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Crosstalk between synovial macrophages and fibroblasts in rheumatoid arthritis

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Summary. Rheumatoid arthritis (RA) is an autoimmune disease associated with chronic inflammation of joints. Abnormally activated cells such as synovial macrophages and synovial fibroblasts induce RA pathogenesis and ultimately joint destruction. Since macrophages can change their own characteristics depending on the microenvironmental condition, it has been suggested that activation and remission of RA are regulated by crosstalk between synovial macrophages and other cells. Moreover, recent findings of heterogeneity of synovial macrophages and fibroblasts support the idea that complex interactions regulate RA from its onset to remission. Importantly, an understanding of the intercellular crosstalk in RA is far from complete. Here, we summarize the molecular mechanisms underlying the pathological development of RA with particular reference to the crosstalk between synovial macrophages and fibroblasts.

Key words: Rheumatoid arthritis, Crosstalk, Synovial macrophages, Synovial fibroblasts

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by systemic chronic inflammation. Immune disorders caused by genetic factors and/or environmental factors such as infection, smoking and aberrant epigenetics disrupt homeostasis in the joints, resulting in their destruction (McInnes and Schett, 2011; Smolen et al., 2016; Saeki et al., 2022). Recent RA therapeutics such as disease-modifying anti-rheumatic drugs (DMARDs), biologics and molecularly-targeted drugs have achieved substantial benefits in many RA patients. However, important issues remain, i.e., about 20% of RA patients fail to respond to currently available therapeutics and these therapeutics increase patients' susceptibility to infection (Bécède et al., 2019; Yamanaka et al., 2020). Thus, clarification of the molecular mechanisms in RA pathogenesis followed by identification of novel therapeutic targets is required.

The synovium (also known as the synovial membrane) is a thin lining inside the joint cavity in healthy joints. Histologically, the synovium is divided into two distinct layers. The lining layer is composed of a sheet of resident macrophages and fibroblasts that maintains homeostasis in the joint cavity. In addition, the sub-lining interstitial layer consists of loose connective tissue with a fat pad, blood vessels and lymph vessels, and is a region that includes stromal cells, macrophages and other immune cells (Smith, 2011) (Fig. 1). In joints with RA, chronic inflammation induces abnormal activation of synovial cells and infiltration of immune cells followed by hyperplasia of the synovium and destruction of bones and cartilage (Lindblad and Hedfors, 1987; van de Sande and Baeten, 2016) (Fig. 1). Several studies using RA specimens and mouse models of inflammatory arthritis have shown that crosstalk between synovial macrophages and fibroblasts is important for both the pathogenesis and the resolution of synovitis (Kuo et al., 2019; Alivernini et al., 2020; Saeki and Imai, 2020). It has been suggested that macrophages, which contribute to both pro-inflammatory and anti-inflammatory processes, and tissue repair, play key roles in the regulation of RA pathogenesis (Kemble and Croft, 2021). Indeed, macrophages can alter physiological characteristics through their impact on the microenvironment (Guilliams et al., 2020; Park et al., 2022). In this review, we summarize our current understanding of the activation mechanisms in general macrophages. We also discuss activation of synovial macrophages via crosstalk with synovial fibroblasts in inflammatory arthritis conditions including RA.

Macrophages

Macrophages play a central role in the innate immune system. They localize in multiple tissues (tissue-resident macrophages) to maintain homeostasis

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and they accumulate at pathological sites, contributing to immune responses and the repair of injured tissues in pathological conditions and the elimination of pathogens (Davies et al., 2013). Historically, macrophages were believed to be derived from blood monocytes, i.e., the mononuclear phagocyte system (MPS) (Van Furth and Cohn, 1968). Monocytes differentiate from hematopoietic progenitor cells in bone marrow and infiltrate into tissue via blood vessels, followed by maturation into macrophages. However, fate-mapping and lineage tracing analyses revealed that tissue-resident macrophages are derived from embryonic progenitors of the yolk sac and fetal liver (Christensen et al., 2004; Gomez Perdiguero et al., 2015; Hoeffel et al., 2015). The embryonic macrophages possess self-renewal ability and longevity in many tissues (Sieweke and Allen, 2013). The tissue-resident macrophages are progressively replaced by bone marrow-derived macrophages (BMDMS), although the degree of replacement of cells differs between organs. Thus, it has been suggested that appropriate numbers of tissue-resident macrophages are preserved by both self-renewal of embryonic macrophages and infiltration of BMDMs in the postnatal period (Sieweke and Allen, 2013; Guilliams and Scott, 2017). Macrophages are heterogeneous in nature because they can alter biological characteristics in response to external signals from the microenvironment, a process called polarization. Therefore, macrophages acquire unique functions with the expression of marker genes dependent on the tissue. Tissue-resident macrophages are termed microglia in the brain, Kupffer cells in liver, osteoclasts in bone and Langerhans cells in skin (Davies et al., 2013). In addition, several studies indicated that the polarization of macrophages is plastic. For example, Lavin et al. showed that peritoneal macrophages transplanted into the lung decreased their expression of markers characteristic of peritoneal macrophage and increased lung alveolar macrophage markers (Lavin et al., 2014). Polarization and plasticity of macrophages are observed in pathological states from onset to remission, suggesting that controlling macrophages may help to regulate several disease states.

Macrophage reprogramming and polarization

The M1/M2 polarization concept is a long-standing model that explains the heterogeneity of macrophages (Gordon, 2003). M1 polarization is induced by stimulation by lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), leading to macrophages' production of reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS) as well as pro-inflammatory cytokines

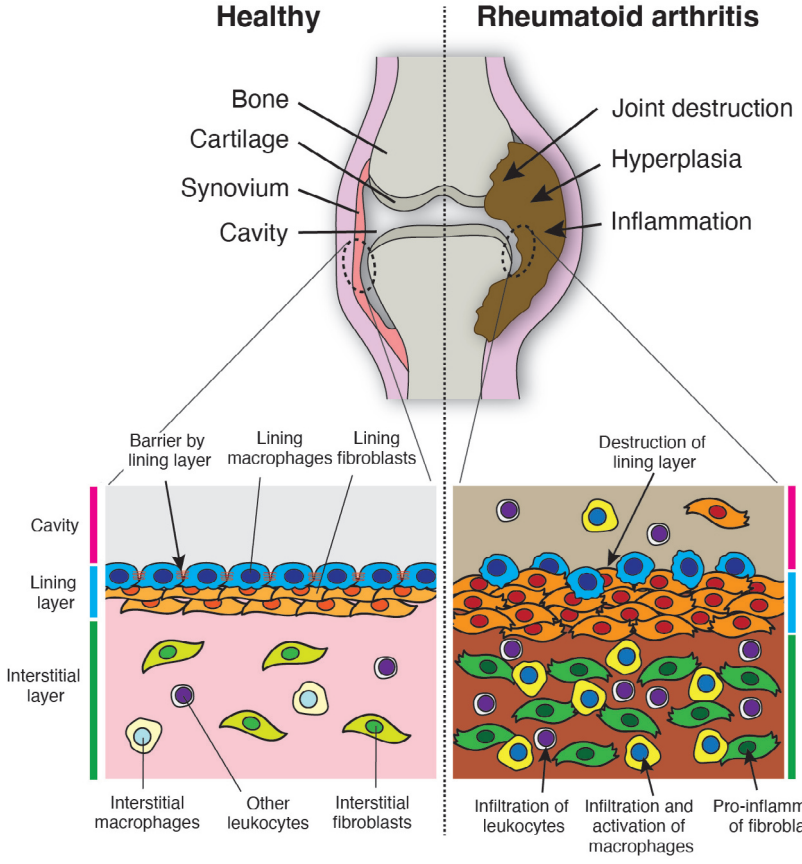

Fig. 1. Upper. Schema comparing a healthy joint and rheumatoid arthritis joint. **Lower.** Schema comparing healthy synovium and rheumatoid arthritis synovium.

such as TNF-α, IL-1β, IL-6, and IL-12 (Sica and Mantovani, 2012). M2 polarization is induced by IL-4, IL-10 or IL-13, and these cells suppress inflammatory processes and support tissue repair and vascularization (Sica and Mantovani, 2012). Several studies have shown that functional alterations such as M1/M2 polarization are closely associated with cellular metabolic reprogramming (Viola et al., 2019). G.C. Hard found that pro-inflammatory (M1 type) macrophages increase the rates of glycolysis and decrease the rate of oxygen consumption (Hard, 1970). Elevated expression levels of *GLUT1* and *PFKB3* in M1 macrophages enhance glycolysis and biological defenses (Obach et al., 2004; Freemerman et al., 2014). Also, activation of the pentose phosphate pathway (PPP), which is a metabolic pathway of glucose-6-phosphate, generates NADPH for ROS and NO production, contributing to microbial killing (Tan et al., 2016). In addition, the tricarboxylic acid (TCA) cycle is fragmented by suppression of metabolic reactions, which results from low expression levels of *IDH1* and high expression levels of *IRG1* (Li et al., 2013; Abhishek et al., 2015). Arrest of the TCA cycle leads to accumulated succinic acid and stabilization of transcription factor HIF-1A that induces expression of pro-inflammatory cytokines such as IL-1β (Tannahill et al., 2013).

In contrast to M1 macrophages, glycolysis and PPP are modest in M2 macrophages (Haschemi et al., 2012; Tavakoli et al., 2017). Instead, the uptake of glutamine and fatty acids is enhanced by upregulated ASCT2 and CD36, increasing energy production via oxidative metabolism (Huang et al., 2014; Tavakoli et al., 2017). Activated STAT6 followed by upregulation of PGC-1β by IL-4 stimulation induces fatty acid oxidation and mitochondrial biogenesis (Vats et al., 2006). The PPARs transcription factors, which interact with PGC-1β, also have key roles in regulating the expression of β-oxidation-related genes and anti-inflammation-related genes (Chawla et al., 2001). Indeed, increased levels of ARG1 catalyze the hydrolysis of arginine to ornithine and urea followed by synthesis for polyamine, which inhibits the production of pro-inflammatory cytokines and NO, through ornithine decarboxylase (Rath et al., 2014). Based on these findings, biological alterations associated with metabolic reprogramming have been advocated in M1/M2 macrophages. However, these findings were largely obtained by *in vitro* experiments. *In vivo*, it has been found that gene expression patterns and cellular metabolic responses following stimulation by external factors are rather more complex and cannot be simply classified as M1 and M2 types in macrophages (Sun et al., 2022).

Resident macrophages in healthy and RA synovium

Several types of macrophages are present in both the lining and sub-lining layers of the synovium (Kemble and Croft, 2021). Macrophages in lining layer are known as macrophage-like synoviocytes (MLS) or type A cells. The origin of synovial macrophages was examined by Tu et al. They showed that embryonic macrophages (defined as $F4/80^{+}CD11b^{-}$ cells) were present in synovium from E12.5 (before myelopoiesis). Infiltrated BMDMS (defined as $F4/80^{-}CD11b^{+}$ cells) then appeared from E20.5 during the development of synovial tissue. Those observations suggest that synovial macrophages have at least two origins (Tu et al., 2019). Postnatal replacement of synovial macrophages by BMDMs is controversial. Bone marrow chimera analysis revealed that recipient $MHCII^{-}$ or $F4/80^{+}CD11b^{-}$ macrophages showed radio-resistance and could not be replaced by donor cells, although recipient $MHCII^{+}$ or $F4/80^{-}CD11b^{+}$ macrophages were rapidly replaced in ankle tissue in the steady state (Misharin et al., 2014). On the other hand, Culemann's study using parabiotic chimera mice exhibited very little replacement of synovial macrophages by circulating donor cells in steady state (Culemann et al., 2019). Further investigations are required to clarify the replacement of macrophages in the synovium.

Understanding of the heterogeneity of macrophages has been dramatically enhanced by recent single-cell RNA-sequence (scRNA-seq) analysis. In murine and human synovia, several macrophage populations were identified based on specific gene expression and/or protein marker patterns. In healthy murine synovia, a single population of $Cx3cr1^{+}$ macrophages (also defined by high expression of *Trem2*) is localized on the synovial fibroblast lining layer. In the sub-lining layer, interstitial macrophages are distributed in four different clusters defined by high expression of *Aqp1, H2-Eb1* (MHCII), *Retnla* (Relm-α) and *Stmn1*, excluding the osteoclast lineage. *Stmn1*$^{+}$ macrophages are suggested to be *Aqp1*$^{+}$ and *H2-Eb1*$^{+}$ macrophages that entered the cell cycle. Pseudo-time trajectory analysis indicates that both $Cx3cr1^{+}$ and Relm-α^{+} macrophages are derived from proliferating $MHCII^{+}$ macrophages. After experimental arthritis induction in mice, a cluster of monocyte-derived macrophages (defined by high expression of *Ccr2*) newly appeared and expanded, a process associated with the progression of arthritis. The synovial barrier constituted by a lining of $Cx3cr1^{+}$ macrophages is disrupted in arthritis conditions (Culemann et al., 2019) (Fig. 1). In humans, nine clusters of macrophages were identified by scRNA-seq and analogous clusters based on the expression of orthologous genes were found in the synovium as shown in Table 1. Among $MerTK^{neg}$ subpopulations, the proportion of $S100A12^{pos}$, $SPP1^{pos}$ and $CLEC10a^{pos}$ macrophages was increased in active RA compared with healthy and remission RA. In contrast, the proportion of $MerTK^{pos}$ $TREM2^{pos}$ and $MerTK^{pos}$ $LYVE1^{pos}$ macrophages was increased in remission RA (Alivernini et al., 2020).

As reported in several cohort studies, the number of bulk synovial macrophages is positively correlated with disease activity in active RA patients (Kinne et al., 2000). Hypoxic conditions are present in the hyperplastic synovia of RA patients. The micro-

environment suppresses oxidative phosphorylation and promotes glycolysis. These conditions are associated with enhanced HIF-1A expression and ROS production in synovial macrophages, supporting pro-inflammatory processes (Guo and Chen, 2020). However, the relationship between synovial macrophage subpopulations and alteration of specific metabolic signatures is unknown.

Resident fibroblasts in healthy and RA synovia

Fibroblasts are ubiquitously present in connective tissue, where they produce extracellular matrix. Although they have common biological features across tissues, a recent study suggested that they might support tissue-specific functions (Lemos and Duffield, 2018). Indeed, tissue-resident fibroblasts have been known as fibroblast-like synoviocytes (FLS) or type B cells in the lining layer of the synovium. In healthy tissues, they contribute to tissue homeostasis in the joint cavity by producing collagens and laminin. It is notable that immune cells as well as synovial fibroblasts contribute to RA pathogenesis. For example, the number of synovial fibroblasts in RA is expanded due to the acquisition of resistance to apoptosis, forming pannus (Zhao et al., 2021). Also, they secrete growth factors for stromal cells, immunoregulatory factors (chemokines and cytokines) and matrix metalloproteases (MMPs) that degrade the extracellular matrix.

The heterogeneity of synovial fibroblasts has been confirmed by scRNA-seq studies. Synovial fibroblasts from murine arthritis tissue were divided into five distinct clusters by gene expression patterns. Subsequent gene ontology analysis suggested functional diversity in these clusters (Croft et al., 2019). The pathology of murine inflammatory arthritis is not completely consistent with RA. However, at least three subpopulations of synovial fibroblast with orthologous genes are found in RA tissue (Croft et al., 2019; Zhang et al., 2019). By broad classification, synovial fibroblasts were divided into $THY1^-$ cells in the lining layer and $THY1^+$ cells in the sub-lining layer. Higher levels of cytokines and chemokines were produced by $THY1^+$ subpopulation whereas $THY1^-$ subpopulations produced bone metabolism-related factors such as MMPs, RANKL and CCL9 (Croft et al., 2019). In a separate investigation using spatial transcriptomics, $THY1^+$ and $THY1^-$ synovial fibroblasts could not be divided into distinct populations. Moreover, the expression levels of THY1 were gradually altered in RA synovial fibroblasts depending on the microanatomical position. Those data suggested that subpopulations constitute a wide spectrum of differentiation from $THY1^-$ to $THY1^+$ synovial fibroblasts (Wei et al., 2020).

Crosstalk between synovial macrophages and fibroblasts via direct cell-cell interactions

In the healthy synovium, $Cx3cr1^+$ macrophages are localized on the lining fibroblasts (Culemann et al., 2019). In the microenvironment, direct interaction is expected via cell-cell contact through several ligand/receptor systems (Fig. 2). For example, pan-macrophages express integrin α4β1 (also known as VLA-4) and the representative ligand, VCAM1 (vascular cell adhesion molecule 1), is expressed on synovial fibroblasts (Weber and Springer, 1998; Li et al., 2000). VCAM1 expression is up-regulated in synovial fibroblasts via NF-κβ activation after TNF-α stimulation, suggesting that both the recruitment and retention of macrophages are supported by the enhanced adhesion ability of synovial fibroblasts in RA synovium (Li et al., 2000). In general, the binding of RANKL to its receptor, RANK, in macrophage lineage cells induces osteoclastogenesis (Wada et al., 2006). In an inflammatory arthritis model, RANKL is mainly expressed on synovial fibroblasts following stimulation by TNF-α and IL-1. In this instance, a specific population of macrophages (defined as $CX3CR1^{high}$ $Ly6C^{intermediate}$) is derived from classical monocytes ($CX3CR1^{low}$ $Ly6C^{high}$) that express RANKL (Danks et al., 2016; Hasegawa et al., 2019). Those cells are called arthritis-associated osteoclastogenic macrophages (AtoMs). They can differentiate into pathological osteoclasts by direct interaction via

Table 1. Representative marker expression of human synovial macrophage subpopulations and clusters, and closely related murine synovial macrophage subpopulations.

HUMAN			Mouse
Population	Subpopulation	Cluster	Subpopulation
$MerTK^{pos}$	$TREM2^{pos}FOLR^{pos}$	$TREM2^{pos}TIMD4^{pos}CD163^{pos}$	$Cx3cr1^+$
		$TREM2^{low}$	
	$FOLR2^{high}TREM2^{neg}$	$ID2^{pos}$	$MHCII^+$
		$LYVE1^{pos}$	$Relm\text{-}\alpha^+$
		$ICAM1^{pos}$	-
$MerTK^{neg}$	$HLA^{high}CD48^{pos}$	$ISG15^{pos}$	$Ccr2^+Arg1^+$
		$CLEC10a^{high}$	$Aqp1^+$
	$CD48^{pos}$	$S100A12^{pos}$	$Ccr2^+Il\text{-}1\beta^+$
		$SPP1^{pos}$	

RANKL on synovial fibroblasts (Hasegawa et al., 2019). In addition, fractalkine/CX3CL1 expression is promoted in RA synovial fibroblasts by TNF-α and IFN-γ. CX3CL1 is present in two forms, soluble and membrane-bound. It has been suggested that CX3CL1 induces chemotaxis in non-classical monocytes that express high levels of the receptor CX3CR1, and osteoclastogenesis. It is notable that lining macrophages also express CX3CR1. That fact suggests a bidirectional signal via CX3CR1-CX3CL1 interaction between synovial macrophages and fibroblasts in the setting of RA. However, detailed information about this interaction remains lacking.

Crosstalk between synovial macrophages and fibroblasts via secreted factors

In RA patients and inflammatory arthritis models, the normal structure of synovial tissue composed of lining macrophages and fibroblasts is disrupted (Culemann et al., 2019; Saeki and Imai, 2020). The synovial cells are discontinuously and randomly localized in hyperplastic synovium. Also, infiltrated macrophages and invasive fibroblasts are found in synovial fluid. In such spatial arrangements, synovial macrophages, synovial fibroblasts and other cells are expected to interact with one another via paracrine pathways (Neumann et al., 2010; Bai et al., 2022; Knab et al., 2022) (Fig. 3). Recent biologics for RA therapeutics have targeted cytokine-related molecules (Findeisen et al., 2021). Representative pro-inflammatory cytokines such as TNF-α and IL-1β are derived from macrophages, while IL-6 is derived from fibroblasts in the RA synovium (Neumann et al., 2010). These cytokines induce MMP production in synovial fibroblasts, resulting in degradation of cartilage and bone (Hanemaaijer et al., 1997; Konttinen et al., 1999; Schulze Westhoff et al., 1999). Macrophages stimulated by tissue-specific factors from synovial fibroblasts and TNF-α produce HBEGF (heparin-binding EGF-like growth factor), a protein that induces invasiveness of synovial fibroblasts (Kuo et al., 2019). These findings suggest that in inflammatory conditions such as RA, the presence of synovial macrophages increases the aggressive behavior of synovial fibroblasts. On the other hand, cell culture supernatants derived from inflammatory synovial fibroblasts enhance both glycolysis and oxidative phosphorylation in primary synovial macrophages associated with up-regulated cytokine expression. Those results suggest that synovial macrophages acquire long-lived pro-inflammatory phenotypes after exposure to secreted factors from synovial fibroblasts, contributing to chronic inflammation in RA (Saeki and Imai, 2020). Also, GAS6 is produced by THY1^{+} synovial fibroblasts during remission of RA. That finding suggests those cells contribute to anti-inflammatory processes in GAS6 receptor MerTK-positive macrophages (Alivernini et al., 2020). However, it remains unclear how GAS6 expression is regulated in sub-lining fibroblasts during the switch from active to remission RA. Collectively, these findings suggest that synovial macrophages have important roles in controlling both progression and remission in RA pathogenesis. Regulating the behaviors of macrophages may contribute to the development of effective and novel RA therapeutics.

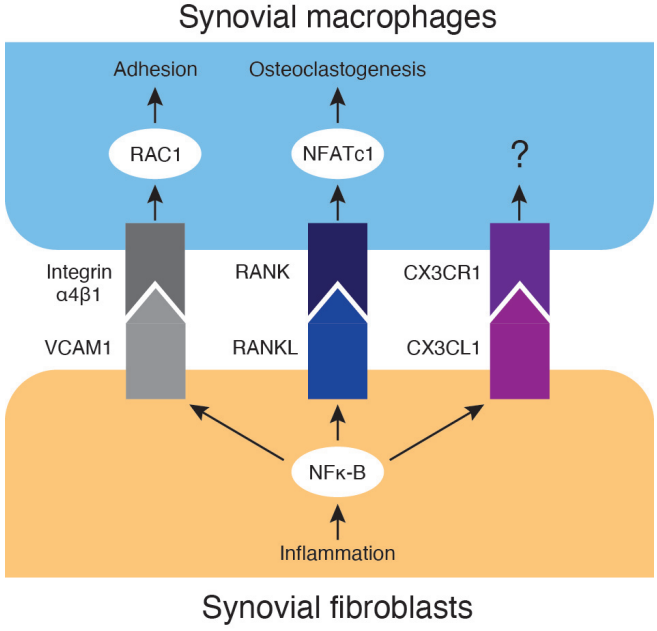

Fig. 2. Schema outlining the crosstalk between synovial macrophages and fibroblasts via direct cell-cell interactions through ligand/receptor systems.

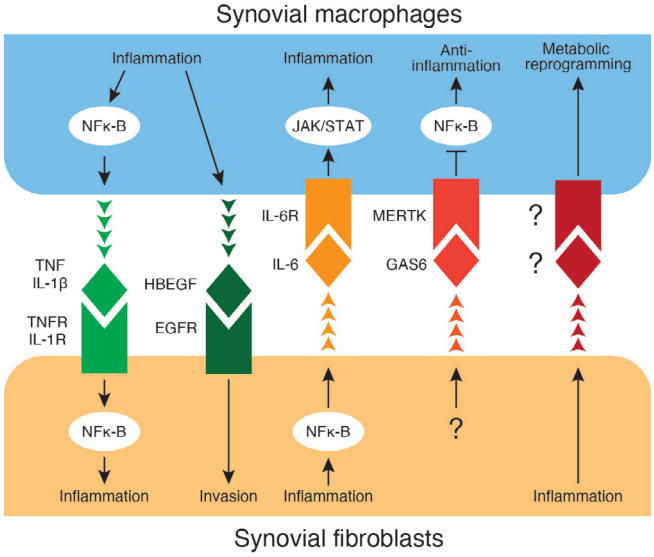

Fig. 3. Schema of the crosstalk between synovial macrophages and fibroblasts via secreted factors.

Conclusions

Microenvironmental niches in healthy synovium consist of subpopulations of synovial macrophages and synovial fibroblasts. Those cells have unique functions that support joint homeostasis. It has been suggested that the difference of pathological stages in RA patients is based on multiple factors by specific cells (Guo et al., 2018). The cellular niches are transformed (cellularly, spatially and functionally) during the onset and remission of inflammatory arthritis, including RA. The formation of abnormal niches is closely associated with alteration of the crosstalk between synovial macrophages and synovial fibroblasts, although other types of cells such as lymphocytes and adipocytes in synovial tissue would be also involved in the crosstalk at different stages of RA (Cope, 2008; Guo et al., 2018; Usher et al., 2019; Toussirot, 2020; Wu et al., 2021). Improved understanding of the crosstalk between different cell types and between different stages in RA should assist researchers to develop novel strategies for RA treatment.

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Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. NS and YI planned the review and wrote the manuscript.

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