Review

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A brief review of current treatment options for osteoarthritis including disease-modifying osteoarthritis drugs (DMOADs) and novel therapeutics

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Abstract

Osteoarthritis (OA) is a chronic disorder caused by degenerative changes in articular cartilage, which are mainly manifests as degeneration of cartilage, subchondral bone remodeling, as well as synovial inflammation. Over the next few decades, OA and its burden will continue to increase worldwide, posing a major public health challenge for the foreseeable future. Treatment for OA includes non-pharmacological, pharmacological, and surgical treatments. Existing conservative treatments and joint surgery can only alleviate the symptoms and cannot be cured, so new therapies for OA are urgently needed. Since advances in the understanding of OA pathophysiology, researchers have identified some potential therapeutic targets against degeneration of cartilage, subchondral bone remodeling and synovial inflammation, enabling development of the disease-modifying OA drugs (DMOADs). Additionally, a number of new technologies are also being investigated for treating OA, such as RNA interference (RNAi), CRISPR/Cas9 and PROTAC. The goal of this review is to describe the current development status of DMOADs and to discuss the potential of emerging therapeutic approaches for treating OA, thus providing a reference for OA treatments.

Keywords: CRISPR/Cas9, disease-modifying OA drugs, osteoarthritis, PROTAC, RNAi

Introduction

Osteoarthritis (OA), a degenerative joint disease, poses serious health risks to patients, with the main symptoms of joint pain and tenderness, limited joint motion, and joint deformities, which will impose a heavy economic burden on individuals and society. Multiple risk factors contribute to OA, including aging, sex, and increased BMI and prior joint injury, which is the leading cause of physical disability in the world[1]. It is estimated that most people usually suffer from OA when they are 40–50 years old, and 9.6% of men and 18.0% of women older than 60 years of age have symptomatic OA worldwide[2]. Due to the aging of the population and the increasing prevalence of obesity, OA incidences are also increasing.

HIGHLIGHTS

- Osteoarthritis (OA) is a very common and poses serious health risks to patients, thus new drugs are needed to alleviate OA symptom and progression.
- Degeneration of cartilage, subchondral bone remodeling, as well as synovial inflammation are the main characteristics of OA, so as the important targets for treatment of OA.
- The clinical heterogeneity of OA needs to develop disease-modifying OA drugs (DMOADs) to relieve pain or improve patients' physical function.

Current OA management focuses on relieving pain, delaying disease progression, restoring joint function, and improving the quality of life of patients using anti-inflammatory drugs (NSAIDs), opioid analgesics, and intra-articular injection steroids and hyaluronic acids. In most cases, surgical restorative interventions are only a last option. The disease-modifying OA drugs (DMOADs) hold the most promise for treatment OA, which targeting key factors for the pathologic process of OA, aiming to inhibit the deterioration in the biological, structural of joint and improving physical function, not only reducing pain. Currently, DMOADs delays cartilage degeneration by targeting inflammatory factors, matrix-degrading proteases, Wnt signaling pathway or promoting cartilage repair factors. Additionally, drugs based

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on RNAi, CRISPR/Cas9, and PROTAC are being developed to stimulate cartilage regrowth.

The objective of this review is to summarize the evidence supporting the role of drugs in OA pathology, as well as to review potential mechanisms within each of these drugs to develop disease-modifying therapeutics. The literature search was conducted on the search engines PubMed and keywords included osteoarthritis and DMOADs.

Inhibition of the degeneration of cartilage

Inhibition of extracellular matrix degradation

The degradation of extracellular matrix including type II collagen and the proteoglycan aggrecan, which are important features of OA. Targeting cartilage matrix degradation is a fully explored field of drug discovery. Study has been demonstrated that dual deletion of ADAMTS-4 and ADAMTS-5 generated mice significant protection against proteoglycan degradation and decreased the severity of murine OA[3,4]. Thus, these key enzymes of anabolic and catabolic pathways, such as MMPs, ADAMTS-4 and ADAMTS-5 protease, which regulate ECM in the cartilage, have potential to be as drug targets.

MMP-13 is expressed specifically in OA cartilage, whereas normal adult cartilage is not, thus MMP13 has been the focus of the most research in OA. ALS1-0635, an MMP-13 inhibitor, has been found to inhibit bovine articular cartilage degradation in a dose-dependent manner (48.7% and 87.1% inhibition at 500 nM and 5000 nM, respectively). The results of intra-articular injection of ALS1-0635 into a model of cartilage damage rat knee joint indicated that the area of cartilage damage in the ALS1-0635 treated rats was significantly reduced compared with vehicle-treated rats[5]. Another inhibitor of MMP13 is PF152, which has been demonstrated to reduce cartilage lesions and increase biomarkers of type II collagen and aggrecan in adult dogs with OA[6]. In a clinical trial involving human subjects, the MMP inhibitor PG-116800 was administered to patients with knee osteoarthritis. Following a year of treatment, there was no discernible difference of statistical significance in the joint space width of the knee or the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) between the placebo group and the group receiving PG-116800. Furthermore, the side effect rate of musculoskeletal toxicity was 35%, suggesting that the MMP inhibitor is unsuitable for use in osteoarthritis[7]. Thus, in spite of the fact that those MMP inhibitors may provide significant therapeutic benefits in OA animal model, all clinical trials of MMP inhibitors have failed, thus no such molecules have been approved by the FDA, indicating that there are still need for alternative drug candidates and therapeutic targets.

ADAMTSs, a group of zinc metalloendopeptidases, are involved in a wide range of biological processes, including but not limited to procollagen processing, extracellular matrix remodeling, inflammation, cell migration, and vascular biological processes. Aggrecan is susceptible to cleavage by various members of the ADAMTS family, such as ADAMTS1, ADAMTS4, ADAMTS5, ADAMTS8, and ADAMTS15. In particular, the significant protective outcomes observed in surgically induced OA mouse models through Adamts5 gene knockout and the use of ADAMTS5-specific antibodies underscore the predominant role of ADAMTS5 as the primary enzyme responsible for aggrecan degradation in OA. Recently, blocking ADAMTS5 catalytic activity and reducing cartilage damage by antibody-based inhibitors, such as CRB0017, GSK2394002, and M6495 have demonstrated promising effectiveness in the treatment of OA *in vivo*[8].

M6495, an antibody that exhibits selective binding to ADAMTS5, has a high affinity KD of 3.65 pM. In OA human cartilage, the IL-1α induced GAG release was dose-dependently inhibited by M6495, the oncostatin M (10 ng/ml) + TNFα (20 ng/ml) induced huARGS release in healthy human cartilage was inhibited by M6495 at 50 nM[9]. Therefore, M6495 shows the protective effect of cartilage *in vitro* by inhibiting the degradation of cartilage mediated by ADAMTS-5 and the whole cartilage degradation in a dose-dependent manner. To assess the safety, two randomized, placebo-controlled, double-blind studies were performed. Pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple injections of M6495 was detected in healthy volunteers and patients with OA. M6495 in single and multiple doses of less than or equal to 300 mg s.c. weekly was well tolerated with no clinically significant changes in any safety parameter. Adverse events reported more frequently in the M6495 groups were primarily mild cases of injection site reactions, myalgia, and nausea, which resolved following cessation of treatment[9,10]. These results suggested that M6495 is safe enough for further clinical evaluation.

GSK2394002 were generated with specific targeting capabilities towards both ADAMTS-5 and ADAMTS-4, and their efficacy in inhibiting and modulating OA was evaluated. After systemic administration of GSK2394002 in an OA model, the results showed that monoclonal antibodies could penetrate cartilage to the anticipated site of action. In accordance with research on knockout mouse, the functional results indicated that the cartilage degradation and pain-related behavior were significantly alleviated after treatment with GSK2394002[11]. However, as a result of potential adverse reactions, the majority of antibodies do not meet preclinical expectations, with only a limited number currently undergoing or having advanced beyond phase 1 clinical trials. GLPG1972/S201086, a potential ADAMTS-5 inhibitor developed by Brebion and colleagues, which displayed high potency against ADAMTS-5 in a mouse cartilage. Furthermore, GLPG1972/S201086 evinced a decrease in proteoglycan loss and subchondral bone sclerosis while also promoting the repair of cartilage injury in menisectomized rats[12]. Clinical trials involving GLPG1972/S201086 have been conducted in patients with knee osteoarthritis in phase 2 (NCT03595618), which started in August 2018 and was completely recruited (N = 938) by June 2019. Nevertheless, the findings from a phase 2 randomized clinical trial revealed that S201086/GLPG1972 did not yield statistically significant reductions in cartilage loss rates or symptom modification among adults with symptomatic knee osteoarthritis, even though the study included participants who had experienced considerable cartilage loss over a span of 52 weeks[13].

Taken together, the target of inhibition of ECM degradation such as ADAMTS4, ADAMTS5, MMP13 are effective therapeutic targets for OA at the animal experiment level. However, in the clinic, the inhibitors of MMP13 exhibited severe side effects, suggesting that the MMP13 is not an ideal target or the inhibitors have multiple targets that could induce side effects. Meanwhile, the effect of ADAMTS4 and ADAMTS5 inhibitors are not good, suggesting that it is necessary to find some new small-molecule drugs for that target ADAMTS4 and ADAMTS5.

Inhibition of Wnt pathway

Wnt family is a highly conserved secreted signaling pathway, which contributes to regulating the differentiation of chondrocytes and maintenance of metabolic balance between catabolism and anabolism in joint[14]. Wnt proteins can activate different signaling pathways, including the classical Wnt/β-catenin signaling pathway and non-classical Wnt pathway. During the progression of OA, the differentiation of proliferating chondrocytes into hypertrophic chondrocytes is accelerated, which is usually accompanied by the activation of the classical Wnt/β-catenin signaling pathway[15]. Key molecules of Wnt signaling pathway such as Wnt3a, β-catenin, Wnt16, Wnt2, Wnt3a and Wnt5b are found to be highly expressed in OA cartilage, and the antagonists of Wnt signaling pathway such as osteopenin, Sirt1 and WISP-1 are down-regulated, while collagen II was reduced[16,17]. Activation of Wnt/β-catenin signaling pathway increases of the expressions of metalloproteinases, leads to the degradation of the extracellular matrix, which in turn leads to the development of OA[18]. Thus, the Wnt signal is a promising target for osteoarthritis treatment.

Loricivint (LOR), formerly known as SM04690, showed a protective effect on cartilage in the process of joint destruction in the preclinical model of knee OA by inhibiting the Wnt signaling pathway of CDC-like kinase 2 (CLK 2) and bispecific tyrosine phosphorylation kinase 1 a (DYRK 1A) which are the key regulators in the Wnt signaling for regulation of chondrogenesis and inflammation[18]. Additionally, LOR exhibited an upregulation of Wnt16 expression, along with cartilage anabolic factors, namely COL2A1, SOX9, and aggrecan, while concurrently suppressing the expression of cartilage catabolic factors. Furthermore, LOR demonstrated a protective effect on chondrocytes against TNF-α-induced inflammatory response. *In vivo*, LOR increased the quantity of superficial zone cells in the temporomandibular joint condyle, thereby underscoring the therapeutic potential of LOR in the context of temporomandibular joint osteoarthritis (TMJOA)[19]. In a previous 52-week Phase II trial (NCT 02536833), a total of 695/700 subjects received treatment, which indicated that the symptoms of unilateral knee OA were significantly improved compared with placebo. Comparison Procedure-Modeling (MCP-Mod) identified that 0.07 mg LOR was the lowest effective dose[20,21]. Subsequently, the safety and efficacy of 0.07 mg LOR was evaluated in a Phase 3 28-week trial (OA-10, NCT04385303). The results showed that LOR seemed to be safe and well tolerated, but it did not reach the primary or secondary end point of the trial. Therapeutic signals were found among participants with less serious structural disease, indicating that early intervention may be more effective. Future trials of LOR in the treatment of knee OA will focus on less serious structural disease and evaluate higher dose (0.23 mg LOR).

Verapamil, an FDA-approved drug, which was a commonly prescribed calcium channel blocker that suppressed Wnt/β-catenin signaling in human OA chondrocytes. Takamatsu *et al.*[22] demonstrated that Verapamil increased the expression of FRZB, a soluble antagonist of Wnt signal transduction, which led to the improvement of Wnt3A-induced proteoglycan loss in chondrogenically differentiated ATDC5 cells. Further experiments confirmed that as well as inhibiting hypertrophic differentiation of mouse chondrocytes in an explant culture of mouse tibia, verapamil also inhibited nuclear localization of β-catenin in a rat OA model, thus inhibiting OA progression[22].

Wnt signaling pathway is a complex protein network, whose function is most common in embryonic development and cancer, but it also participates in the normal physiological process of adult animals. Although inhibitors specific target to Wnt signaling pathway have exhibited ani-OA effect in the clinic or animal experiment, it will take further investigations to determine whether inhibitors like Verapamil is safe and therapeutically effective.

Promotion of cartilage repair

LNA043, a derivative of angiopoietin-like 3 (ANGPTL3), has been identified as a potential drug for the treatment for OA, because it can promote the cartilage formation by regulating primary human bone marrow mesenchymal stem cells and promoting the synthesis of cartilage matrix in rat and pig models. Researchers found that LNA043 combined with recombinant integrin α5β1 mediated the secretion of WNT signal inhibitor Dkk1 in chondrocytes of human OA cartilage, suggesting that LNA043 induces cartilage repair by binding to integrin α5β1 receptors on chondrocytes[23]. The first human clinical trial enrolled 28 patients with knee OA for intra-articular injection of LNA043 or placebo 2 h, 7 days, or 21 days before total knee replacement. LNA043 was found to be safe and well tolerated, consistent with the primary safety end point of the trial[23]. In comparison to patients taking placebo, transcriptome analysis of cartilage collected from post-operatively patients treated with LNA043 showed that anabolic signaling pathways were stimulated. Treatment with 20 mg LNA0434 weekly injected by i.a. (NCT03275064) resulted in regeneration of cartilage in patients with femoral articular cartilage lesions indicating that LNA0434 could be a new disease-modifying OA drug candidate[24]. LNA043 is currently being evaluated in phase 2b trials (NCT04864392).

In 2012, Johnson *et al.*[25] developed Kartogenin (KGN), a small molecule intended for the regeneration of cartilage. KGN shows chondroprotective effects through promotes chondrocyte differentiation in the OA animal models. The mechanism studies showed that KGN binds to vitamin A, destroying its interaction with the transcription factor core binding factor β subunit (CBFβ), and regulating cartilage formation by regulation of CBFβ-RUN1 transcription program. Furthermore, KGN was found to promote chondrogenic differentiation of human umbilical cord MSCs mainly by activating the JNK/Runt-related transcription factor (RUNX)1 pathway, and suppressing the b-catenin/RUNX2 pathway[26]. Upon enzymatic cleavage, KGN can be converted into 4-aminobiphenyl (4-ABP) and phthalic acid (PA). One study indicated that oral or intra-articular delivery of KGN effectively improved the OA phenotype of mice, but only 4-ABP could be detected in cartilage. Subsequent investigation revealed that 4-ABP has the capacity to stimulate chondrogenic differentiation and proliferation of mesenchymal stem cells *in vitro* by augmenting the population of CD44 + /CD105 + stem cells and impeding matrix degradation, thereby facilitating the restoration of cartilage in a mouse model of OA. Based on transcriptional profiling, RPS6KA2 and the PI3K-Akt pathway were identified as 4-ABP targets, and 4-ABP could promote stem cells proliferation and repair OA damage by activating the PI3K-Akt pathway, suggesting that 4-ABP is the main active substance of KNG and KGN promotes proliferation of stem cell and

chondrogenic differentiation, as well as osteoarthritic repair through RPS6KA2 and PI3K-Akt signaling pathway[27]. Recently, in order to improve potency and chemical stability of KGN, an analog of KGN was developed and named as KA3475 which showed excellent safety and cartilage protection. A phase I trial of KA34^{75} on 60 OA patients (NCT03133676) has recently been completed, but the results have not yet been published[28].

Additionally, a recombinant human fibroblast growth factor 18 (rhFGF18) known as Sprifermin, has also been verified to promote anabolic growth in articular cartilage, which is considered promising DMOADs. Intra-articular injections of sprifermin to patients with KOA significantly improvement of WOMAC total scores, compared with the placebo. Patients' treatment with sprifermin gained more cartilage thickness and volume in total femorotibial joint and showed no specific adverse effects. Thus, well-designed phase 3 clinical trials are needed to evaluate its effects on symptoms and cartilage loss in KOA[29].

The Krüppel-like factor (KLF) family of transcription factors is composed of 17 members in mammals and is involved in various biological and pathological mechanisms. Among them, KLF4 has been reported to enhance expression of chondrogenic genes in human chondrocytes, meniscal cells, and BM-derived mesenchymal stem cells (BMSCs), including SOX9, COL2A1 and ACAN, COMP, and PRG4. Meanwhile, KLF4 suppresses the expression of inflammation and ECM-degrading enzymes, such as ADAMTS5, MMP3, MMP13, IL-6, and PTGS2, in human chondrocytes, meniscal cells, and synovial cells. Thus, molecules increasing KLF4 expression would be novel therapeutic candidates for OA. Through high-throughput screening with 11 948 clinical-stage compounds, small molecules mocetinostat, a selective histone deacetylase (HDAC) inhibitor, was identified to upregulate the expression of KLF4 and regulate the expression of anabolic and catabolic genes, which served as a candidate to be used as a DMOAD[30].

OA is characterized by the degeneration or damage of articular cartilage, which has very limited ability to self-heal after damage or degradation because of its avascular nature. Thus, articular cartilage repair is considered one of the most challenging in in clinical orthopedics. Small molecules that enhanced the chondrogenic ability of chondrocytes or BMSCs with low side effects may be ideal DMOADs for OA, such as rhFGF18, which has also been repeatedly proved to have a beneficial effect on OA and promote cartilage healing. Merck initiated the first clinical trial of recombinant human FGF18 (Sprifermin) for the treatment of OA and the effector genes of FGF18 in OA were also confirmed, which brings us hope for the treatment of OA in the future.

Inhibition of inflammatory response

It is important to note that inflammation is associated with both the onset and development of OA. Reducing inflammation is one of the key goals in treating OA. Metformin is widely used as a first-line drug in the treatment of type 2 diabetes because of its good efficacy, safety and tolerance. At the same time, it also suggests that metformin has anti-inflammatory and anti-aging effects, which shows that metformin has great potential in treating OA[31]. A comparative analysis involving more than 40 000 patients with type II diabetes found that compared with non-users, the risk of joint replacement of users of metformin was reduced by about 30–40%, which indicated that metformin might have a protective effect on cartilage. On the middle meniscus instability (DMM) model induced by high-fat diet, metformin not only directly affect articular chondrocytes to reduce their apoptosis and the expression of matrix-degrading enzymes, but also reduce OA by inhibiting the infiltration of synovial macrophages and the polarization of pro-inflammatory macrophages. In obese mice, metformin can also play a combined protective role by reducing the secretion of leptin, which suggests that metformin has good therapeutic potential for obese OA patients and the AMP-activated protein kinase (AMPK) and growth differentiation factor 15 (GDF-15) can be potential therapeutic targets for OA[31,32].

TPCA-1 and Tofacitinib (Tofa) are the inhibitors of κB kinase (Ikk) and Janus kinases (Jak), respectively. A preclinical experiment showed that the TPCA-1 and Tofa significantly prevented cartilage degradation and rescued type II collagen production when inflammation is present, which reduced the loss of proteoglycans induced by inflammation and decreased AGNx1 release compared to controls 43- and 32-fold, respectively[33]. The preclinical data indicate that TPCA-1 and Tofa are capable of protecting cartilage ECM under inflammatory conditions and could eventually be used as DMOADs to treat inflammation-induced OA.

A number of inflammatory cytokines are responsible for the development and progression of OA, which is characterized as an inflammatory disease. Inflammatory cytokines and relative signaling pathways are considered related to the pathogenesis of KOA, which plays an important role in cartilage matrix degradation and bone destruction. Metformin can protect cartilage by reducing the secretion of leptin through regulating AMPK signaling pathway with good safety and tolerance. The inhibitors of Ikk and Janus kinases Jak also have displayed chondroprotective effects in various animal models. These studies suggested that inhibitors for inflammatory response have potential to be as DMOADs. However, inhibiting inflammation has been proved to reduce the progress of OA, but it usually shows little cartilage repair ability.

Inhibition of abnormal remodeling of subchondral bone

OA is acknowledged as a joint disease that impacts the entire joint, with the subchondral bone playing a pivotal role. Irrespective of whether subchondral bone modifications occur prior to cartilage damage or emerge during the progression of the disease, subchondral bone is presently acknowledged as a critical focus in the treatment of OA. Indeed, bone irregularities, particularly heightened bone turnover, have been identified in the initial stages of certain types of OA[34].

During the process of OA, structural modifications occur in subchondral bone, which include augmented bone turnover, microfractures, angiogenesis, and bone sclerosis in advanced stages[35]. These changes have an impact on the biomechanical properties of the joint cartilage above and their interdependent biological relationship. In addition, the activation of osteoclasts can lead to the genesis of pain by inducing acidic conditions at the osteochondral junction, thereby stimulating acid-sensing receptors of sensory neurons. The subchondral bone undergoes significant changes in both composition and structural organization, which can have detrimental effects on the articular cartilage that

overlies it. Hence, the suppression of anomalous subchondral bone remodeling presents a promising approach for the management of osteoarthritis. Additionally, contemporary research indicates that certain pharmacological agents may be useful for the treatment of this processes[36]. These drugs include anti-resorptives (e.g. estrogens, SERMs and bisphosphonates), bone-forming agents (e.g. parathormone/teriparatide), anti-osteoporotic drugs with dual mechanisms of action (e.g. strontium ranelate) and others[37]. Additionally, several pharmaceutical drugs, including Zoledronic Acid, Denosumab, Vitamin D, TPX-100, Teriparatide, and MIV-711, have entered phase 2 and 3 stages of development to combat abnormal remodeling of subchondral bone.

Zoledronic acid (ZOL) is a third-generation bisphosphonate (BIS) that exhibits a higher efficacy compared to its counterparts. It is frequently employed in the management of osteoporosis, particularly in post-menopausal women. Recent research has revealed that ZOL effectively suppresses bone resorption by inhibiting Wnt5a signaling in early OA, rectifies the imbalance of subchondral bone remodeling, mitigates cartilage degeneration, and delays the progression of OA in rat models[38]. Furthermore, ZOL exhibited a capacity to enhance subchondral bone density, ameliorate microstructural abnormalities, and mitigate articular cartilage degeneration in osteoarthritis, as evidenced by both morphological and quantitative assessments in a rabbit model of the disease[39]. The findings of a randomized clinical trial involving 223 individuals diagnosed with knee osteoarthritis and bone marrow lesions indicated that ZOL did not significantly mitigate cartilage volume loss over a 24-month period when compared to a placebo (Clinical Trial Registry Number ACTRN12613000039785). Subsequently, a phase 3 clinical trial was conducted with 70 participants who were administered either Zoledronic Acid or a placebo (Clinical Trial Registry Number NCT04303026)[40].

MIV-711, a cathepsin K inhibitor with high potency and selectivity, demonstrated a significant reduction in HP-1 levels by up to 72% ($P < 0.001$) and CTX-II levels by up to 74% ($P < 0.001$) in ACLT rabbits when compared to ACLT vehicle controls. In dogs, MIV-711 exhibited a substantial decrease in CTX-I and CTX-II levels by 86% ($P < 0.001$) and 80% ($P < 0.001$), respectively, which significantly improved the symptoms of OA[41]. MIV-711 100 mg treatment can significantly reduce WOMAC pain and bone area change. The phase IIa study indicated that MIV-711 200 mg had an acceptable safety and tolerability profile with 6 months of additional treatment with 200 mg MIV-711 (Clinical Trial Registry Number NCT02705625).

TPX-100, which promotes the differentiation of osteoblasts and chondroblasts, has been recognized as a prospective therapy for OA. A randomized trial was conducted wherein 104 participants with bilateral moderate to severe knee cartilage defects were subjected to either TPX-100 (200 mg) or placebo. The TPX-100-treated group demonstrated a noteworthy decrease in pathologic bone shape alteration in comparison to the placebo-treated group at 6 and 12 months. (ClinicalTrials.gov Identifier: NCT01925261)[42].

Overall, inhibitors developed for subchondral bone demonstrate efficacy in reducing OA symptoms and are well tolerated, which may provide a potential direction for the drug development of OA.

New technology-based therapeutics

In OA, articular cartilage destruction and intra-articular inflammation are the main pathological features of the disease. Interfering the expression of inflammation-related genes, catabolic and anabolic gene in chondrocytes at the DNA or mRNA level is an alternative method. With the development of specific genome editing technologies, regulating the expression of certain genes appears feasible. The CRISPR-Cas system is found in bacteria and archaea, and can target foreign sequences and then silence or modify them in hosts by combining multiple single guide RNAs (sgRNAs). Chondrocytes have been targeted using CRISPR/Cas9 to regulate expression levels of MMP-13 and enzyme activity. As a result of CRISPR/Cas9-mediated genome editing, MMP-13 levels were significantly reduced and cartilage matrix proteins were accumulated[43]. Additionally, an AAV expressing CRISPR/Cas9 with specific sgRNAs targeting MMP13, IL-1β and nerve growth factor (NGF) were developed and delivered into mice via intra-articular injection, the results showed that NGF ablation could alleviate the pain caused by partial meniscectomy, while disruption of MMP13 and IL-1β in healthy and osteoarthritis human articular chondrocytes significantly enhanced type II collagen accumulation[43,44].

MicroRNA (miRNA) is a single-stranded small molecular RNA with a length of 21–25 nt, which exists widely in eukaryotes. MiRNA can combined RISC to form a complex and then completely combined with the non-coding region at the 3' end of target mRNA, which prevents mRNA translation. MicroRNA is an endogenous RNA that controls the expression of post-transcriptional genes and plays an important role in some biological processes. Silencing of the p66shc gene by MiR-320c via intra-articular injection to osteoarthritic mice resulted in alleviation of cartilage damage and pain behavior as well was suppression of IL-1β, TNFα and Cyclooxygenase 2 (COX2) expression levels. Among the studies found, MiR-320c was decreased in OA chondrocytes and late stage of hADSCs chondrogenesis, while β-catenin was increased[45]. Overexpression of miR-320c and knockdown of β-catenin had similar effects on OA chondrocytes. Through downregulation of NIMA-related kinase 2 (NEK2), miR-138 could regulate WNT/β-catenin signaling pathway and then promote chondrocyte proliferation and suppress apoptosis in OA chondrocytes[46]. Taken together, CRISPR-Cas9-mediated genome editing and endogenous RNA-mediated RNA regulation has the potential to greatly promote current cell-based therapies for cartilage repair.

Proteolytic targeting chimera (PROTAC) is a chemical knockout method based on protein level that works quickly and reversibly, which consists of three elements: a binding ligand that binds to a target POI, a recruiter ligand of E3, and a flexible linker between the two ligands. Several PROTAC-based drugs have already been developed. For instance, ARV825, that acts as a protein degradation agent of the BET family and promotes the degradation of BRD4, which displays high activity for the clearance of senescence even at nanomolar concentrations. Predictably, targets of OA such as MMPs, ADAMTDs, IL-1β etc. also available for PROTAC drug development. PROTAC is an emerging drug discovery paradigm, but as PROTACs generally have larger molecular weight than traditional small molecules, which may result in less optimal pharmacokinetics.

In summary, although new technology-based therapeutics seem to be very promising for the treatment OA, clinical

Table 1

The main emerging therapies being investigated in OA

Type of drug	Name	Target	Clinicaltrials.gov identifier
MMP-13 inhibitor	ALS1-0635	MMP-13	None
MMP-13 inhibitor	PF152	MMP-13	None
MMP-13 inhibitor	PG-116800	MMP-13	NCT00041756
Monoclonal antibodies	GSK2394002	ADAMTS-4/5	None
ADAMTS-5 inhibitor	GLPG1972	ADAMTS-5	NCT03595618
Wnt inhibitor	Loricivin	Wnt pathway	NCT 02536833
Wnt inhibitor	Verapamil	FRZB	None
Wnt inhibitor	Salinomycin	Lrp6	None
Cartilage repair factor	LNA043	Integrin α5β1 receptors	NCT04864392
Cartilage repair factor	TD-198946	Runx1	None
Cartilage repair factor	Kartogenin	Vitamin A	NCT03133676
Inflammation inhibitor	Metformin	AMPK/GDF-15	None
Inflammation inhibitor	TPCA-1	Ikk	None
Inflammation inhibitor	Tofacitinib	Jak	None
BIS	Zoledronic Acid	Subchondral bone	NCT04303026
Cathepsin K inhibitor	MIV-711	Subchondral bone	None
Peptide	TPX-100	Subchondral bone	NCT01925261
AAV	CRISPR/Cas9	MMP-13	None
AAV	CRISPR/Cas9	IL-1β	None
AAV	CRISPR/Cas9	NGF	None
RNAi	MiR-320c	p66shc	None
RNAi	miR-138	β-catenin	None
PROTACs	ARV825	BRD4	None

OA, osteoarthritis.

effectiveness have not been proved. Additionally, CRISPR/Cas9 and similar systems have low transfection efficiency and possibility of off-target effects, which is the major drawback concern with the CRISPR/Cas9 system. MiRNA is easily degraded by exonuclease of XRN-2 or SDN, thus is difficult to silence the target gene stably. Therefore, it is necessary to develop nanobiomaterials to enhance the stability of miRNAs. Compared with other strategies, PROTAC advantage of better safety and potency. However, current research has been mainly focused on the cancer.

Conclusions

At present, most of the approved drugs only alleviate the clinical symptoms of OA but fail to cure the degeneration of articular cartilage. In this review, we highlight the current methodologies and strategies against OA including DMOADs, RNA interference, CRISPR/Cas9 system and PROTAC that impact on multiple aspects of cartilage such as degeneration of cartilage, subchondral bone remodeling and synovial inflammation and hope to provide information for the current and future anti-OA drug development. Their final approval and availability on the pharmaceutical market are coming soon, which will help to treat the most destructive joint diseases. Furthermore, this study provides a comprehensive summary of clinical trials and animal trials pertaining to the development of DMOADs, as well as an analysis of the efficacy and safety profiles of various targeted drugs (Table 1). These findings offer valuable insights for future research endeavors.

Ethical approval

This article does not contain original human or animal data, so it does not involve ethical approval.

Consent

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The data in the article can be provided upon reasonable request.

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