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Cartilage Tissue Engineering

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ABSTRACT

Cartilage has a poor regenerative potential with very low cell-density that contributes to its poor capability for self -repair .For this reason, autologous cartilage grafts have been used in reconstructive surgery .Today; the rapidly emerging field of tissue engineering holds great promises for the generation of functional cartilage tissue substitutes. The technique was initiated by harvesting cartilage cells (chondrocytes) from a donor site such as the nasal septum or the auricle. However, in clinical use of human chondrocytes for tissue engineering, extensive expansion of cell numbers from a small donor site biopsy was required and this could limit the chondrogenic potential of cells after proliferation. Therefore, the ability of chondrocytes to replicate in- vitro allowed the expansion of cell numbers to produce theoretically limitless supplies of cartilage autografts .Stem cell technology presents an alternative , immunoprivileged resource of cells with unlimited replicative capacity . These cells exist in a wide selection of tissues and provide the option of multi-lineage differentiation. This paper reviews the current evidence that stem cells may provide a superior cell resource for tissue engineered cartilage and outlines the methodology for their isolation and chondrogenic induction. ***(Tanaffos 2005; 4(14): 9-18)***

Key words: *Tissue engineering; cartilage; chondrogenesis; stem cells; biomaterials*

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INTRODUCTION

Cartilage is a type of dense connective tissue, composed of cells called chondrocytes. There are three main types of cartilage (hyaline, elastic, and fibrocartilage).

Hyaline cartilage is found in the knee, fibrocartilage and elastic cartilage are seen in other areas of the body. All three composed of chondrocytes and extracellular matrix macromolecules, elastic cartilage forms the ear and nose and is characterized by the presence of elastin in the extracellular matrix (ECM). Fibrocartilage has a higher proportion of collagen in the ECM than hyaline cartilage and is found at the ends of tendons and ligaments in apposition to bone. Hyaline cartilage has a white, glassy appearance, and unlike fibrocartilage, shows no macroscopic evidence of fibers (1, 2, 3). Usually, there are three main types of cartilage injury: matrix disruption, partial thickness defects, and full thickness defects. In addition, diseases or congenital abnormalities and trauma caused degeneration of cartilage that could be managed by reconstructive surgery, implants, prosthesis or a combination of these options (4, 5, 6, 7). However, in these reconstructive surgeries, infection and dislocation frequently occurred. As a

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consequence, other attempts i.e. ., curettage, spongialization, autologous osteochondral transplantation, drilling holes through subchondral bone, periosteal and cartilage transplantation and injection of chondrogenic agents were also investigated (8, 9, 10, 11, 12). Overall, the success of total joint replacement and /or treatment for repair of cartilage damage was less than satisfactory.

Today, the rapidly emerging field of tissue engineering holds great promises for the generation of functional tissue substitutes, by constructing tissue *in vitro* and implanting it *in-vivo* .For example, a trachea reconstructed by using calf articular chondrocytes seeded onto synthetic biomaterial polyglycolic acid (PGA) in athymic mice (13, 14).

The basic principal is to utilize a sound scaffold that is seeded with an appropriate cell source which is loaded with bioactive molecules to promote cellular differentiation and/or maturation. Although, in clinical practice the potential for harvested autologous chondrocytes, especially for trachea is limited by their restricted replicative capacity (15, 16, 17, 18, 19, 20, 21, 22, 23). This is due to dedifferentiation to a fibroblastic phenotype in monolayer culture. Recent discoveries point to a solution. Investigators have been able to identify and culture rare "stem cells" from various crucial tissues for many months (24, 25, 26, 27, 28). These cells are pluripotent and have an infinite self renewal capacity and can be induced into a mesenchymal lineage to produce chondrocytes.

This review aims to present the current status and prospects of tissue engineered cartilage and the role of stem cells in propelling this field towards clinical applications.

The Promise of Mesenchymal Progenitor or Stem cells

There have been several promising advances in the use of stem cells for tissue regeneration. Only a few stem cells would be required to produce large numbers of cells following serial sub cultivation *in-vitro*. There are several sites from which these cells can be acquired; some of which yield high stem cell populations and involve minimally invasive harvesting techniques (29, 30, 31, 32, 33). In addition, stem cells are immuno-privileged and therefore offer a future potential for large scale stem cell banks that can be utilized to generate a wide variety of cell populations. Cartilage remains closer to this end-point because it is not dependent on the currently theoretical development of an integral capillary network within tissue engineered constructs (34, 35, 36, 37, 38, 39).

A) Different types of stem cells

Two types of stem cells are available: embryonic and adult stem cells.

A.1) Embryonic Stem Cells (ESCs)

Embryonic stem cells are pluripotent; they have the ability to differentiate into any cell specification whilst maintaining full regenerative capacity. There are three types of ESCs ; embryonic stem cells (ESC), embryonic carcinoma cells (ECC) and embryonic germ cells (EGC). ESCs are derived from the inner cell mass of blastocysts during gastrulation. The latter two are derived from primordial germ cells.

A.2) Adult Stem Cells (ASCs)

Adult stem cells have been found in a variety of differentiated tissues including bone, deciduous teeth, adipose tissue, umbilical cord blood, synovium, brain and blood vessels.

However, the most researched postnatal stem cells are the two discrete populations found in bone marrow; hemopoietic and mesenchymal stem cells (15).

Jiang et al. (40) found a pluripotent cell type in bone

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marrow which could be induced to develop cells from all three germ cell lineages. He named this population multipotent adult progenitor cells (MAPC) and was later to find such cells in other tissues such as muscle and brain.

This phenomenon of transgermal plasticity challenges previous conceptions that ASCs have a restricted repertoire of cells into which they can differentiate. The advantages of ASCs for use in tissue regeneration are being less tumorogenic than their embryonic counterparts and are accessible from a diversity of tissues.

B) Stem cell source

ASC can be found in a variety of tissues. The selection criteria should consider site of harvest, yield and pluripotency of the cell type (40, 41, 42, 43, 44, 45). Currently, most stem cell derived neocartilage constructs have been engineered using bone marrow and adipose tissue. Bone marrow is the most widely used source for stem cells as it harbour two unique stem cell populations; HSCs and MSCs. MSCs can be expanded many-fold with little effect on the tissue that is eventually formed and have been shown to differentiate into both bone and cartilage cells (46).A 30ml aspirate produces an average of 10^5 cells. Recent studies have shown that MSCs may be harvested from umbilical cord blood (31). This is a valuable source of stem cells because it is readily available, its collection harbours no risks to the donor and the risk of immune rejection to an allogenous implant of this derivation is small. They may also be cryopreserved for storage. This cell population has been shown to possess multi-lineage differentiation but its role as a viable cell source in tissue engineering still remains undetermined.

C) Isolation techniques

MSCs are generally aspirated in a heparin loaded syringe and cultured in basal medium. The standard choice is high glucose Dulbecco's modified Eagle's medium (DMEM), 10% fetal bovine serum and sometimes antimicrobial agents. The MSCs will express a fibroblastic phenotype and adhere to tissue culture plastic. The non adherent cells will die over a period of two weeks or can be washed away earlier by PBS. Centrifugation may be used to produce cell pellets which are then re-suspended in basal medium and plated until they reach confluence (46, 47, 48, 49, 50, 51, 52, 53).

This technique is unfortunately not specific to MSCs; haemopoietic cell types can also adhere to tissue culture plastic.

There are more accurate isolation and characterization methods now available involving monoclonal antibodies, fluorescent activated cell sorting (FACS), magnetic activated cell sorting (MACS), polymerase chain reaction (PCR) and flow cytometry.

Monoclonal antibodies have been particularly useful in classification of cell populations within tissue. One of the first antibodies found to correspond to an antigen on colony forming unit-fibroblasts (CFU-Fs), clonogenic stromal progenitor cells capable of prolonged replication, is STRO-1 (53-54). Simmons et al (54) separated human bone marrow using a murine antibody which was named STRO-1. Paramagnetic beads conjugated to antibodies against known hemopoietic cell surface markers (CD11b, CD34, CD45) can be used to extract these cell lineages from murine bone marrow (55, 56, 57).

The cell surface antigens Sca-1, CD29, CD44, CD81, CD106 and stem cell marker nucleostemin (NST) on these immunodepleted cells were analysed using FACS. These cells could be induced to differentiate into adipocytes, chondrocytes and osteoblasts in vitro (56). Immunoprecipitation, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), matrix-assisted laser desorption/ionisation time of flight (MALDI-TOF), mass spectrometry and amino

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acid analysis have been used in the isolation and characterization of the SB-10 antigen in human, rat, canine and rabbit MSCs (57, 58, 59).

D) The important adjuncts

Various adjuncts for stem cell propagation and differentiation have been explored such as biomaterials, bioreactors and growth hormones.

D.1) Exogenous factors

The role of growth factors in stem cell derived chondrogenesis has been extensively studied. It is well documented that MSCs centrifuged to a pelleted micromass and cultured in a serum free medium containing "Tumour Growth Factor"-betaTGF-1 or TGF-3 will differentiate into chondrocytes (60, 61). The TGF super family has been found to promote chondrogenic induction and cartilage matrix production (32, 60, 62, 63).

Barry et al. (59) compared the effects of TGF-1, TGF-2 and TGF-3 on chondrogenesis of human MSC cell pellets. All three growth factors maintained at similar cellular content over three weeks but TGF-2, and TGF-3 produced significantly more GAGs and collagen 2 than TGF-1. With availability of this extra-cellular matrix, the cartilage would be designed. Without a TGF-(analogue) cells were small and secreted minimal matrix (64, 65, 66). Bone morphogenic proteins (BMP) and the sonic hedgehog gene (Shh) are members of the TGF- super family which can be transfected into stem cells to enhance chondrogenesis. Chondrogenesis is regulated by factors of the wnt family. Among these, wnt-7a has found to be implicated in chondrogenesis inhibition whereas wnt-4 and wnt-14 are expressed at sites of future joint development. Wnt-5 and wnt-11 are found in the prehypertrophic chondrocytes and wnt-5b characterizes prehypertrophic ones in the growth plate (67). Fibroblast growth factor (FGF)-FGF receptor 3 signaling is sufficient to induce chondrogenic differentiation (68).

ASCs share the requirement with chondrocytes for three dimensional constructs to produce chondrocytes and extra cellular matrix. Huang et al reported that human adipose derived stem cells could be induced to chondrocytic differentiation in micromass culture but not in monolayer cultures even with TGF-(1) (62) Disease can modify the replicative senescence of MSCs. The proliferative capacity of human MSCs with respect to adipogenic and chondrogenic activity in patients with osteoarthritis was reported.

Basic Fibroblast growth factor (bFGF) has been shown to improve chondrogenesis in stem cells of osteoarthritic patients (69, 70, 71, 72).

In addition, nanofibrous scaffold (NFSs) in the presence of TGF- differentiated to a chondrocytic phenotype, as evidenced by chondrocyte-specific gene expression and synthesis of cartilage -associated extra cellular matrix (ECM) proteins .This is because the NFSs can be readily fabricated in any shape and size as needed clinically and also provides sound mechanical stability .Thereby , the three dimensional NFS can be a good candidate of bioactive carrier for MSC transplantation in tissue engineering based cartilage repair.

D. 2) Biomaterials for cartilage engineering

The extra cellular matrix and basement membrane are the two biological scaffolds which guide cell growth and function. A biomaterial should be easily producible, non-cytotoxic, non-immunogenic, compatible with physiological environments, adaptable by manipulation of cell-matrix communications, porous and biodegradable. It should also ideally possess self assembling spatial geometry similar to that found in living tissues and provide mechanical strength. The construct must not only enable cell adherence and orientation but also provide specific antigens and growth factors to

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trigger cellular proliferation and matrix production (39).

D. 2a) Non synthetic

Natural materials used to produce a bioactive scaffold include agarose, alginate, hyaluronic acid, fibrin glue, collagen derivatives, cellular dermis, porcine intestine submucosa, cadaveric fascia and amniotic membrane. The overriding disadvantage of these constructs is their mechanical fragility. Cartilage is tough but pliable and hence an integral ingredient to successful regeneration lies in an equivocal structural support. Issues regarding variable host related degradation rates, antigenicity and disease transfer also need to be considered (13).

Collagen is a widely used polymer in cartilage regeneration. The ECM of cartilage predominantly comprises of collagen 2. Both collagen 1 and 2 have proved to be effective substrates for chondrogenesis. Mechanical integrity has been improved by various techniques involving cross-linking and sponge formation.

Pieper et al (44) showed that crosslinked collagen 2 matrices elicited an evenly distributed cell population whereas the collagen 1 matrix located chondrocytes on its periphery. Both types of polymer, however, stabilised phenotype and supported matrix production. Collagen matrices have been found to have the proper molecular cues to stimulate new collagen production by transplanted cells as compared with other scaffold types (73).

Chitosan is a relatively unexplored bioactive scaffold for engineering cartilage. It is a partially de-acetylated derivative of chitin, found in the exoskeletons of arthropods. Hence, this is a naturally occurring, infinitely available polymer (74, 75, 76).

Itosan is a polysaccharide based analogue of GAG which is degraded in vivo by lysosyme. A large repertoire of moieties may be added to this polymer to modify its biochemical behavior. It has a propensity to form hydrogels and was first used as a bioactive substrate for chondrogenesis by Sechriest et al (77). Alginate and agarose beads or gels have problems with degradation in mammalian cartilage as they are derived from sea-weed. They are also difficult to handle. Some forms of alginate have been found to be immunogenic, as evidenced by increased lymphocyte number and presence of anti-alginate antibodies (78).

Recently, chitosan has been processed into porous matrices. This is produced by freezing and lyophilising chitosan-acetic acid, the pore size of which is modulating the rate of freezing. The use of this substrate to induce stem cell derived chondrogenesis is not reported.

D.2 b) Synthetic

The mechanical, biochemical and degradable qualities of a synthetic biomaterial are much easier to modify than that found in naturally occurring polymers. They do not possess the same problems with availability and their shapes and sizes can be tailored to specific requirements. Polyglycolide (PGA), polylactides (PLLA, PLGA,PDLA,PLC), polycaprolactone (PCL), polyethylene glycol (PEG), polyesterurethane (PEU), polyamide, expanded polytetrafluoroethylene (ePTFE), polyethylene oxide (PEO), polyN-isopropyl acrylamide (PNIPAAm), polybutylene and polystyrene have all been used to produce cartilage. Copolymers, polymer blends and composites are also continually investigated in the quest to find the ideal engineering matrix (60, 79, 80, 81, 82, 83, 84).

PGA is a well studied substrate which will continue to be used in engineering cartilage. It has been shown to maintain significantly higher chondrocyte differentiation than PLLA and PLGA and has comparable adhesivity and matrix production to non-absorbable scaffolds such as polyamide and ePTFE (60, 83, 85). It is most often used in its non-woven

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form which has a high porosity. However, PGA fibrous polymer is weaker and degrades at a faster rate than most synthetic scaffolds. This can be modified in copolymers and composite compounds.

Hybrid scaffolds have also been presented as promising candidates for engineering cartilage. Chen et al. (83) invented a novel composite web of PLGA knitted mesh filled with collagen microsponges. The thickness of the chondrocyte seeded implant was altered by rolling or laminating the web. The same group of scientists modified their matrix using PLGA sponge filled with collagen microsponges. Both forms of this hybrid scaffold promoted chondrocyte phenotype and new tissue formation in vivo. PLGA offered the mechanical strength and shape whilst the collagen provided the 3-D environment for cellular differentiation. PLGA, like most synthetic polymers, is hydrophobic and lacks cell signaling mitosis. Collagen enhanced homogenous cell seeding because it is hydrophilic and exhibits surface cell adhesion receptors (84, 85, 86, 87, 88).

Future direction:

Further research should thus be aimed at investigating and evaluating tissue-engineering approaches to cartilage repair in diseases-compromised animal models to gain a better understanding of clinically feasible designs. The results of such studies should have direct therapeutic applications and should also provide a model system for the study of normal and pathological cartilage tissues.

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