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Self-assembled hyaluronic acid nanoparticles for osteoarthritis treatment

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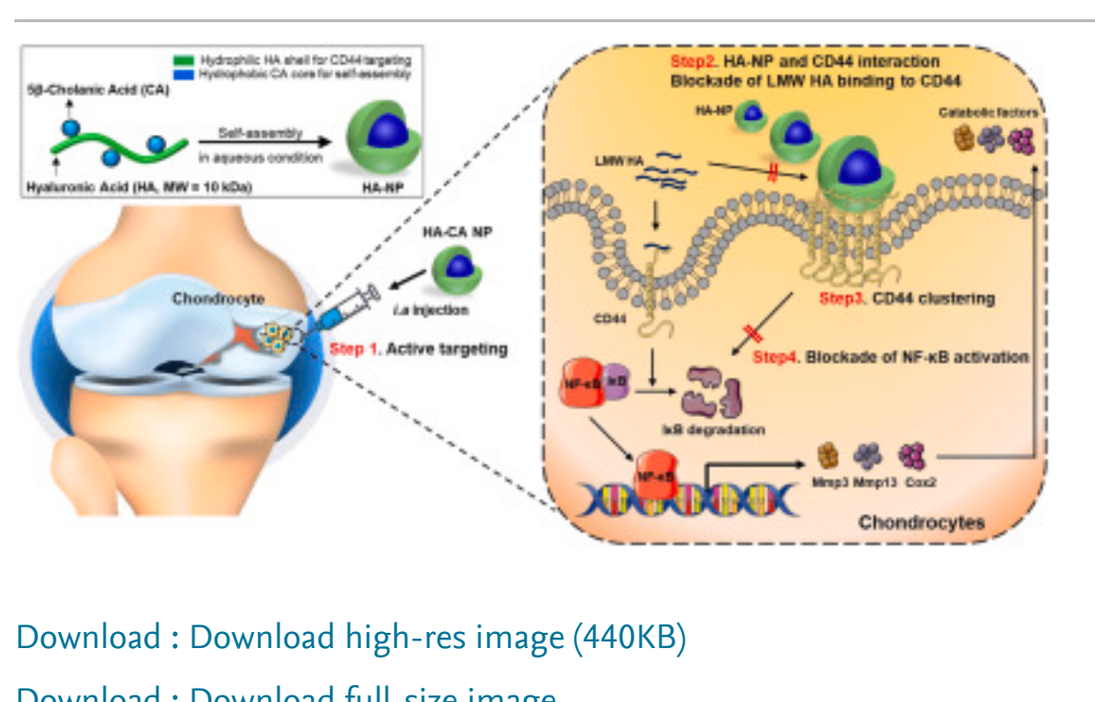
Abstract

Although osteoarthritis (OA) is the most prevalent degenerative joint disease, there is no effective disease-modifying therapy. We report an empty self-assembled hyaluronic acid nanoparticle (HA-NP) as a potential therapeutic agent for OA treatment. In mouse primary articular chondrocytes, HA-NPs blocked the receptor-mediated cellular uptake of free low-molecular-weight HA, and the cellular uptake of HA-NPs increased by ectopic expression of CD44, using an adenoviral delivery system (Ad-*Cd44*). HA-NP showed *in vitro* resistance to digestion with hyaluronidase and *in vivo* long-term retention ability in knee joint, compared with free high-molecular-weight (HMW) HA. CD44 expression increased in the damaged articular cartilage of patients and mice with OA. Ad-*Cd44* infection and IL-1β treatment induced *in vitro* phenotypes of OA by enhancing catabolic gene expression in primary articular chondrocytes, and these effects were attenuated by HA-NP, but not HMW HA. Both *Cd44* deficiency and intra-articular injection of HA-NP protected joint cartilage against OA development in the OA mouse model. NF-κB was found to mediate CD44-induced catabolic factor expression and HA-NP inhibited CD44-induced NF-κB activation in chondrocytes. Our results identify an empty HA-NP as a potential therapeutic agent targeting CD44 for OA treatment, and the CD44-NF-κB-catabolic gene axis as an underlying mechanism of destructive cartilage disorders.

Graphical abstract



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Introduction

Osteoarthritis (OA) is the most common degenerative joint disease and cause of disability, with a large socioeconomic cost; however, there is currently a lack of effective disease-modifying therapy for OA [1]. OA is characterized by progressive cartilage destruction, thickening of the subchondral bone plate, and variable degrees of inflammation in the synovium, leading to joint stiffness, chronic pain, and functional disturbance [2,3]. A major component of articular cartilage in the joint is a dense extracellular matrix (ECM) including collagens and glycosaminoglycans, especially hyaluronic acids (HAs); OA manifestations are caused by the upregulation of ECM-degrading enzymes [4]. These pathogenic factors are first triggered by mechanical stress, which then alters biochemical pathways in chondrocytes, resulting in ECM degradation and inflammation through matrix metalloproteinases (MMPs) and cyclooxygenase 2 (COX2) expression, respectively [5]. Among MMPs, MMP3 and MMP13 are known to play crucial roles in OA pathogenesis. COX2 is primarily involved in inflammation, eventually leading to MMP activation and ECM degradation [6].

Ideal OA therapy involves blocking pathogenic factors prior to the development of severe OA [7]. Conventional drugs have been developed to target these pathways, including several classes of cytokine receptor antagonists and small anti-inflammatory molecules that neutralize inflammatory cytokines or block pathogenic receptors [8]. Although such drugs relieve the symptoms and delay the advancement of deterioration, no current treatments can effectively restore the damaged cartilage. It has been also reported that interactions between the ECM and chondrocytes, mediated by matrix receptors, including integrin and CD44, respectively, are responsible for maintaining cartilage homeostasis. Altered ECM-chondrocyte interaction due to ECM decomposition under pathological conditions, including inflammation and tissue injury, plays a critical role in destruction and progressive loss of cartilage by triggering the expression of MMP3, MMP13, and COX2 [[9], [10], [11]]. These catabolic factors promote cartilage destruction and release of fragmented ECM molecules, such as fragmented fibronectin, which further triggers catabolic gene expression in chondrocytes [9,11]. Therefore, the inhibition of fragmented ECM molecule-chondrocyte interactions might be a potential therapeutic strategy for the treatment of OA.

Intra-articular (*i.a.*) injection of high-molecular-weight (HMW, MW > 1000 kDa) HAs, one of the currently available treatment options for OA, can relieve pain and have disease-modifying effects in the knee joint of mild OA [12]. However, there are conflicting results regarding their efficacy and several side effects, such as local inflammation, likely due to the degradation of HMW HAs into fragmented low-molecular-weight (LMW, MW < 500 kDa) HA molecules by hyaluronidases (HYALs) [13]. Indeed, fragmented LMW HA molecules in the knee joint are known to be responsible for increased catabolic gene expression as well as pro-inflammatory cytokine production [9,10,14,15].

Self-assembled HA nanoparticles (HA-NPs) have been extensively investigated as target-specific and long-acting drug carriers to actively target pathological sites that express HA receptors, particularly CD44 [16,17,18]. Recent studies, including ours, have identified a HA-NP as a potential therapeutic agent for the treatment of obesity and related metabolic disorders, including type 2 diabetes (T2D) and atherosclerosis [[19], [20], [21]]. Here, we demonstrated that, apart from its role as a drug carrier, an empty HA-NP without any drug has therapeutic potential for the treatment of OA by interfering with fragmented LMW HA-CD44 interaction as well as the underlying mechanism involved in the pathogenesis and progression of OA using *in vitro* and *in vivo* models (Fig. 1A).

Section snippets

Synthesis and characterization of HA-NPs

Sodium hyaluronate (MW = 10 kDa) was purchased from Lifecore Biomedical (Chaska, MN, USA). Ethylenediamine, 5β-cholanic acid (CA), N-hydroxysuccinimide (NHS), and 1-ethyl-3(3-(dimethylamino)propyl)-carbodiimide·hydrochloride (EDC·HCl) were obtained from Sigma-Aldrich (St. Louis, MO, USA). An amphiphilic HA conjugate bearing 3.35 CAs per 100 sugar residues of HA was synthesized in the presence of EDC and NHS, as previously reported [19,20,22]. The chemical structure of the conjugate was…

Characterization of self-assembled HA-NPs

The therapeutic effects of HA-NP were evaluated using *in vitro* and *in vivo* OA model systems. We first synthesized amphiphilic HA conjugates by chemical conjugations of free LMW HA backbone (MW = 10 kDa) with hydrophobic 5β-cholanic acid (CA), as previously reported [19,20,22]. Due to their amphiphilic nature, the conjugates self-assemble into NPs via hydrophobic interactions among CAs in aqueous conditions, in which CAs and HAs compose the hydrophobic core for self-assembly and the hydrophilic…

Conclusions

HMW HAs are the most widely distributed native forms of HAs in the articular joint and are responsible for its structure and the normal functions of synovial fluid. Indeed, *i.a.* injection of sodium hyaluronate, which is an injectable HMW HA that is approved by the FDA, has disease-modifying effects in mild OA of the knee [12]. However, HMW HAs are easily decomposed by degrading enzymes present in OA synovial fluid. Here, we identified the protective effects of HA-NP against CD44-mediated…

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Data availability

The raw data required to reproduce these findings are available on request….

Credit author statement

Li-Jung Kang: Conceptualization, Investigation, Methodology, Formal analysis, Writing—original draft, review, and editing. Juhwan Yoon: Investigation, Methodology, Formal analysis, Writing—review and editing. Jun GI Rho: Investigation, Writing—review and editing. Hwa Seung Han: Investigation, Writing—review and editing. Seulbi Lee: Investigation, Writing—review and editing. Young Soo Oh: Investigation, Writing—review and editing. Hwan Kim: Investigation, Writing—review and editing. Eunha Kim:…

Declaration of competing interest

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

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2022, Biomaterials

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…Thereafter, 5-μm-thick sections were obtained and stained with 0.1% Safranin-O and 0.025% fast green solutions. Each section was imaged and scored using the OARSI and synovitis grading system [44]. The expression pattern of Cox-2, JNK, p-JNK, and p-c-Jun within the cartilage was evaluated using immunohistochemistry.…

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…Overall, the above results indicated that the CLX@Lipo@HA-gels have good biocompatibility and can be applied to biological interfaces to reduce friction. In addition to abnormal mechanical stress, excessive production of pro-inflammatory cytokines can also cause chondrocyte damage, leading to the biodegradation and synthesis imbalance of ECM [42–44]. Type II collagen (Col2) and aggrecan are the principal constituents of cartilage ECM synthesized by chondrocytes and can be degraded by matrix metalloproteinase 13 (MMP13) and A disintegrin and metallopeptidase with thrombospondin type 1 motif 5 (ADAMTS5) in osteoarthritis conditions [45–48].…

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