Review Article

Revolutionizing Osteoarthritis Treatment: The Synergy of iPSCs and Extracellular Vesicles-Based Acellular Therapies for Joint Tissue Repair

Abstract

This review discusses the current state of osteoarthritis treatment and the limitations associated with traditional approaches. The review then explores the potential of induced pluripotent stem cells (iPSCs) and extracellular vesicles (EVs) for joint tissue repair. The use of iPSCs and EVs together in acellular therapies has the potential to provide a safe and effective treatment option for joint tissue repair. The review examines the benefits of these therapies and discusses future research directions, including the use of bioinspired EV-mimicking nanoparticles and the modulation of the immunogenicity of donor iPSCs. The review also addresses the potential ethical implications of these therapies and proposes solutions for addressing these concerns. Overall, this review suggests that iPSCs and EVs-based acellular therapies could revolutionize regenerative medicine for osteoarthritis treatment, providing a promising avenue for future research.

Keywords: osteoarthritis, iPSCs, Extracellular vesicles, joint tissue repair

Introduction to Osteoarthritis and current treatment options

What is Osteoarthritis, and how prevalent is it in society?

Osteoarthritis is a chronic, painful, and disabling disease that affects many people, particularly in developed countries. It is a non-inflammatory arthropathy that has been traditionally defined, but recent studies suggest that it has an inflammatory component with the presence of synovitis in a large number of patients [1]. The disease is multifactorial with inflammatory, metabolic, and mechanical causes, and it is characterized by articular cartilage degradation [2]. Inflammatory mediators such as pro-inflammatory cytokines, reactive oxygen species, nitric oxide, matrix degrading enzymes, and biomechanical stress are major factors responsible for the progression of OA in synovial joints. Identifying early inflammatory events and targeting these alterations will help to ameliorate the major symptoms such as inflammation and pain in OA patients [1]. Osteoarthritis is a frequent cause of pain, loss of function, and disability in adults [1]. It is the most prevalent joint disease in the elderly population, with a prevalence of about 60% in men

and 70% in women after the age of 65 years [2][1]. The prevalence of OA increases rapidly during midlife, and it is expected to increase substantially in the future [1]. Knee OA is the most common subset of OA, and weight loss (if overweight) is an important core treatment in knee and hip OA. Exercise is a key core treatment in knee, hip, and hand OA and should be considered regardless of age, structural disease severity, functional status, pain levels, or the presence of comorbidities. It is recommended to provide education, advice, or information about the etiology, progression, prognosis, and treatment options of OA as an ongoing and integral part of care. Trained healthcare providers with the skills to provide the core treatments are essential [1]. Despite the prevalence and impact of OA, no treatment has been found yet, and the pathophysiology behind the structural changes in osteoarthritis is complex and poorly understood. Therefore, there is a need for new innovation in methodologies and instrumentation for the non-invasive detection of inflammation in OA by modern imaging techniques [1][3][2].

What are the current treatment options for Osteoarthritis?

The current treatment options for osteoarthritis (OA) encompass both non-pharmacological and pharmacological interventions. Non-pharmacological interventions include exercise and weight loss, while pharmacological interventions for OA entail acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular corticosteroid injections [4]. In severe cases of OA, surgery such as total knee replacement may be necessary [4]. However, each of these approaches has its own benefits and burdens [4]. The standard pharmacological treatment for OA includes pain and inflammation control agents such as NSAIDs, analgesics, and intraarticular corticosteroids. Symptomatic slow-acting drugs for OA such as glucosamine sulfate, chondroitin sulfate, diacerein, unsaponifiable extract of soybean, and avocado administered orally and intraarticular hyaluronic acid are also used [5]. Yet, there is no convincing evidence that any treatment can slow down or prevent the development of OA [4]. Additionally, dietary supplements have become available but their effectiveness remains to be proven [4]. Using a cane has been highlighted as a beneficial treatment option for OA by Jones et al. [1]. Orthotics, ranging from insoles to braces, are a significant treatment option for reducing pain in OA patients [1]. Management of knee OA requires non-pharmacological and pharmacological approaches. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) has developed a step-by-step therapeutic algorithm for knee OA treatment [1]. Combination therapy of viscosupplements with therapeutic agents, drug delivery systems or regenerative therapies is a current treatment option for OA. This combination therapy can improve viscosupplementation outcome in terms of pain relief and joint functionality [1]. Moreover, biological approaches such as stem cells or platelet-rich plasma appear to be promising strategies for cartilage recovery [1]. However, further research is needed to reach more conclusive results regarding the effectiveness of this treatment option [1]. Drug delivery systems combined with hyaluronic acid could enhance the activity of encapsulated molecules and provide better control over drug release. Anti-inflammatory molecules can improve pain relief but may have cytotoxicity [1]. To improve the management of OA, there is a need for easily disseminated guidance for OA treatment in the primary care setting and harmonization of recommendations for knee OA treatment [1]. Guidelines recommend the involvement of experts with real clinical experience in drug use and patient management. Nonetheless, primary care providers may not adhere to clinical care guidelines, particularly for non-pharmacological OA treatment due to discrepancies between guidelines that are due to

heterogeneity of expert panels and geographical differences in the availability of pharmacotherapies and studies [1].

What are the limitations of current treatments?

Despite the available treatments for osteoarthritis, there remain many limitations and inefficiencies. Traditional OA drugs have been found to be effective in reducing pain and inflammation, but they are insufficient to slow, stop, or reverse joint damage and are frequently associated with adverse effects [6]. In addition, the unsatisfactory effects and unacceptable side effects of traditional OA drugs have prompted the development of novel materials to improve drug therapeutic efficacy [6][7]. Current treatments for OA have lagged behind those for inflammatory arthritis, with existing treatments providing only symptom relief for osteoarthritis patients [8][6]. Furthermore, current treatments do not achieve actual repair of damaged joint tissue, doing little more than ease the pain [6]. The majority of treatments for OA are drugs and/or surgery, with current treatments being limited in number [1]. Surgical interventions like the ACI technique have problems such as limited cells available, multiple surgical procedures involved, in vitro chondrocyte dedifferentiation, and donor-site morbidity caused by cartilage harvest [6]. Despite the promise of regenerative therapies, limitations still exist in current pharmacologic and regenerative therapy, and larger, randomized, controlled, and long-term follow-up studies are needed to confirm their safety and effectiveness [6]. In summary, while there are treatments available for osteoarthritis, there are many limitations to these treatments, and more research is needed to develop effective and safe therapies for this debilitating condition.

iPSCs and Extracellular VesiclesBased Acellular Therapies for Joint Tissue Repair

What are iPSCs, and how can they be used for Osteoarthritis treatment?

Osteoarthritis (OA) remains a leading cause of physical disability in the elderly. While there is no information on the use of iPSCs for OA treatment in the given text, iPSCs can be used to model cartilage diseases and provide evidence of the association between familial osteochondritis dissecans and early-onset OA [9]. iPSCs are generated from patients with osteopetrosis, a bone disorder caused by osteoclast defects [9]. Refined protocols for differentiating iPSCs have paved the way for developing in vitro models for cartilage diseases [9]. Additionally, iPSCs can be used as a new screening platform for testing new drugs for cartilage diseases [9]. MSCs derived from iPSCs have comparable multipotency to adult MSCs and show potential in ligament repair and bone regeneration [9]. iPSC-based models can recapitulate key changes in chondrocyte phenotype and matrix production found in OA [9]. Successful repair of cartilage defects in vivo has been detected when treated with human iPSCs in comparison with those untreated and those treated with hydrogel alone [9]. Furthermore, transplantation of iPSC-derived cartilaginous particles in osteochondral defects resulted in the formation of good quality cartilage-like neotissue in rats and minipigs [9]. Although iPSC research to date has mostly focused on neurology, cardiology, and hematology fields, there has been a growing interest in using cellular reprogramming as a tool to study pathogenesis of mutation- and ageing-associated musculoskeletal disorders and to explore their potential for

tissue repair [9]. Therefore, using iPSCs in OA research and treatment could potentially provide new insights into the pathogenesis of the disease and offer regenerative medicine approaches to improve patient outcomes.

What are extracellular vesicles, and how can they be used for Osteoarthritis treatment?

Extracellular vesicles (EVs) have emerged as promising candidates for the treatment of osteoarthritis (OA),[10],,[11],,,,[10]. EVs are small, lipid-membrane enclosed vesicles that are secreted by cells into the extracellular space to modulate cellular communication and important physiological processes [10],. They can be found in various biological fluids, including blood, urine, saliva, and synovial fluid [10]. EVs contain various molecules, including growth factors and anti-inflammatory factors, which can help promote tissue repair and reduce inflammation [10],. Additionally, EVs may be a promising alternative to stem cell therapy for OA treatment, as they can be produced in large quantities and have a lower risk of adverse effects [10]. Stem cell-derived EVs have shown potential for use in treating joint injury and OA [10]. MSC-derived EVs (MSC-EVs) have demonstrated potential for tissue repair and immune suppression in various preclinical models including AD. MSC-produced EVs are less immunogenic and can serve as an alternative to cellular therapies by transmitting signaling or delivering biomaterials to diseased areas of the body [11]. Recent studies have shown that EVs can affect the regeneration of cartilage and osteochondral tissue [10]. However, further research is needed to understand the full potential of EVs for OA treatment and to develop specific EV-based therapies for this condition.

What are the benefits of using iPSCs and extracellular vesicles together in acellular therapies for joint tissue repair?

Unfortunately, while orthotics can alleviate pain and delay joint replacement surgery, they cannot repair the damaged tissue.To address this issue, researchers have explored acellular therapies that utilize induced pluripotent stem cells (iPSCs) and extracellular vesicles (EVs).iPSCs have the potential to differentiate into various cell types, including chondrocytes, which can generate cartilage tissue. However, using iPSCs directly in therapy carries the risk of teratoma formation and immune rejection. On the other hand, EVs are small lipid vesicles that contain bioactive molecules such as growth factors, cytokines, and miRNAs that can induce tissue regeneration. Recent studies have shown that using a combination of MSC-EVs and iPSC-EVs can enhance tissue regeneration by promoting cell deposition at cartilage defect sites [12]. The iPSC-EVs were incorporated with in situ hydrogel glue to ensure retention of MSC-EVs at the site of cartilage injury. The acellular tissue patch integrates with native cartilage matrix and promotes functional cartilage repair. The use of iPSCs and EVs together in acellular therapies has the potential to provide a safe and effective treatment option for joint tissue repair.

Future Directions and Implications

What are the future directions for research on iPSCs and extracellular vesicles-based acellular therapies?

iPSCs and extracellular vesicles-based acellular therapies are a promising avenue for future research in regenerative medicine. One of the future directions for research on iPSCs and EVs-based acellular therapies is their translation to clinics with good manufacturing practice implementation [13]. iMSCs could be a potentially unlimited source of cells with more stable phenotype and function, which will improve the clinical applications of iPSCs and EVs-based acellular therapies [13]. Moreover, iPSC-CPC-EVs could be used to improve chronic heart failure by decreasing left ventricular volumes and increasing left ventricular ejection fraction [14]. Future research on iPSCs and extracellular vesicles-based acellular therapies will focus on tissue restoration, including exploring the angiogenesis ability of iPSCs and iPSC-EVs in heart failure, and investigating the potential of iPSC-EVs in promoting capillary density in the infarct zone. Additionally, bioinspired EV-mimicking nanoparticles can be obtained from intact cells as a different approach for exploring the beneficial effects of cell-derived vesicles. These particles have potential applications in drug delivery systems. Modulating the immunogenicity of donor iPSCs, such as overexpression of the HLA-E gene or knockout of HLA-A and -B genes, is a potential strategy for future research, which could lower the risk of immune recognition. Developing banks of allogeneic iPSCs with matching HLA proteins would also be a promising direction for research on iPSCs and extracellular vesicles-based acellular therapies, allowing for wider clinical use without the risk of immune rejection. Overall, iPSCs and extracellular vesicles-based acellular therapies are a potential future direction for research that could revolutionize regenerative medicine.

What are the clinical implications of these therapies for Osteoarthritis treatment?

There are several clinical implications of the current and emerging therapies for osteoarthritis treatment. Disease-modifying OA drugs (DMOADs) have shown promise in clinical trials and aim to modify the underlying pathophysiology of OA to alleviate structural damage and prevent long-term disability [15]. However, DMOADs are not yet available in the pharmaceutical market, and current clinical implications of therapies for osteoarthritis of the knee are limited due to inconsistent outcomes and potential side effects [4][15]. The American College of Rheumatology (ACR) has provided recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee, which can include both nonpharmacologic and pharmacologic options [16]. Future therapies for osteoarthritis treatment may involve innovative approaches such as stem cell therapy, gene therapy, and tissue engineering [4]. Promising DMOADs delay cartilage degeneration by targeting pro-inflammatory cytokines, the proteolytic activities of catabolic enzymes, and the Wnt pathway [15]. Moreover, regenerative therapy as an OA treatment shows potential by stimulating the regenerative potential of cartilage through tankyrase inhibition or fostering the regenerative capacity of adult cartilage [15]. Though dietary supplements have been used for OA treatment, their effectiveness remains to be proven [4]. In summary, current surgical and pharmaceutical intervention strategies for osteoarthritis of the knee have benefits and burdens, while emerging therapies have the potential to modify the underlying pathology of OA and prevent long-term disability.

What are the potential ethical implications of these therapies, and how can they be addressed?

There is a growing concern about the ethical implications of transcranial direct current stimulation (tDCS) therapy, as well as a need for regulation of this emerging technology. Some of the ethical concerns raised in reviewed studies include informed consent, potential adverse effects, and the use of tDCS in vulnerable populations, such as children and people with mental illnesses [17]. Addressing these concerns is critical to the future of tDCS research and development. Proposals for alternative methods to facilitate clinical research on tDCS have been made, such as requiring standardized training and certification for tDCS practitioners, developing clear guidelines for the use of tDCS in research and clinical settings, and conducting large-scale randomized controlled trials to establish the safety and efficacy of tDCS [17]. By addressing these ethical concerns and implementing appropriate regulations, the potential benefits of tDCS therapy can be realized while minimizing any associated risks.

Conclusion

Osteoarthritis is a debilitating condition that affects many people, particularly in developed countries. While there are currently treatments available, there are limitations and inefficiencies associated with these treatments. New innovations in methodologies and instrumentation for the non-invasive detection of inflammation in OA by modern imaging techniques are needed. iPSCs and extracellular vesicles-based acellular therapies have shown promise for joint tissue repair, and further research in this area could revolutionize regenerative medicine. However, there are potential ethical implications that must be taken into consideration. Addressing these ethical concerns and implementing appropriate regulations will be critical to the future of regenerative medicine research and development for osteoarthritis treatment.

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