The use of stem cells in articular cartilage defects: where are we now?

Wasim Khan
Co-authors: Prof James Richardson & Prof Andrew McCaskie

The management of injuries of the knee cartilage has evolved over the years with advances in minimally invasive surgical techniques, cell-based therapies and sophisticated rehabilitation. These therapies have been augmented by greater knowledge of biomechanics and tissue engineering.

Tissue engineering aims to construct biomaterials, using in vitro and in vivo techniques, capable of integrating bioactive molecules and cells. Tissue engineering has four critical elements. Any given therapy does not always include all four:

1. Stem cells or progenitor cells: These cells are at varying levels of maturity, ranging from embryonic stem cells to adult multipotent cells, which are further down the differentiation pathway;

2. Matrices or scaffolds: These organic or inorganic structures promote cell attachment and cell growth;

3. Induction using signalling proteins, cytokines and growth factors: biochemical signals trigger the proliferation and differentiation of stem cells;

4. Biomechanical force stimulation: such as shear or strain stress using a bioreactor, which can also promote the proliferation and differentiation of stem cells.

What is a stem cell?

It is important to distinguish cell therapy in general from stem cell therapy in particular. ‘Cell therapy’ includes many cell types, for example a chondrocyte in autologous chondrocyte implantation but stem cell therapy uses stem cells, which have different properties, such as self-renewal and the potential to differentiate into varying cell types. Stem cell behaviour is demonstrated by embryonic stem cells, where the blastocyst cells are pluripotent and able to give rise to a vast array of the body’s cells. Pluripotency can also be induced in adult somatic cells – induced pluripotent stem cells (iPSC).

At the current time, clinical practice is focused on the role of another type of adult stem cell - mesenchymal stem cells (MSC). Originally called bone marrow stromal cells, MSCs were popularised in the 1990s, as they are multipotent and can differentiate in the laboratory into bone, cartilage and fat, so-called trilineage differentiation.

There is a question over whether the MSCs should be considered a stem cell, or simply a cell therapy, because it has other important properties in relation to immunomodulation and has recently been renamed a "medicinal signalling cell". These cells are identified by the expression of various cell surface markers (Figure 1). Whether acting as a stem or signalling cell the ease of acquisition and apparent safety profile have made the MSCs a popular target for cell therapy. This review will focus on this type of cell.
Stem cell therapy opens up many therapeutic opportunities in cartilage repair and has the potential to deal with symptomatic lesions at the cellular and molecular level. The limited healing capacity of cartilage and its avascular, aneurial and alymphatic structure make it an ideal target for tissue engineering and regenerative medicine. There has been a gradual increase in the clinical evidence over the years including some early well-designed comparative clinical studies.

Laboratory-based cell culture studies, gene transfer techniques, biomechanical analysis of scaffolds and small animal models, although important, have their limitations. The cell culture techniques to preserve the expression of certain stem cell surface markers, and enhance the gene expression of lineage-specific markers of differentiation may show how best to form cartilage tissue in the tightly-regulated incubator. However, the question remains, will all these factors still be relevant in the complex human body with its myriad of internal and external factors? Small animal models are useful to investigate some aspects of a tissue-engineered meniscus, but how relevant are these to a patient’s joint? There is a shift from laboratory studies to pre-clinical studies, from small animal models to large animal models, and from pre-clinical studies to clinical applications.

Clinical Studies Exploring Stem Cell Therapy for Cartilage Repair

Some of the recent clinical studies into cartilage repair are illustrative. Kim et al. showed better results in talar osteochondral lesions in patients over 50 years treated with adipose-derived MSCs and marrow stimulation when compared to patients treated with marrow stimulation alone. The patients receiving intraarticular MSCs had a better VAS, AOFAS, Roles and Maudsley, and Tegner activity scale scores, especially for defects greater than 109mm². Wong et al. conducted a prospective randomised controlled trial studying 56 patients with unicompartmental knee osteoarthritis and genu varum. All patients underwent microfracture and a medial opening high tibial osteotomy, some were also treated with culture-expanded bone-marrow derived MSCs injected into the knee. The patients receiving the MSCs had better Lysholm, Tegner, IKDC and MOCART scores.

Koh et al. showed that culture expanded adipose-derived MSCs were effective in cartilage healing, reducing pain, and improving function in 30 patients aged over 65 years with grade 2 or 3 knee osteoarthritis in multiple compartments. Stem cell injections were combined with arthroscopic lavage. Outcome measures included the Knee Injury and Osteoarthritis Outcome Scores, VAS, and Lysholm score. All clinical results were significantly improved at 2-years when compared to 12-month follow-up. Only five patients demonstrated worsening of Kellgren-Lawrence grade. At a second-look arthroscopy in 16 patients, 14 had improved or
maintained cartilage at 2-years post-operatively. None of the patients underwent total knee arthroplasty during this 2-year period.

In a more recent study13, 1,128 patients with Kellgren–Lawrence grades II–IV osteoarthritis underwent standard liposuction under local anaesthesia. The stromal cells were isolated and injected into one to four large joints, mainly the knee and hip. 1,114 patients were followed for a mean of 17 months. No serious side effects, systemic infection or cancer was associated with the cell therapy. Modified knee and hip scoring confirmed that most patients gradually improved for three to 12 months following therapy. A greater than 50% improvement in the score was documented in 91% of patients, 12 months after cell therapy.

Evaluating Clinical Stem Cell Studies

The first author conducted a review of clinical, cell-based studies for cartilage repair in 201314 and concluded that more high level human trials were required to evaluate the true effect of such techniques in repairing human cartilage defect. A recent meta-analysis15 on the effect of MSCs on articular cartilage degeneration treatment concluded that clinical symptoms and cartilage morphology showed significant improvement after stem cell treatment. However, the more comprehensive evaluation indices, such as the American Knee Society Score, the HSS Knee Scale and the IKDC Score were not improved by stem cell treatment. Thus we need to better evaluate this technology.

When assessing the quality of stem cell-based studies, important considerations are the study design, the evidence level and the outcome measures. A number of studies described in the literature combine stem cells with additional procedures, and these confounding variables make interpretation difficult. The nature of the lesion, its size and location, have a significant effect on the outcome. It is also important to note the stem cell harvest procedure and implantation technique. It is also important that any adverse effects are reported.

Conclusions

Regenerative therapies using stem cells represent a promising treatment option for cartilage defects. Our knowledge base of stem cells, growth factors, scaffolds and bioreactors is expanding. These techniques are beginning to be translated into daily clinical practice, with early evidence of safety and efficacy. There is considerable uncertainty as to the precise mechanism by which these therapies work, and extensive translational bench to bedside research is required. Although the early studies have shown positive outcomes, additional, well-designed and appropriately powered clinical trials are needed to confirm the efficacy and long term safety of stem cell treatment.

Wasim Khan is a University Lecturer and Honorary Consultant Orthopaedic Surgeon in Cambridge. He has an interest in stem cells and tissue regeneration. He aims to identify better ways of treating cartilage and meniscal lesions.

Correspondence

Email: wasimkhan@doctors.org.uk

References

References can be found online at www.boa.ac.uk/publications/JTO or by scanning the QR Code.
References


