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Review

Chondrocyte and mesenchymal stem cell-based therapies for cartilage repair in osteoarthritis and related orthopaedic conditions

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ABSTRACT

Osteoarthritis (OA) represents a final and common pathway for all major traumatic insults to synovial joints. OA is the most common form of degenerative joint disease and a major cause of pain and disability. Despite the global increase in the incidence of OA, there are no effective pharmacotherapies capable of restoring the original structure and function of damaged articular cartilage. Consequently cell-based and biological therapies for osteoarthritis (OA) and related orthopaedic disorders have become thriving areas of research and development. Autologous chondrocyte implantation (ACI) has been used for treatment of osteoarticular lesions for over two decades. Although chondrocyte-based therapy has the capacity to slow down the progression of OA and delay partial or total joint replacement surgery, currently used procedures are associated with the risk of serious adverse events. Complications of ACI include hypertrophy, disturbed fusion, delamination, and graft failure. Therefore there is significant interest in improving the success rate of ACI by improving surgical techniques and preserving the phenotype of the primary chondrocytes used in the procedure. Future tissue-engineering approaches for cartilage repair will also benefit from advances in chondrocyte-based repair strategies. This review article focuses on the structure and function of articular cartilage and the pathogenesis of OA in the context of the rising global burden of musculoskeletal disease. We explore the challenges associated with cartilage repair and regeneration using cell-based therapies that use chondrocytes and mesenchymal stem cells (MSCs). This paper also explores common misconceptions associated with cell-based therapy and highlights a few areas for future investigation.

Contents

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[1] http://cordis.europa.eu/projects/rcn/105314_en.html; http://ec.europa.eu/research/health/medical-research/severe-chronic-diseases/projects/d-board_en.html.

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1. Introduction

Cell-based therapy is a form of biological therapy. It involves the process of introducing new cells into tissues in order to treat a degenerative or age-related disease. The advent of cell-based therapies as a novel therapeutic platform has the potential to revolutionise the future of healthcare, driving a shift from the management of disease symptoms to their cure. Thus far, research in the area of cell therapy has mainly focused on the treatment of hereditary diseases, with or without the addition of gene therapy. However, cell therapy is also a form of regenerative medicine and is increasingly used in combination with tissue engineering and biomaterials. Although the combination of cell therapy, regenerative medicine and tissue engineering are relatively novel areas of therapeutic research, each individual element by itself is not novel and goes back several decades. Current cell therapy initiatives are deeply rooted in blood transfusion, bone marrow and organ transplantation, tissue banking and reproductive *in vitro* fertilisation. However, cell-based therapy is now an established component of modern healthcare and is predicted to grow exponentially as modern healthcare systems evolve and integrated knowledge of cell biology, biomaterials and regenerative medicine expands. The aim of this article is to provide an overview of chondrocyte-based therapies for the treatment of osteoarticular lesions, or "focal defects" in articular cartilage. It could be argued that these types of cell-based therapy are a contra-indication for OA due to the geometry of osteoarthritic lesions and the fact that inflammatory joint disease is rarely focal, unlike cartilage defects in younger patients and elite athletes. However, in the absence of effective pharmacological agents [1], novel biological [2] and cell-based therapies need to be developed for OA and related orthopaedic conditions. Therefore, in this review article we approach this problem from basic science viewpoint rather than a clinical perspective and refer readers to relevant clinical papers and trials instead of discussing them in significant detail. Our aim is to describe the significance of this topic in the context of the biology of the joint and the osteoarthritic disease process, discuss the current state-of-the-art and speculate on the impact of autologous and allogeneic chondrocyte-based therapies in orthopaedics, rheumatology and sports medicine. This paper also summarises key concepts and developments in the area of mesenchymal stem cell (MSC) based therapy.

2. The burden of musculoskeletal diseases and osteoarthritis

Age-related musculoskeletal and joint diseases are currently a major cause of morbidity globally and result in enormous costs for health and social care systems. Chronic and inflammatory diseases of joints are major causes of disability in the middle-aged and the elderly. With increasing life expectancy, the burden of musculoskeletal diseases is progressively growing, highlighting the need for a radical shift in healthcare strategies that involve interventions that can either prevent or significantly reduce the risk of development of these diseases.

Arthritic diseases are a group of conditions involving inflammatory damage to synovial joints. Arthritis literally means inflammation (*itis*) of the joints (*arthr*) and involves pain, redness, heat, swelling and other harmful effects of inflammation. Although there are over 200 different forms of arthritis, OA is the most prevalent and chronic form joint disease and a major cause of pain and disability affecting the ageing population with increasing prevalence as this population expands [3]. OA leads to joint pain, stiffness and loss of function predominantly in the knees, hips, hands and other weight-bearing joints. Although advancing age is a major risk factor for the development of OA, there are other significant contributing factors including obesity, a history of joint trauma and other co-morbidities such as diabetes, metabolic and endocrine diseases. OA is one of the top five causes of disability amongst non-hospitalised adults (source: Centers for Disease Control and Prevention (CDC, http://www.cdc.gov/), USA). According to estimates from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS, http://www.niams.nih.gov/) more than 20 million Americans currently suffer from OA. Conservative estimates suggest that 35–40 million Europeans have OA. Statistical data from epidemiological studies suggest that arthritis is the number one condition associated with functional limitation and physical disability among US population aged 65 and older and affects 30% of the population [4]. It is expected that by 2030, 20% of adults will have developed OA in Western Europe and North America. OA is an important cause of disability-adjusted-life years in both the developed and developing world [5]. Therefore, OA is expected to be a heavy economic burden on healthcare systems and community services in Europe, North America and the rest of the world as the population expands and the number of older people increases.

3. Cartilage degeneration in osteoarthritis

Classically OA has been considered a 'wear and tear' degenerative condition of joints. However, OA is a systemic disease that affects the whole joint, including cartilage, subchondral bone, synovium, tendons, and muscles [6–9]. The disease is characterised by degeneration of articular cartilage, low grade synovial inflammation (synovitis) [7], and alterations in peri-articular soft tissues and subchondral bone [10]. The synovitis that occurs in both the early and late phases of OA is associated with alterations in cartilage. Catabolic and pro-inflammatory mediators such as cytokines, nitric oxide, prostaglandin E_2 (PGE_2) and neuropeptides are produced by the inflamed synovium and alter the balance of cartilage matrix degradation and repair, leading to excess production of the proteolytic enzymes responsible for cartilage breakdown [7]. Cartilage alterations induce further synovial inflammation, creating a vicious circle and the progressing synovitis exacerbates clinical symptoms and stimulates further joint degradation in OA [7]. Fig. 1 outlines the major molecular and cellular changes that occur in the synovial joint in arthritis and synovitis.

Recent studies have demonstrated that systemic factors regulate the metabolism of joint tissues, and that there is substantial

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