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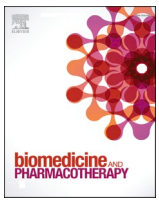

Review

Therapeutic strategies targeting synovial cells to treat osteoarthritis

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ABSTRACT

Osteoarthritis is a chronic degenerative joint disorder that significantly impairs the quality of life of millions of patients and for which there is no reliable cure to date, showing the crucial need for new, effective treatments capable of alleviating this disease. Numerous studies have evidenced the critical roles played by synovial cells during the progression of the disease, including synovial macrophages and synovial fibroblasts. In response to the altered osteoarthritic environment, synovial macrophages undergo polarization towards a pro-inflammatory M1 phenotype with the secretion of inflammatory mediators and cartilage-degrading enzymes (*versus* an anti-inflammatory M2 phenotype) while synovial fibroblasts become inappropriately activated, producing inflammatory mediators and undergoing abnormal cell proliferation and migration that contribute to synovial fibrosis, aggravate inflammation, and promote angiogenesis, all exacerbating the disease. Regulating the polarization of synovial macrophages and preventing the abnormal activation of synovial fibroblasts may therefore provide adapted strategies to counteract the progression of osteoarthritis. This review recapitulates the roles of synovial cells in the disease and describes the potential of classical and more highly innovative treatments to target synovial cells *in vivo* as a means to manage the progression of osteoarthritis.

1. Inflammation in osteoarthritis

Weight-bearing joints are the primary target of osteoarthritis (OA), a chronic degenerative and highly prevalent human disease [1–5] due to mechanical stress, obesity, aging, joint instability, and trauma [6,7] for which there is no definitive cure thus far. More than 600 million people worldwide suffer from OA, and older people have extremely high rates of morbidity and impairment, which are rising as a result of obesity and population aging [6,8–12]. A number of symptoms and features, including pain, stiffness, dysfunction, and deformity, are frequently observed, potentially leading to a severe disability and loss of motor function with a negative impact on the individual's quality of life, thus imposing a substantial burden and a significant financial strain on the society (total direct medical costs: ~$107 billion in the USA) [6,8,11–14].

A large body of evidence shows that, among many factors involved in the pathogenesis of OA, synovial inflammation (synovitis or synovialitis) plays a significant role in the initiation of the disease [15–55] via the abnormal production of inflammatory mediators and cartilage-degrading enzymes by pathologically activated synovial cells in the inflamed OA synovium [24,48,53,56–58], ultimately leading to the degradation of the articular cartilage in OA joints [28,40,56,59–63] (Fig. 1).

The synovium (Fig. 1) [64] is constituted of:. an intimal lining layer with:

– CD68-positive immune synovial macrophages involved in tissue homeostasis and repair [40,65–70]. These cells regulate the progression of OA [26,55,65,66,71–75] with an increased number in the OA synovium [21,31,67,68]. During the progression of the disease, they develop different phenotypes under specific stimuli of the microenvironment [76], from an unstimulated (M0) phenotype to either a pro-inflammatory (M1) phenotype or to an anti-inflammatory (M2) phenotype [40,47,52,72–74,77], the physiological ratio of which (M1/M2) in healthy joints is shifted in OA by polarization towards a pro-inflammatory (M1) phenotype according to the disease severity [72,73,78–80] and- CD55-positive synovial fibroblasts (~75 % of the synovial cells) involved in the maintenance of the synovial extracellular matrix (ECM) and in the synovial fluid homeostasis [40,81]. These cells become inappropriately activated in OA, driving inflammation and contributing to the advancement of the disease [40,82–84];

. a synovial sublining layer of fibrous connective tissue with blood

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vessels containing a small number of macrophages as well as activated immune B and T lymphocytes ($CD4^+/CD8^+$ of ~ 5/1; imbalanced T helper Th1/Th2 with polarization to a pro-inflammatory (Th1) phenotype; infiltrating regulatory T lymphocytes - Tregs), plasma cells, mast cells, and natural killer - NK - cells that all may contribute to inflammation and pain via the secretion of cytokines responsible for the further activation of macrophages (interleukin 2 - IL-2, interferon gamma - IFN-γ, IL-1β, tumor necrosis alpha - TNF-α, IL-6, etc) and of cartilage-degrading enzymes involved in joint destruction (matrix metalloproteinases - MMPs, a disintegrin and metalloproteinases with thrombospondin motifs - ADAMTSs) [15,16,21,30,31,46,55,85–109].

1.1. Synovial macrophages

Inflammation in OA is associated with increases in pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that produced and/or released in the joint space by damaged cells upon high mechanical stress including bacterial lipopolysaccharide (LPS), cartilage components and fragments (type-II collagen, aggrecan, biglycan, hyaluronan, heparin sulfate, tenascin C, decorin, fibromodulin, fibronectin, lubricin/proteoglycan 4 - PRG4, lumican), alarmins (S100 family of calcium-binding proteins S100A8 and S100A9, high mobility group box 1 - HMGB-1 - non-histone DNA-binding protein), advanced glycation end products (AGEs), plasma proteins (fibrinogen, Gc-globulin, α1-microglobulin, α2-macroglobulin), and crystals (basic calcium phosphate - BCP, calcium pyrophosphate dehydrate - CPPD, uric acid crystals) [15,47,69,110–149] (Fig. 2).

DAMPs are recognized by pattern-recognition receptors (PRRs) such as toll-like receptors (TLRs), nucleotide-binding, oligomerization domain (NOD)-like receptors (NLRs), receptors for AGEs (RAGEs), and the NLR pyrin domain containing 3 (NLRP3) inflammasome expressed on resident macrophages, chondrocytes, osteoblasts, and synovial cells [69,114,118,120–122,125,126,128,129,131,134,136,137,140,142–145,147,148,150–158], with crosstalks with the complement system [159,160] (Fig. 2). Interactions between DAMPs and PRRs activate various signaling pathways (nuclear factor kappa B - NF-κB, mitogen-activated protein kinase - MAPK, Janus kinase - JAK/signal transducer and activator of transcription - STAT, phosphoinositide 3-kinase - PI3K/protein kinase B - AKT/mammalian target of rapamycin - mTOR, extracellular signal-regulated kinase - ERK/c-jun - N-terminal kinase - JNK, transforming growth factor beta - TGF-β) [23,73,161–167], promoting the release of mediators that trigger innate immune responses via macrophage polarization [69,155] (Fig. 2).

The pro-inflammatory M1 phenotype (CD80, CD86, CD14, CD11c, MHC II) [65,67,68,74,79,166,168–171] is activated in response to LPS, IFN-γ, and TNF-α, promoting the release of pro-inflammatory TNF-α, IL-1β, −6, −8, −12, and −23, oncostatin M (OSM), nitric oxide (NO), cyclooxygenase 2 (COX-2), reactive oxygen species (ROS), hypoxia-inducible factor 1 alpha (HIF-1α), chemokines (CC motif ligand 5 - CCL5) and chemokine ligands (CXC motif chemokine ligand 9, 10, and 11 - CXCL9, CXCL10, CXCL11), MMPs (-1, −3, −9, −13), and ADAMTSs (-4, −5) while repressing the production of IL-10 [21,65,73,171–175], leading to ECM breakdown, chondrocyte cell death, and cartilage degradation [72,73,78,172,173,176–178] (Fig. 3). The anti-inflammatory M2 phenotype (CD163, CD206) [67,68,74,79] is activated in response to IL-4, −10, and −13 and TLR agonists, promoting

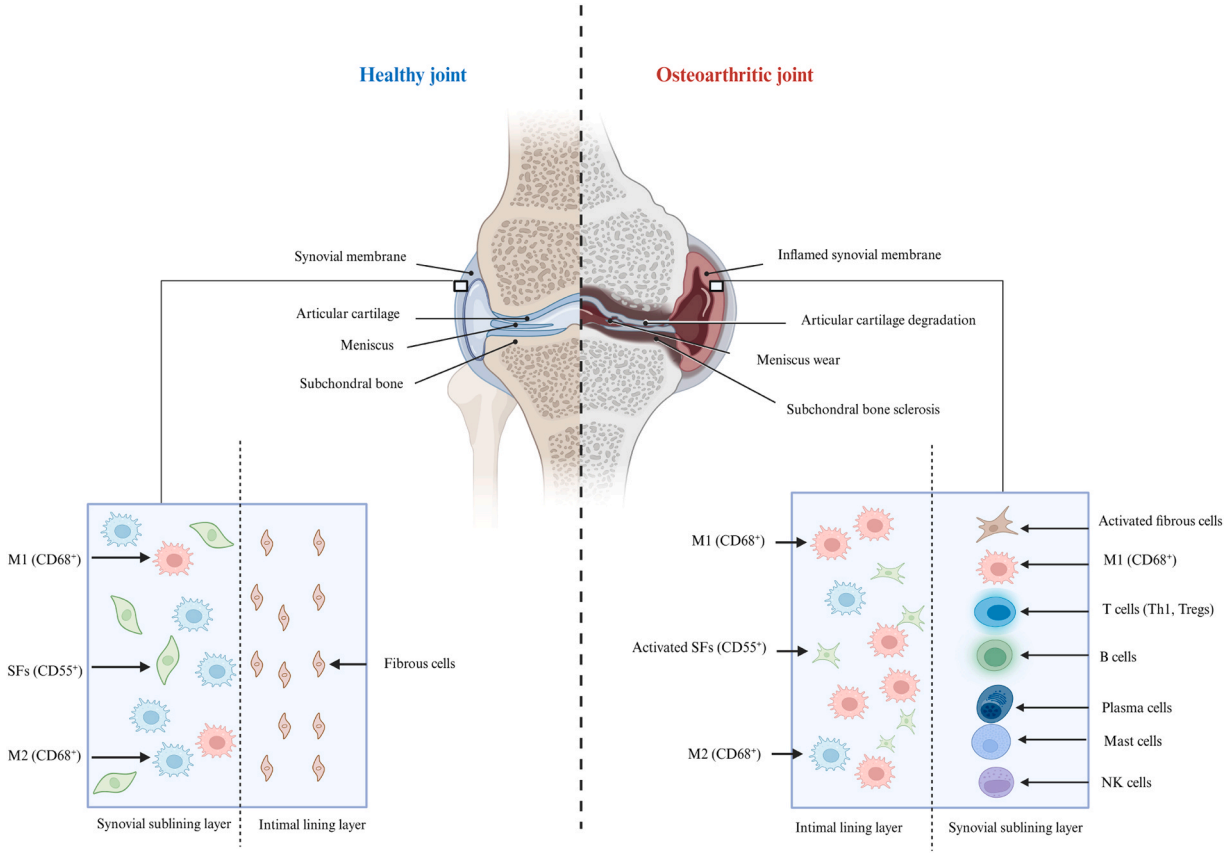

Fig. 1. Synovial inflammation in OA. Healthy and osteoarthritic joints are depicted with an overview of the tissues involved in an OA *versus* normal articulation. The boxes present the natural (left) and OA (right) cell composition of the synovium in the intimal lining and synovial sublining layers, with an imbalanced M1/M2 ratio shifted in OA by polarization towards a pro-inflammatory M1 phenotype. Abbreviations: OA, osteoarthritis; M0, unstimulated macrophages; SFs, synovial fibroblasts; M1, pro-inflammatory macrophages; Th1, pro-inflammatory T helper lymphocytes; Tregs, regulatory T lymphocytes; NK, natural killer cells (Created in BioRender. Li, F. (2025) https://BioRender.com/5b8mhg6).

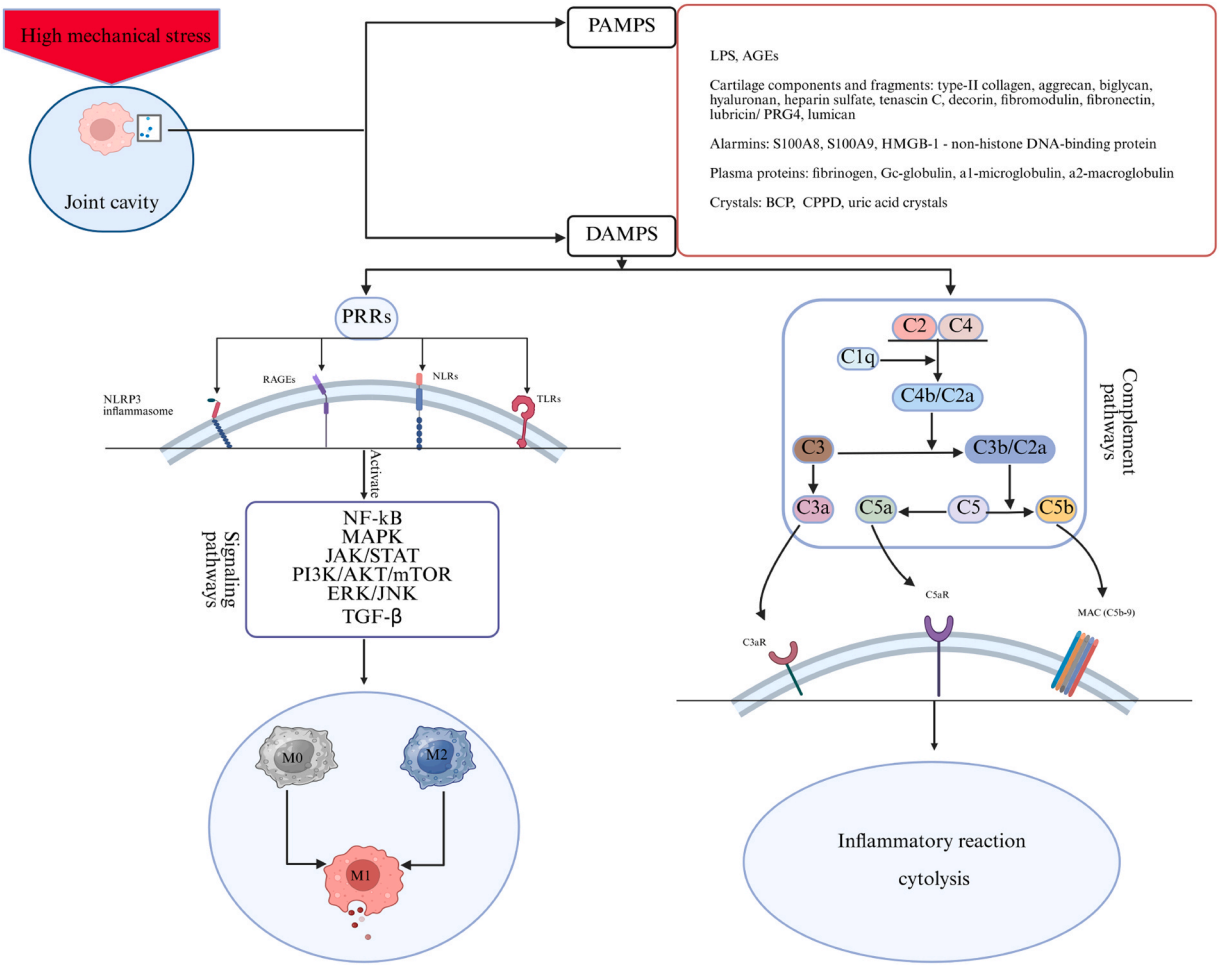

Fig. 2. Macrophage activation during synovial inflammation in OA. Under high mechanical stress, damaged cells release PAMPs and DAMPs in the joint space that are recognized by PRRs at the surface of resident cells (macrophages, chondrocytes, osteoblasts, synovial cells) with crosstalks with the complement system. These interactions activate various signaling pathways leading to the further release of mediators inducing macrophage polarization. Abbreviations: OA, osteoarthritis; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; LPS, lipopolysaccharide; AGEs, advanced glycation end products; PRG4, proteoglycan 4; S100A8, S100A9, S100 family of calcium-binding proteins; HMGB-1, high mobility group box 1; BCP, basic calcium phosphate; CPPD, calcium pyrophosphate dehydrate; PRRs, pattern-recognition receptors; TLRs, toll-like receptors; NLRs, NOD-like receptors; NOD, nucleotide-binding, oligomerization domain; RAGEs, receptors for AGEs; NLRP3, NLR pyrin domain containing 3; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; ERK, extracellular signal-regulated kinase; JNK, c-jun - N-terminal kinase; TGF-β, transforming growth factor beta; MAC, membrane attack complex (Created in BioRender. Li, F. (2025) https://BioRender.com/5jnsmc4).

the release of anti-inflammatory and protective/reparative IL-10, IL-1 receptor antagonist (IL-1Ra), insulin-like growth factors (IGFs), TGF-β, CCLs (CCL4, CCL8, CCL13, CCL18), and arginase 1 (ARG-1) [72,73,162,173,174,179] (Fig. 3).

1.2. Synovial fibroblasts

In response to the inflammatory environment in OA as described above, including originating from adipose tissues like the infrapatellar fat pad (IPFP) producing adipokines (leptin, adiponectin, visfatin, resistin, nefastin-1) [25,36,44,58,180–185] and upon TLR and RAGE engagement, the synovial fibroblasts become inappropriately activated with:

1. excessive cell proliferation and migration,
2. enhanced production of OA-associated inflammatory mediators and expressing particular markers (TNF-α, IL-1β, −6, −8, and −17, connective tissue growth factor - CTGF/CCN2, NO, prostaglandin E2 - PGE2, COX-2, ROS, NO synthetase - NOS, HMGB-1, CCL5, CCL19, CCN4, pain-inducing nerve growth factor - NGF, angiogenic and adhesion molecules like vascular endothelial growth factor - VEGF, monocyte chemoattractant protein 1 - MCP-1/CCL2, intercellular adhesion molecule type 1 - ICAM-1, vascular cell adhesion molecule 1 - VCAM-1, and integrin $\alpha_v\beta6$, ECM-degrading enzymes like MMP-1, −3, −9, −10, −13, ADAMTS-4, −5, −7, −12), and
3. the potential development of a myofibroblast phenotype (alpha-smooth muscle actin - α-SMA, type-I collagen alpha 1 - COL1A1) under pro-fibrotic stimuli (TGF-β)

via activation of signaling pathways (activator protein 1 (AP-1)/NF-κB, ERK/JNK, apoptosis signal-regulating kinase 1 - ASK1, MAPK, PI3K/AKT/mTOR, Wingless-type - Wnt/β-catenin), leading to an altered metabolic balance with the excessive accumulation of particular ECM compounds (fibrin, fibronectin, collagen degradation fragments - C1M/C3M) [21,23,28,82,84,124,128,186–222] (Fig. 4).

These abnormal activities of the synovial fibroblasts lead to synovial hyperplasia (thickening) and fibrosis with an increased vascularization and additional infiltration/adherence of inflammatory cells like monocytes, contributing to joint adhesion, rigidity, and pain and exacerbating the disease by also aggravating the inflammation in OA and cartilage

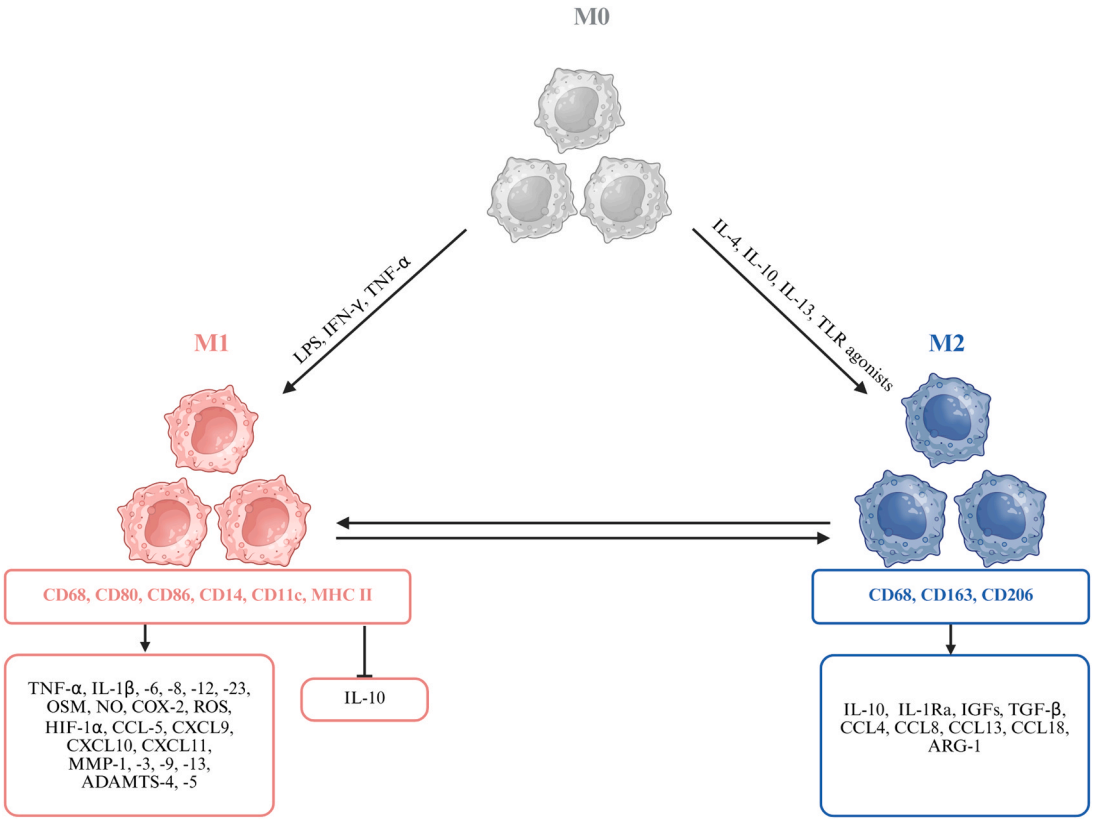

Fig. 3. Macrophage polarization. The synovium contains CD68-positive synovial macrophages that may develop different phenotypes under specific stimulation from the microenvironment, from an unstimulated M0 phenotype either to a pro-inflammatory M1 phenotype or to an anti-inflammatory M2 phenotype. In OA, the synovial macrophages undergo M1 polarization, shifting the M1/M2 ratio relative to the physiological balance in the healthy synovium. Abbreviations: M0, unstimulated macrophages; M1, pro-inflammatory macrophages; OA, osteoarthritis; LPS, lipopolysaccharide; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor alpha; IL-4, −6, −8, −10, −12, −13, −23, interleukins; TLRs, toll-like receptors; OSM, oncostatin M; NO, nitric oxide; COX-2, cyclooxygenase 2; ROS, reactive oxygen species; HIF-1α, hypoxia-inducible factor 1 alpha; CCL, CC motif ligand; CXCL, CXC motif chemokine ligand; MMP, matrix metalloproteinase; ADAMTS, a disintegrin and metalloproteinases with thrombospondin motifs; IL-1Ra, IL-1 receptor antagonist; IGFs, insulin-like growth factors; TGF-β, transforming growth factor beta; ARG-1, arginase 1 (Created in BioRender. Li, F. (2025) https://BioRender.com/m6fk4oh).

degradation [20,28,30,40,43,82,115,212,220,223,224] (Fig. 4).

1.3. Therapeutic concepts to target the synovial cells in osteoarthritis

While various clinical treatments for OA are available to the patients, ranging from non-pharmacological treatments (education, self-management, load relief, weight loss, exercise, physical therapy, strength training) to established and experimental pharmacological therapy (analgesics: paracetamol/acetaminophen, duloxetine; non-steroidal anti-inflammatory drugs, i.e. NSAIDs: cyclooxygenase - COX - inhibitors such as diclofenac - DCF, aceclofenac, ibuprofen, celecoxib; glucocorticoids: steroidal anti-inflammatory drugs, corticosteroids, and corticoids such as triamcinolone acetonide - TAA, dexamethasone - dex; viscosupplementation: hyaluronic acid - HA, chondroitin sulfate - CS, glucosamine; drugs targeting pro-inflammatory mediators and OA-associated processes such as the IL-1Ra anakinra, the TNF antagonists adalimumab, etanercept, infliximab, the NGF antagonists tanezumab and fasinumab, and various other drugs like methotrexate - MTX, lorecivivint - a CDC-like kinase/dual-specificity tyrosine kinase - CLK/DYRK - inhibitor modulating the Wnt pathway, the glucagon-like peptide 1 receptor agonists semaglutide and liraglutide used in type 2 diabetes and obesity, the fibroblast growth factor 18 - FGF-18/sprifermin and bone morphogenetic protein 7 - BMP-7, kartogenin - KGN, metformin, denosumab - a receptor activator of NF-κB ligand inhibitor, etc), orthobiologics (progenitor cells and concentrates, extracellular vesicles - EVs/exosomes - Exos, platelet-rich plasma - PRP), and surgical options (osteotomy, arthroplasty) [4,6,166,225–355], none of them can reliably prevent or reverse the pathogenesis of OA, while many are associated with a number of hurdles, risks, and/or adverse events [1,282,324,327,356–365], supporting the concept of developing new therapies and disease-modifying anti-OA drugs (DMOADs).

In this regard, approaches that may (1) inhibit the pro-inflammatory (M1) phenotype and/or induce the anti-inflammatory (M2) phenotype to re-establish the physiological M1/M2 ratio by repolarizing synovial macrophages, (2) prevent the deleterious activities of synovial fibroblasts, and/or (3) target the activated immune cells in the synovial sublining layer represent potential strategies to tackle the pathogenesis of OA. In the next chapter, we present such possible approaches to treat OA by specifically targeting these various cells.

2. Therapeutic strategies targeting synovial cells in OA

Several approaches have been developed to target the synovial cells (macrophages, fibroblasts, other activated immune cells) in OA using direct (biomaterial-free) pharmacological and drug therapy (Table 1), orthobiologics and surgical options (Table 2), biomaterial-based therapy (Table 3), gene therapy (Table 4), and combined gene- and biomaterial-based therapy (Table 5) (Fig. 5).

2.1. Direct pharmacological and drug therapy

2.1.1. NSAIDs

Naproxen [366–368], nimesulide [366,369–371], and aceclofenac [244] were shown to reduce the expression of pro-inflammatory PGE2

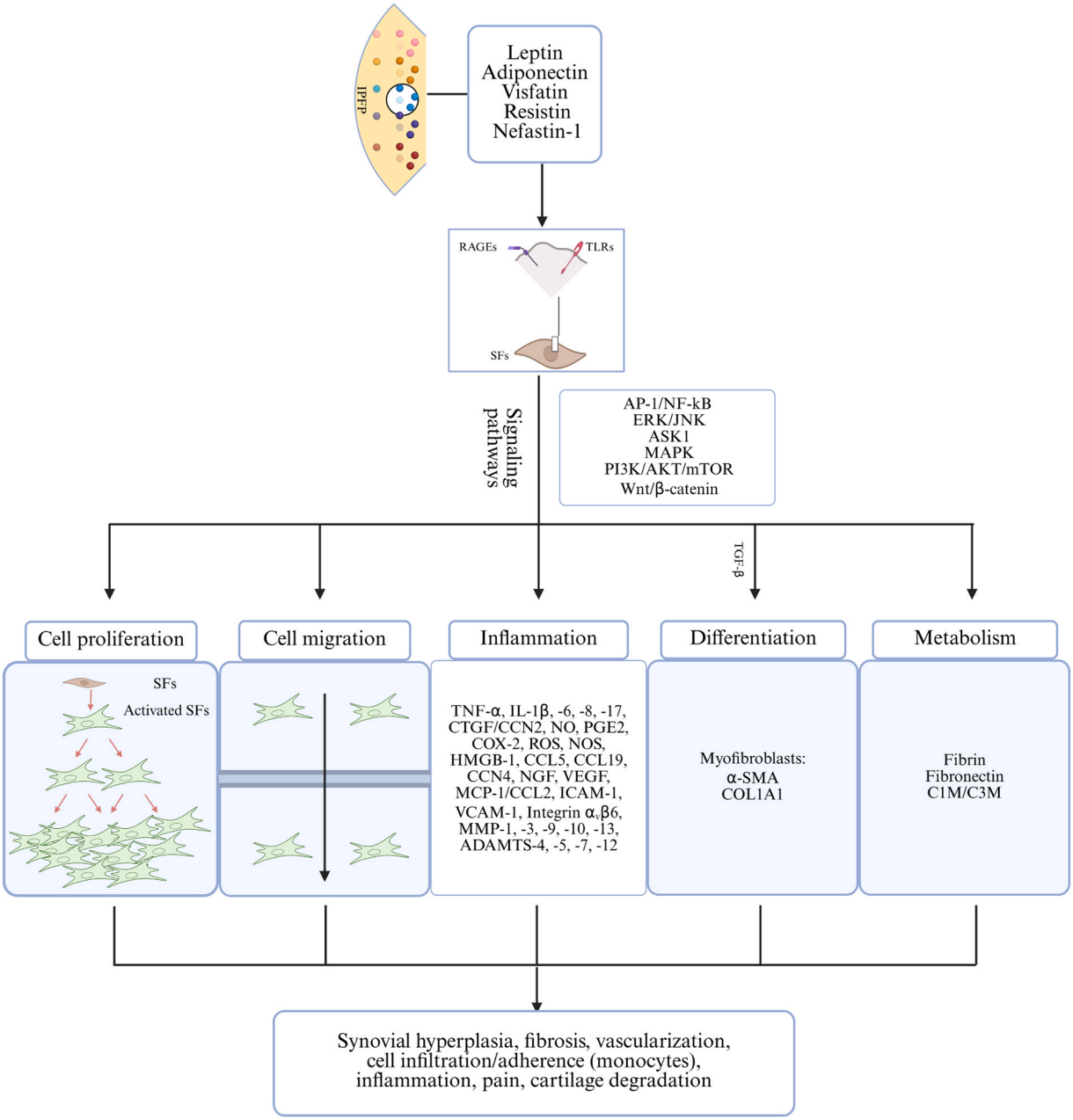

Fig. 4. Synovial fibroblast activation during synovial inflammation in OA. In response to the OA inflammatory environment (including from adipose tissues/IPFP), the synovial fibroblasts become activated via TLR and RAGE engagement and various signaling pathways, leading to abnormal cell proliferation and migration, production of OA-associated inflammatory mediators and markers, differentiation (myofibroblast phenotype), and excessive accumulation of particular ECM components that promote synovial hyperplasia, fibrosis, vascularization, cell infiltration/adherence (monocytes), pain, inflammation, and cartilage degradation. Abbreviations: OA, osteoarthritis; IPFP, infrapatellar fat pad; RAGE, receptors for advanced glycation end products; TLRs, toll-like receptors; SFs, synovial fibroblasts; AP-1, activator protein 1; NF-κB, nuclear factor kappa B; ERK, extracellular signal-regulated kinase; JNK, c-jun - N-terminal kinase; ASK1, apoptosis signal-regulating kinase 1; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; Wnt, Wingless-type; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis alpha; IL-1β, interleukin 1 beta; CTGF/CCN2, connective tissue growth factor; NO, nitric oxide; PGE2, prostaglandin E2; COX-2, cyclooxygenase 2; ROS, reactive oxygen species; NOS, NO synthetase; HMGB-1, high mobility group box 1; CCL, CC motif ligand; NGF, nerve growth factor; VEGF, vascular endothelial growth factor; MCP-1/CCL2, monocyte chemoattractant protein 1; ICAM-1, intercellular adhesion molecule type 1; VCAM-1, vascular cell adhesion molecule 1; MMPs, matrix metalloproteinases; ADAMTS, a disintegrin and metalloproteinases with thrombospondin motifs; α-SMA, alpha-smooth muscle actin; COL1A1, type-I collagen alpha 1; C1M/C3M, collagen degradation fragments (Created in BioRender. Li, F. (2025) https://BioRender.com/5x52p4o).

and COX-2 in OA patients [244] and of pro-inflammatory IL-1β, IL-6, PGE2, urokinase (uPA), and the glucocorticoid receptor (GR) while increasing that of the plasminogen activator inhibitor (PAI-1) in human OA synovial fibroblasts [366–371]. Celecoxib was evidenced to decrease the expression of pro-inflammatory IL-1β, TNF-α, PGE2, and COX-2 and synovial macrophage infiltration in OA patients [244], displaying a pro-apoptotic effect on human OA synovial fibroblasts [372]. Meloxicam was reported to inhibit the production of pro-inflammatory MMP-1, −2, −3, and −13 via the NF-κB/AP-1 signaling pathways in human OA synovial fibroblasts [373] and to mitigate synovitis for up to 20 weeks in an anterior cruciate ligament transection (ACLT) model of OA in rats via the p38/JNK and ERK signaling pathways [374].

Table 1
Pharmacological and drug therapy to target synovial cells in OA.

Family	Compounds	OA systems	Effects	Refs.
NSAIDs	naproxen, nimesulide, aceclofenac, celecoxib	OA patients, human OA synovial fibroblasts	decreased expression of pro-inflammatory OA mediators	[244, 366–372]
	meloxicam	human OA synovial fibroblasts, ACLT (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[373,374]
	indomethacin	MMT (rats)	reduced synovial inflammation	[375]
Glucocorticoids	dex, prednisolone, TAA	human OA synovial tissue and synovial fibroblasts, PTOA (rabbits), MMT (rats), papain (rats)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[375–382]
Viscosupplementation	HA, CS, lubricin	human OA synovial fibroblasts and biopsies, TRR (mice), DMM (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[137, 383–389]
Cytokines, anti-cytokine therapeutics	IL−4, IL−10, IL−13	human OA synovial tissue and synovial fibroblasts, DMM (mice)	decreased expression of pro-inflammatory OA mediators, M2 polarization	[376, 390–392]
	etanercept, infliximab, adalimumab, ESBA105, IL−1Ra/anakinra	human OA synovial fibroblasts, human monocytes, ACLT/MMT (rabbits), PTOA (rats, mice)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[393–399]
Drugs (released factors, metabolites)	CRF, VIP, α-defensin−1, MFG-E8, itaconate, resolvin D1, omentin−1, carveol, MMF, DMF	human OA synovial fibroblasts and tissue, MLI (rats), DMM (mice), MIA (rats), ACLT (mice)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[175, 400–407]
Drugs (inhibitors/ activators, agonists/ antagonists)	tenidap, mevastatin, panobinostat, vorinostat, RO100, RO919, lorecivivint, XAV−939, forskolin, bortezomib, dexmedetomidine, capsaicin, K−80003, HC067074	human OA synovial fibroblasts, ACLT (dogs, rabbits), DMM (mice), MIA (rats), MMT (mice, rats), papain (rats)	decreased expression of pro-inflammatory OA mediators, decreased M1 infiltration and polarization, reduced synovial inflammation	[393, 408–422]
Drugs (repurposed drugs)	DC32, liraglutide, metformin, suramin, nintedanib, MED	human OA synovial fibroblasts, papain (mice), MIA (mice), DMM (mice), ACLT (mice)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[423–429]
Drugs (medicinal/vegetal compounds)	EGCG, boswellic acid, icariin, TRB-N0224, quercetin, casticin, chrysin, FGS, AGN, fargesin, ANG, CA, AT-III, SPD, songorine	human OA synovial fibroblasts, DMM (mice), ACLT (rabbits, rats), ACLT/MMT (rats), MIA (rats), collagenase (mice)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[165, 430–436, 438–445]

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; dex, dexamethasone; TAA, triamcinolone acetonide; HA, hyaluronic acid; CS, chondroitin sulfate; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; CRF, corticotrophin-releasing factor; VIP, vasoactive intestinal peptide; MFG-E8, milk fat globule-epidermal growth factor factor 8 (lactadherin); MMF, monomethyl fumarate; DMF, dimethyl fumarate; DC32, (9α,12α-Dihydroartemisinyl) bis(2′-chlorocinnamate); MED, medermycin; EGCG, (-)-epigallocatechin-3-gallate; FGS, frugoside; AGN, agnuside; ANG, angelicin; CA, cinnamic aldehyde; AT-III, atractylenolide-III; SPD, spermidine; OA, osteoarthritis; ACLT, anterior cruciate ligament transection; MMT, medial meniscal transection; PTOA, post-traumatic OA; TRR, Treadmill Running; DMM, destabilization of the medial meniscus; MLI, meniscal/ligamentous injury; MIA, monosodium iodoacetate.

Indomethacin was described to reduce synovial inflammation and angiogenesis for 5 weeks in a medial meniscal transection (MMT) model of OA in rats [375].

2.1.2. Glucocorticoids

Dex was demonstrated to diminish the expression of M1 pro-inflammatory IL-1β and TNF-α in human OA synovial tissue [376–378] while increasing the expression of M2 anti-inflammatory IL-4 and IL-10 in this evaluation model [378], with also a reduction of the expression of pro-inflammatory MMP-3 for up to 3 weeks in a post-traumatic OA (PTOA) model in rabbits [379] and in synovial inflammation for 5 weeks in an MMT model of OA in rats [375]. Prednisolone was shown to decrease macrophage infiltration in OA patients [380] and fibrosis in human OA synovial fibroblasts [381]. TAA was evidenced to increase the expression of M2 anti-inflammatory IL-10 for 12 weeks in a papain-induced model of OA in rats [382].

2.1.3. Viscosupplementation

HA was reported to inhibit the expression of uPA and its receptor (u-PAR), PAI-1, CTGF, TGF-β1, VEGF, MMP-3, aggrecanase-2, and M1 pro-inflammatory IL-1β and TNF-α in human OA synovial fibroblasts [383–387] and synovial fibrosis for 19 days in a TGF-β1 injection and treadmill running (TTR) model of OA in mice [388]. CS was described to protect human OA synovial membrane biopsies and synovial fibroblasts against the expression of VEGF and thrombospondin-1 (TSP-1) as well as synovial angiogenesis [389]. Lubricin was demonstrated to inhibit synovial inflammation and pain for 3 weeks in a destabilization of the medial meniscus (DMM) model of OA in rats [137].

2.1.4. Cytokines and anti-cytokine therapeutics

Different anti-inflammatory cytokines such as IL-4 [376,390,391], IL-10 [390], and IL-13 [390,392] were shown to suppress the production of pro-inflammatory IL-1β and TNF-α in human OA synovial tissue and synovial fibroblasts [376,390] and to promote M2 polarization for up to 20 weeks in a DMM model of OA in mice [391].

Anti-cytokine agents were also evidenced for their beneficial effects to target synovial cells in OA. Etanercept (a soluble TNF receptor-Ig fusion protein) was also reported to reduce the expression of pro-inflammatory IL-6, MMP-1, and MMP-3 in OA synovial fibroblasts [393] while infliximab, adalimumab, and ESBA105 (anti-TNF-α antibodies) [394–397] decreased the expression of pro-inflammatory TNF-α in human OA synovial fibroblasts [396] and inhibited synovial inflammation for up to 8 weeks in an ACLT/MMT model of OA in rabbits [395] and in a PTOA model in rats [397]. IL-1Ra/anakinra was described to alleviate synovial inflammation for up to 8 weeks in a PTOA model in mice [398] and rats [397] and to reduce the expression of pro-inflammatory TNF-α and IL-8 in human monocytes [399] while anti-IL-1β antibodies decreased the expression of pro-inflammatory IL-6, MMP-1, and MMP-3 in OA synovial fibroblasts [393].

2.1.5. Drugs

A broad spectrum of drugs of various origins have also been tested for

Table 2
Orthobiologics and surgical options to target synovial cells in OA.

Family	Origin	OA models	Effects	Refs.
Cells	MSCs (synovial fluid)	ACLT (rats)	reduced synovial inflammation	[446]
	MSCs (bone marrow)	ACLT (dogs, rabbits), amphotericin-B-induced (horses)	M2 polarization, reduced synovial inflammation	[447–449]
	MSCs (adipose tissue)	human OA synovial fibroblasts, human M1 macrophages, collagenase (mice), MMT (mice), spontaneous OA (guinea pigs), MIA (rat), ACLT/MMT (rats), papain (rats), DMM (rats)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[332, 450–457]
	MSCs (umbilical cord)	ACLT (rats)	M2 polarization	[458]
	MSCs (amniotic fluid)	human OA synovium	M2 polarization	[459]
EVs, Exos, secretome	Exos (synovial membrane-derived MSCs)	collagenase (mice)	reduced synovial inflammation	[460]
	Exos (bone marrow-derived MSCs)	collagenase (mice), MIA (rats), Hulth (rats), ACLT (rats)	M2 polarization, reduced synovial inflammation	[461–464]
	EVs, Exos (adipose-derived MSCs)	MIA (rats), DMM (mice), ACLT (mice)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[465,466]
	EVs, Exos, (umbilical cord-derived MSCs)	ACLT (rats), MMT (rats), ACLT/MMT (rats), DMM (mice)	decreased expression of pro-inflammatory OA mediators, M2 polarization	[458, 467–470]
	Exos (iPSC-derived MSCs)	collagenase (mice), ACLT (rabbits)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[460,471]
	Exos (chondrocytes)	ACLT (mice)	M2 polarization	[472]
	secretome (human fetal cartilage progenitor cells)	collagenase (rats)	M2 polarization, reduced synovial inflammation	[473]
Blood derivatives	PRP, derivatives	human OA synovium and synovial fibroblasts, human monocytes, collagenase (mice), MIA (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[399, 474–478]
Surgical options	HTO	OA patients	M2 polarization	[479]

Abbreviations: EVs, extracellular vesicles; Exos, exosomes; MSCs, mesenchymal stromal cells; iPSCs, induced pluripotent stem cells; PRP, platelet-rich plasma; HTO, high tibial osteotomy; OA, osteoarthritis; ACLT, anterior cruciate ligament transection; MMT, medial meniscal transection; MIA, monosodium iodoacetate; DMM, destabilization of the medial meniscus.

their potential effects on synovial cells in OA, including released factors and metabolites, inhibitors/activators and agonists/antagonists, repurposed drugs, and medicinal/vegetal compounds.

The corticotrophin-releasing factor (CRF) and the vasoactive intestinal peptide (VIP) (neuropeptides) were shown to reduce the expression of ADAMTSs in human OA synovial fibroblasts [400]. α-Defensin-1 (a molecule released from apoptotic neutrophils, augmenting the antimicrobial capacity of macrophages) was evidenced to promote M2 polarization in human synovial fibroblasts tissue and to mitigate synovial inflammation for 9 weeks in a meniscal/ligamentous injury (MLI) model of OA in rats [175]. Lactadherin (i.e. milk fat globule-epidermal growth factor 8 - MFG-E8, a secreted body glycoprotein) was reported to relieve synovial inflammation and to promote M2 polarization for 8 weeks in a DMM model of OA in mice [401]. Itaconate (a metabolite of macrophages) was described to alleviate synovial inflammation for 8 weeks in a DMM model of OA in mice [402]. Resolvin D1 (an omega 3 derivative) was demonstrated to inhibit the expression of pro-inflammatory IL-1β and MMP-3 in human OA synovial fibroblasts [403]. Omentin-1 (an adipokine) was evidenced to promote M2 polarization with an increased expression of anti-inflammatory IL-4 in OA synovial fibroblasts [404]. Carveol (an endogenous metabolite) was reported to inhibit synovial inflammation and to promote M2 polarization for 8 weeks in a DMM model of OA in mice [405]. Monomethyl fumarate and dimethyl fumarate (MMF and DMF, respectively, metabolites of methyl esterases in the liver) were described to reduce synovial inflammation, to promote M2 polarization, and to decrease the expression of pro-inflammatory TNF-α while increasing that of anti-inflammatory IL-10 for up to 6 weeks in a monosodium iodoacetate (MIA)-induced model of OA in rats [406] and in an ACLT model of OA in mice [407].

Tenidap (a COX- and 5-lipoxygenase inhibitor) was demonstrated to reduce synovial inflammation [408] and to decrease the expression of pro-inflammatory IL-1β, collagenase-1, and MMPs for up to 8 weeks in an ACLT model of OA in dogs [409–411]. Mevastatin (an inhibitor of the hydroxymethylglutaryl coenzyme A - HMG-CoA - reductase) was demonstrated to mitigate synovial inflammation and to diminish macrophage infiltration for 6 weeks in an ACLT model of OA in rabbits [412]. Panobinostat and vorinostat (histone deacetylase inhibitors) were shown to inhibit the expression of pro-inflammatory IL-1β in OA synovial fibroblasts [413]. RO100 and RO919 (NF-κB inhibitors) were evidenced to reduce the expression of pro-inflammatory IL-6, MMP-1, and MMP-3 in OA synovial fibroblasts [393]. Lorecivivint and XAV-939 (Wnt inhibitors) were reported to alleviate synovial inflammation for up to 10 weeks in a DMM model of OA in mice [414] and in an MIA-induced model of OA in rats [415]. Forskolin (an adenylyl cyclase activator) was described to mitigate synovial fibrosis in human OA synovial fibroblasts [416]. Bortezomib (an anti-VEGF receptor 3 antibody) was demonstrated to reduce inflammation and the number of M1 macrophages for 7 weeks in an MMT model of OA in mice [417]. Dexmedetomidine (an α2 receptor agonist) was shown to attenuate synovial inflammation and to inhibit the NLRP3 inflammasome for 4 weeks in papain-induced [418] and MIA-induced models of OA in rats [419]. Capsaicin (an agonist of the transient receptor potential vanilloid 1 - TRPV1 - cation channel involved in inflammation and pain perception) was evidenced to alleviate synovitis and M1 infiltration for 8 weeks in an MMT model of OA in rats [420]. K-80003 (a modulator of the retinoid X receptor α - RXRα) was reported to reduce synovial inflammation and to down-regulate the expression of pro-inflammatory TNF-α, IL-6, MMPs, and ADAMTSs for 24 days in an MIA-induced model of OA in rats [421]. HC067074 (a TRPV4 inhibitor) was demonstrated to mitigate synovial inflammation and to decrease M1 polarization for 8 weeks in an MMT model of OA in rats [422].

(9α,12α-Dihydroartemisinyl) bis(2′-chlorocinnamate) (DC32, an anti-malaria drug) was shown to inhibit the expression of pro-inflammatory IL-1β and IL-6 in OA synovial fibroblasts and synovial inflammation for 4 weeks in a papain-induced model of OA in mice [423]. Liraglutide was described to promote M2 polarization for 29 days in an MIA-induced model of OA in mice [424]. Metformin (a drug used for type-2 diabetes) was evidenced to decrease synovial inflammation and to inhibit M1 polarization for up to 10 weeks in a DMM model of OA in mice [425,426]. Suramin (a drug used for trypanosomiasis) was

Table 3
Biomaterial-based therapy to target synovial cells in OA.

Family	Compounds, Origin	Biomaterials	OA models	Effects	Refs.
Pharmacological and drug therapy (NSAIDS)	DCF	type-I collagen/lipid conjugates, liposomes with HA or type-I collagen, hyalomer formulations, F127/COS NSs, GelMA/DMA/MPC MSs	MIA (rats), ACLT/DMM (rats), DMM (rats)	reduced synovial inflammation	[492,493, 495,496]
	lornoxicam	TPP MSs	MIA (rats)	reduced synovial inflammation	[497]
	celecoxib	polyesteramine MSs, ME/HA MNs, methacrylate/HA microgel, hyaluronan NCs, P407/GS97/alginate/PVP/HA hydrogel, amino acid-based polyesteramid MSs	ACLT/MMT (rats), MIA (rats), chronic OA (dogs)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[498–503]
	naproxen	gelatin/dextran/HA hydrogel	collagenase (rabbits)	reduced synovial inflammation	[504]
	flurbiprofen	CV−2 carriers	ACLT/MMT (rats)	reduced synovial inflammation	[505]
	parecoxib	PVA/PLGA MSs	ACLT/MMT (rats)	M2 polarization	[506]
Pharmacological and drug therapy (glucocorticoids)	dex	liposomes/gels with HA or type-I collagen, PLGA MSs, P407/GS97/alginate/PVP/HA hydrogel, PEG/PCL/TSPBA/GelMa NPs, HA hydrogel, pNiPAM NPs, chitosan/glycerol/borax hydrogel, HPMA gel, gelatin/dextran/HA hydrogel, PEG/pPAD NPs	MIA (rats, mice), ACLT (rats), DMM (mice), collagenase (rabbits), papain (rats), PTOA (mice)	reduced synovial inflammation	[493,502, 504, 507–514]
	TAA	PEA MSs, dextran sulfate NPs	collagenase (rats), MIA (mice)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[515,516]
Pharmacological and drug therapy (viscosupplementation)	HA	p(HPMam-lac)/PEG hydrogel, PLGA NPs	collagenase (mice), DMM (mice)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[517,518]
Pharmacological and drug therapy (cytokines, anti-cytokine therapeutics)	IL−1Ra	ELP depots, PLGA MSs	PTOA (mice), ACLT (rats)	reduced synovial inflammation	[519,520]
Pharmacological and drug therapy (drugs: released factors, metabolites)	resolvin D1	clodronate liposomes	DMM (mice)	reduced synovial inflammation	[521]
	EPA	gelatin hydrogel	DMM (mice)	reduced synovial inflammation	[522]
	bilirubin	PLL NPs, CS NPs	ACLT (rats), ACLT/MMT (rats)	reduced synovial inflammation	[523,524]
	substance P	self-assembled peptide hydrogels	ACLT (rabbits)	reduced synovial inflammation	[525]
Pharmacological and drug therapy (drugs: inhibitors/activators, agonists/antagonists)	bortezomib	PEG NPs	DMM (mice)	M2 polarization, reduced synovial inflammation	[526]
	DEF	DIPEA/Ce NPs	DMM (mice)	reduced synovial inflammation	[527]
	V−9302	self-assembling Fe^{3+} NPs	ACLT (rats)	M2 polarization, reduced synovial inflammation	[528]
Pharmacological and drug therapy (drugs: repurposed drugs)	simvastatin	gelatin hydrogel	DMM (mice)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[529]
	rebamipide	PEG/PDLLA NPs, PLGA NPs	MIA (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[530]
	metformin	PLGA MSs	DMM (rats)	M2 polarization, reduced synovial inflammation	[531]
	rapamycin	gelatin hydrogel, PEG/type-II collagen NPs, MOF-decorated MPDA platforms, HPMDA/PDSE/PEG NPs	DMM (mice), ACLT (rats, mice)	reduced synovial inflammation via Tregs	[532–535]
Pharmacological and drug therapy (drugs: other agents or factors)	3,4,6-O-Bu3GalNAc	PLGA MSs	MMT (rats)	reduced synovial inflammation	[536]
	KGN	F127/COS NSs, HA/PEG hydrogel, CV−2 carriers, PLGA/PEG/PLGA gels, PEG/PCL/TSPBA/GelMA NPs, alendronate-grafted HA NPs, HA/ZIF−8 nanogels, aldehyde-modified PLGA MSs, PLGA/CuBG MSs	ACLT/DMM (rats), ACLT/MMT (rats), ACLT (rabbits), MIA (rats, mice), DMM (mice), MMT (rats)	M2 polarization, reduced synovial inflammation	[495,505, 509,531, 537–541]
	SASP	HA formulation	MIA (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[542]
	TTS	DGME/OMG/POE/PEG hydrogel	papain (rabbits)	reduced synovial inflammation	[543]

(*continued on next page*)

Table 3 (*continued*)

Family	Compounds, Origin	Biomaterials	OA models	Effects	Refs.
	SMT	ZIF−8 NPs	ACLT (mice)	M2 polarization, reduced synovial inflammation	[544]
	catalase	ZIF−8 NPs, PLL/$Mn_{1.8}Co_{1.2}O_4$ NPs, G2-OH_{24} dendrimers	ACLT (mice), MMT (rats), MIA (mice)	decreased expression of pro-inflammatory OA mediators, M2 polarization, reduced synovial inflammation	[544–546]
	CORMs	peptide dendrimer nanogel	MIA (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[547]
	FGF−18	CS/PEG/PDLLA NPs	ACLT (mice)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[548]
	TGF-β	CS/methacrylate/liposome MSs	ACLT (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[549]
	PDGF-AB	PLGA MSs	DMM (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[531]
	SCDF−1	PLGA/CuBG MSs	MMT (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[541]
Pharmacological and drug therapy (drugs: medicinal/ vegetal compounds)	curcumin	TMOS/PEG/chitosan NPs, PMPC nanoplatform	DMM/MMT (mice), MIA (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[550,551]
	PCA	MOFs	ACLT (rats)	reduced synovial inflammation	[552]
	AG	mesoporous silica NPs	ACLT (rats)	reduced synovial inflammation	[553]
	berberine	PLL NPs	ACLT (rats)	reduced synovial inflammation	[523]
	LQ	CS/liposome MSs	DMM (rats)	decreased M1 polarization, reduced synovial inflammation	[554]
	icariin	TA NDs	MIA (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[555]
	baicalin	MOFs, HEA hydrogels	ACLT (rats, mice)	M2 polarization, reduced synovial inflammation	[556,557]
	quercetin	ZIF−8 hydrogels, G2-OH_{24} dendrimers	MIA (rats, mice)	reduced synovial inflammation	[546,558]
	PTE	DIPEA/Ce NPs	DMM (mice)	reduced synovial inflammation	[527]
	chrysin	self-assembling Fe^{3+} NPs	ACLT (rats)	M2 polarization, reduced synovial inflammation	[528]
Orthobiologics (cells)	MSCs (bone marrow)	Hymovis	DMM (mice)	M2 polarization, reduced synovial inflammation	[559]
	MSCs (adipose tissue)	HA-EGCG hydrogel, alginate hydrogel	DMM (rats), ACLT (rabbits)	M2 polarization, reduced synovial inflammation	[560,561]
	Artificial M2 macrophages	CS/gelatin nanogel	papain (mice)	decreased M1 polarization, reduced synovial inflammation	[562]
Orthobiologics (Exos)	MSCs (bone marrow)	GelMA hydrogel, PDA NPs	DMM (mice), ACLT (rats)	M2 polarization, reduced synovial inflammation	[563–565]
	MSCs (umbilical cord)	HA hydrogel	ACLT (rats)	M2 polarization, reduced synovial inflammation	[566]
	M2 macrophages	F127/HA hydrogel, PLGA/MnO_2/S-methylisothiourea NPs, HA hydrogel	ACLT (rats), collagenase (mice)	decreased M1 polarization, M2 polarization, reduced synovial inflammation	[567–569]
	chondrocytes	F127/HA hydrogel	DMM (rats)	M2 polarization, reduced synovial inflammation	[570]
Orthobiologics (blood derivatives)	PRP and derivatives	gelatin hydrogel, PNAAA hydrogel, P407/ HA hydrogel	ACLT (rabbits, rats), MIA (rats)	M2 polarization, reduced synovial inflammation	[571–573]

Abbreviations: NSAIDS, non-steroidal anti-inflammatory drugs; Exos, exosomes; DCF, diclofenac; dex, dexamethasone; TAA, triamcinolone acetonide; HA, hyaluronic acid; IL-1Ra, interleukin 1 receptor antagonist; EPA, eicosapentaenoic acid; DEF, deferasirox; 3,4,6-O-Bu3GalNAc, tri-butanoylated N-acetyl-D-galactosamine; KGN, kartogenin; SASP, sulfasalazine; TTS, 3,5,4'-trimethoxy-trans-silbene; SMT, S-methylisothiourea hemisulfate salt; CORMs, CO release molecules; FGF-18, fibroblast growth factor 18; TGF-β, transforming growth factor beta; PDGF-AB, platelet-derived growth factor AB; SCDF-1, stromal cell-derived factor 1; PCA, protocatechuic acid; AG, andrographolide; LQ, liquiritin; PTE, pterostilbene; MSCs, mesenchymal stromal cells; PRP, platelet-rich plasma; F127, pluronic 127; COS, chitosan oligosaccharide; NSs, nanospheres; GelMA, methacrylate gelatin; DMA, dopamine methacrylamide; MPC, 2-methacryloyloxyethyl phosphorylcholine; MSs,

microspheres; TPP, tripolyphosphate; ME, microemulsion; MNs, microneedles; NCs, nanocapsules; P407, poloxamer 407; GS97, Gantrez® S97; PVP, polyvinylppyrrolidone; CV-2, zwitterion-modified cavitand; PVA, polyvinyl alcohol; PLGA, polylactic acid glycolic acid; PEG, poly(ethyleneglycol); PCL, polycaprolactone; TSPBA, N1-(4-boronobenzyl)-N3-(4-boronobenzyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diaminium; NPs, nanoparticles; pNiPAM, poly(N-isopropyalacrylamide); HPMA, N-(2-hydroxypropyl) methacrylamide; pPAD, L-DOPA pro-antioxidant; DOPA, dopamine; PEA, polyester amide; p(HPMam-lac), poly(hydroxypropyl methacrylamide lactate); ELP, elastin-like polypeptide; PLL, polylysine; CS, chondroitin sulfate; DIPEA, diisopropylethylamine; PDLLA, poly(D,L-lactide); MOFs, metal-organic frameworks; MPDA, MOF-decorated mesoporous polydopamine; HPMDA, 1,2,4,5-cyclohexanetetracarboxylic dianhydride; PDSE, 1,2,4,5-cyclohexanetetracarboxylic dianhydride (HPMDA)/2,2′-(propane-2,2-diylbis(sulfanediyl))bis(ethan-1-o1); ZIF-8, zeolotic imidazolate frameworks-8; CuBG, copper-doped bioactive glass; DGME, diethylene glycol monoethyl ether; OMG, oleoyl macrogolglyceride; POE, polyoxyethylene; G2-OH_{24}, hydroxyl-terminated bioactive phosphorus; TMOS, tetra-methyl-orthosilicate; PMPC, zwitterionic poly(2-methacryloyloxyethyl phosphorylcholine; TA, tannic acid; NDs, nanodiamonds; HEA, 2-hydroxyethyl acrylate; EGCG, (-)-epigallocatechin-3-gallate; PDA, polydopamine; PNAAA, poly(N-acryloyl alaninamide); OA, osteoarthritis; MIA, monosodium iodoacetate; ACLT, anterior cruciate ligament transection; DMM, destabilization of the medial meniscus; MMT, medial meniscal transection; PTOA, post-traumatic OA.

Table 4
Gene therapy to target synovial cells in OA.

Family	Sequences (vectors)	OA models	Effects	Refs.
DNA	IL−1Ra (AdV, scAAV, rAAV)	PTOA (horses), ACLT/DMM (mice, rats)	reduced synovial inflammation	[591–596]
	IκBα (AdV)	human OA synovial fibroblasts	decreased expression of pro-inflammatory OA mediators	[597]
	TSP−1 (AdV)	ACLT (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[598]
	ChM−1 (LV)	DMM (rats)	reduced synovial inflammation	[599]
	PRG4 (AdV)	ACLT/DMM (mice)	reduced synovial inflammation	[593]
	relaxin (AdV)	human OA synovial fibroblasts	decreased expression of pro-inflammatory OA mediators	[600]
	CAB39 (NV)	DMM (mice)	reduced synovial inflammation, M2 polarization	[601]
	Sirt6 (LV)	MMT (mice)	reduced synovial inflammation, M2 polarization	[602]
	SOX9 (rAAV)	ACLT/MMT (rats)	reduced synovial inflammation	[596]
	MSCs (bone marrow)/IL−10 (AdV)	collagenase (mice)	decreased immune T lymphocytes	[603]
	synovial fibroblasts/IL−1Ra (RV)	ACLT (dogs)	reduced synovial inflammation	[604]
	macrophages/IL−4 (NV)	Hulth (rats)	reduced synovial inflammation	[605]
	chondrocytes/TGF-β (RV)	MIA (rats)	reduced synovial inflammation, M2 polarization	[164]
RNA (siRNA)	NF-κBp65 (AdV)	ACLT (rats)	reduced synovial inflammation	[606]
	MMP−13 (n/a)	DMM (mice)	reduced synovial inflammation	[607–609]
	ADAMTS−5 (n/a)	DMM (mice)	reduced synovial inflammation	[608]
	hsa_circ_0134111 (LV)	MMT (rats)	reduced synovial inflammation	[610]
	Peli1 (AdV)	DMM (mice)	reduced synovial inflammation	[611]
	WWC1 (rAAV)	DMM (mice)	reduced synovial inflammation	[612]
RNA (shRNA)	MIP−1γ (LV)	ACLT (mice)	decreased macrophage infiltration, reduced synovial inflammation	[613]
	cadherin−11 (LV)	human OA synovial fibroblasts	decreased expression of pro-inflammatory OA mediators, decreased invasive capacity	[614]
	Ob-Rb (LV)	ACLT (rats)	reduced synovial inflammation	[615]
	SP-D (rAAV)	ACLT (rats)	reduced synovial inflammation	[616]
	MAP3K7 (LV)	OA synovial fibroblasts	decreased expression of pro-inflammatory OA mediators, decreased proliferation levels	[617]
	circ_0000423 (rAAV)	ACLT (mice)	reduced synovial inflammation	[618]
	FSHR (rAAV)	DMM (mice)	reduced synovial inflammation	[619]
	NEK7 (rAAV)	ACLT (mice)	reduced synovial inflammation	[620]
	STIP1 (LV)	ACLT (rats)	reduced synovial inflammation	[621]
	ECM1 (rAAV)	DMM (mice)	reduced synovial inflammation	[622]
RNA (miR)	miR−10a (LV)	OA synovial fibroblasts	decreased expression of pro-inflammatory OA mediators, decreased proliferation levels	[617]
	miR−29a (LV)	collagenase (mice)	reduced synovial inflammation	[623]
	miR−140 agomir (n/a)	ACLT/MMT (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[624]
	M2 macrophage-derived EVs/miR−21–5p (NV)	ACLT (mice)	M2 polarization, reduced synovial inflammation	[625]
	Synovial MSC-derived EVs/miR−31 (LV)	ACLT/MMT (mice)	reduced synovial inflammation	[626]
	synovial fibroblast-derived Exos/miR−126–3p, miR−146a, miR−150–3p, miR−214–3p (NV)	ACLT/MMT (rats)	reduced synovial inflammation	[627–630]
	bone marrow-derived MSC-derived Exos/miR−125b (NV)	ACLT (rats)	M2 polarization, reduced synovial inflammation	[631]
	umbilical cord-derived MSC-derived Exos/miR−223 (LV)	MIA (rats)	reduced synovial inflammation	[632]
	adipose-derived MSC-derived Exos/miR−376c−3p (NV)	MIA (rats)	reduced synovial inflammation	[633]
RNA (circRNA)	circPDE4D (rAAV)	DMM (mice)	reduced synovial inflammation	[634]
	circSPI1_005 (rAAV)	DMM (mice)	reduced synovial inflammation	[635]

Abbreviations: siRNA, small interfering RNA; shRNA, small hairpin RNA; miR, microRNA; circRNA, circular RNA; IL-1Ra, IL-1 receptor antagonist; AdV, adenoviral vector; scAAV, self-complementary adeno-associated viral vector; rAAV, recombinant adeno-associated viral vector; IκBα, IkappaBalpha; TSP-1, thrombospondin 1; ChM-1, chondromodulin 1; LV, lentiviral vector; PRG4, proteoglycan 4; CAB39, Calcium-binding protein 39; Sirt6, sirtuin 6; SOX9, sex-determining region Y-type high mobility box 9; MSCs, mesenchymal stromal cells; IL-10, interleukin 10; RV, retroviral vector; IL-4, interleukin 4; TGF-β, transforming gerowth factor beta; NF-κBp65, nuclear factor kappa B subunit p65; MMP-13, matrix metalloproteinase 13; n/a, not applicable (injection); ADAMTS-5, a disintegrin and metalloproteinases with thrombospondin motifs 5; Peli1, Pellino1; MIP-1γ, macrophage inflammatory protein 1 gamma; Ob-Rb, leptin receptor; SP-D, surfactant protein D; MAP3K7, mitogen-activated protein kinase kinase kinase 7; FSHR, follicle-stimulating hormone receptor; NEK7, never in mitosis A (NIMA)-related kinase 7; STIP1, stress-inducible protein 1; ECM1, extracellular matrix protein 1; EVs, extracellular vesicles; Exos, exosomes; NV, nonviral vector; PDE4D, phosphodiesterase 4D; OA, osteoarthritis; PTOA, post-traumatic OA; ACLT, anterior cruciate ligament transection; DMM, destabilization of the medial meniscus; MMT, medial meniscal transection; MIA, monosodium iodoacetate.

Table 5
Combined gene- and biomaterial-based therapy to target synovial cells in OA.

Family	Sequences (vectors)	Biomaterials	OA models	Effects	Refs.
DNA	crmA (NV)	HA-chitosan NPs	ACLT (rats)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[638]
	IGF-I (rAAV)	alginate hydrogel	PTOA (minipigs)	reduced synovial inflammation	[639]
RNA (siRNA)	HIF−2α (n/a)	CAP/PEI NPs	ACLT (mice)	reduced synovial inflammation	[640]
	NF-κB (n/a)	p5RHH peptide NPs	PTOA (mice)	reduced synovial inflammation	[641]
	Notch1 (n/a)	PLGA/PEG NPs	papain (mice)	reduced synovial inflammation	[642]
	p47phox (n/a)	PLGA NPs	MIA (rats)	reduced synovial inflammation	[643]
	p66shc (n/a)	PLGA NPs	MIA (rats)	reduced synovial inflammation	[644]
	periostin (n/a)	p5RHH peptide NPs	DMM (mice)	reduced synovial inflammation	[645]
	MMP−13 (n/a)	PLGA/PVA microplates, poly(DMAEMA-co-BMA)/PEG NPs	PTOA (mice)	reduced synovial inflammation	[646, 647]
	CA9 (n/a)	NAHA/CaP NPs	MIA (mice), DMM (rats)	reduced synovial inflammation	[648]
	Cd61 (n/a)	PNIPMAM nanogel	DMM (mice)	reduced synovial inflammation	[649]
RNA (shRNA)	IL−1β (n/a)	yeast MCs	DMM (mice)	decreased expression of pro-inflammatory OA mediators, reduced synovial inflammation	[650]
	LEPR (n/a)	KAFAK/M2H NPs	ACLT/MMT (rats)	reduced synovial inflammation	[651]
RNA (miR)	miR−140 (n/a)	Lnxc-CL	DMM (rats)	reduced synovial inflammation	[652]
	miR−224–5p (n/a)	urchin-like NPs, G5-AHP/GelMA NPs	DMM (mice)	reduced synovial inflammation	[653, 654]
	miR−365 antagomir (n/a)	YCWP nanotubes	PTOA (mice)	reduced synovial inflammation	[655]
RNA (mRNA)	FGF−18 (n/a)	MC3/DOPE/cholesterol/PEG and SM−102/DSPC/cholesterol/PEG NPs	ACLT (mice), DMM (mice)	reduced synovial inflammation	[656, 657]

Abbreviations: siRNA, small interfering RNA; shRNA, small hairpin RNA; miR, microRNA; crmA, cytokine response modifier A; IGF-I, insulin-like growth factor I; HIF-2α, hypoxia-inducible factor 2 alpha; n/a, not applicable (injection); NF-κB, nuclear factor kappa B; MMP-13, matrix metalloproteinase 13; CA9, carbonic anhydrase IX; Cd61, integrin β3; IL-1β, interleukin 1 beta; LEPR, leptin receptor; FGF-18, fibroblast growth factor 18; HA, hyaluronic acid; NPs, nanoparticles; CAP, chondrocyte-affinity peptide DWRVIIPPRPSAC; PEI, polyethylenimine; p5RHH, VLTTGLPALISWIRRRHRRHC peptide; PLGA, polylactic acid glycolic acid; PEG, poly(ethyl-eneglycol); PVA, polyvinyl alcohol; DMAEMA, 2-(dimethylamino) ethyl methacrylate; BMA, butyl methacrylate; NAHA, NO, alendronate and o-phenylenediamine; CaP, calcium phosphate; PNIPMAM, poly(*N*-isopropylmethacrylamide); MCs, microcapsules; KAFAK, cell-penetrating peptide KAFAKLAARLYRKALARQLGVAA; M2H, M2 macrophage membrane-coated; Lnxc-CL, lornoxicam cationic liposomes; G5-AHP, phenylalanine-modified generation 5 polyamidoamine; GelMA, methacrylate gelatin; YCWP, yeast cell wall particle; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; DSPC, 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine; OA, osteoarthritis; ACLT, anterior cruciate ligament transection; PTOA, post-traumatic OA; MIA, monosodium iodoacetate; DMM, destabilization of the medial meniscus; MMT, medial meniscal transection.

reported to inhibit synovial inflammation and to promote M2 polarization for 12 weeks in an ACLT model of OA in mice [427]. Nintedanib (a drug used for pulmonary fibrosis) was described to reduce synovial inflammation for 8 weeks in a DMM model of OA in mice [428]. Medermycin (MED - an antibiotic) was demonstrated to diminish the expression of pro-inflammatory IL-1β, IL-6, IL-8 in human OA synovial fibroblasts [429].

A variety of medicinal/vegetal compounds were also employed to target synovial cells in OA. Among them, (-)-epigallocatechin-3-gallate (EGCG, a catechin) was demonstrated to inhibit the expression of pro-inflammatory COX-2, PGE2, and IL-8 in human OA synovial fibroblasts [430]. Boswellic acid was shown to reduce synovitis and to inhibit the expression of pro-inflammatory IL-1β and the TLR4 signaling pathway for 12 weeks in a DMM model of OA in mice [431]. Icariin was evidenced to decrease the expression of pro-inflammatory IL-1β and MMP-14 in human OA synovial fibroblasts [432]. TRB-N0224 (a curcumin derivative) was reported to attenuate synovial inflammation for 12 weeks in an ACLT model of OA in rabbits [433]. Quercetin was described to reduce synovial inflammation and to promote M2 polarization with a decreased expression of pro-inflammatory MMPs and ADAMTSs for up to 6 weeks in ACLT/MMT [434] and MIA-induced models of OA in rats [435]. Casticin was demonstrated to mitigate synovial inflammation and to inhibit the NLRP3 inflammasome for 8 weeks in an MIA-induced model of OA in rats [436]. Chrysin was shown to alleviate synovial inflammation and to inhibit the activation of the NLRP3 inflammasome for 4 weeks in MIA-induced model [437] and ACLT models of OA in rats [438]. Frugoside (FGS) was evidenced to reduce synovial inflammation and to inhibit M1 polarization, decreasing the expression of pro-inflammatory TNF-α and IL-6 for 6 weeks in a collagenase-induced model of OA in mice [439]. Agnuside (AGN) was reported to decrease synovial fibrosis and to inhibit the NLRP3 inflammasome and the expression of pro-inflammatory IL-1β, TGF-β, and VEGF in OA synovial fibroblasts and for 3 weeks in an MIA-induced model of OA in rats [440]. Fargesin was described to attenuate synovitis and to promote M2 polarization for 6 weeks in a collagenase-induced model of OA in mice [165]. Angelicin (ANG) was demonstrated to promote M2 polarization for 2 weeks in a DMM model of OA mice [441]. Cinnamic aldehyde (CA) was shown to inhibit inflammation by blocking the TLR4/MyD88 signaling pathway in human OA synovial fibroblasts [442]. Atractylenolide-III (AT-III) was evidenced to alleviate synovial inflammation and to promote M2 polarization for one week in an ACLT model of OA in rats [443]. Spermidine (SPD) was reported to mitigate synovial inflammation and to promote M2 polarization for 8 weeks in a DMM model of OA in mice [444]. Songorine was described to reduce synovial inflammation and to promote M2 polarization for 8 weeks in an ACLT model of OA in rats [445].

2.1.6. *Summary, highlights*

The direct administration of pharmacological and drug therapies is capable of effectively enhancing M2 polarization while reducing synovial inflammation in experimental models *in vivo* and in human OA synovial cells, tissues, and patients, especially when applying NSAIDs (celecoxib, meloxicam), glucocorticoids (TAA), viscosupplementation (lubricin), cytokines and anti-cytokine therapeutics (IL-4, IL-10, IL-13, etanercept, IL-1Ra/anakinra), and drugs (metformin) [137,244,373, 374,376,382,390,391,393,397–399,425,426].

2.2. *Orthobiologics and surgical options*

2.2.1. *Cells*

A number of cells have been applied to relevant models of OA to target synovial cells, mostly progenitor cells. Mesenchymal stem/

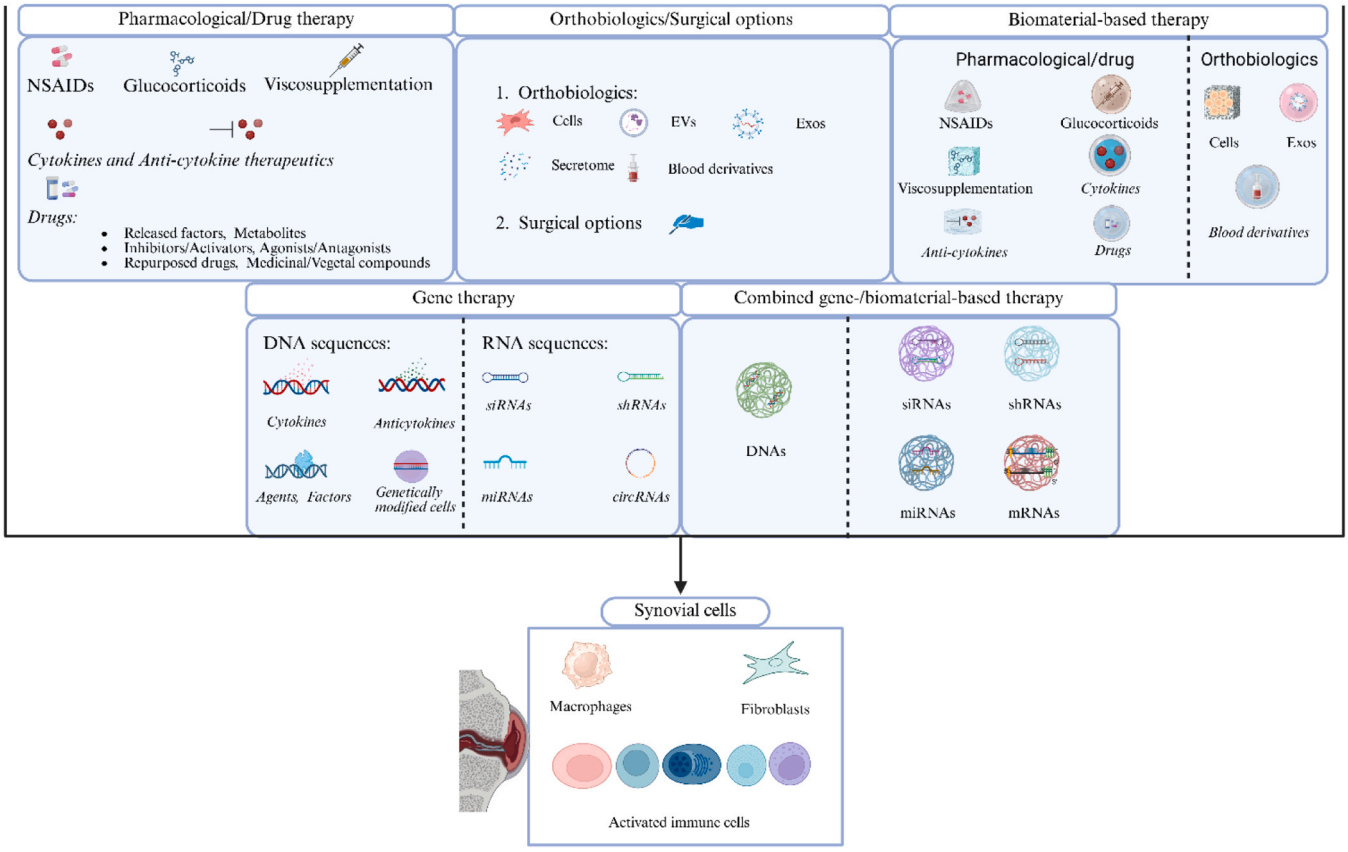

Fig. 5. Therapeutic strategies targeting synovial cells in OA. A variety of therapeutic strategies have been developed in order to target the synovial cells (macrophages, fibroblasts, other activated immune cells) in OA using pharmacological and drug therapy, orthobiologics and surgical options, biomaterial-based therapy, gene therapy, and combined gene- and biomaterial-based therapy. Abbreviations: OA, osteoarthritis; NSAIDS, non-steroidal anti-inflammatory drugs; EVs, extracellular vesicles; Exos, exosomes; siRNA, small interfering RNA; shRNA, small hairpin RNA; miRNA, microRNA; mRNA, messenger RNA (Created in BioRender. Li, F. (2025) https://BioRender.com/ejqbzhf).

stromal cells (MSCs) from the synovial fluid were demonstrated to alleviate synovial inflammation for 12 weeks when injected in an ACLT model of OA in rats [446]. Bone marrow-derived MSCs were shown to suppress inflammation and to enhance M2 polarization for 6 months when injected in an ACLT model of OA in dogs [447] and rabbits [448] and in an amphotericin-B-induced model of OA in horses [449]. Adipose-derived MSCs were evidenced to inhibit synovial inflammation and fibrosis, to reduce M1 polarization, to promote M2 polarization, and to decrease the expression on pro-inflammatory IL-1β, IL-6, TNF-α, MCP-1, and PGE2 for up to 8 weeks when injected in collagenase-induced [450] and MMT models of OA [451] in mice, in a spontaneous model of OA in guinea pigs [452], and in MIA [332], ACLT/MMT [453], papain-induced [454], and DMM models of OA [455] in rats and to diminish the expression of M1 pro-inflammatory IL-β, TNF-α, IL-6, chemokine ligands, and CCLs in human OA synovial fibroblasts [456] and in human M1 macrophages [457]. Umbilical cord-derived MSCs were reported to reduce M1 polarization and to increase the expression of M2 anti-inflammatory IL10 for 9 weeks when injected in an ACLT model of OA in rats [458]. Amniotic fluid-derived MSCs were described to promote M2 polarization in human OA synovium [459].

2.2.2. EVs, Exos, and secretome

Synovial membrane MSC-derived Exos were demonstrated to mitigate synovial inflammation for 4 weeks when injected in a collagenase-induced model of OA in mice [460]. Bone marrow-derived MSC Exos were shown to decrease synovial inflammation, to decrease the expression of pro-inflammatory IL-1β, IL-6, TNF-α, MMP-13 and inducible NOS (iNOS), and to promote M2 polarization for up to 8 weeks when injected in a collagenase-induced model of OA in mice [461] and in MIA-induced, Hulth, and ACLT models of OA in rats [462–464]. Adipose-derived MSC EVs and Exos were evidenced to attenuate synovial inflammation and inhibit M1 polarization with a decreased expression of pro-inflammatory IL-1β, IL-6, and TNF-α for up to 11 weeks when injected in an MIA-induced model of OA in rats and in DMM and ACLT models of OA in mice [465,466]. Umbilical cord-derived MSC EVs and Exos were reported to reduce M1 polarization and the expression of pro-inflammatory IL-6, TNF-α, iNOS, MMP-13 and ADAMTS-5 while increasing that of M2 anti-inflammatory IL-10 for up to 9 weeks when injected in ACLT, MMT, and ACLT/MMT models of OA in rats [458,467–469] and in a DMM model of OA in mice [470]. Induced pluripotent stem cell (iPSC)-derived MSC Exos were described to alleviate synovial inflammation and to promote M2 polarization with a decreased expression of pro-inflammatory MMP-13 and ADAMTS-5 for up to 6 weeks when injected in a collagenase-induced model of OA in mice [460] and in an ACLT model of OA in rabbits [471]. Chondrocyte Exos were demonstrated to reduce M1 polarization while promoting M2 polarization for 8 weeks when injected in an ACLT model of OA in mice [472]. Human fetal cartilage progenitor cell secretome was shown to mitigate synovial inflammation and to promote M2 polarization for 4 weeks when injected in a collagenase-induced model of OA in rats [473].

2.2.3. Blood derivatives

Platelet-rich plasma (PRP) and derivatives were evidenced to reduce synovial inflammation for up to 3 weeks when injected in a collagenase-induced model of OA in mice [474] and in an MIA-induced model of OA in rats [475] and to decrease the expression of pro-inflammatory TNF-α and IL-8 in human monocytes [399] and that of pro-inflammatory

TNF-α, NO, MMP-13, ADAMTS-5, and VEGF in human OA synovium and synovial fibroblasts [476–478].

2.2.4. Surgical options

High tibial osteotomy (HTO) was reported to promote M2 polarization with an increased expression of anti-inflammatory IL-1Ra, IL-10, and CCL18, while that of pro-inflammatory IL-1β and IL-6 decreased in OA patients [479].

2.2.5. Summary, highlights

The direct administration of orthobiologics and the use of surgical options can effectively enhance M2 polarization and reduce synovial inflammation in experimental models *in vivo* and in human OA synovial cells, tissues, and patients, particularly when applying bone marrow-derived and amniotic fluid-derived MSCs, adipose-derived MSC EVs and Exos, PRP and derivatives, and HTO [399,447–449,459,465,466,475–479].

2.3. Biomaterial-based therapy

Biomaterial-based therapy employs tissue engineering concepts and procedures using biocompatible (non-toxic, non-immunogenic) materials for the controlled delivery of therapeutics in a spatiotemporal manner in target locations in order to circumvent their short pharmacological half-lives [480–491].

2.3.1. Pharmacological and drug therapy

2.3.1.1. NSAIDS. DCF was demonstrated to mitigate synovial inflammation for up to 8 weeks when injected via type-I collagen/lipid conjugates [492], via liposomes carrying HA or type-I collagen [493], and via hyalomer formulations [494] in MIA-induced models of OA in rats, via pluronic 127/chitosan oligosaccharide (F127/COS) nanospheres (NSs) in an ACLT/DMM model of OA in rats [495], and via methacrylate gelatin (GelMA)/dopamine methacrylamide (DMA)/2-methacryloyloxyethyl phosphorylcholine (MPC) microspheres (MSs) in a DMM model of OA in rats [496]. Lornoxicam was described to reduce synovial inflammation for 3 weeks when injected via chitosan/tripolyphosphate (TPP) MSs in an MIA-induced model of OA in rats [497]. Celecoxib was shown to alleviate synovial inflammation, to reduce the expression of pro-inflammatory TNF-α, IL-6, and PGE2, and to promote M2 polarization for up to 8 weeks when injected via polyesteramine MSs [498] and microemulsion (ME)-incorporated/HA-based microneedles (MNs) [499] in ACLT/MMT models of OA in rats, via a methacrylate/HA microgel in an ACLT model of OA in rats [500], via hyaluronan nanocapsules (NCs) [501] and via a poloxamer 407 (P407)/Gantrez® S97 (GS97)/alginate/polyvinylppyrrolidone (PVP)/HA hydrogel [502] in MIA-induced models of OA in rats, and via amino acid-based polyesteramid MSs in a chronic model of OA in dogs [503]. Naproxen was evidenced to attenuate synovial inflammation for 3 weeks when injected via a gelatin/dextran/HA hydrogel in a collagenase-induced model of OA in rabbits [504]. Flurbiprofen was reported to reduce synovial inflammation for 8 weeks when injected via zwitterion-modified cavitand (CV-2) carriers in an ACLT/MMT model of OA in rats [505]. Parecoxib was demonstrated to promote M2 polarization for 4 weeks when injected via polyvinyl alcohol (PVA)/polylactic acid glycolic acid (PLGA) MSs in an ACLT/MMT model of OA in rats [506].

2.3.1.2. Glucocorticoids. Dex was described to mitigate synovial inflammation for up to 12 weeks when injected via liposomes or gels composed of HA or type-I collagen [493,507], via PLGA MSs [508], via a P407/GS97/alginate/PVP/HA hydrogel [502], and via poly(ethyleneglycol) (PEG)/polycaprolactone (PCL)/N1-(4-boronobenzyl)-N3-(4-boronobenzyl)-N1,N1,N3,N3-tetramethylpropane-1,3-diaminium (TSPBA)/GelMA NPs in MIA-induced models of OA in rats [493,502,507,509] and mice [508], via an HA hydrogel in an ACLT model of OA in rats [510], via HA-poly (N-isopropyalacrylamide) (pNiPAM) nanoparticles (NPs) [511], via a chitosan-glycerol-borax hydrogel [512], and via N-(2-hydroxypropyl) methacrylamide (HPMA) gel [513] in DMM models of OA in mice [511–513], via a gelatin/dextran/HA hydrogel in a collagenase-induced model of OA in rabbits [504], and via PEG/L-dopamine (DOPA) pro-antioxidant (pPAD) NPs in a papain-induced model of OA in rats [514]. TAA was demonstrated to reduce synovial inflammation, to decrease the expression pro-inflammatory IL-1β, IL-6, and TNF-α, and to promote M2 polarization for up to 7 weeks when injected via polyester amide (PEA) MSs in a collagenase-induced model of OA in rats [515], and via dextran sulfate NPs in an MIA-induced model of OA in mice [516].

2.3.1.3. Viscosupplementation. HA was shown to alleviate synovial inflammation and to decrease the expression of pro-inflammatory TNF-α for up to 3 weeks when injected via a poly(hydroxypropyl methacrylamide lactate) (p(HPMam-lac))/PEG hydrogel in a collagenase-induced model of OA in mice [517] and via PLGA NPs in a DMM model of OA in mice [518].

2.3.1.4. Cytokines and anti-cytokine therapeutics. An IL-1Ra was evidenced to attenuate synovial inflammation for up to 8 weeks when injected via elastin-like polypeptide (ELP) depots in a PTOA model in mice [519] and via PLGA MSs in an ACLT model of OA in rats [520].

2.3.1.5. Drugs. A variety of drugs delivered using biomaterials have also been examined for their ability to influence the behavior of synovial cells in OA, among which released factors and metabolites, inhibitors/activators and agonists/antagonists, repurposed drugs and other agents or factors, and medicinal/vegetal compounds.

Resolvin D1 [521] and eicosapentaenoic acid (EPA) (both omega 3 derivatives) [522] were reported to reduce synovial inflammation for 8 weeks when injected via clodronate liposomes [521] and via gelatin hydrogels [522] in DMM models of OA in mice. Bilirubin (a product of bile acid metabolism) was described to inhibit synovial inflammation for up to 9 weeks when injected via opsonized polylysine (PLL) NPs [523] and via CS NPs [524] in ACLT and ACLT/MMT models of OA in rats. Substance P (involved in nociception and inflammation) was demonstrated to alleviate synovial inflammation for 3 weeks when injected via self-assembled peptide hydrogels in an ACLT model of OA in rabbits [525].

Bortezomib was shown to attenuate synovial inflammation and to promote M2 polarization for 12 weeks when injected via PEG NPs in a DMM model of OA in mice [526]. Deferasirox (DEF, a ferroptosis inhibitor) was described to reduce synovial inflammation for 8 weeks when injected via diisopropylethylamine (DIPEA)/cerium ions (Ce) NPs in a DMM model of OA in mice [527]. V-9302 (an inhibitor of glutamine uptake) was evidenced to mitigate synovial inflammation and to promote M2 polarization for 4 weeks when injected via self-assembling Fe^{3+} NPs in an ACLT model of OA in rats [528].

Simvastatin (a drug used for hypercholesterolaemia) was reported to reduce synovial inflammation and to decrease the expression of pro-inflammatory IL-1β and MMP-13 for 8 weeks when injected via a gelatin hydrogel in a DMM model of OA in mice [529]. Rebamipide (a drug used to protect the gastrointestinal mucosa) was shown to decrease synovial inflammation and the expression of pro-inflammatory IL-1β, TNF-α, IL-6, COX-2, and MMPs for 8 weeks when injected via PEG/poly (D,L-lactide) (PDLLA) and PLGA NPs in an MIA-induced model of OA in rats [530]. Metformin was described to diminish synovial inflammation and to promote M2 polarization for 6 weeks when injected via PLGA MSs in a DMM model of OA in rats [531]. Rapamycin (sirolimus, an immunomodulator) was demonstrated to alleviate synovial inflammation via Tregs for up to 16 weeks when injected via a gelatin hydrogel [532] and

via PEG/type-II collagen NPs [533] in DMM models of OA in mice and via metal-organic framework (MOF)-decorated mesoporous polydopamine (MPDA) platforms [534] and via 1,2,4,5-cyclohexanetetracarboxylic dianhydride (HPMDA)/2,2′-(propane-2,2-diylbis(sulfanediyl))bis (ethan-1-o1) (PDSE)/PEG NPs [535] in ACLT models of OA in rats [534] and mice [535].

Other agents and factors were also used to target synovial cells in OA. Among them, tri-butanoylated N-acetyl-D-galactosamine analog (3,4,6-O-Bu3GalNAc, a carbohydrate-based drug) was shown to mitigate synovial inflammation for 4 weeks when injected via PLGA MSs in an MMT model of OA in rats [536]. KGN was evidenced to attenuate synovial inflammation and to promote M2 polarization for up to 12 weeks when injected via F127/COS NSs in an ACLT/DMM model of OA in rats [495], via HA/PEG hydrogels [537] and via CV-2 carriers [505] in ACLT/MMT models of OA in rats [505,537], via PLGA/PEG/PLGA gels in an ACLT model of OA in rabbits [538], via PEG/PCL/TSPBA/GelMA NPs [509] and via alendronate-grafted HA NPs [539] in MIA-induced models of OA in rats [509] and mice [539], via HA/zeolotic imidazolate frameworks-8 (ZIF-8) nanogels in a DMM model of OA in mice [540], and via aldehyde-modified PLGA MSs [531] and via PLGA/copper-doped bioactive glass (CuBG) MSs [541] in MMT models of OA in rats. Sulfasalazine (SASP) was reported to reduce synovial inflammation and to decrease the expression of pro-inflammatory TNF-α, IL-6, COX-2, and MMP-3 for 8 weeks when injected via HA formulation in an MIA-induced model of OA in rats [542]. 3,5,4'-Trimethoxy-trans-silbene (TTS) was described to diminish synovial inflammation for 4 weeks when injected via a diethylene glycol monoethyl ether (DGME)/oleoyl macrogolglyceride (OMG)/polyoxyethylene (POE)/PEG hydrogel in a papain-induced model of OA in rabbits [543]. S-Methylisothiourea hemisulfate salt (SMT) and catalase were demonstrated to alleviate synovial inflammation and to promote M2 polarization for 4 weeks when injected via ZIF-8 NPs in an ACLT model of OA in mice [544]. Catalase was further shown to reduce synovial inflammation and to promote M2 polarization with a decreased expression of pro-inflammatory IL-1β, TNF-α, iNOS, and MMP-13 for 12 weeks when injected via PLL/$Mn_{1.8}Co_{1.2}O_4$ NPs in an MMT model of OA in rats [545] and via hydroxyl-terminated bioactive phosphorus (G2-OH_{24}) dendrimers in an MIA-induced model of OA in mice [546]. CO release molecules (CORMs) were evidenced to mitigate synovial inflammation and to decrease the expression of pro-inflammatory IL-1β, TNF-α, and IL-6 for 3 weeks when injected via peptide dendrimer nanogels in an MIA-induced model of OA in rats [547]. Several growth factors were reported for their beneficial effects in the activities of synovial cells in OA. FGF-18/sprifermin [548], TGF-β [549], the platelet-derived growth factor AB (PDGF-AB) [531], and the stromal cell-derived factor 1 (SCDF-1) [541] were described to diminish synovial inflammation and to promote M2 polarization for up to 8 weeks when injected via CS/PEG/PDLLA NPs [548] and via CS/methacrylate/liposome MSs [549] in ACLT models of OA in mice [548] and rats [549], via PLGA MSs in a DMM model of OA in rats [531], and via PLGA/CuBG MSs in an MMT model of OA in rats [541].

Various medicinal/vegetal compounds were also tested to determine their impact the activities of synovial cells in OA. For instance, curcumin was demonstrated to alleviate synovial inflammation and to decrease the expression of pro-inflammatory IL-1β, TNF-α, MMPs, and ADAMTS-5 for up to 8 weeks when injected via tetra-methyl-orthosilicate (TMOS)/PEG/chitosan NPs in a DMM/MMT model of OA in mice [550] and via zwitterionic poly(2-methacryloyloxyethyl phosphorylcholine (PMPC) nanoplatform in an MIA-induced model of OA in rats [551]. Protocatechuic acid (PCA) was shown to reduce synovial inflammation for 8 weeks when injected via MOFs in an ACLT model of OA in rats [552]. Andrographolide (AG) was evidenced to attenuate synovial inflammation for 8 weeks when administered via mesoporous silica NPs in an ACLT model of OA in rats [553]. Berberine was reported to inhibit synovial inflammation for 9 weeks when injected via opsonized PLL NPs in an ACLT model of OA in rats [523]. Liquiritin (LQ) was described to reduce synovial inflammation and to inhibit M1 polarization for 3 weeks when administered via CS/liposome MSs in a DMM model of OA in rats [554]. Icariin was demonstrated to protect against synovial inflammation and to suppress the expression of pro-inflammatory TNF-α, IL-6, and MMP-3 for 4 weeks when injected via tannic acid (TA) nanodiamonds (NDs) in an MIA-induced model of OA in rats [555]. Baicalin was shown to alleviate synovial inflammation and to promote M2 polarization for up to 8 weeks when injected via MOFs [556] or via 2-hydroxyethyl acrylate (HEA) hydrogels [557] in ACLT models of OA in rats [556] and mice [557]. Quercetin was evidenced to mitigate synovial inflammation for up to 4 weeks when injected via ZIF-8 hydrogels [558] and via G2-OH_{24} dendrimers [546] in MIA-induced models of OA in rats [558] and mice [546]. Pterostilbene (PTE) was reported to reduce synovial inflammation for 8 weeks when injected via DIPEA/Ce NPs in a DMM model of OA in mice [527]. Chrysin was described to diminish synovial inflammation and to promote M2 polarization for 4 weeks when injected via self-assembling Fe^{3+} NPs in an ACLT model of OA in rats [528].

2.3.1.6. Summary, highlights. Biomaterial-based pharmacological and drug therapy is able to effectively enhance M2 polarization and reduce synovial inflammation in experimental models *in vivo*, especially when applying NSAIDS (celecoxib), glucocorticoids (dex), anti-cytokine therapeutics (IL-1Ra), and drugs (metformin, FGF-18/sprifermin) via various hydrogels (HA, alginate, gelatin, pluronics), MSs (PLGA), and NPs (PDLLA) [500,502,504,510,511,520,531,548].

2.3.2. Orthobiologics

2.3.2.1. Cells. Bone marrow-derived MSCs were demonstrated to decrease synovial inflammation and to promote M2 polarization for 12 weeks when injected via a hyaluronan hexadecylamide derivative (Hymovis) in a DMM model of OA in mice [559]. Adipose-derived MSCs were shown to alleviate synovial inflammation and to promote M2 polarization for 12 weeks when injected via an HA-EGCG hydrogel in a DMM model of OA in rats [560] and via an alginate hydrogel in an ACLT model of OA in rabbits [561]. Artificial M2 macrophages were evidenced to reduce synovial inflammation and to block M1 stimulation for 26 days when injected via a CS/gelatin nanogel in a papain-induced model of OA in mice [562].

2.3.2.2. Exosomes. Bone marrow-derived MSC Exos were described to mitigate synovial inflammation and to promote M2 polarization for up to 8 weeks when injected via GelMA hydrogels in DMM models of OA in mice [563,564] and via polydopamine (PDA) NPs in an ACLT model of OA in rats [565]. Umbilical cord-derived MSC Exos were demonstrated to attenuate synovial inflammation and to promote M2 polarization for 12 weeks when injected via HA hydrogels in an ACLT model of OA in rats [566]. M2 macrophage Exos were reported to diminish synovial inflammation, to block M1 stimulation, and to promote M2 polarization for up to 8 weeks when injected via F127/HA hydrogels in an ACLT model of OA in rats [567] and via PLGA/MnO_2/ S-methylisothiourea NPs [568] and via HA hydrogels [569] in collagenase-induced models of OA in mice. Chondrocyte Exos were shown to alleviate synovial inflammation and to promote M2 polarization for 12 weeks when injected via F127/HA hydrogels in a DMM model of OA in rats [570].

2.3.2.3. Blood derivatives. PRP and derivatives were evidenced to decrease synovial inflammation and to promote M2 polarization for up to 10 weeks when injected via a gelatin hydrogel [571] and via a poly (N-acryloyl alaninamide) (PNAAA) hydrogel [572] in ACLT models of OA in rabbits [571] and rats [572] and via a P407/HA hydrogel in an MIA-induced model of OA in rats [573].

2.3.2.4. Summary, highlights. Biomaterial-based application of orthobiologics is capable of effectively enhancing M2 polarization while

reducing synovial inflammation in experimental models *in vivo*, particularly when applying bone marrow- and adipose-derived MSCs, Exos (umbilical cord-derived MSCs, chondrocytes), and PRP and derivatives via various hydrogels (HA, alginate, gelatin, pluronics) [559–561,566,570,573].

2.4. Gene therapy

Gene therapy, the concept of treating human disorders via delivery of genetic sequences (DNA, RNA) in sites of injury via *in vivo* (direct injection of selected gene carriers) or *ex vivo* (indirect administration of cells and tissues genetically modified by selected gene carriers) strategies [574–590], has been also applied to target synovial cells in OA using a variety of gene vehicles such as nonviral (NV) vectors and virus-derived (adenoviral - AdV, recombinant adeno-associated viral vectors - rAAV, self-complementary AAV - scAAV, lentiviral - LV, retroviral - RV) vectors.

2.4.1. DNA sequences

Different DNA sequences have been manipulated to evaluate their potential to overexpress various candidate products capable of tackling the activities of synovial cells in OA, among which cytokines and anti-cytokine therapeutics, other agents and factors, and genetically modified cells.

2.4.1.1. Cytokines and anti-cytokine therapeutics. An IL-1Ra sequence was reported to alleviate synovial inflammation for up to 14 weeks via AdV [591–593], scAAV [594], and rAAV [595,596] gene transfer in PTOA models in horses [591,592,594] and in ACLT/DMM models of OA in mice [592,593] and rats [595,596].

2.4.1.2. Other agents and factors. An inhibitory subunit IkappaBalpha (IκBα, an inhibitor of NF-κB) sequence was shown to inhibit the expression of pro-inflammatory IL-6, MCP-1, MMPs, and ADAMTS-4 via AdV gene transfer in human OA synovial fibroblasts [597]. A TSP-1 (angiogenesis inhibitor) sequence was evidenced to mitigate synovial inflammation with reduced microvessel density and macrophage infiltration and to decrease the expression of pro-inflammatory IL-1β for 13 weeks via AdV gene transfer in an ACLT model of OA in rats [598]. A chondromodulin 1 (ChM-1) sequence was reported to delay synovial inflammation via LV gene transfer for 5 weeks in a DMM model of OA in rats [599]. A PRG4 sequence was shown to delay synovial inflammation via AdV gene transfer for 14 weeks in an ACLT/DMM model of OA in mice [593]. A relaxin (anti-fibrogenic agent) sequence was described to diminish the expression of pro-inflammatory MMPs in via AdV gene transfer in human OA synovial fibroblast [600]. A calcium-binding protein 39 (CAB39) was demonstrated to attenuate synovial inflammation and to promote M2 polarization for 4 weeks via NV gene transfer in a DMM model of OA in mice [601]. A sirtuin 6 (Sirt6) sequence was reported to alleviate synovial inflammation and to promote M2 polarization for 8 weeks via LV gene transfer in an MMT model of OA in mice [602]. IL-1Ra and cartilage-specific sex-determining region Y-type high mobility box 9 transcription factor (SOX9) sequences were shown to reduce synovial inflammation for 8 weeks via rAAV gene transfer in an ACLT/MMT model of OA in rats [596].

2.4.1.3. Genetically modified cells. Bone marrow-derived MSCs overexpressing an IL-10 sequence via AdV gene transfer were evidenced to decrease the amounts of activated immune CD4 and CD8 T lymphocytes for 6 weeks when injected in a collagenase-induced model of OA in mice [603]. Synovial fibroblasts overexpressing an IL1-Ra sequence via RV gene transfer were described to mitigate synovial inflammation for 4 weeks when injected in an ACLT model of OA in dogs [604]. Macrophages overexpressing an IL-4 sequence via NV gene transfer were demonstrated to alleviate synovial inflammation for 4 weeks when injected in an Hulth model of OA in rats [605]. Chondrocytes overexpressing a TGF-β sequence via RV gene transfer were reported to attenuate synovial inflammation and to promote M2 polarization for 8 weeks when injected in an MIA-induced model of OA in rats [164].

2.4.2. RNA sequences

Various types of RNA sequences have also been employed to determine their potential to impact the activities of synovial cells in OA, among which non-coding small interfering RNA (siRNA), small hairpin RNA (shRNA), microRNA (miRNA, i.e. miR), and circular RNA (circRNA) promoting gene silencing and gene regulation.

2.4.2.1. siRNA sequences. An siRNA sequence specific to NF-κBp65 was shown to mitigate synovial inflammation for 5 weeks via AdV gene transfer in an ACLT model of OA in rats [606]. siRNA sequences specific to MMP-13 were evidenced to reduce synovial inflammation for up to 8 weeks when injected in DMM models of OA in mice [607–609]. An siRNA sequence specific to ADAMTS-5 was described to diminish synovial inflammation for 8 weeks when injected in a DMM model of OA in mice [608]. An siRNA sequence specific to hsa_circ_0134111 (a circRNA upregulated in OA) was demonstrated to alleviate synovial inflammation for 8 weeks via LV gene transfer in an MMT model of OA in rats [610]. An siRNA sequence specific to Pellino1 (Peli1) (an E3 ubiquitin ligase) was reported to attenuate synovial inflammation for 8 weeks via AdV gene transfer in a DMM model of OA in mice [611]. An siRNA sequence specific to WWC1 (an upstream effector of the Hippo signaling pathway involved in tissue homeostasis and upregulated in OA) was shown to protect against synovial inflammation for 8 weeks via rAAV gene transfer in a DMM model of OA in mice [612].

2.4.2.2. shRNA sequences. An shRNA sequence specific to the macrophage inflammatory protein 1 gamma (MIP-1γ) was evidenced to mitigate synovial inflammation and to decrease macrophage infiltration for 13 weeks via LV gene transfer in an ACLT model of OA in mice [613]. An shRNA sequence specific to cadherin-11 was described to reduce the invasive capacity and MMP-2 expression via LV gene transfer in human OA synovial fibroblasts [614]. An shRNA sequence specific to the leptin receptor (Ob-Rb) was demonstrated to alleviate synovial inflammation for 12 weeks via LV gene transfer in an ACLT model of OA in rats [615]. An shRNA sequence specific to the surfactant protein D (SP-D) was reported to diminish synovial inflammation for 10 weeks via rAAV gene transfer in an ACLT model of OA in rats [616]. An shRNA sequence specific to the mitogen-activated protein kinase kinase kinase 7 (MAP3K7) was shown to decrease the expression of pro-inflammatory MMPs and ADAMTSs and the levels of proliferation via LV gene transfer in OA synovial fibroblasts [617]. An shRNA sequence specific to circ_0000423 (a circRNA upregulated in OA) was evidenced to attenuate synovial inflammation for 8 weeks via rAAV gene transfer in an ACLT model of OA in mice [618]. An shRNA sequence specific to the follicle-stimulating hormone receptor (FSHR) was described to delay synovial inflammation for 3 weeks via rAAV gene transfer in a DMM model of OA in mice [619]. An shRNA sequence specific to the never in mitosis A (NIMA)-related kinase 7 (NEK7, an NLRP3 mediator) was demonstrated to reduce synovial inflammation for 8 weeks via rAAV gene transfer in an ACLT model of OA in mice [620]. An shRNA sequence specific to the stress-inducible protein 1 (STIP1) homology and U-box-containing protein 1 (STUB1, i.e. carboxyl terminal of heat shock protein 1 - Hsp70-interacting protein - CHIP, a chaperone-dependent E3 ubiquitin ligase) was reported to ameliorate synovial inflammation for 8 weeks via LV gene transfer in an ACLT model of OA in rats [621]. An shRNA sequence specific to the ECM protein 1 (ECM1) was shown to alleviate synovial inflammation for 8 weeks via rAAV gene transfer in a DMM model of OA in mice [622].

2.4.2.3. miR sequences. miR-10a was evidenced to decrease the

expression of pro-inflammatory MMPs and ADAMTSs and the levels of proliferation via LV gene transfer in OA synovial fibroblasts [617]. miR-29a was described to lessen synovial inflammation for 8 weeks via LV gene transfer in a collagenase-induced model of OA in mice [623]. An miR-140 agomir was demonstrated to diminish synovial inflammation and the expression of pro-inflammatory MMP-13 and ADAMTS-5 for 2 weeks when injected in an ACLT/MMT model of OA in rats [624].

Various miRNAs present in genetically modified EVs and Exos have also been tested for their potential to target synovial cells in OA. M2 macrophage-derived EVs enriched in miR-21–5p via NV gene transfer were reported to alleviate synovial inflammation and to promote M2 polarization for 5 weeks when injected in an ACLT model of OA in mice [625]. Synovial MSC-derived EVs enriched in miR-31 via LV gene transfer were shown to reduce synovial inflammation for 12 weeks when injected in an ACLT/MMT model of OA in mice [626]. Synovial fibroblast-derived Exos enriched in miR-126–3p [627], miR-146a [628], miR-150–3p [629], and miR-214–3p [630] via NV gene transfer were evidenced to prevent synovial inflammation for up to 10 weeks when injected in ACLT/MMT models of OA in rats [627–630]. Bone marrow-derived MSC-derived Exos enriched in miR-125b via NV gene transfer were described to moderate synovial inflammation and to promote M2 polarization when injected in an ACLT model of OA in rats [631]. Umbilical cord-derived MSC-derived Exos enriched in miR-223 via LV gene transfer were demonstrated to decrease synovial inflammation for 4 weeks when injected in an MIA-induced model of OA in rats [632]. Adipose-derived MSC-derived Exos enriched in miR-376c-3p via NV gene transfer were reported to attenuate synovial inflammation for 2 weeks when injected in an MIA-induced model of OA in rats [633].

2.4.2.4. circRNA sequences. CircPDE4D (derived from the phosphodiesterase 4D and down-regulated in OA) was shown to mitigate synovial inflammation for 2 weeks via rAAV gene transfer in a DMM model of OA in mice [634]. CircSPI1_005 (down-regulated in OA) was evidenced to reduce synovial inflammation for 8 weeks via rAAV gene transfer in a DMM model of OA in mice [635].

2.4.3. Summary, highlights

Gene therapy can effectively enhance M2 polarization and reduce synovial inflammation in experimental models *in vivo*, especially when applying DNA sequences (IL-1Ra, PRG4, and Sirt6 via AdV and LV gene transfer, genetically modified chondrocytes overexpressing TGF-β via RV gene transfer) and RNA sequences (shRNA specific to MIP-1γ via LV gene transfer, M2 macrophage-derived EVs enriched in miR-21–5p via NV gene transfer) [164,591–596,602,613,625].

2.5. Combined gene- and biomaterial-based therapy

Controlled delivery of genetic sequences (DNA, RNA: siRNA, shRNA, and miR and coding mRNA for gene supplementation) via biomaterials [485–488,491,587,589,636,637] has also been attempted to tackle the activities of synovial cells in relevant models of OA.

2.5.1. DNA sequences

A cytokine response modifier A (CrmA) sequence was described to alleviate synovial inflammation and to decrease the expression of pro-inflammatory IL-1β and MMPs for 3 weeks via NV gene transfer using HA-chitosan NPs in an ACLT model of OA in rats [638]. An IGF-I sequence was demonstrated to inhibit synovial inflammation for one year via rAAV gene transfer using an alginate hydrogel in a PTOA model in minipigs [639].

2.5.2. RNA sequences

2.5.2.1. siRNA sequences. An siRNA sequence specific to HIF-2α was reported to attenuate synovial inflammation for 7 weeks using chondrocyte-affinity peptide (CAP: DWRVIIPPRPSAC)/poly-ethylenimine (PEI) NPs when injected in an ACLT/MMT model of OA in mice [640]. An siRNA sequence specific to NF-κB was shown to mitigate synovial inflammation for 2 weeks using p5RHH (VLTTGLPA-LISWIRRRHRRHC) peptide NPs when injected in a PTOA model in mice [641]. An siRNA sequence specific to the Notch1 (an important component of development and embryogenesis) was shown to inhibit synovial inflammation for 3 weeks using PLGA/PEG NPs when injected in a papain-induced model of OA in mice [642]. An siRNA sequence specific to p47phox (cytosolic subunit of the nicotinamide adenine dinucleotide phosphate ester - NADPH - oxidase) was evidenced to relieve synovial stress for 6 weeks using PLGA NPs when injected in an MIA-induced model of OA in rats [643]. An siRNA sequence specific to p66shc (an isoform of the shcA adaptor protein family involved in the generation of mitochondrial ROS) was described to reduce synovial inflammation for 3 weeks using PLGA NPs when injected in an MIA-induced model of OA in rats [644]. An siRNA sequence specific to periostin was demonstrated to diminish synovial inflammation for 8 weeks using p5RHH peptide NPs when injected in a DMM model of OA in mice [645]. siRNA sequences specific to MMP-13 were reported to alleviate synovial inflammation for up to 4 weeks using PLGA/PVA microplates [646] and 2-(dimethylamino) ethyl methacrylate/butyl methacrylate (poly(DMAEMA-co-BMA)/PEG NPs [647] when injected in PTOA models in mice. siRNA sequences specific to the carbonic anhydrase IX (CA9) were shown to moderate synovial inflammation for up to 8 weeks using NO, alendronate and o-phenylenediamine (NAHA)-calcium phosphate (CaP) NPs when injected in an MIA-induced model of OA in mice [648] and in a DMM model of OA in rats [539]. An siRNA sequence specific to Cd61 (integrin β3) was evidenced to attenuate synovial inflammation for 8 weeks using a poly(*N*-isopropylmethacrylamide) (PNIPMAM) nanogel when injected in a DMM model of OA in mice [649].

2.5.2.2. shRNA sequences. An shRNA sequence specific to IL-1β was described to decrease synovial inflammation and the expression of pro-inflammatory MMP-13 for 5 weeks using yeast microcapsules (MCs) when injected in a DMM model of OA in mice [650]. An shRNA sequence specific to the leptin receptor (LEPR) was demonstrated to mitigate synovial inflammation for 12 weeks using cell-penetrating peptide (KAFAK: KAFAKLAARLYRKALARQLGVAA)/M2 macrophage membrane-coated/PEI/HA (M2H) NPs when injected in an ACLT/MMT model of OA in rats [651].

2.5.2.3. miR sequences. miR-140 was reported to alleviate synovial inflammation for 4 weeks using lornoxicam cationic liposomes (Lnxc-CL) when injected in a DMM model of OA in rats [652]. miR-224–5p was shown to reduce synovial inflammation for up to 9 weeks using urchin-like ceria NPs [653] and arginine, histidine, and phenylalanine-modified generation 5 polyamidoamine (G5-AHP)/-GelMA NPs [654] when injected in DMM models of OA in mice [653, 654]. An miR-365 antagomir was evidenced to attenuate synovial inflammation for 7 weeks using yeast cell wall particle (YCWP) nanotubes when injected in a PTOA model in mice [655].

2.5.2.4. mRNA sequences. An mRNA sequence coding for FGF-18 was described to improve synovial inflammation for 8 weeks using MC3/1,2-dioleoyl-sn-glycero-3-phosphoethanolamine - DOPE/cholesterol/PEG NPs [656] and SM-102/1,2-dioleoyl-sn-glycero-3-phosphatidylcholine - DSPC/cholesterol/PEG NPs [657] when injected in ACLT [656] and DMM [657] models of OA in mice.

2.5.3. Summary, highlights

Combined gene- and biomaterial-based therapy is able to effectively enhance M2 polarization and reduce synovial inflammation in experimental models *in vivo*, particularly when applying DNA sequences (IGF-I

via rAAV gene transfer) and RNA sequences (miR-224–5p, mRNA coding for FGF-18) via various hydrogels (alginate) and NPs (urchin-like ceria, G5-AHP/GelMA, DOPE/ and DSPC/cholesterol/PEG) [639,653,654,656,657].

3. Conclusions and future directions

The most important finding of this study is the rather large body of data originating from preclinical animal models *versus* the paucity of clinical data. Despite the availability of numerous clinical options to treat OA in patients including non-pharmacological treatments, pharmacological and drug therapy, orthobiologics, and surgical options, none can definitively reverse or prevent its advancement, demonstrating the need for new therapies and DMOADs against this highly prevalent, debilitating disease and public health concern. A large body of the literature showed the key roles played by activated synovial cells in OA inflammation (synovial macrophages with polarization towards a pro-inflammatory M1 phenotype, synovial fibroblasts with inappropriate activation via secretion of pro-inflammatory mediators and abnormal cell proliferation/migration), a central pathophysiological process involved in the disease progression and leading to the irreversible degradation of the articular cartilage.

In this regard, numerous novel strategies have been developed to re-establish a physiological M1/M2 ratio by stimulating the anti-inflammatory M2 phenotype in synovial macrophages and/or to inhibit the detrimental activities of the synovial fibroblasts, including pharmacological and drug therapy, orthobiologics and surgical options, biomaterial-based therapy for the controlled release of therapeutics in a spatiotemporal manner, gene therapy via delivery of genetic sequences, and combined gene- and biomaterial-based therapy. While promising results have been reported in various relevant experimental (preclinical) models of OA *in vivo* as demonstrated here, little information is available in human OA individuals to date, with merely studies reporting the clinical benefits of aceclofenac and celecoxib administration [244] and of surgical HTO [479] on M2 polarization with reduced expression of pro-inflammatory mediators (IL-1β, TNF-α, IL-6, PGE2, COX-2) and increased expression of anti-inflammatory agents (IL-1Ra, IL-10, CCL18) in OA patients. This reflects the challenges to implement and conduct new clinical trials for this disease (regulatory issues, costs, benefit-risk assessment *versus* current therapies including drug repurposing) [324,342,354,662–666], especially when using gene therapy approaches [329,354,590,658–661,667–677], even though this concept became an applicable strategy worldwide like for the coronavirus disease 2019 (COVID-19) pandemic [678–680].

In addition, for the treatment of a complex disorder like OA [681], it will be important to take into account its particular stage [3,682,683], phenotypes [684–686], and patient-specific (personalized) features (age, sex, gender, etc) [687–690] that may directly impact the choice of an optimal therapy (class, formulation, dose, frequency of application, etc), while addressing the specific OA environment and joint barriers (inflamed synovial fluid, ECM, enzymes, oxygen, pH, etc) to enable joint entry and avoid premature clearance/dissemination and possible deleterious effects of the therapeutic compound [77,378,691–695]. Nevertheless, despite certain remaining challenges, the progress made thus far provides certain optimism to further explore strategies targeting synovial cells to alleviate OA in patients in the near future.

Statement of significance

Therapies like based on the application of biocompatible materials, capable of managing the critical synovial inflammation in osteoarthritis, a highly prevalent uncurable chronic degenerative joint disorder, may provide attractive approaches to treat millions of patients affected worldwide. This work reports the manipulation of therapeutic options capable of alleviating osteoarthritis in clinically relevant models *in vivo* by tackling pathological changes in synovial cells (synovial macrophage polarization towards a pro-inflammatory M1 phenotype compared with the anti-inflammatory M2 phenotype, inappropriate synovial fibroblast activation). The novelty and originality of this work relies on thoroughly reporting, for the first time, innovative options to regulate synovial macrophage polarization and prevent synovial fibroblast activation as a means to significantly counteract the progression of osteoarthritis.

Author contributions

FL acquired and interpreted the data and drafted the manuscript; JKV played an important role in interpreting the data and revised the manuscript; HM played an important role in interpreting the data and revised the manuscript; MC conceived and designed the work, interpreted the data, and revised the manuscript. All authors approved the final version of the manuscript and agreed to its publication.

CRediT authorship contribution statement

Henning Madry: Writing – review & editing, Visualization, Validation, Funding acquisition, Formal analysis. **Jagadeesh Kumar Venkatesan:** Writing – review & editing, Visualization, Validation, Formal analysis. **Magali Cucchiarini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Fanfan Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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