Bone Marrow-derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis

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Forty percent of people over 70 years of age suffer from knee osteoarthritis. Stem cell based therapy is one of a number of promising strategies for osteoarthritis treatment. Mesenchymal stromal /stem cells (MSCs) derived from the bone marrow are the most commonly described source of MSCs and have been widely used to promote tissue regeneration in orthopaedic conditions, particularly in osteoarthritis. A fundamental knowledge of stem cells is very important prior to translating this technology into clinical practice. Although the mechanism of MSC therapy is still uncertain, several studies have reported on the safety and outcome of using bone marrow-derived MSCs for treating osteoarthritis. However, we still cannot conclude that MSCs can regenerate long lasting cartilage tissue. The long term clinical studies need to be evaluated in the future.

Key words: *Knee Osteoarthritis, Cell based therapy, Mesenchymal stem cells*

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Introduction

Knee osteoarthritis (knee OA) is characterised by joint space narrowing, osteophyte formation, and subchondral sclerosis and manifests primarily as joint pain[(1)], resulting in the physical disability of patients. Around 40% of people over 70 years of age suffer from this condition[(2)]. Knee OA in particular is a major cause of morbidity and is the primary diagnostic indication for total knee replacement[(3)], the volume of which continues to grow unabated globally. However, the procedure is a major operation and may pose several complications[(4)]. Recently, scientific evidence has strongly demonstrated that novel treatments can modify or change the disease progression of knee OA[(5-8)]. One potential strategy in osteoarthritis treatment is stem cell based therapy. The fundamental knowledge of stem cells is very important prior to translating this technology into clinical practice. Thus, the objectives of this review are to describe stem cells, including bone marrow derived mesenchymal stem cells (MSCs), and to summarise the recent evidence from animal to clinical studies in stem cell based approaches in treating knee osteoarthritis.

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Stem cells

There are two types of natural stem cells based on their origin; embryonic stem (ES) cells and adult stem cells. ES cells are derived from the inner cell mass of blastocysts. They are pluripotential stem cells with the capacity to differentiate into cells of all primary germ layers: ectoderm, mesoderm, and endoderm[(9)]. However, they are limited by a number of factors including technical limitations such as isolation and culture techniques, concerns regarding tumour formation, and major ethical controversy[(10,11)]. Recently, it has been reported that somatic cells can be genetically induced to pluripotent stem cells by introducing the four factors Oct3/4, Sox2, c-Myc, and Klf4[(12,13)]. These cells are known as induced pluripotent stem (iPS) cells. Although these cells have high proliferative potential and pluripotency, the induction of these cells is an artificial process which may also increase the risk of forming teratomas[(14)]. For these reasons, it is unlikely that ES and iPS cells will be used for orthopaedic clinical applications in the near future. Adult stem cells are found in adult tissue. These cells can be used autologously, negating much of the ethical controversy. They have been isolated from several tissue types[(15-19)]. Mesenchymal stromal /stem cells (MSCs) derived from the bone marrow are the most commonly described source of MSCs and have

been widely used to promote tissue regeneration in orthopaedic conditions.

Bone marrow mesenchymal stem cells

Bone marrow from iliac bone contains MSCs that constitute approximately 1 in 10,000 of all nucleated cells[20]. In 1970, Friedenstein et al. reported that this rare population of cells could be isolated on the basis of their ability to adhere to culture plastic[21]. These cells were capable of proliferating and differentiating into multiple mesodermal lineages[22,23]. There is controversy concerning which antigens identify MSCs and immunological techniques are therefore not widely used to isolate MSCs. Currently, most MSCs used in studies are isolated by plastic adherence in a process similar to that described by Friedenstein et al. A direct bone marrow plating method is commonly used for cells from small animals[24,25]. With human bone marrow, density gradient centrifugation is the most commonly used method for isolating MSCs.

MSCs are identified by their ability to proliferate and undergo multilineage differentiation. The colony-forming unit-fibroblast (CFU-F) is defined as a highly adherent colony of fibroblastic-like cells formed from a single mother cell. Thus, the CFU-F assay has been used to assess bone marrow progenitors. The number of colonies formed from the total number of seeded marrow cells indicates colony-forming efficiency (CFE). This assay indicates the percentage of cells in the marrow that are capable of clonogenic expansion. It has been demonstrated that CFU-F populations are not homogeneous, but rather contain a hierarchy of progenitors including multipotential MSCs and committed progenitors[26,27].

MSCs express a number of surface markers. These markers include a mixture of cell surface receptors, adhesion molecules, extracellular matrix proteins, cytokines, and other molecules whose function is to communicate with other cells. These markers are used to characterise MSCs. However, controversy remains regarding the set of surface markers that are expressed by bone marrow-derived stem cells. MSCs do not express: CD45 which is expressed in hematopoietic stem cells (HSC)[28], CD14 which is expressed in innate immune cells[29], and CD34 which is expressed in HSCs, satellite cells, and endothelial progenitors[30,31].

Mesenchymal stem cells have been reported to express: STRO-1, CD105, CD90, CD73, CD166, CD44, CD29, and CD54. These markers are expressed on all isolated MSCs from bone marrow[22,32]. STRO-1 is an early marker for stromal precursors and the subpopulations of cells from bone marrow which are STRO-1 positive are able to generate CFU-F as well as to differentiate into multiple mesenchymal lineages[33].

Up until now, no unique marker for MSCs has been described. Thus, a combination of markers is used to identify and sort MSCs. The combination of CD10+, CD13+, CD56+, and MHC Class-I+ markers has been reported to identify a population of lineage-committed progenitor cells and lineage-uncommitted pluripotent cells[34]. The combination of VCAM+, STRO-1+, CD73+, and CD105+ markers has been reported to isolate MSCs from human trabecular bone[17]. D7-FIB+, CD13+, CD45-, GPA-, and LNGFR+ have been reported to select adherent cell monolayers that undergo chondrogenesis, osteogenesis, and adipogenesis[35].

MSCs constitute a heterogeneous population of cells, in terms of their morphology, physiology, and expression of surface antigens. The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy has proposed criteria necessary to define human MSCs. First, MSCs must be plastic-adherent when maintained in standard culture conditions. Second, MSCs must express CD105, CD73, and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR surface molecules. Third, MSCs must differentiate into osteoblasts, adipocytes, and chondroblasts *in vitr* [36].

The differentiation potential of MSCs

MSCs have an ability to differentiate *in vitro* in specific culture media (Fig. 1). For osteogenic differentiation, dexamethasone, ascorbate, and β-glycerophosphate are required[37]. 1, 25-vitamin D3 has been reported to increase mineralization in human bone marrow-derived stem cell cultures[38]. Their morphology and cytoskeletal components are changed when they differentiate into osteoblasts. Furthermore, they express several different markers with osteogenesis such as Runx-2/Cbfa-1, osterix, alkaline phosphatase, bone sialoprotein, osteopontin, osteocalcin, osteonectin, and osteocrin[39]. For chondrogenesis, transforming growth factor beta, ascorbate, and dexamethasone are required. MSCs are capable of chondrogenesis and the expression of biochemical markers including transcription factors (SOX-9, scleraxis) and extracellular matrix (ECM) genes (collagen types II and IX, aggrecan, biglycan, decorin, and cartilage oligomeric matrix protein) which can be found during chondrogenesis[22,40,41]. To induce adipogenesis, adipogenic media consisting of dexamethasone, insulin, isobutylmethylxanthine, and indomethacin is required[42]. In these conditions, cells will differentiate increasing PPAR-γ (peroxisome proliferator-activated receptor gamma) and other adipose specific factors such as lipoprotein lipase. PPAR-γ has been found to be important in the development of adipocytes[43]. It can also be used as a marker for adipogenic differentiation.

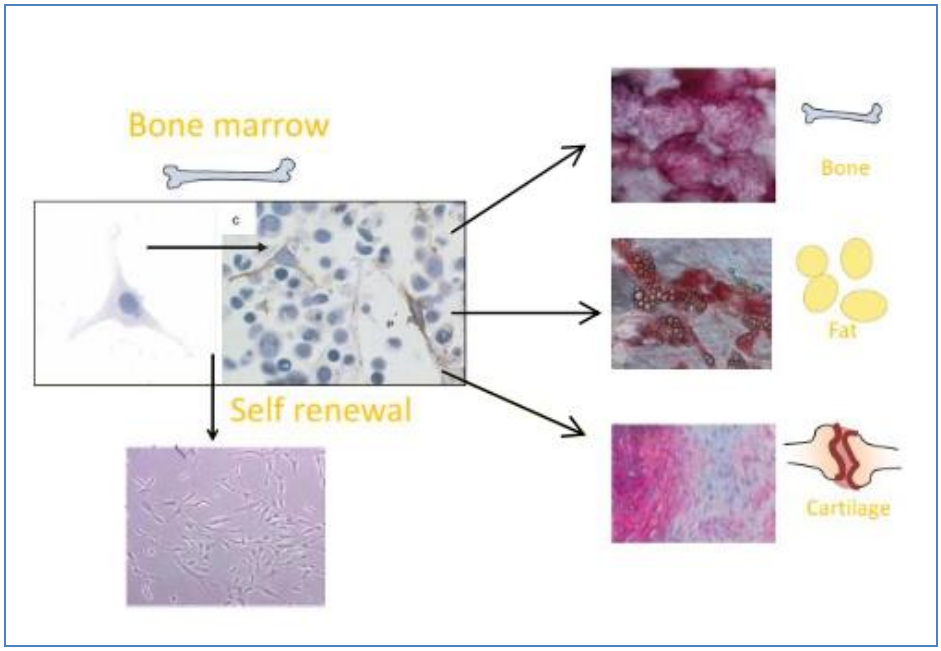

Fig.1 Mesenchymal stem cells: MSCs are capable of proliferation and differentiation into bone, fat and cartilage cells.

Mechanism of action using MSCs in osteoarthritis from preclinical studies

Osteoarthritis can be induced either by surgical (anterior cruciate ligament resection and/or meniscectomy) or by medical intervention (collagenase induced intra-articular injection) prior to injections of MSCs in a preclinical study. Therapeutic outcomes of MSC treatment have been well documented in previous studies. In the MSC treated groups, the rate of osteoarthritis deterioration was less compared to the control groups. This was supported by the evidence from histological findings; such as a) decreased area of cartilage lesion, b) decreased degree or depth of cartilage destruction, c) decreased osteophyte formation, and d) decreased subchondral sclerotic changing[44,45].

The mechanisms of MSCs' action can be explained either by the migration of the MSCs or by an anti-inflammatory process. From previous reports, the migration of MSCs was detected under fluorescence microscopy by GFP-transduced cells (MSCs that produced green fluorescence protein). In the MSC treated group, areas of cell engraftment were found on the sub-intimal synovial layer, fat pad, lateral meniscus, posterior cruciate ligament, and extensor digitorum longus. Additionally, more fibroblastic formation with Type I collagen than Type II collagen was found in those areas, but in articular cartilage only chondrification and fibrohyaline formation was seen and MSCs were not engrafted[44,46,47]. MSCs may promote suitable conditions for cartilage and tissue repair by the anti-inflammatory process. The results from synovial fluid analysis showed the level of catabolic enzymes was decreased in the MSCs treated group and the gene expression analysis showed significantly decreased expression of ADAMTS-4 and ADAMTS-5 (primary functions are cartilage formation and remodeling). In addition, MSCs showed high expression of tissue inhibitors of metalloproteinase (TIMP-1 and TIMP-3) that could inhibit the function of metalloproteinase enzymes, resulting in the declination of inflammatory cytokines such as PGE-2, TNF-α and TGF-β[48]. In a histology study, it was found that synovial thickening and the number of migrating macrophages in the MSC injection group decreased compared to the control group[47].

From an animal functional assessment, the MSCs treated group in dog models showed improvement in function of OA-limbs by gait analysis. This study also showed significantly increased peak vertical force (PVF) and vertical impulse (VI) in OA compared with the control group[49].

Cultured bone marrow mesenchymal stem cells in knee osteoarthritis

Wakitani et al. reported the first stem cell study for the treatment of knee OA in humans. They aspirated bone marrow blood from both sides of the iliac crest. After approximately 20 days of cell culture, they embedded the stem cells in collagen gel which was produced from porcine tendon. They performed high tibial osteotomies (HTO) in 24 patients with medial compartmental knee OA. The cultured cell-gel composite was

embedded into the cartilage defect using periosteal patches in 12 patients at the time of HTO. The other 12 subjects served as cell-free controls. Second-look arthroscopies were performed twice at 6 and 42 weeks after implantation. They found that the cartilage defects were covered with hyaline cartilage-like tissue in the cell-transplanted group. Furthermore, the arthroscopic and histological grading scores of the cell-transplanted group were significantly better than that of the cell-free group at both the first and second-look operations. However, in this study, the clinical improvement was not significantly different[50].

Wong et al. reported a prospective, randomized clinical trial in 56 patients. They injected cultured bone marrow-derived mesenchymal stem cells into varus knees with cartilage defects after performing high tibial osteotomy and microfracture procedures. They harvested about 49 mL of bone marrow from the iliac crest and cultured it in the laboratory for 3 weeks. The total number of cells was 1.46×10^7 and the cell viability was 87.1%. One group received a stem cell + HA injection and the other group had only a HA injection. The 2 year follow-up results showed that the stem cell group was better than the HA alone group. There were improvements of 7.65 for IKDC scores, 7.61 for Lysholm scores, and 0.64 for Tegner scores. MRI scans performed 1 year after surgical intervention showed significantly better MOCART scores for the cell-recipient group. They concluded that an intra-articular injection of cultured MSCs is effective in improving both short-term clinical and MOCART outcomes in patients undergoing HTO and microfracture for varus knees with cartilage defects[51].

Other cell sources without culture expansion in knee osteoarthritis

In the year 2009, Saw KY et al. began their investigations of stem cell therapy in a goat model using subchondral drilling in 3 groups: one with no postoperative injections, one with postoperative injections of hyaluronic acid (HA) alone, and one with postoperative injections of bone marrow aspirate (BMA) and HA. Histological grading illustrated the best outcomes in the group treated with injections of BMA and HA; the worst outcomes were observed in the group with no postoperative injections[52].

This promising result led the investigators to initiate a pilot clinical study in humans. Peripheral blood stem cells (PBSC) were used as opposed to cultured mesenchymal stem cells (MSCs) or marrow aspiration. They recently published the methodology, scientific basis, and results of a case series, including 5 cases with histological evaluation. They concluded that articular hyaline cartilage regeneration is possible with arthroscopic subchondral drilling followed by postoperative intra-articular injections of autologous PBSC in combination with HA[53].

After that, in 2013, the authors reported a randomized controlled trial (RCT) comparing postoperative injections of HA alone to postoperative injections of PBSC in combination with HA in 50 patients. Both groups received 5 weekly injections after arthroscopic drilling surgery. Three additional injections of either HA or PBSC + HA were given at weekly intervals 6 months after surgery. Subjective IKDC scores and MRI scans were obtained preoperatively and postoperatively at serial visits. They also performed second-look arthroscopy and biopsy at 18 months on 16 patients in each group. The total ICRS II histological scores for the control group averaged 957 and they averaged 1,066 for the intervention group. The biopsy result found hyaline cartilage in the PBSC + HA group. They concluded that after arthroscopic subchondral drilling into grade 3 and 4 chondral lesions, postoperative intra-articular injections of autologous PBSC in combination with HA resulted in an improvement of the quality of articular cartilage repair over the same treatment without PBSC, as shown by histological and MRI evaluation. However, clinical improvements were not significantly different. They predicted that the hyaline cartilage in the PBSC group will last longer than the HA alone group, and the long term clinical results will be different[54].

Conclusion

Cellular based therapy is a promising strategy for osteoarthritis treatment. Studies have reported on the safety and outcome of using bone marrow-derived MSCs for treating osteoarthritis[55,56]. They have shown improvements in clinical scores and MRI results. Second-look arthroscopy and cartilage biopsy results also demonstrated that bone marrow-derived MSCs can regenerate the hyaline cartilage covering defects. However, these studies have only short-term results (less than 3 years follow-up). At the present time, we still cannot conclude that MSCs can regenerate long lasting cartilage tissue. The long term clinical results have to be evaluated in the coming future. Other cell sources such as PBSC may be alternative cell based therapies as their therapeutic potential has been reported. A multicentre trial may be needed to warrant reproducible results on different settings. Further studies should be focused on the justification of the cell type, processes of preparation and standardisation, indication for treatment, and the regulation on cell based therapy in osteoarthritis.

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ตุลยพฤกษ์ ถาวรสวัสดิ์รักษ์, พบ, ไตร พรหมแสง, พบ, ปวีณ ตั้งจิตต์พิสุทธิ์, พบ,
พงศ์ศักดิ์ ยุกตะนันทน์, พบ

ปัจจุบันผู้ป่วยโรคข้อเข่าเสื่อมมีจำนวนสูงขึ้น เนื่องจากจำนวนประชากรผู้สูงอายุที่มากขึ้นในประเทศ การรักษาโดยการใช้เซลล์ต้นกำเนิดเป็นความหวังในการรักษา หรือช่วยชะลออาการของข้อเข่าเสื่อมในอนาคต มีการศึกษาทั้งจากห้องปฏิบัติการ ในสัตว์ทดลอง รวมถึงในมนุษย์ ที่สนับสนุนถึงความปลอดภัย และประสิทธิผลของการรักษาโดยวิธีนี้ ดังนั้นความรู้พื้นฐานเกี่ยวกับเซลล์ต้นกำเนิดนั้นมีความสำคัญ ในการที่จะนำเทคโนโลยีเซลล์ต้นกำเนิดไปใช้ในทางคลินิก อย่างไรก็ตาม ข้อมูลเรื่องกลไกในการรักษาของเซลล์ต้นกำเนิดยังไม่ชัดเจน และยังต้องการการศึกษาเพิ่มเติม รวมถึงข้อมูลผลการรักษาทางคลินิกในการติดตามการรักษาในระยะยาวยังไม่มีการรายงาน การรักษาโดยใช้เซลล์ต้นกำเนิดอาจจะมีบทบาทในการดูแลผู้ป่วยโรคข้อเสื่อมในอนาคต หลังจากที่มีข้อมูลมาสนับสนุนกลไกการรักษา รวมถึงข้อมูลทางคลินิกที่มีคุณภาพดี และมีการติดตามผู้ป่วยในระยะยาว หลังจากการรักษา