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Mesenchymal Stem Cells and Cartilage Regeneration in Traumatic and Osteoarthritic-Cartilage Defects

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Abstract

Osteoarthritis (OA) affects several hundred million people and is one of the leading causes of disability around the world. Aging is the most influential risk factor for developing OA. Cartilage has a limited ability to spontaneously heal; therefore, it needs surgical intervention in case of cartilage defects caused by traumatic injury or degenerative disease. Due to the shortage of autologous chondrocytes and autografts that require additional defects, adult human mesenchymal stem cells (MSCs), the precursors of chondrocytes, become possible options for cartilage regeneration in traumatic and Osteoarthritic cartilage defects.

Keywords

osteoarthritis, cartilage defects, mesenchymal stem cells.

Osteoarthritis (OA), which affected at least 27 million Americans in 2005 and an estimated 67 million Americans are projected to have arthritis by 2030, is the leading cause of disability in USA [1,2]. Worldwide estimates are that 9.6% of men and 18.0% of women aged over 60 years have symptomatic osteoarthritis [3]. Aging is the most influential risk factor for developing OA. Many traumatic injuries to joints can also develop into OA with its chronic disabilities. The degeneration of articular cartilage as part of the clinical syndrome of osteoarthritis is one of the most common causes of pain and disability in middle-aged and older people. Both clinical and experimental studies have provided evidence for the sensitization of pain pathways during OA, involving pronounced changes in joint nociceptors and changes of the nociceptive processing in the spinal cord, brain stem, and thalamocortical system [4]. Animals treated with MSCs distributed significantly more weight to the affected limb after treatment, suggesting that injected MSCs were able to reduce pain in a rat model of OA [5].

Cartilage Regeneration in Osteoarthritis and Traumatic Articular Cartilage Defects

Articular cartilage is a unique tissue that provides life-long weight-bearing and mechanical lubrication with extraordinary biomechanical performance and simple structure.

Adult articular cartilage is composed of a proteoglycan and collagen type II-rich extracellular matrix, and free of blood vessels. Only about 5% of cartilage tissue volume is occupied by chondrocytes that arespherical, embedded in lacunae filled with pericellular matrix, and no contact to the distant neighbor cells [6], in addition to no access to abundant nutrients or circulationing progenitor cells [7], cartilage has a limited ability to spontaneously heal in case of cartilage damaged by trauma or disease. Therefore, an unavoidable surgical intervention is needed to regenerate articular cartilage [8]. The success of cartilage repair may differ depending on whether the lesion is restricted to the cartilage itself or penetrates the underlying bone to form an osteochondral lesion. Numerous surgical approaches have been developed to repair articular cartilage: abrasive chondroplasty, micro-fracture, spongialization, autologous transplants of periosteum orperichondrium and osteochondral matrix (mosaicplasty) etc. [9]. Thus far, no surgical technique has ever been completely successful in stimulating articular cartilage repair and regeneration, and then, the focus has shifted in potentially utilizing the patient's own autologous chondrocytes to initiate a more desirable chondrogenic repair.

The first cell therapy for cartilage repair named autologous chondrocyte transplantation (ACT) Osteoarthritic chondrocyte implantation (ACI) was reported in 1994 that relied on implantation of *in vitro* expanded chondrocytes, obtained from an uninvolved area of the injured knee, into the area of the defect [10]. Although ACI is currently used in clinical repair cartilage defects worldwide, the major disadvantages of ACI are ascribed to the need for two invasive procedures and the extensive expansion of cells for each patient [7,8]. The use of autologous chondrocytes for cartilage regeneration raises several major issues such as morbidity at the donor site, low cell number upon harvest, de-differentiate during culture expansion with concomitant down regulation of cartilage-specific genes and limited life span following transplantation with a 5.8% failure rate in a mean time of 22 months [11,12].

Mesenchymal Stem Cells and Cartilage Regeneration

Human adult bone marrow-derived skeletal stem cells, a.k.a. mesenchymal stem cells or marrow stromal cells (MSCs), have been identified as precursors of several different cellular lineages, including osteoblasts, chondrocytes, myoblasts, adipocytes, and fibroblasts, as well as non mesenchymal lineages, including neurons and glial cells [13]. MSCs or MSC-like cells are not a unique feature of the bone marrow, as they also are found in non-marrow tissues such as fat, umbilical cord blood, amniotic fluid, placenta, dental pulp, tendons, synovial membrane, and skeletal muscle, though the complete equivalency of such populations has not been formally demonstrated using robust scientific methods [13,14]. Mesenchymal stem cells (MSCs) have gained significant attention of studied, since they hold great promise as a source for cell-based transplantation therapies for bone and cartilage [15]. In addition, MSCs have anti-inflammatory properties of potential benefit when regeneration has to occur in a hostile inflammatory environment [16]. There has been a growing interest in tissue engineering, which is the use of a combination of cells, biochemical and physiochemical factors, engineering and biomaterials to create functional tissue replacements to treat cartilage injuries. Similar to other tissue engineering/cell-based therapies for articular cartilage repair, it has three major requirements for successful cartilage regeneration by MSCs: optimal sources of MSCs and *in vitro* expansion, signal molecules that induce chondrogenesis, and matrix scaffolds that support cartilage regeneration. Among of them, the biggest challenge is to find the most appropriate matrix scaffolds for MSCs transplantation and chondrogenic differentiation. A wide array of materials has been used in various *in vitro* and *in vivo* studies for articular cartilage engineering, including hydrogels made from poly(ethylene glycol) diacrylate (PEGDA), collagen, fibrin, agarose, and synthetic peptides; sponge-like scaffolds manufactured from materials such as collagen, polyglycolic acid, polylactic acid, and polyurethane; materials with a naturally occurring porous structure, such as coral, devitalized articular cartilage, and hyaluronan based scaffolds [18]. Each of these scaffolds has strengths and limitations, more studies are needed to further identify the most optimal combination of MSCs, growth factors, and supporting matrix scaffolds to induce regeneration of injured cartilage.

The feasibility, efficacy and safety of autologous MSCs implantation for the treatment of cartilage defects were reported in early of 1990s [19,20]. Since then, there are a lot of published pre-clinical studies of MSC-based treatment of chondral and osteochondral lesions [15,21]. The first clinical study describing the implantation of expanded MSCs into OA kneelesions was reported by Wakitani et al. [18]. Twelve patients received transplantation with expanded autologous MSCs, which were embedded in a gel composed of type I collagen and implanted as a collagen sheet, and 12 patients served as cell-free controls receiving the collagen sheet alone. Approximately a year later clinical scores did not differ between the groups, but arthroscopy and histological scores were better in the cell-transplanted group [22]. Recently, Orozco et al. [23] reported that twelve patients with chronic knee pain and radiologic evidence of osteoarthritis were treated with autologous expanded bone marrow MSCs by intra-articular injection and showed that patients exhibited rapid and progressive improvement of algofunctional indices and a highly significant decrease of poor cartilage areas with improvement of cartilage quality in 11 of the 12 patients. Centeno et al. showed that in a study involving a larger group of patients, there is no evidence of malignant transformation in vivo following re-implantation of culture expanded mesenchymal stem cells into peripheral joints or into intervertebral discs [24]. Wong et al. [25] reported that in 56 patients, intra-articular injection of cultured MSCs is effective inimproving both short-term clinical and MOCART outcomes in patients with cartilage defects. MSCs-related clinical study procedures, follow-up times, cell sources, and biomaterials differgreatly among the studies [21], thereby preventing generalized conclusions on clinical and functional outcomes. However, preliminary results of pre-clinical and clinical studies are promising. In general, after cell-based therapy—irrespective of cell type—clinical and functional scores are clearly improved and defects are filled with newly formed cartilage like tissue, sometimes even with hyaline-like characteristics [15,21]. Although promising, these clinical data on MSC delivery to cartilage defects still have to be considered as very preliminary since these clinical studies are mostly uncontrolled case reports including only a few patients. Several randomized controlled clinical studies that investigate the use of bone marrow concentrates and MSCs via delivery as suspension or three-dimensional constructs to cartilage defects are under way [15]. More data from controlled in vivo studies need to be analyzed to determine whether MSC-based treatments can compete with current treatment modalities.

Summary and Prospectives

Human MSCs (hMSCs) obtained from either patient's bone marrow or non-marrow tissues, e.g. fat, umbilical cord blood, amniotic fluid, placenta, dental pulp, tendons, synovial membrane, and skeletal muscle etc., or donors can be injected directly into intra-articular cavity or implanted within scaffolds as naive hMSCs or chondrocytes differentiated from MSCs in vitro for cartilage regeneration in osteoarthritis and articular cartilage defects (Figure 1).

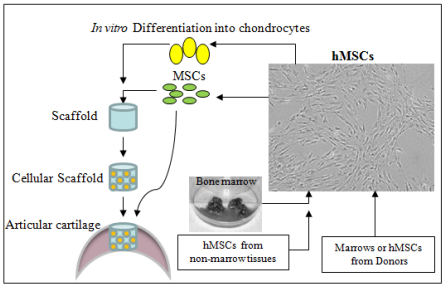

Fig. 1 Prospective MSC therapies for cartilage regeneration in osteoarthritis and articular cartilage defects. Human MSCs (hMSCs) obtained from either patient's bone marrow or nonmarrow tissues, e.g. fat, umbilical cord blood, amniotic fluid, placenta, dental pulp, tendons, synovial membrane, and skeletal muscle etc., or donors can be injected directly into intraarticular cavity or implanted within scaffolds as naive hMSCs or chondrocytes differentiated from MSCs in vitro.

Accumulating evidence indicates that the main advantages of MSCs for regenerative medicine and tissue engineering applications are their easy isolation from a variety of sources, potential for cell-number expansion, ability to readily differentiate into the cells of interest, lack of immunogenicity, limited capability to form tumors and not ethically restricted. However, special attention must be given to improve the quality of repair tissue formed following MSCs transplantation into the cartilage defect: (1) While some studies have attempted to demonstrate the engraftment and/or differentiation of the transplanted MSCs, none has convincingly shown that cellular differentiation in vivo was responsible for these cells' therapeutic effects. This troubling deficit ismainly due to the lack of standardized specific cell surface markers of MSCs *in vivo* and tracking molecules. Thus, it is need to consider these reliability issues when designing and interpreting preclinical and clinical trials that concern MSCs engraftment and differentiation [26]. (2) Human MSCs proliferation and differentiation potential can deteriorate with age and under certain conditions with disease [30-32]. Thus, more basic biological studies are needed to improve clinically MSCs regenerative outcome in cartilage defects. (3) Most expansion protocols still use fetal bovine serum/fetal calf serum as a growth factor supplement, which is a potential source of undesired xenogeneic pathogens and raises concerns when used in clinical-grade preparations [27]; substitutes for FBS/FCS may be needed. (4) Cultured MSCs are versatile in producing cytokines, chemokines and modulatory factors and the therapeutic effects afforded by MSCs transplantation that are likely to be short-lived and related to dynamic, paracrine interactions between MSCs and host cells [28]; therefore, more research is needed to help understand their basic biology and mutual regulatory roles. (5) Chondrocyte expansion is complicated by the fact that monolayer-cultured chondrocytes de-differentiate, lose their characteristic phenotype. Efficient protocols must be developed to prevent hypertrophy and dedifferentiation of chondrocytes produced by MSCs differentiation [29]. (6) Determination of an optimized combination of genetically modified MSCs with scaffolds is importance for producing a high quality repair tissue *in vivo* [29], but the clinical safety of genetically modified MSCs need to be further evaluated. (7) The protocols and technologies of human MSCs for therapeutic strategies need more clinical trials; the guidelines from governmental and Inter governmental agencies for their use in clinical applications also need to be established [29]. Future research may need to focus on a combination of biodegradable scaffolds and MSCs to produce a mechanically functional hyaline repair tissue. With a worldwide extensive effort, MSCs will be routinely applicable in articular cartilage defects in the near future.

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