

Cell Therapies-Engineered Cartilage Tissue-New Horizons

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Abstract

Cartilage tissue engineering is required for the repair of injured cartilage and osteoarticular diseases. Since cartilage cells at the site do not grow to form new cartilage cells, therefore, tissue engineered cartilage approaches aim at cultivating chondrocytes *in vitro*, and to reintroduce the engineered cultured cartilage tissue into the damaged region. In our study, human cartilage cells cultured on novel microcarrier made of ECM (Extracellular matrix) proteins exhibited hyaline cartilage differentiation, cell proliferation and biocompatibility. Engineered cartilage tissue will be a promising method for the treatment of cartilage defects.

Keywords: Extracellular Matrix (ECM); Cartilage; Engineering; Microcarrier

Introduction

Repair of injured cartilage and osteoarticular diseases is a major challenge for Orthopedic surgeons. Cartilage injuries among professional and recreational athletes are increasingly encountered and diagnosed and demand a quick return to preinjury level of sporting activities [1].

Current high-field Magnetic Resonance Imaging (MRI) techniques provide a sensitive and reliable diagnostic tool for the evaluation of cartilage and osteochondral injury [2]. In the athlete, untreated articular cartilage defects can represent a career-threatening injury and create a significant obstacle in returning to full athletic participation. The markedly limited healing potential of articular cartilage often leads to continued deterioration and progressive functional limitations [3]. Because cartilage cells at the site do not grow to form new cartilage cells, cartilage tissue engineering is required for the repair of injured cartilage. Tissue-engineered cartilage approaches aim at cultivating chondrocytes *in vitro* and to reintroduce the engineered cultured cartilage tissue into the damaged region. Our proposed cell therapy besides being useful in repairing traumatic cartilage lesions can also serve as bioenhancement procedure after joint surgeries like ACL (Anterior cruciate ligament) repair, microfractures, and arthroscopic debridement. Bio enhancement with a bioactive scaffold, like our micro carrier can stimulate healing [4]. At present, cartilage injury cases are treated with multiple drilling, abrasion arthroplasty, mosaicplasty, Autologous Chondrocyte Implantation (ACI), and Matrix-Induced ACI (MACI). Articular cartilage injuries remain a prime target for regenerative techniques such as tissue engineering. In contrast to the surgical techniques mentioned above, which often lead to the formation of fibrous or fibrocartilaginous tissue, tissue engineering aims at fully restoring the complex structure and properties of the original articular cartilage by using the chondrogenic potential of transplanted cells [5]. MACI by Genzyme Corporation is proven for cartilage trauma. Collagen I and collagen III are used for MACI that provide Extracellular Matrix (ECM) environment and hence potentially useful.

Methods

I propose two novel and hypothetical variation of MACI for cartilage injuries and Osteoarthritis. In first approach, autologous chondrocyte are cultured on ECM microcarrier and transplanted. Chondrocyte phe-

notype can be preserved during culture expansion [6]. In the second approach, autologous Mesenchymal Stem Cells (MSCs) are cultured on ECM microcarrier and differentiated into hyaline cartilage and used for transplantation. Bone marrow has been shown as a possible source of Multipotent Stem Cells (MSCs) with chondrogenic potential [7]. MSCs seeded in hydrogel composites can improve cartilage repair [8]. Effective chondrogenesis can be achieved by directing the MSCs toward chondrocyte lineage [9]. Both approaches have high degree of feasibility as per the published literature. In the last decades, a wide number of researchers/clinicians involved in tissue engineering field published several works about the possibility to induce a tissue regeneration guided by the use of biomaterials [10] like our ECM microcarrier. In our study primary chondrocytes were isolated from discarded human cartilage during joint replacement surgeries. The patient's consent was taken for the study. The cartilage cells are isolated after enzyme digestion and are cultured on ECM particle (microcarrier) in spinner bottle set up for required period. Similarly, MSCs isolated from bone marrow concentrates are differentiated into chondrocytes and expanded on ECM microcarrier. The ECM carrier laden with cells is then transplanted in nude mice for study of collagen and GAG expression. *In vivo*, cartilage matrix formation can be assessed by histology after subcutaneous transplantation of chondrocyte-seeded scaffolds in immuno compromised mice [11]. The principle of porous microcarrier culture of human or animal cells is described with help of (Figure 1 and 2).

Results

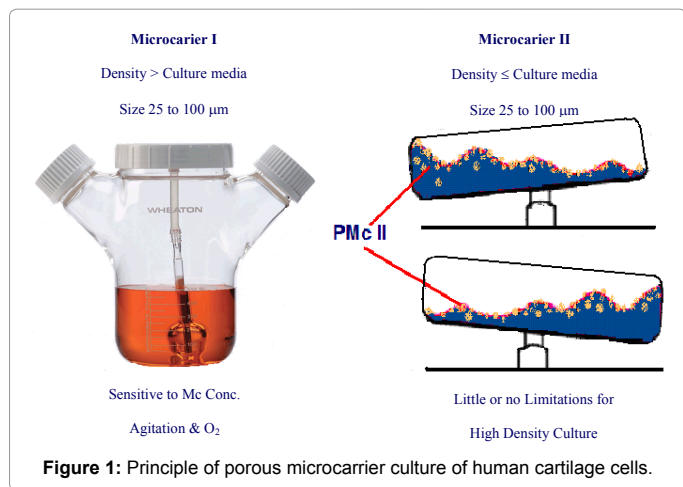
The studies on the construction of engineered cartilage tissue on a ECM composite have high degree of feasibility. The cell attachment ratio to our novel microcarrier, proliferation, and extracellular matrix proteins secretion are superior and reproducible. They have appropriate mechanical and structural properties for clinical applications.

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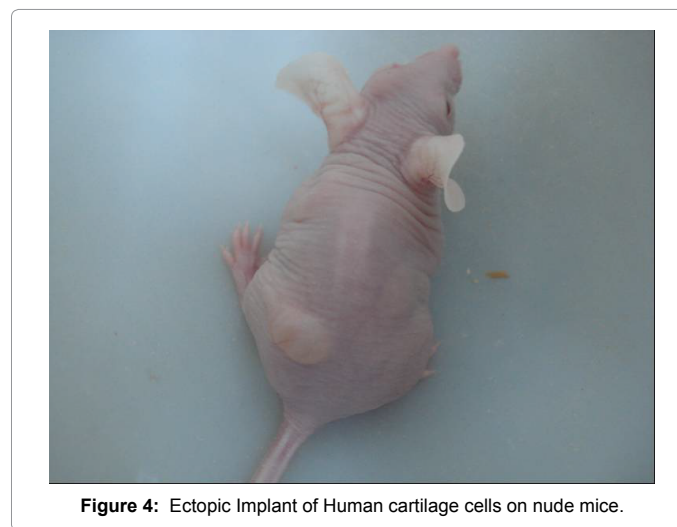
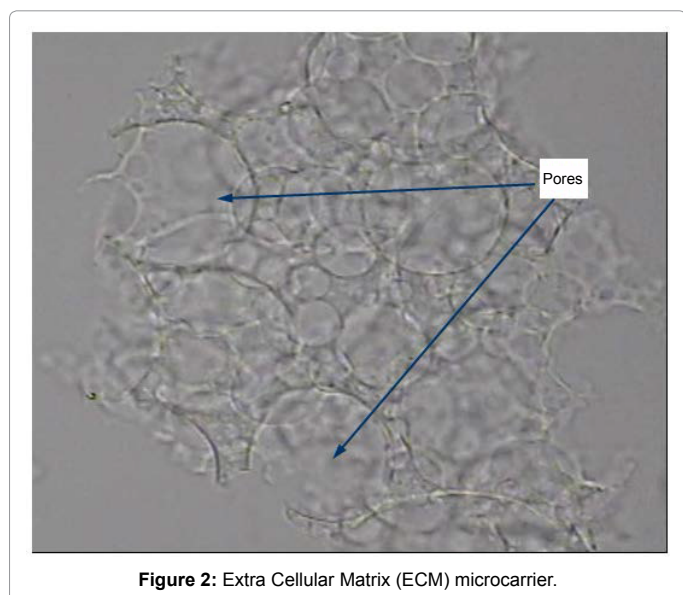
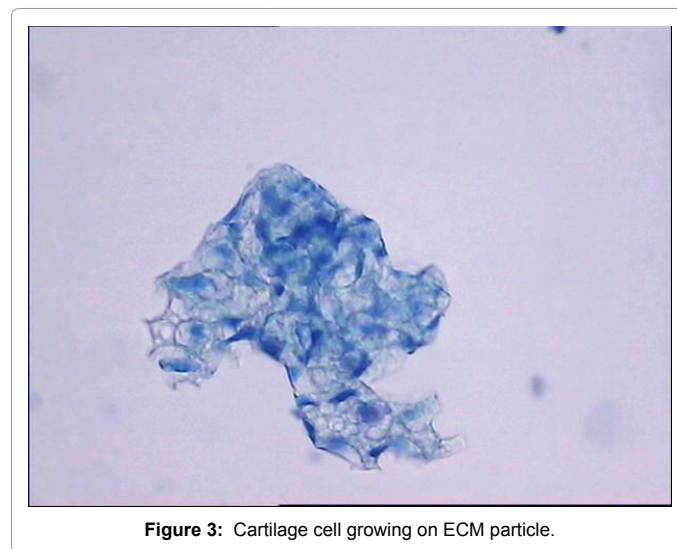
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that currently exist, a multidisciplinary field, in which bioengineering and medicine based on integrative approaches using scaffolds, cell populations from different sources, growth factors, and nanomedicine should emerge [12].

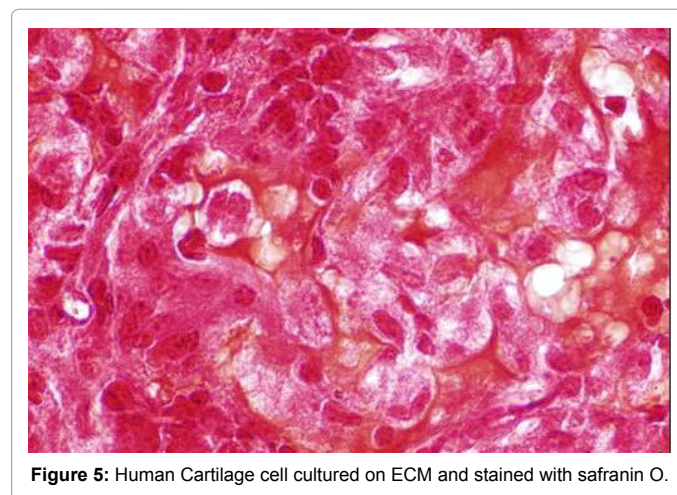


The Scanning electron microscope (Figure 3 and 4) and confocal fluoroscope examinations showed that the ECM microcarrier has a regular interconnected porous structure.

The novel ECM microcarrier is effective in engineered chondrocyte culture. The cell viability test (WST-1 assay), cell toxicity (lactate dehydrogenase assay), cell survival rate, extracellular matrix protein production (glycosaminoglycans contents), cell proliferation (DNA quantification), and gene expression (real-time PCR) all revealed good results for chondrocyte culture (Figure 5). The chondrocytes can maintain normal phenotypes, highly express aggrecan and type II collagen, and secrete a great deal of extracellular matrix when seeded in our novel microcarrier. This study demonstrated that a highly organized “Sol-cell” can be prepared with an ECM microcarrier device which is effective in engineering cartilage tissue.

Conclusions

The engineered cartilage tissue will be a promising method for the treatment of cartilage defects. The downsides associated with present treatment regimens like multiple drilling, abrasion arthroplasty, mosaicplasty and joint replacement can be addressed with our novel, fluidic yet robust cartilage engineering to overcome the limitations



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