Editorial

Stem Cell Applications and Tissue Engineering Approaches in Orthopaedic Surgery and Musculoskeletal Medicine

Musculoskeletal tissue is frequently damaged or lost in injury and disease. Orthopaedic surgery has been highly successful in repairing, realigning and replacing damaged musculoskeletal structures. The coming years will establish whether a paradigm shift from fixation towards regeneration of tissue is possible, clinically feasible and financially viable. There has been an increasing interest in stem cell applications and tissue engineering approaches in surgical practice to deal with damaged or lost tissue [1-3]. Tissue engineering is an exciting strategy being explored to deal with damaged or lost tissue. It is the science of generating tissue using molecular and cellular techniques, combined with material engineering principles, to replace tissue. This could be in the form of cells with or without matrices. Although there have been developments in almost all surgical disciplines [1], the greatest advances are being made in orthopaedics, especially in bone repair [3]. This is due to many factors including the familiarity with bone marrow derived mesenchymal stem cells and bone grafting.

STEM CELLS

Stem cells are a self-renewing, slow-cycling cell population that exhibits a high proliferation potential and the ability to undergo multilineage differentiation. They can be isolated from tissues of individuals of various ages and maintain capacity for multilineage differentiation. Protocols for the culture [4] and, chondrogenic, osteogenic and adipogenic differentiation of bone marrow derived mesenchymal stem cells have been described [5, 6]. The rationale behind these protocols is discussed in this issue as well as highlighting the different regulators which determine the lineage a particular mesenchymal stem cell will differentiate into. By the end of last century, there was considerable interest in the use of mesenchymal stem cells for clinical tissue engineering applications. Unlike embryonic stem cells, the use of autologous postnatal mesenchymal stem cells is generally well accepted by society. Mesenchymal stem cells are less tumourogenic than their embryonic counterparts [7] and provide an autologous source of cells eliminating concerns regarding rejection and disease transmission. Cells with mesenchymal stem cell characteristics have been isolated from many different adult tissues including bone marrow, liver, dental pulp, periosteum, skin, retina, adipose tissue, skeletal muscle, synovial tissue, the infrapatellar fat pad, and more recently, cartilage [8-14].

Although bone marrow-derived mesenchymal stem cells are multipotent with good differentiation potential, their use does have limitations. These cells are scarce and form only 0.001-0.01% of the total nucleated cells in bone marrow aspirates [15]. Human bone marrow-derived mesenchymal stem cells from older donors have been shown to be fewer in number [16, 17] and have a reduced lifespan, proliferation [18] and differentiation potential [19]. There is an urgent need to identify the optimal source of mesenchymal stem cells for various musculoskeletal applications in an increasingly elderly population and to determine the effects of ageing in these cells [20]. The ideal mesenchymal stem cell source would deliver a good cell yield, not require long culture expansion and exhibit good proliferation and differentiation potential. Work by others and by us has shown that compared to cells harvested from the bone marrow, some other sources e.g. synovial fat pad derived mesenchymal stem cells are easier to obtain and are associated with a higher yield of mesenchymal stem cells [11, 21, 22]. Adult mesenchymal stem cells of bone marrow origin are the cells which are heavily investigated in many studies and have been shown capable of producing a variety of connective tissues especially cartilage and bone. Clinical trials have shown that these cells are able to be successfully used to regenerate tissues with good clinical outcome. Other sources are showing promise, however, is yet to be brought to the clinical level in humans. Mesenchymal stem cells from different tissues vary in their differentiation potential [23, 24] and in this issue we look at the advantages and disadvantages of using mesenchymal stem cells from various sources of particular interest to musculoskeletal applications including bone marrow, blood, adipose tissue, synovium, periosteum and cartilage. We also discuss the nature of stem cells and the increasing data that supports pericytes as candidate mesenchymal stem cells [22, 25].

In this issue we also highlight the fundamental principles and challenges of engineering products which can mimic both the structure and function of these tissues in their healthy state. We discuss the recent progress in the field with its implications for revolutionising healthcare in the future. The issue of ensuring governance of these novel technologies falls upon both the scientific community and the established licensing authorities and this is also discussed in this issue.

One of the features of musculoskeletal disease and injury is the varying tissue distribution that can be affected ranging from bone and cartilage to ligaments, tendons, blood vessels, nerves and skin. In addition to cartilage and bone, developments in the multidisciplinary field of tissue engineering have yielded advances in the reconstruction of tendons, skin, peripheral nerves and blood vessels as well, and these are highly relevant to orthopaedics.

BONE

Tissue engineering of bone has the potential to overcome the limitations of using autologous, allogeneic or synthetic bone grafts to treat extensive bone defects and fracture non-unions [26]. It involves culturing of osteogenic cells within appropriate scaffold materials under conditions that optimize bone development. Stem cells, progenitor cells, terminally differentiated cells or genetically modified cells may be used. Scaffold materials include polymers, ceramics or composites which are used to maintain the desirable characteristics of the individual materials. Preclinical and clinical studies on the use of growth factors such as bone morphogenetic proteins to increase bone formation have had

promising results. This issue discusses the challenges associated with producing tissue engineered bone, and evaluates the preclinical and clinical evidence for stem cell applications and tissue engineering approaches.

More than one million patients are treated annually to manage and regenerate bone tissue in sites of congenital defects, tumour resection or fractured bones [27]. This regeneration process is very complex and requires a morphogenetic signal, responsive host cells, a viable well-vascularised host bed and a suitable scaffold [28]. During fracture healing, scaffolds serve as a template for cell interactions and the formation of bone extracellular matrix, and provide a structural support to the newly formed tissue. The use of autografts and allografts is restricted by donor site shortage and morbidity, immunologic barriers and risks of infectious diseases' transmission. A growing array of synthetic scaffolds for bone regeneration has become commercially available over the last century [27]. These scaffold aim to provide a three dimensional substrate for cells to populate on and function appropriately. They should have mechanical properties similar to those of the bone repair site, biocompatibility and biodegradability at a rate commensurate with remodelling [29]. In this issue we look at synthetic bone regeneration scaffolds focussing on basic sciences principles and properties of clinical available or experimental synthetic bone scaffolds.

CARTILAGE

Articular cartilage is frequently damaged by trauma and in joint disease but shows only a limited capacity for repair. If focal cartilage lesions are left untreated or are treated inadequately, they progress to more extensive secondary osteoarthritic lesions. Osteoarthritis is the most prevalent disorder of the musculoskeletal system affecting approximately 15% of the total UK population [30]. The frequent outcome for arthritis in large joints such as the knee is surgical intervention for joint replacement that costs the National Health Service around £8,000. A joint replacement tends to be successful in older sedentary patients but the limited lifetime of prostheses makes it much less desirable for younger and more active patients [31]. This means a greater likelihood of needing a revision procedure with its associated increased operative complications. The numbers of primary and revision total knee replacements are projected to increase six-fold by 2030 [32]. This is the driving force behind numerous ongoing efforts to develop new strategies for the treatment of focal cartilage defects to prevent secondary osteoarthritis [2].

Options for the repair of focal cartilage lesions include abrasive chondroplasty, subchondral drilling and microfracture, but these result in the formation of fibrocartilage rather than the desired hyaline cartilage, with inferior mechanical and hydroelastic characteristics and unsatisfactory clinical outcome [33]. Autologous Chondrocyte Implantation (ACI) is a cell-based strategy being used for the repair of focal cartilage defects in younger patients [34]. It involves injury to non-weight bearing cartilage, it is expensive and technique-dependant. With prolonged expansion in culture chondrocytes lose their ability to proliferate and to express cartilage specific proteins [35]. Although short-term clinical results have been good, evidence suggests formation of fibrocartilage and progression of degenerative changes in the joint [36].

Tissue engineering applications using mesenchymal stem cells present an interesting and promising new approach for the repair of articular cartilage defects [2, 37]. To date there have been only limited reports of human autologous bone marrow derived cell implantation for cartilage repair [38-40] where expanded cells were used to repair a full-thickness cartilage defect in the knee. Histological studies suggest that the defect was filled with hyaline-like type of cartilage. This issue covers the limitations of the current treatment strategies and then builds on these by emphasising the role of stem cells and tissue engineering in this important orthopaedic area.

MENISCI

The menisci are important fibrocartilaginous structures which give lubrication, shock absorption, nutrition and stabilisation to the knee joint, and also helps transfer load. The meniscus' extracellular matrix possesses a complex architecture which is not uniform throughout the tissue. The inner third of the meniscus is composed of hyaline cartilage and the outer meniscus is composed of fibrocartilage. In a mature meniscus only the outer 10-25% is vascularised. There are various types of pathology associated with the meniscus. In the past, surgical techniques used to be considered as conventional treatment for meniscal lesions. However lesions in the avascular regions of the meniscus would rarely heal appropriately. It has been found that total menisectomies in patients may increase their chance of suffering from osteoarthritis in the future.

Meniscal tissue engineering has been developed in an attempt to help improve the healing potential of avascular meniscal regions. Many different concepts and approaches have been tried and tested, such as the application of natural and synthetic scaffolds, mesenchymal stem cells, growth factors, fibrin glue and more. In this issue we summarise the different approaches that have been used in the development of meniscal tissue engineering. The focus of this is to evaluate the strengths and weaknesses of the studies have been carried out, and from there determine what we have learnt from them in order to further the development in meniscal tissue engineering.

In this issue the important topic of governance is discussed followed by stem cell applications and tissue engineering approaches relevant to bone, cartilage and meniscus repair as well as other soft tissues of relevance to musculoskeletal medicine. This follows a brief outline of mesenchymal stem cells, their sources and their differentiation. We should however bear in mind that significant hurdles remain to be overcome before tissue engineering becomes more routinely used in surgical practice.

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Wasim S Khan
(*Guest Editor*)
University College London Institute of Orthopaedic and Musculoskeletal Sciences
Royal National Orthopaedic Hospital
Stanmore, Middlesex, HA7 4LP
United Kingdom

Atif Malik
Department of Trauma and Orthopaedics
Chase Farm Hospital
Barnet and Chase Farm Hospitals NHS Trust
Ridgeway, Enfield, Middlesex, EN2 8JL
United Kingdom