation – are central mechanisms governing the aggressive phenotype of RA-FLS. Improved understanding of these epigenetic pathways offers novel therapeutic avenues to mitigate RA-FLS-driven inflammation, invasiveness and joint destruction, ultimately improving patient outcomes.

Immunometabolism of FLS in RA

Discoveries in immunology have highlighted the importance of metabolic adaptations during the early stages of immune responses, now recognized as essential processes (Refs. 90, 91, 92, 93, 94). Increasing evidence has shown that metabolic changes affect stromal and immune cells (Refs. 95, 96, 97) and play a role in autoimmune diseases (Refs. 98, 99, 100). Various factors within the cellular microenvironment activate key signalling pathways that influence cellular metabolism, supporting cell growth and survival (Refs. 101, 102). Notably, metabolic disruption has been associated with RA (Ref. 103). In RA, FLS exhibit a unique metabolic profile within the inflamed joint milieu. Characterized by a hypermetabolic phenotype, FLS undergo substantial metabolic shifts that augment their proliferative and invasive capacities (Refs. 104, 105, 106).

Glucose metabolism of FLS in RA

As the first step of glucose metabolism, glycolysis often occurs in the cytoplasm of cells and produces only a small amount of total energy stored in adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NADP). Unlike normal cells, cancer cells tend to favour glycolysis to metabolize glucose over the more efficient oxidative phosphorylation, even in the presence of oxygen (the Warburg effect) (Ref. 107). Similar to cancer cells, RA-FLS also exhibit a Warburg-like metabolism, marked by increased glucose consumption and glycolytic flux (Ref. 102). Garcia-Carbonell et al. (Ref. 108) have observed an increased expression of glucose transporter 1 (GLUT1) mRNA in the synovial lining cells in a model of inflammatory arthritis. Additionally, glucose uptake and glycolytic gene expression were increased in the stromal compartment of arthritic mouse joints, indicating significant alterations in glucose metabolism in RA-FLS. This study also has highlighted the effectiveness of 3-bromopyruvate (BrPA) in alleviating RA in a mouse model of inflammatory arthritis by targeting hexokinase-2 (HK2) through inhibiting glycolysis. Other glycolytic inhibitors, such as 2-deoxyglucose (2-DG) (Ref. 109) and lonidamine (Ref. 110), have also been shown to inhibit glycolysis and regulate the inflammatory phenotype of RA-FLS, offering potential therapeutic approaches for managing RA.

Lactate metabolism of FLS in RA

Lactate production primarily occurs during conditions of increased aerobic glycolysis (Ref. 111). In the inflamed joint, there is a notable decrease in synovial fluid pH alongside an increase in lactate concentration, stemming from the intense cellular turnover within the synovium (Ref. 112). Monocarboxylate transporter 4 (MCT4) plays a role in transporting lactate out of tumour cells, supporting metastasis and angiogenesis (Refs. 113, 114). The expression levels of MCT4 mRNA and protein were markedly increased in RA-FLS compared to OA-FLS (Ref. 115). Using specific siRNA to silence MCT4 has demonstrated a reduction in arthritis severity in mouse models of RA, underscoring MCT4 as a promising therapeutic target for RA (Ref. 115).

Lipid metabolism of FLS in RA

Although our understanding continues to evolve, it is acknowledged that lipids play a pivotal role in both fuelling adaptive immunity and dampening inflammation (Refs. 103, 116). A notable finding was impaired mitochondrial fatty acid β-oxidation in FLS from individuals at risk of RA and RA patients, compared to healthy controls (Ref. 117). This deficiency, associated with decreased gene expression in the β-oxidation pathway, suggests a lipid metabolic inflexibility that could contribute to the onset of RA. In addition, there was a marked increase in phospholipid levels, notably phosphocholine (PCho), in tumour cells (Ref. 118). These increases in PCho were partially attributed to the increased activity of the enzyme choline kinase α (ChoKα), crucial for phosphatidylcholine (PtdCho) biosynthesis (Ref. 119). Guma et al. (Ref. 120) have found that ChoKα was increased in RA synovium, further demonstrating that targeting ChoKα could be effective in reducing migration and promoting apoptosis in RA-FLS. The ChoKα inhibitor MN58b has proven to be effective in the reduction of harmful behaviours in FLS, such as migration and resistance to apoptosis, which are vital in the progression of RA (Ref. 120).

Mitochondrial metabolism of FLS in RA

Mitochondria consume oxygen to generate ATP and produce metabolic intermediates of the tricarboxylic acid (TCA) cycle, participating in numerous metabolic pathways (Ref. 121). In RA

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

patients' synovial fluid, TCA intermediates like glutamate, citrate and succinate act as inflammation promoters (Ref. 105). Increased glutamate levels in arthritic joints enhance IL-6 release through the activation of glutamate receptors, contributing to arthritic pain (Ref. 122). Research has indicated that glutaminase (GLS) 1, which catalyses the conversion of glutamine to glutamate, is upregulated in RA-FLS. Inhibiting GLS1 through siRNA transfection or with inhibitors can suppress the growth of RA-FLS (Ref. 123). Furthermore, the mitochondrial complex I inhibitor IACS-010759 disrupts RA-FLS metabolic rewiring by interfering with hypoxia-inducible factor (HIF) 1α and enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) regulation, reducing citrate or succinate accumulation (Ref. 124). However, IACS-010759 showed inefficacy in a collagen-induced arthritis (CIA) preclinical model, cautioning its clinical application (Ref. 124). Consequently, targeting mitochondrial metabolism, particularly the metabolic intermediates, offers a promising therapeutic approach for managing RA, potentially affecting both cell proliferation and the inflammatory response.

In conclusion, research has shown that the immune microenvironment in RA induces metabolic reprogramming in FLS, leading to dysfunction and imbalance in immune homoeostasis. Therefore, targeting this metabolic reprogramming could open new avenues for RA treatment.

Using computational biology in the characterization of RA-FLS

Bioinformatics is one of the most dynamic fields in biological research, with numerous studies utilizing computational platforms to delineate the developmental progress and tissue specification of various cell lines. A notable example included the work by Zhang et al. (Ref. 125), who developed Taiji, an advanced algorithm for identifying key TFs essential for lineage-specific and stage-dependent tissue differentiation. This system-level strategy integrated transcriptomic and epigenomic data to accurately pinpoint essential TFs. Using the Taiji platform, Ainsworth et al. (Ref. 126) conducted a comprehensive analysis of primary RA-FLS cell lines, focussing on their distinct TF biology at the transcriptional level. Through their analysis, they identified that RA-FLS cell lines can be divided into two distinct groups, CL1 and CL2, based on their Personalized PageRank scores. This classification revealed significant differences in phenotypic traits and pathway activities between the groups. They identified cluster-specific TFs that played differential roles in the function of RA-FLS. Notably, retinoic acid receptor alpha (RARα) emerged as a crucial factor, exhibiting unique regulatory effects on TGFβ signalling pathways across the clusters. Further experimental validation confirmed the distinct roles of RARα within these clusters, particularly in its impact on gene expression, protein levels and cellular behaviours such as proliferation and invasion. These findings highlighted divergent TGFβ signalling and biological outcomes between the clusters, highlighting the molecular complexity of RA pathogenesis. This research not only biologically validated the predictions for the key subtype-specific TF, RARα, but also demonstrated the differential regulation of TGFβ signalling in the two subtypes, providing deeper insights into the variable clinical responses observed in RA treatments.

Various studies have employed different computational systems to explore the characteristics of RA-FLS. Aghakhani et al. (Ref. 127) introduced a hybrid modelling approach to studying metabolic reprogramming in RA-FLS. Their model merged a qualitative regulatory network with a global metabolic network, using flux balance analysis to assess the impact of regulatory outcomes on metabolic flux distributions. It demonstrated how RA-FLS transition towards functioning as metabolic factories, potentially exacerbating RA pathology through increased energy and nutrient production, driven by HIF1 activation. Singh et al. (Ref. 128) developed a comprehensive Boolean model to investigate FLS in RA. This model predicted drug synergies and identified potential new therapeutic targets by simulating various phenotypes such as inflammation and bone erosion. Additionally, it employed drug repurposing analysis to identify candidate drugs, thereby aiming to improve treatment strategies through a system-level understanding of RA pathophysiology. Ge et al. (Ref. 72) provided a detailed genomic atlas of FLS, highlighting their role in the genetic predisposition to RA. By integrating DNA architecture, chromatin interactions and gene expression data, the study pinpointed genes and pathways that contribute to the heritability of RA, emphasizing the critical role of FLS in the disease's pathogenesis. You et al. (Ref. 129) focussed on the molecular signatures that characterize the invasive behaviour of RA-FLS. The study used transcriptome profiling and network modelling to identify key regulators of FLS invasiveness, offering insights into the cellular mechanisms underlying RA pathogenesis and identifying potential therapeutic targets. Together, these studies improved our understanding of RA by covering various aspects, from metabolic changes and drug response predictions to genetic susceptibility and the invasive characteristics of FLS.

Signalling pathways in RA-FLS and prospects for therapeutic interventions

Several intracellular signalling pathways regulate the pathogenic behaviour of FLS, including the JAK/STAT, MAPK, NF-κB, Notch and IRAK4 signalling pathway. Given their crucial role, these signalling cascades represent promising therapeutic targets for RA treatment.

JAK/STAT signalling pathway

The JAK/STAT pathway plays a critical role in regulating the pathogenesis and progression of RA (Ref. 143). More than 50 cytokines are known to activate the JAK/STAT pathway through interactions with type I or type II cell-surface receptors, underscoring the importance of this signalling cascade in immune regulation and inflammation (Refs. 144, 145). The JAK family comprises four members: JAK1, JAK2, JAK3 and tyrosine kinase-2 (TYK2) (Ref. 146). These kinases transmit extracellular cytokine signals to the intracellular environment, initiating downstream cascades via the JAK/STAT pathway and thereby influencing key biological processes such as apoptosis, proliferation, immune responses and inflammation (Ref. 147). In the context of RA, cytokines such as IL-6 bind to IL-6 receptor (IL-6R) on FLS, activating JAK enzymes that subsequently phosphorylate STAT proteins, particularly STAT3 (Ref. 148). Once activated, STAT3 translocates to the nucleus, where it induces the expression of numerous pro-inflammatory genes, cytokines and MMPs (Ref. 149). This contributes significantly to synovial inflammation, FLS proliferation, invasiveness and, ultimately, joint damage. Given the crucial role of JAK/STAT signalling,

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

Table 2. Summary of drugs for RA and their effects on FLS

Target type	Drug name	Biological functions
JAK	Upadacitinib	Inhibited the development of HLA-DR + CD90 + FLS (Ref. 130).
	Tofacitinib	Modulated autophagy of FLS, dampening chemokine synthesis by FLS (Refs. 131, 132).
	Baricitinib	Suppressed the pro-inflammatory behaviour of RA-FLS, accelerated cell death and abrogated thickening of the synovium (Ref. 133).
	Filgotinib	Inhibited the production of vascular endothelial growth factor (VEGF) in IL–6 stimulated RA-FLS (Ref. 134).
	Peficitinib	Suppressed monocyte chemotaxis and proliferation of FLS through inhibition of pro-inflammatory cytokines (Ref. 135).
CDK	Seliciclib	Suppressed FLS proliferation (Refs. 136, 137, 138).
TNF	Etanercept Infliximab Adalimumab	Induced apoptosis and reducing autophagy in FLS (Refs. 139, 140). Degraded MMP–1 in FLS (Ref. 14). Induced apoptosis in FLS (Ref. 140).
IL–6R	Tocilizumab	Suppressed FLS inflammation by regulating the MIR31HG-miR–214-PTEN-AKT pathway (Ref. 141).
Dihydrofolate reductase	Methotrexate	Reduced growth rate of RA-FLS (Ref. 142).

pharmacological inhibition of JAK enzymes represents a promising therapeutic strategy for RA. JAK inhibitors, including upadacitinib (JAK1-specific), tofacitinib (JAK1–3), baricitinib (JAK1, JAK2), filgotinib (JAK1) and peficitinib (JAK3) (see Table 2), effectively block JAK enzyme activity, preventing the phosphorylation and activation of STAT3. This interruption halts STAT3 nuclear translocation and reduces the expression of inflammatory mediators and tissue-degrading enzymes (Ref. 148). Moreover, preclinical studies have demonstrated that selective targeting of JAK3 can significantly reduce cartilage and bone erosion in animal models of RA, highlighting the therapeutic benefits of pathway-specific interventions (Ref. 150). Thus, targeting the JAK/STAT pathway, particularly through STAT3 suppression, offers considerable promise for improving disease management in RA patients by addressing inflammation at the molecular and cellular levels.

MAPK signalling pathway

The MAPK signalling pathway includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 as its main family members. This pathway involves various signalling molecules that regulate cellular processes such as differentiation, apoptosis, proliferation and stress responses (Refs. 151, 152, 153). In RA, pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 can activate ERK, JNK and p38 MAPK (Refs. 154, 155). A cascade of dual-specificity kinases known as MAPK kinases (MKK) induces the phosphorylation of conserved threonine and tyrosine residues, activating MAPK. One study revealed that MKK7 is the most crucial MKK for activating JNKs in RA-FLS (Ref. 156).

NF-κB signalling pathway

In RA, FLS play a critical role in signalling pathways that counteract apoptosis by upregulating the expression of anti-apoptotic proteins. Activation of NF-κB also influences FLS proliferation, leading to hyperplasia of FLS in the synovium affected by RA. RANKL, the primary differentiation factor for osteoclastogenesis from myeloid precursors, is upregulated in its expression within the RA synovium due to activated T cells and FLS (Ref. 11). NF-κB proteins comprise a family of inducible TFs that regulate numerous genes involved in various immune-inflammatory responses. Once activated, NF-κB promotes FLS proliferation and increases its invasion and infiltration capabilities, while simultaneously reducing apoptosis. The NF-κB signalling pathway significantly contributes to the regulation of many genes involved in inflammation, immune responses, and cell proliferation and survival (Ref. 157). The NF-κB signalling pathway consists of NF-κB, NF-κB inhibitor (IκB) and IκB kinases (IKK) (Ref. 158). It has been shown that an IKK inhibitor can effectively reduce the activation and proliferation of RA-FLS without causing cellular toxicity (Ref. 159). Detailed exploration of the complex dynamics of the NF-κB signalling pathway in RA-FLS has been previously documented (Ref. 160).

Notch signalling pathway

The Notch signalling pathway is evolutionarily conserved, operating across multiple cell types and developmental stages. It is particularly noted for its role in governing the differentiation of sublining fibroblasts, having been extensively documented to promote the differentiation of mural cells during development. In both humans and mice, there exist Notch ligands, namely delta-like ligand 1 (DLL1), delta-like ligand 3 (DLL3), delta-like ligand 4 (DLL4), Jagged-1 (JAG1) and Jagged-2 (JAG2), along with four Notch receptors (Notch1–4). This signalling pathway is a highly conserved method of intercellular communication and plays a crucial role in cell fate decisions and tissue homoeostasis (Ref. 161). Its involvement in RA development is well established, functioning downstream of inflammatory signalling to regulate skeletal development and bone remodelling. Recent scRNA-seq analysis of FLS has highlighted the significance of Notch signalling in the pathogenesis of RA, providing a molecular basis for therapeutically targeting stromal cells in RA through the regulation of Notch3 signalling (Ref. 162). The expression of Notch3 and Notch target genes is upregulated in RA-FLS. Additionally, studies on Notch3-deficient mice have shown promising potential for RA treatment, potentially alleviating inflammation and joint damage in RA (Ref. 162). Based on these findings (Ref. 162), an unbiased method called covarying neighbourhood analysis (CNA) has been developed to capture the Notch activation gradient implicated in RA (Ref. 163). This method highlights the role of endothelium-derived Notch signalling in regulating FLS and the resulting inflammation and pathology observed in RA.

IRAK4 signalling pathway

In addition to the direct involvement in joint inflammation and destruction, FLS express various toll-like receptors (TLRs) that activate the IRAK4 signalling pathway. Activation of IRAK4 significantly increases the production of pro-inflammatory cytokines such as IL-6 and MMPs, further promoting inflammation and joint damage (Ref. 164). Among the IRAK family members, IRAK4 plays the most critical role due to its ability to initiate downstream

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

inflammatory signals. IRAK4 activates these signals through an essential self-phosphorylation step, without which subsequent signalling molecules remain inactive. Additionally, IRAK4 acts structurally by assembling a multi-protein complex known as the myddosome. This complex, including IRAK1 and MyD88 proteins, stabilizes and amplifies inflammatory signals, ensuring the sustained activation of inflammatory pathways (Ref. 165). Recent studies have highlighted IRAK4 as a promising therapeutic target. PF-06650833 (zimlovisertib), a small-molecule inhibitor of IRAK4, has demonstrated promising results by effectively reducing cytokine and MMP release *in vitro* and significantly alleviating arthritis symptoms in animal models (Ref. 166). Currently, zimlovisertib is being evaluated in phase 2 clinical trials, with interim results at week 12 indicating superior clinical efficacy compared to placebo. Furthermore, emerging approaches involving IRAK4 degradation, such as the selective IRAK4 degrader KT-474 (SAR444656), represent innovative strategies aiming to further suppress inflammation by directly reducing IRAK4 protein levels (Ref. 167). Collectively, targeting the IRAK4 signalling pathway offers substantial therapeutic promise for RA by directly addressing critical inflammatory mechanisms driven by FLS. Such targeted approaches could provide improved disease management, ultimately benefiting RA patients by intervening precisely at the molecular level.

Epigenetic modulations of FLS as a therapeutic strategy

The epigenetic landscape of RA-FLS suggests that therapeutic potential lies in targeting genes or pathways that are differentially regulated. By examining individual epigenetic markers and conducting comprehensive analyses, we can uncover and prioritize genes and pathways that have been previously overlooked but hold promise for drug development. A particularly intriguing approach would be to reshape the RA epigenome, restoring it to a state of normalcy. Although epigenetic alterations are long-lasting, it is feasible to influence the epigenome by targeting the machinery responsible for these modifications, such as histone-modifying enzymes. In animal models of arthritis, several HDAC small-molecule inhibitors have shown promising efficacy. Additionally, givinostat, an oral inhibitor of class I and class II HDACs, has undergone phase 2 trials in treating systemic-onset juvenile idiopathic arthritis and demonstrated moderate clinical efficacy (Ref. 168). While the precise mechanism of action of HDAC inhibitors is largely unknown, they appear to regulate the acetylation status of histones; for instance, givinostat inhibits cytokine production and has anti-inflammatory effects in RA-FLS (Ref. 169). Moreover, HDAC inhibitors decrease the mRNA level of pro-inflammatory factors such as IL-6 and PTGS2 (Ref. 170).

Targeting FLS surface markers and novel therapeutic approaches

In addition to signalling pathways, targeted therapy against specific FLS surface receptors has been explored. The potential presence of disease-associated FLS phenotypes can play a role in categorizing illnesses and enable a more precise strategy for dealing with synoviocytes in RA. For instance, current treatments aim at targeting FLS-specific surface receptors, such as CDH11. Notably, mice lacking CDH11 exhibit resistance to inflammatory arthritis. Although a phase 1 trial evaluating the efficacy of RG6125, a monoclonal antibody targeting CDH11, has been completed, subsequent phase 2 trials and further development for treating RA are halted due to inadequate effectiveness (Ref. 171). The monoclonal antibody ASP5094, which specifically targets integrin alpha-9, abundantly expressed by RA-FLS and contributing to both cell adhesion and inflammation, unfortunately did not yield favourable results in a phase 2a trial. It failed to demonstrate any discernible difference in disease activity scores compared to a placebo (Refs. 172, 173).

Despite this setback, several other promising therapeutic candidates are currently undergoing human trials. Seliciclib, an orally available inhibitor of cyclin-dependent kinases (CDKs), has shown potential in suppressing the proliferation of FLS by inhibiting CDK2 and inducing the CDK inhibitor p21 (Refs. 136, 137). A recent study has reported the findings of a non-randomized, open-label, dose-exploratory phase 1b clinical trial, which aimed to determine the appropriate therapeutic dose, pharmacokinetics and safety of seliciclib, while also providing a preliminary assessment of its potential in targeting the proliferation of FLS for the treatment of RA (see Table 2). The trial involved a total of 37 RA patients who had an inadequate response to TNF inhibitors. Among them, 15 patients were assigned to five different treatment dose groups of seliciclib. The results revealed that the maximum tolerated dose of seliciclib was 400 mg, once daily, with no unexpected safety concerns, thus suggesting the need for further investigation in future studies (Ref. 138).

In the realm of clinical practice, traditional Chinese medicine (TCM) has been used as a therapeutic and supplementary modality for patients in the early stages of RA. Although TCM lacks specific targets, emerging research has highlighted its impact on FLS in RA. For instance, schisandrin, the bioactive component of *Schisandra chinensis*, inhibits FLS proliferation and invasion, thereby ameliorating RA pathology (Ref. 174). Beyond individual drugs, research has also focussed on the anti-arthritis mechanisms of TCM formulas. Qufeng Tongluo formula, a clinical prescription for RA treatment, has shown the ability to inhibit FLS proliferation, migration and invasion *in vitro* (Ref. 175). Additionally, a two-herb formula RL (consisting of Rosae Multiflorae Fructus and Lonicerae Japonicae Flos) has significantly alleviated arthritis in a CIA rat model and attenuated the expression of RANKL in IL-6/sIL-6R-stimulated RA-FLS, which is linked to the STAT3 signalling pathway (Ref. 176). These findings provide mechanistic insights into targeting FLS as an approach for TCM treatment against RA.

Conclusion

Within autoimmune arthritis, particularly RA, synovial tissue represents a critical area of interest. This review has explored the physiological roles and pathological transformations of FLS and highlighted their significant impact on RA progression. We have further summarized how these cellular alterations shape therapeutic strategies. The metabolic reprogramming and distinct phenotypic changes of RA-FLS have been extensively discussed, emphasizing potential therapeutic targets derived from both immune pathways and bioinformatics analyses. Overall, targeting FLS in RA presents an attractive therapeutic approach, underscoring the need for continued research into both standalone treatments and synergistic combination therapies.

Signalling pathways such as JAK/STAT, MAPK, NF-κB, Notch and IRAK4, along with epigenetic modifications including DNA methylation, histone modifications, SUMOylation and ncRNA regulation, have been established as critical mediators driving the pathological behaviours of RA-FLS. Therapeutic interventions designed to target these pathways offer considerable promise for

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

effective RA management. However, despite significant progress, limitations remain. Current research often faces challenges such as variability in patient response, nonspecific targeting effects and inadequate clinical translation of promising preclinical results. Additionally, RA-FLS exhibit substantial heterogeneity, complicating efforts to design universally effective therapies. Addressing these challenges will require further mechanistic studies, refined patient stratification and innovative therapeutic designs that effectively bridge basic science discoveries with clinical practice.

Author contribution. CL, AL and DH supervised and revised the manuscript. SY, JF and DX wrote and edited the manuscript. CC, ZW, JH, FQ and XY provided their suggestions. All authors contributed to the article and approved the submitted version.

Funding statement. This work is supported by the National Key R&D Program of China (2024YFC3506200 to DH and 2024YFC3506205 to CL), the National Natural Science Foundation Council of China (82472394 and 82172386 to CL, and 82074234 to DH), the 2020 Guangdong Provincial Science and Technology Innovation Strategy Special Fund (Guangdong-Hong Kong-Macau Joint Lab) (2020B1212030006 to AL), the Guangdong Basic and Applied Basic Research Foundation (2022A1515012164 to CL), the Shenzhen Science and Technology Program (JCYJ20210324104201005 and SGDX20240115112400001 to C.L.), the Hong Kong General Research Fund (12102722 and 12106424 to AL), and the Hong Kong RGC Theme-based Research Scheme (T12–201/20-R to AL).

Competing interests. The authors declare none.

References

1. **You S**, **Koh JH**, **Leng L**, et al. (2018) The tumor-like phenotype of rheumatoid Synovium: Molecular profiling and prospects for precision medicine. *Arthritis and Rheumatology* **70**, 637–652.
2. **Smith MH and Berman JR** (2022) What is rheumatoid arthritis? *JAMA* **327**, 1194–1194.
3. **Smolen JS**, **Landewé RBM**, **Bergstra SA**, et al. (2022) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 Update. *Annals of the Rheumatic Diseases* **82**, 3–18.
4. **Fraenkel L**, **Bathon JM**, **England BR**, et al. (2021) 2021 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Care & Research* **73**, 924–939.
5. **Alivernini S**, **Firestein GS and McInnes IB** (2022) The pathogenesis of rheumatoid arthritis. *Immunity* **55**, 2255–2270.
6. **Aletaha D and Smolen JS** (2018) Diagnosis and management of rheumatoid arthritis: A review. *JAMA* **320**, 1360–1372.
7. **Nagy G**, **Roodenrijs NMT**, **Welsing PMJ**, et al. (2022) EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. *Annals of the Rheumatic Diseases* **81**, 20–33.
8. **Svensson MND**, **Zoccheddu M**, **Yang S**, et al. (2020) Synoviocyte-targeted therapy synergizes with TNF inhibition in arthritis reversal. *Science Advances* **6**, eaba4353.
9. **Dakin SG**, **Coles M**, **Sherlock JP**, et al. (2018) Pathogenic stromal cells as therapeutic targets in joint inflammation. *Nature Reviews Rheumatology* **14**, 714–726.
10. **Nygaard G and Firestein GS** (2020) Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes. *Nature Reviews Rheumatology* **16**, 316–333.
11. **Noss EH and Brenner MB** (2008) The role and therapeutic implications of fibroblast-like synoviocytes in inflammation and cartilage erosion in rheumatoid arthritis. *Immunological Reviews* **223**, 252–270.
12. **Pradhan RN**, **Krishnamurty AT**, **Fletcher AL**, et al. (2021) A bird's eye view of fibroblast heterogeneity: A pan-disease, pan-cancer perspective. *Immunological Reviews* **302**, 299–320.
13. **Wei K**, **Nguyen HN and Brenner MB** (2021) Fibroblast pathology in inflammatory diseases. *The Journal of Clinical Investigation* **131**, e149538.
14. **Bartok B and Firestein GS** (2010) Fibroblast-like synoviocytes: Key effector cells in rheumatoid arthritis. *Immunological Reviews* **233**, 233–255.
15. **Zhang F**, **Wei K**, **Slowikowski K**, et al. (2019) Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. *Nature Immunology* **20**, 928–942.
16. **Floudas A**, **Smith CM**, **Tynan O**, et al. (2022) Distinct stromal and immune cell interactions shape the pathogenesis of rheumatoid and psoriatic arthritis. *Annals of the Rheumatic Diseases* **81**, 1224–1242.
17. **Carmona-Rivera C**, **Carlucci PM**, **Moore E**, et al. (2017) Synovial fibroblast-neutrophil interactions promote pathogenic adaptive immunity in rheumatoid arthritis. *Science Immunology* **2**, eaag3358.
18. **Croft AP**, **Campos J**, **Jansen K**, et al. (2019) Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* **570**, 246–251.
19. **Smolen JS**, **Aletaha D**, **Barton A**, et al. (2018) Rheumatoid arthritis. *Nature Reviews Disease Primers* **4**, 18001.
20. **Firestein GS and McInnes IB** (2017) Immunopathogenesis of rheumatoid arthritis. *Immunity* **46**, 183–196.
21. **Németh T**, **Nagy G and Pap T** (2022) Synovial fibroblasts as potential drug targets in rheumatoid arthritis, where do we stand and where shall we go? *Annals of the Rheumatic Diseases* **81**, 1055–1064.
22. **Smith MD** (2011) The normal synovium. *Open Rheumatology Journal* **5**, 100–106.
23. **Beckmann D**, **Römer-Hillmann A**, **Krause A**, et al. (2021) Lasp1 regulates adherens junction dynamics and fibroblast transformation in destructive arthritis. *Nature Communications* **12**, 3624.
24. **Wu Z**, **Ma D**, **Yang H**, et al. (2021) Fibroblast-like synoviocytes in rheumatoid arthritis: Surface markers and phenotypes. *International Immunopharmacology* **93**, 107392.
25. **Alivernini S**, **MacDonald L**, **Elmesmari A**, et al. (2020) Distinct synovial tissue macrophage subsets regulate inflammation and remission in rheumatoid arthritis. *Nature Medicine* **26**, 1295–1306.
26. **Buckley CD** (2011) Why does chronic inflammation persist: An unexpected role for fibroblasts. *Immunology Letters* **138**, 12–14.
27. **Buckley CD and McGettrick HM** (2018) Leukocyte trafficking between stromal compartments: Lessons from rheumatoid arthritis. *Nature Reviews Rheumatology* **14**, 476–487.
28. **Muller-Ladner U**, **Pap T**, **Gay RE**, et al. (2005) Mechanisms of disease: The molecular and cellular basis of joint destruction in rheumatoid arthritis. *Nature Clinical Practice. Rheumatology* **1**, 102–110.
29. **Bottini N and Firestein GS** (2013) Duality of fibroblast-like synoviocytes in RA: Passive responders and imprinted aggressors. *Nature Reviews Rheumatology* **9**, 24–33.
30. **Lafyatis R**, **Remmers EF**, **Roberts AB**, et al. (1989) Anchorage-independent growth of synoviocytes from arthritic and normal joints. Stimulation by exogenous platelet-derived growth factor and inhibition by transforming growth factor-beta and retinoids. *Journal of Clinical Investigation* **83**, 1267–1276.
31. **Korb A**, **Pavenstadt H and Pap T** (2009) Cell death in rheumatoid arthritis. *Apoptosis* **14**, 447–454.
32. **Kato M**, **Ospelt C**, **Gay RE**, et al. (2014) Dual role of autophagy in stress-induced cell death in rheumatoid arthritis synovial fibroblasts. *Arthritis and Rheumatology* **66**, 40–48.
33. **Shin YJ**, **Han SH**, **Kim DS**, et al. (2010) Autophagy induction and CHOP under-expression promotes survival of fibroblasts from rheumatoid arthritis patients under endoplasmic reticulum stress. *Arthritis Research & Therapy* **12**, R19.
34. **Steenvoorden MM**, **Tolboom TC**, **van der Pluijm G**, et al. (2006) Transition of healthy to diseased synovial tissue in rheumatoid arthritis is associated with gain of mesenchymal/fibrotic characteristics. *Arthritis Research & Therapy* **8**, R165.
35. **Marinova-Mutafchieva L**, **Williams RO**, **Funa K**, et al. (2002) Inflammation is preceded by tumor necrosis factor-dependent infiltration of mesenchymal cells in experimental arthritis. *Arthritis and Rheumatism* **46**, 507–513.
36. **Chu CQ** (2020) Fibroblasts in rheumatoid arthritis. *New England Journal of Medicine* **383**, 1679–1681.

37. **Orange DE**, **Yao V**, **Sawicka K**, et al. (2020) RNA identification of PRIME cells predicting rheumatoid arthritis flares. *New England Journal of Medicine* **383**, 218–228.
38. **Buckley CD**, **Ospelt C**, **Gay S**, et al. (2021) Location, location, location: How the tissue microenvironment affects inflammation in RA. *Nature Reviews Rheumatology* **17**, 195–212.
39. **Mendez-Huergo SP**, **Hockl PF**, **Stupirski JC**, et al. (2018) Clinical relevance of Galectin-1 and Galectin-3 in rheumatoid arthritis patients: Differential regulation and correlation with disease activity. *Frontiers in Immunology* **9**, 3057.
40. **Donlin LT**, **Rao DA**, **Wei K**, et al. (2018) Methods for high-dimensional analysis of cells dissociated from cryopreserved synovial tissue. *Arthritis Research & Therapy* **20**, 139.
41. **Mizoguchi F**, **Slowikowski K**, **Wei K**, et al. (2018) Functionally distinct disease-associated fibroblast subsets in rheumatoid arthritis. *Nature Communications* **9**, 789.
42. **Stephenson W**, **Donlin LT**, **Butler A**, et al. (2018) Single-cell RNA-seq of rheumatoid arthritis synovial tissue using low-cost microfluidic instrumentation. *Nature Communications* **9**, 791.
43. **Croft AP**, **Naylor AJ**, **Marshall JL**, et al. (2016) Rheumatoid synovial fibroblasts differentiate into distinct subsets in the presence of cytokines and cartilage. *Arthritis Research & Therapy* **18**, 270.
44. **Lee DM**, **Kiener HP**, **Agarwal SK**, et al. (2007) Cadherin-11 in synovial lining formation and pathology in arthritis. *Science* **315**, 1006–1010.
45. **Berckmans RJ**, **Nieuwland R**, **Kraan MC**, et al. (2005) Synovial microparticles from arthritic patients modulate chemokine and cytokine release by synoviocytes. *Arthritis Research & Therapy* **7**, R536–R544.
46. **Umar S**, **Hedaya O**, **Singh AK**, et al. (2015) Thymoquinone inhibits TNF-α-induced inflammation and cell adhesion in rheumatoid arthritis synovial fibroblasts by ASK1 regulation. *Toxicology and Applied Pharmacology* **287**, 299–305.
47. **Dorst DN**, **Rijpkema M**, **Boss M**, et al (2020) Targeted photodynamic therapy selectively kills activated fibroblasts in experimental arthritis. *Rheumatology* **59**, 3952–3960.
48. **Culemann S**, **Gruneboom A**, **Nicolas-Avila JA**, et al. (2019) Locally renewing resident synovial macrophages provide a protective barrier for the joint. *Nature* **572**, 670–675.
49. **Naylor AJ**, **Filer A and Buckley CD** (2013) The role of stromal cells in the persistence of chronic inflammation. *Clinical and Experimental Immunology* **171**, 30–35.
50. **Lee A**, **Qiao Y**, **Grigoriev G**, et al. (2013) Tumor necrosis factor alpha induces sustained signaling and a prolonged and unremitting inflammatory response in rheumatoid arthritis synovial fibroblasts. *Arthritis and Rheumatism* **65**, 928–938.
51. **Migita K**, **Iwanaga N**, **Izumi Y**, et al. (2017) TNF-alpha-induced miR-155 regulates IL-6 signaling in rheumatoid synovial fibroblasts. *BMC Research Notes* **10**, 403.
52. **Donlin LT**, **Jayatilleke A**, **Giannopoulou EG**, et al. (2014) Modulation of TNF-induced macrophage polarization by synovial fibroblasts. *Journal of Immunology* **193**, 2373–2383.
53. **Kuo D**, **Ding J**, **Cohn IS**, et al. (2019) HBEGF(+) macrophages in rheumatoid arthritis induce fibroblast invasiveness. *Science Translational Medicine* **11**, eaau8587.
54. **Alvaro-Gracia JM**, **Zvaifler NJ and Firestein GS** (1989) Cytokines in chronic inflammatory arthritis. IV. Granulocyte/macrophage colony-stimulating factor-mediated induction of class II MHC antigen on human monocytes: A possible role in rheumatoid arthritis. *Journal of Experimental Medicine* **170**, 865–875.
55. **Firestein GS** (2003) Evolving concepts of rheumatoid arthritis. *Nature* **423**, 356–361.
56. **Yellin M**, **Paliienko I**, **Balanescu A**, et al. (2012) A phase II, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of MDX-1100, a fully human anti-CXCL10 monoclonal antibody, in combination with methotrexate in patients with rheumatoid arthritis. *Arthritis and Rheumatism* **64**, 1730–1739.
57. **Burmester GR**, **McInnes IB**, **Kremer J**, et al. (2017) A randomised phase IIB study of mavrilimumab, a novel GM-CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis. *Annals of the Rheumatic Diseases* **76**, 1020–1030.
58. **Yoshitomi H** (2019) Regulation of immune responses and chronic inflammation by fibroblast-like synoviocytes. *Frontiers in Immunology* **10**, 1395.
59. **Fuller K**, **Wong B**, **Fox S**, et al. (1998) TRANCE is necessary and sufficient for osteoblast-mediated activation of bone resorption in osteoclasts. *Journal of Experimental Medicine* **188**, 997–1001.
60. **Lacey DL**, **Timms E**, **Tan HL**, et al. (1998) Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* **93**, 165–176.
61. **Pincus T and Sokka T** (2004) Should contemporary rheumatoid arthritis clinical trials be more like standard patient care and vice versa? *Annals of the Rheumatic Diseases* **63**(Suppl 2), ii32–ii39.
62. **Cohen SB**, **Dore RK**, **Lane NE**, et al. (2008) Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: A twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis and Rheumatism* **58**, 1299–1309.
63. **Diarra D**, **Stolina M**, **Polzer K**, et al. (2007) Dickkopf-1 is a master regulator of joint remodeling. *Nature Medicine* **13**, 156–163.
64. **Nakano K**, **Boyle DL and Firestein GS** (2013) Regulation of DNA methylation in rheumatoid arthritis synoviocytes. *Journal of Immunology* **190**, 1297–1303.
65. **Ai R**, **Whitaker JW**, **Boyle DL**, et al. (2015) DNA Methylome signature in synoviocytes from patients with early rheumatoid arthritis compared to synoviocytes from patients with longstanding rheumatoid arthritis. *Arthritis and Rheumatology* **67**, 1978–1980.
66. **Ai R**, **Laragione T**, **Hammaker D**, et al. (2018) Comprehensive epigenetic landscape of rheumatoid arthritis fibroblast-like synoviocytes. *Nature Communications* **9**, 1921.
67. **Igarashi H**, **Hashimoto J**, **Tomita T**, et al. (2010) TP53 mutations coincide with the ectopic expression of activation-induced cytidine deaminase in the fibroblast-like synoviocytes derived from a fraction of patients with rheumatoid arthritis. *Clinical and Experimental Immunology* **161**, 71–80.
68. **Da Sylva TR**, **Connor A**, **Mburu Y**, et al. (2005) Somatic mutations in the mitochondria of rheumatoid arthritis synoviocytes. *Arthritis Research & Therapy* **7**, R844–R851.
69. **Promila L**, **Joshi A**, **Khan S**, et al. (2023) Role of mitochondrial dysfunction in the pathogenesis of rheumatoid arthritis: Looking closely at fibroblast- like synoviocytes. *Mitochondrion* **73**, 62–71.
70. **Li X-F**, **Xin C**, **Jing B**, et al. (2019) PTEN negatively regulates the expression of pro-inflammatory cytokines and chemokines of fibroblast-like synoviocytes in adjuvant-induced arthritis. *Artificial Cells, Nanomedicine, and Biotechnology* **47**, 3687–3696.
71. **Li XF**, **Wu S**, **Yan Q**, et al. (2021) PTEN methylation promotes inflammation and activation of fibroblast-like Synoviocytes in rheumatoid arthritis. *Frontiers in Pharmacology* **12**, 700373.
72. **Ge X**, **Frank-Bertoncelj M**, **Klein K**, et al. (2021) Functional genomics atlas of synovial fibroblasts defining rheumatoid arthritis heritability. *Genome Biology* **22**, 247.
73. **Tharuka MDN**, **Courelli AS and Chen Y** (2025) Immune regulation by the SUMO family. *Nature Reviews Immunology* 1–13.
74. **Dehnavi S**, **Sadeghi M**, **Johnston TP**, et al. (2019) The role of protein SUMOylation in rheumatoid arthritis. *Journal of Autoimmunity* **102**, 1–7.
75. **Wang C**, **Xiao Y**, **Lao M**, et al. (2020) Increased SUMO-activating enzyme SAE1/UBA2 promotes glycolysis and pathogenic behavior of rheumatoid fibroblast-like synoviocytes. *JCI Insight* **5**, e135935.
76. **McHugh J** (2020) SUMOylation links metabolic and aggressive phenotype of RA FLS. *Nature Reviews Rheumatology* **16**, 668–668.
77. **Li F**, **Li X**, **Kou L**, et al. (2014) SUMO-conjugating enzyme UBC9 promotes proliferation and migration of fibroblast-like Synoviocytes in rheumatoid arthritis. *Inflammation* **37**, 1134–1141.
78. **Ryu HY and Hochstrasser M** (2021) Histone sumoylation and chromatin dynamics. *Nucleic Acids Research* **49**, 6043–6052.
79. **Sheng Z**, **Luo S**, **Huang L**, et al. (2025) SENP1-mediated deSUMOylation of YBX1 promotes colorectal cancer development through the SENP1-YBX1-AKT signaling axis. *Oncogene* **44**, 1361–1374.

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

80. **Maciejewska-Rodrigues H**, **Karouzakis E**, **Strietholt S**, et al. (2010) Epigenetics and rheumatoid arthritis: The role of SENP1 in the regulation of MMP-1 expression. *Journal of Autoimmunity* **35**, 15–22.
81. **Kawabata T**, **Nishida K**, **Takasugi K**, et al. (2010) Increased activity and expression of histone deacetylase 1 in relation to tumor necrosis factor-alpha in synovial tissue of rheumatoid arthritis. *Arthritis Research & Therapy* **12**, R133.
82. **Fan L**, **Yang X**, **Zheng M**, et al. (2022) Regulation of SUMOylation targets associated with Wnt/β-catenin pathway. *Frontiers in Oncology* **12**, 943683.
83. **Trenkmann M**, **Brock M**, **Gay RE**, et al. (2011) Expression and function of EZH2 in synovial fibroblasts: Epigenetic repression of the Wnt inhibitor SFRP1 in rheumatoid arthritis. *Annals of the Rheumatic Diseases* **70**, 1482–1488.
84. **Wijesinghe SN**, **Lindsay MA and Jones SW** (2022) Long non-coding RNAs in rheumatology. *Advances in Experimental Medicine and Biology* **1363**, 35–70.
85. **Chang C**, **Xu L**, **Zhang R**, et al. (2022) MicroRNA-mediated epigenetic regulation of rheumatoid arthritis susceptibility and pathogenesis. *Frontiers in Immunology* **13**, 838884.
86. **Yang S and Yang Y** (2015) Downregulation of microRNA-221 decreases migration and invasion in fibroblast-like synoviocytes in rheumatoid arthritis. *Molecular Medicine Reports* **12**, 2395–2401.
87. **Pandis I**, **Ospelt C**, **Karagianni N**, et al. (2012) Identification of microRNA-221/222 and microRNA-323-3p association with rheumatoid arthritis via predictions using the human tumour necrosis factor transgenic mouse model. *Annals of the Rheumatic Diseases* **71**, 1716–1723.
88. **Huh YH**, **Lee G**, **Song WH**, et al. (2015) Crosstalk between FLS and chondrocytes is regulated by HIF-2alpha-mediated cytokines in arthritis. *Experimental & Molecular Medicine* **47**, e197.
89. **Gupta RA**, **Shah N**, **Wang KC**, et al. (2010) Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* **464**, 1071–1076.
90. **Febbraio MA**, **Hiscock N**, **Sacchetti M**, et al. (2004) Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. *Diabetes* **53**, 1643–1648.
91. **Hotamisligil GS**, **Shargill NS and Spiegelman BM** (1993) Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. *Science* **259**, 87–91.
92. **Pearce EL**, **Walsh MC**, **Cejas PJ**, et al. (2009) Enhancing CD8 T-cell memory by modulating fatty acid metabolism. *Nature* **460**, 103–107.
93. **Wieman HL**, **Wofford JA and Rathmell JC** (2007) Cytokine stimulation promotes glucose uptake via phosphatidylinositol-3 kinase/Akt regulation of Glut1 activity and trafficking. *Molecular Biology of the Cell* **18**, 1437–1446.
94. **Lercher A**, **Baazim H and Bergthaler A** (2020) Systemic Immunometabolism: Challenges and opportunities. *Immunity* **53**, 496–509.
95. **Ghesquière B**, **Wong BW**, **Kuchnio A**, et al. (2014) Metabolism of stromal and immune cells in health and disease. *Nature* **511**, 167–176.
96. **Wang R and Green DR** (2012) Metabolic checkpoints in activated T cells. *Nature Immunology* **13**, 907–915.
97. **Pearce EL**, **Poffenberger MC**, **Chang CH**, et al. (2013) Fueling immunity: Insights into metabolism and lymphocyte function. *Science* **342**, 1242454.
98. **Yin Y**, **Choi SC**, **Xu Z**, et al. (2015) Normalization of CD4+ T cell metabolism reverses lupus. *Science Translational Medicine* **7**, 274ra218.
99. **Yang Z**, **Matteson EL**, **Goronzy JJ**, et al. (2015) T-cell metabolism in autoimmune disease. *Arthritis Research & Therapy* **17**, 29.
100. **McDonald G**, **Deepak S**, **Miguel L**, et al. (2014) Normalizing glycosphingolipids restores function in CD4+ T cells from lupus patients. *Journal of Clinical Investigation* **124**, 712–724.
101. **Cairns RA**, **Harris IS and Mak TW** (2011) Regulation of cancer cell metabolism. *Nature Reviews. Cancer* **11**, 85–95.
102. **Vander Heiden MG**, **Cantley LC and Thompson CB** (2009) Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science* **324**, 1029–1033.
103. **Ahn JK**, **Kim S**, **Hwang J**, et al. (2016) GC/TOF-MS-based metabolomic profiling in cultured fibroblast-like synoviocytes from rheumatoid arthritis. *Joint, Bone, Spine* **83**, 707–713.
104. **Falconer J**, **Murphy AN**, **Young SP**, et al. (2018) Review: Synovial cell metabolism and chronic inflammation in rheumatoid arthritis. *Arthritis and Rheumatology* **70**, 984–999.
105. **Weyand CM and Goronzy JJ** (2017) Immunometabolism in early and late stages of rheumatoid arthritis. *Nature Reviews Rheumatology* **13**, 291–301.
106. **Aghakhani S**, **Zerrouk N and Niarakis A** (2021) Metabolic reprogramming of fibroblasts as therapeutic target in rheumatoid arthritis and cancer: Deciphering key mechanisms using computational systems biology approaches. *Cancers* **13**, 35.
107. **Hsu PP and Sabatini DM** (2008) Cancer cell metabolism: Warburg and beyond. *Cell* **134**, 703–707.
108. **Garcia-Carbonell R**, **Divakaruni AS**, **Lodi A**, et al. (2016) Critical role of glucose metabolism in rheumatoid arthritis fibroblast-like Synoviocytes. *Arthritis and Rheumatology* **68**, 1614–1626.
109. **Abboud G**, **Choi SC**, **Kanda N**, et al. (2018) Inhibition of glycolysis reduces disease severity in an autoimmune model of rheumatoid arthritis. *Frontiers in Immunology* **9**, 1973.
110. **Song G**, **Lu Q**, **Fan H**, et al. (2019) Inhibition of hexokinases holds potential as treatment strategy for rheumatoid arthritis. *Arthritis Research & Therapy* **21**, 87.
111. **Rabinowitz JD and Enerbäck S** (2020) Lactate: The ugly duckling of energy metabolism. *Nature Metabolism* **2**, 566–571.
112. **Pucino V**, **Certo M**, **Varricchi G**, et al. (2020) Metabolic checkpoints in rheumatoid arthritis. *Frontiers in Physiology* **11**, 347.
113. **Ullah MS**, **Davies AJ and Halestrap AP** (2006) The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1alpha-dependent mechanism. *The Journal of Biological Chemistry* **281**, 9030–9037.
114. **Pettersen EO**, **Ebbesen P**, **Gieling RG**, et al. (2015) Targeting tumour hypoxia to prevent cancer metastasis. From biology, biosensing and technology to drug development: The METOXIA consortium. *Journal of Enzyme Inhibition and Medicinal Chemistry* **30**, 689–721.
115. **Fujii W**, **Kawahito Y**, **Nagahara H**, et al. (2015) Monocarboxylate transporter 4, associated with the acidification of synovial fluid, is a novel therapeutic target for inflammatory arthritis. *Arthritis & Rhematology* **67**, 2888–2896.
116. **O'Neill LA**, **Kishton RJ and Rathmell J** (2016) A guide to immunometabolism for immunologists. *Nature Reviews. Immunology* **16**, 553–565.
117. **de TA**, **Semmelink JF**, **Denis SW**, et al. (2023) Altered lipid metabolism in synovial fibroblasts of individuals at risk of developing rheumatoid arthritis. *Journal of Autoimmunity* **134**, 102974.
118. **Glunde K**, **Bhujwalla ZM and Ronen SM** (2011) Choline metabolism in malignant transformation. *Nature Reviews. Cancer* **11**, 835–848.
119. **Lacal JC** (2001) Choline kinase: A novel target for antitumor drugs. *IDrugs* **4**, 419–426.
120. **Guma M**, **Sanchez-Lopez E**, **Lodi A**, et al. (2015) Choline kinase inhibition in rheumatoid arthritis. *Annals of the Rheumatic Diseases* **74**, 1399–1407.
121. **Kelly B and O'Neill LA** (2015) Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Research* **25**, 771–784.
122. **Bonnet CS**, **Williams AS**, **Gilbert SJ**, et al. (2015) AMPA/kainate glutamate receptors contribute to inflammation, degeneration and pain related behaviour in inflammatory stages of arthritis. *Annals of the Rheumatic Diseases* **74**, 242–251.
123. **Takahashi S**, **Saegusa J**, **Sendo S**, et al. (2017) Glutaminase 1 plays a key role in the cell growth of fibroblast-like synoviocytes in rheumatoid arthritis. *Arthritis Research & Therapy* **19**, 76.
124. **Umar S**, **Palasiewicz K**, **Volin MV**, et al. (2021) Metabolic regulation of RA macrophages is distinct from RA fibroblasts and blockade of glycolysis alleviates inflammatory phenotype in both cell types. *Cellular and Molecular Life Sciences* **78**, 7693–7707.
125. **Zhang K**, **Wang M**, **Zhao Y**, et al. (2019) Taiji: System-level identification of key transcription factors reveals transcriptional waves in mouse embryonic development. *Science Advances* **5**, eaav3262.
126. **Ainsworth RI**, **Hammaker D**, **Nygaard G**, et al. (2022) Systems-biology analysis of rheumatoid arthritis fibroblast-like synoviocytes implicates cell line-specific transcription factor function. *Nature Communications* **13**, 6221.

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

127. **Aghakhani S**, **Soliman S and Niarakis A** (2022) Metabolic reprogramming in rheumatoid arthritis synovial fibroblasts: A hybrid modeling approach. *PLoS Computational Biology* **18**, e1010408.
128. **Singh V**, **Naldi A**, **Soliman S**, et al. (2023) A large-scale Boolean model of the rheumatoid arthritis fibroblast-like synoviocytes predicts drug synergies in the arthritic joint. *npj Systems Biology and Applications* **9**, 33.
129. **You S**, **Yoo SA**, **Choi S**, et al. (2014) Identification of key regulators for the migration and invasion of rheumatoid synoviocytes through a systems approach. *Proceedings of the National Academy of Sciences of the United States of America* **111**, 550–555.
130. **Zhao S**, **Grieshaber-Bouyer R**, **Rao DA**, et al. (2022) Effect of JAK inhibition on the induction of Proinflammatory HLA-DR+CD90+ rheumatoid arthritis synovial fibroblasts by interferon-γ. *Arthritis and Rheumatology* **74**, 441–452.
131. **Vomero M**, **Caliste M**, **Barbati C**, et al. (2022) Tofacitinib decreases autophagy of fibroblast-like Synoviocytes from rheumatoid arthritis patients. *Frontiers in Pharmacology* **13**, 852802.
132. **Rosengren S**, **Corr M**, **Firestein GS**, et al. (2012) The JAK inhibitor CP-690,550 (tofacitinib) inhibits TNF-induced chemokine expression in fibroblast-like synoviocytes: Autocrine role of type I interferon. *Annals of the Rheumatic Diseases* **71**, 440–447.
133. **Weston S**, **Macdonald JL**, **Williams LM**, et al. (2020) The JAK inhibitor baricitinib inhibits oncostatin M induction of proinflammatory mediators in ex-vivo synovial derived cells. *Clinical and Experimental Rheumatology* **40**, 1620–1628.
134. **Anjiki K**, **Hayashi S**, **Ikuta K**, et al. (2024) JAK inhibitors inhibit angiogenesis by reducing VEGF production from rheumatoid arthritis-derived fibroblast-like synoviocytes. *Clinical Rheumatology* **43**, 3525–3536.
135. **Ikari Y**, **Isozaki T**, **Tsubokura Y**, et al. (2019) Peficitinib inhibits the chemotactic activity of monocytes via proinflammatory cytokine production in rheumatoid arthritis fibroblast-like synoviocytes. *Cells* **8**, 561.
136. **Alessi F**, **Quarta S**, **Savio M**, et al. (1998) The cyclin-dependent kinase inhibitors olomoucine and roscovitine arrest human fibroblasts in G1 phase by specific inhibition of CDK2 kinase activity. *Experimental Cell Research* **245**, 8–18.
137. **Perlman H**, **Bradley K**, **Liu H**, et al. (2003) IL-6 and matrix metalloproteinase-1 are regulated by the cyclin-dependent kinase inhibitor p21 in synovial fibroblasts. *Journal of Immunology* **170**, 838–845.
138. **Pratt AG**, **Siebert S**, **Cole M**, et al. (2021) Targeting synovial fibroblast proliferation in rheumatoid arthritis (TRAFIC): An open-label, dose-finding, phase 1b trial. *Lancet Rheumatology* **3**, e337–e346.
139. **Vomero M**, **Manganelli V**, **Barbati C**, et al. (2019) Reduction of autophagy and increase in apoptosis correlates with a favorable clinical outcome in patients with rheumatoid arthritis treated with anti-TNF drugs. *Arthritis Research and Therapy* **21**, 39.
140. **Pattacini L**, **Boiardi L**, **Casali B**, et al. (2010) Differential effects of anti-TNF-α drugs on fibroblast-like synoviocyte apoptosis. *Rheumatology* **49**, 480–489.
141. **Cao L**, **Jiang H**, **Yang J**, et al. (2021) LncRNA MIR31HG is induced by tocilizumab and ameliorates rheumatoid arthritis fibroblast-like synoviocyte-mediated inflammation via miR-214-PTEN-AKT signaling pathway. *Aging* **13**, 24071–24085.
142. **Lories R**, **Derese I**, **De Bari C**, et al. (2003) In vitro growth rate of fibroblast-like synovial cells is reduced by methotrexate treatment. *Annals of the Rheumatic Diseases* **62**, 568–571.
143. **Malemud CJ** (2018) The role of the JAK/STAT signal pathway in rheumatoid arthritis. *Therapeutic Advances in Musculoskeletal Disease* **10**, 117–127.
144. **Morris R**, **Kershaw NJ and Babon JJ** (2018) The molecular details of cytokine signaling via the JAK/STAT pathway. *Protein Science* **27**, 1984–2009.
145. **Gadina M**, **Le MT**, **Schwartz DM**, et al. (2019) Janus kinases to jakinibs: From basic insights to clinical practice. *Rheumatology (Oxford)* **58**, i4–i16.
146. **Ghoreschi K**, **Laurence A and O'Shea JJ** (2009) Janus kinases in immune cell signaling. *Immunological Reviews* **228**, 273–287.
147. **Schwartz DM**, **Kanno Y**, **Villarino A**, et al. (2017) JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nature Reviews Drug Discovery* **17**, 78.
148. **Tanaka Y**, **Luo Y**, **O'Shea JJ**, et al. (2022) Janus kinase-targeting therapies in rheumatology: A mechanisms-based approach. *Nature Reviews Rheumatology* **18**, 133–145.
149. **Dutzmann J**, **Daniel JM**, **Bauersachs J**, et al. (2015) Emerging translational approaches to target STAT3 signalling and its impact on vascular disease. *Cardiovascular Research* **106**, 365–374.
150. **Milici AJ**, **Kudlacz EM**, **Audoly L**, et al. (2008) Cartilage preservation by inhibition of Janus kinase 3 in two rodent models of rheumatoid arthritis. *Arthritis Research & Therapy* **10**, R14.
151. **Kim EK and Choi E-J** (2010) Pathological roles of MAPK signaling pathways in human diseases. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* **1802**, 396–405.
152. **Cargnello M and Roux PP** (2011) Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiology and Molecular Biology Reviews* **75**, 50–83.
153. **Kyriakis JM and Avruch J** (2012) Mammalian MAPK signal transduction pathways activated by stress and inflammation: A 10-year update. *Physiological Reviews* **92**, 689–737.
154. **Schett G**, **Tohidast-Akrad M**, **Smolen JS**, et al. (2000) Activation, differential localization, and regulation of the stress-activated protein kinases, extracellular signal-regulated kinase, c-JUN N-terminal kinase, and p38 mitogen-activated protein kinase, in synovial tissue and cells in rheumatoid arthritis. *Arthritis and Rheumatism* **43**, 2501–2512.
155. **Thalhamer T**, **McGrath MA and Harnett MM** (2008) MAPKs and their relevance to arthritis and inflammation. *Rheumatology* **47**, 409–414.
156. **Inoue T**, **Hammaker D**, **Boyle DL**, et al. (2006) Regulation of JNK by MKK-7 in fibroblast-like synoviocytes. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology* **54**, 2127–2135.
157. **Carlsen H**, **Alexander G**, **Austenaa LM**, et al. (2004) Molecular imaging of the transcription factor NF-kappaB, a primary regulator of stress response. *Mutation Research* **551**, 199–211.
158. **Hayden MS and Ghosh S** (2008) Shared principles in NF-kappaB signaling. *Cell* **132**, 344–362.
159. **Okazaki Y**, **Sawada T**, **Nagatani K**, et al. (2005) Effect of nuclear factor-kappaB inhibition on rheumatoid fibroblast-like synoviocytes and collagen induced arthritis. *Journal of Rheumatology* **32**, 1440–1447.
160. **Nejatbakhsh Samimi L**, **Farhadi E**, **Tahmasebi MN**, et al. (2020) NF-κB signaling in rheumatoid arthritis with focus on fibroblast-like synoviocytes. *Autoimmunity Highlights* **11**, 1–10.
161. **Artavanis-Tsakonas S**, **Rand MD and Lake RJ** (1999) Notch signaling: Cell fate control and signal integration in development. *Science* **284**, 770–776.
162. **Wei K**, **Korsunsky I**, **Marshall JL**, et al. (2020) Notch signalling drives synovial fibroblast identity and arthritis pathology. *Nature* **582**, 259–264.
163. **Reshef YA**, **Rumker L**, **Kang JB**, et al. (2022) Co-varying neighborhood analysis identifies cell populations associated with phenotypes of interest from single-cell transcriptomics. *Nature Biotechnology* **40**, 355–363.
164. **Ospelt C**, **Brentano F**, **Rengel Y**, et al. (2008) Overexpression of toll-like receptors 3 and 4 in synovial tissue from patients with early rheumatoid arthritis: Toll-like receptor expression in early and longstanding arthritis. *Arthritis and Rheumatism* **58**, 3684–3692.
165. **Feng Y**, **Chen C**, **Shao A**, et al. (2024) Emerging interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitors or degraders as therapeutic agents for autoimmune diseases and cancer. *Acta Pharmaceutica Sinica B* **14**, 5091–5105.
166. **Winkler A**, **Sun W**, **De S**, et al. (2021) The Interleukin-1 receptor-associated kinase 4 inhibitor PF-06650833 blocks inflammation in preclinical models of rheumatic disease and in humans enrolled in a randomized clinical trial. *Arthritis and Rheumatology* **73**, 2206–2218.
167. **Ackerman L**, **Acloque G**, **Bacchelli S**, et al. (2023) IRAK4 degrader in hidradenitis suppurativa and atopic dermatitis: A phase 1 trial. *Nature Medicine* **29**, 3127–3136.
168. **Vojinovic J**, **Damjanov N**, **D'Urzo C**, et al. (2011) Safety and efficacy of an oral histone deacetylase inhibitor in systemic-onset juvenile idiopathic arthritis. *Arthritis and Rheumatism* **63**, 1452–1458.
169. **Angiolilli C**, **Kabala PA**, **Grabiec AM**, et al. (2017) Histone deacetylase 3 regulates the inflammatory gene expression programme of rheumatoid

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press

arthritis fibroblast-like synoviocytes. *Annals of the Rheumatic Diseases* **76**, 277–285.

170. **Grabiec AM**, **Korchynskyi O**, **Tak PP**, et al. (2012) Histone deacetylase inhibitors suppress rheumatoid arthritis fibroblast-like synoviocyte and macrophage IL-6 production by accelerating mRNA decay. *Annals of the Rheumatic Diseases* **71**, 424–431.
171. **Finch R**, **Sostelly A**, **Sue-Ling K**, et al. (2019) OP0224 Results of a Phase 2 Study of RG6125, an Anti-Cadherin-11 Monoclonal Antibody, in Rheumatoid Arthritis Patients with an Inadequate Response to Anti-TNFalpha Therapy. *Annals of the Rheumatic Diseases* **78**, 189.
172. **Emori T**, **Hirose J**, **Ise K**, et al. (2017) Constitutive activation of integrin α9 augments self-directed hyperplastic and Proinflammatory properties of fibroblast-like Synoviocytes of rheumatoid arthritis. *Journal of Immunology* **199**, 3427–3436.
173. **Takeuchi T**, **Tanaka Y**, **Erdman J**, et al. (2020) ASP5094, a humanized monoclonal antibody against integrin alpha-9, did not show efficacy in patients with rheumatoid arthritis refractory to methotrexate: Results from a phase 2a, randomized, double-blind, placebo-controlled trial. *Arthritis Research & Therapy* **22**, 252.
174. **Lin W**, **Liu Y**, **Zhang S**, et al. (2023) Schisandrin treatment suppresses the proliferation, migration, invasion, and inflammatory responses of fibroblast-like synoviocytes from rheumatoid arthritis patients and attenuates synovial inflammation and joint destruction in CIA mice. *International Immunopharmacology* **122**, 110502.
175. **Lu M**, **He J**, **Wang X**, et al. (2023) Exploring the pharmacological mechanism of Qufeng Tongluo formula in the treatment of rheumatoid arthritis using network pharmacology methods and in vitro experimental validation. *Pharmacological Research – Modern Chinese Medicine* **8**, 100298.
176. **Chen Y-J**, **Wu J-Y**, **Leung W-C**, et al. (2020) An herbal formula inhibits STAT3 signaling and attenuates bone erosion in collagen-induced arthritis rats. *Phytomedicine* **76**, 153254.

https://doi.org/10.1017/erm.2025.11 Published online by Cambridge University Press