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Signalling and putative therapeutic molecules on the regulation of synoviocyte signalling in rheumatoid arthritis

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetrical and chronic polyarthritis. Fibroblast-like synoviocytes are mainly involved in joint inflammation and cartilage and bone destruction by inflammatory cytokines and matrix-degrading enzymes in RA. Approaches that induce various cellular growth alterations of synoviocytes are considered as potential strategies for treating RA. However, since synoviocytes play a critical role in RA, the mechanism and hyperplastic modulation of synoviocytes and their motility need to be addressed. In this review, we focus on the alteration of synoviocyte signalling and cell fate provided by signalling proteins, various antioxidant molecules, enzymes, compounds, clinical candidates, to understand the pathology of the synoviocytes, and finally to achieve developed therapeutic strategies of RA.

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Article focus

- Apoptosis or proliferation of fibroblastic synoviocytes (FLS) controls excessive multiplication of FLS, which causes pannus formation of joint.
- The inflammation and migration of FLS involved in rheumatoid arthritis (RA) pathogenesis.
- Current strategies for targeting inflammation and pathognomonic parameters for RA FLS.

Key messages

- FLS-related signalling is involved in FLS hyperplasia, joint destruction, and pain. To regulate the excessive multiplication of FLS, mechanisms of various signalling molecules related to proliferation and apoptosis of FLS are summarized in this review.
- Activated FLS tends to migrate to and invade synovial tissues following aggravation of RA. We elucidate the signalling molecules, enzymes, and various compounds focused on the migration and invasion of FLS.
- We also describe our current knowledge of FLS signalling and several agents related to FLS signalling as candidates for therapeutic opportunities.

Strengths and limitations

- We describe the numerous molecules and mechanisms, which are directly involved in RA, to regulate FLS characteristics. This paper could be the initiation for build-up therapies of RA to focus on pathognomonic parameters for RA FLS.
- Signalling pathways are integrated in various compounds or signalling molecule-related FLS pathogenesis. Assessment or prioritization of the potential translational value of such targets and compounds still needs to be substantially improved.

Introduction

The goal of treatment for rheumatoid arthritis (RA) is remission for early RA and low disease activity for long-standing disease.[1-3] Most current treatments for RA, including non-steroidal anti-inflammatory drugs (NSAIDs),

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synthetic or biological disease-modifying antirheumatic drugs (DMARDs), and glucocorticoids, are targeted to eliminate inflammation rapidly. This is because inflammation is established as the driving force for the clinical symptoms, joint damage, disability, and comorbidity in RA.[4,5] The biological DMARDs are specifically developed to target inflammatory cytokines and their receptors such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-6 receptor (IL-6R), interleukin-17 (IL-17), B cells (rituximab), or T cells (abatacept). Moreover, they are highly efficient in decrement of disease activity in about 75% to 80% of the RA patients.[5,6] However, there is still a requirement for development of new therapies for RA because 20% to 25% of patients do not reach low disease activity. Recent guidelines from the American College of Rheumatology (ACR) recommend an initial use of methotrexate and then adding or switching to other conventional synthetic DMARDs (csDMARDs) in patients with insufficient improvement in disease activity.[2] The European League Against Rheumatism (EULAR) recommends administration of biological DMARDs in patients with high titres of autoantibodies, early joint damage on radiography, and high disease activity with the previous therapy and after failure of the first treatment cycle.[1] It is clear that joint damage can occur if inflammation persists despite these reasonably successful treatments.

In RA, there occurs a massive cellular influx of immune cells such as T lymphocytes, macrophage-like synoviocytes, and fibroblastic synoviocytes (FLS) to the synovium. Their activation, proliferation, and differentiation contribute remarkably to synovial inflammation.[7] Moreover, hyperplasia of FLS is one of the major contributors of this synovial inflammation. It could be explained by the imbalance between apoptosis and proliferation of existing FLS by environmental and somatic mutation, besides increased differentiation of mesenchymal stem cells to FLS.[8,9] These FLS migrate to the inflammatory site in the joint and form hyperplastic synovial lining containing activated FLS and macrophages called the pannus. Additionally, these activated FLS play many roles in the joints of patients with RA. They can increase the expression of adhesion molecules and activate several signalling pathways such as nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases (MAPK), and transcription factor activator protein-1 (AP-1) in early RA.[10-12] This is caused by the response to not only the pro-inflammatory environment of the immune cells, but also to autoantibodies, mechanical stimulus, and citrullination, which induces autoimmune diseases such as RA and activates the calcium channels in FLS directly.[13] This is strong evidence that FLS autonomously contribute to RA pathogenesis by driving joint inflammation and destruction. Moreover, FLS migrate, attach to, and invade the cartilage, produce matrix metalloproteinase (MMP), express receptor activator of NF-κB ligand (RANKL), and can be resistant to apoptosis by tumour-like transformation with epigenetic changes in joint destruction.[14-16] These molecular mechanisms of activated FLS are not fully understood and it is difficult to evaluate their degree of contribution to active RA or refractory RA or to current treatment strategies. Nevertheless, the current evidence indicates FLS as strong potential targets for the treatment of RA.

To understand RA, various signalling mechanisms and targets of FLS have been investigated to study cellular homeostasis and clinical implications. In this review, we summarize the novel therapeutic targets and valuable treatments in RA pathogenesis. In view of the applications of various antibodies such as TNF- α, IL-1β, and IL-6 receptor as treatments for RA, the establishment of alternative targets may be an expanded therapeutic market for RA. On the other hand, the modulation of cell fate involves tissue homeostasis and structural modification. The identification of new therapeutic strategies on RA involves the study of modulation of proliferation or apoptosis, resistance to apoptosis, and tumour cell-like features of FLS in RA.[17-19] The regulation of FLS involves the various molecules mentioned below. This section will discuss the proliferative and apoptotic signalling agents of FLS in RA. Beneficial effects of various agents on FLS may attenuate FLS hyperplasia, joint destruction, and pain. Here, we describe our current knowledge of FLS signalling and review target molecules and potential molecules before approval for RA treatment and depict articles in accordance with scope of the mode of action in FLS as proliferation, apoptosis, inflammatory activity, migration, and invasion.

Proliferative and apoptotic modulation of RA FLS

FLS of RA forms pannus with accumulated FLS, which is the result of hyperplasia of FLS. In this section, we will describe factors or molecules related to apoptosis or proliferation of FLS to control excessive multiplication of FLS and schematic summary, represented in Figure 1 and represented mode of action and working dose of molecules in Table I.

Endogenous factors

Lymphotoxin-like herpes simplex virus glycoprotein D, a receptor expressed by T lymphocytes. The expression level of lymphotoxin-like herpes simplex virus glycoprotein D, a receptor expressed by T lymphocytes (LIGHT) is up-regulated in both the synovial fluid (SF) and the synovium.[20,54,55] LIGHT significantly enhances the proliferation of FLS and induces the expression of adhesion molecules such as the intercellular adhesion molecule-1 (ICAM-1) and various cytokines such as the monocyte chemoattractant protein-1, IL-8, macrophage inflammatory protein (MIP)-1α, and NF-κB translocation through the lymphotoxin β receptor.[20] Moreover, LIGHT also stimulates macrophage-mediated osteoclastogenesis in the SF. A higher concentration of LIGHT is revealed in RA SF compared with that in the OA SF.[54]

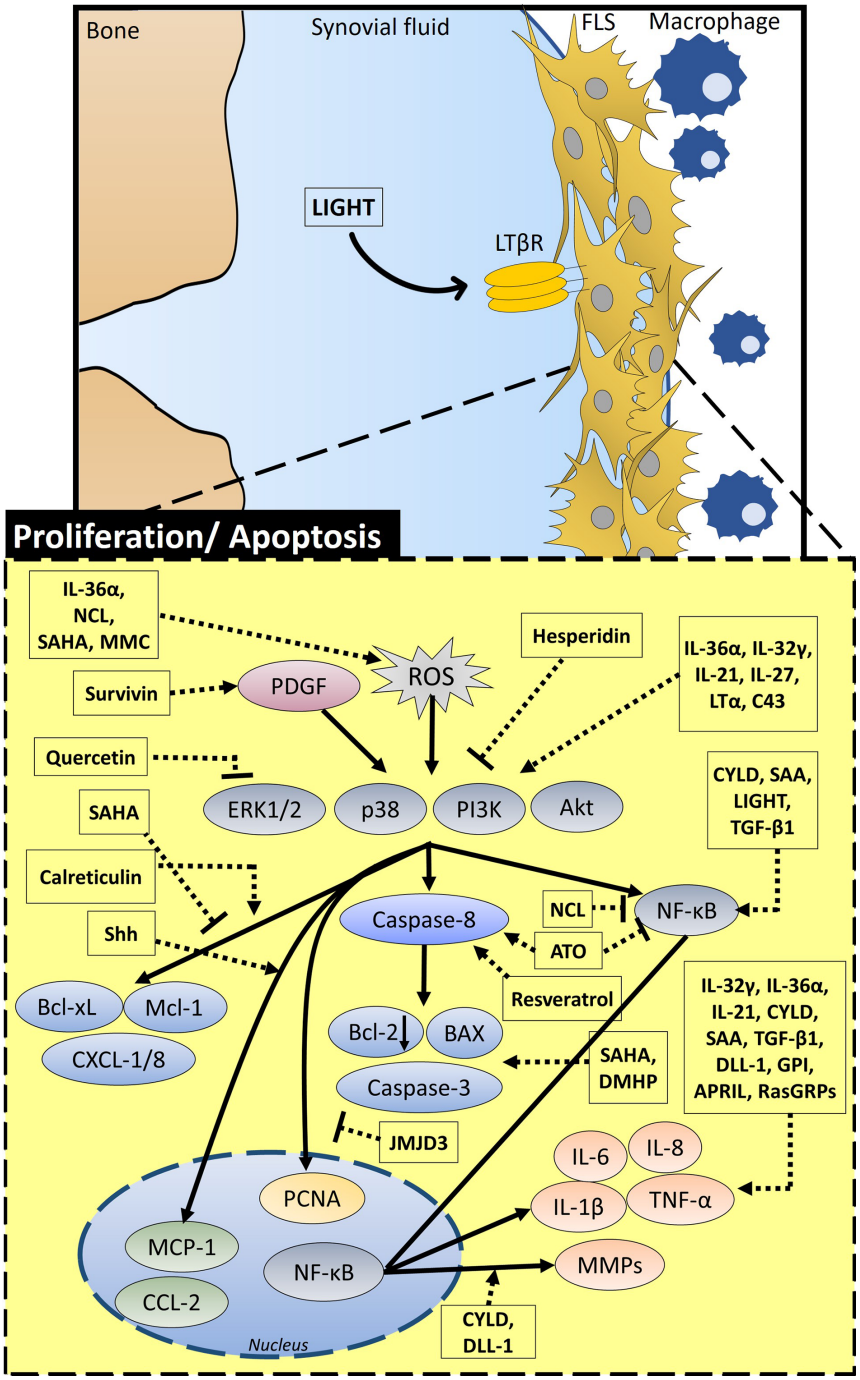

Fig. 1

Schematic diagram of the overall signalling mechanism and related factors of proliferative and apoptotic modulation in the fibroblastic synoviocytes (FLS) of rheumatoid arthritis (RA). Proliferation and apoptosis in FLS are regulated by various signalling factors. IL-36α, NCL, SAHA, and MMC increase reactive oxygen species (ROS) and survivin activates platelet-derived growth factor (PDGF) signalling. PDGF and ROS affect extracellular signal-regulated protein kinase 1/2 (ERK1/2), p38, phosphoinositide 3-kinase (PI3K), and protein kinase B (Akt) signalling. SAHA inhibits B-cell lymphoma-extra large (Bcl-xL) and myeloid cell leukemia-1 (Mcl-1) expression. NCL inhibits nuclear factor kappa-B (NF-κB). Quercetin and hesperidin inhibit extracellular signal-regulated kinase (ERK)/PI3K/Akt signalling, whereas IL-36α, IL-32γ, IL-21, IL-27, LTα, and C43 activate this signalling. While calreticulin stimulates Bcl-xL, Mcl-1, and C-X-C motif chemokine ligand (CXCL)-1/8 through this signalling, ATO and resveratrol enhance caspase-8 activity, and CYLD, SAA, LIGHT, and TGF-β1 activate NF-κB signalling. In the nucleus, Shh activates MCP-1 and CYLD and DLL-1 increase MMPs and IL-1β through NF-κB signalling. GPI, APRIL, and RasGRPs increase inflammatory factors such as TNF-α and IL-8. JMJD3 inhibits the activity of PCNA in the nucleus. SAHA and DMHP enhance expression of Bcl-2-associated X protein (BAX) and caspase-3, and they also attenuate Bcl-2 expression. LIGHT, lymphotoxin-like, herpes simplex virus glycoprotein D, a receptor expressed by T lymphocytes; LTα, lymphotoxin α; APRIL, a proliferation-inducing ligand; Shh, Sonic hedgehog; GPI, glucose-6-phosphate isomerase; IL, interleukin; JMJD3, Jumonji C family of histone demethylases; CYLD, cylindromatosis; RasGRPs, Ras guanine nucleotide-releasing proteins; TGF-β1, transforming growth factor-β1; SAA, serum amyloid A; DLL-1, δ like Notch ligand 1; C43, compound 43; ATO, arsenic trioxide; DMHP, 7,3'-dimethoxy hesperetin; NCL, niclosamide; MMC, mitomycin C; MCP-1, monocyte chemoattractant protein-1; SAHA, suberoylanilide hydroxamic acid; PCNA, proliferating cell nuclear antigen.

Table I. Summary of molecular mechanism of fibroblastic synoviocytes (proliferation and apoptosis).

Molecules	Mode of action	Species	Dose		Ref
			In vivo	In vitro	
Endogenous factors					
LIGHT	Enhanced the proliferation of FLS, expression of ICAM-1, MCP-1, IL-8, MIP-1α, and NF-κB translocation	RA-FLS		10 ng/ml	20
APRIL	Produced IL-6, TNF-α, IL-1β, and enhanced FLS proliferation	RA-FLS, Rat adjuvant-induced arthritis (AA) model		30 to 300 ng/ml	21,22
Shh signalling	Mediated the proliferation and migration through MAPK/ERK pathway	RA-FLS		1, 10 μM	23
GPI	Stimulated the secretion of TNF-α and IL-1β	RA-FLS, arthritic synovial tissues from RA patients		1 to 10 μg/ml	24
Survivin	Promoted proliferation	RA-FLS			25
JMJD3	Activated proliferation and migration	RA-FLS, CIA mice			26
CYLD	Enhanced cell growth and cytokine production	RA-FLS			27
RasGRPs	Enhanced cell motility and IL-6 production	RA-FLS, CIA mice			28
TGF-β1	Activated NF-κB, AP-1, migration, and invasion	RA-FLS, SF from RA patients		1 to 100 ng/ml	29,30
SAA	Promoted migration, angiogenesis through MMP-2/9, activation of NF-κB, and cytokine production	RA-FLS, RA synovial/SCID mouse	50 μg/ml	10 to 50 μg/ml	31,32
DLL-1	Suppressed IL-6 and MMP-3				33
Calreticulin	Induced Bcl-xL, Mcl-1 through PI3K/Akt and STAT3 pathways	RA-FLS			34
Cytokines					
LTα	Activation of MAPK, ERK1/2, p38, PI3K/Akt pathway, NF-κB translocation, IL-6/8, and MMP-3	RA-FLS		0.5 nM	35
IL-21	Stimulated the proliferation and secretion of TNF-α and IL-6 through ERK1/2, PI3K/Akt, and STAT3	RA-FLS		1 to 100 ng/ml	36
IL-32γ	Enhanced expression of IL-6 and IL-8 through activation of ERK1/2	RA-FLS		50 to 100 ng/ml	37
IL-27	Induced expression of adhesion molecules, inflammatory cytokines, and activated inflammatory signalling pathways	RA-FLS		10 to 100 ng/ml	38
IL-36α	Activated p38 MAPK signalling and pro-inflammatory cytokines	RA/Murine FLS, IL-36R-deficient FLS			39
Synthetic compounds					
C43	Inhibited proliferation, inflammation, and bone injury	RA-FLS, SIA mice, and CIA mice	6 to 30 mg/kg	30 μM	40,41
ATO	Induced apoptosis through caspase signalling	RA-FLS, CIA rats	1 to 6 mg/kg	0.1 to 8 μM	42,43
DMHP	Induced apoptosis through enhancing BAX and caspase-3	RA-FLS, AA rats	20 to 150 mg/kg	2.5 to 20 μM	44
NCL	Reduced E-selectin, ICAM-1, and VCAM-1 and inhibited migration and invasion	RA-FLS, RA patients	1,000 mg/day	20 to 100 nmol/l	45,46
SAHA	Induced apoptosis through enhancing caspase-3 and ROS	RA-FLS		5 μM	47
Natural compounds					
Resveratrol	Mediated apoptosis and inhibited IL-1β, MMP-3, and phosphorylated Akt	RA-FLS, RA patients	1 g/person	6.25 to 50 μM	48,49
Hesperidin	Down-regulated TNF-α and reduced MMPs	RA-FLS, AIA and CIA mice	20 to 150 mg/kg	2.5 to 20 μM	50,51
MMC	Induced apoptosis through ROS production	RA-FLS		10 to 100 μg/ml	52
Quercetin	Enhanced apoptosis through inhibition of PI3K/Akt pathway	RA-FLS		200 μM	53

APRIL, A proliferation-inducing ligand; ATO, arsenic trioxide; Bcl-xL, B-cell lymphoma-extra large; C43, compound 43; CYLD, cylindromatosis; DLL-1, delta like canonical notch ligand 1; DMHP, 7,3'-dimethoxy hesperetin; ERK1/2, extracellular signal-regulated protein kinase 1/2; GPI, glucose 6-phosphate isomerase; IL-21, interleukin-21; IL-27, interleukin-27; IL-32γ, interleukin-32γ; IL-36α, interleukin-36α; JMJD3, Jumonji C family of histone demethylases; LIGHT, lymphotoxin-like herpes simplex virus glycoprotein D, a receptor expressed by T lymphocytes; LTα, lymphotoxin α; Mcl-1, myeloid cell leukemia-1; MMC, mitomycin C; NCL, niclosamide; RasGRPs, Ras guanine nucleotide-releasing proteins; Ref, reference; SAA, serum amyloid A; SAHA, suberoylanilide hydroxamic acid; Shh signaling, Sonic hedgehog signaling; STAT3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor-β1.

A proliferation-inducing ligand. High level of A proliferation-inducing ligand (APRIL) is detected in RA serum and in the adjuvant-induced arthritis (AA) synovium of rat model.[21,22] APRIL stimulates the FLS to produce various cytokines including APRIL itself.[21] APRIL-stimulated T or B cells also enhance the FLS proliferation in a co-culture system.[22]

Sonic hedgehog signalling. Sonic hedgehog (Shh) signalling is involved in various cell functions such as proliferation, differentiation, and embryonic development.[56,57] Higher expression of Shh messenger RNA (mRNA) in the RA synovium than that in the control synovium and treatment with cyclopamine (a specific inhibitor of Shh signalling) on FLS results in cell cycle arrest.[58] Currently, it is reported to mediate the proliferation and migration of FLS by the MAPK/extracellular signal-regulated kinase (ERK) pathway in RA.[23] Two Shh inhibitors, sonidegib and vismodegib, have received Food and Drug Administration (FDA) approval for basal cell carcinoma.[59]

Glucose-6-phosphate isomerase. The biochemical role of glucose-6-phosphate isomerase (GPI) is the isomerization of glucose-6-phosphate to fructose 6-phosphate. GPI plays various roles in cell growth and motility and has been robustly studied for its pathological roles in tumour proliferation.[60–62] More recently, the pathophysiological role of GPI has been revealed in RA. The level of GPI is increased in RA FLS and it also stimulates the secretion of cytokines such as TNF-α and IL-1β in FLS.[24]

Survivin. Survivin is considered a proto-oncogene and is involved in joint destruction in RA.[63–65] Enhanced expression of wild type and splice variant type 2B of survivin is demonstrated in the RA synovium.[65] Extracellular survivin is also increased in the SF of RA.[25] Platelet-derived growth factor (PDGF)-dependent survivin 2B expression and subsequent promotion of FLS proliferation suggest that survivin 2B plays an emerging role in RA.

Jumonji C family of histone demethylases. The expression of Jumonji C family of histone demethylases (JMJD3) is low in normal tissue; its expression is stimulated by various stress conditions such as amino acid deprivation and hypoxia.[66,67] The enhanced expression of JMJD3 in RA FLS activates proliferation and migration.[26]

Cylindromatosis. Cylindromatosis (CYLD) is a condition involving multiple tumours of the skin appendages.[68,69] The gene of CYLD, a tumour suppressor, is associated with deactivation of the NF-κB signalling pathway.[27,70,71] CYLD suppression enhances cell growth and cytokine production in RA FLS.[27]

Ras guanine nucleotide-releasing proteins. Ras guanine nucleotide-releasing proteins (RasGRPs) are identified in the FLS of RA. The overexpression of RasGRP2 enhances cell motility and IL-6 production, whereas the knockdown of RasGRP2 attenuates pannus formation in an experimental arthritis model.[28]

Transforming growth factor-β1. Transforming growth factor (TGF)-β1 is expressed in the synovium of patients with RA. It enhances the DNA-binding activities of NF-κB and AP-1,[29,30,72] and promotes migration and invasion by activating Smad2/3 in the RA FLS.[73]

Serum amyloid A. Serum amyloid A (SAA) is identified as a biomarker for acute phase inflammation in RA.[74,75] It promotes the migration of FLS and angiogenesis by induction of MMP-2 and MMP-9 in the synovium; thus, it supports the proliferation of synovium and formation of pannus.[31] SAA is enhanced in RA synovium,[76] and stimulates the transcriptional activation of NF-κB and the expression of IL-6 and IL-8 with the involvement of receptor for advanced glycation end-products (RAGE).[32] The SAA/RAGE/NF-κB signalling process is involved in the pathogenesis of RA.[32]

δ like canonical Notch ligand 1. Blocking the δ like canonical Notch ligand 1 (DLL-1) protein improves arthritis in collagen-induced arthritis (CIA) mouse model and suppressed IL-6 and MMP-3.[33] Although the ameliorating effect of DLL-1 blocking on inflammatory cytokines is partial, DLL-1 has proved to be a new target for joint inflammation treatment.

Calreticulin. Calreticulin is known as the calcium-binding endoplasmic reticulum (ER) resident chaperone. Extracellular calreticulin is involved in apoptotic cell clearance as a recognition ligand.[77] Extracellular application of recombinant calreticulin inhibits inflammation-mediated bone resorption.[78] Although the intra-/extracellular functions of calreticulin are diverse, it is also considered as a biomarker of juvenile idiopathic arthritis.[34] In addition, enhanced expression of calreticulin is revealed in RA synovium, and it induces the expression of B-cell lymphoma-extra large (Bcl-xL) and myeloid cell leukaemia-1 (Mcl-1) proteins through the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB or Akt) and signal transducer and activator of transcription 3 (STAT3) pathways.[79]

Cytokines

Lymphotoxin α. Lymphotoxin α (LTα), previously known as tumour necrosis factor-β (TNF-β), is a pro-inflammatory cytokine produced by T lymphocytes and is very similar to TNF-α.[35,80] LTα possesses high affinity for both TNF receptor 1 (TNFR1) and TNFR2.[81] It mediates the activation of MAPKs extracellular signal-regulated protein kinase 1/2 (ERK1/2), p38, the PI3K/Akt pathway, NF-κB translocation, and the secretion of cytokines such as IL-6, IL-8, and MMP-3.[35] Being homologous to the cytokine TNF-α, LTα is also a stimulant of RA FLS as well as lymphocytes such as macrophages. However, the subcutaneous injection of pateclizumab, an anti-LTα antibody, does not show any clinical improvements in RA symptoms and signs, while adalimumab, a TNF-α inhibitor, demonstrates the clinical efficacy in RA patients with poor response to csDMARDs.[82]

IL-21. Increased serum IL-21 levels and enhanced expression of IL-21 receptors in the synovium of RA patients are associated with the pathology of RA.[83,84] The treatment of IL-21-activated signalling pathways such as ERK1/2, PI3K/Akt, and STAT3 subsequently stimulate the proliferation and secretion of cytokines in RA FLS.[36] Recently, the first in-human phase 2 trial with recombinant anti-IL-21 monoclonal Ab has shown to be well tolerated in RA patients.[85]

IL-32γ. IL-32γ is identified in the monocytes of active RA SF.[37] Stimulation of IL-32γ enhances the expression of IL-6 and IL-8 in RA FLS. Phosphorylated ERK1/2 is also involved in RA, and inhibition of ERK1/2 in RA FLS attenuates

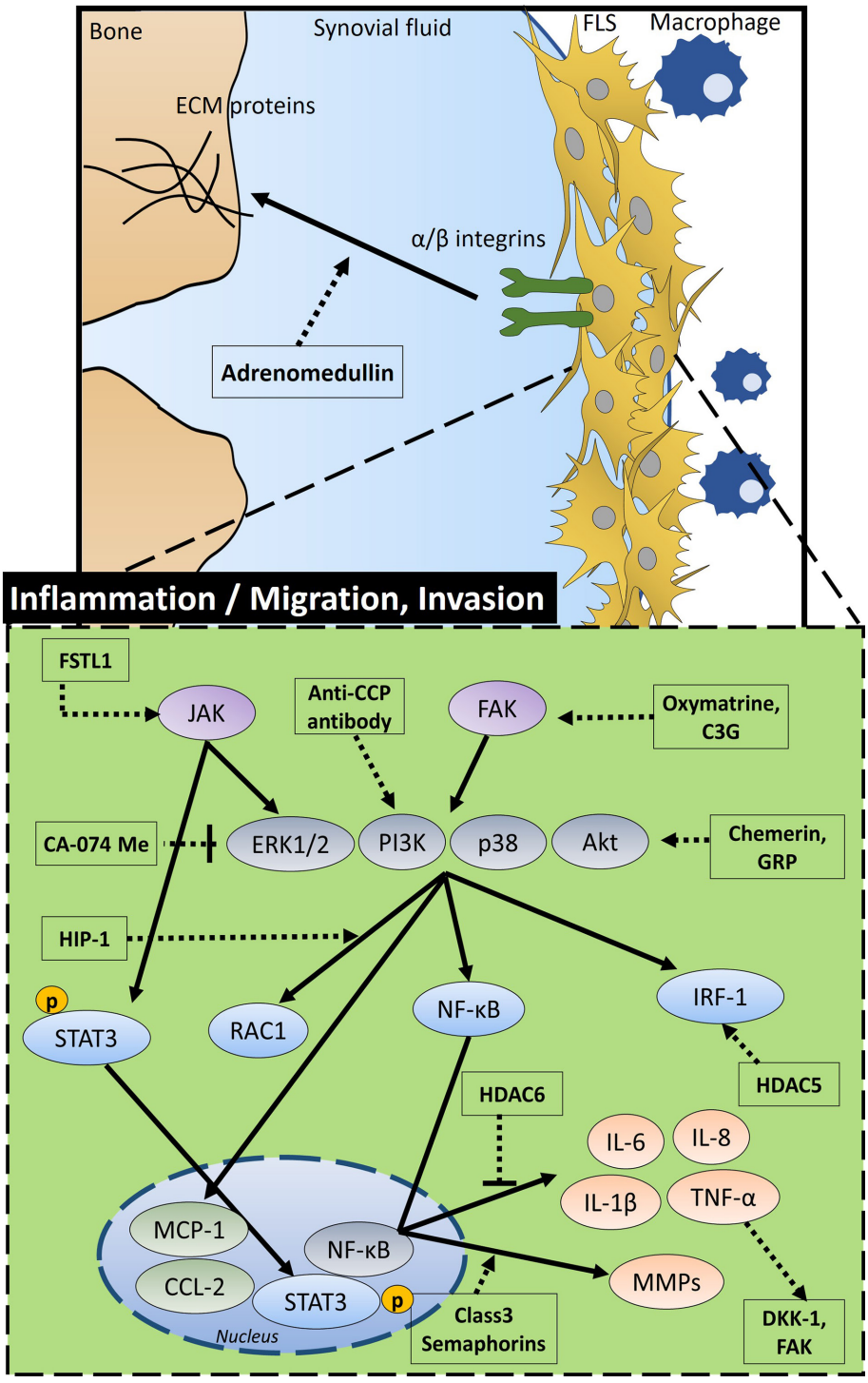

Fig. 2

Schematic diagram of the overall signalling mechanism and related factors of inflammatory activity, migration, and invasion in the fibroblastic synoviocytes (FLS) of rheumatoid arthritis (RA) FSTL1 stimulates JAK signalling. Oxymatrine and C3G enhance FAK signalling. Anti-CCP antibody activates PI3K. JAK induces activation of extracellular signal-regulated protein kinase 1/2 (ERK1/2) and pSTAT3, FAK activates phosphoinositide 3-kinase (PI3K), p38, and protein kinase B (Akt) signalling. Chemerin and GRP activate PI3K/Akt signalling, but CA-074Me inhibits this signalling. HIP-1 activates RAC1 and HDAC5 activates interferon regulatory factor 1 (IRF-1) through PI3K/Akt signalling. HDAC6 inhibits inflammatory factors such as interleukin (IL)-6 and tumour necrosis factor-α (TNF-α) through nuclear factor kappa-B (NF-κB) transcription in the nucleus, whereas class 3 semaphorins increase levels of matrix metalloproteinases (MMPs). In addition, increased TNF-α enhances DKK-1 and FAK. This signalling is involved in the inflammation, migration, and invasion of FLS. C3G, cyanidin-3-glucoside; DKK-1, Dickkopf-1; FAK: integrin-related focal adhesion kinase; pSTAT3: phosphorylated signal transducer and activator of transcription 3; GRP, gastrin-releasing peptide; HIP-1, Huntingtin-interacting protein-1; HDAC, histone deacetylase; FSTL1, follistatin-like protein 1; ECM proteins, extracellular matrix proteins; anti-CCP, anti-cyclic citrullinated peptide.

Table II. Summary of molecular mechanisms of fibroblastic synoviocytes (inflammation, migration, and invasion).

Molecules	Mode of action	Species	Dose		Ref
			In vivo	in vitro	
Endogenous factors					
Chemerin	Activation of cytokine production, MMP-3 expression, and FLS migration	RA-FLS		10 to 50 μM	113
DKK-1 and FAK	Enhancement of FLS migration	RA-FLS			114
GRP	Enhancement of FLS invasion through Akt activation	RA-FLS		10 μM	115
Class 3 semaphorins	Activation of RAC1 and increasing effect on RA-FLS invasion	RA-FLS		10 μM	116
HIP-1	Enhancement of FLS migration	RA-FLS			117
Adrenomedullin	Increase of FLS adhesion	RA-FLS		100 nM	118
HDAC	Increase of IL-6 and IL-1β expression	RA-FLS, CIA mice			119
FSTL1	Enhancement of MMP expression and invasion of FLS	RA-FLS		1 to 5 μg/ml	120
Cadherin-11	Enhancement of FLS adhesion and proliferation	RA-FLS			121,122
Anti-CCP antibody	Increase of FLS migration through PI3K activation	RA-FLS		1 μg/ml	123
Synthetic compounds					
CA-074Me	Inhibition of cathepsin B with decrease of MMP-2, F-actin, and phosphorylation of p38 MAPK/JNK	RA-FLS		10 μM	124
Natural compounds					
C3G	Inhibition of LPS-induced IL-6 and IL-1β production	RA-FLS, CIA mice	50 mg/kg	10 to 40 μM	125
Oxymatrine	Protection of joint destruction	RA-FLS, CIA mice	100 mg/kg	10 to 100 μM	126

C3G, cyanidin-3-glucoside; CIA, collagen-induced arthritis; DKK-1, Dickkopf-1; FAK, focal adhesion kinase; FLS, fibroblastic synoviocytes; FSTL1, follistatin-like protein 1; GRP, gastrin-releasing peptide; HDAC, histone deacetylase; HIP-1, Huntingtin-interacting protein-1; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; MMP, matrix metalloproteinase; PI3K, phosphoinositide 3-kinase; RA, rheumatoid arthritis.

IL-32γ-induced IL-6 and IL-8 mRNA expressions.[86] It also mediates proinflammatory cytokines through the activation of ERK1/2.

IL-27. Increased level of IL-27 is observed in RA patients and IL-27 receptor is expressed in FLS. Stimulation of IL-27 induces the expression of adhesion molecules, release of inflammatory chemokines such as the C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 9 (CXCL9), and CXCL10, and activates inflammatory signalling pathways such as STAT1, JAK-2, Akt, PI3K, and c-Jun N-terminal kinase (JNK) signalling in RA FLS.[38,87]

IL-36α. Increased expression of IL-36α, an IL-1 family member, is identified in the synovium of patients with inflammatory arthritis such as RA and psoriatic arthritis.[88] As an inflammatory signalling mediator, IL-36α stimulation activates p38-MAPK signalling and enhances the production of proinflammatory cytokines in FLS.[39] This study of IL-36α receptor-depleted condition demonstrates that the IL-36α receptor provides a link between FLS and plasma or B cells in synovium.[39]

Synthetic compounds

Compound 43. Compound 43 (C43) is an agonist of the formylpeptide receptor identified in various cells, such as endothelial cells[89] and fibroblasts,[90] and has been discovered as the receptor for the tripeptide N-formylmethionyl-leucyl-phenylalanine (fMLF).[91] C43 inhibits inflammation and bone injury, and decreases FLS proliferation and joint damage in RA.[40,41]

Arsenic trioxide. Arsenic trioxide (ATO, As_2O_3) has been studied with reference to cellular apoptosis, and has been approved by the FDA for the treatment of acute promyelocytic leukaemia. ATO shows a beneficial effect for some solid tumours and haematological malignancies.[42,92] The action of ATO is also effective against the pathogenesis of RA by inducing apoptosis of FLS through the activation of caspase signalling and subsequently rebuilding the synovial tissue.[43] Although the molecular mechanism of ATO is poorly understood in RA, more recently ATO has been shown to improve RA symptoms by regulating autophagic signalling in combination with vitamin D.[42]

7,3'-dimethoxy hesperetin. 7,3'-dimethoxy hesperetin (DMHP) is a derivative of the bioflavonoid compound hesperidin.[44] It induces FLS apoptosis through enhanced

expression of BAX (Bcl-2-associated X protein) and caspase-3 mRNA and caspase-3 activity in an experimental adjuvant arthritis model.[44]

Niclosamide. Niclosamide (NCL) is known as a multifunctional agent with anti-inflammatory, antitumour, and antioxidative properties,[45,93–95] and is used for therapy of tapeworm infection.[96] Moreover, its role in the suppression of cell viability and ROS production through the mitochondrial-Akt signalling pathways has also been investigated.[45,97] A phase 2 clinical trial of NCL for RA was conducted as an adjuvant treatment along with administration of etanercept, and it showed a reduction of disease activity with marked decrease of E-selectin, ICAM-1, and vascular cell adhesion molecule-1 (VCAM-1).[46]

Suberoylanilide hydroxamic acid. Suberoylanilide hydroxamic acid (SAHA, vorinostat), a class I histone deacetylase (HDAC) inhibitor, is an anticancer agent[98,99] and was approved by the FDA for treatment of cutaneous T cell lymphoma.[100] It induces the apoptosis of RA FLS through the involvement of enhanced caspase-3 activity and ROS production.[47]

Natural compounds

Resveratrol. Polyphenol resveratrol, trans-3,5,4'-trihydroxystilbene, is an antioxidant abundant in red wines and displays a positive effect on cardiac protection.[101,102] Resveratrol mediates cell apoptosis through the modulation of mitochondrial signalling in RA FLS. It is a different strategy to reduce synovial hyperplasia.[102] Currently, it is reported that resveratrol inhibits inflammatory cytokine IL-1β, MMP-3, and phosphorylated Akt expression.[48] Moreover, a clinical trial has shown the efficacy of resveratrol as an adjuvant therapy to the conventional RA treatment.[49]

Hesperidin. Hesperidin, a bioflavonoid, has revealed various protective roles in cognition, heart function, and inflammation.[103–105] Oral administration of hesperidin suppresses the clinical scores of RA patients.[50] More recently, hesperidin has shown an anti-inflammatory effect on FLS and reduces the polarization of macrophages in antigen-induced arthritis mouse model.[51]

Mitomycin C. Mitomycin C (MMC) is an antibiotic and anti-tumour agent.[106,107] It has also been studied as an apoptotic agent of fibroblasts.[108–110] Treatment with MMC induces apoptosis of RA FLS through the production of ROS and disruption of the mitochondrial membrane potential.[52]

Quercetin. Quercetin (3,3',4',5,7-pentahydroxyflavone) is a polyphenolic flavonoid and antioxidant in the human diet.[111,112] The treatment of quercetin enhances the apoptosis of RA FLS through the inhibition of the PI3K/Akt pathway.[53]

Inflammatory activity, migration, and invasion

A characteristic inflamed synovium possesses dynamic FLS that reveals migration and invasive properties. This section focuses on the modulation of inflammation and migration of FLS and signalling molecules or enzymes on RA pathogenesis. A schematic diagram of migration and invasive properties is shown in Figure 2, and a summary of the mode of action and working dose of molecules is given in Table II.

Endogenous factors

Chemerin. Chemerin is an agonist of chemokine-like receptor 1 (known as ChemR23) and identified in macrophages and dendritic cells.[127,128] The enhanced expressions of chemerin and its receptor ChemR23 are revealed in the RA synovium and related to disease severity.[113,129] Chemerin activates cytokine production, MMP-3 expression, and enhances FLS migration through the involvement of the p38-MAPK and Akt pathways.[113]

Dickkopf-1 and integrin-related focal adhesion kinase. Stimulation by TNF-α causes the FLS-induced activation of Dickkopf-1 (DKK-1) and integrin-related focal adhesion kinase (FAK), and enhances migration of these FLS.[114] High levels of FAK, p-JNK, paxillin, and cell division control protein 42 (cdc42) expression are reported in the FLS migration machinery.

Gastrin-releasing peptide. Gastrin-releasing peptide (GRP) and its receptor GRPR are involved in inflammation processes such as gastritis and sepsis.[130] Activation of GRP enhances FLS invasion through Akt activation whereas RC-3095, the GRPR antagonist reduces it in a RA mice model.[115]

Class 3 semaphorins. The semaphorins are implicated in autoimmune diseases such as RA and in the migration of immune cells and FLS.[116,131] Type-specific expression of semaphorin reveals the severity of RA.[116,132]

Huntingtin-interacting protein 1. Huntingtin-interacting protein 1 (HIP-1) gene is identified using DNA sequencing by a phenotype-driven strategy in rats and patients with RA; it is involved in the enhanced invasiveness of RA FLS.[117] HIP-1 deficient human RA FLS decreased their invasion by nearly 50%,[133] suggesting that HIP-1 can be used for deteriorated joints in RA patients.

Adrenomedullin. Adrenomedullin is a secreted peptide from the FLS and is associated with the pathogenesis of RA.[118,134] Its stimulation mediates the adhesion of FLS by association of extracellular matrix proteins, integrin-α2 and -β1.[135]

Histone deacetylase. The role of HDAC in RA FLS is not yet clear. Although the HDAC inhibitor SAHA mediates apoptosis in RA FLS,[47] the stimulation of inflammatory cytokines such as IL-1β and TNF-α suppresses the expression of HDAC5 in RA FLS.[136] In addition, application of HDAC6 inhibitor tubastatin A suppresses synovial inflammation and protects joint damage in CIA mice.[119]

Follistatin-like protein 1. Follistatin-like protein 1 (FSTL1) is identified in RA synovium[137] and enhanced in the early stage of CIA in mice.[138] It is also involved in the progression of osteoclasts.[139] Its mechanism of pathogenesis in RA involves NF-κB, MAPK, and JAK/STAT3 signalling

pathways.[120] MicroRNA-27a-targeted FSTL1 inhibits the migration and invasion of RA FLS.[140]

Cadherin-11. Cadherin-11 is an adhesion molecule involved in various functions of the FLS. Cadherin-11-deficient FLS display diminished migration and invasion to cartilage under stimulation of serum or PDGF.[141] Cadherin-11 is selectively expressed on the FLS and supports the lining layer of the synovium via mediating FLS-to-FLS adhesion.[121] Knockdown of cadherin-11 reduces the IL-1β-induced proliferation of FLS.[122]

Anti-cyclic citrullinated peptide antibody. The serum of RA patients is positive for anti-cyclic citrullinated peptide (anti-CCP).[142] Anti-CCP is used as a serological marker to diagnose RA.[143] Recently, it has been reported that FLS migration is increased by stimulation of anti-CCP polyclonal antibody through activating PI3K.[123]

Synthetic compounds

Cathepsin B inhibitor, CA-074 Me. Cathepsin B, a proteinase, displays a higher activity in RA synovium.[144] Application of its inhibitor, CA-074 Me, inhibits invasion signalling through the reduced expression of MMP-2 mRNA, F-actin protein, and phosphorylation of P38-MAPK/JNK in FLS.[124]

Natural compounds

Cyanidin-3-glucoside. Cyanidin-3-glucoside (C3G) is the most distributed anthocyanin compound in the flavonoid family. Being an antioxidant, it is studied for its inhibitory role on inflammation.[145] Treatment with C3G inhibits LPS-induced cytokine production in FLS and attenuates RA severity in the CIA mouse model.[125]

Oxymatrine. Oxymatrine, a quinolizidine alkaloid, is an extract from the roots of *Sophora flavescens*.[126] It has demonstrated an inhibitory role in breast cancer cell migration and invasion,[146] an anti-inflammatory and antioxidant role,[147] and a protective effect on amyloid beta-induced neurotoxicity.[148] From the massive study conducted on oximatrine, it is found to be involved in the protection of joint destruction in RA.[126]

Future perspectives and clinical strategies

Current medications, focused on inflammation and immunity, can influence FLS in RA. A therapeutic dose of methotrexate, the first choice for initial RA treatment, may attenuate the effects of PDGF and IL-1β on tumour suppressor expression and inhibit the proliferation and migration of FLS.[149,150] Hydroxychloroquine, a csDMARD, can also sensitize FLS to Fas-mediated apoptosis.[151] TNF-α inhibitors can influence FLS apoptosis via phosphoinositide-3-kinase Akt signal transduction and proliferation via the NF-κB pathway.[152,153] IL-6 and IL-6R inhibitors can also function well, since IL-6 is reported to promote proliferation of FLS[154] and facilitate angioneogenesis for pannus formation.[155] It is reported that IL-17 impairs FLS apoptosis through activation of autophagy[156] and enhances proliferation of FLS via STAT3 activation.[157] Thus, IL-17 inhibitors can attenuate the contribution of FLS in RA. Janus kinase inhibitors, which are targeted synthetic DMARDs (sDMARDs), may inhibit the FAK-mediated activation and invasion of FLS in RA.[158] Rituximab, a CD20 monoclonal antibody, might inhibit cellular adhesion and the production of MMP by FLS through LIGHT up-regulated B-cell depletion.[159] Abatacept, a cytotoxic T-lymphocyte-associated antigen 4-Ig that antagonizes CD28-medicated T cell activation, inhibits the FLS migration and expression of MMPs by inhibiting the MAPK pathway.[160] Although the influences of these medications on RA FLS have been reported, it is not known whether or not they can sufficiently control the RA FLS under therapeutic dose.

Research has been focusing on the greatest unmet needs of novel targeted therapies, including research of novel combination therapies for patients with refractory RA to available therapies, since the patients with remission are less than half of RA patients and there is no cure yet.[161] Current available therapies for RA including various synthetic and biological DMARDs, glucocorticoids, and their combination therapies should be used carefully due to hazards such as increased risk of infection and malignancy. Thus to minimize systemic adverse events from immune suppression and increase the response to these current treatments, more specific target molecules that have a weaker effect on immune cells may be needed. In this respect, molecules that regulate synoviocyte signalling may be one of the more efficient therapeutic targets for RA, and we review these here. Add-on or combination therapies with synoviocyte-targeting therapies may increase their treatment efficacy and decrease systemic adverse events by reducing dose of current therapies. For example, NCL, as mentioned earlier, in combination with etanercept increases the proportion of patients achieving an ACR 20% response (ACR20), ACR50 response, and ACR70 response, and improves tender joint count, swollen joint count, and disease activity score of 28 joints (DAS-28) in RA patients who show an inadequate response to etanercept.[46] Interestingly, this treatment does not reduce CRP and ESR compared to placebo,[46] and this suggests that adding NCL can improve the treatment response without having a certain effect on systemic inflammation. In this regard, GPI is also prudently suggested as one of the best prospective targets, although this treatment option is in the early stages since GPI could be involved in the pathogenesis of RA with joint-specific inflammation as an autoantigen.[162] GPI has also shown to be correlated with disease activity such as DAS-28, swollen and tender joint count, and GPI levels decreased in response to infliximab treatment in RA patients.[163]

In this review, we have tried to highlight the unmet need to target FLS as one of the novel therapies for RA. Several therapeutic approaches may have a weak anti-inflammatory effect or no effect at all. However, it is clear that inflammation is at the heart of the pathogenesis of

RA. In this respect, innovative strategies are required to target inflammation and pathognomonic parameters for RA FLS concurrently. This approach will provide us with a wide perspective to identify the appropriate target from multiple signalling of RA.

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