Editorial

Tissue Engineering in Orthopaedics and Musculoskeletal Sciences

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Orthopaedic surgery as a speciality lends itself well to tissue engineering. Many musculoskeletal tissues are frequently damaged or lost in injury and disease, and show a limited capacity for repair. Although orthopaedic surgery has been successful in replacing cartilage, the coming years will establish whether a shift from replacement towards regeneration of tissue is feasible. There has been an increasing interest in tissue engineering approaches to deal with damaged or lost tissue [1-3]. Tissue engineering is an exciting strategy that employs stem cells, scaffolds and growth factors or mediators either in isolation or in combination. It is the expanding science of generating tissue using molecular and cellular techniques, combined with material engineering principles, to replace tissue surgically. This could be in the form of cells with or without matrices. Many tissue engineering advances are being made in orthopaedics and this is partly due to the familiarity with bone marrow derived mesenchymal stem cells. In this review we will cover mesenchymal stem cells, scaffolds, bioreactors and growth factors applicable to orthopaedics and musculoskeletal sciences. This is followed by specific discussions on Dupuytren's disease where there is early evidence of stem cell etiology, and bone and cartilage tissue engineering.

STEM CELLS

Stem cells are a self-renewing cell population with a high proliferation potential and the ability to undergo chondrogenic, osteogenic and adipogenic differentiation. Protocols for the culture and differentiation of bone marrow derived mesenchymal stem cells have been described [4-6]. Over the last decade, there has been considerable interest in the use of mesenchymal stem cells and tissue engineering principles in orthopaedics and musculoskeletal sciences. The use of autologous postnatal mesenchymal stem cells is generally well accepted by society and does not involve many of the ethical, political and religious considerations that surround embryonic stem cells [7]. Cells with mesenchymal stem cell characteristics have been isolated from many different adult tissues including bone marrow, periosteum, skin, adipose tissue, skeletal muscle, synovial tissue, the infrapatellar fat pad, and more recently, cartilage [8-15], and we provide a systematic review of the literature outlining the sources of mesenchymal stem cell used in musculoskeletal applications.

Human bone marrow-derived mesenchymal stem cells exhibit age-related changes; with increasing age, they are fewer in number [16, 17], have reduced proliferation [18] and reduced differentiation potential [19]. There is uncertainty whether these age-related changes are also exhibited by mesenchymal stem cells from other sources, and what the extent of these changes is in these other sources. There is a need to determine not only the effects of patient age on mesenchymal stem cells [20] but also the effect of senescence. There are many known growth factors involved in controlling and influencing stem cell growth that are also related to cell senescence, and we review these *in vitro* considerations.

Work by others and by us has shown that mesenchymal stem cells from the synovial fat pad are easier to obtain and are associated with a higher yield of mesenchymal stem cells compared to bone marrow [11, 21, 22]. Although mesenchymal stem cells from different tissues vary in their differentiation potential [23,24], it is possible that there are more similarities between stem cells from various sources than differences; increasing data supports pericytes as candidate mesenchymal stem cells in a number of sources [22,25]. These cells are identified using cell surface markers but there are no papers in the literature that bring together and summarize these cell surface markers. We present a systematic review that summarizes all the available information about the cell surface characterization of adult human MSCs by identifying and evaluating all the published literature in this field. We have found that the most commonly reported positive markers are CD105, CD90, CD44, CD73, CD29, CD13, CD34, CD146, CD106, CD54 and CD166, and the most frequently reported negative

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markers are CD34, CD14, CD45, CD11b, CD49d, CD106, CD10 and CD31.

SCAFFOLDS, BIOREACTORS AND GROWTH FACTORS

The use of scaffolds remains an integral part of the tissue engineering applications in orthopaedics and musculoskeletal sciences. We provide a summary of the principals of using material scaffolds in musculoskeletal tissue engineering applications and how these materials may eventually come to be incorporated in clinical practice. This is followed by a review of bioreactors that engineered tissue can be generated in. We discuss the role of bioreactors in tissue engineering and evaluate the principles of bioreactor design. We evaluate the methods of cell stimulation and review the bioreactors in common use today. Research has shown the importance of growth factors in guiding and modulating the differentiation of mesenchymal stem cells in order to obtain the required cell type. Gene-based delivery systems have aided the delivery of sustained quantities of these growth factors. The evidence from growth factor enhanced tissue engineering studies for tissue healing looks very positive. This is a multi-disciplinary approach that integrates molecular, biochemical and clinical techniques with developmental and engineering processes. Initial studies indicate an immense potential for cell based strategies to enhance current orthopaedic approaches in skeletal tissue reconstruction and this is also covered in a review.

E-GOVERNANCE

The rules of governance are changing. They are necessarily becoming more stringent as interventions offered to treat conditions carry unpredictable side effects, often associated with novel therapeutic vectors. The clinical relevance of this relates to the obligations of those involved in research, to ensure the best protection for subjects whilst encouraging the development of the field. Existing evidence supports the concept of e-Governance both in operational health research and more broadly in the strategic domain of policy formation. Building on the impact of the UK Comprehensive Research Network and recent EU Directives, it is now possible to focus on the issues of regulation for cell therapies in musculoskeletal science through the development of the Advanced Therapeutic Medicinal Products (ATMP) category of research products. We provide a review that covers the framework that has borne this and the need for more detailed Virtual Research Integration and Collaboration (VRIC) systems to ensure regulatory compliance. Technology research and development plans must develop in close association between tissue engineering and treating clinicians. The scope of this strategy relates to the handling of human tissues the transport and storage of specimens in accordance with current EU directives and the Human Tissue Authority (HTA) regulations.

DUPUYTREN'S DISEASE

Dupuytren's disease is the most common condition seen by hand surgeons. It is not only prevalent but can also be a most debilitating condition resulting in significant loss of function of the fingers involved. The cause of this disease, however still remains largely unknown although some recent evidence suggests a stem cell etiology. We provide a review article that summarizes the current known knowledge of Dupuytren's as well as the clinical findings, investigations, treatments available and looks at preliminary evidence of stem cell etiology.

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]. Over a million patients are treated annually to manage and regenerate bone tissue in sites of congenital defects, tumor resection or fractured bones [27]. This regeneration process is very complex and requires a morphogenetic signal, responsive host cells and a suitable scaffold [28]. An increasing variety of synthetic scaffolds for bone regeneration has become commercially available over the last century [27] that aim to provide a three dimensional substrate for cells to populate on and function appropriately. They should have appropriate mechanical properties, biocompatibility and biodegradability at a rate commensurate with remodelling [29].

Stem cells have shown to be excellent carriers for gene transfer having the capability to be transduced. Gene transfer could enable growth factors and bone morphogentic proteins to enhance bone repair. Stem cells are implanted onto scaffolds, which are structures capable of supporting tissue formation by allowing cell migration, proliferation and differentiation. Research aims to produce scaffolds that deliver and retain cells, allow for cell attachment has adequate biodegradability, biocompatibility and non-immunogenicity. However, having tried and testing numerous materials including synthetic and natural products research into the perfect scaffold product continues. We provide a review that aims to explain how stem cells were discovered, the techniques used to isolate stem cells, identify and manipulate them down different cell lineages and discuss the research into using stem cells to reconstruct bone using genetic modification and scaffolds.

CARTILAGE

Osteoarthritis is the most prevalent disorder of the musculoskeletal system [30] and the frequent outcome for arthritis in large joints such as the knee is surgical intervention for joint replacement. 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]. The numbers of primary and revision total knee replacements are projected to increase six-fold by 2030 [32] and this is the driving force behind numerous ongoing efforts to develop new cell-based strategies for the treatment of focal cartilage defects to prevent secondary osteoarthritis [2]. Current options for the repair of focal cartilage lesions include abrasive chondroplasty, subchondral drilling and microfracture. These result in the formation of fibrocartilage rather than the desired hyaline cartilage, with inferior mechanical and hydroelastic characteristics [33]. Autologous Chondrocyte Implantation is a cell-based strategy currently in clinical practice [34, 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 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]. We include a review that looks at the current treatment strategies for articular cartilage, describes use of mesenchymal stem cells for articular cartilage repair along with the results of clinical studies, and describes the future direction that these strategies are likely to take.

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