Advantages and challenges of stem cell therapy for osteoarthritis (Review)

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Abstract. Osteoarthritis (OA) is a degenerative disorder of the cartilage and is one of the leading causes of disability, particularly amongst the elderly, wherein patients with advanced-stage OA experience chronic pain and functional impairment of the limbs, thus resulting in a significantly reduced quality of life. The currently available treatments primarily revolve around symptom management, and is thus palliative rather than curative. The aim of the present review is to briefly discuss the limitations of some of the currently available treatments for patients with OA, and highlight the value of the potential use of stem cells in cellular therapy, which is widely regarded as the breakthrough that can address the present unmet medical needs for treatment of degenerative diseases, such as OA. The advantages of stem cell therapy, particularly mesenchymal stem cells, and the challenges involved are also discussed in this review.

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1. Introduction

Arthritis is an umbrella term used to refer to diseases that cause pain and inflammation of the joints, and it characterized by painful inflammation and stiffness of the joints (1). Osteoarthritis (OA) is one of the most commonly diagnosed types of arthritis, and it is considered a chronic, debilitating and prevalent joint disease, accounting for ~23% of all cases of musculoskeletal disorders, according to the Global Burden Disease study 2017 (2). In brief, OA occurs due to the loss of articular cartilage within the synovial joints with the natural propensity to occur in elderly individuals (3,4). The high count of years lived with disability of patients with OA makes it one of the leading causes of disability, where patients with advanced-stage OA tend to experience chronic pain and functional impairment of the limbs, thus resulting in a poor quality of life (1).

Generally, a healthy joint possesses a layer of slippery tissue known as the articular cartilage, which is comprised primarily of chondrocytes and extracellular matrix (ECM). The ECM is predominantly made up of proteoglycan and type II collagen fiber (5). With several roles in the musculoskeletal system, the articular cartilage lubricates the bones during angular movements and absorbs shock to prevent the bones from impacting one another. This involves the spreading of the load evenly across the joints during weight-bearing activities (such as walking and weight-lifting), as well as high-intensity activities (such as running and jumping). Additionally, the articular cartilage also acts as a reservoir that stores synovial fluid; a fluid that transports nutrients to the joints (1).

Cartilage can be damaged through several factors, such as injuries as well as autoimmune diseases including rheumatoid arthritis (6). However, it can also be damaged from wear-and-tear over time. Typically, the occurrence of wear-and-tear are often counteracted by the repair and renewal of articular cartilage. However, the regenerative capacity is dependent on several aspects, including genetic background, age, sex, body weight and the level of physical activity an individual partakes in (7). When the cartilage damage outweighs the regenerative capacity of the body, thinning of the articular cartilage occurs followed by a progressive loss of articular cartilage. Under such circumstances, the individual will thus be diagnosed with OA (5).

OA is also referred to as degenerative arthritis due to its tendency to develop as a person ages, as well as the fact that it is characterized by the loss of the cartilage that leads to constant friction followed by the eventual deformation of the bones (1,8). In such events, the patient will experience inflammation and subsequently, pain and stiffness to the joints (7,8). OA can affect any joint in the body, but often occurs in the knees, small joints of the fingers, lower back, neck and hips (9). Though it was typically accepted that it occurs as part of the aging process, there are other causes of OA including congenital bone deformities, joint overuse, traumatic injuries, obesity and genetic diseases, such as Paget's disease and diabetes (7,10,11).

2. Challenges of conventional treatment methods for OA

The primary process that underlies the development of OA is the substantial degeneration of the structures within the articular cartilage, thus causing severe pain and reduced mobility. Unfortunately, the treatment options available for patients with OA are palliative measures rather than curative. Symptom management, with a focus on halting or slowing the progression of OA range from physical and nonsurgical therapies to surgery, including: i) Exercise programs for muscle strengthening and weight loss, and the use of supporting devices such as braces; ii) pharmacological interventions to alleviate pain; and iii) surgical interventions (12,13). However, there are certain challenges and limitations to all of these approaches as discussed in the following subsections.

Physical measures. A basic attempt to treat OA involves the introduction of an exercise program to strengthen the muscles surrounding the affected joints, and to promote weight loss if required. With regards to knee OA, where the knees act as the pillar of support to the human body, a study demonstrated the association between muscle weakness, particularly the quadriceps, and the development of knee OA (14). In addition to weak muscle strength, obesity which is suggested to be secondary to inactivity, is well-established to favor the development of knee OA through increased leverage, whereby the risk of knee OA is reported to increase by 36% with every 2 units of body mass index (BMI) gained, and the likelihood of developing knee OA by 4.2x in individuals with a BMI >30 kg/m^2 (15,16). Hence, it was recommended that patients with OA increase the amount of exercise they do, such as weight lifting and strength training to increase muscle strength, as this has been proven to reduce pain and improve physical function, as well as aid in weight-loss (17-20). However, the pain and physical restrictions that come with OA often act as hurdles that keep OA patients from implementing and sustaining such activities. In addition, maintaining a healthy weight is another challenge faced by patients with OA, as it requires (often substantial) changes to their lifestyle, long term determination, and commitment to achieve noticeable results.

Use of braces. The general purpose of the braces is to provide support, as well as align and immobilize the area of the affected the joint (21). They prevent and correct deformities, thereby improving function and assisting in slowing the progression of the disease (22). There are several categories of braces available for various purposes. The unloader knee brace is used specifically for patients with OA to alleviate pain and improve physical function. Other categories of braces include the prophylactic knee brace, which is used to provide protection of the healthy knees against injuries during athletic activities; the patellofemoral knee brace which is used for anterior knee pain; and the functional knee brace is used to improve stability of an unstable knee in ligament injuries, such as a torn anterior cruciate ligament (ACL) or post-ACL reconstruction (22). Studies have reported that the use of braces has beneficial effects for patients with OA by reducing the pain they experience, improving the physical function of the affected joint, as well as delaying the need for surgical interventions (23,24). However, despite the benefits of these braces, it is only able to provide short-term pain relief, and are inefficient for long-term management (25). Furthermore, the efficacy of the knee braces varies between patients with OA; as indicated in certain studies, the use of braces lacks symptomatic relief, may fit poorly, and may cause discomfort when wearing the braces as well as skin irritation (26,27).

Medication. The use of pharmacological treatments for OA is often considered as a supplement in cases of severe OA, following failure to relieve symptoms by non-pharmacological methods (28). Some of the drugs used are analgesics, such as acetaminophen and opioids, NSAIDs and COX-2 inhibitors (29). Although the complementary usage of drugs and non-pharmacological regimen has been shown to be most effective for pain management of OA, there are safety concerns regarding the adverse effects of the drugs on the human body, such as liver toxicity as well as renal, cardiovascular and gastrointestinal side effects (29).

Surgical intervention. Surgery is considered as the final resort, when both pharmacological and non-pharmacological regimens fail to relieve the symptoms in patients with severe OA, particularly when their joints have entered a state of severe damage, causing unbearable pain, as well as deterioration of function in the affected patient. The types of surgical treatments for OA include arthroscopic lavage and debridement, cartilage repair, osteotomies and joint arthroplasty (30). Arthroscopic lavage and debridement are often performed as an initial surgical option that entails the removal of fragments of the meniscus, loose cartilage or osteophytes, and shaving of rough cartilage, and has been shown to alleviate pain and improve physical function (31). However, it has been demonstrated in randomized controlled trials that arthroscopic surgery was no more effective than a placebo surgery for treating knee OA. In the early 2000's, two seminal studies by Kirkley *et al* (32) and Moseley *et al* (33), made an impact on the use of arthroscopy for OA, in which the authors reported that patients with OA who received arthroscopy lavage and debridement did not show any improvements in the pain score and physical functions compared with a placebo group who underwent a sham surgery, a group that received optimized therapy, and a group that underwent physical therapy. The publication of these two landmark studies was followed by the update of the guidelines for the treatment of OA by the United Kingdom's National Institute for Health and Care Excellence, which no longer recommends arthroscopy as a treatment for OA (1).

The final resort for a patient with OA who has progressed to the most severe grade would be a total joint replacement. However, the procedure for joint replacements may cause unbearable pain and requires a long duration for rehabilitation. The adverse outcomes observed in patients who undergo total knee replacement surgery include myocardial infarction, infections and pulmonary embolism (34).

3. Stem cell therapy

The inconsistency of palliative treatments for OA highlight the need for a more reliable and curative approach that targets the root cause of OA; the degeneration of articular cartilage. Hence, the notion of stem cell therapy has galvanized intensive investigation into its potential use for treatment of OA, due to its regenerative properties. Owing to their excellent self-renewing capacity as well the ability to differentiate into >200 cell types, the use of stem cells in cellular therapy has ushered in an exciting new epoch for the fields of regenerative medicine with grounds for optimism to address the present unmet medical needs to treat a variety of degenerative diseases, including OA (35). At present, three types of stem cells are commonly studied with regard to stem cell therapy: Embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult stem cells, and these are discussed below.

ESCs. ESCs are considered to be totipotent stem cells derived from the fertilized zygote cell, wherein the embryo is usually 4-5 days old (35,36). The use of embryonic stem cells has generated ethical concerns, particularly with regard to how they are obtained (37). Hence, it is restricted for use in biomedical research only, and is to date, illegal for use as a treatment of any diseases, as their remains a notable bone of contention over the considerable ethical issues that arise, given that an embryo must be aborted to obtain the ESCs (37,38).

iPSCs. As one of the major revolutions in stem cell research, the identification and interest in research on iPSCs was spurred on by the ethical issues raised over the sourcing of ESCs (39,40). iPSCs were first discovered in 2006 by Takahashi and Yamanaka (39) who successfully reprogrammed the terminally differentiated fibroblast to an iPSC via introduction of four transcription factors, the so called Yamanaka factors; Sox2, Oct3/4, Klf4 and c-Myc (39,41). Similar to ESCs, iPSCs exhibit a high degree of pluripotency, with the additional benefit of circumventing the ethical concerns regarding the use of ESCs.

Despite its initial promise as a potential substitute for ESCs however, the transition to iPSC research for clinical applications highlighted several obstacles inherent to the use of iPSCs for cellular therapy, which includes genomic instability, immunogenicity, teratoma formation and clonal variations amongst iPSCs derived from the same donor cells, thus raising major concerns over the safety of their use clinically (40,42,43).

Adult stem cells. Adult stem cells are usually found in differentiated cells of specific tissues after birth, and are further categorized into hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) (44). The regeneration of the damaged tissues using adult stem cells was greeted as a breakthrough in relatively recent years, and has exhibited encouraging outcomes when used for treatment of several chronic degenerative conditions, such as degenerative disc disease, Parkinson's disease and amyotrophic lateral sclerosis. Numerous studies have demonstrated the safety and efficacy of adult stem cells for the treatment of several diseases (45-47).

HSCs. HSCs are the building blocks for the production of blood cells, including the erythrocyte and leukocyte lineages, as well as platelets (48,49). HSCs are found in the bone marrow and the umbilical cord, and are now primarily used for the treatment of the majority of disorders of blood cells, including primary immune deficiencies, congenital cytopenia, and storage and metabolic disorders (50,51). The transplantation of HSCs has been shown to ameliorate bone lesions, a decline in cognitive and central nervous function, as well as improving the survival of children diagnosed with Hurler's syndrome (the most severe form of mucopolysaccharidoses) (52). Furthermore, the use of HSCs has been deemed to be curative in the treatment of sickle cell diseases (53). There have been attempts to assess the efficacy of HSCs for the treatment of OA, wherein a study by Abdelmoaty *et al* (54) showed that patients who received repeated injections of autologous peripheral blood stem cells experienced improvements in physical function as well as improved articular cartilage quality. At present, the only FDA-approved stem cell products consist of hematopoietic progenitor cells that are derived from umbilical cord blood, solely for the treatment of blood disorders involving the hematopoietic system (55).

MSCs. MSCs are multipotent stem cells that are found ubiquitously throughout the musculoskeletal system in the human body, and can differentiate into various cell types including, but not limited to, osteoblasts, chondrocytes, adipocytes, astrocytes and cardiomyocytes (56-61). They can be isolated from the HSCs based on their ability to adhere readily to the plastic surfaces of tissue culture plates (56). MSCs can be derived from various tissues in the body, including bone marrow, adipose tissue, synovium, umbilical cord blood, dental pulp, amniotic fluid, dermis and peripheral blood (62-67). The characterization of MSCs are defined based on a guideline proposed by the International Society for Cellular Therapy (ISCT); the minimum criteria being that cells exhibit expression of specific markers, including CD44, CD90 and CD105, but lack expression of CD34, DC45 and CD133, as these are markers of HSCs (68). The revelation of the intrinsic nature of MSCs to regenerate and differentiate into chondrocytes has increased interest in the investigation of MSCs, and they show potential as an excellent alternative treatment option for OA. One study that used bone marrow aspirates in treating knee OA has successfully entered clinical trial phase 4, and was registered in ClinicalTrials.gov (Identifier, NCT03289416). In this clinical trial, undifferentiated cells found in the bone marrow aspirate concentrate (BMA) were shown to promote healing of damaged tissue, and aid in growth, repair and tissue regeneration. Whereas the full benefits of BMA remain to be elucidated, studies have shown that this treatment can relieve pain, and improve healing in articular cartilage and bone grafts (69). Although MSCs can be derived from numerous tissues in the body as mentioned previously, the two types of

MSCs that are widely studied for the treatment of OA are bone marrow-derived MSCs (BMSCs) and adipose-derived stem cells (ASCs) (70,71).

4. Types of MSC therapy for the treatment of OA

BMSCs. BMSCs are a population of fibroblast-like cells that reside in the stroma of the bone marrow (66). These MSCs were initially isolated from the bone marrow aspirate of the iliac crest, before the subsequent emergence of MSCs derived from other tissues, such as adipose tissue, umbilical cord and amniotic fluid (72,73). Currently, BMSCs are regarded as the gold standard and remain the most frequently investigated cell type, as they are hypothesized to possess higher potential for chondrogenic differentiation (70). There are 58 registered clinical trials in Clinicaltrials.gov (as of March 2021), on the use of BMSCs for treatment of osteoarthritis using the key words 'osteoarthritis' and 'bone marrow stem cells'. However, only a handful of studies have been completed and have published their results (74-81).

ASCs. ASCs are stem cells isolated from adipose tissues. They were first identified as an MSC in 2001 (82), following which, they have been widely studied for their potential therapeutic value in regenerative medicine and tissue engineering (63,83-85). Although ASCs exhibit similarities to the BMSCs, there are several distinct characteristics between these 2 types of stem cells, such as their differentiation potential and the complement of cell surface markers. BMSCs express CD106 (a marker that is involved in MSCs-mediated immunosuppression and the binding of hematopoietic progenitor cells) which was found to be absent on ASCs (86,87) and the ASCs express CD49d (α4 integrin that is involved in facilitating leukocyte migration) which was not detected on BMSCs (86). Unlike BMSCs, ASCs can be obtained in high yields from adipose tissues, which can be found abundantly in the body (84). It has been estimated that MSCs account for 0.001-0.004% of the bone marrow aspirate cells, whereas ASCs account for ~2% of the lipoaspirate cells (84). The isolation of ASCs can be performed via liposuction aspirates or from subcutaneous adipose tissue fragments, and is less invasive compared to BMSCs (63). As of March 2021, 52 registered clinical studies were found on Clinicaltrials.gov using the key words 'osteoarthritis' and 'adipose stem cells'.

5. General advantages of MSCs over other types of stem cells for therapeutic purposes

MSCs are favored over the other types of stem cells, as they exhibit numerous advantages for therapeutic purposes, such as their relative abundance, ease of isolation, their multilineage differential potential, lower risk of malignant transformation, immunomodulatory properties and the lack of ethical issues.

Abundance and ease of isolation. Previous reports have suggested that MSCs originate from the perivascular niche, thus making it possible to isolate them from various tissues in the body such as bone marrow, adipose tissue, peripheral blood, the placenta and the umbilical cord (72,73). However, the bone marrow and subcutaneous adipose tissues remain the preferential sources of obtaining MSCs, due to their relative abundance in the human body, particularly in the subcutaneous adipose tissue (88).

Multilineage differential potential. MSCs can be differentiated into various cell lineages. Over the years, in addition to the production of osteocytes, chondrocytes and adipocytes from MSCs, studies have also successfully induced MSCs to differentiate into oligodendrocytes (89-91), insulin-producing cells (71,92,93) and cardiomyocytes (94), highlighting their potential for the treatment of various degenerative diseases, including diabetes mellitus (95), cardiovascular diseases (96,97) and bone diseases (98).

Lower risk of malignant transformation. MSCs are endogenously programmed to exhibit limited proliferation capacity in cultures, after which cells enter a state of senescence, preventing their ability to divide; this is termed the 'Hayflick limit' (99). Senescence is defined as a stress response that results in the arrest of cell proliferation, thus preventing the propagation of damaged cells and lowering the risk of malignant transformation in the body (100).

Immunomodulatory properties. Another characteristic of MSCs that contributes to the advantage of using MSCs is that they have been shown to exhibit immunomodulatory properties, wherein they secrete anti-inflammatory cytokines to suppress both the adaptive and innate immune responses, thus permitting their use as universal donor cells without the need for immunosuppressants (101-103). This is due to the presence of unique surface markers that permit the MSCs to remain undetected by the immune system, including the lack of expression of major histocompatibility complex class II and co-stimulatory cluster of differentiation (CD) molecules such as CD40 ligand, CD40, CD80 and CD86 (104-107). This highlights the possibility for the use of allogeneic MSCs to treat patients who do not meet the criteria for autologous stem cell therapy.

Lack of ethical issues. Unlike ESCs, MSCs can be derived from various tissues in the body and hence, the ethical concerns associated with ESCs do not apply to MSCs. Although ESCs have received significant interest due to their high-degree of pluripotency, the use of ESCs in clinical applications remains controversial due to the safety concerns over teratoma formation, as well as the ethical issues with regard to sourcing (108,109).

6. MSC therapy offers analgesic, chondroprotective and regenerative properties when used for the treatment of OA

Studies on MSC therapy for OA that have been performed globally to evaluate their safety and efficacy, ranging from proof-of-concept studies to randomized controlled clinical trials, and have yielded positive results. Additionally, there are no studies showing notable side effects of the use of BMSCs and ASCs, and they have seen progressive improvements when used to reduce pain, physical function, stabilization of cartilage defects and even the thickening of articular cartilage in patients with OA. Table I summarizes the randomized controlled trials of BMSCs and ASCs as a treatment for OA performed between

Table I. Summary of randomized clinical trials of BMSCs and ASCs for the treatment of knee osteoarthritis between 2010 and 2020.

Author, year	MSC source/type	Type of study	Experimental design	Intervention	Measurement	Outcomes	(Refs.)
Lamo-Espinosa et al, 2016	Autologous BMSC	Case series (n=32). Final follow-up, 12 months	Multicenter, randomized, controlled, phase I/II clinical trial	Administration, Single intra-articular injection of MSCs. Cell dose, $1x10^7$ cells (low-dose), and $1x10^8$ cells (high-dose).	VAS, WOMAC, X-ray and MRI	Pain reduction at 3 months. The group of patients injected with $1x10^8$ cells exhibited the best response to MSC treatment, which reduced pain and preserved knee joint space at month 12.	(75)
Bastos et al, 2018	Autologous BMSC	Case series (n=18). Final follow up, 12 months	Double-blinded, randomized, phase I clinical trial	Administration, Single intra-articular injection of MSCs vs. MSCs/PRP. Cell dose, Not mentioned	KOOS	MSCs alone or in combination with PRP were safe and resulted in significant clinical improvement in patients with knee OA for up to 12 months.	(136)
Bastos et al, 2020	Autologous BMSC	Case series (n=47). Final follow up, 12 months	Double-blinded, randomized, controlled clinical trial	Administration, Single intra-articular injection of MSCs vs. MSCs/PRP vs. Corticosteroid. Cell dose, $4x10^7$ cells	KOOS and Knee ROM	MSCs/PRP groups showed the highest percentages of improvement for the KOOS domains and global score.	(137)
Emadedin et al, 2018	Autologous BMSC	Case series (n=47). Final follow up, 6 months	Triple-blinded, randomized, placebo-controlled phase I/II clinical trial	Administration, Single intra-articular injection of MSCs. Cell dose, $4x10^7$ cells	VAS and WOMAC	Significantly reduced pain in 6 months.	(138)
Hernigou et al, 2018	Autologous BMSC	Case series (n=30). Final follow up, 12 years	Prospective, randomized, controlled trial	Administration, Single intra-articular injection of MSCs. Cell dose, 40 ml of bone marrow graft with an average of $6.5x10^3$ MSCs/ml.	Knee society score, radiograph and MRI	Reduction in pain, increase in cartilage volume, and reduction in bone marrow lesions in patients who received MSC treatment.	(139)
Vega et al, 2015	Allogeneic BMSC	Case series (n=30). Final follow up, 12 months	Multicentered, randomized, controlled phase I/II clinical trial.	Administration, Single intra-articular injection of MSCs. Cell dose, $4x10^7$ cells.	VAS, WOMAC, Lesquesne algofunctional indices, SF-12 and MRI	Allogeneic BMSC transplantation is safe and feasible with no major adverse outcomes; provides pain relief and significantly improves cartilage quality.	(77)
Gupta et al, 2016	Allogeneic BMSC	Case series (n=60). Final follow up, 12 months	Randomized, double-blind, multicentric, placebo-controlled, phase II study	Administration, Single intra-articular injection of MSCs Cell dose, $2.5x10^7$ cells, $5x10^7$, $7.5x10^7$, and $1.5x10^8$ cells	VAS, WOMAC, ICOAP, X-ray and MRI	Maximum symptoms reduction in patients treated with $25x10^6$ cells, at 12 months. However, no improvements in the morphology of cartilage were observed in any of the groups of patients.	(140)

Table I. Continued.

Author, year	MSC source/type	Type of study	Experimental design	Intervention	Measurement	Outcomes	(Refs.)
Song et al, 2018	Autologous ASC	Case series (n=18). Final follow up, 96 weeks	Double-blinded, randomized, phase I/IIa clinical trial	Administration, Repeated intra-articular injection of MSCs. Phase I, 1×10^7 cells (low-dose), 2×10^7 cells (mid-dose), and 5×10^7 cells (high-dose), repeated; Phase II, 5×10^7 cells (high-dose)	WOMAC, NRS-11, SF-36 and MRI	Significant reduction in pain and increase in volume of cartilage at week 48 onwards, particularly in the high dose group. Furthermore, the cartilage increased to a higher degree after the third injection.	(141)
Freitag et al, 2019	Autologous ASC	Case series (n=30). Final follow up, 12 months	Unblinded randomized controlled trial	Administration, Single or two intra-articular injections of MSCs. Cell dose, 1×10^7 cells	WOMAC, KOOS, NPRS and MRI	Significant reduction in pain and functional improvements in all patients who received the treatment. OA did not progress by the time of the final follow-up period in 89% of the patients who received two-injections.	(85)
Lee et al, 2019	Autologous ASCs	Case series (n=24). Final follow up, 6 months	Double-blinded, randomized, placebo-controlled phase IIb clinical trial	Administration, Single intra-articular injections of MSCs. Cell dose, 1×10^8 cells	VAS, WOMAC, KOOS, physical examination and MRI	Reduced pain and preserved size of cartilage defect of medial femoral condyle over 6 months.	(142)

MSC, Mesenchymal stem cell; BMSC, bone marrow-derived stem cell; ASC, adipose-derived stem cell; PRP, platelet-rich plasma; IL, interleukin; OA, osteoarthritis; TKA, total knee arthroplasty; MRI, magnetic resonance imaging; VAS, Visual Analogue Scale; WOMAC, The Western Ontario and McMaster Universities osteoarthritis index; KOOS, Knee Injury and Osteoarthritis Outcome score; Knee ROM, Knee range of motion; SF-12, 12-item Short Form health survey; SF-36, 36-item Short Form health survey; WORMS, Whole Organ Magnetic Resonance Imaging Score; NRS-11, The 11-point Numerical Rating Scale; ICOAP, The Measure of Intermittent and Constant Osteoarthritis Pain; NPRS, Numeric Pain Rating Scale
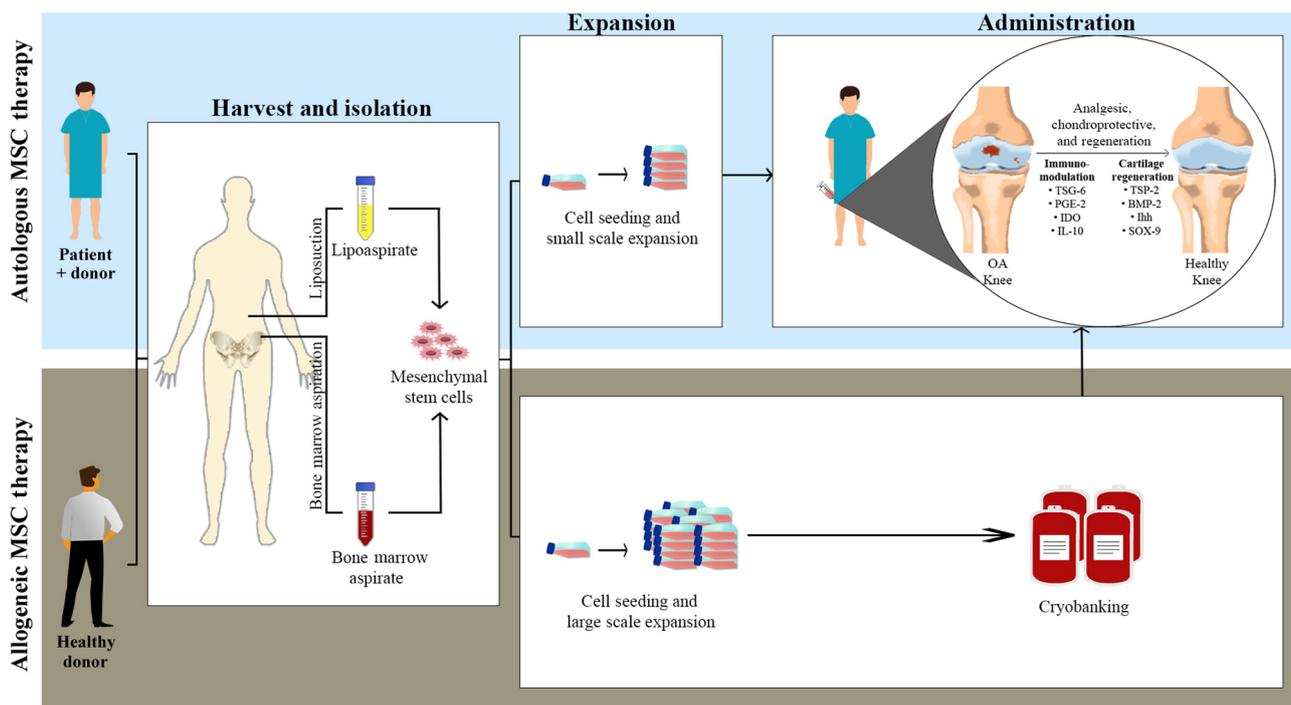
Figure 1. General procedures in using BMSCs and ASCs for the treatment of OA. Autologous MSCs are isolated from the patient's own tissue, whereas allogeneic MSCs are isolated from a healthy donor who is not a patient. The BMSCs and ASCs are harvested via bone marrow aspiration and liposuction, respectively, followed by the isolation of MSCs. The expansion of MSCs is performed on a small scale for autologous MSCs and large scale for allogeneic MSCs, and the latter are stored in a cryobank, to be later administered to patients with OA when required. MSCs are administered to the patients via intra-articular injection, and the expected beneficial outcomes post-treatment are analgesia, chondroprotective effects and cartilage regeneration. MSC, mesenchymal stem cell; BMSC, bone marrow-derived stem cells; ASC, adipose-derived stem cells; OA, osteoarthritis.

2010 and 2020. The general procedures used are as shown in Fig. 1. Collectively, the studies highlight their beneficial properties, exhibiting analgesic, chondroprotective and anatomical regenerative properties.

Analgesic and chondroprotective effects. Although the specific molecular mechanisms by which MSCs exert an analgesic effect remain to be elucidated, it is hypothesized that they revolve around its immunomodulatory effects, by inducing the synthesis of anti-inflammatory cytokines, such as IL-10, and downregulating the production of pro-inflammatory cytokines, such as IL-1, IL-6, TNFα and interferon (IFN)-γ (110-114). MSCs are able to secrete numerous soluble growth factors and cytokines, including TNFα-stimulated gene/protein 6 (TSG-6), prostaglandin E2 (PGE-2) and indoleamine 2,3-dioxygenase (IDO), which contribute to their ability to mitigate pain (103,115-117). It has been shown that the presence of MSCs results in the production of TSG-6, leading to inhibition of the toll-like receptors-2/nuclear factor κ-light-chain-enhancer of activated B cells signaling pathway, followed by the subsequent downregulation of inflammatory mediators, such as nitric oxide, TNFα and IL-1 (103,115). Upregulation of PGE-2 by MSCs leads to inhibition of the IFN-γ, inducing the differentiation of M1-type macrophages to M2-type macrophages (116). Similarly, the production of IDO by MSCs also promotes the conversion of M1 macrophages to M2 macrophages (117).

The homing migratory ability of MSCs to sites of injury and inflammation provides beneficial relief in both BMSC and saline-treated knee in patients with bilateral OA (118-120).

Chondrocyte regenerative effect. The regenerative effect of MSCs on the cartilage has been shown to involve the high expression of several genes responsible for inducing chondrogenesis, and the subsequent development of normal cartilage. These genes include the production of thrombospondin-2, which promotes the Notch signaling pathway; the production of bone morphogenetic protein 2, which induces the SMAD signaling pathway; and the Indian hedgehog signaling pathway, which promotes the expression of SOX9 followed by increased expression of the Col2a1 gene, thus stimulating the production of proteoglycans and type II collagen, all of which are involved in cartilage regeneration (121-123). The likely mechanism by which MSCs exert their anti-inflammatory and cartilage regenerative effects is summarized in Fig. 2.

Several studies have highlighted the analgesic effects of MSCs is addition to their cartilage regenerative effects; however, follow-up is usually limited to 6-12 months post-treatment. The long-term potential of MSC therapy may thus be underrated, as the structural changes required for a prominent effect take at least a year to occur (79,124).

In general, numerous reports have shown that as little as a single injection of a $1x10^6$ cell dose is sufficient for initiation of their analgesic effects, although eliciting chondrocyte regeneration response in cartilage requires a much higher dose of at least $1x10^8$ cells (81,125). Hence, higher quality randomized, controlled clinical studies with larger cohorts are required to strengthen the evidence and evaluate the quality of its therapeutic outcomes. Additionally, established protocols for consideration of the optimal dose, time of intervention, method of delivery and safety precautions also require extensive study.
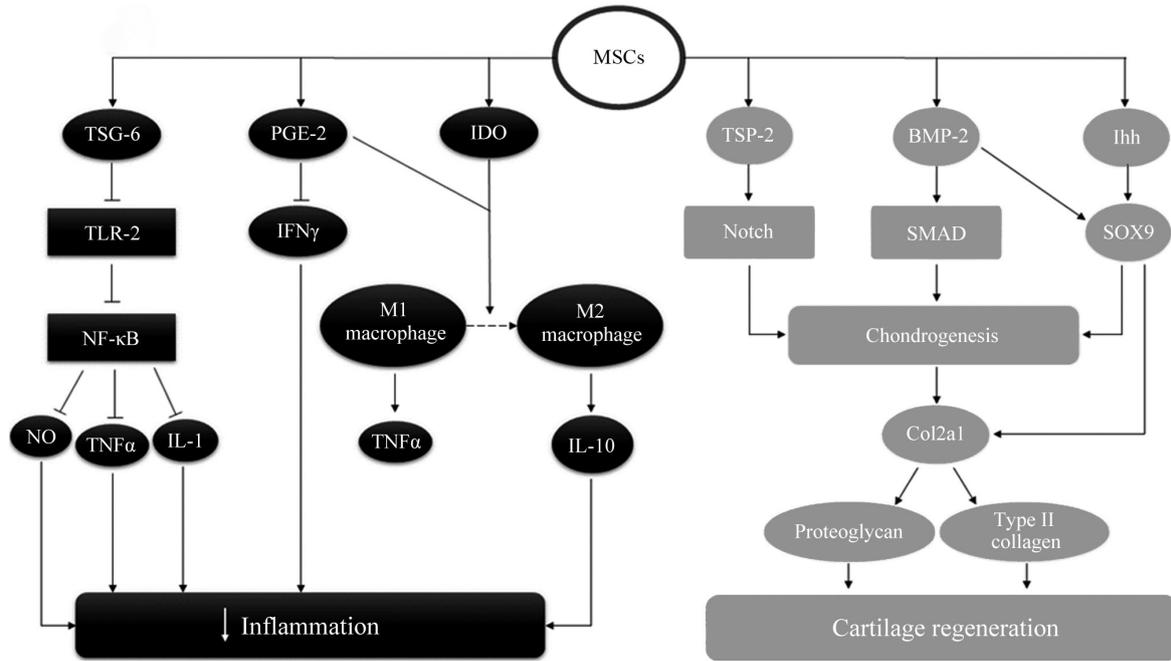
Figure 2. Summary of the likely mechanism by which MSCs exert their anti-inflammatory (black) and cartilage regeneration (grey) effects. Solid arrows indicate stimulation; dashed arrows indicate differentiation; flatheaded arrows indicate inhibition. MSC, mesenchymal stem cell; Col2a1, collagen type 2 α1 chain; IDO, indoleamine 2,3-dioxygenase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NO, nitric oxide; PGE-2, prostaglandin E2; SOX9, SRY-box transcription factor 9; TLR-2, toll-like receptor-2; TNF, tumor necrosis factor; TSG-6, TNFα-stimulated gene/protein 6; TSP-2, thrombospondin-2.

7. Challenges involved in the use of MSC therapy for OA

Despite the promising aspects for the use of MSCs clinically, this approach is considered relatively new and is surrounded by challenges involved in its use for OA, and these are discussed below.

Effects of the donor's health condition and age on stem cell properties. The differentiation potential and proliferation capacity of the MSCs are known to be affected by patients requiring autologous MSC therapy. Certain metabolic conditions, such as diabetes and obesity, can generate microenvironmental cues that predispose the differentiation potential of MSCs towards adipocyte differentiation rather than chondrocyte differentiation (126-128). Besides, the proliferative capacity of MSCs decreased with age (126).

Instability of chondrocyte-like phenotypes. One of the major challenges accompanying the use of MSCs for treatment of OA is the unsustainable cellular and hyaline cartilage phenotype of differentiated chondrocytes. Previous studies have documented the possible involvement of these cells in the development of heterotopic ossification, a process where bone formation occurs in non-skeletal tissues (129-132). These studies reported on the transient secretion of type II collagen from the MSCs, followed by the up-regulated expression of collagen type X, matrix metalloproteinase and alkaline phosphatase activity, thus indicating a shift from the chondrogenic to a hypertrophic phenotype that precedes osteogenesis, a phenomenon that does not normally occur amongst the chondrocytes found in the hyaline cartilage in the joints.

Limited replicative lifespan. As mentioned earlier, the MSCs will enter a state of senescence whereby they lose their ability

to proliferate. This is a double-edged characteristic, as it may lower the risk of malignant tumors, but limit the therapeutic use of stem cells. It was documented that the MSCs exhibited abnormalities in the morphology of the cells, such as enlargement, reduced expression of specific surface markers, and finally senescence as they reached higher passage numbers (133,134). The entry into a state of senescence in MSCs was shown to affect the differential potential of the cells, the immunomodulation capability and their migratory ability (133). Although cryopreservation of MSCs can be used to address this issue, the process comes with its own challenges; a decrease in viability, colony forming units and integrin expression were observed after cryopreservation and thawing of the cells (135).

Technical challenges. MSC therapy requires highly skilled professionals, as the culturing of MSCs must be performed with utmost care to prevent contamination of the cells. Additionally, considerably more research is required in order to establish a clear protocol for the isolation, expansion, differentiation and pre-conditioning of MSCs, and to determine the appropriate concentration of MSCs for use in patients with OA.

Social. While stem cell therapy may offer an attractive option for treatment of currently uncurable diseases, the costs are currently considerably high, owing to the need to cover the cost of the individual harvesting, isolation, and expansion of cells in a sterile facility. Additionally, the increasing popularity of stem cell therapy has warranted the use widespread biobanking, and an increased access to the various highly multipotent stem cells, which could be at risk of exploitation. Hence, policies on biobanking of stem cells must be regulated to address the possible issues regarding its usage, control as well as patients' consent.

8. Conclusions

The emergence of stem cell-based therapies has brought about novel avenues to address the, as of yet, unmet curative treatment for various degenerative disorders, including OA. The multipotency of the MSCs, along with its self-renewal and immunomodulatory properties, availability and ease of isolation highlight the potential use of MSCs for cellular therapeutic approaches in OA, and promising results have been demonstrated in various pre-clinical and clinical trials. However, several challenges are involved in this process, and this requires standardized solutions before they can be recommended clinically. Efforts on investigating and establishing protocols to increase the stability of the chondrocyte-like phenotype of the MSCs is required to raise the success rates of MSC-based treatment in patients with OA, and to lower the cost. In addition, the appropriate concentration of stem cells for specific treatments, and the long-term follow-ups of patients with OA treated with MSCs should be performed to investigate the long-term safety and efficacy of MSC-based therapy.

Availability of data and materials

Not applicable.

Authors' contributions

SJQL and NKW both wrote and revised the article. Both authors read and approved the final manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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