

# Cartilage Regeneration: How Do We Meet the Increasing Demands of an Ageing Population?

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## Editorial

Globally, hundreds of millions of people are affected by musculoskeletal disorders (~10 million in the UK) [1]. Data presented from a pan-European study showed that one in three people are affected by musculoskeletal pain and disorders of the musculoskeletal system are the most common work-related health problem. From a survey of individuals who retired early on medical grounds or were on long-term sickness benefit, up to 60% cited musculoskeletal pain as the cause [2]. As well as these societal implications there is a significant economic cost associated with musculoskeletal health. The National Health Service (NHS) spends over £4 billion per year on the treatment of these conditions. It is estimated that approximately ten million working days are lost each year (second only to the stress, depression and anxiety category) bringing the cost to the wider UK economy to over £5.4 billion. In the US this figure has been reported as \$849 billion (approximately 7.7% of the Gross Domestic Product (GDP)) [3]. It is widely accepted that these figures will continue to increase as a result of the ageing population and as such intensive clinical and scientific research is focused on developing and implementing strategies that promote the maintenance of tissue physiology and function – a theme often termed ‘healthy ageing’.

Hyaline cartilage tissue is present on the surface of long bones where it provides resistance to compressive forces, permits dissipation of biomechanical loads that would otherwise be placed on the subchondral bone and contributes to the low-friction movement of the diarthrodial joint. The functional properties of hyaline cartilage are directly related to the biochemistry and macromolecular architecture of the Extracellular Matrix (ECM) components, which are synthesised and organised by one cell type, the chondrocyte. Aggrecan is the predominant proteoglycan of hyaline cartilage and is largely responsible for creating the hydrostatic pressure that resists loading through the osmotic imbalance brought by the heavily sulphated, negatively charged Glycosaminoglycan (sGAG) sugars attached to the core protein. Between 50-80% of the dry weight of hyaline cartilage is collagen, principally the fibrillar collagen type II, which lends torsional stability and tensile strength to counter the swelling pressure inside the tissue and through intermolecular interactions influences the organisation of the ECM. Minor components such as small leucine-rich proteoglycans (SLRPs; e.g. decorin, biglycan), cell surface proteoglycans (e.g. perlecan, syndecans, glypicans) and Fibril-Associated Collagens with Interrupted Triple Helices (FACIT) collagens (e.g. type, IX, XI, XIV, XVI) fine tune the tissue structure and regulate cell signalling events by controlling the release of bio-active growth factors and cytokines [4].

The homeostasis of hyaline cartilage is vital to the health and function of the tissue and disruption of the exquisite balance of ECM anabolism and catabolism results in the slow and progressive loss of macromolecular components and eventual degradation and failure of the tissue associated with chronic diseases such as OA. Because of its hypocellular and avascular properties, hyaline cartilage has a limited capacity for self-repair [4]. OA is now widely accepted as a whole organ disease affecting all of the tissues within the joint and whilst being an obvious target for regenerative medicine, given the societal burden of the ageing population, clinical interventions are restricted to weight reduction, physiotherapy and Non-Steroidal Anti-Inflammatory Drug (NSAIDs) regimens with surgical replacement of the joint in the advanced stages [5,6].

In the UK, surgical intervention may be performed in the treatment of symptomatic focal defects if conservative measures have failed. In some centres in Europe and the USA, prophylactic treatment in asymptomatic cases may be offered with their clinical aim being to resurface the articular defect delaying the onset of chronic degenerative disease. These patients, typically within the younger demographic of the population (< 40 years), can return to occupational and recreational activity with minimal societal and economic impact.

The most common cartilage regeneration strategy is microfracture or marrow stimulation which involves arthroscopic abrasion of the calcified layer and puncturing the subchondral plate with a pick into the cancellous bone to encourage the infiltration of mesenchymal progenitor cells that differentiate into chondrogenic cells capable of ECM synthesis, deposition and organisation. This technique is limited in that the de novo cartilage has a fibro cartilage phenotype with higher ratios of collagen type I: collagen type II and versican: aggrecan than the biomechanically superior hyaline cartilage [7]. It is limited to the defect sizes of < 2cm<sup>2</sup> and focal arthroplasties, either metal or BioPoly™, are available for medium-sized defects in older patients.

There is therefore a significant clinical need to develop cartilage tissue regeneration strategies that not only meet the growing demand for surgeries within the younger population demographic, but also to improve the quality of the cartilage that is formed and thus the likelihood for successful clinical outcome. The options available include implantation of whole tissue grafts or the use of chondrogenic cellular therapies.

Osteochondral tissue grafts are used to repair large full thickness cartilage defects created by trauma or pathology. Pioneering research investigating the potential for storing allogeneic osteochondral grafts at low temperature with nutrient supplementation to prolong chondrocyte viability, metabolic activity and maintenance of tissue integrity has increased the amount of available donor tissue, enabling the devolution of the procedure away from specialised centres and into routine surgical practice as more patients can be treated [8]. It is likely that further knowledge of bio-processing parameters including media formulations, gaseous tension and pH will continue to prolong the maintenance of tissue quality during storage. This, together with an increased knowledge regarding the biological changes that occur within different clinical cohorts of donor tissue (e.g. the effect of age or underlying co-morbidity) will serve to stratify and broaden the spectrum of available tissue to meet increasing demand.

The advent of multi-disciplinary tissue engineering strategies bringing together expertise in cell biology, natural and synthetic scaffold materials and bioengineering has expanded the potential for advanced regeneration approaches for the treatment of larger lesions. The first of these, Autologous Chondrocyte Implantation (ACI), has been used clinically for over twenty years and is carried out as a two-stage procedure in which a biopsy of cartilage tissue is harvested for the isolation and ex vivo expansion of chondrocyte populations that are transplanted back at the site of the cartilage lesion. ACI and third generation techniques are challenged by the ability to harvest sufficient tissue and the rapid loss of chondrocyte phenotype as they divide in culture. Currently these procedures are indicated for use in larger lesions up to 20cm<sup>2</sup>. Research has over the past decade sought to investigate the use of stem cell populations as an alternative or additional choice of cell source. Mesenchymal stem cells (MSCs) are adult stem cells that can be isolated from multiple tissues (e.g. Bone marrow, synovium, muscle, adipose), expanded through many population doublings and differentiated into cell lineages relevant to the treatment of orthopaedic clinical indications including chondrocytes [9]. Furthermore embryonic stem cells, derived from the inner cell mass of embryos can undergo in vitro directed differentiation toward a chondrogenic cell lineage

which lacks expression of hypertrophic collagen type X, leading to the suggestion that these cells have a more developmentally-relevant hyaline cartilage phenotype in contrast to MSC-derived chondrocytes [10, 11]. An additional benefit to ESCs as an allogeneic cell source is the potential for scaled-up manufacture and production of multiple treatment units from a single batch and hence a prospective reduced cost of per patient over the long term.

The number of ground-breaking scientific developments being made in the laboratory will open up a future of more personalised treatment options yielding more successful clinical outcomes. However, classification of these cell-based therapies as Advanced Therapy Medicinal Products (ATMPs) subjects them to what may be perceived as a complex regulatory framework with extensive and robust pre-clinical evaluations during the R&D stage and multicentre Randomized Clinical Trials (RCTs) to demonstrate safety and efficacy profiles for licensing by the European Medicines Agency (EMA). Presently ACI and third generation techniques are the only cell-based therapies licensed for surgical use by clinicians in the knee. An evidence-based UK consensus statement prepared by 104 clinicians concluded that ACI was the preferred treatment option for cartilage defects over microfracture with particular consideration for larger-sized defects [12]. Despite this the decision for ACI to be widely offered through the UK's largest healthcare provider, the NHS, is still being debated with questions over the evidence of efficacy and cost-reimbursement still being considered.

The creation of the UK Regenerative Medicine Platform (UKRMP) to develop technologies that meet the challenges associated with the application of regenerative medicine (e.g. Delivery of cells and drugs, manufacture, safety and immunological modulation) alongside the Cell Therapy Catapult aims to provide the necessary infrastructure for facilitating and streamlining efficient clinical translation, placing the UK at the forefront of delivering regenerative medicine into clinical practice.

Nevertheless, the delivery of cell-based chondrogenic cell therapies into widespread clinical practice remains a long way off and a two-pronged strategy of research into the development of protocols that optimise the quality of osteochondral grafts together with robust RCTs for evaluating chondrogenic cell therapies will be required to meet the increasing demand brought by the ageing population.

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