Biomaterial-Mediated Gene Therapy in Cartilage Repair

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Articular cartilage defects caused by various reasons are relatively common in clinical practice, but the lack of efficient therapeutic methods remains a substantial challenge due to limitations in the chondrocytes' repair abilities. In the search for scientific cartilage repair methods, gene therapy appears to be more effective and promising, especially with acellular biomaterial-assisted procedures. Biomaterial-mediated gene therapy has mainly been divided into non-viral vector and viral vector strategies, where the controlled delivery of gene vectors is contained using biocompatible materials. Genetic therapy, on the other hand, aims to transfer exogenous genes into target cells in order to induce endogenous gene expression to complete treatment. It has been extensively used in cartilage repair. Genetic editing is used to promote stable expressions of various growth factors for osteochondral regeneration. Meanwhile, biomaterial mediation could further localize the effect of genetic therapy by providing a scaffold to limit the genetically modified cells and vectors to within the targeted region; this increases the precision of the treatment, and makes it an ideal approach for treating osteochondral injuries.

biomaterial gene therapy cartilage repair virus vector

1. Introduction

Articular cartilage is indispensable in joint movement; its injury and the subsequent osteoarthritis that is secondary to trauma or degeneration can be highly detrimental to patients' quality of life [1]. Chondral lesions are not self-repairing due to limits in the capabilities of cartilage tissue, making its treatment a contemporary challenge in orthopedics. In recent years, researchers have witnessed a rise in cartilage injuries secondary to competitive sports and traffic accidents. The increasing awareness of health and participation in sports is, however, coupled with more sports injuries, causing wide concern in sports medicine.

Cartilage injuries are currently treated medically and surgically. During the initial stage, medicine and rehabilitation may be used among patients with mild injuries. Microfracture and autologous chondrocyte implantation (ACI) may also be used in selected patients [2]. However, joint replacement is usually indicated for patients in end stages of the disease with severe cartilage damage and osteoarthritis [3]. Despite the definitive efficacy that has been proven for arthroplasty, this surgical intervention is not considered ideal due to its high medical costs, the risks of postoperative periprosthetic joint infections (PJIs), deep venous thromboses, prostheses loosening, and the limited lifespans of implants [4][5].

Developments in tissue and genetic engineering have created new perspectives for the treatment of cartilage injuries in the past decade. Compared to traditional surgical intervention, tissue and genetic engineering focuses on complete regeneration of articular cartilage [6][7], with the potential to regenerate tissue, which is comparable to human cartilage in its quality and function. Considering the nature of cartilage's lack of ability to self-repair or regenerate, the application of tissue and genetic engineering in cartilage repair becomes more appealing. Three core factors form the basis of tissue engineering for cartilage repair: seed cells, scaffold material, and growth factors [8]. researchers will not further discuss seed cell selection, as there are existing literature research on this topic [9][10]. Scaffold material plays an important role in tissue engineering, as it provides the environment and platform for seed cells as an extracellular matrix, and supports the growth of new tissues. Ideal scaffold material should demonstrate no immunogenicity, good biocompatibility, satisfactory biomechanical features, and be easy to produce. In recent years, the development of scaffold material has become popular in the field of cartilage repair [11]. Moreover, cellular factors are also indispensable in chondral or osteochondral repair. While promoting cartilage repair, specific cellular factors may skew stem cells in the direction of chondrocyte differentiation [12]. Previous mainstream studies incorporated growth factors directly into scaffold materials, but reported limited efficiency as a result of rapid degradation, unstable repairing outcomes, etc. [12]. The advances in genetic engineering now allow entry of exogenous genes into the cells to express various growth factors that promote cartilage repair. The combination of tissue engineering and genetic engineering has undoubtedly propelled the development of cartilage repair techniques. Researchers will discuss the progress as well as the pros and cons of tissue and genetic engineering in the treatment of cartilage injury.

2. Non-Viral Gene Delivery System

Vectors used in the non-viral gene delivery system mainly include lipid-based vectors, peptide and protein vectors, and polymeric vectors. Vector-free delivery systems have also been studied under this category.

2.1. Lipid-Based Vectors

Lipid-based vectors, or liposomes, are widely applied carriers in the nano-drug delivery system. Liposomes are sealed spherical vesicles consisting of phospholipid bilayers, and are capable of protecting the genetic materials from degradation during transfection. Therefore, they are well suited for mediated genetic therapy [13]. Their special structure confers advantages such as low toxicity, high biocompatibility, biodegradability, good target gene loading capacity, and easy preparation and modification. Based on their electronic charge, liposomes may be divided into cationic, anionic, and neutral liposomes. The cationic liposome, also known as lipofectamine, is capable of transfecting not only cationic DNA, but also RNA [14], making it the most commonly used lipid-based vector at present.

Many studies have confirmed the feasibility of transferring various growth factors (IGF-1, FGF-2, and TGF-β) via liposomes into the chondrocytes to promote repair. Li et al. [15] developed a PLGA/fibrin gel hybrid scaffold to load lipofectamine/pDNA-TGF-β1 complexes and mesenchymal stem cells (MSCs) as a cartilage-mimetic tissue platform, which demonstrated good cartilage repairing. Other studies reported different outcomes using liposome-

combined vectors. Lolli et al. [16] constructed a fibrin/hyaluronan (FB/HA) hydrogel scaffold to deliver antimiR-221 to the injured area, and compared antimir-221 delivery rates and repair outcomes with and without lipofectamine. The results showed a significant two-fold increase in the amount of repaired cartilage, which contained abundant type II collagen, using FB/HA loaded with antimiR-221/lipofectamine, compared to that without lipofectamine.

2.2. Polymeric Vectors

Polymeric vectors and liposomes are the top two common non-virus-based gene delivery vectors, and have long been the gold standard for transfection of this kind. When compared to liposomes, polymeric vectors embody satisfactory variability and stability through the regulation of synthesis processes [17]. Polyethylenimine (PEI), poly (lactide-co-glycolide) (PLGA), and chitosan are all common polymeric vectors, among which PEI is the one most commonly used. Previous studies have proven its effectiveness in inducing stem cell differentiations into different cell lines after transfection [18][19], including chondrogenesis [20][21]. Additionally, researchers have made attempts to use PEI to transfer SOX9 and anti-Cbfa-1 siRNA to MSCs simultaneously, in order to enhance chondrogenesis [22]. However, studies also warned about the cytotoxicity of PEI on stem cell differentiation [23].

PLGA, a common scaffold material, can also perform the role of vectors in gene transfection. Shi et al. [24] devised a poly (L-lactic-co-glycolic acid) (PLLGA) scaffold, and utilized the PLGA vector to incorporate bone morphogenetic protein 4 (BMP-4) into rabbit adipose-derived stem cells (ADSCs) by transfection for cartilage repair. Results of this showed good repair efficacy and outcomes using the PLGA-based scaffold and transfection vector in full-thickness articular cartilage defects, featuring a large amount of regenerated hyaline cartilage. Another widely used polymeric vector is chitosan; it exhibits good biocompatibility, low cytotoxicity, biodegradability, and no immunogenicity. Wang et al. [25] designed a composite construct comprising bone marrow mesenchymal stem cells (BMSCs), fibrin gel, and PLGA sponge. Chitosan chloride was employed as the vector to transfect transforming growth factor-β1 (TGF-β1) into BMSCs. In vivo experiments resulted in successful repair of leporine cartilage defects by the composite constructs. Histological examination confirmed a similar amount and distribution of type II collagen and glycosaminoglycans in the regenerated cartilage as those in hyaline cartilage. Effectiveness in cartilage repair has also been reported using nanohydroxyapatite (nHA) [26], composite polymeric vectors, etc. [27].

2.3. Peptide and Protein Vectors

Another approach used to perform targeted gene delivery is through DNA-carrying peptides. Peptides are short amino acid chains of different structures with various physiological functions; these can be utilized as a part of a gene delivery system to optimize transfection. Peptides are incorporated to overcome certain systemic barriers; for example, cationic peptides with basic residues such as lysine or arginine could enhance affinity when binding to nucleic acids to form nanoparticulate complexes. Peptide and protein vectors are utilized based on their high stabilities and binding capacities, as well as their biodegradability and low toxicity. However, similar to other non-viral vectors, the transfection rate of peptide and protein vectors needs to be further improved in order to be comparable to that of viral vectors.

In a rabbit cartilage model study by Li et al. [28], a PLGA scaffold was constructed mainly with fibrin gel and mesenchymal stem cells, and a poly-l-lysine (PLL) vector was used to transfect the TGF-β1 gene into MSCs for cartilage repair. Results of this showed that neo-cartilage could be regenerated at the lesion site, with abundant subchondral deposition of type II collagen and glycosaminoglycans. Research also discovered specific peptide sequences (for example, chondrocyte-affinity peptide (CAP)) that could target certain membrane receptors in chondrocytes. Attempts have also been made to combine the peptide vector with other carriers; for example, a CAP-PEI complex carrier designed by Pi et al. [29] demonstrated better transfection rate compared to PEI alone during in vivo experiments. It has the potential to become a cartilage-specific vector for cartilage disorders. Despite the current performance of peptide and protein vectors in studies, and their low toxicity profiles [30][31], their use in cartilage repair remains relatively underexplored, warranting further validation studies in this area.

2.4. Vector-Free Delivery Systems

Vector-free delivery systems denote the use of multiple techniques, such as electroporation, microinjection, sonoporation, and hydrodynamic gene transfer. Due to low transfection rates and a lack of tissue-specificity, microinjection and hydrodynamic gene transfer are rarely used for gene therapy in cartilage repair [32].

Electroporation is a commonly used vector-free technology that temporarily enhances the permeability of cell membranes using pulses of high-voltage electricity, in order to promote the uptake of exogenous molecules such as DNA, RNA, or nucleic acids [33]. Nucleofection by electroporation has been performed successfully on primary chondrocytes in a high-throughput format [34]. In a study by Im et al. [35], SOX trio was transfected via electroporation into adipose stem cells (ASCs), and greatly enhanced chondrogenesis. In a study by Khoury et al. [36], electroporation was used to transfect interleukin-10 in a collagen-induced arthritis murine model. The study failed to show sufficient therapeutic efficacy despite a relatively high transfection rate, due to very unstable genetic expression that was observed during the study.

Sonoporation is another commonly used vector-free technology. It refers to the formation of small pores in cell membranes using ultrasound for the transfer of nucleic acid materials. An in vivo study revealed highly efficient BMP-6 transfection into MSCs via sonoporation to improve fracture healing [37]. This technique is also being applied to transfect genes into the intravertebral disks in some studies [38]. The effect of using sonoporation in cartilage injury repair has not been reported in the literature, and future studies are warranted to further demonstrate its efficacy.

Despite having lower costs and better safety profiles compared to virus-based therapy, solutions to low gene expressions and transfection rates are yet to be found in order to revolutionize non-virus-based genetic therapy [39]. Additionally, the efficacy of combining vector-free delivery systems and biomaterials to improve cartilage repair outcomes has not been extensively discussed in the literature. The application of this combined technique also warrants future exploration in this field.

3. Virus Gene Delivery Vectors

Due to its high efficiency in cell infection and its ability to integrate with the host cell genome, viral vectors are a commonly applied delivery system for gene therapy, such as retroviruses/lentiviruses, adenoviruses, adeno-associated viruses (AAVs), and baculoviruses.

3.1. Retrovirus/Lentiviral

Retroviruses can integrate their own genes into the host chromosome, thus ensuring the continuity of the integrated genes that can be expressed in the cell [40]. They have the advantages of a wide spectrum of infection, effective infection of cells at the dividing and resting stages, and long-term stable expressions of exogenous genes [41]. Therefore, retroviruses are a powerful tool for introducing exogenous genes. Clinical trials have been conducted to achieve gene therapy by transfecting the synovial cells of inflammatory joints with retroviruses that express IL-1 receptor antagonist (IL-1 Ra), and then inserting these cells into the joint cavity of rheumatoid arthritis [42]. However, retroviruses will preferentially integrate the genes that are carried into the transcription starting point as well as highly expressed genes, which will lead to tumor side effects [43], such as leukemia in x-linked patients with severe combined immune deficiency [44]. Lentiviral vectors are mostly integrated into sites that are far from the transcription starting point. Thus, compared with retrovirus vectors, lentiviral vectors appear to be less likely to cause cancer, and may be safer for clinical use.

Many studies focused on generating gene-modified scaffold-mimicking cartilaginous extracellular matrix (ECM) through retrovirus/lentivirus-based methods, in order to improve cartilage repair [45]. A gene-modified silk cable-reinforced chondroitin sulfate–hyaluronate acid–silk fibroin (CHS) hybrid scaffold was developed to reconstruct the fibrocartilage layer [46]. Mesenchymal stem cells (MSCs) were able to distribute uniformly throughout the scaffold with the lentiviral-mediated transforming growth factor-β3 (TGF-β3) gene, and showed chondral differentiation. Polycaprolactone (PCL)-hydroxyapatite (HA) scaffold [47] and poly(e-caprolactone) scaffold [48] were also explored to enable lentiviral-mediated TGF-β3 gene overexpression, and showed promising cartilage defect repair. Moreover, Lee et al. [49] used retroviruses to transfect the SOX gene into adipose stem cells and compound the transfected cells with fibrin hydrogel. In the rat model of cartilage injury, it was found that the composite material could promote the repair of articular cartilage defects and delay the degeneration of arthritis. Inducing overexpression of the IL-1 receptor antagonist (IL-1Ra) in MSCs via scaffold-mediated lentiviral gene delivery was also able to enhance the long-term success of therapies for cartilage injuries or osteoarthritis by resisting the IL-1-induced upregulation of matrix metalloproteinases [8].

3.2. Adenovirus

Adenovirus (AdV) is a double-stranded DNA without an envelope, containing approximately 26–48 kBP in its genome [50]. More than 60 human adenoviruses have been identified, with adenovirus serotypes 5 (Ad5) widely used as a gene delivery vector [50]. Adenoviruses have low or no toxicity in humans, and high transduction efficiency in both mitotic and non-mitotic cells [50][51]. Moreover, adenoviruses have a very low risk of insertion mutation because they cannot be integrated into the host genome; however, they also have the disadvantage of not being able to express the carrying genes for long [50][51].

Recombinant adenoviruses can be successfully transfected into cells derived from bone marrow fluid, such as BMSCs, ASCs, and induced pluripotent stem cells [52]. Adenovirus-mediated Sox9 gene transfer of bone marrow mesenchymal stem cells was able to induce chondrogenesis in a PGA scaffold [53]. In a rabbit model with full-thickness cartilage defects, the PGA scaffold and BMSCs with Sox9 transduction-grafted joints showed more newly formed cartilage tissue and hyaline cartilage-specific extracellular matrix, and greater expressions of several chondrogenesis marker genes. Another study synthesized a chitosan/silk fibroin (CS/SF) porous scaffold with bone-marrow-derived mesenchymal stem cells (BMSCs), using transfection with recombinant adenovirus containing C-type natriuretic peptide (CNP) gene; this also showed good chondrogenic differentiation ability and promising cartilage lesion repair in a rat model [54].

The biggest obstacle to the clinical application of adenoviruses is the strong humoral and cellular immune responses caused by them [55]. Researchers developed “gutless” vectors, containing only virus terminal repeat sequences and packaging sequences, in order to minimize the immune response [56]. However, the production of “gutless” adenovirus vectors is more complicated due to the absence of most viral components, and the need for auxiliary plasmids or viruses [57].

3.3. Adeno-Associated Virus

Adeno-associated virus (AAV), a prospect for widely applicable gene vector delivery, is a low-pathogenic parvovirus. Its replication requires helper viruses, for example, adenoviruses. Its genome is linear, single-stranded DNA with a size of about 4.7 kB. AAVs may provide long-term transgene expression in numerous dividing and non-dividing cells without triggering potent host immune responses, which make them non-pathogenic to humans. These advantages enable AAVs to demonstrate clinical potential in the treatment of tumors, hemophilia, lipoprotein lipase deficiency and other diseases. Researchers have developed an AAV vector that expresses TNF antagonists for the treatment of RA, which has successfully entered phase I and II clinical trials.

Some studies have used intra-articular injections of recombinant adeno-associated viruses to affect cartilage metabolism through cytokines such as IL-1β, L-1R, and TNF-α, in order to achieve the effect of cartilage injury repair. However, the transfection efficiency of the simple virus is not high. Some scholars have combined recombinant adeno-associated virus with cells and biological materials, in order to improve transfection efficiency and repair effects. Jagadeesh et al. [58] found that recombinant adeno-associated virus and biocompatible mechanostable poly(E-caprolactone) (PCL) films grafted with poly(sodium sulfonate) (pNaSS) could still achieve 90% transfection efficiency after 21 days, with no biotoxicity detected. Fibrin scaffolds can also serve as long-term releasers of recombinant adeno-associated virus vectors [59]. These results suggest that scaffold-guided gene transfer offers strong systems to develop promising therapeutic options for the treatment of articular cartilage defects. Moreover, Ana et al. [60] developed poly (ethylene oxide) (PEO) and poly(propyleneoxide) (PPO) polymeric (PEO−PPO−PEO) micelles to control release-transferring SOX9 rAAV gene vectors. Controlled delivery of recombinant rAAV via polymeric micelles overexpresses the levels of SOX9, leading to increased proteoglycan deposition and a stimulated proliferation of OA chondrocytes. In 1-year minipig cartilage defect models [61], alginate hydrogel guided with rAAV-mediated IGF-1 overexpression was able to enhance long-term cartilage repair and

protection against perifocal osteoarthritis without deleterious or immune reactions. These results suggest that hydrogels, micelles, and scaffolds have great potential in gene therapy mediated by recombinant adeno-associated viruses.

3.4. Baculovirus

Baculoviruses can naturally infect insect cells, and have been widely employed to transmute many mammalian cells. They have demonstrated efficient gene delivery-mediated expression of growth factors (TGF-b1, IGF-1, and BMP-2) to therapeutic levels in chondrocytes, thus showing their potential for application in cartilage tissue engineering [62]. Chen et al. [63] developed baculovirus-transduced chondrocytes, and then seeded them in PLGA porous scaffold, which consequently demonstrated chondrogenic abilities. However, due to the non-replicating nature of baculoviruses, they mediate transient (<7 days) transgenic expressions; this hinders the application of baculoviruses in situations where ongoing expression is required [64][65].

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