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

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Review

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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

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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

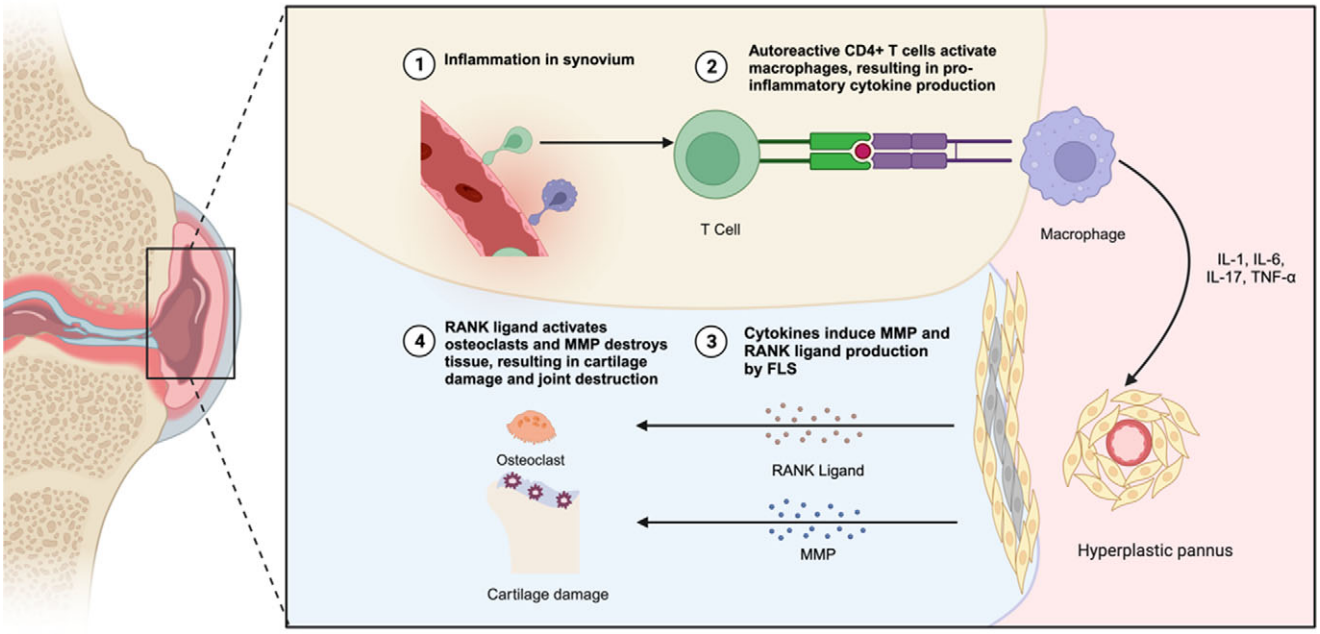

Figure 1. The pathological changes in the RA synovial joint. In RA, the synovial lining undergoes hyperplasia, forming an invasive pannus that contributes to joint destruction. FLS play a central role in this process by producing pro-inflammatory cytokines, matrix metalloproteinases (MMPs) and chemokines 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.

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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

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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

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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

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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,

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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

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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

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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.

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