Review Paper
Insights Into Gene Therapy Innovations for Orthopedic Disorders: A Mini-review

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A B S T R A C T

A thorough review of the available scientific works related to the use of gene therapy to address orthopedic disorders was performed. This review highlights the considerable promise of gene therapy in transforming clinical practice in this domain. Orthopedic conditions, including a range of problems, such as spinal fusion failure, disc degeneration, fractures, segmental bone defects, bone tumors, joint disorders, soft-tissue injuries, genetic disorders, and nerve and muscle disorders, often pose significant challenges for traditional surgical or medical treatments. Consequently, a concerted effort has been made to explore gene therapy as a viable alternative. This innovative approach has made significant progress, although several hurdles must be addressed before widespread clinical application in humans. However, gene therapy has considerable potential as a promising treatment option for orthopedic disorders in the 21st century. As gene transfer techniques continue to advance, the potential applications of gene therapy for orthopedic disorders are expected to expand significantly.

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Introduction

Genes act as fundamental building blocks of heredity, governing individuals' physical traits and functional characteristics. At birth, individuals inherit a predetermined genetic blueprint, which, when coupled with environmental influences, dictates susceptibility to various disease conditions. Gene therapy has emerged as a strategy for correcting aberrant genes associated with disease development, involving the transfer and activation of genes within individuals for therapeutic purposes [1, 2]. Gene therapy consists of the delivery of genes to individuals with a therapeutic aim. Human gene transfer can be achieved through ex vivo and in vivo approaches. Ex vivo gene therapy involves the transfer of genes into cells outside the body, typically in a tissue culture environment. Subsequently, genetically modified cells are reintroduced into the host organism. In contrast, the in vivo approach entails the direct transfer of genes into specific somatic cells of the host organism in its native environment [3]. Ex vivo techniques are notably more intricate but offer relatively higher safety profiles. Additionally, the ex vivo approach provides an opportunity to select cells expressing the desired genes at elevated levels in vitro. In contrast, in vivo gene delivery techniques are more straightforward from a technical standpoint and are currently more widely employed. The application of gene therapy to germline cells, initially envisioned as a remedy for hereditary genetic conditions, raises ethical dilemmas owing to the far-reaching implications of modifications, impacting all future generations and potentially evoking concerns related to eugenics. As a result, while experimental somatic cell gene therapy represents a relatively emerging domain, substantial advancements have been made in the last decade. The widespread recognition of the potential of gene therapy to transform medical practices in the 21st century is evident [4]. This review underscores this innovative approach's utilization and prospective benefits in tackling orthopedic disorders.

Strategies for Gene Therapy

Gene therapy can be categorized into two main branches: Somatic cells and germline cells. It is crucial to highlight that all clinical trials conducted thus far exclusively examined somatic cell gene therapy [5, 6]. In somatic gene therapy, a plethora of tissues are available for consideration. Additionally, once the target tissue is identified, selecting the target cell in that tissue presents a considerable challenge, often surpassing the complexity of choosing the target tissue itself. The decision regarding which cell to target frequently depends on the method employed for vector delivery [7]. In gene therapy, the synthesis of a functional protein involves several sequential processes. First, exogenous complementary DNA (cDNA) must traverse the cell membrane, evade degradation within the lysosomes, and subsequently access the nucleus for transcription. After transcription, the resulting messenger ribonucleic acid (mRNA) is translated into amino acids, culminating in the production of the intended peptide or protein [8]. Gene therapy holds promise for delivering growth factors in a biologically active manner because the protein is synthesized endogenously in the body. This can result in more accurate post-translational modifications and the formation of tertiary structures with ligands that are more readily recognizable, thereby augmenting their ability to bind to cell surface receptors compared with recombinant proteins [9, 10].

Gene Delivery Vectors

For gene expression to occur, the transferred DNA must successfully enter the host cell's nucleus, where it can integrate into the host cell's chromosomes or remain in episomes. Introduction is the process of gene transfer using a viral vector. Viral vectors employed in human clinical trials include retroviruses, adenoviruses, adeno-associated viruses, lentiviruses, and HSVs [11, 12]. The Moloney murine leukemia retrovirus is one of the most well-established viral vectors used in gene therapy. The essential attributes of any viral vector pertinent to gene therapy include simplicity, cost-effectiveness of production, potential for evoking immune responses, integration into the host genome, titer, and safety profile [13]. The specific advantages and limitations of each available viral vector system have been comprehensively examined in the literature [14].

Viral Vectors

Vectors derived from retroviruses

Retroviruses are RNA viruses that replicate via an intermediate step involving DNA [3]. The primary advantage of retroviral vectors is their exceptional efficiency in transferring genes into actively dividing cells. This level of accuracy and durability of gene transfer is unmatched by other types of viruses [15]. Retroviral vectors have a substantial cloning capacity, accommodating up to 8 kilobases (kb) of genetic material, and can be manufactured in significant quantities with relative ease for clinical applications. However, their utility is constrained by

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factors such as a limited host range, inadequate transduction of non-dividing cells, and potential risk of insertional events that trigger tumorigenesis [16]. These delivery systems can transduce osteoblasts, bone marrow stromal cells, and muscle-derived stem cells, positioning them as promising candidates for skeletal gene therapy [17-19]. Investigators found that periosteal mesenchymal stem cells, engineered to express bone morphogenetic protein (BMP)-7 via retroviral vector manipulation, markedly improve the healing process of critical-sized defects. Researchers in a mouse calvarial model noted synergistic advantages in bone regeneration by co-implanting muscle-derived stem cells, genetically modified ex vivo using retroviral vectors to produce BMP-2/4 and vascular endothelial growth factor (VEGF) [20, 21].

Vectors derived from adenovirus

Adenoviruses, DNA viruses featuring a double-stranded genome approximately 35 kb in length, have been extensively evaluated in both preclinical and clinical trials for gene therapy applications [22]. These vectors can accommodate approximately eight kb of genetic material within an expression cassette. However, newer "gutless" adenoviral vectors can accommodate significantly larger DNA sequences [23]. Adenovirus vectors exhibit remarkable efficiency, facilitating their production in significant quantities and resulting in elevated levels of expression following transduction. Furthermore, they demonstrate the capacity to transfer genes to replicating and non-replicating cells [3]. The primary hurdle associated with using adenoviruses in gene therapy pertains to the immune response elicited by the host, which restricts transgene expression in animals with intact immune systems [10]. Adenoviral vectors expressing *lacZ* and transforming growth factor β1 (TGF-β1) efficiently transduced osteoblasts and osteoclasts, resulting in notable alterations within the epiphyseal plate [24, 25].

Vectors derived from herpes simplex virus (HSV)

HSV vector, known for its remarkable DNA virus and infectivity, remains latent in nerve cells. However, its extensive genome and cytotoxic properties make it less favorable for consideration as a vector [26]. Researchers have recently employed a second-generation, low-toxicity HSV vector to deliver an interleukin-1 receptor antagonist (*IL-1Ra*) gene and a soluble tumor necrosis factor-α (TNF-α) receptor gene. This approach significantly reduced arthritis symptoms, primarily through *IL-1Ra* [27].

Vectors derived from lentiviral

For the most part, lentiviral vectors are derived from human immunodeficiency virus (HIV). Consequently, prioritizing safety is crucial when employing this gene delivery platform. Lentiviral vectors engineered from HIV demonstrate efficient transduction of human macrophages and primary tissues, such as the brain and muscle [28, 29]. Despite persistent safety concerns, the capacity of lentiviral vectors to infect non-dividing osteogenic cells, their compatibility with osteoblast-specific promoters, and their reduced propensity to induce gene silencing or activate host cell genes strongly indicate that these vectors exert a significant influence on future skeletal gene therapy strategies.

Vectors derived from adeno-associated virus

Recently, recombinant adeno-associated viral (AAV) vectors have emerged as promising substitutes for adenoviral and retroviral vectors for gene therapy. AAV vectors demonstrate non-cytotoxic properties, exceptional safety profiles, and the ability to deliver genes to non-dividing cells. They can be integrated explicitly into the 19th chromosome, ensuring targeted gene insertion. Furthermore, they enable prolonged and consistent gene expression and can be produced at high titers, facilitating their application using in vivo methods [1]. The researchers utilized AAV vectors to deliver marker genes to the arthritic knees of mice overexpressing TNF-α using in vivo techniques. AAV has demonstrated effectiveness as a vector and is expected to be applied in a broader spectrum of clinical treatments [30].

Vectors derived from non-viral

There has been a push for developing non-viral delivery systems owing to concerns regarding safety, immunogenicity, and production limitations associated with viral vectors. These systems involve a combination of genes (DNA) and various chemical formulations. The technique referred to as transfection illustrates a form of gene transfer that does not include viruses. Non-viral delivery systems encompass a diverse range of materials, such as plasmids, peptides, positively charged liposomes, DNA complexes with ligands targeting particular cell receptors to enhance cellular uptake, and Gene-gun technology, which employs gold-coated particles loaded with DNA and introducing them into cells through high-speed bombardment [31-33]. However, their effectiveness typically falls short of that of viral vectors. Non-viral delivery systems demonstrate lower efficiency than viral techniques because no intrinsic biological mechanism

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is found to integrate the desired DNA material into the genome. These approaches can be classified as physical, mechanical, or chemical approaches. The researchers injected plasmid DNA encoding TGF-α1 directly into the muscles of mice with streptococcal cell wall-induced arthritis. They observed substantial suppression of chronic diseases, which was marked by reduced inflammation at the peak of the acute phase. Additionally, cartilage, bone damage, and pannus formation decrease is observed during the chronic phase [34].

Clinical Applications

Cartilage repair

Impairment of adult articular cartilage frequently results in early-onset arthritis, mainly due to the tissue's limited regenerative ability. This limitation can be attributed to insufficient availability of stem cells, inadequate vascularization, and low cellular turnover [35]. Numerous methods have been devised to enhance the healing of articular cartilage [36, 37]. Mason et al. used a retroviral vector to genetically modify mesenchymal stem cells by introducing a *BMP-7* gene. These modified cells were transplanted onto a polyglycolic acid scaffold to a rabbit osteochondral defect [38, 39]. They demonstrated significantly improved healing of the articular defect compared to control groups at both 8 and 12 weeks post-implantation. More recently, researchers have investigated the effects of in vitro gene transfer of insulin-like growth factor-1 (IGF-1), BMP-2, and TGF-β to rabbit articular chondrocytes [39]. Studies indicate that *BMP-7* also stimulates the chondrogenic differentiation of precursor cells derived from the periosteum. Research has shown that incorporating periosteal cells genetically modified to express *BMP-7* or sonic hedgehog cDNAs improves the healing of osteochondral defects in rabbits [40]. Given their limited intrinsic capacity for cartilage repair and remodeling, gene therapy cells have often been integrated with diverse scaffolds to replicate the architecture of cartilage tissues. This approach has shown promising results in cartilage repair in rabbits, mainly using periosteal mesenchymal stem cells transfected with *BMP-7* and sonic hedgehog genes [41].

Meniscus

Various methods, such as sutures, arrows, and staples, have been devised to conserve the menisci. Nonetheless, tears located solely in the vascularized outer third of the meniscus exhibit healing potential [42]. Preconditioning meniscus allografts using viral vectors expressing growth factors holds promise for expediting graft heal-

ing and restructuring while mitigating immunogenic responses. The rationale for employing gene-based approaches to preserve and repair the articular cartilage can be extended to the meniscus. Meniscal cells are responsive to adenoviral and retroviral transduction. Specifically, the delivery of *TGF-β1* cDNA into these cells in monolayer culture resulted in a significant increase in proteoglycan and collagen production, with no changes detected in the cells' collagen phenotype [43-47].

Osteoporosis

Osteoporosis leads to reduced bone density and osteopenia [48]. Osteoporosis manifests as two distinct types. Type 1 osteoporosis is characterized by escalated osteoclastogenesis stemming from estrogen depletion, whereas type 2 is characterized by diminished osteogenesis originating from aging marrow stem cells. Gene therapy for type 2 osteoporosis can be implemented using ex vivo methods involving the transduction of marrow stem cells from osteoporotic donors with adenoviral vectors encoding the *BMP-2* gene. This potent growth factor promotes bone formation. Studies have shown that genetically engineered cells significantly enhance osteogenic activity in vivo [49]. Systemic intravenous delivery of adenoviral or AAV vectors containing osteoprotegerin (OPG) cDNA results in elevated levels of OPG in circulation, thereby eliciting a sustained anti-osteoporotic effect in mice [50, 51].

Osteopetrosis

Osteopetrosis, a genetic disorder characterized by excessive bone formation and bone marrow obliteration, presents an opposite phenotype to osteoporosis. Surplus bone formation in osteopetrosis is caused by decreased osteoclastogenesis, which is associated with genetic abnormalities affecting the colony-stimulating factor 1 (CSF-1) gene. Gene therapy offers potential by introducing marrow stem cells modified to overexpress the *CSF-1* gene, thereby stimulating heightened osteoclastogenesis [52-54].

Spinal fusion

Spinal fusion is a common procedure in spinal surgery, frequently requiring internal fixation devices for temporary stabilization. However, achieving enduring stability requires a successful bone fusion. Nonetheless, the failure rate to achieve robust bone fusion can reach 45%. Although autogenous bone grafts are efficacious, they are constrained in volume and can induce considerable morbidity at the donor site. Research indicated that the

Table 1. Genes related to gene therapy in spinal fusion

Gene	Effect	Vector Type	Ref
BMP-2	Stimulating the generation of fresh bone tissue and effectively facilitating spinal fusion	Adenoviral	[57, 58]
BMP-7	Stimulating the generation of fresh bone tissue and effectively facilitating spinal fusion	Adenoviral	[57, 58]
LMP-1	Promoting the production of a secreted osteoinductive protein capable of influencing neighboring cells to stimulate bone formation	Adenoviral	[59, 60]
BMP-9	Promoting spinal fusion	Adenoviral	[61]

morbidity rate associated with harvesting autogenous iliac crest bone grafts may reach 30%. Allograft bone carries risks of antigenicity and disease transmission. Additionally, alloplastic materials are associated with higher infection rate and extrusion and inferior biomechanical properties [55]. Extensive animal studies have demonstrated the exceptional effectiveness of BMPs in enhancing bone formation at fusion sites, offering strong support for advancing BMP gene therapy to clinical applications. Unlike systemic gene therapy, local gene therapy for spinal fusion is less complex because it requires sustained gene expression for only a brief period, potentially less than a week, to trigger the endochondral osteoinduction cascade. Although several hurdles must be overcome before this innovative approach can be clinically deployed, local gene therapy shows promise as a more favorable method of osteoinduction than the administration of pharmacological doses of recombinant or extracted osteoinductive proteins in spinal surgery. With further refinement, BMP gene therapy stands poised to facilitate bony union across various spinal regions, including transverse processes, facets, laminae, and spinous processes, in a minimally invasive manner, offering numerous applications in spine surgery [56].

Genes related to gene therapy in spinal fusion are presented in Table 1.

Degeneration of the intervertebral disc

Disc degeneration and related spinal disorders are a significant cause of morbidity, leading to considerable pain and heightened healthcare expenses. Despite extensive clinical research focused on intervertebral discs, current surgical interventions or pharmaceutical treatments do not address the underlying pathology of intervertebral disc degeneration. This degeneration is characterized by weakened or ruptured collagen and proteoglycan structures, reducing water content, and decreased flexibility. Although protein-based agents show promising therapeutic potential with precise targeting, they often face challenges reaching spinal compartments (Table 2) [62, 63].

Bone regeneration

Fracture healing in humans commonly exhibits resilience, requiring only stabilization of the injured area and pain management as medical measures. However, inadequate fracture healing is associated with chronic pain and prolonged mobility limitations, often necessitating surgical intervention. External fixation devices can stabilize fractures prone to inadequate healing; however, insufficient bone at the defect site may lead to structural instability and, in some cases, infection and bone erosion. Although bone grafts are another option, they carry the risk of infection and may not provide sufficient bone for specific applications, making contouring difficult. Microsurgical transfer of free bone grafts, including attached soft tissue and blood vessels, can help reduce the risk of infection; however, it is a complex and specialized procedure with an elevated risk of complications. As a result, modern orthopedic practice often lacks an effective treatment for fractures prone to poor healing tendencies (Table 3) [66-68].

Table 2. Genes related to gene therapy in intervertebral disc degeneration

Gene	Effect	Vector Type	Ref
TGF-α	Induction of ECM production	Adenoviral	[64]
IL-1Ra	Induction of ECM production	Adenoviral	[65]

ECM: Extracellular matrix.

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Table 3. Genes related to gene therapy in bone healing

Gene	Effect	Vector Type	Ref
BMP-2	Results of bone stimulation and bone tissue healing	Adenoviral	[69]
BMP-3	Results in bone stimulation and bone tissue healing	Adenoviral	[70, 71]
BMP-4	Results in bone stimulation and bone tissue healing	Adenoviral	[72]
PTH1-34	Results in bone stimulation and bone tissue healing	Adenoviral	[72]
BMP-5	Results in bone stimulation and bone tissue healing	Adenoviral	[73]
BMP-6	Results in bone stimulation and bone tissue healing	Adenoviral	[74, 75]
TGF-α	Results in bone stimulation and bone tissue healing	Adenoviral	[76]

Arthritis

Gene therapy has emerged as a prospective tactic for providing continuous therapeutic concentrations of anti-arthritic gene products to afflicted joints. Viral and non-viral vectors can be used to convey these genes directly into the body (in vivo) or to cells outside the body before re-implantation (ex vivo). Encouraging preclinical outcomes have been attained through implementing these methodologies in diverse animal models of arthritis. Advancements in crafting gene therapies for arthritis have been swift, instilling confidence to enhance the management of this category of ailments (Table 4) [77, 78].

Soft-tissue healing

Injuries to musculoskeletal tissues, such as ligaments and tendons, are prevalent; however, these tissues do not always undergo optimal healing. In healthy individuals, wound healing and tissue repair typically involve multiple stages. Following birth, this process commences with an inflammatory response, upon which subsequent stages are predicted. While wound healing normally restores the injured site, it does not achieve tissue regeneration, which is particularly relevant for mechanically active tissues, such as ligaments and tendons. The complex interplay between mechanical forces and biological processes significantly influences the healing process's effectiveness. Moreover, host biology is affected by factors such as age, sex, genetics, and tissue history, all of which can influence the healing process [87, 88]. However, their clinical delivery poses significant challenges. In recent years, considerable progress has been made to explore whether gene therapy can overcome these limitations. These encouraging outcomes suggest that this innovative gene therapy approach holds promising potential for advancing soft tissue healing in the foreseeable future (Table 5).

Bone tumor

The traditional treatment for osteosarcoma is aggressive, with relatively modest success rates, and a significant proportion of cases experience relapse. Moreover,

Table 4. Genes related to gene therapy in arthritis

Gene	Effect	Vector Type	Ref
TGF-α	Inhibit inflammatory	Plasmid	[79]
IL-13	Dampen autoimmune reactions and persistent inflammation	Adenovirus	[80, 81]
IL-1Rα	Mitigate autoimmune reactions and persistent inflammation	Retrovirus plasmid	[82, 83]
IL-10	Inhibits the progression of the condition.	Adenovirus	[84]
IL-4	Reduced radiographic indication of bone deterioration	Retroviral	[85]
FADD	Fas-induced apoptosis of synovial	Adenoviral	[86]

Table 5. Genes related to gene therapy in soft-tissue healing

Gene	Effect	Vector Type	Ref
Fibroblasts	Migrated away from the point of injection and assimilated into the crimp of the tendon	Adenovirus	[9, 89]
PDGF	Increased PDGF expression during ligament healing facilitates angiogenesis initially and subsequent augmentation of collagen deposition within the wound site	HVJ-liposome	[9, 45]
TGF-α	Improved ACL healing and facilitated graft maturation	Plasmid	[9]
EGF	Abled to improve healing of the ACL and facilitate graft maturation	Adenovirus	[90, 91]
BMP-13	Potential for advancement in ligament and tendon repair	Adenovirus	[92]
BMP-12	Enhanced healing of posterior cruciate ligaments	Adenovirus	[93]

Abbreviations: HVJ: The hemagglutinating virus of Japan; PDGF: Platelet-derived growth factor; ACL: Anterior cruciate ligament.

traditional treatments for metastatic osteosarcoma primarily focus on palliative care, and metastatic osteosarcoma invariably leads to mortality. As a result, metastatic osteosarcoma is a plausible candidate for gene therapy (Table 6) [94, 95].

Gaucher disease

Gaucher disease, characterized by glycolipid storage dysfunction, arises from numerous mutations in the glucocerebrosidase gene. Approximately 80% of patients with Gaucher exhibit osseous complications, manifesting as bone loss, osteosclerosis, osteonecrosis, and impaired remodeling. Consequential bone loss heightens skeletal fragility, often culminating in pathological fractures that exhibit slow healing tendencies and commonly result in nonunion or malunion [97, 98]. The elucidation of the cDNA for the human glucocerebrosidase gene has ushered in the prospect of gene therapy for Gaucher disease. Investigations have illustrated that introducing this gene into fibroblasts from patients with Gaucher syndrome can rectify this defect. In mice, the retroviral transduction of hematopoietic stem cells has successfully achieved sustained glucocerebrosidase gene expression. However, translating this approach into clinical practice requires bone marrow ablation followed by autologous bone marrow transplantation, which poses a significant procedural challenge. Researchers have explored alter-

native strategies for targeting circulating hematopoietic progenitor cells expressing the CD34 marker to overcome these obstacles. These progenitor cells can be harvested from peripheral blood, genetically modified ex vivo, and reintroduced into the patient through intravenous infusion. Moreover, inherited genetic disorders caused by collagen gene mutations, including chondrodysplasia, Stickler syndrome, and spondyloepiphyseal dysplasia, are candidates for gene therapy. Current efforts aim to optimize these innovative techniques for treating such conditions effectively [9, 99-101].

Disorders affecting nerves and muscles

Gene therapy holds immense promise for revolutionizing the treatment of nerve and muscular injuries. Conditions such as amyotrophic lateral sclerosis and spinal muscular atrophy, which are characterized by progressive paralysis and frequently result in premature mortality, may benefit from novel therapeutic approaches. Although neurotrophic factors have been proposed as potential treatments for these disorders, their clinical use as injected recombinant proteins faces challenges, including toxicity and limited availability. However, research has shown that adenovirus-mediated gene transfer of NT-3 offers significant promise for addressing motor neuron diseases. For instance, intramuscular delivery of this construct demonstrated substantial therapeutic

Table 6. Genes related to gene therapy in bone tumor

Gene	Expression in Osteosarcoma	Vector Type	Effect	Ref
CCG1	Up	Retroviral	Reduced mitotic rates and heightened stromal development in the remaining tumors	[9]
Type 1 helper T (Th1)	Down	Adenovirus	Efficient in eliciting anti-tumor responses by enhancing cell-mediated immune reactions	[9, 96]

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effectiveness in a mouse model of progressive motor neuronopathy [102]. A recent laboratory study introduced a tetracycline-regulated construct encoding nerve growth factor (NGF), demonstrating its dose-dependent modulation and responsiveness to the tetracycline analog doxycycline. These results provide a foundation for future research exploring regulated neurotrophin delivery in animal models of neurodegenerative diseases and nerve injury. Ischemic peripheral neuropathy (IPN) is a common and irreversible complication of lower-extremity vascular insufficiency. Current research efforts aim to evaluate the potential of gene therapy to prevent and/or reverse IPN. In a rabbit model, intramuscular delivery of naked DNA encoding VEGF during hindlimb ischemia effectively prevented a significant decline in motor and sensory nerve functions, facilitating rapid nerve recovery. This positive outcome was partly attributed to improved hindlimb perfusion. Furthermore, the discovery of functional VEGF receptor expression in Schwann cells indicated a direct role for VEGF in maintaining neural integrity [103]. These discoveries represent a novel approach to addressing IPN. The diminishment or alteration of the survival of motor neuron 1 (*SMN1*) gene results in decreased levels of intracellular survival motor neuron protein, likely contributing to the initiation of spinal muscular atrophy. This effect may occur through potential disruption of spliceosome assembly [104].

Rotator cuff tears

Rotator cuff tears represent frequent soft tissue injuries, often necessitating surgical intervention. Surgical repair of tendon tears markedly enhances pain relief and functional outcomes [105-107]. Previous studies have revealed that up to half of these tears do not heal, as confirmed by ultrasound or magnetic resonance imaging (MRI) [108-110]. Early efforts to improve tendon healing focused on strengthening the repair using more robust suture materials and knots and restoring the rotator cuff's anatomical footprint using double-row repair techniques. More recent research has focused on the biological augmentation of the healing process [111, 112]. Tissue engineering is an interdisciplinary domain that applies scientific principles to develop living tissues to replace, repair, or enhance diseased tissues [113, 114]. Gene therapy involves the transfer of a specific gene into a cell, prompting the cell to produce a particular protein. The advantage of gene therapy combined with a tissue engineering approach for healing lies in the physician's ability to select growth factors that play crucial roles in tendon healing. Ideally, enhancing the current repair technique would result in improved tendon healing and, consequently, better clinical outcomes [45, 115, 116].

PDGF- is pivotal in accelerating and enhancing tissue healing by facilitating several critical processes. These include chemotaxis, fibroblast proliferation, induction of extracellular matrix components such as fibronectin, and revascularization. Numerous studies have demonstrated that PDGF promotes DNA and matrix synthesis in tendon cells while enhancing the expression of cell-surface integrins, which are essential for tendon repair [117]. IGF-1 also boosts reparative mechanisms by augmenting DNA, collagen, and glycosaminoglycan synthesis. Studies conducted in controlled laboratory settings and within living organisms have clarified IGF-1's capacity to reduce inflammation and concurrently promote cellular proliferation, collagen generation, and DNA levels [118, 119].

Conclusion

Gene therapy is a promising approach for treating various orthopedic conditions, with research showing feasibility in laboratory and initial clinical trials. Understanding the molecular genetics of skeletal disorders has led to innovative treatments involving the introduction of specific genes into patient cells to influence bone repair and regeneration. This method can potentially manage genetic disorders, such as osteogenesis imperfecta, chronic conditions, such as arthritis, and injuries, such as bone and cartilage damage. Animal studies have shown positive results in osteoarthritis, bone healing, and ligament healing. However, challenges remain in identifying optimal cellular targets, therapeutic genes, and safe delivery methods. Future research should aim to understand the genes and signaling pathways involved in bone cell growth, identify more effective therapeutic genes, and explore combining genes for better outcomes. Non-viral vectors have emerged as alternatives to viral vectors. The integration of gene therapy with existing treatments, such as protein therapy and tissue engineering, is also being explored. Advances in genetic markers, genomics, and proteomics will help identify treatment targets, and molecular imaging technology will aid in studying the role of expressed molecules, leading to further progress in this field.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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