JSAMR
Journal of the National Student Association of Medical Research
Volume 4, Issue 1

Can stem cells revolutionise therapy for osteoarthritis?

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Peer-reviewed
Received: 12th July 2020
Revised: 27th August 2020
Accepted: 8th September 2020
Available online: 27th December 2020

Keywords: Stem Cells | Osteoarthritis

Abstract

Osteoarthritis is a debilitating joint condition which primarily causes damage to the articular cartilage, but also affects surrounding joint tissues such as the subchondral bone and overlying synovium. The condition presents itself through impaired joint function, reduced movement, increased pain and stiffness. There are various molecular mechanisms underlying osteoarthritis from abnormal activation of proteolytic enzymes to pathological inflammatory pathways; the end result is gradual cartilage (and ultimately other joint tissue) damage. Current therapy involves symptomatic management, with most patients undergoing total joint replacement eventually. New research into the functional mechanisms of stem cells introduces exciting opportunities for osteoarthritis therapy. Mesenchymal stem cells make an ideal candidate for the role. These cells possess the ability of self-renewal and are also able to produce a variety of anti-inflammatory molecules, which are hugely beneficial for the osteoarthritic joint. Numerous clinical studies have been analysed in this study to determine the efficacy of mesenchymal stem cells. This review aims to outline mechanisms underlying osteoarthritic pathology and potential therapeutic options for the future.

1 Introduction

Osteoarthritis (OA) is a chronic progressive functional and structural degenerative joint disease (Hunter & Feldon, 2006). It is estimated that approximately 8.5 million individuals in the UK have clinical OA, as defined by signs and symptoms such as joint pain, joint stiffness and functional limitations (Al-Najar M, Khalil H, Al-Ajlouni J, Al-Antary E, Hamdan M, Rahmeh R, Alhattab D, Samara O, Yasin M, Al Abdullah A, 2017). Prevalence increases with age, 13.9% of adults over the age of 25 experience OA in at least one joint while for individuals over the age of 65 that statistic jumps up to 33.6% (Peach CA, Carr AJ, 2005). By the end of 2020, OA is set to become the fourth most disabling disease globally. Its negative consequences don't just end there; OA was also found to have evident links with other conditions such as depression, sleep disorders and neuropathic pain (Makris EA, Gomoll AH, Malizos KN, Hu JC, 2015a; Malchau H, Herberts P, 1993). Unfortunately, left to its own resources the dysfunctional osteoarthritic joint has little hope of convalescence as it does not possess healing properties unlike most other tissues in the body (Klatt E, 2015). The aim of this review is to critically analyse the current prognosis and treatment of OA and evaluate the potentially different patient outcomes through the introduction of stem cell therapy.

2 Osteoarthritis

OA is a degenerative disease resulting in gradual joint dysfunction. Although all joints can be affected the knee,

hip and hand joints are the most common (Makris EA, Gomoll AH, Malizos KN, Hu JC, 2015b). The resulting pain is usually significant enough to hinder other physiological processes evidenced by knee OA being associated with a 1.55-fold increased risk for all-cause mortality (Tchetverikov I, Lohmander LS, Verzijl N, Huizinga TW, TeKoppele JM, Hanemaaijer R, 2005). All joint tissues undergo pathology in OA; from bone and menisci to ligaments and synovium. However it's the hyaline articular cartilage (AC) which is most affected; the eventual destruction of which prompts the need for surgical intervention. From a macroscopic prospective the AC goes through three phases of destruction; fibrillation, erosion and cracking. Eventually inflammatory alterations to the synovium and subchondral bone results in chondrocyte necrosis, extensive loss of cartilage and marked subchondral bone changes. The whole process is termed 'eburnation'. On a cellular level the AC undergoes an increase in water content and a reduction in proteoglycan and collagen. In maintaining homeostasis chondrocytes can synthesise new extra cellular matrix (ECM) to replace the degraded matrix although this process is incredibly timely; proteoglycan turnover can take upwards of 2 decades (Endres M, Andreas K, Kalwitz G, Freymann U, Neumann K, Ringe J, Sittinger M, Häupl T, 2010). In OA the rate of ECM destruction is higher than the rate of synthesis leading to an overall net reduction (Goldman L, 2011). These changes limit the AC's compressible properties and increase the permeability to tissue breakdown products.

AC is composed of sparse specialised chondrocytes and (mainly) ECM. ECM consists of type II collagen proteins which form a structural skeleton, elastin micro fibrils and aggrecan (aggregated proteoglycans) all of which are synthesised by AC chondrocytes (Malchau H, Herberts P, 1993). The swelling pressure of aggrecan and the tension of the collagen matrix is equal and opposing, giving AC the property of resilience under compression. Through the course of OA it is these molecules which undergo proteolysis. Enzymes of the 'A disintegrin Metalloproteinase with Thrombospondin motif' (ADAMTS) family are responsible for the damage that occurs to the aggrecan, especially ADAMTS 4/5. Whereas it's the 'collagenolytic matrix metalloproteinases' (MMPs) which provoke collagen breakdown. MMPs are secreted from chondrocytes and synovial lining cells undergoing physiological stress. These enzymes hydrolyse the collagen network effectively softening it, leading to the initiation of the superficial layer of AC into the fibrillation phase. This process of cartilage softening is called 'chondromalacia'. It was found that chondrocyte mRNA for various MMPs was significantly higher in OA versus non-OA patients (Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, Bridgett L, Williams S, Guillemin F, Hill CL, 2014).

Ultimately, the entire joint suffers. As the AC erodes it exposes the underlying subchondral bone. The unprotected bone is susceptible to wear and tear which results in the formation of micro fractures on the bony trabeculae. This induces osteoblast activity to regenerate the bone on a microscopic scale. Osteophyte formation and focal pressure necrosis is quick to follow leading to the formation of cysts on the subchondral surface. As a result of these alterations, subchondral bone is less able to dissipate energy upon excursion, thus increasing the force exerted on the joint which further enhancing cartilage damage (B Marcu K, Otero M, Olivotto E, Maria Borzi R, 2010; Scanzello CR, Umoh E, Pessler F, Diaz-Torne C, Miles T, Dicarlo E, Potter HG, Mandl L, Marx R, Rodeo S, 2009). Bone marrow oedema can build up in the subchondral bone along with vascular engorgement and reduced blood flow to the bone marrow, all of which contribute to the clinical features of pain in OA. Prevailing therapeutic options are aimed at targeting these features.

3 Current Treatment

Current therapeutic options for OA are limited. Often treatment is targeted towards alleviating the signs and symptoms of OA, rather than targeting the underlying pathology (Klatt E, 2015). Obesity is a fundamental risk factor for OA, and consequently weight loss is effective in non-pharmacological management. Clinical trials from 2005 showed that patients with knee OA experienced a 28% improvement in knee function (stiffness and joint pain) following a 10% reduction in body weight (B, 2006). Contrastingly pharmacological interventions focus mainly on pain management, ranging from NSAIDs (Non-steroidal anti-inflammatory drugs) to opioid use. NSAIDs and paracetamol are widely prescribed (Cryer B, 1998; Towheed T, Maxwell L, Judd M, Catton M, Hochberg MC, 2006) however the effects, while statically significant, are minimal as found by a Cochrane review in 2006 (Chalmers JP, West MJ, Wing LM, Bune AJ, 1984). Nonetheless chronic use of NSAIDs and paracetamol pose their own risks including cardiovascular, respiratory and GI side effects. More invasive therapeutic options include intra-articular corticosteroid injections and total joint replacement (TJR). TJR application introduces its own complications. While (for knee joints) 82% of TJRs last for 25 years (on average); TJRs are not completely effective and have numerous complications both during and after surgery (Sophia Fox AJ, Bedi A, 2009). Ranging from risk of infection and technical error during surgery to instability, misalignment, recurrent dislocation and osteolysis thereafter (Goldring MB, 2004; Moore K, 1998). Surgery for many is still not the preferred option for management. Finding an alternative therapeutic cure for OA is therefore a necessity, especially one which targets the elemental pathology in OA. Upcoming research into the regenerative abilities of stem cells introduces exciting new prospects for OA treatment.

4 Stem cells

Stem cells are defined as cells which possess the capability of self-renewal for a prolonged period, along with the ability to differentiate to produce at least one type of mature cell. These cells have the capacity to become all (totipotent) or most (pluripotent/multipotent) tissue types within the body. Subpopulations of stem cells are classified as embryonic stem cells (ESCs), adult stem cells (ASC) and cancer stem cells (CSCs). ESCs are pluripotent, giving rise to all cell types. CSCs are the basis for cancer development and have more sinister implications such as escaping physiological apoptosis

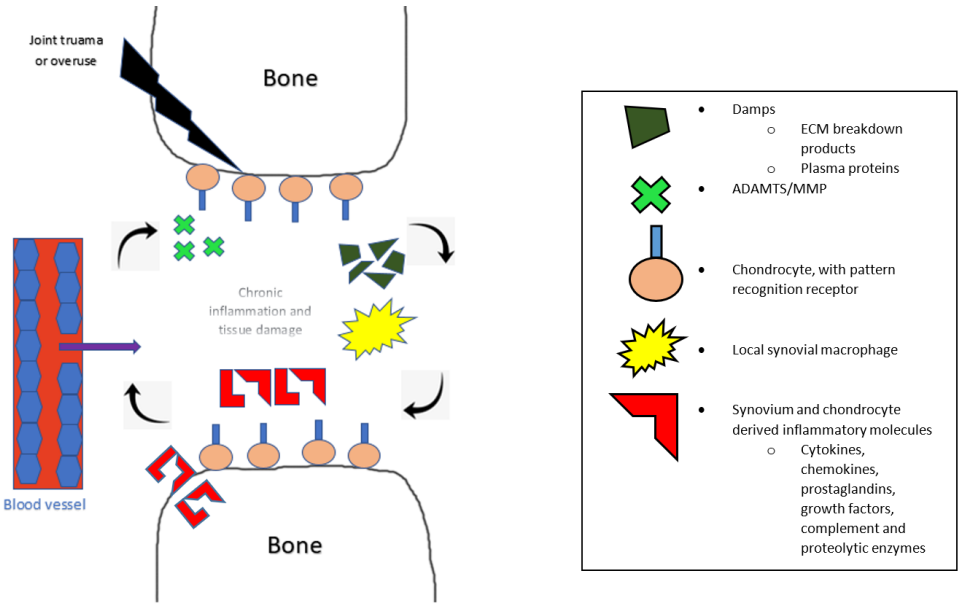

Figure 1: Schematic representation of chronic inflammation and pathological occurrences in an OA joint (Sokolove J, 2013)

(Goldman L, 2011). Induced pluripotent stem cells (IPSCs) are another prospective area of study. These cells exhibit many similarities to ESCs but are derived from somatic cells. These cells can be genetically re-engineered in vitro to regain proliferative properties and the potential to differentiate into various cell types (Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, 2007). The most important stem cells for OA therapy however are ASCs. ASC's main function is to replenish cells which undergo stress or death due to physiological wear and tear or pathology (Goldman L, 2011). Examples of such cells are mesenchymal stem cells (MSCs).

4.1 Mesenchymal stem cells

MSCs can differentiate into osteoblasts, adipocytes, myocytes and chondrocytes and (in adults) are derived from two main sources; adipocytes and bone marrow (Caplan AI, 2007; Somoza RA, Correa D, Labat I, Sternberg H, Forrest ME, Khalil AM, West MD, Tesar P, 2018). MSCs possess immunomodulatory and trophic properties through the release of growth factors and cytokines (Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, Grisanti S, 2002). Cytokines including TGF-β, HGF (hepatocyte growth factor) and PGE2 are all released. These function to reduce immune cell function, mainly by upregulating T-cell function (Dyer DP, Thomson JM, Hermant A, Jowitt TA, Handel TM, Proudfoot AE, Day AJ, 2014; Engela AU, Hoogduijn MJ, Boer K, Litjens NH, Betjes MG, Weimar W, 2013). TSG-6 (TNF-alpha stimulated gene/protein 6) is also expressed by MSCs and is a key component in the regulation of inflammation by inhibiting neutrophil chemotaxis while also possessing chondroprotective properties (Vonk LA, De Windt TS, Slaper-Cortenbach IC, 2015). Other T cells (CD4+ and CD8+) are also affected by MSCs. By releasing inflammatory soluble factors MSCs induce G0 arrest of the cell cycle of these cells or even cause apoptosis, exhibiting inhibition of both innate and adaptive immune pathways (Pers YM, Ruiz M, Noël D, 2015; Vonk LA, De Windt TS, Slaper-Cortenbach IC, 2015). MSCs also disrupt the local inflammatory response by suppressing B cell activation and antibody secretion which effectively eradicates the risk of tissue rejection for prospective stem cell transplantation.

5 Clinical Application

Before application to the patient stem cells often undergo in vitro 'expansion' (induced mitotic divisions) (Lai RC, Yeo RW, 2015). Although it is difficult to prevent phenotypic instability during this process there are numerous studies which show that factors such as TGF-β, Proline, Insulin, BMPs and FGF all enhance chondrogenesis and cartilage formation (Lefebvre V, 2015). In clinical application the MSCs are generally obtained from healthy donors, often from the posterior superior iliac spine region and expanded to large number before transplant. Minimal amounts of BM aspirate are required (between 2-4ml) which is mixed with heparin to prevent blood clotting. Clinical trial studies of MSC application are critical to analyse, in order to determine the efficacy and potential success of stem cell therapy.

6 Clinical Data

From all the studies that have been discussed intra-articular injections containing autogenic or allogenic MSCs showed positive clinical manifestations with no graft-related death, tumorigenesis or infection (Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A, Orozco L, Soler R, Fuertes JJ, Huguet M, 2015). Since the method of transfer of stem cells is minimally invasive and does not require surgery this significantly reduces risks of many surgical side effects unlike TJR.

Key:

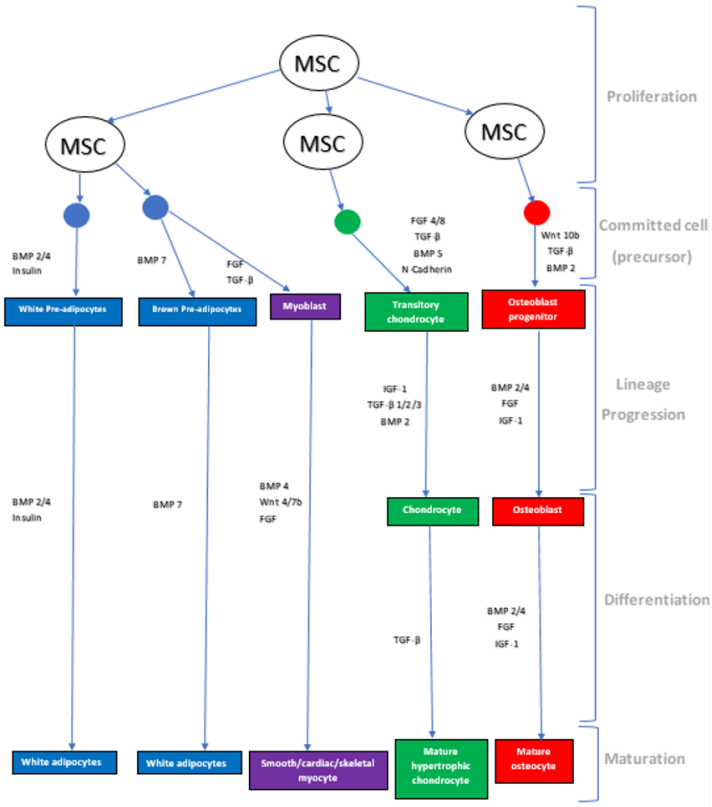

Figure 2: Schematic showing multiple differentiation pathways of MSCs. A diverse range of growth factors, receptors, intracellular signalling molecules and transcription factors are involved in aiding differentiation. Chondrogenic differentiation is displayed as the green lineage (Kolf CM, Cho E, 2007).

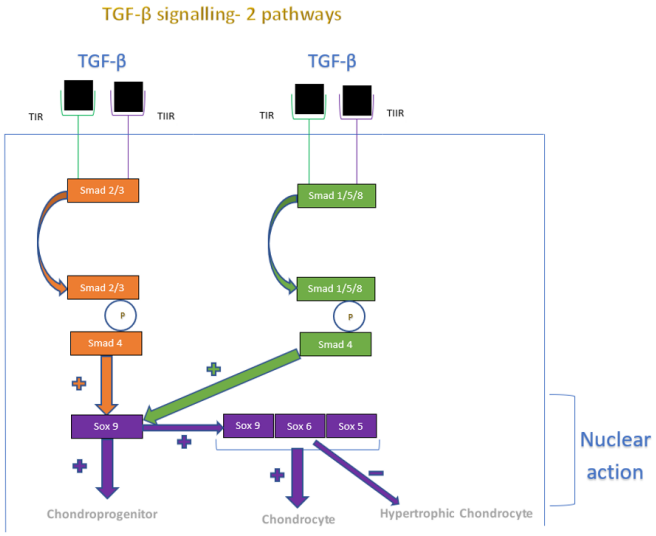

Figure 3: Schematic diagram displays two signalling pathways of TGF-β. Signals are transmitted via a pair of transmembrane serine/threonine kinases (TIR/TIIR). Multiple intracellular molecules are subsequently phosphorylated, resulting in an increase in activity of various transcription factors (Sox molecules). These molecules aid differentiation of the chondroprogenitor, while preventing excessive hypertrophy (chiefly through the action of Sox6) (Szychlinska MA, Stoddart MJ, D'Amora U, Ambrosio L, Alini M, 2017; Tang X, Fan L, Pei M, Zeng L, 2015).

1. KOOS: Knee injury osteoarthritis outcome score (measures 5 different categories, pain, other symptoms, ADL, function in sport and recreation and knee related QOL).
2. WOMAC: Western Ontario and McMaster universities osteoarthritis index (questionnaire with 3 categories measures, joint pain, stiffness, and functional limitations). Used in conjunction with HOOS (Hip injury osteoarthritis outcome score).
3. VAS: Visual analogue scale. Patients specify their level of agreement to particular statements; a more subjective scale.
4. Phase I/II clinical trials: Trials which determine the safety, side effects and best dosage of a new treatment and monitors disease progression. Usually different doses of drug are given in phase I and phase II of the trial.
5. Tegner activity scale: Sports based scoring system, on a scale of 0 to 10. 0 is disability, 10 represents international level sporting ability.
6. OARSI: Osteoarthritis research society international. Scoring system for the progression of OA.
7. PRP: Platelet- rich plasma.

All studies had expanded their initial harvest of cells. As can be seen from the numerous studies in the table there is overwhelming evidence to support the use of MSCs for OA treatment from both BM and AD sources, both allogenic and autologous, with many of the clinical trials reporting no tissue rejection. Testing categories ranged from safety to clinical outcomes and numerous studies have found MSCs to be effective in improving function and inducing repair in osteoarthritic joints. It is interesting to note however that certain studies, such as the one done by Pers et al in 2016 suggests the lowest dosage of cells given gave the most successful results. Hence investigating the optimal cell dosage is something which still requires further research. Potential use of a scaffold, most appropriate timing of intervention and method of MSC delivery are all among the components of methodology which require further investigation (Montoya F, Martínez F, García-Robles M, Balmaceda-Aguilera C, Koch X, Rodríguez F, Silva-Álvarez C, Salazar K, Ulloa V, 2013). The minimally invasive mechanism of intra-articular injections minimises risk of infection and significantly lowers risk of technical error during the procedure. While MSCs are an incredibly effective treatment option, costs of application to the NHS need to be considered.

7 Economic Implications

OA itself represents an enormous economic burden on the NHS. In 2000 there were 3 million GP consultations and 115,000 hospital admissions due to OA. Patients with OA often have multiple comorbidities, further adding to the complexity of care required. £250 million is spent annually on community and social services (as of 2010) and the total cost to the gross national product is estimated to be around 1%. In 2000 the economy suffered £3.2 billion in 'lost production', this brings into prospective the impact this condition has on our wider community. Surgical treatment introduces its own costs. There were 116,000 hip and knee TJR surgeries in 2010 which ultimately cost the NHS around £890 million (Pers YM, Rackwitz L, Ferreira R, Pullig O, Delfour C, Barry F, Sensebe L, Casteilla L, Fleury S, Bourin P, 2016). Demand for TJR has increased significantly with more than 160,000 TJR surgeries taking place in 2019 (Clinic, 2020a). Data on the costs of stem cells is limited although it is estimated that stem cell regeneration for one total knee OA would cost £6,400 (Clinic, 2020b). Affordability may not be the only hindrance; several eligibility criteria also prevent individuals from receiving stem cell treatment (such as needing to have a BMI of less than 35) (Clinic, 2020b).

8 Conclusion

There is overwhelming evidence to support the efficacy and safety of MSC application for OA therapy. After analysing multiple clinical studies I have found numerous positive outcomes from MSC therapy; not just to alleviate patient symptoms (as current OA therapy does) but to target and cure the fundamental underlying pathology. Nonetheless certain aspects of treatment require further research such as the correct dosage of cells and appropriate timing of intervention. Thus the need for a gold standard is necessary, to ensure maximum safety for patients. The nature of stem cells themselves however pose some ethical dilemmas which need to be addressed. Concerns regarding intentions for stem cell use, especially in the domain of ESCs, are often raised. Some argue this could violate the respect for nascent human life. Often in IPS/ASC research donors are not explicitly informed of which research procedures their donated cells will be part of, and who will be performing the study. As these databases are often accessed by large numbers of people, those who oppose this kind of research would argue that potential breach of data would be an invasion of privacy and confidentiality. These concerns can be addressed with more robust legislation, although the ethical stigma would still likely be associated. It is also critical to consider the expense of MSC therapy which as it stands would generate further economic strain on an already financially struggling NHS. However, with technological advancements and improvements in culturing and application methods, MSC therapy holds a very promising stance in the future of OA therapy.

Author statements

Conflicts of interest statement

No conflicts of interest have been declared by any authors.

Authorship statement

All authors fulfill ICMJE authorship criteria, which can be accessed at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. All authors have read and approved the final version, and accept responsibility for information published.

Type of study	Type of MSC /scaffold used	Number of participants/length of study	Cell dosage	Measurement technique used	Findings/results	Reference /year of study
Phase I/II study.	Autologous AD-MSCs with saline.	18 participants, with knee OA, 6 months follow up.	Three doses of cells administered: 1*10^7, 5*10^7, 1*10^8.	WOMAC.	Cartilage defect was reduced, while volume increased. Most significantly in higher dosage. Hyaline cartilage regeneration detected with clinical improvement in pain and function.	36. Year of study 2017 Jo Ch et al.
Phase I/II study.	Autologous BM-MSCs.	13 participants with knee OA, 24 months follow up.	One dose of cells administered: 30.5*10^6.	MRI and KOOS.	Significant KOOS improvements, and knee cartilage thickness had improved detected by MRI.	2. Year of study 2017 Mahasen Al Najar et al.
Phase I/II study.	Autologous BM-MSCs.	30 participants with knee OA, 12 months follow up.	Two doses of cells administered: 10*10^6 and 10*10^7.	VAS, WOMAC, X-ray and MRI.	Injection of the highest dose showed most clinical/functional improvement. Significant improvement in joint pain.	37. Year of study 2016 Lamo-Espinosa JM et al.
Phase I study.	Autologous BM-MSCs.	4 participants with knee OA, 60 months follow up.	One dose of cells administered: 8-9*10^6.	Walking time, X-ray and VAS.	Significant improvement in clinical knee function. Earlier transplantation had better results.	38. Year of study 2016 Soler R et al.
Phase I/II study.	Autologous AD-MSCs.	18 participants with knee OA, 24 months follow up.	Three doses of cells administered: 10*10^6, 50*10^6, 100*10^6.	VAS, WOMAC and MRI.	The highest dosage of cells were most effective in improving clinical joint function/mobility.	39. Year of study 2017 Jo CH et al.
Case series study.	Autologous AD-MSCs with PRP.	30 participants with knee OA, 24 months follow up.	One dose of cells administered 1.9*10^6.	VAS, Tegner activity scale.	Significant reduction in pain and improved joint function after 24 months of follow up.	40. Year of study 2012 Koh YG et al.
Case series, Phase I study.	Autologous AD-MSCs.	18 participants with knee OA, 20 months follow up	Three doses of cells administered, 2*10^6, 10*10^6, 50*10^6.	WOMAC, VAS, KOOS and OARSI.	Lowest dosage group showed best results. Improvements in joint pain/mobility.	41. Year of study: 2016, Pers et al.
Case series study.	Allogenic AD-MSCs.	30 participants with knee OA, 12 months of follow up.	One dose of cells administered: 40*10^6.	VAS, WOMAC and MRI.	Improvement in joint cartilage quality and reduction in pain.	42. Year of study, 2015, Vega et al.
Case series study.	Allogenic BM-MSCs.	30 participants with knee OA, 12 months of follow up.	One dose of cells administered: 40*106. Control group given 60mg of hyaluronic acid (15 participants in each group).	VAS and MRI (Figure 1).	Improvements in functional/structural properties of joint. Increases in cartilage size and quality.	35. Year of study, 2015, Vega Aurelio et al.

Table 1: In reference to Section 6 (Clinical Data)

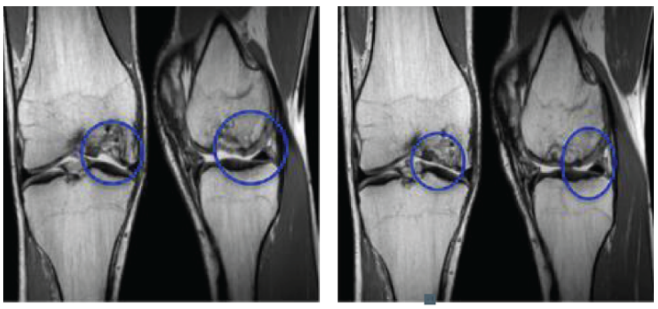

Figure 4: Schematic of MSC bases therapies in OA. MSC self-renewal properties and methods of application (left) and their molecular mechanisms in maintaining joint homeostasis (right) are all shown. Notably the immunomodulatory and anti-inflammatory effects via alterations to anti/pro-inflammatory molecules (Zhang R, Ma J, Han J, Zhang W, 2019).

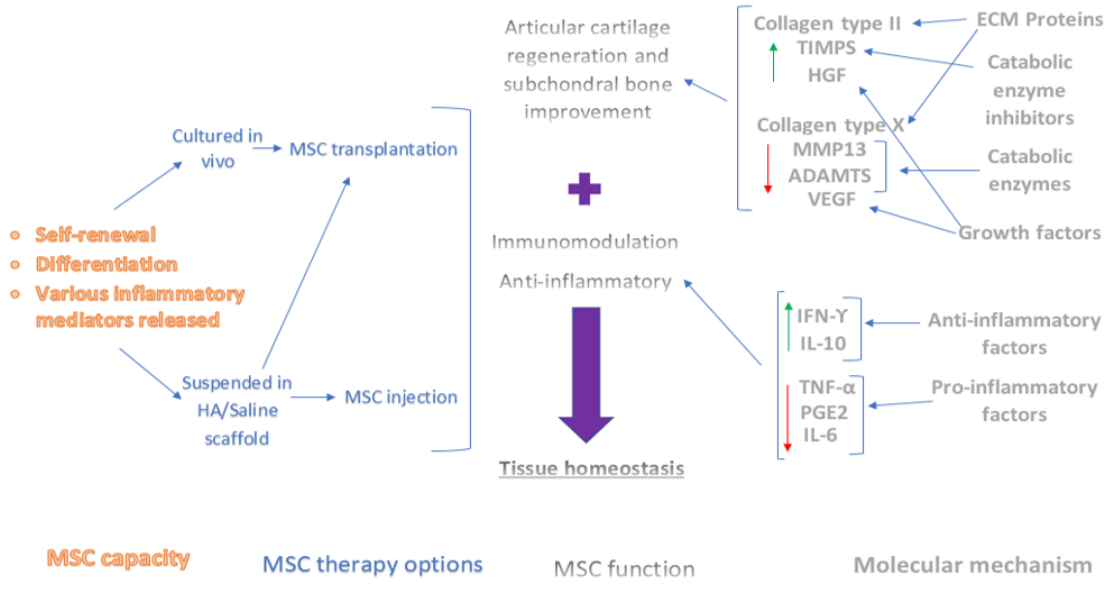

Figure 5: (Freitag J, Shah K, Wickham J, Boyd R, 2017) MRI of knee joint. Coronal (left) and sagittal (right) T2 weighted MRI images shown. A is pre-treatment, B is post treatment 12 months after initiating treatment. B shows significant regeneration of the articular cartilage.

Ethics statement

Authors declare that no ethical approval was required for this article.

Editorial and peer review statement

The review process for this manuscript was double blind, where authors and peer reviewers were blinded to each others identity and institution.

Open access and distribution statement

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