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Review Article

Breaking Boundaries: Stem Cell Breakthroughs Reshaping Osteoarthritis Treatment

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Abstract

Osteoarthritis (OA) is significant global health issues, severely affect the joint mobility by stiffness and pain. In this review we emphasize how stem cells hold the potential to aid patients affected by this illness. We discuss current transformative approaches for OA treatment, pathogenesis of OA, including molecular and cellular mechanism, genetic and environmental factors involved in developing this illness. We also discuss current treatments methods and unmet challenges in handling this global disease. We find that different stem cell has the differential potential to regenerate the defective tissue and give quality of life for affected individuals. We highlight how stem cells assist in personalized treatment and their therapeutic applications. Additionally, this review emphasizes the animal models, the preclinical and clinical studies, challenges and risks, outcomes of patients and their responses, and ethical considerations, including mitigating risks and adverse effects to standardize the regulation of stem cell therapy (Figure 1).

Keywords: Osteoarthritis, Stem cell therapy, Cartilage regeneration, Cellular therapies, Regenerative medicine, Mesenchymal stem cell (MSCs), Personalized treatment, Joint Degeneration

Abbreviations: OA: osteoarthritis; MSCs: Mesenchymal Stem Cells; BM-MSCs: Bone Marrow- Derived mesenchymal stem cells; iPSCs: Induced Pluripotent stem cells; ESCs: Embryonic Stem Cells; ADMSCs: Adipose-Derived Mesenchymal Stem Cells; TNF-α: Tumor Necrosis Factor Alpha.

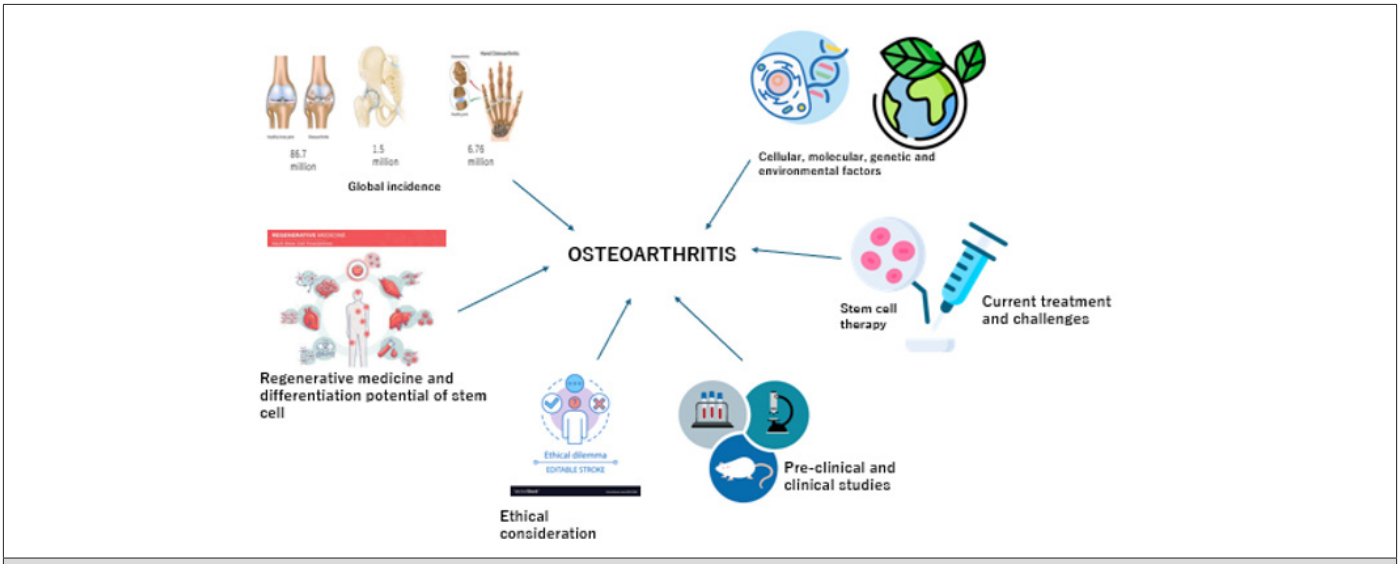

Figure 1: Graphical Abstract.

Introduction

Osteoarthritis: A Global Health Challenge

Millions of people worldwide, particularly the elderly, suffer from osteoarthritis, a serious global health concern. It results in stiffness of joints, decreased mobility, and joint pain [135]. Its rising incidence is caused by several factors, including age, sedentary lifestyles, obesity, joint traumas, and heredity [10]. The costs are borne by economies and healthcare systems, with a considerable economic impact [114]. Multiple joints are impacted by osteoarthritis, which degrades cartilage, produces inflammation, and limits movement. Current treatments for osteoarthritis are not much effective for long term, but regenerative medicine provide promising treatment [59]. Awareness of osteoarthritis treatment is essential as it is most common diseases globally and addressing osteoarthritis enhance the standard of living in the world [61].

Need for Transformative Approaches in Osteoarthritis Treatment

There is a need of novel treatment approaches for osteoarthritis because of the limitations in the current treatment methods, as osteoarthritis is globally increasing and the demand of new approaches for its treatment also increasing to improve the patient's quality of life [105]. Conventional therapies are not enough good to identify the underlying cause of osteoarthritis and are not effective for long term [149]. As osteoarthritis is globally increasing and leading to significant financial repercussions, With the increasing demand of new treatment approaches [22]. Transformative approaches in osteoarthritis treatment can bring a dramatic change in the life of patients by providing long-term relief from this disease. Novel treatment approaches like regenerative and personalized medicine could transform the life of effected people globally [66].

Pathogenesis of Osteoarthritis

Osteoarthritis (OA) caused by interaction of different factors such as genetical, environmental factors, metabolic alterations and mechanical stress [8]. In OA the impairment of cartilage occurs resulted into the breakdown of joint. Repetitive stress or damage results into the extensive stress on joints which leads to the impairment of cartilage [134]. Different biochemical variables such as enzymes and inflammation involve speeding up the damage of joint [166]. The changes in the underlying bone and cartilage cells as well as genetic predisposition also involves in the development of osteoarthritis [91]. By understanding the complex processes related with the OA leads to the development of novel and personalize treatment to control this disease [117] (Figure 2).

Figure 2: Pathogenesis of Osteoarthritis.

Molecular and Cellular Mechanisms Driving Osteoarthritis

Various cellular and molecular mechanisms are involved in a complex joint disorder known as Osteoarthritis (OA) [148]. Many other factors like inflammatory chemicals, Enzymes and many growth factors are involved in altering the outer layer of the joint which are involved in osteoarthritis OA [23]. Inflammation in joints is activated by the activation of enzymes which results in the breakdown of joint, while growth hormones influence the joints equilib rium [42]. Modifications in cellular activities, modification in the underlying bone, genetic variations, many enzymes and chemical reactions influence the development of Osteoarthritis (OA) [46-49,118], Understanding all these factors and pathways they followed which are involved in the development of OA can be a great assistance for focused therapies to overcome this disorder and in the improvement of patient's life [9].

Genetic and Environmental Factors Influencing Disease Progression

Various Genetical and environmental factors interact in a complex way resulted into an OA *Ibounig, et al.,* Any changes in the genes specially which are related to joint structure, inflammation, and cartilage metabolism can potentially increases the risk of having OA in individual *Mendez, et al., Grässel, et al., Muschter, Burton, et al.,* Similarly, Various environmental factors such as any trauma in joint, obesity, exposure to allergens, level of physical activity influence the OA progression *Bortoluzzi, et al., Courties, et al.,* [118]. Comprehending these genetic and environmental factors how they interact can assist in the early detection of OA, along with the preventive measures to control its progression *Bortoluzzi, et al., Millar, et al.,* [9].

Inflammatory Pathways and Cartilage Degeneration

Inflammation is considered one of the main factors involve in the progression of Osteoarthritis (OA) by degenerating the cartilage [158]. Many inflammatory pathways and chemicals involved in the degeneration of cartilage such as cytokines like TNF-α and IL-1β, prostaglandins and nitric oxide [15]. Inflammatory signals are produced by the breakdown of cartilage, injury in the tissue or by mechanical stress [32]. Inflammation in the cartilage for the long period not just results into the damage of cartilage but also breaks the synovium and subchondral bone of the joint [151]. Understanding these inflammatory pathways assisted in the development of personalized treatment of OA which not only can reduce the inflammation but will also assist in the maintenance of the cartilage (Table 1).

Table 1: Current treatment and limitations of osteoarthritis.

Treatment	Limitations	Reference
Conventional treatment	Temporal pain relief, surgical approach leads to adverse complications such as increased morbidity and long-term pain.	(*Shah et al.* [137])
Minimal invasive therapies	Cell survival and retention after delivery is a considerable challenge.	(*O'Cearbhaill et al.* [125])
Physical Therapy	Consistent efforts required, not applicable for chronic osteoarthritis.	
Surgical interventions	Risk of infection and other complications.	(*Charlesworth et al.* [19])

Current Treatment Landscape

Novel treatments such as stem cell therapy are revolutionizing the treatment of Osteoarthritis (OA) by reducing the inflammation and by healing the damaged cartilage [71]. among stem cells mostly mesenchymal stem cells are used because of their ability to develop into the cartilage cells, it also releases some chemicals which assisted in the regeneration of damaged tissue and by reducing the inflammation [86]. Such kind of personalized approaches resulted into a promising treatment by alleviating the symptoms of disease from the patients.

Medications for Symptom Management: Advantages and Limitations

Stem cell approach brings the drastic change in personalized therapy, but medication still have great implications in the management of disease like Osteoarthritis. Different painkillers, NSAIDs, visco-supplementation, corticosteroid injections are still being used to reduce pain and inflammation. Each have its own adverse effect but still they have their own worth in handling diseases like OA [147,155,162]. Even though stem cell treatments have the potential to regenerate damaged cartilage, medicines are still necessary to successfully manage the symptoms of osteoarthritis [6]. It's critical to comprehend the advantages and disadvantages of drugs in the context of developing stem cell therapies to provide patients with OA with complete care.

Physical Therapy and Rehabilitation: Enhancing Joint Function

For those with osteoarthritis, physical therapy and rehabilitation are essential to restoring joint function [28]. They promote mobility and general functionality, optimize joint health, and support stem cell therapy [29]. Physical therapy enables individuals to take charge of their health, reduce discomfort, and enhance their quality of life through exercises, modalities, and teamwork [113].

Surgical Interventions: Addressing Advanced Osteoarthritis Cases

When non-surgical therapy has failed to improve an advanced case of osteoarthritis, surgical interventions become critical [24]. The goals of treatments including arthroscopy, joint osteotomy, total joint replacement, and partial joint replacement are to reduce pain, restore joint function, and enhance quality of life [101]. For severe situations, total joint replacement is frequently done, although partial joint replacement is a less intrusive option for limited injury [20]. Joint osteotomy entails reshaping bones to lessen stress on the injured joint, while arthroscopy enables diagnostic and therapeutic procedures [5]. These procedures have possible hazards, therefore selecting patients carefully and ensuring proper rehabilitation after surgery are necessary for the best outcomes.

Unmet Needs and Challenges in Existing Treatment Modalities

Stem cell discoveries present a prospective remedy for Osteoarthritis (OA), as the available treatments for the condition have drawbacks and unmet needs [95]. Current therapies frequently fall short of providing long-term treatment or halting the progression of the disease. But stem cell treatments can change the course of the illness and repair injured tissues, so they can help with these difficulties [64]. Stem cell treatments have the potential to completely transform OA care by customizing medications and focusing on disease pathways [106]. They also have the benefit of perhaps prolonging the efficacy of treatment, which lessens the need for surgery. Apart from getting stem cell therapies, there is a need to learn efficient way of their delivery with safety by understanding ethical and legal issues [34]. Embracing innovation in regenerative medicine could transform the OA therapy and give a quality of life to effected individuals [38].

Regenerative Potential of Stem Cells

Stem cells have the potential to regenerate, it holds fascinating potential for the treatment of osteoarthritis OA [82]. Stem cells have ability to transform into cartilage-producing cell named as chondrocytes. It would significantly contribute to repair and regeneration of damaged cartilage in affected joints [51]. Moreover, stem cells produce anti-inflammatory molecule and provide the best possible healing environment on the affected area [57]. Scientists are finding the novel techniques for the efficient use of stem cell including their effective delivery methods, using scaffolds to assist cell growth, and encouraging the body`s natural production of stem cells [165]. However, challenges still exist in choosing the best source of stem cells, in their delivery methods, ethical issues, and long-term efficiency and safety [17]. Despite these limitations regenerative therapy holds a great potential to transform the treatment of Osteoarthritis (OA).

Stem Cells: Nature's Building Blocks for Regeneration

Stem cells have the great potential to revolutionize OA treatment because of its natural potency to regenerate [41]. Stem cells are considered one of the most enticing options in personalized or regenerative treatment and bring a new hope for the patients of untreatable diseases, offering a great potential by healing and regenerating common diseases via treatment [77]. Abnormal activity or depletion of these cell reservoirs is linked to the start of degenerative changes in the joint, resulting in a loss of chondrogenic potential and an increased prevalence of a fibro-genic phenotype. Ex vivo MSC cultures delivered locally have shown encouraging results

in preclinical models of joint dysfunction. To replace conventional assays based on cell-surface markers and differentiation, paracrine factors must be evaluated as indicators of MSC therapeutic effectiveness. Mechanistically, paracrine signaling by MSCs may be more significant than differentiation in generating repair responses [7]. The appropriate regulation of immune cells that cause inflammation and bioactive substances present in the injured microenvironment is necessary for the successful regeneration of functioning tissues [121]. But there are difficulties in maximizing stem cell selection and taking ethical and safety issues into account [54,112].

Immunomodulatory Properties and Tissue Repair Mechanisms

In addition to showing promise for the treatment of common chronic diseases, regenerative therapies provide hope for several diseases that were previously incurable [28]. In patients with osteoporosis, stem cells maintained their anti-inflammatory capacity and resulted in the preservation of bone homeostasis. Stem cells demonstrated resilience in a damaged milieu and the capacity to retain a variety of characteristics, such as stemness and the ability to control T cell survival [77]. For cell-based therapy of Osteoarthritis (OA), Mesenchymal Stem Cells (MSCs) have been the most widely studied due to their ability to differentiate into chondrocytes and their immunomodulatory features. The primary properties of MSCs that allow for their therapeutic use in OA are their ease of acquisition, rapid proliferation, maintenance of differentiation potential after multiple passages in vitro, minimal immunological rejection because of the low surface expression of major histocompatibility complex antigens, effective engraftment, and long-term coexistence in the host [54]. MSC-based therapy is one of the more promising OA treatment methods. Preclinical research provided positive findings about MSCs' potential for treatment in OA animal models. bone marrow on 16 artificially created osteochondral defects in rabbits, MSCs were transplanted. Rabbits implanted with MSCs showed superior histology scores and increased matrix synthesis of collagen type II [67,124]. Another major obstacle is determining the safety, effectiveness, benefits, and drawbacks of employing these therapy modalities in regenerative medicine [45]. Still, stem cell injections appear to have a lot of promise for treating OA. restoring patients' hope and revolutionizing the regenerative medicine industry [25,16].

Insights into Stem Cell Differentiation and Chondrogenic

The treatment of osteoarthritis is being revolutionized by new findings on stem cell differentiation and their chondrogenic potential (OA). The treatment of osteoarthritis is being revolutionized by new findings on stem cell differentiation and their chondrogenic potential [26]. Numerous studies have concentrated on using BM-MSCs in conjunction with various scaffold types to create cartilage tissue in animal models [48,30]. The development of stem cell-based therapies has been spurred by the shortcomings of conventional treatments for cartilage repair [96]. Thus, knowing how stem cells and biomaterials interact will enable the identification of novel biomaterials for use in clinical therapeutic applications for tissue regeneration in the future [63]. This combo technique provides a multimodal approach to improve the results of therapy and promote cartilage regeneration.

Revolutionizing Osteoarthritis Treatment: Exploring the Diverse Landscape of Stem Cell Types

The potential of stem cells to treat Osteoarthritis (OA) is considerable, and several varieties have been studied. The two forms of stem cells under investigation are Induced Pluripotent Stem Cells (iPSCs) and Embryonic Stem Cells (ESCs), which are extracted from embryonic mammalian cells. Both cells have the pluripotent capacity to differentiate into chondrocytes or any other kind of cell; animal models have shown that ESCs enhance cartilage regeneration, and [72]. have created iPSCs from human OA chondrocytes and then stimulated the cells to differentiate into chondrocytes [98,156,13]. Although Embryonic Stem Cells (ESCs) offer a wide range of applications, there are ethical concerns [142]. Human-Induced Pluripotent Stem Cells (hiPSCs) have highly promising clinical prospects, but there are still certain ethical questions surrounding them that researchers studying iPSCs and the relevant authorities in the area must acknowledge [2]. Different MSC subpopulations and doses may be required for the therapy of different diseases. Additionally, the dosage of MSCs varies for various tissue-derived MSCs for the same condition [107]. Adipose-derived Stem Cells (ASCs) represent a subclass of Mesenchymal Stem Cells (MSCs) that exhibit numerous regenerative characteristics and are readily extracted from adipose tissues [141]. Selection of stem cell source depends on different factors such as the age of both recipient and donor, The decision on which stem cell source to use depends on several factors, including the recipient's and donor's ages, coexisting medical conditions, stage of diseases, Preferences of donor and center, ethical concerns, and treatment objectives [75]. In depth study is required to understand different types of stem cell which could result into development of innovative and efficient treatment methods of OA.

Regenerative Power of MSCs: Reshaping Osteoarthritis Treatment

Among all the stem cell types, MSCs are mostly used for the treatment of Osteoarthritis (OA) which revolutionized the way of treatment. Up till now MSCs are studied extensively in the regenerative medicine. MSCs showed potential in treatment of different diseases especially in osteoarthritis by regenerating cartilage and by reducing the inflammation, also have a proven safety record [164]. MSCs have ability to produce extracellular matrix (enrich in type II collagen and proteoglycans), promote the regeneration of cartilage by developing into chondrocyte-like cells [157]. MSCs are well known to induce transformation of M1 macrophages into M2 macrophages which assist in the reduction of inflammation and bone regeneration. According to research by Maggini and associates, MSCs transform macrophages into a regulatory profile characterized by a decreased ability to secrete inflammatory cytokines and an enhanced capacity to phagocyte apoptotic cells [104,110]. Numerous clinical studies have demonstrated the MSC therapy's encouraging potential for pain relief and cartilage healing [9]. MSCs are a promising new frontier in the treatment of Osteoarthritis

(OA), with the potential to completely transform the field despite certain obstacles [147]. Since the identification of Mesenchymal Stem Cells (MSC) as potential therapeutic agents, bone marrow-derived stem cells, liposuction-derived adipose tissue, and biopsy-derived adipose tissue have all shown promise in rebuilding cartilage. Higher cell counts, population doublings, and a reduced senescence assay were all used to support the observation that BM-MSCs proliferated more effectively than both sets of ASCs. These cells can also be extracted by sorting or centrifugation [52]. The creation of culture media that are optimally prepared for the separation and growth of Human Mesenchymal Stem Cells (hMSCs) is a crucial procedure that is acknowledged to be highly complex [74]. When human mesenchymal stem cells are cultured at physiological oxygen levels (between 1% and 5%), more cell proliferation as well as an increase in their adipogenic and osteogenic differentiation have been noted [150,128]. Furthermore, there is less oxidative stress, DNA damage, telomere shortening, and chromosomal aberrations in hMSCs grown under these low oxygen circumstances [39,79]. In the last ten years, OoC (Organ on cChips) platforms have advanced quickly. By combining previously established technologies—such as biomaterials, bioreactors, and 3D bioprinting-they improve the expansion process and replicate the environment of natural tissue [97,76]. Through successful and transformational stem cell-based therapies, researchers hope to change the treatment of OA by utilizing varied sources and improving isolation and expansion procedures.

Multilineage Differentiation Potential and Therapeutic Applications

Treatment for Osteoarthritis (OA) may be revolutionized by stem cells' capacity for multilineage differentiation and their therapeutic uses [171]. Multipotent bone marrow-derived cells called Mesenchymal Stem Cells (MSCs) can differentiate into a variety of specialized cells, such as osteoblasts, adipocytes, and chondrocytes *Q Li, et al.,* Likewise, the progenitor cells obtained from humaniPSCs grew along several mesenchymal lineages and had immunophenotypic characteristics of Mesenchymal Stem Cells (MSCs) [57]. Due to its regenerative potential, it grants a relief from cartilage abnormalities. It is evident that undifferentiated stem cells have little potential and exhibits variety of responses. By understanding stem cells, it shows that therapeutic potential of stem cell could increase by modifying their characteristics and behavior via different engineering techniques. Furthermore, stem cell can potentially reduce the inflammation and speed up the tissue healing process due to their immunomodulatory capabilities [87]. MSC-based technologies have ability to alleviate pain, enhance mobility, and regenerate cartilage in joints with cartilage abnormalities [93]. Few issues need to be raised such as their delivery method, effectiveness and safety, ethical concerns. We can get advantage from regenerative and immunomodulatory capabilities of MSCs in development of innovative treatment of OA [50,48].

Induced Pluripotent Stem Cells (iPSCs)

While Induced Pluripotent Stem Cells (iPSCs) discovery brings dramatic change in the field of Biomedicine. iPSCs gained recognition because of their potential in tissue regeneration, drug screening and disease modeling. Most of the iPSC research focused on cardiology, neurology, and hematology [89]. different reprogramming cell technologies are used to create iPSCs, such as biotechnological, chemical, and physical modulation techniques. Each have its own pros and cons, with the innovations in research, they have the potential to differentiate into any type of body cell, which open new doors in the field of medicine to control diseases in future [108]. Because of their limitless cell supply and capacity to maintain modified genotypes that replicate the characteristics of patients' cells and tissue, Induced Pluripotent Stem Cells (iPSCs) are the most advantageous tool for CRISPR/Cas9-assisted disease modeling [154]. Because of their pluripotency and limitless potential for proliferation, Human Induced Pluripotent Stem Cells (hiPSCs) offer great potential as cell sources for cartilage regenerative therapies and in vitro disease-modeling systems [123,145,163,3]. iPSCs offer a way to create genetically modified or patient-specific cartilage for use in medication screening for medications that alter osteoarthritis [4]. But there are inherent difficulties in achieving safe and effective clinical translation (Desgres and Menasché). IPSCs offer a promising way to change the way OA is treated, offer individualized regenerative therapies, and give patients hope globally [94].

Reprogramming Strategies and iPSC Generation

The method we treat Osteoarthritis (OA) has radically changed because of Induced Pluripotent Stem Cells (iPSCs) [91]. iPSCs as the ideal instrument for creating cellular models unique to each patient and enabling so-called personalized treatment [127]. More recent advancements in iPSC technology include the characterization of alternate reprogramming factors and improved reprogramming techniques using cutting-edge delivery systems including non-integrating viral and non-viral vectors. Simultaneously, tiny chemical compounds (epigenetic regulators or inhibitors of signaling) have emerged as critical components of iPSC reprogramming; they could enhance and replace potential reprogramming factors [132]. Nonetheless, there are still significant problems that need to be resolved, including the technological difficulties in creating iPSCs and the safety risks with using them in clinical settings [70]. Numerous small compounds that can be substituted for external transcription factors have been found, greatly increasing the effectiveness and caliber of iPSC reprogramming *Lin, et al., Wu, et al.,* We conduct a complete assessment of their pluripotency markers and chondrogenic lineage differentiation capacity [92]. In the future, we hope to improve reprogramming techniques even more and learn more about the epigenetic changes that take place throughout the procedure. The potential of iPSCs to offer individualized and potent therapies that can completely transform the lives of people with OA is what holds the key to the future of OA treatment [94].

Differentiation into Chondrocytes: Toward Personalized Therapies

Treatment for osteoarthritis may be completely changed if stem cells are differentiated into chondrocytes, which are specialized cells that produce cartilage [83]. The use of tissue engineering techniques has greatly aided in cartilage restoration. Since nano-

materials have unique mechanical, biological, and biomimetic qualities, they are particularly superior in controlling the behaviors of stem cells. They have so received a lot of attention in tissue regeneration. They offer the milieu necessary to encourage stem cell development. Nanoparticles It would be advantageous for cartilage tissue regeneration to induce stem cells to differentiate into chondrocyte phenotypes, hence fostering the advancement of cartilage tissue engineering [90]. By utilizing stem cells from the patient's own body, personalized therapy lowers the chance of immunological rejection and customizes care to meet each patient's needs [40]. Many kinds of stem cells are being researched, including those that come from different tissues, reprogrammed adult cells, and embryos. Additionally increasing its efficacy are developments in genetic engineering and alterations. The progress made thus far can help translate modified cartilage products into the future, which will benefit the millions of patients suffering from arthritides and cartilage injuries [94]. The goal of this research is to enhance treatment results and offer a fresh method of osteoarthritis management.

Emerging Stem Cell Types: Exploring New Avenues

Investigating many stem cell kinds, including newly discovered ones, OA treatment could be transformed by stem cell therapy. Stem cells, such as ESCs, iPSCs, and MSCs, have shown encouraging outcomes in the regeneration of injured cartilage [61]. Scientists from all over the world are looking for stable, secure, and very accessible sources of stem cells that have a lot of promise for regenerative medicine. Examples of these sources include synovial fluid-derived stem cells, induced neural crest stem cells, and amniotic fluid stem cells. Researchers have assessed how well tissue engineering and stem cell therapy work to treat osteoarthritis. All forms of stem cells, such as adult, fetal, induced pluripotent, and embryonic stem cells, may be used in stem cell therapy, which offers a long-term biological remedy and represents a revolutionary development in the treatment of this crippling illness [18].

Mechanisms of Stem Cell Therapy

The use of stem cells in OA treatment is essential for creating cutting-edge treatment plans. It might be able to create safer and more efficient methods of treating OA by utilizing the immunomodulatory and regenerative capacities of SCs [26]. The mechanisms which are under the Stem cell transplantation is a viable approach because of the Stem Cells' (SCs') strong proliferative capability and ability to develop into chondrocytes, which are cells that produce cartilage [12]. They also release good chemicals that help reduce inflammation and repair tissue [139]. SCs have demonstrated that they also have strong anti-inflammatory and immunosuppressive properties. Additionally, SCs can affect the local tissue environment and exert protective benefits by secreting several soluble substances, which successfully stimulates regeneration in situ. SCs' ability to perform this function may be used to treat degenerative joint conditions including RA and OA [21]. It is essential to comprehend these mechanisms to optimize therapeutic strategies (Figure 3).

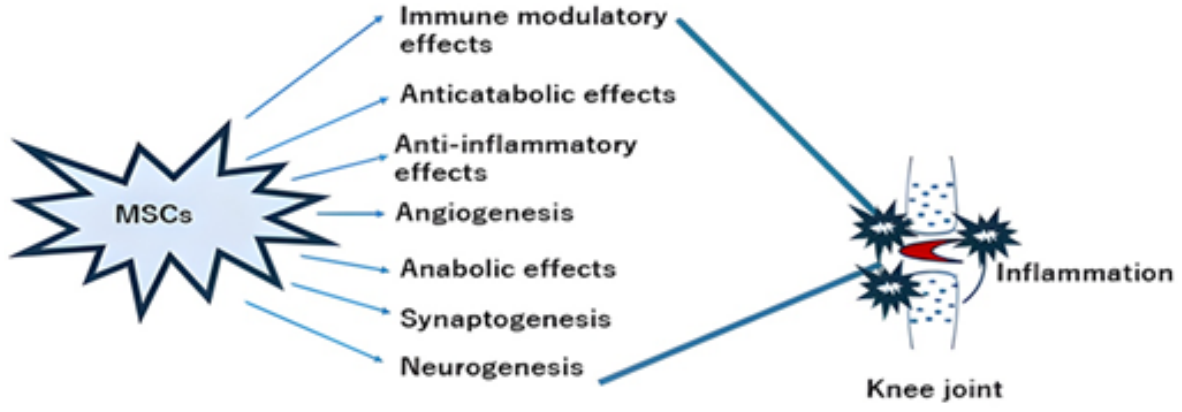

Figure 3: MSCs play an important role in regeneration of damage tissue and in anti-inflammation.

Cartilage Regeneration and Tissue Engineering Approaches

Tissue engineering and cell treatment Techniques for cartilage regeneration or repair have fascinating opportunities to transform osteoarthritis treatment [109]. The ability of stem cells, such as MSCs, ESCs, and iPSCs, to promote cartilage repair is essential [93]. These techniques enable stem cells to differentiate into chondrocyte-like cells for the formation of cartilage through tissue engineering [100]. It appears that the reprogrammable methods used today to encourage stem cell differentiation into cartilage tissues are ineffective. Furthermore, it appears that methods for gene editing, and genetic modification will help to get around the present drawbacks of stem cell-based therapy. Gene therapy drugs delivered locally promote a safer and more efficient recovery from OA. Adeno-associated virus vectors that have been recombinant (rAAV) are also employed as genetic vectors to transfer genetic sequences in situ and encourage cartilage regeneration [102,103]. Technological developments in stem cell research, tissue engineering, and tailored therapy revolutionized the treatment of osteoarthritis and improved patient outcomes.

Immunomodulation and Anti-inflammatory Effects

The potential of stem cells to treat Osteoarthritis (OA) is enhanced by their capacity to differentiate into chondrocytes and their capacity to regulate the immune system and decrease inflammation [171]. Mesenchymal Stem Cells (MSCs) are the most

frequently used stem cells as therapeutic agents in the treatment of immune-mediated disorders because of their differentiation and immuno-modulatory properties. MSCs move to the site of inflammation and alter the immune system's reaction [152]. It has been shown that MSCs inhibit both pro- and anti-inflammatory reactions [88]. MSCs will induce the therapeutic activity of memory T cells by reestablishing the balance between pro- and anti-inflammatory memory T cell populations that are dysregulated in RA [99]. With the availability of many stem cell types, including MSCs, ESCs, and iPSCs, customized treatments for OA are now feasible [61]. Because cell-based therapy aims to reverse the pathophysiology and symptoms of OA, it has proven to be a viable approach [168].

Paracrine Signaling and Trophic Factor Secretion

The production of trophic factors and paracrine signaling are essential for stem cells to transform Osteoarthritis (OA) treatment. MSCs could release a variety of substances that can alter pain signaling pathways, including cytokines and neurotrophic factors. These elements may prevent pain signals from being transmitted and lessen the impression of pain in OA patients [26]. The primary method by which MSCs aid in tissue regeneration is their capacity to generate a wide range of bioactive trophic factors, which in turn encourage nearby parenchymal cells to begin mending injured tissues [90]. The complete potential of paracrine signaling in revolutionizing OA treatment will continue to be investigated as further studies and clinical trials move forward.

Preclinical and Clinical Studies

Clinical and preclinical research has been essential in transforming osteoarthritis treatment. As OA therapy is still in its infancy, preclinical and clinical studies are being conducted to confirm its efficacy and safety [65]. MSCs can effectively prevent the OA-related degradation of cartilage and subchondral bone, according to preclinical and clinical research. Researchers have shown the regenerative potential of stem cells in preclinical studies utilizing animal models, which improve cartilage quality, reduce inflammation, and improve joint function [118]. By demonstrating notable improvements in pain and function, as well as more reliable OA stability with improved mobility and an overall increase in quality of life, stem cell therapy outperformed traditional approaches [47,26]. These studies demonstrate how individualized therapies have improved the quality of life for people with osteoarthritis and solved its associated issues. Several scientific techniques were used to identify research hotspots, productivity, and partnerships pertaining to the application of stem cells for cartilage regeneration. Research hotspots that might provide positive results shortly include double-blind clinical trials, 3D printing, and extracellular vesicles. Additional research is required to enhance our comprehension of this domain, and longer follow-up periods and larger sample numbers in clinical trials are necessary for therapeutic transformation [44].

Preclinical Findings: Promising Efficacy in Animal Models

Promising results from preclinical research utilizing animal models have shown how beneficial stem cell therapies can be in transforming the treatment of Osteoarthritis (OA). According to their research, different kinds of stem cells, such as MSCs, iPSCs, and ESCs, ADSC, may encourage the regeneration of cartilage, lessen inflammation, and enhance joint function [120]. Comparable anatomy and joint function are crucial considerations when choosing the optimal repair model, but translational preclinical investigations also need to take other elements into account [121] (Table 2).

Table 2: discussed the animal models, stem cell sources and delivery method, outcomes.

Animal Models Small animals	Delivery Method	Stem Cell Sources	Outcomes	Refs
Mice	Intramuscular and subcutaneous route	Human mesenchymal stem cells (hMSCs)	In two distinct animal models of arthritis, hsTNFR-transduced hMSCs could reverse or reduce arthritic inflammation.	(*L. N. Liu et al.* [92])
Rats	Intramuscular and subcutaneous route	Human mesenchymal stem cells (hMSCs)	//	(*L. N. Liu et al.* [92])
Rabbits	intra-articular injection	ADSC	Compared to the control group, the ADSC sheets group shown a modest inhibition of cartilage deterioration, but there was no statistically significant difference.	(*Takagi et al.* [144])
Guinea pigs	Intra-articular injection in knee joint	hWJ-MSCs	Compared to HA plus MSCs or only HA, the administration of HA plus hWJ-MSCs-derived chondrocytes (HA-CHON) resulted in a higher healing rate of degenerative cartilages.	(*Nadeem et al.* [120])
Dogs	Intra-articular injection	Umbilical Cord Derived Mesenchymal Stem Cell.	After therapy, the UMSC group's success rate was noticeably higher than that of the placebo group at both one and six months.	(*S. E. Kim et al.* [81])
Sheep	Intra-articular injection	Adipose-Derived Mesenchymal Stem Cells	This study showed that in a sheep OA model, intraperitoneal injection of allogeneic AD-MSCs in combination with HA could successfully inhibit the development of OA and accelerate cartilage regeneration.	(*Feng et al.* [44])

Goats	Intra-articular directly into the joint section	hUCB-MSCs combined with cartilage acellular matrix injection (CAM Inj.)	In a goat model, therapy with a combination of hUCB-MSCs and CAM Inj. decreased the symptoms of OA and effectively repaired the cartilage.	(*M. Kim et al.* [44])
Horses	Intra-articular injection	Allogeneic bone-marrow (BM) derived MSCs and umbilical cord blood (UCB) derived MSC	The findings suggest that allogeneic BM-MSCs are a potentially effective therapy for OA in equines.	(*Bertoni et al.* [11])
caprine	Direct intraarticular injection into injured knee	Adult mesenchymal stem cells	Resulted into regeneration of meniscal tissue and retards the progressive destruction	(*J. M. Murphy et al.* [116])

In the above-mentioned table different animal model showed with their outcomes for the treatment of OA. Other practical factors that impact the choice of animal model are financial concerns, availability of resources, skilled labor, and housing options, as well as ethical issues [36,121]. Three solid justifications exist for carrying out animal research: 1) repeated failures of therapies, 2) methodological errors in research with animals, and 3) significant discrepancies between the results of clinical trials and animal models [136,82]. In preclinical models as well as in clinical settings, Stem Cells (SCs) generated from bone marrow, umbilical cord, and adipose tissue have demonstrated strong immunomodulatory and anti-inflammatory properties. They have also been proven to improve tissue repair and regeneration [138]. Furthermore, during the past few years, greater quality data has arisen to support SCs therapy; hence, more technique improvement will be required to enable its frequent clinical use [31].

The application of stem cell therapies in clinical practice will be significantly impacted by successful pre-clinical investigations [115]. The goal of employing an OA animal model is to offer the greatest data regarding the presence, mechanism, timing, and location of a chemical, pathway, cell, or process in clinical disease to develop individualized OA treatments for human patients [167]. Through the identification of optimal delivery methods and investigation of various stem cell types and their corresponding therapy regimens, researchers hope to enhance the quality of life for individuals afflicted with osteoarthritis [115]. To progress the research and get closer to effective stem cell-based treatments for osteoarthritis, scientists, physicians, and regulatory agencies must work together continuously.

Clinical Trials: Safety Profiles and Patient Responses

Clinical trials, which evaluate the safety profiles and patient responses to stem cell therapies, have been essential in transforming the treatment of Osteoarthritis (OA) [115]. Studies conducted in vivo and in vitro should be used to establish the effective range of administration (i.e., dose) of stem cells or stem-cell-derived products employed in treatment. It is necessary to estimate the minimal effective capacity as well as the safe and effective treatment capacity, whenever possible [115]. These studies investigate the efficaciousness of stem cell therapies in mitigating pain, promoting joint function, and improving quality of life, as well as their safety and doses. Studies with extended follow-ups demonstrate the advantages of stem cell therapies in terms of their effectiveness and safety [130]. Despite obstacles such as long-term safety and optimal dosage, the platform trial strategy presents an opportunity to include personalized medicine into trial design and future clinical practice [62]. Clinical studies help develop tailored medicines and improve treatment strategies for OA *Yang Song, et al.,* To further improve the treatment of OA using stem cell therapies, ongoing research and collaboration are necessary.

Challenges and Considerations

The use of different kinds of stem cells to revolutionize Osteoarthritis (OA) treatment comes with a unique set of considerations and limitations. The biggest problem in striking a balance between safety and innovation is stem cell-based therapy regulation and accessibility, which is why a new approach is needed to distinguish between treatments that have been shown to work and those that reuire additional research [84]. Many countries have experienced different scandals. For example, the US Food and Drug Administration has created a stringent three-tier regulatory framework known as "regulations-regulation-guidance principles" for stem cell research. In contrast, Japan's regulations are laxer and more permissive, allowing stem cell products to be approved conditionally after just ten patients have provided positive clinical data [140]. Based on risk, authorities throughout the world are putting limits and rules on regenerative therapies. In order to guarantee the product's safety, purity, and potency before it reaches a patient, these measures include demonstrating that the product is manufactured in accordance with Current Good Manufacturing Practices (cGMP), complying with applicable premarket or post-market approval requirements, and regulatory oversight of the investigational product's preclinical and clinical evaluation [133]. Another difficulty is determining the ideal stem cell type and treatment schedule [33]. Prior to beginning cell-based therapy, a few things need to be considered, including availability, specificity, immunogenicity, regenerative potential, and ethical issues. More research is required to assess and compare the effectiveness of various stem cell types, including MSCs, iPSCs, and ESCs, to determine which treatments are best for certain patients.

To produce standardized treatment procedures that finally show the best injectate composition, dose, timing interval, frequency, and patient selection, more research is required [67]. More than 110 organizations make up the OAAA, and together they strive to

raise public awareness of OA prevention and management, offer educational materials, and increase target audiences' access to evidence-based programs, which include OA patients, community-based organizations, healthcare systems and providers, and policymakers [14]. It's critical to design pricing and reimbursement schemes that encourage investment in R&D without endangering the long-term viability of healthcare systems. Therefore, to guarantee that patients receive their medicines on time, payers and manufacturers must accept each other's limits, including budgetary constraints and limitations in the manufacturer's ability to generate proof. They also need to welcome creative thinking and new methods [27].

Ethical Considerations in Stem Cell Research and Clinical Translation

To revolutionize the treatment of Osteoarthritis (OA), stem cell research must take ethical factors into account [87]. Determining who owns stem cells, forbidding the trade of human bodies, monitoring biobanks, and providing information about the Oversight Committee on Stem Cell Research are some of the ethical, legal, and jurisprudential tactics for employing adult/somatic stem cells. Well-designed studies, adherence to biomedical research codes of ethics (particularly those pertaining to stem cell research, clinical trial studies, and animal studies), suitable cooperation with ethics committees, and respecting research participants' rights (including both human and animal rights) are some suggestions for addressing ethical issues for conducting stem cell research. Furthermore, expanding international bioethics networks is essential for bolstering regional and global organizational communications, fortifying legal frameworks, and creating easily accessible cooperative education programs at various levels [43]. Rapid advancements in stem cell-based regenerative medicine have raised stricter ethical guidelines for employing these treatments on patients [73,119]. The formulation of a relevant question precedes the clinical translation of the technology at hand, which may result in an answer that has both scientific and social significance. This is the first step towards addressing the ethical difficulties that all stem cell researchers encounter [37,119]. At every level of their study, the therapy's risks and benefits to patients and society must be considered [35,119]. To promote stem cell therapies for OA in an ethically and socially acceptable manner, it is imperative to uphold ethical values and carefully address these challenges.

Ensuring Safety: Mitigating Risks and Adverse Effects

Although cell therapy has been shown to be safe, more extensive controlled research is required to determine whether it can reduce pain and promote structural benefits in OA. To ascertain efficacy and enable meaningful comparisons of clinical research outcomes, standardization of cell product production (including potency evaluation), frequency and mode of delivery, and determination of target patient populations through stratification will be required [33]. The need of maximizing benefits, minimizing risks, and addressing any potential drawbacks with stem cell therapy for OA is emphasized in this note. Thorough examination is necessary at every stage of the development of stem cell therapies, from the source of the cells used to their expansion, modification, and preclinical testing to their eventual engraftment in the host [53]. To protect patients' wellbeing, it's also critical to create secure delivery systems for stem cells and to closely follow legal and moral requirements [80]. Enhancing efficacy and safety through optimal stem cell types, administration methods, dosage plans, and long-term safety evaluations are some of the next prospects in stem cell-based HF therapy. Crucial elements of the changing environment include personalized treatment, combining therapies, resolving moral and legal issues, and increasing access while cutting costs [126]. There is a lot of potential for improving patient outcomes, cutting healthcare costs, and meeting unmet clinical requirements in the treatment of musculoskeletal illnesses using stem cell technology in orthopedics [1].

Standardization and Regulation of Stem Cell Therapies

To successfully include various types of stem cells into the revolution of treating Osteoarthritis (OA), standardization and control are essential. There is a lack of uniformity in control groups, cell dosage and application, and stem cell procurement methodologies in the current studies [131]. This comment emphasizes how crucial it is to set up standardized procedures and robust regulatory frameworks to guarantee the ethical, effective, and safe application of stem cell treatments for osteoarthritis. A quality control analysis's cellular identity, purity, sterility, viability, and potency are crucial components to produce stem cells and their medicinal uses. For the generation of stem cells and their therapeutic applications, a quality control analysis's cellular identity, purity, sterility, viability, and potency are essential elements [31]. Working together, academics, doctors, and regulatory agencies may create comprehensive laws that strike a balance between safety, innovation, and accessibility [137]. This method, which uses potent stem cell therapy, completely transforms how OA is treated.

Patient Outcomes and Success Stories

Promising outcomes and heartwarming patient success stories have resulted from the investigation of various types of stem cells in OA treatment [110]. These days, medication- or surgery-based conventional treatments are ineffective, and one of the most promising approaches to cartilage regeneration is cell-based therapy. This leads to decreased discomfort, increased joint mobility, and an overall higher quality of life [68]. Statistically significant better results were reported by patients treated at earlier stages of deterioration. The patient's participation in recreational activities and quality of life significantly increased because of the significant improvement in pain and function scores [111]. Gathering thorough information on patient outcomes and follow-up outcomes is essential for improving treatment strategies and customizing medications for each patient to get the best outcomes. These encouraging results show that stem cell therapies have the potential to transform the way that OA is treated and improve the lives of those who are impacted, giving hope to those who suffer from the condition.

Improved Pain Relief and Enhanced Joint Function

Application of several stem cell types to treat Osteoarthritis (OA) is transforming the condition and shows promising outcomes

in terms of greater pain alleviation and improved joint function [10]. Damaged cartilage can be repaired by the multilineage potential of stem cells, appropriate scaffolds, and chondrogenic agents (chemical and mechanical stimulation) [87,79,143-149]. Following these therapy, patients' pain is significantly reduced, giving them back control over their everyday activities. Furthermore, these therapies aid in the repair of damaged cartilage, which enhances the affected joints' mobility and functionality. To fully realize the potential of stem cell therapies in transforming the treatment of osteoarthritis, ongoing research and treatment protocol modification are essential.

Enhanced Quality of Life and Functional

Continuous advancements have been made in the clinical application of stem cell treatment for osteoarthritis in recent years. A few new stem cell medications are being applied for approval in China for OA clinical trials. In China, the therapeutic application of stem cells for the treatment of osteoarthritis is evolving quickly. Additionally encouraging on a global scale is the clinical use of stem cell therapy for osteoarthritis [116]. The use of Stem Cell therapies (SCs) improved the functional state of OA affected joints by promoting cartilage regeneration and reducing joint inflammation. A small number of case studies showed that OA modification and cartilage volume regeneration improved people's quality of life [54,55-60]. Numerous studies describe how fully developed chondrocytes can be used to generate a population of cartilage stem/progenitor cells under culture conditions. These cells have the capacity to revert to their chondrocytic phenotype for effective cartilage regeneration [72-81]. The patient's functional improvement and significant pain alleviation were achieved with stem cell treatment [122-129,85]. This study demonstrated the safety, tolerability, and preliminary efficacy of AD-MSCs in the treatment of knee OA; however, bigger, more stringent long-term trials are required for additional assessment [10-19]. Although cell-based therapy shows promise, further research is required to ensure treatment safety and change how OA is managed, ultimately helping those who suffer from the illness [69,153-170].

Conflict of Interest

None.

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