Experimental Therapeutics for the Treatment of Osteoarthritis

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Abstract: Osteoarthritis (OA) therapy remains a large challenge since no causative treatment options are so far available. Despite some main pathways contributing to OA are identified its pathogenesis is still rudimentary understood. A plethora of therapeutically promising agents are currently tested in experimental OA research to find an opportunity to reverse OA-associated joint damage and prevent its progression. Hence, this review aims to summarize novel emerging experimental approaches for OA. Due to the diversity of strategies shown only main aspects could be summarized here including herbal medicines, nanoparticulate compounds, growth factors, hormones, antibody-, cell- and extracellular vesicle (EV)-based approaches, optimized tools for joint viscosupplementation, genetic regulators such as si- or miRNAs and promising combinations. An abundant multitude of compounds obtained from plants, environmental, autologous or synthetic sources have been identified with anabolic, anti-inflammatory, -catabolic and anti-apoptotic properties. Some ubiquitous signaling pathways such as wingless and Integration site-1 (Wnt), Sirtuin, Toll-like receptor (TLR), mammalian target of rapamycin (mTOR), Nuclear Factor (NF)- κ B and complement are involved in OA and addressed by them. Hyaluronan (HA) provided benefit in OA since many decades, and novel HA formulations have been developed now with higher HA content and long-term stability achieved by cross-linking suitable to be combined with other agents such as components from herbals or chemokines to attract regenerative cells. pH- or inflammation-sensitive nanoparticulate compounds could serve as versatile slow-release systems of active compounds, for example, miRNAs. Some light has been brought into the intimate regulatory network of small RNAs in the pathogenesis of OA which might be a novel avenue for OA therapy in future. Attraction of autologous regenerative cells by chemokines and exosome-based treatment strategies could also innovate OA therapy.

Keywords: osteoarthritis, chondrocyte, cytokine, chemokine, hyaluronan, nanoparticle, exosome, mesenchymal stromal cell, miRNA

Introduction

Osteoarthritis (OA) is the most common joint disease. It has an increasing prevalence in the more and more aging population¹ and presents a large burden for the healthcare systems since it remains so far untreatable. A huge bulk of novel literature arises daily in OA research presenting a demanding challenge for OA researchers to notice the emerging innovations. In regard to therapeutical targets in OA, several reviews of literature have recently been published which can be studied.^{2–10} However, mesenchymal stromal cell (MSCs) or exosome-based approaches, interrelation of OA with the microbiome, novel strategies of improved viscosupplementation as well as the arising knowledge concerning the impact of micro RNAs (miRNAs) in the OA therapy are

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less addressed and hence, present a topic of this review. In view of the abundant novel literature related to these issues, this review remains mainly confined to most recent findings of the last three years. Its purpose is to discuss currently emerging experimental strategies to treat OA. It will introduce into currently known facts about the pathogenesis of OA. Then, as research tools, the in vitro and in vivo OA models will be shortly summarized before therapeutically addressed targets and signaling pathways in OA will be presented and some promising groups of remedies will be discussed in more detail.

OA Pathogenesis

Diverse pathogenetic factors in OA have been identified including its initiation by insufficient cartilage healing after injury representing posttraumatic OA (PTOA), loss of function of cartilage during aging,¹¹ genetic predispositions (eg, less stable cartilage ECM through mutations

in ECM genes or less effective protective mediators due to mutations in their genes) or joint overload (by misalignment of leg axis or adipositas/obesity as well as meniscus damage or loss).^{12,13} The contribution of metabolic dysbalances (metabolic syndrome, diabetes mellitus) to OA has been underlined in the last years.^{14,15} Joint pain, stiffness and swelling are typical clinical features of OA.¹⁶ The progradient cartilage deterioration and subsequent loss (Figure 1) associated with OA is clinically detectable as joint space narrowing on X-ray images. Other changes include formation of osteophytes, subchondral bone sclerosis, cracks and possibly, subchondral bone marrow edema,¹⁷ as well as low-grade synovitis.^{18,19} OA is triggered by episodic inflammation^{1,18,19} and local inflammation in the affected joints which correlates with systemic inflammation markers.¹⁸ OA is a whole joint disease affecting all joint-associated tissues.^{13,20,21}

Figure 1 Osteoarthritic joint cartilage. (A) A femur head affected by OA explanted during joint replacement surgery is shown. Histological images (Hematoxylin Eosin staining) of (B1) nearly unaffected human cartilage, (B2 and B3) mild (hypocellularity, superficial clefts) and severely (cartilage absent, bone marrow activated, fibrosis) affected human joint cartilage. A histological image of healthy (C1) and severely osteoarthritic (C2) articular cartilage of the rat knee joint.

Typical molecular features of OA in joint cartilage are an accelerated cartilage ECM degradation enforced by a dysbalance between extracellular matrix (ECM) degrading enzymes such as matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) and regulatory tissue inhibitors of metalloproteinases (TIMPs).^{3,22} Particularly the cleavage of aggrecan in cartilage is a hallmark of cartilage degeneration in OA.^{22,23} Furthermore, ECM neosynthesis is suppressed in OA chondrocytes.²¹ Episodic joint inflammation is triggered by an enhanced release of pro-inflammatory cytokines including TNF α , IL-1 β and IL-6 which play a crucial role in OA.^{1,24,25} In addition to the aforementioned well-known cytokines increased levels of other cytokines such as IL-8 and IL-18 can also be observed.²⁶ Cytokines are released by synovial fibroblasts (SF), macrophages or chondrocytes themselves.^{27–29} Chondrocytes change their cell membrane protein expression pattern comprised as surfactome in response to the presence of TNF α and IL-1 β .²⁴ The loss of maturational arrest of chondrocytes has been reported in OA³⁰ leading to cell cluster formation due to uncontrolled focal cell proliferation. OA chondrocytes can undergo preterm senescence³⁰ or perish due to apoptosis.³ Apoptosis can arise from extrinsic, which includes death receptor-mediated, or intrinsic mitochondria-associated signaling pathways. Mitochondrial pathways are affected by OA reflecting oxidative stress.^{30,31} Mitophagy, which represents the selective uptake of mitochondria by autophagosomes of the cells, has been observed as a correlate of mitochondrial disturbances in OA.^{32,33} In addition, apoptosis in OA can be induced by lysosomal dysfunction as recently reported.³⁴

Enhanced cell death and ECM degradation propagate the presence of damage products including so-called alarmins, some of them released from the cytosol.²⁹

Alarmins which represent so-called damage-associated molecular patterns (DAMPs) are delivered as normal cellular constituents such as ECM components, S100 proteins, histones or nucleic acids³⁵ from degraded ECM, damaged or dying cells and subsequently bind to cell membrane receptors or intracellular receptors of other cells initiating inflammatory responses. In OA an enhanced release of alarmins can be postulated.²⁹ One receptor class binding DAMPs is the Toll-like receptor (TLR) family.³⁵ Alarmins are involved in OA pathogenesis as recently reviewed by Minguzzi et al³⁰. Cell and ECM fragments can also initiate complement activation³⁶

and thereby, contribute substantially to OA pathogenesis.^{37,38} Despite the changes in cartilage are so far more intensively studied, the contribution of other tissues than cartilage to OA pathogenesis has to be strongly considered such as of menisci and infrapatellar fat pad (IFP).^{13,39,40} An intimate interplay between inflamed synovium and meniscus tissue of early and late OA patients could be observed in co-culture studies characterized by elevated release of inflammatory and catabolic mediators in co-cultures compared to monocultures.⁴¹ A closer focus on the IFP indicated inflammatory and fibrotic changes as well as enhanced vascularization associated with OA.^{39,42} The synovial membrane and IFP might act as anatomo-functional unit involved in OA pain generation^{43,44} and both tissues are inflamed in OA.³⁹ Future research should elucidate more details of the interplay of all these tissues in the scenario of OA.

OA is so Far Untreatable

There are no approved effective disease-modifying OA drugs (DMOADs) available for OA treatment.¹² Only symptomatic treatment of OA can be performed. Hence, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) addressing pain and inflammation are the therapeutic options for OA^{45,46} with adverse effects in long-term use.⁴⁷ NSAIDs are widely prescribed for the treatment of symptomatic OA of the knee.⁴⁵ Therefore, the search for valuable targets requires the understanding of the interaction of different signaling pathways and has to go on remaining a challenging topic in current research.⁴⁸

In vitro and in vivo Disease Models for Elucidation of OA Therapeutics

Suitable OA models are required to decipher OA pathogenesis. Many studies are completely performed in vitro using primary chondrocytes from healthy persons or individuals suffering from OA, synovial fibroblasts (SF), several chondrocytic, synovial fibroblast (SF) or macrophage cell lines (eg, human chondrosarcoma SW1353 and OUMS-27 cell lines, murine teratocarcinoma-derived chondrocyte cell line ATDC5, SF K4IM and murine macrophage Raw 264.7 cell lines) or even cartilage explants to simulate natural three-dimensional (3D) conditions (Table 1).^{8,27,49–53} Cells were usually stimulated with probably mostly hyperphysiological concentrations

Table 1 Examples of in vitro Models

		Anatomic origin of main cell types from the knee joint used as in vitro model. BM: bone marrow C: cartilage IFP: infrapatellar fat pad M: meniscus SB: subchondral bone SM: synovium/synovial membrane	
Primary cells	Cell lines	Explants	OA induction
Chondrocytes (articular cartilage) from unaffected or OA cartilage	OUMS-27, ⁵⁰ SW1353, ^{87,88} (both: human), ATDC5 ⁴⁹ (mouse), fetal fibroblasts immortalized with hTERT from bone+cartilage CHON-001 ⁸⁹	Cartilage ⁹⁰ (unaffected or OA)	Key cytokines: TNF α , ⁸⁷ IL-1 β , ⁸⁹ LPS ⁹¹ conditioned media from OA cells ⁶⁰ oxidative stress ⁹² oncostatin ⁸⁸
Fibrochondrocytes ⁹³ (menisci)		Meniscus ⁴¹	
Stem cells (IFP-, synovium-, bone marrow-derived)		Synovium ⁴¹	
Synovial fibroblasts ²⁷	K41M ²⁷ (human)		
Macrophages	Raw 264.7 ⁵² (murine) U937 ⁹⁴ (human)		
Osteoblasts ⁹⁵ from unaffected or OA subchondral bone		Osteochondral unit ⁶¹	
Adipocytes		IFP	
Endothelial cells (fat pad, synovium)			

Abbreviations: IFP, infrapatellar fat pad; IL, interleukin; LPS, lipopolysaccharide; OA, osteoarthritis; TNF, tumor necrosis factor.

of cytokines IL-1 β , TNF α or lipopolysaccharide (LPS) to simulate inflammation associated with OA.^{27,28,52,54} On first glance, LPS does not play a role in OA. However, it has recently been suggested that LPS released from the disturbed gut microbiome might provide a pathogenetic link between obesity, metabolic syndrome and OA.⁵⁵ One has to consider that chondrocyte cell lines usually do not reflect all features of primary chondrocyte responses.^{50,56} These in vitro studies focus in the most cases only on chondrocytes and mostly neglect the interplay with other cell types in the joint such as synoviocytes (SF and macrophages), Hoffa fat pad- or subchondral bone derived-cell types. However, some co-culture models were used. Co-culture models of OA were established which consisted, eg, of cartilage and synovial membrane explants from human OA patients activated with IL-1 β to simulate inflammation before treated with hyaluronan (HA) and

MSC-derived conditioned medium (CM) to visualize effects of this treatment approach.⁵⁷ In other studies either synovium-derived MSCs and ATDC5 chondrocytes⁵⁸ or human SF and articular chondrocytes were co-cultured.⁵⁹ The latter study was undertaken to show the exchange of stem cell-derived extracellular vesicles (EVs) under 2D and 3D conditions in regard to OA.⁵⁹ One should critically think about the in vitro models in regard to the fact that inflammation is refined to the presence of either TNF α or IL-1 β . Meanwhile it is known that other cytokines and mediators among them IL-6 or IL-18 might contribute to OA pathogenesis.^{26,41} In this regard studies using conditioned media from OA tissues are important.⁶⁰ Most of the in vitro studies are performed in 2D culture, but there exist differences in cell behavior of 2D and 3D cultured cells.⁵⁹ More sophisticated in vitro models are required, particularly more complex co-cultures including several cell

types or tissues, eg, addressing also menisci, the osteochondral unit, synovium and the IFP of the osteoarthritic joint to reflect interactions.^{41,61}

Several experimental settings combine in vitro analyses with preclinical in vivo models. To fully address OA as a whole joint disease, which does not exclusively affect the cartilage layer²⁰ and to assess complex symptoms like pain in vivo models are indeed required. Preclinical OA models have already previously been thoroughly discussed and summarized.^{62,63} Models are performed in various animal species such as mice, rats, rabbits and dogs.^{5,62,64–66} Rodent models are broadly used.^{63,67–70} Approaches to induce OA differ (Figure 2). OA can be induced by direct damage of knee joint cartilage by application of monosodium iodoacetate (MIA model) or other harmful agents.^{71,72} The other models are based on creating knee instability by destabilization of the medial meniscus (DMM model) through transection of the medial

anterior meniscotibial ligament (MAMTL) which fixes the medial meniscus at the tibial plateau⁷³ or by transection of the medial collateral ligament (MCL) together with removal of the medial meniscus (MCL-MMx model), transection of the medial meniscus (medial meniscus transection: MMT model)^{71,73,74}, of the ACL (ACLT model)^{75,76} or combinations of them.⁷⁶ Novel models based on joint cartilage overloading by high impact or cyclic overloading (inducing non-invasively posttraumatic joint injury leading to posttraumatic OA [PTOA]) have also been proposed.^{68,77} In addition, more specific models have been described such as creating surgically patellofemoral OA by shortening the patellar ligament and thereby, changing the position of the patella and hence, its fitting accuracy in the femoropatellar groove⁷⁸ or facet joint OA in the spine of rats.⁷⁹ Finally, estrogen-deprivation by ovariectomy is also used⁶² to induce OA, being simultaneously a well-known model for osteoporosis.

Figure 2 Most commonly used OA in vivo models. In vivo models are either established in the knee joint by application of MIA through the patellar ligament (PL) or other destructive agents (eg tamoxifen for age-related OA) which directly affect joint cartilage integrity or by creation of instability due to ligament transection, meniscus injury or even removal. Except for MIA (sagittal) frontal views of the knee joint are depicted. OA induced by repetitive loading: by cyclic tibial compression. Joint overload by obesity. Ovariectomy impairs bone- and chondroprotective estrogen. Application of tamoxifen induces age-related OA.⁸⁷ The image was created by G. Schulze-Tanzil using Krita 4.1.7 Software.

Abbreviations: MIA, monosodium iodoacetate application; MCL-MMx, medial collateral ligament (MCL) transection and medial meniscus (MM) removal (x); DMM, destabilization of the medial meniscus by transection of the medial anterior meniscotibial ligament (MAMTL); ACLT, anterior cruciate ligament (ACL) transection; PCLT, posterior cruciate ligament (PCL) transection; PTOA, post-traumatic OA; LCL, lateral collateral ligament.

In contrast to MIA, surgical models might be more preferable reflecting more closely one crucial aspect of the natural OA pathogenesis, namely, inhomogenous joint loading by instability.⁴⁸ They can display early and late OA depending on the time point of investigation selected after OA induction to perform the experiments. Aülo Rasser et al, (2020) pointed to MMT as preferable model in comparison to MIA investigating early OA.⁸⁰ High fat diet contributes to OA development in mice,⁸¹ hence, also obesity models exist.^{82,83} In addition, in mice, a couple of strains which spontaneously develop OA such as the STR/Ort mice model have been described.⁸⁴ Mice models present the advantage of studying diverse gene knock outs to elucidate signaling pathways contributing to OA.⁸⁵ Data from man and mice have to be brought in overlap to deduce novel therapeutic strategies in OA. Convincing concordance could be demonstrated^{48,86} supporting the further use of rodent models as valuable tool to improve the understanding of OA pathogenesis. Depending on the model, different compartments of the joint are affected by OA. Most studies are performed in the knee joint; however, OA is a heterogenous disease affecting different joints or even joint regions involving possibly diverse pathogenetic factors depending on the topographical environmental conditions. Despite cartilage is a key structure affected by OA and responsible for impaired joint function, other tissues impaired by OA such as menisci should be more thoroughly addressed by models.⁴¹ The limitation of in vivo models mostly performed in rodents is that it is often not possible to separate certain tissues from each other, eg, the synovial membrane from the IFP to get a simplified model to study distinct tissue-related aspects of OA pathogenesis.

One has to consider that the severity of OA and velocity of its progression differs in the various models.

Therapeutically Addressed Signaling Pathways of OA

A search for biomarkers has been undertaken to identify the early disease stages of OA.⁹⁶ Chondroprotective agents effective in OA generally exert anabolic, anti-catabolic-, -inflammatory, -apoptotic and mitoprotective properties. Accordingly, there exist a couple of known general approaches to address these key features.

Antagonists/inhibitors of MMPs have been tested⁹⁷ to stop cartilage ECM degradation in OA. Suramin,

historically used as antiparasitic and antihelminthic drug, is able to restore the expression of chondroprotective tissue inhibitor of metalloproteinase (TIMP)-3, thereby inhibiting OA cartilage degradation by MMPs.⁹⁸

The direct inhibition of inflammation by neutralizing pro-inflammatory cytokines such as IL-1 β and TNF α was less effective in OA.⁹⁹

Anti-inflammatory cytokines could antagonize pro-inflammatory cytokine effects. IL-10, a member of the IL-10 family, exerts some chondroprotective effects such as inhibiting TNF α -induced apoptotic pathways in chondrocytes and partly restoring the aggrecan expression suppressed by TNF α in OA in vitro models.^{28,100–102} Hence, an agonistic IL-4/IL-10 fusion antibody seems to be promising for OA therapy.¹⁰³ This therapeutical approach based on human IL-10 reduced pain in the dogs, as reported by the veterinarians and dog owners observations, without any detectable adverse effects. These results might provide a starting point for clinical trials to confirm it in future as effective.¹⁰⁴

There is clinical evidence implicating TLRs in OA pathogenesis and OA associated pain, depending on disease activity as reviewed by Miller et al^{29,35}. TLR are cell surface receptors which recognize microbial-associated molecular patterns and NF κ B is a critical transcription factor for TLR downstream signaling.¹⁰⁵ TLR2 is expressed in chondrocytes, its immunoreactivity was correlated with expression of NF κ B, higher body mass index (BMI) and Western Ontario and McMaster Universities OA Index (WOMAC) scores in patients and related to OA associated changes.¹⁰⁵ Typical ligands of TLR, which belong to the group of pattern recognition receptors are DAMPs representing ECM fragments (eg, from aggrecan, tenascin C, HA, fibronectin), S100 proteins and other factors.⁹⁹ Chondrocyte apoptosis is a critical event which can be mediated by TLR signaling.¹⁰⁶ This part of the innate immunity, the TLR mediated signaling cascades could be addressed in future in OA as reviewed by Barreto et al¹⁰⁶.

Another part of the innate immune system is the complement system which is dysregulated in OA.³⁸ It represents a cascade of components activated by proteolytic cleavage. Split fragments are released during activation. The important anaphylatoxins C3a and C5a result from the cleavage of the components C3 and C5 and bind to cellular receptors (eg, C3aR and C5aR) initiating inflammatory responses. The finally arising complement complex at the end of the cascade, the membrane attack complex, forms pores after integrating into target cell membranes, thereby

leading to cell lysis.¹⁰⁷ Accordingly, the expression of inflammatory and degradative molecules was lower in chondrocytes from destabilized joints of complement C5-deficient mice than C5-sufficient mice. Activation of complement is abnormally high in human osteoarthritic joints.³⁸ Due to the involvement of complement activation in OA, complement inhibitors could serve as promising agents in future OA therapy.^{37,38}

The sirtuin (SIRT) signaling pathway (SIRT)/p53 axis has strongly been implicated in OA.⁸⁶ Sirtuins and Forkhead box O (FoxOs), the latter a target of sirtuins have chondroprotective properties. SIRT1 is known to exert anti-apoptotic effects. The FoxO signaling pathway is one of the most dysregulated pathways in human OA cartilage compared to normal tissue, but SIRT1 might not be exclusively beneficial.^{108,109} Melatonin, a hormone regulating circadian rhythm released from the pineal gland, is known to inhibit the SIRT1 pathway and possesses chondroprotective effects.^{110,111}

The mammalian target of rapamycin (mTOR) signaling pathway, initiated by mTOR as a critical serin/threonine protein kinase, plays a crucial role for chondrocyte homeostasis and its dysbalance contributes to OA associated joint degeneration. Inhibition of this pathway and mTOR knock outs lead to reduction of the severity of OA in mouse models as reviewed recently.^{112–114}

The reactive oxygen species (ROS)/extracellular signal regulated kinase (ERK)/Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathways have been implicated in OA.¹¹⁵

Adenosine monophosphate-activated protein kinase (AMPK) activation - a cell energy sensor,^{116,117} acting via SIRT3, limits oxidative stress and improves mitochondrial DNA integrity and function in OA chondrocytes. These effects likely contribute to chondroprotective effects of AMPK activity.³¹

The wingless and integration site-1 (Wnt) pathway is strongly implicated in OA. Signaling molecules and regulators of Wnt are abnormally activated or suppressed under OA conditions. Hence, agonists and antagonists of this pathway have attracted interest for future OA treatment as reviewed previously.^{48,118} First attempts have been undertaken to modulate this pathway: inhibition of the Wnt/beta-catenin signaling with the compound lorecivint prevented cartilage degradation and impaired pain in a preclinical model of posttraumatic OA (PTOA) probably via reduced signal transducer and activator of transcription (STAT) signaling. Lorecivint has

already entered Phase I and Phase 2 trials, reducing pain and joint narrowing.¹¹⁹

The Runt related transcription factor (RUNX) 2 regulates osteoblast and chondrocyte differentiation and was induced in murine OA models underlining an involvement in OA development. Hence, it has been postulated as a potential novel target for therapeutical intervention.¹²⁰

The observation that the transmembrane protein aquaporin (AQP)-1, responsible for water transport was upregulated in OA cartilage initiated more detailed investigations which showed that this surface protein facilitated caspase-3 activation promoting chondrocyte apoptosis as a typical feature of OA.¹²¹

In addition, it has been shown that PTEN-induced kinase (Pink)1 mediated chondrocytic mitophagy, initiated chondrocyte death and contributed thereby, to cartilage degeneration in OA.¹²² Not only Pink1 but also Parkin proteins were increased in OA.¹²³ The Parkin protein might protect from ROS accumulation mediating chondrocyte survival.¹²⁴

One shared target of several above-mentioned signaling pathways is the NF-κB signaling.¹²⁵ However, NF-κB is involved in many pathways mediating anabolic and catabolic processes in cartilage.¹²⁵ This transcription factor is inhibited by many potential agents of OA (Table 2) including herbal medicines.

The endocannabinoid-associated signaling pathway is involved in pain regulation in OA.¹²⁶

Herbal Medicines and Dietary Phytochemicals (Nutraceuticals)

Herbal medicines and other compounds from natural resources, eg, uptaken as nutraceuticals represent an emerging field in OA therapy and novel candidates have been summarized in several very recent reviews.^{8,9,127} Some agents have been used empirically since centuries, eg, in Chinese traditional medicine (see Table 2).¹²⁸ More systematical screening has been undertaken to identify novel promising compounds¹²⁹ and chemoinformatic recherche exploring suitable compounds based on their putative properties deduced from chemical structure and composition was also applied to identify valuable agents for OA.⁸ Nutrigenomics is an additional strategy to find potential therapeutics tailored for individual patients.¹³⁰ This novel field implicates that nutrients affect the expression of an individual's gene setting, translation of proteins and arising metabolites or protect its genes from damage.¹³¹ A problem of natural compounds is the fact to be extracted from herbals or other environmental sources. The content of active compounds is influenced by extraction and

Table 2 Synopsis of Some Compounds Extracted from Natural Resources

Compound	Effects/Models Used	Reference
Artemisinin	<i>Artemisia annua</i> , inhibiting Wnt/catenin pathway, anti-inflammatory, IL-1 β ↓, TNF α ↓, IL-6↓, MMP-13↓, models: rat ACLT+MMx, human/rat articular chondrocytes+IL-1 β	[76]
Berberine	<i>Rhizoma coptidis</i> , protein kinase B (AKT) signaling, NO↓, inhibited PG, ACAN and collagen degradation by IL-1 β , →cartilage degeneration↓ models: rat articular chondrocytes+IL-1 β , ACLT+MMx	[133]
Blue mussel water extract	<i>Mytilus edulis</i> , pro-inflammatory mediators↓ oxidative stress↓, cartilage degradation↓ and pain↓, anti-obesity effect in obese OA rats, NF- κ B inhibition could be hypothesized model: rat ACLT+MMx (high fat diet obese rats)	[75]
Butein	Bark of cashews and <i>Rhus verniciflua</i> IL-1 β mediated NO↓ and PGE2↓, COX-2↓, iNOS↓, TNF- α ↓, IL-6↓ and MMP-13↓, degradation of COL-2 and SOX-9↓, MMP-1↓, MMP-3↓, ADAMTS-4↓ and -5↓ gene expression, NF κ B activation↓ synovitis↓, cartilage erosion↓, GAG loss↓ autophagy in OA chondrocytes via AMPK/TSC2/ULK1/mTOR pathway↑ models: human OA chondrocytes+IL-1 β , DMM mice	[134,135]
Carnosol	Rosemary, MMP-3↓, IL-6↓, NO↓, ADAMTS-4↓, collagen type II↑ models: human osteoarthritic chondrocytes, co-cultured with sclerotic or non-sclerotic osteoblasts	[95,136]
<i>Centella asiatica</i> , <i>Boswellia serrata</i>	<i>Centella asiatica</i> and <i>Boswellia serrata</i> , NO↓, iNOS↓ (in vitro in macrophages), pain↓ models: MIA and RAW 264.7 macrophages	[52]
Curcumin	<i>Curcuma longa</i> , AKT/mTOR, pain↓, inhibits NF- κ B, restored type II collagen, autophagy capacity. Apoptosis↓, MMP-3↓ models: chondrocytes (human, mice and rat articular chondrocytes+IL-1 β or oxidative stress), spontaneous OA mice model, DMM mice model, aging related OA mice model via tamoxifen administration	[92,137–139]
<i>Comarum palustre</i> L.	Traditional medicine drug, TNF α ↓, IL-10↑, adiponectin↑ in patients, pain↓, disability↓, OA symptoms↓ model: human patients	[140]
Daphnetin	Traditional chinese drug, inhibition of the phosphoinositol-3 kinase (PI3K)/AKT, MAPK and NF- κ B pathways, IL-6↓, IL-12↓, MMP-3↓, -9↓, -13↓, BAX↓, caspase-3↓, IL-10↑ induced by IL-1 β models: rabbit articular chondrocytes+IL-1 β , rabbit OA (ACLT+PCLT+meniscectomy)	[141]
Dehydrocostus lactone	Medicinal plants, NF- κ B inhibition, inhibited oxidative stress: ROS↓, IL-1 β ↓, IL-6↓, restored collagen type II and ACAN, MMPs+ADAMTS↓ by TNF α model: SW1353 chondrocytes+TNF α	[87]
Grape seed oil, in combination with avocado	Grape seed oil, cartilage degradation↓, inhibits loss of chondrocytes, PGs, osteophytes↓, ROS↓, MMP-3, -13↓, nitrotyrosine↓, and IL-1 β ↓ model: ACLT rat	[142]
Green tea polyphenols, theanine	L-theanine, Epigallocatechin 3-gallate (=polyphenol), pro-inflammatory mediators↓, COX-2↓, PGE2↓, iNOS↓, NO↓, diverse MMPs↓, ADAMTS↓, MMP regulator CITED2, IL-1 β ↓, TNF α ↓, chemokine receptor (CCR)2↓, NF- κ B inhibition (p65 activation↓), OA lesions↓ (in vivo and in vitro) models: rat chondrocytes+IL-1 β , ACLT rats, DMM mice	[9,143,144]

(Continued)

Table 2 (Continued).

Compound	Effects/Models Used	Reference
<i>Harpagophytum procumbens</i>	<i>Harpagophytum procumbens</i> extract, MMP-1↓, -3↓, -9↓ induced by IL-1β, cannabinoid receptor (CBR)2↑, pain↓, probably via NF-κB and endocannabinoid system model: articular chondrocytes+IL-1β (human)	[145]
Icariin	Extract of Epimedium, NOD-, LRR- and pyrin domain-containing protein (NLRP)3/caspase-1 signaling mediated pyroptosis in OA models: rat articular chondrocytes+LPS, MIA rat	[146]
Isoliquiritigenin	Licorice flavonoids, progression of OA↓, bone resorption↓ and angiogenesis↓ in subchondral bone, MMP-2↓, Receptor Activator of NF-κB Ligand (RANKL)-RANK-TNF receptor associated factor (TRAF)6 signaling model: ACLT mice	[147]
Kaempferol	Polyphenolic component of diverse herbals and fruits. Co-treatment of kaempferol and apigenin: collagen IIa↑, aggrecan↑, SOX-9↑ gene expression. model: ACLT rat	[148,149]
Krill oil mixture with astaxanthin and HA	Serum levels of articular cartilage degeneration biomarkers cartilage oligomeric matrix protein (COMP)↓ and crosslinked C-telopeptide of type II collagen↓, TNF-α↓, IL-1β↓, IL-6↓, mRNA of iNOS↓, COX-2↓, MMP-2 and -9↓, in knee joint tissue, probably via NF-κB model: MIA rat	[150]
Olive-derived polyphenols	Olive, contains polyphenols: including hydroxytyrosol, tyrosol, oleocanthal and oleuropein anti-inflammatory, with antioxidant and autophagy-enhancing activities (via SIRT1) models: rabbit articular cartilage defect, human trials	[151]
Paeonia (P.) lactiflora and the gum resin of <i>C. myrrha</i>	Traditional medicines, <i>P. lactiflora</i> root and <i>C. myrrha</i> gum resin, NO↓, iNOS↓, IL-1β↓, IL-6↓, COX-2↓, cartilage erosion and subchondral bone damage↓ model: MIA rat	[128]
<i>Phyllanthus emblica</i>	Fruit extract, hyaluronidase and collagenase 2 activity↓, chondroprotection model: human OA articular cartilage explants	[90]
Quercetin	<i>Achyranthes bidentata</i> , (Quercetin, baicalein, and berberine are contained), inhibitors of TNFα and IL-6 signaling, and tumor suppressor protein (TP)53, inflammation↓, apoptosis↓ model: rat chondrocytes+IL-1β	[129]
Resveratrol	Grape seed extract, inhibits NF-κB signaling, TNFα↓, IL-1β↓, IL-6↓, IL-18↓, caspase-9/3 activity↓, SIRT1↓, PGE2↓ and NO↓, MMP-1↓, -3↓, -13↓, COX-2↓, collagen type II and ACAN restored, heme oxygenase 1 (HO-1) and nuclear factor erythroid 2-related factor 2 (Nrf-2)↑, hence, it negatively regulates genes involved in apoptosis, cell stress, autophagy, catabolism models: OA articular chondrocytes+IL-1β, MIA rat	[152,153]
Stinging nettle	Stinging nettle, MMP-1↓, MMP-3↓, MMP-9↓ Hypothesized: inhibits NF-κB signaling model: human articular chondrocytes+IL-1β	[154]
Sulforaphane	Vegetables, broccoli-derived isothiocyanate, regulates Nuclear factor (erythroid-derived)-like (Nrf2) and histone deacetylase activity, cytokine-induced MMP expression↓, inhibits NF-κB signaling models: SW1353, human articular chondrocytes+IL-1β and oncostatin, bovine nasal cartilage explants, DMM mice	[88]
Tanshinone	Traditional Chinese medicine Danshen, progression of OA↓, synovitis↓, restores collagen type II and aggrecan, apoptosis↓, MMP-13↓, ECM degradation↓ induced by IL-1β, probably via NF-κB models: CHON-001 fetal fibroblasts from bone and cartilage, immortalized with hTERT+IL-1β, ACLT mice	[89]

(Continued)

Table 2 (Continued).

Compound	Effects/Models Used	Reference
Trans-capsaicin	Chili peppers, improved pain with walking, knee stiffness, and physical function in OA patients with knee pain, Phase II study model: human patients	[6]
Thymoquinone	<i>Nigella sativa</i> , immunomodulatory, anti-inflammatory and anti-oxidant properties, IL-4 $\uparrow$, IL-10 $\uparrow$, survivin $\uparrow$, Bax $\downarrow$, cytokine levels: IFN- γ , TNF- α , COX-2, IL-6, IL-8, IL-12A and IL-16 depended on concentrations of thymoquinone, regulation of canonical pathways directly related to synaptogenesis, neuroinflammation, TGF- β , and interleukin signaling was predicted in silico model: human bone marrow MSCs and in silico analysis	[155]
Ursolic acid	Peels of fruits, herbs and spices, NF- κ B/NLRP3 inflammasome pathway, inhibits phosphorylation of AKT and p65 unit of NF- κ B, MMP-13 $\downarrow$, IL-1 β $\downarrow$, IL-6 $\downarrow$, P20 $\downarrow$, NLRP3 $\downarrow$ and prostaglandin-endoperoxide synthase 2 (PTGS2) $\downarrow$ restored ACAN and collagen type II, suppressed by TNF α models: rat articular chondrocytes, ACLT rat	[156]
Verbascoside	Eg in olives, pro-inflammatory cytokines $\downarrow$, targeting purinergic type 2 receptor (P2X7R) expression, production of MMPs, PGE2, NF- κ B signaling pathway $\downarrow$ model: MIA rats	[25]
Wogonin	Root extract of <i>Scutellaria baicalensis</i> , IL-6 $\downarrow$, COX-2 $\downarrow$, PGE2 $\downarrow$, iNOS $\downarrow$ and NO $\downarrow$, disrupts kelch-like ECH associated protein (KEAP)-1/Nrf-2 interaction models: human OA articular chondrocytes+IL-1 β , DMM mice	[115,157]
Yellow oil of <i>Zingiber montanum</i>	<i>Zingiber montanum</i> pain $\downarrow$ inhibition of COX and lipoxygenase (LOX) pathways, possibly via NF- κ B $\downarrow$ model: human patients	[45]

Abbreviations: ACAN, aggrecan; ACLT, anterior cruciate ligament transection; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AKT, protein kinase B; BAX, Bcl-2 associated protein X; CBR, cannabinoid receptor; CITED2, Cbp/P300 Interacting Transactivator With Glu/Asp Rich Carboxy-Terminal Domain 2; COX, cyclooxygenase; DMM, destabilized medial meniscus; ECM, extracellular matrix; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; KEAP, kelch-like ECH-associated protein; LOX, lipoxygenase; MAPK, MAP kinase; MIA, monosodium iodoacetate application; MMP, matrix metalloproteinase; MMx, medial meniscus removal; mTOR, mammalian target of rapamycin; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NO, nitric oxide; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; OA, osteoarthritis; PCLT, posterior cruciate ligament transection; PG, proteoglycans; PGE, prostaglandin E; PI3K, phosphoinositol-3 kinase; PTGS2, prostaglandin-endoperoxide synthase 2; P2X7R, purinergic type 2 receptor; RANK(L), Receptor Activator of NF- κ B (Ligand); ROS, reactive oxygen species; SIRT, Sirtuin; TRAF, TNF receptor associated factor; TP53, tumor suppressor protein 53; Wnt, wingless and Integration site-1.

purification strategies, local growth conditions of plants (eg, soil composition) and further, the often used oral application route which is associated with inhomogeneous intake and limited possibly, inconsistent bioavailability.¹³² On the contrary, one has also to consider that compounds when systemically uptaken have to pass the blood-joint barrier consisting of the connective tissue between synovial capillaries and synovocytes cell layers. The density of this barrier changes due to synovitis associated with OA.

Novel Synthetic Compounds as Candidates for OA Treatment: Nanoparticular Compounds and Antibodies

Candidate therapeutics for OA treatment are selected based on the current understanding of its molecular pathogenesis.³

Various nanoparticular compounds have been developed with putative implication in OA treatment.¹⁰ Nanoparticular compounds such as dendritic polyglycerol sulfates (dPGS) could act as anti-inflammatory agents in OA.^{74,100,158,159} A challenge for nanoparticular compounds is to penetrate the cartilage ECM for internalization by articular chondrocytes as key player cell population in OA which depends on their size, loading and binding motifs allowing receptor interaction for uptake into target cells.^{100,159} Particles with high affinity to the targets or even inflamed tissues are of particular interest.¹⁵⁹ Such compounds could act locally in the joint despite of being administered systemically impairing the overall risk of adverse effects adherent with this class of compounds.

Nanoparticles could also present a versatile slow release system and be combined with other agents. Rhein-

loaded pH-responsive nanoparticles have been developed.¹⁶⁰ pH responsiveness of loaded nanoparticles allows accumulation or even the release of the effective agent in inflamed tissue which are usually characterized by lower pH values.¹⁶⁰ Rhein has approved anti-inflammatory capacity.^{132,160} Nanoparticles were also used to deliver siRNA of 66 kDa proto-oncogene Src homologous-collagen homologue (p66shc) which is involved in cartilage degeneration in OA and known to mediate oxidative stress-induced apoptosis.¹⁶¹ By delivering p66shc-siRNA-loaded Poly(lactide-co-glycolide) (PLGA) nanoparticles into the osteoarthritic knee joints, mitochondrial dysfunction-induced cartilage damage was significantly impaired suggesting them as an option for the treatment of OA.¹²²

In addition to being effective, nanoparticles should be highly cytocompatible, or capable to be easily eliminated, eg, by self-degradation to disappear, and not to accumulate and produce unwanted adverse effects.

In addition to nanoparticles, other therapeutical compounds have been investigated such as the H₂S-producing enzyme 3-mercaptopyruvate sulfurtransferase (3-MST) which could be loaded in future on nanoparticles. H₂S generated by 3-MST protects against joint calcification and experimental OA progression. Hence, enhancing H₂S production in chondrocytes may represent a potential disease modifier to treat OA.¹⁶² Other compounds belong to the group of bisphosphonates such as tiludronate, which impaired pain, joint effusion, synovitis, MMP-13 and ADAMTS expression in OA knees of dogs suggesting efficacy in OA.¹⁶³

To directly neutralize harmful mediators upregulated in OA such as pro-inflammatory cytokine antibody therapy presents a strategy. Some antibody-based approaches have been developed. Antibody-based anti-cytokine therapy was effective in rheumatoid arthritis (RA) but bears also risks such as immunosuppression and malignancies.¹⁶⁴ However, anti-cytokine therapy like in RA was less effective in OA.⁴⁸ Antibodies against pro-inflammatory mediators including IL-1 β and TNF α have failed in recent OA clinical trials as reviewed by Mimpen and Snelling.⁶ Other options to utilize antibodies have been tested in OA such as anti-ADAMTS-5 monoclonal antibodies as a tool to directly inhibit aggrecanase in OA.²² Increased vascularization of the synovial membrane but also vessels penetrating into cartilage can be observed in OA and both are associated with increased vascular endothelial growth factor (VEGF) activity. Bortezomib, a vascular endothelial growth factor receptor 3 (VEGFR3) neutralizing antibody

reduced joint tissue damage in a mouse model of experimental PTOA, which was associated with improved synovial lymphatic function.¹⁶⁵

Antibody-based complement inhibitors could be interesting as OA therapeutics.^{36–38,166} Unfortunately, so far not enough is known about the role of distinct complement components in OA.³⁷

However, therapeutical antibodies have to be stable enough to be administered and one has to consider that this therapy is indeed expensive.

Anabolic Factors: Growth Factors and Hormones, Hormone Analogues

The insufficiency of chondrocytes to respond to different growth factors has been implicated in OA pathogenesis.¹⁶⁷ The anabolic growth factor insulin-like growth factor (IGF)-1 is important to maintain cartilage ECM homeostasis. The decreased levels of IGF-1 may play a critical role for the loss of the balance between catabolic and anabolic processes in cartilage metabolism during the development of OA. Thus, increasing IGF-1 may be applicable to restore homeostasis and as an approach in future OA therapy.¹⁶⁸

The anabolic growth factor fibroblast growth factor (FGF) 18 acts chondroprotective via regulating TIMP-1 expression and hence, inhibiting ECM degradation.^{48,169}

The female sex hormone estrogen is known to have chondroprotective effects.¹⁷⁰ Accordingly, estrogen deprivation by ovariectomy is used as OA model.⁶² A lack in estrogen explains the high predisposition of postmenopausal woman for OA.¹⁷⁰ Genistein is the major active component of isoflavone, with a chemical composition and a biological effect that is very similar to that of estrogens, which prevents the degradation of articular cartilage.¹⁷¹

Glucagon is an anabolic hormone regulating carbohydrate metabolism. The glucagon-like peptide-1 receptor (GLP-1R) leads to anti-inflammatory and anti-apoptotic effects in cartilage. Activating GLP-1R suppressed the NF- κ B pathway, decreased the release of pro-inflammatory key mediators (TNF α , IL-6), and reduced ECM catabolism in triglyceride-treated chondrocytes. These effects were reversed by GLP-1R knockdown.^{172,173}

Melatonin is an epiphyseal hormone strongly associated with the circadian rhythm. Melatonin was able to impair IL-1 β -induced MMP production by inhibiting SIRT1-dependent pathways in chondrocytes, suggesting melatonin as a potential therapeutic candidate in OA.¹¹⁰

Recently the putative involvement of melatonin, the hypothalamic hormone thyroid stimulating hormone (TSH), and suprarenal gland-derived cortisol have been implicated in OA pathogenesis with respect to influencing the circadian clock as reviewed by Hossain et al.¹¹¹ which opens a novel perspective on the multifaceted nature of OA pathogenesis.

The hormone oxytocin (OT) induced increased aggrecan, collagen type X, and COMP levels in vitro, and a normalization of cartilage markers such as SRY-box transcription factor 9 (SOX9) and collagen type II. There was a significant correlation between OA and impaired OT in rats. OT stimulated chondrogenesis. Systemic OT levels in the serum were also impaired in human patients with hand OA. This suggests that OT might be involved in the pathophysiology of OA.¹⁷⁴

The hormone prolactin and its cleavage products, the vasoinhibins, can be implicated in regulation of angiogenesis in OA. Prolactin could be a candidate for OA therapy.³⁷

Pain is the main symptom in OA impairing patient's life quality. Nerve growth factor (NGF) sensitizes pain sensory nerve fibers; hence, inhibition of its signaling pathway could modulate pain sensation.⁴⁸

Irisin represents a myokine which has also effects on cartilage. It is a cleaved form of fibronectin type III domain containing 5 (FNDC5), and normally regulates bone turnover and muscle homeostasis. A study revealed that human osteoarthritic articular chondrocytes express decreased level of FNDC5 and the autophagosome marker light chain (LC) 3-II, but upregulated levels of the oxidative DNA damage marker 8-hydroxydeoxyguanosine and apoptosis. Irisin repressed inflammation-mediated oxidative stress and ECM underproduction through retaining mitochondrial biogenesis, dynamics and autophagic program.¹⁷⁵

Recently, the small molecule kartogenin regulating the core binding factor subunit (CBF) β -RUNX1 pathway was reported to promote the differentiation of bone marrow (BM)-derived MSCs (BM-MSCs) into chondrocytes in vitro. Kartogenin exhibited chondroprotection when injected i.a. in two mouse models of OA.¹⁷⁶

A more comprehensive understanding of OA: influence of the microbiome

A more comprehensive image of OA becomes visible showing that OA is to some degree indeed a systemic

disease since systemic hormone and factor disbalances are involved in its pathogenesis as outlined before and also systemic cytokine levels are substantially changed in OA.¹⁸ The gut-associated microbiome contributes also to OA. In this regard a microbiome-joint connection has been postulated by Favazzo et al.¹⁷⁷ A dysbiosis of the gut microbial flora might trigger the systemic release of potentially harmful bacterial components which could affect the homeostasis of the joints making them more susceptible for OA development or progression. LPS might accumulate in response to microbiome imbalance (dysbiosis) and present a link by mediating low-grade inflammation between obesity and metabolic syndrome.⁵⁵ In this regard, the biotransformation of curcumin, for example, by gut microbiota might explain its beneficial health effects¹³⁸ and this important mechanism might also influence other compounds. Therefore, this interrelation has to be addressed in more detail in future.

Cell-Based Approaches in OA: MSCs

There exist already results from several clinical trials using MSCs in OA.^{178,179} MSCs have various protective effects which might be mediated by trophic mediators released by MSCs (Figure 3). Different MSC species can be applied either allogenic or autologous. Adipose tissue-derived mesenchymal stromal cells (ASCs) have the advantage of easy and less invasive accessibility by liposuction.¹⁷⁹ Intraarticular application (i.a.) of autologous ASCs without culturing them inhibited the progression of cartilage degeneration¹⁸⁰ but also allogenic ASCs expanded by culturing attenuated cartilage degeneration in an experimental rat OA model.¹⁸¹ Allogenic BM-MSCs were expanded under hypoxic conditions before injected in combination with HA into rat knees in a rat ACLT model leading to superior results compared to controls and revealing that an engraftment of MSCs into joint cartilage takes indeed place.¹⁸²

In contrast to these promising results, i.a. injection of xenogenic SF-MSCs did neither exert chondroprotection nor does it impair inflammation in ACLT-induced OA in the rat knee.¹⁸³

Encouraging were the results with allogenic amniotic MSCs which impaired OA progression in a synovial macrophage-mediated in vitro cartilage explant co-culture model.¹⁸⁴

The adipose tissue-derived stromal vascular fraction (SVF) represents a potent precursor cell population which can be harvested from adipose tissue.¹⁷⁹ SVFs have been tested as promising healing approach in OA.^{17,185} SVF fraction acts

Figure 3 Capacities which could stimulate cartilage healing exerted by mesenchymal stromal cells. The image was created by G. Schulze-Tanzil.

Abbreviations: FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IL, interleukin; LIF, leukemia inhibitory factor; MHCII, major histocompatibility complex II; MIP1α, macrophage inflammatory protein; NK, natural killer cells; NO, nitric oxide; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

anti-inflammatory in temporomandibular joint OA.¹⁸⁶ It was concluded that the i.a. application of SVFs to treat knee OA was safe and chondroprotective for the tested time period of 1 year. SVFs might induce a cascade of molecular and structural responses mediated through complex interactions between infrapatellar fat pad fatty tissue and SVFs, and enforcing the intraarticular fatty tissue back to homeostasis, protective, and anti-inflammatory functions, as an explanation for the inhibition of OA progression observed.¹⁸⁵

Chemokines

Chemokines are able to attract regenerative stem cells. The application of chemokines might be less invasive compared to preparing and injecting stem cells. The term of in situ tissue engineering was postulated to describe this strategy to support cartilage defect healing.¹⁸⁷ There are some hints indicating that chemokine signaling might be

disturbed in OA. The CXC-motif-chemokine receptor (CXCR) 4 which has probably chondroprotective capacities was downregulated by miR-146a in chondrocytes under inflammatory conditions. Its overexpression attenuated inflammation.⁴⁹ A comprehensive transcriptome analysis of OA versus non-OA samples with clinical data integration reflected that many chemokine genes were significantly downregulated under OA conditions.¹⁸⁸ On the contrary, the chemokine IL-8 (CXC motif chemokine [CXCL]8) was increased in synovial fluid and plasma of OA patients²⁶ and the chemokine CXCL1 contributed to pro-inflammatory IL-6 expression in OA SF mediated by the CXC-motif-chemokine receptor 2, rapidly accelerated fibrosarcoma (c-Raf), MAPK, and activator protein (AP)-1 signaling pathways.^{188,189} Hence, the intimate interplay between chemokine subtypes and other key pathways has to be further addressed in future.

Platelet-Rich Plasma

Platelet-rich plasma (PRP) contains growth factors and diverse mediators such as cytokines and chemokines. It is used for stem cell culturing and to promote tissue regeneration. The study of Mariani et al, 2020⁵¹ in SF summarizes reference data on the concentration and release kinetics of biomolecules that could represent potential specific effectors in the modulation of inflammatory processes and in tissue repair after treatment with PRP. Another research team reported that PRP combined with alendronate delayed OA progression by inhibiting the NF- κ B signaling pathway.¹⁹⁰

Conditioned Media

Chemokines, cytokines, growth factors are released by chondrogenic cells during culturing mediating paracrine signaling. Conditioned media (CM) harvested from cultured cells contain these diverse products of cells. Since CM can influence cell differentiation they have also been tested in OA models as therapeutic option. CM from notochordal cells, which represent embryonic precursor cells found as leftovers in the immature intervertebral disc cartilage, revealed protective effects in OA.¹⁹¹ CM of ASCs was also used for cartilage stimulation and found to be a promising treatment strategy for OA in experimental models.⁵⁷ CM contained also so-called exosomes harboring the above-mentioned mediators.

Extracellular Vesicles: Microvesicles and Exosomes

Exosomes and microvesicles are extracellular vesicles (EV), surrounded by a phospholipid membrane either cell membrane- or endosomal-derived, of different sizes (30–100 nm or 0.1–1 μ m). EVs are released by diverse cell types including those of the joint. EVs mediate paracrine cell-cell communication, being produced by cell membrane budding of donor cells and are internalized by recipient cells including joint-derived cells such as chondrocytes and SF.^{54,59,192} An uptake of ASC-derived EVs by SF and chondrocytes could be observed in in vitro co-culture models of SF and chondrocytes from the same OA patient which differed under 2D and 3D conditions. Interestingly, SFs showed a faster uptake of EVs than chondrocytes.⁵⁹

BM-MSC-derived EVs can prevent OA-associated catabolic features simulated by IL-1 β exposure by

reinduction of cartilage ECM marker gene expression such as collagen type II alpha 2 chain (COL2A1) and aggrecan (ACAN), inhibition of MMP and ADAMTS (MMP-13 and ADAMTS-5) gene expression, suppression of pro-inflammatory mediators such as NO production, apoptosis and macrophage activation, thereby modulating immune reactivity as shown in chondrocytes in vitro.^{54,192}

Chondrocyte proliferation and migration capacity were also restored by EVs in vitro.⁵⁴ Using the rat MIA OA model, exosome treatment significantly reconstituted collagen type II and impaired MMP-13 protein expression in the knee joint cartilage of the OA rats.⁵⁴

ASCs are easier to harvest compared to BM-MSCs. Nevertheless, also ASC-derived EVs are effective in modulating features associated with OA. Activated SF treated with exosomes suppressed their expression of pro-inflammatory mediators such as IL-6, NF- κ B and TNF α , while the expression of anti-inflammatory IL-10 was elevated.¹⁹³ Exosomes can be used clinically,¹⁹⁴ being harvested by sequential centrifugation techniques from cultured MSCs before i.a. injected.¹⁹² The immunogenicity of EVs, since they expose membrane proteins on their surface, remains unclear, and hence, the necessity to isolate them from autologous cell populations. Nevertheless, EVs can also be isolated from autologous plasma or serum.¹⁹⁵ The treatment of chondrocytes with EVs isolated from autologous blood products (hyperactive serum and citrate-anticoagulated PRP) induced the expression of anabolic markers such as the chondrogenic transcription factor SOX9, type II collagen and aggrecan, compared to the original complete full blood products, but it induced also the ECM degradative MMP-3. The blood product-derived EVs but not the blood product itself increased SOX9 protein expression and inhibited IL-6 release in human chondrocytes from OA patients.¹⁹⁵

The content of EVs depends on diverse factors, such as cell source, culturing time and conditions and this might explain some heterogeneity of results studying the effect of EVs and their perspective for OA.^{91,196,197} In addition to diverse proteins, lipids, cytokines and chemokines, they contain also mRNA or miRNA.¹⁹⁸ However, contents depend largely on the methods of purification. An important question to be answered in future concerns whether these particles are able to penetrate the cartilage ECM.

Restorage of Joint Function by Viscosupplementation and Restored Osmolarity

Viscosupplementation implies the application of natural components of cartilage ECM and synovial fluid to restore its viscoelastic properties and provide lubrication of joint cartilage surface to reduce friction. HA is most important for this unique properties of the synovial fluid. In a healthy joint, it has a content of 2–4 mg/mL HA with an MW of 4–6 MDa.¹⁹⁹ Hence, viscosupplementation is mostly based on application of HA which represents a well-established OA therapy,²⁰⁰ but other compounds such as glucosamine are also proposed.^{201,202} HA is a natural non-sulfated high molecular weight (MW) glycosaminoglycan (GAG)²⁰³ with broad medical application.⁵³ In OA, the content of HA in the synovial fluid is reduced which, hence, loses its viscoelasticity/thixotropic properties²⁰³ and is not any longer able to impair friction during joint movement. It gets a lower MW during aging.²⁰³ HA is responsible to maintain aggrecan aggregates of sufficient sizes in the cartilage ECM.²⁰⁴ It exerts anti-inflammatory, -apoptotic, -catabolic, -nociceptive and anabolic effects.^{205–207} HA binding to chondrocytes is mediated by the HA receptor,

CD44.²⁰⁴ The full mechanism of action of exogenous HA is uncertain, but studies indicate that it may promote endogenous HA production, reduce joint inflammation, prevent degeneration of cartilage and facilitate its healing.²⁰⁸

However, there exist diverse variants of HA²⁰³ possessing different MWs.²⁰⁹ High MW would provide longer lasting protective effects in OA-affected joints.²¹⁰ The capacity of HA to penetrate the cartilage ECM and directly modulate chondrocyte activity remains a matter of debate. A drawback of HA therapy is the preferred i.a. application route. Multiple HA injections are recommended to achieve effects of sufficient duration.²¹¹ Hence, in regard to the necessity of multiple i.a. injection which bears the risk of joint infection longterm stability of HA is desired which can be achieved by cross-linking, eg, represented by Hylan G-F.^{202,212} HA, but also chondroitin sulfate as another effective GAGs for viscosupplementation, have extensively been tested in rat OA models.⁶⁹ Chondroitin sulfate has been used for years to ameliorate OA as reviewed in detail by Mimpen and Snelling.^{6,69} Another compound used since many years for viscosupplementation in OA is glucosamine, an aminosugar of the natural cartilage ECM.²¹³

Lubricin (also called proteoglycan 4 [Prg4]) is naturally produced by superficial zone articular chondrocytes

Table 3 Some miRNAs with Implication in OA Restricted to 2018–2020

Type	Implication	Reference
miR-140	Promoting cartilage formation↑, inhibiting degeneration↓, role in chondrogenesis (MSCs)	[227]
miR-23b-3p	Promotes ECM degradation by activating p38 MAPK in chondrocytes and OA cartilage	[228]
lncRNA HOTAIR	Silencing inhibited Wnt/β-catenin pathway, declined synovial inflammation and synoviocyte proliferation, and promoted apoptosis in OA rats	[229]
miR-103a-3p	Upregulation: cell proliferation↑, apoptosis↓, inflammation↓, caspase-3↓, Poly(ADP-ribose)-Polymerase (PARP)↓, IL-1β↓, IL-6↓, IL-10↓ and TNF-α↓. High mobility group box 1 (HMGB1), an inflammatory mediator of OA, is a target of miR-103a-3p	[230]
miR-145 and miR-221	Upregulation of miR-145 and miR-221: proliferation of periosteal cells↑ and chondrogenic potential↑. Evidence in support for the use of patient-derived exosomes (from ASCs), for potential amelioration of OA	[193]
miR-136-5p	BM-MSC-derived exosomal miR-136-5p: chondrocyte migration↑ in vitro and cartilage degeneration↓ in vivo, OA pathology↓	[231]
miR-495	CircSERPINE2 could mediate TGFBR2 expression by binding with miR-495. As a conclusion, CircSERPINE2 attenuated IL-1β-caused apoptosis and ECM degradation of chondrocytes by regulating miR-495/TGFBR2 axis → new target for OA treatment.	[232]
miR-17-5p	OA cartilage and IL-1β-induced chondrocytes: miR-17-5p↓, Fucosyltransferase (FUT) I↑	[233]
miR-296-3p	CircCDH13 contributes to OA pathogenesis by acting as a sponge of miR-296-3p and regulating the miR-296-3p-PTEN pathway. Silencing of CircCDH13: chondrocyte apoptosis↓, ECM catabolism↓, anabolism↑, in vivo: alleviated OA.	[234]

Abbreviations: ASC, adipose tissue-derived mesenchymal stromal cells; FUT, Fucosyltransferase; HMGB1, High mobility group box 1; i.a., intra-articular; MAPK, MAP kinase; miR, microRNA; PARP, Poly(ADP-ribose)-Polymerase; TGFBR2, Transforming growth factor β receptor 2; Wnt, wingless and integration site-1.

and SF in the joint and important for cartilage lubrication to minimize friction during movements within the joint. Gene therapy by inducing overexpression of the Prg4 gene in the joint was protective in OA.^{214,215} Gene therapy was also performed by combination of Prg4 and interleukin receptor antagonist (IL-1ra) genes which protected against hyperalgesia and cartilage degeneration in the PTOA model.²¹⁶ The receptor antagonist transgene was also tested locally in an equine OA joint model leading to substantial increase in IL-1ra mediating reduced lameness, lesser joint pathology revealed by imaging, alleviated synovitis and improved healing of osteochondral lesions whereas no systemic increase in IL-1ra was observed.²¹⁷

Adaption of dysbalanced osmolarity could present a future strategy in OA therapy. Osmolarity intimately regulates growth factor expression.^{218,219} Decreased

osmolarity contributes to sustained inflammation and catabolic activities in OA chondrocytes and impairs their responsiveness to the growth and differentiation factor (GDF)-5. This suggests that osmolarity represents a critical factor in OA pathogenesis²²⁰ and should be further addressed. HA is often combined with other therapeutic agents,²²¹ eg, cells²²² or chemokines.²²³

Genetic Regulators of Inflammatory/Catabolic Gene Expression

Genetic and epigenetic regulation has been implicated in OA pathogenesis.²²⁴ OA-associated epigenetic aberrations have been recognized at the level of DNA methylation and histone modification in chondrocytes.²²⁵ DNA methylation is known to destinate gene expression as reviewed by Kim et al.²²⁶

Figure 4 Synopsis of some current experimental therapeutic strategies in OA. **(A)** viscosupplementation such as i.a. application of HA to improve gliding properties of damaged cartilage as well as stimulate regenerative capacity of chondrocytes. **(B)** application of MSCs with immunomodulatory and trophic properties. **(C)** administering antibodies to inhibit inflammatory pathways in the joint. **(D)** provide exosomes as vehicles for chondroprotective cellular products. **(E)** apply microparticles. **(F)** give nanoparticulate compounds with anti-inflammatory properties. **(G)** apply inhibitory and regulatory small RNA or DNA interfering with inflammatory pathways in the joint. **Abbreviation:** i.a., intraarticular; miRNA, micro ribonucleic acid; MSC, mesenchymal stromal cells; siRNA, small interfering ribonucleic acid. The image was created by G. Schulze-Tanzil using Krita 4.1.7 software.

Micro RNAs (miR) are important regulators of gene expression. They represent a class of regulatory but non-coding RNAs (around 22 nucleotides in length). Despite the knowledge about their regulatory network is still limited a growing number of miRs has been implicated in OA pathogenesis based on their aberrant expression profiles under OA conditions (Table 3). miRs and small interfering RNAs (siRNAs) could present future tools in OA therapy being, eg, combined with nanoparticles, microvesicles or other carriers.^{122,193} Limitations to be addressed in future could be to maintain stability and achieve sufficient high local concentrations of therapeutical miRNAs.

Conclusion

It has to be considered that OA is a systemic and generally heterogenous disease.^{7,46} Many players (growth factors, diverse hormone networks, circadian clock factors, gut microbiome, nutrigenomics, epigenetics: eg miRs ...) and several dysregulated signaling pathways are involved in its pathogenesis which might differ dependent on individual patients. NF- κ B dysregulation seems to play a major role. There exist meanwhile various novel or further optimized experimental strategies to alleviate OA progression (Figure 4). Approaches for treatment have possibly to be adapted in future to disease subtypes and individual patients. Hence, personalized OA therapy should be a future vision.

Abbreviations

ACAN, aggrecan gene; ACL, anterior cruciate ligament; ACLT, anterior cruciate ligament transection; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AKT, protein kinase B; AMPK, Adenosine monophosphate-activated protein kinase; AP-1, activator protein-1; ASCs, adipose tissue-derived mesenchymal stromal cells; Aqp, aquaporin; BM, bone marrow; BM-MSCs, bone marrow-derived mesenchymal stromal cells; BMI, body mass index; CBF β , core binding factor subunit β ; CM, conditioned media; COL2A1, gene for alpha1 chain of collagen type II; COMP, cartilage oligomeric matrix protein; COX, cyclooxygenase; CXCR4, CXC-motif-chemokine receptor 4; DMM, destabilized medial meniscus; dPGS, dendritic polyglycerol sulfates; ECM, extracellular matrix; ERK, extracellular signal regulated kinase; EV, extracellular vesicles; FGF, Fibroblast growth factor; FNDC5, fibronectin type III domain containing 5; FoxOs, Forkhead box O; FUT1, Fucosyltransferase 1; GAG, glycosaminoglycans; GDF, growth and differentiation factor; GLP-1R, glucagon-

like peptide-1 receptor; GM-CSF, granulocyte-macrophage colony stimulating factor; HA, hyaluronan; HGF, hepatocyte growth factor; IPF, intrapatellar fat pad; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; iNOS, inducible nitric oxide synthetase; IGF-1, insulin-like growth factor-1; KEAP, Kelch-like ECH-associated protein; LCL, lateral collateral ligament; LIF, leukemia inhibitory factor; LPS, lipopolysaccharide; MAMTL, medial anterior meniscotibial ligament; MAPK, MAP kinase; MCL, medial collateral ligament; MHCII, major histocompatibility complex II; MIA, monosodium iodoacetate; MIP1 α , macrophage inflammatory protein; miRNA, micro ribonucleic acid; MMP, matrix metalloproteinase; MMT, medial meniscus transection; 3-MST, 3-mercaptopyruvate sulfurtransferase; mTOR, mammalian target of rapamycin; MW, molecular weight; NGF, nerve growth factor; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NK, natural killer cells; NO, nitric oxide; Nrf, Nuclear factor (erythroid-derived)-like; OA, osteoarthritis; OT, oxytocin; PARP, Poly(ADP-ribose)-Polymerase; PCL, posterior cruciate ligament; PG, proteoglycan; PGE, Prostaglandin E; Pink1, PTEN induced kinase 1; PI3K, phosphoinositol-3 kinase; PRP, platelet-rich plasma; PTGS2, prostaglandin-endoperoxide synthase 2; PTOA, posttraumatic OA; P66shc, 66 kDa proto-oncogene Src homologous-collagen homologue; RANK(L), Receptor Activator of NF- κ B (Ligand); Raf, rapidly accelerated fibrosarcoma; ROS, reactive oxygen species; RUNX, runt related transcription factor; SF, synovial fibroblasts; SIRT, sirtuin; siRNA, small interfering ribonucleic acid; SOX9, SRY-box transcription factor 9; SVF, stromal vascular fraction; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TLR, Toll like receptor; TIMP, tissue inhibitors of metalloproteinases; TNF, tumor necrosis factor; TRAF, TNF receptor associated factor; TSH, thyroid stimulating hormone; VEGF, vascular endothelial growth factor; VEGFR3, vascular endothelial growth factor receptor 3; Wnt, wingless and integration site-1; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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