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Cell Based Therapy for Articular Cartilage Regeneration; Past, Present & Future

Goyal AD*

Department of Pathology, Smt. Nathiba Hargovandas Lakhmichand Municipal Medical College, India

***Corresponding author:** Anjali Deepak Goyal, Department of Pathology, Smt. Nathiba Hargovandas Lakhmichand Municipal Medical College, Pritan Rai Cross Road, Ellise Bridge, Paldi, Ahmedabad, Gujarat 380006, India, Email: anjali@knee.in

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Abstract

The articular cartilage around the knee joint is specialized for load bearing along with the transmission of sheer forces to the underlying bone. A damage to the cartilage following injuries, loading & aging can lead to the development of degenerative joint disorders (osteoarthritis). Treatment of large articular cartilage defects is technically difficult and complex, often accompanied by failure. Articular cartilage cannot repair itself after injury due to a lack of blood vessels, lymph, and nerves. The repair has been attempted by the various cartilage repair surgeries with a varying success rate & none with a perfect solution.

New minimally invasive and effective techniques are being developed. The development of cell based & tissue engineering technology has created a hope for articular cartilage reconstruction. This technology supplies stem cells with various sources of pluripotent and mesenchymal stem cells directed towards a hyaline cartilaginous differentiation to augment the repair techniques & holds a promise for the future [1].

The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The search terms used were Articular Cartilage Repair & Knee with 23,8864 results: further narrowing down to 303 studies over the past 10 years involving the use of PRP (Platelet Rich Plasma), chondrocytes & exosomes.

Keywords: Cartilage Regeneration; PRP; MSC; OA; Chondrocytes; Articular Cartilage Repair

Abbreviations

MF: Microfracture; ACI- Autologous Chondrocyte Implantation; CACI: Collagen Cover ACI; MACI: Collagen Bilayer seeded with Chondrocytes; PACI: Periosteum covered ACI; OCD: Osteochondral Defects; OATS: Osteochondral Autologus Transfer Surgery; OCT: Osteochondral Cylinder Transfer Technique; PBPCs- Peripheral Blood Progenitor Cells; IPSC: Induced Pluripotent Stem Cells; IHC: Immunohistochemistry; HA: Hyaluronic Acid; OA: Osteoarthritis; BMSC: Bone Marrow stem cells; ADSC: Adipose Derived Stem Cells; HADSC: Human Adipose Derived Stem Cells; DPSC: Dental Pulp Derived Stem Cells; PLSC: Peridontal Ligament derived Stem Cells; SDSC: Synovial Derived Stem Cells; WJMSC- Wharton Jelly Derived Stem Cells; PDSC: Periosteum Derived Stem Cells; AMIC: Autologous Matrix Induced Chondrogenesis; ECM: Extracellular Matrix; BEC: Bio Engineered Cartilage; TGF: Transforming Growth Factor; IGF 1: Insulin Like Growth Factor; HGF: Hepatocyte Growth Factor; FGF: Fibroblast Growth Factors; EGF: Epidermal Growth Factor; MCAM: Melanoma Cell adhesion Molecule; cDNA: Complementary DNA; BMP: Bone Morphogenetic Proteins; COMP: Cartilage Oligomeric Matrix Protein.

Introduction

Normal Structure of the Articular Cartilage

The Articular cartilage of the knee joint is a specialised form of hyaline cartilage which transforms the articulating ends of the bones into lubricated, wear-proof, slightly compressible surfaces exhibiting very little friction.

It comprises of cells called chondrocytes & highly specialized extracellular matrix (ECM) making up 95% of the total cartilage volume. The ECM is solid, firm and pliable. It plays a paramount role in opposing shear, tensile & compressive forces borne by the knee joint. It comprises of collagen (mainly type II), glycosaminoglycans (GAGs) for chondrocyte nutrition) along with proteoglycan aggregates which are important for weight bearing & nutrition of the chondrocytes by diffusion.

On histology the articular cartilage is 2-5mm in thickness in adults & is divided into four layers according to the structure of chondrocytes & the extracellular matrix, supported by the underlying subchondral bone. The lowermost or the basal zone comprises of the uncalcified & calcified zone separated by a tidemark. Whereas the superficial zone is associated with a primary load bearing, the deep layer transmits the load to the underling subchondral bone.

The adult articular cartilage around the knee is subject to a constant wear & tears with a limited regenerative capacity owing to the avascularity of the articular cartilage, immobility of the entrapped chondrocytes & a limited ability of mature chondrocytes to proliferate.

Hence the focal articular cartilage defects are progressive leading to deterioration of the cartilage & the development of degenerative joint diseases like osteoarthritis.

The treatment aims for articular cartilage defects are hence aimed at creation of a smooth articular surface with the repair tissue having the structure & composition similar to the original hyaline articular cartilage.

The regeneration of a fibrocartilaginous repair tissue having a variation in the collagen II content & ECM composition leads to an inferior quality of repair with a reduced capacity to bear the stresses & leads to failed repair & progression to degenerative joint disorders.

The treatment approaches include surgical therapies & associated newer cell based therapies.

The key reconstructive surgical therapies for adults include.

- Bone Marrow Stimulation Techniques
- Microfracture, Abrasio etc.
- Osteochondral Cylinder Transfer (OCT)
- Mosaicplasty, OATS
- Autologous Chondrocyte Implantation (ACI)
- P-ACI, C-ACI, Scaffold based ACI (MACI etc.)
- Autologous Matrix Induced Chondrogenesis

The repair tissue following the various intervention is assessed by Clinical & Histopathologic grading systems which include the ICRS (International Cartilage Repair Society) grading (I & II), Modified O'Driscoll score (MODS), Os Score & the Wakitani scores.

Each of the scoring system has points describing surface irregularities, Matrix mineralization, cell distribution & the subchondral bone.

A review of the morphology of repair tissue following various reconstructive therapies with a focus on high-quality randomized clinical trials is done.

Histopathology of Repair following Microfracture

Gudas R, et al. [2] studied patients with a single symptomatic Osteochondral Defects (OCD) or full-thickness articular cartilage lesion in a stable knee randomly divided to have either Osteochondral cylinder transfer technique (OCT) or Microfracture (MF) [2]. 15 of 29 (52%) patients treated by MF had good or excellent results 37 months after the operations with a significant p value.

Biopsies performed after one year in 14 patients with MF showed fibrocartilage and surface fibrillation which was different from the surrounding normal articular cartilage histology.

In a randomised control trial conducted by Knutsen G, et al. [3], 80 patients with a single chronic symptomatic cartilage defect on the femoral condyle in a stable knee without general osteoarthritis were randomised into ACI (Autologous Chondrocyte Implantation) & MF. No correlation between histological quality and clinical outcome was seen. At two and five years, both groups had significant clinical improvement compared with the preoperative status. However at the five-year follow-up interval, there were nine failures in both groups compared with one failure of the MF at two years. Also younger patients did better in both groups. The study found that no patient with the best-quality cartilage (predominantly hyaline) at the two-year mark had a later failure. Knutsen G, et al. [3] concluded that repair cartilage, which is predominantly hyaline, at two years may reduce the risk of later failure.

A study carried out by Saw KY, et al. [4] included Standard Arthroscopic Subchondral drilling along with and postoperative Intra Articular injection of autologous peripheral blood progenitor cells (PBPCs) in combination with Hyaluronic Acid in 5 cases. All biopsy specimens showed histologic features of hyaline cartilage. A comparison of biopsy specimens from Non–Weight Bearing area to the Weight Bearing area in the same patient emphasised that early partial weight bearing is essential for the regeneration and alignment of collagen type II.

Another study carried out by Sakata K, et al. [5] demonstrated results following failed Cartilage Repair after MF for the treatment of Large Cartilage Defect in Medial Compartmental Osteoarthritis of the knee. The results showed regenerated cartilage tissue limited to the deep layer of holes penetrating the subchondral bone plate.

Hence it might be inferred from the above that the repair tissue showing Hyaline morphology at 2 year follow up gives good clinical results. Also, the repair tissue after a microfracture alone results in a fibrocartilaginous repair, which might be seen restricted to the holes penetrating the subchondral bone, resulting in a failed repair.

The addition of regenerative cells like the PBPC to the MF procedure gives a better quality (Hyaline cartilage) repair tissue.

Histopathology of Repair following ACI

A Study done by Brittberg M, et al. [6] in 1994 on 23 patients with isolated cartilage defects in knee following trauma or OCD following autologous chondrocyte implantation showed restoration of function in 14 out of 16 pts with femoral defects in a 3 year follow up. Histopathology revealed formation of new cartilage showing immunoreactivity for type II collagen & metachromatically stained matrix.

Bentley G, et al. [7] studied 100 patients aged 16 to 49 years and with symptomatic articular cartilage lesions of the knee randomised to have either mosaicplasty (42) or ACI (58). 19 biopsies taken from the ACI patients at one year, three were from the patella and 16 from the femoral condyle showed normal Hyaline cartilage in 7 patients; both hyaline & fibrocartilage in 7 patients & fibrocartilage (well-bonded to bone) in 5 patients.

Bentley concluded that more complete healing takes place in patients with ACI which therefore carries a significant superiority over mosaicplasty for the repair of articular defects in the knee. One of graft showing mixed hyaline and fibrocartilage at one year has shown hyaline cartilage alone at the two-year biopsy & hence suggested that the grafts can mature to hyaline cartilage up to two years after surgery.

Horas U, et al. [8] published a similar study on 40 patients with an articular cartilage lesion of the femoral condyle randomly treated ACI/Osteochondral cylinder technique. The biopsy specimens from representative patients of both groups were evaluated with histological staining, IHC (Immunohistochemistry) & scanning electron microscopy. The results at a 2 year follow up showed a complete, mechanically stable resurfacing of the defect in all patients with ACI showing mainly fibrocartilage, with localized areas of hyaline-like regenerative cartilage detected close to the subchondral bone. The patients in the OCT group showed no differences between the osteochondral transplants and the surrounding original cartilage on micromorphological analysis and scanning electron microscopy though a Persistent interface existed between the transplant and the surrounding original cartilage.

Bartlett W, et al. [9] used modifications of the ACI technique & studied chondral defects of the knee in 91 patients, of whom 44 received Porcine derived type I/type III collagen as cover (ACI-C)and 47 Matrix induced grafts using a collagen bilayer seeded with Chondrocytes(MACI). The results showed hyaline-like cartilage with/without fibrocartilage present in (42.9%) ACI graft biopsies and (36.4%) of MACI biopsies. They also concluded that there was evidence to suggest that cartilage grafts continue to remodel after the first post-operative year. The study also stated that a higher frequency of hyaline-like repair to be expected if biopsies were performed 2-3 years after implantation.

Gomoll AH, et al. [10] discussed the use of Type I/III Bilayer Collagen Membrane & observed a decrease in the reoperation rates after ACI for symptomatic hypertrophy.

In a similar study Gooding CR, et al. [11] concluded that a significantly better surface architecture and cellular morphology is seen with C-ACI compared with ACI-P (Periosteum covered ACI). A greater proportion of biopsies were found to be of hyaline or hyaline mix morphology with a greater amount of positive ECM staining for collagen type II with CACI compared to PACI. However no significant differences in – proteoglycan content (both exhibiting normal or near normal matrix metachromasia), tidemark formation or subchondral bone abnormalities was seen between the two patch types.

In a randomised control trial conducted by Knutsen G, et al. [3] between patients treated with MF/ACI no correlation between histological quality and clinical outcome was seen.

At two and five years, the patients had significant clinical improvement compared with the preoperative status.

McCarthy HS, et al. [12] made a Histological Comparison of Repair between PACI & CACI No significant difference between the overall histology scores (ICRS II or OsScore) of the repair tissue was reported. The Presence of any hyaline cartilage (alone /mixture of hyaline & fibrocartilage) was observed in significantly more biopsies in the patients treated with ACI-C than with ACI-P. A Larger proportion of solely fibrocartilage repair tissue was observed with P-ACI than those treated with ACI-C. Also a significantly more staining for collagen type II in C-ACI biopsies was seen than in P-ACI biopsies.

Sally Roberts S, et al. [13] studied the results of cartilage repair and ACI with or without OCT. The cartilage morphology was predominantly hyaline in 5 cases (> 90%); predominantly fibrocartilage in 7 & both hyaline and fibrocartilage in 11. The specimens with hyaline morphology showed positive staining for type II collagen in all cases. However none of the cases with ACI & mosaicplasty showed a significant correlation between the MRI and histology scores.

From the above literature review it is evident that ACI holds a definite advantage over the other cartilage repair techniques.

A further evolution of the techniques has shown better results for C-ACI than the original P-ACI technique.
In almost all the studies the graft maturity to the desirable Hyaline cartilage is seen at a 2 year follow up Biopsy.

Histopathology of Repair following Mosaicplasty

In the study discussed previously by Bentley G, et al [7], to compare the results in ACI & Mosaicplasty, the seven poor results in his study were all in the mosaicplasty group. In four of them, the plugs were in situ, but the tissue between them had not become covered with continuous fibrous tissue. In three patients the plugs had disintegrated altogether. In one patient the area of the mosaicplasty had remained reasonably intact, but the articular cartilage at the margins of the defect had broken down to expose the underlying subchondral bone.

Bentley concluded that Mosaicplasty & ACI give encouraging clinical results after a mean period of one year, but mosaicplasty appears to deteriorate with time. The long-term durability of mosaicplasty appears to be doubtful for biological and technical reasons.

Gudas R, et al. [2] compared the results of Osteochondral Transplantation (OAT) vs MF in a Prospective Randomized Study for the treatment of articular cartilage defects of the knee joint in athletes. There were 28 patients treated by OATS & 29 by MF. Of these patients, 96% had an excellent or good results after a follow up period of 37 months, compared to 52% following MF [2,14]. In this study biopsies were performed in 11 patients treated with OAT. Hyaline cartilage of normal appearance was found in all patients after OAT with normal structure of the cartilage. Histology 3 years after the OAT showed complete connection between calcified cartilage zone and subchondral bone with viable chondrocytes. 93% athletes following OAT & 52% after MF procedure returned to normal preinjury sports activities at 4-8 months.

From the above evidence it appears that a Biopsy performed at 2 years can give a good picture of the repair tissue morphology as it gives adequate time for the graft to mature/disintegrate. Also a biopsy at 3 years (in patients having good clinical results) gives a picture of the integration of the graft with the surrounding tissue.

A systematic trial by Magnussen RA, et al. [15] comparing the surgical techniques for the articular cartilage repair (ACI, MF & OATS) reported an improvement in the clinical outcome scores as compared to the preoperative scores. While no technique consistently had superior results compared to others, the outcome for microfracture tended to be worse in larger lesions.

The era of the surgical therapy is further heralded by the cell based treatments used alone or in association with the other techniques in the cartilage repair.

Tissue Engineering for Cartilage Repair

The newer methods involved the use of Mesenchymal stem cells MSC for cartilage repair. However the therapeutic effects of MSC is unstable due to their heterogeneity [16].

MSC are the pluripotent stem cells which exist in a variety of tissues like the bone marrow (BMSC), adipose tissue, synovial membrane & the umbilical cord whartons jelly.

However MSC exhibit an unstable cell morphology with a suboptimal chondrogenic differentiation due to the inflammatory environment in the joint cavity, leading to a failure to obtain a stable & homogenous cartilage tissue & a sustained therapeutic effect [17].

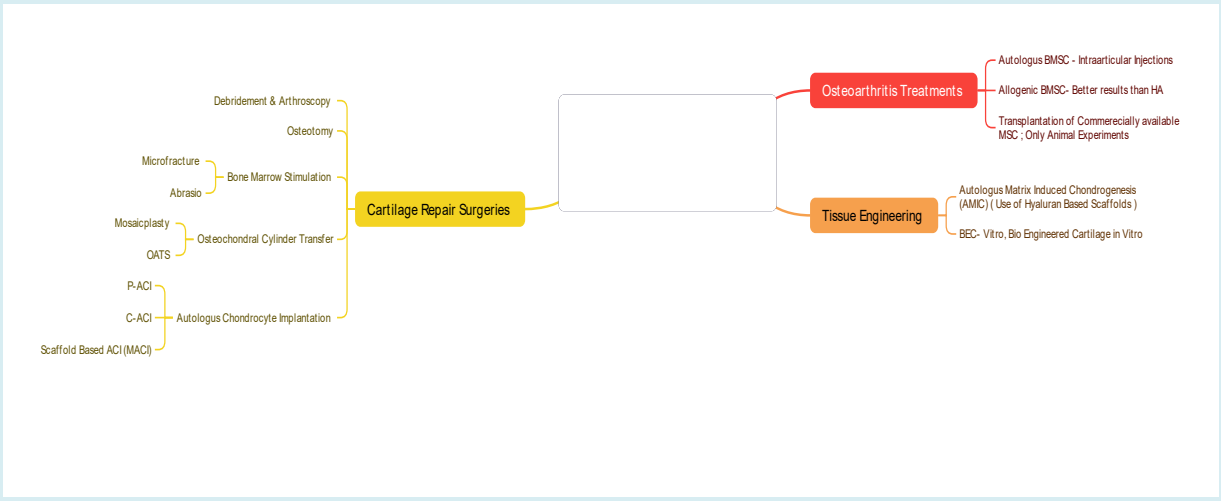

Figure 1: Summary of the Current Treatments For Articular Cartilage Repair.

The cells are able to proliferate & differentiate into chondrocytes to replace the damaged cells, along with an elaboration of various cytokines & immunomodulatory factors.

The transplanted MSC act via differentiation & repopulation of the cartilage defect along with paracrine effects, involving the secretion of a broad range of bioactive molecules such as growth factors, Cytokines & Chemokines [18]. The ECM (Extracellular Matrix) deposition is mediated by the release of trophic factors like the Transforming Growth Factor (TGF-β), Insulin like growth factor (IGF 1). A stable phenotype with a decreased expression of hypertrophic & fibrotic markers takes place due to the secretion of Hepatocyte Growth factor (HGF).

MSC possess low immunogenicity & a weak immune response due to a lack of expression of the MHC class II molecules & costimulatory molecules like CD80.

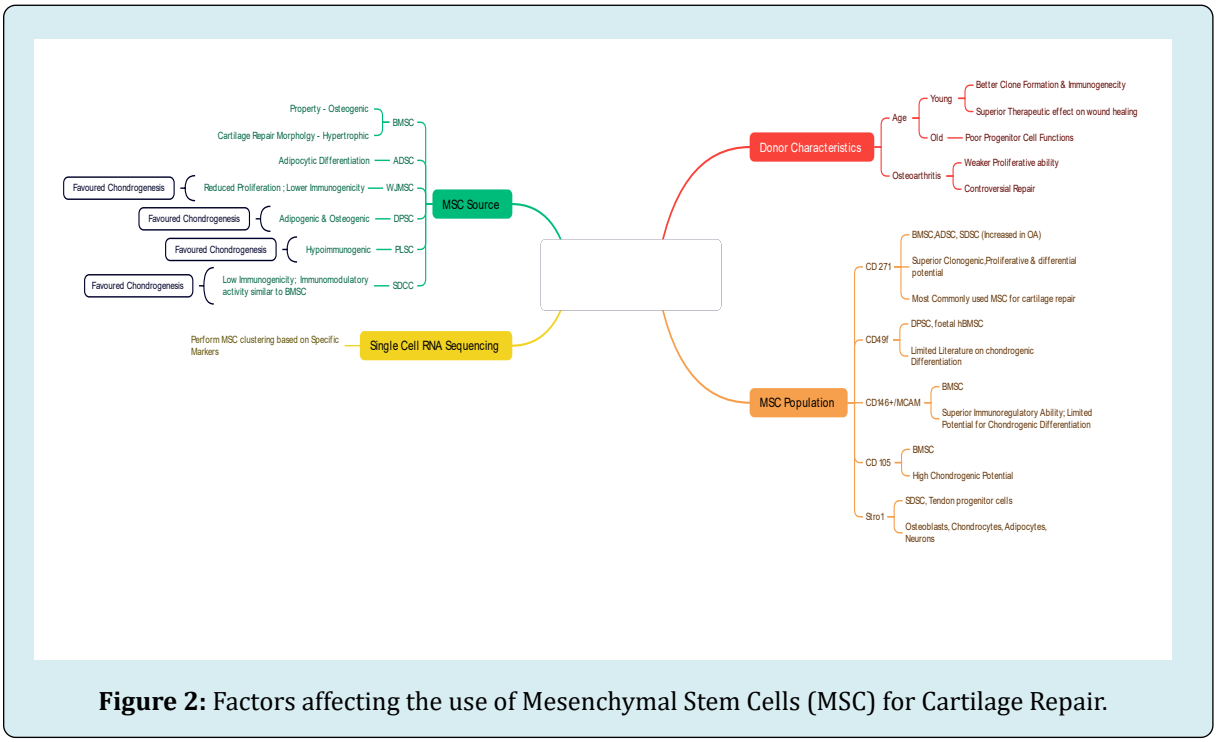

Figure 2: Factors affecting the use of Mesenchymal Stem Cells (MSC) for Cartilage Repair.

Goldberg A, et al. [19] systematically analysed the studies to assess the reparative effect of MSC on cartilage defects. The various types of the stem cells used were The ADSC, SDSC, PDSC (Periosteum derived Stem cells), Embryonic Stem cells & Muscle derived stem cells. Promising results with allogenic MSC compared to autologous cells were seen [20,21]. Poorer repair tissue was seen in the allogenic group in another study comparing the autologous & the allogenic chondroprogenitors [22].

AMIC (autologous matrix induced chondrogenesis) is another technique using stem cells from the adjacent marrow with collagen patches or Hyaluronan based Scaffolds [23-25].

He A, et al. [26] studied the concepts of in vitro cartilage engineering for the repair of the osteochondral defects, & reported a time depended maturation process with BEC-in Vitro (Bioengineered cartilage in Vitro). They concluded that the implantation of BEC-vitro could realise tissue specific repair of the Osteochondral defects with both the cartilage & the subchondral bone [26].

A newer technique involving the use of Bone Marrow Stromal Stem Cells from the patient, suspended in the collagen gel after expanding in culture & placed into the cartilage defect is another technique showing an improvement in the Clinical scores at a 3 year follow up [27]. The repair cartilage was reported to be a fibrocartilage.

Use of Peripheral blood stem cells for the treatment of chondral defects is another step ahead as it avoids a bone marrow harvest. Subchondral Drilling was followed by post-operative intra-articular injection of Hyaluronic acid (HA) with or without peripheral blood stem cells (PBSC). An improvement in the MRI scores at an 18 month follow up was seen along with a better result in the biopsy morphology [28].

Allogenic vs Autologous MSC

The use of Allogenic stem cells could reduce the donor site morbidity & cost of treatment. However, the results are conflicting. Better results from the allogenic cells were seen in some studies, comparing the chondroprogenitors [29,30]. Results from suitable clinical trials to calculate the dose & the types of allogenic stem cells are awaited along with the optimization of the dose of cells required.

The relationship between cell passages, cell dose, use of scaffolds & growth factors along with the efficacy of MSC treatment still needs to be established.

MSC in Osteoarthritis

The use of the autologous BMSC for the repair of articular cartilage in OA dates back to 2013. Orozco L, et al. [31] applied the Autologous Expanded Bone marrow MSC by intra articular injection to patients with unresponsive osteoarthritis related chronic knee pain with encouraging results at a 1 year follow up. Similar results were reported on the clinical trials by Soler R, et al. [32] with a 4 year follow up.

Chahal J, et al. [33] used autologous BMSC in OA patients with positive results after with an improved quality of life were reported, along with a reduction in the synovial inflammation [33].

Vega, et al. reported that the Allogenic BMSC was shown to have a better therapeutic effect for the treatment of OA than hyaluronic acid [34].

The capability of the BMSC from patients with OA had a reduced proliferative, chondrogenic & adipogenic capability with a normal osteogenic ability [35]. Study by Oreffo ROC, et al. [36] reported a reduction in proliferative capacity of the progenitor cells with ageing explaining the inverse relationship between Bone Mass Preservation & development of Generalized Osteoarthritis and Osteoporosis with aging [36].

A study by Fulber, et al. on OA mice showed a weaker chondrogenic differentiation, in contrast with the study by Dudics V, et al. [37] which demonstrated a similar chondrogenic differentiation in the BMSC from OA & normal patients.

Hence we can conclude that the MSC from the patients with Osteoarthritis had a weaker proliferative ability & a controversial chondrogenic ability. Therefore an autologous transplantation of BMSC in patients with OA remains to be further investigated [37].

In a study on Transplantation of Commercially available MSC into the knee joints of guinea pigs with spontaneous osteoarthritis Mitsuhiko, et al. reported a regeneration of the articular cartilage following a scaffold free transplantation of a mixture of HA-MSC. However the long term evaluation & human trials are awaited for the same.

Iijima H, et al. [38] reported no serious side effects following Intra articular injection of MSC along with an improvement in the knee pain, physical functionality & the quality of cartilage [38].

Role of MSC in Cartilage Regeneration following Injury

One of the first attempt to repair cartilage using tissue engineering was reported as early as 1977. Since then, cell based interventions have entered clinical practice while many of them are a part of translational research [39].

Studies using the MSC for articular cartilage injury exhibit a suboptimal chondrogenic differentiation owing to the heterogeneity of the MSC & the Inflammatory Microenvironment in the joint cavity resulting in a suboptimal therapeutic effect [15].

The heterogeneity of the MSC can be based on the donor's characteristics (age, sex & physiologic status), tissues & cell populations and could result in functional differences in the MSC.

Bruna F, et al. [40] studied the age related changes on the regenerative potential of the MSC & concluded that there was no difference in wound healing/ regeneration with age [40].

Rauscher FM, et al. [41] reported a progressive progenitor cell deficit with aging resulting in increased predisposition to the development of atherosclerosis [41].

BMSC

Bornes, et al. demonstrated in a sheep model that a chondrogenic priming ex vivo improves the gene expression profile of BMSC along with a superior cartilaginous repair tissue. However the oxygen tension during the preimplantation culture does not modulate the repair tissue formation.

Immunomodulatory functions of the BMSC helps in a better tissue survival in vivo & the role of CBF (Citrullinated Fibrinogen) in interfering with the same in RA (Rheumatoid Arthritis) [42].

Ding J, et al. [43] demonstrated that the BMSC based engineered cartilage could supress inflammation resulting in better tissue survival for the cartilage scaffolds [43].

The animal studies using the BMSC with tissue engineering & scaffolds have shown positive results for cartilage regeneration. Jin et al used properly pre-differentiated BMSC sheet on fibrous mesh to build an osteochondral interface which favoured the repairing of injured joint cartilage [44].

Sun Y, et al. [42] generated functional knee articular cartilage construct for cartilage repair by 3d-bioprinting a GDF5-conjugated BMSC-laden scaffold with better cartilage repairing effects [42,45].

To summarize, the bio engineered BMSC & use of scaffolds give a superior cartilage regeneration both in human & animal studies.

Adipose Tissue Derived MSC (ADSC)

The ADCC are preferred cells due to their abundance, easy accessibility, & a good capacity for chondrogenic differentiation. They can be obtained from the subcutaneous tissue or the sub-patellar fat pad arthroscopically.

Wu SC, et al. [46] demonstrated that a HA microenvironment enhances the h ADSC mediated cartilage regeneration in chondral defects & hence may be used in tissue engineering. Another study indicated that an intra-articular injection of allogenic ADSC caused an attenuation of the cartilage degeneration in rat OA models, demonstrating the paracrine effects of the MHC mismatched ADSC in reducing inflammation [46].

Various studies on the use of ADSC for cartilage repair have indicated an inferior chondrogenic potential as compared to the BMSC. The chondrogenesis can be improved with a higher growth factor levels. However the ADSC are shown to have better immunoregulatory functions [47].

Various studies & trials using ADSC show encouraging results in the OA patients showing functional improvement & pain relief, used independently or in association with other surgeries like HTO(High Tibial Osteotomy) [48,49].

Hence we can conclude that the ADSC are safe but their clinical utility for cartilage repair needs to be explored more.

Synovial Membrane -Derived MSC (SDCC)

iPSC derived from Synovial fluid MSC could be induced to differentiate into osteogenic, chondrogenic & adipogenic lineages in vitro with a weaker osteogenic capability [50]. The cells possess a lower MHC-II expression & hence low immunogenicity & an immuno-modulatory activity comparable to BMSC.

Synovium -derived cells had the greatest potential for both Proliferation & Chondrogenesis in rat models. Yoshimura H, et al. [51] reported a stronger capacity for proliferation & Chondrogenic differentiation for the SDCC than BMSC & ADSC, along with a stronger intrinsic chondrogenic capacity [51-54]. Coculture of SDSC & chondrocytes could promote deposition of ECM & inhibit the hypertrophy & osteogenic differentiation of Chondrocytes [55]. Studies involving the

implantation of hSDSC in patients with articular cartilage defects showed satisfactory results after 3 years [56]. In another 2 year randomised study, the functional outcome & quality of life was shown to be better for SDCC than ACI [57]. However more studies & more advanced biomaterials are required to enhance the regenerative ability of SDSC.

Wharton Jelly-Derived MSC (WJMSC)

The cells were first isolated from the umbilical cord in 1991 [58]. The collection of the cells is non-invasive, uncontroversial & provides an adequate source for the MSC. Being an intermediate between the embryonic & adult cells the WJMSC a greater capacity for proliferation & chondrogenic differentiation than BMSC [59-61]. Transplantation of hWJMSC Collagen I/III composite scaffold into the site of cartilage injury showed a regenerative tissue well integrated with the surrounding tissue & the subchondral bone [62]. Hence the WJMSC can be the most promising cells for cartilage tissue engineering.

To Summarize, SDSC & WJMSC have better cellular functions than the more commonly used ADSC & the BMSC.

The WJMSC are the most effective for cartilage regeneration when considering the capacity for proliferation, chondrogenic differentiation & immunomodulation.

ADSC is more promising for cartilage regeneration owing to its abundant source, safety & effectiveness.

However more studies are required to evaluate the clinical utility of these cells & cells from other sources like the periosteum, amniotic membranes, peripheral blood & dermis for cartilage regeneration in humans.

MSC Subpopulations in Tissue Engineering

The functional MSC populations which can be used for cartilage repair are CD 271+, CD49f+, CD146+, CD105+ & Stro1+ After harvesting from the tissues , The cells are expanded for 2-3 passages. The MSC subpopulations are isolated using surface markers for cartilage repair using fluorescence activated cell sorting (FACS) or MACS – Magnetic Activated cell sorting. After removing the dead cells, the subpopulations with superior cartilage repair potentials are transplanted into the damaged area to improve treatment outcome [63].

Applying MSC subpopulations has a great prospect in improving the therapeutic effects for cartilage regeneration. The 271+ population exhibits superior clonogenic, proliferative, & differential potential along with a desirable cartilage regenerative ability in Vivo. However more studies are required to characterise the type of cell population & the cell isolation methods (MACS/FACS)

Single Cell RNA Sequencing

Single cell Transcriptome sequencing is used to perform MSC clustering based on specific markers. This is also of great value for application in screening MSC subsets with superior proliferation, Chondrogenic Differentiation or Inflammatory regulation.

Although MSC represent a promising cell source for cartilage repair, an understanding of the heterogeneity is a fundamental step to provide an appropriate selection of the cells for an appropriate treatment for a particular patient.

Future Prospects

The future of cartilage repair aims to have a single stage procedure which would be beneficial to the patients as well as to the surgeons. The Concept of having cell banks for allogenic stem cells can materialize with appropriate clinical trials for the dosage & efficacy.

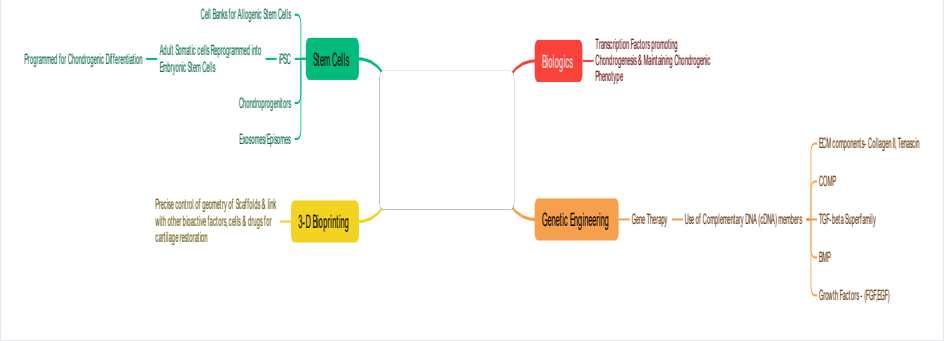

Figure 3: The Future Treatments for Cartilage Repair.

Induced Pluripotent stem cells (iPSC) are adult somatic cells which have been reprogrammed to an embryonic stem cell (https://stemcells.nih.gov/info/basics.htm), & can be programmed into Chondrogenic differentiation [64].

These along with other chondroprogenitors are being studied for their roles as future of cartilage regeneration used alone or in association with cartilage repair surgeries [66].

Three-dimensional (3D) bioprinting, which allows the precise control of internal architecture and geometry of printed scaffolds, has stepped up to be a promising strategy in cartilage restoration.

The mechanical and structural properties of printed constructs can be manipulated & crosslinked with other materials, in addition to cells, drugs, and other bioactive factors such as cytokines, which can enhance the repair and regeneration of cartilage [67].

Another field of research for hyaline cartilage regeneration is the gene therapy making use of Complementary DNA (cDNA) members like extracellular matrix (ECM) components such as collagen type II, tenascin, or cartilage oligomeric matrix protein (COMP) transforming growth factor- (TGF-) β super family, bone morphogenetic proteins (BMPs), growth factors (FGF, EGF) which support production and maintenance of the proper hyaline cartilage matrix. The use of biologics like the transcription factors promote chondrogenesis & maintain chondrocyte phenotype e.g. SOX9, SOX6 & LSOX5 [68].

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