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ARTICULAR CARTILAGE REGENERATION : A LITERATURE REVIEW

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Abstract

Articular cartilage is a highly specialised type of connective tissue found in bones-joints. Its primary function is to provide a smooth, lubricated surface for movement and to reduce the coefficient of friction to facilitate movement. Regenerative medicine has been developed in recent years as an alternative to conventional surgery. The objective is to create a new tissue that is as similar as feasible to the existing cartilage. Due to the close relationship between tissue structure and composition and function, it is believed that the capacity to reconstruct structure is essential for regeneration. Regenerative medicine has become one of the most fascinating areas of biotechnology through the use of cell and gene therapy and tissue engineering. This has given researchers, physicians, and patients a great deal of optimism. The primary objective of advances in this field is to heal damaged tissue, not to supplant it with an external device. In the future, grafts and artificial prostheses may not be necessary.

Keyword: *articular cartilage; osteoarthritis; regeneration; tissue*

INTRODUCTION

Articular cartilage is a highly specialised form of connective tissue found in joints composed of two bones. Its primary function is to provide a smooth, lubricated surface for movement and to facilitate movement by reducing the coefficient of friction. Articular cartilage lacks blood vessels, lymph vessels, and nerves, and must endure a harsh physical environment. Moreover, articular cartilage can only recover and repair itself to a limited degree. Consequently, the health and maintenance of articular cartilage are the most crucial aspects of joint health.[1,2]

It is widely accepted that damage to the articular cartilage can result in considerable morbidity to the musculoskeletal system.[1] Because of its one-of-a-kind and intricate structure, articular cartilage presents a significant obstacle for the patient, the surgeon, and the physical therapist when it comes to the treatment, repair, or restoration of abnormalities. The integrity of the articular cartilage is directly proportional to the degree to which its organised architecture is preserved.[3]

Regenerative medicine has replaced surgery in recent years. Making a tissue that matches the existing cartilage is the goal. Regeneration depends on tissue structure and composition, thus rebuilding structure is vital.[4] Regenerative medicine is the study and creation of new treatments that focus on repairing, regenerating, or replacing cells, tissues, or organs to recover structure and physiological functions that have been lost due to disease, damage, birth defects, or getting older.[5] This article showed the regenerative medicine in articular cartilage.

ARTICULAR CARTILAGE

Articular cartilage is a very specialised type of connective tissue that is found in joints with two bones. Its main job is to provide a smooth, lubricated surface for movement and to make it easier for things to move with a low coefficient of friction.[6] Articular cartilage doesn't have blood vessels, lymph vessels, or nerves, and it has to deal with a rough physical environment. Most importantly, articular cartilage can only heal and fix itself to a certain extent. In this way, the health and maintenance of articular cartilage are the most important things for joint health.[1,7,8]

Hyaline cartilage makes up articular cartilage, which is between 2 and 4 mm thick. Articular cartilage is different from most other tissues because it does not have blood vessels, nerves, or lymphatics. It is made up of a thick extracellular matrix (ECM) and a few chondrocytes, which are very specialised cells. The ECM is mostly made up of water, collagen, and proteoglycans. There are also smaller amounts of glycoproteins and proteins that are not collagen. Together, these parts help the ECM hold on to water, which is important for keeping its special mechanical qualities.[8]

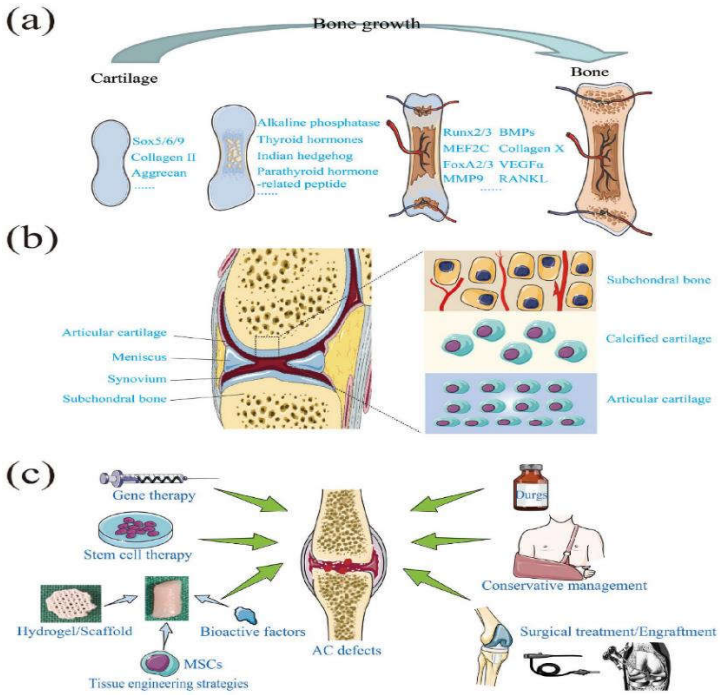

Figure 1. (a) Bone growth process, (b) the joint and AC anatomy, and (c) AC defects therapeutic strategies[9]

The middle (transitional) zone connects the superficial and deep zones. Proteoglycans and thicker collagen fibrils make up 40%–60% of cartilage volume in the middle zone. This layer has spherical, low-density chondrocytes and oblique collagen. Compressive forces first hit the middle zone. Since collagen fibrils are perpendicular to the articular surface, the deep zone resists compressive stresses well. The deep zone has the largest radial collagen fibrils, highest proteoglycan content, and lowest water concentration.[8]

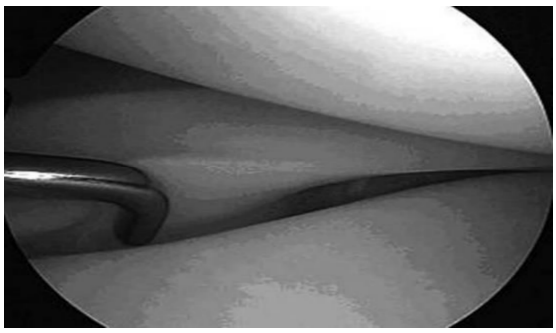

Figure 2. Gross photograph of healthy articular cartilage in an adult human knee[1]

Columnar chondrocytes are parallel to collagen fibres and perpendicular to the joint line. Articular cartilage volume is 30% deep. The tidal mark separates the deep zone from calcified cartilage. Given its high proteoglycan concentration, the deep zone resists compressive stresses best. Collagen fibrils are perpendicular to articular cartilage. The calcified layer anchors deep zone collagen fibrils to subchondral bone, cementing cartilage to bone. This zone has few cells and hypertrophic chondrocytes.[8]

Figure 3. Morphology of human adult articular cartilage. (A), chondrocytes organization in the different tissue zones. (B), arrangement of collagen fibers[10]

The matrix has multiple sections based on closeness to the chondrocytes, composition, collagen fibril diameter and organisation, and zonal structure and composition. Pericellular, territorial, and interterritorial ECM areas exist. The thin pericellular matrix entirely surrounds the chondrocyte. It's mostly proteoglycans, glycoproteins, and noncollagenous proteins. This matrix area may trigger cartilage load-bearing signal transduction. The territorial matrix, a basketlike network of tiny collagen fibrils, surrounds the pericellular matrix.[10]
The territorial matrix is thicker than the pericellular matrix and may protect cartilage cells from mechanical stress and help the articular cartilage structure tolerate heavy loads. The interterritorial zone is the largest of the three matrix regions and most important to articular cartilage biomechanics. The superficial and middle zones have randomly oriented bundles of large collagen fibrils, but the deep zone has them perpendicular to the joint surface. Interterritorial proteoglycans abound.[8,11]

BIOCHEMICAL FUNCTION

Articular cartilage is thin, viscoelastic connective tissue. Its main purpose is to smooth, lubricate, and transmit stresses to the subchondral bone. Articular cartilage is uniquely able to tolerate large cyclic stresses without injury or degeneration. Articular cartilage behaves best as a biphasic medium. Articular cartilage is fluid and solid. Water makes up 80% of the tissue's moist weight. Fluid phase inorganic ions include sodium, calcium, chloride, and potassium. The porous, permeable ECM defines the solid phase.[2]

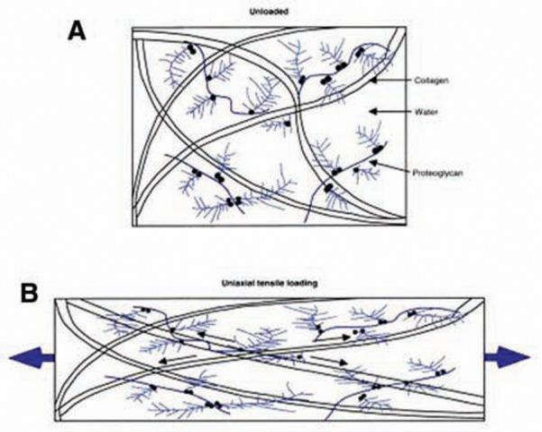

Figure 4. A schematic depiction of the main components of articular cartilage when the tissue is unloaded (A) and when tensile load is applied (B). When the tissue is loaded, collagen fibrils align along the axis of tension[8]

Proteoglycan aggregates and interstitial fluid repel electrostatically, giving cartilage compressive resistance. Articular contact forces during joint loading immediately increase interstitial fluid pressure. This local pressure rise leads fluid to flow out of the ECM, creating a lot of matrix friction. Interstitial fluid returns to tissue after compressive load removal. Articular cartilage's limited permeability prevents liquids from rapidly escaping the matrix. Two opposing bones and surrounding cartilage limit the cartilage under the contact surface.[8,11]

They limit mechanical deformation. When loaded or deformed, viscoelastic articular cartilage behaves time-dependently. Articular cartilage has flow-dependent and flow-independent viscoelasticity processes. Interstitial fluid and frictional drag drive the flow-dependent process. Interstitial fluid drag is biphasic viscoelastic. Macromolecular motion—specifically, the collagen-proteoglycan matrix's inherent viscoelasticity—causes flow-independent viscoelasticity.[8]

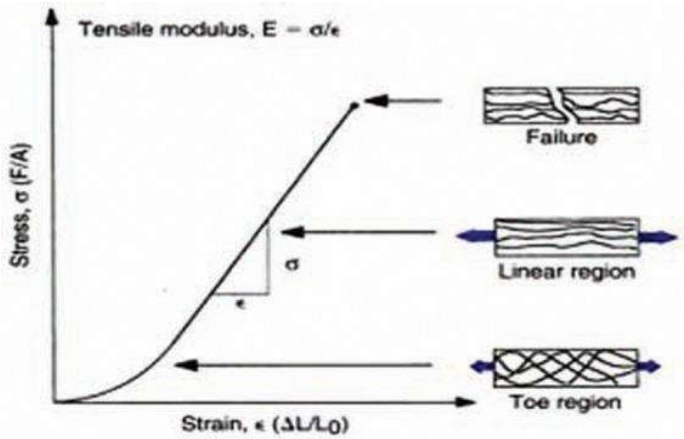

Figure 5. A stress-strain diagram for articular cartilage during tensile loading. The schematic representations on the right illustrate the orientation of the collagen fibrils in response to loading[8]

Thus, fluid pressure contributes to total load support, lowering solid matrix stress. Articular cartilage also creeps and relaxes. Tissue deforms or creeps under constant compressive force until equilibrium is established. When cartilage is deformed and held at a constant strain, stress will peak, then slowly release until equilibrium is attained. Articular cartilage stiffens with strain, hence Young's modulus cannot represent it. Instead, the tissue modulus depends on the force measurement taken during a stress-relaxation test, which was popular in early mechanical testing on articular cartilage.[8]

Currently, a known strain is applied, followed by a peak in measured force and a slow stress-relaxation process. The force/stress value is recorded when equilibrium is attained. The equilibrium modulus is calculated as the stress-strain curve slope throughout a variety of strain values.[6] The middle zones' complex composition and organisation make cartilage shear-resistant. Cartilage responds to shear stress by stretching randomly dispersed collagen fibrils. Collagen fibril molecular arrangement gives it tensile force-resisting capabilities. Intra- and intermolecular cross-links may stabilise and increase collagen fibre tensile strength.[12]

REGENERATION MEDICINE

In the last few years, regenerative medicine has been created as an alternative to traditional surgery. The goal is to make a new tissue that is as similar as possible to the cartilage that is already there. Tissue structure and composition are closely linked to function, so it is thought that the ability to rebuild structure is important for regeneration.[4] Regenerative medicine is the study and creation of new treatments that focus on repairing, regenerating, or replacing cells, tissues, or organs to restore structure and physiological functions that have been lost due to disease, injury, birth defects, or ageing.[5]

Early moderate cartilage injuries (grades I-II) according to the International Cartilage Repair Society (ICRS) and Kellgren & Lawrence (K-L) classification are treated with hyaluronic acid (HA), analgesics, corticosteroids, and hormones. Drugs and corticosteroids have been utilised in clinic/clinical trials or new research to reduce joint inflammation. Kartogenin developing stable nonprotein molecule, can convert bone marrow mesenchymal stem cells (BMSCs) and synovial mesenchymal stem cells (SMSCs) into chondrocytes in vitro and in vivo.[9]

Using bone marrow stimulating techniques, surgeons attempt to stimulate a natural fibrocartilaginous response, with the goals of reducing inflammation and pain and enhancing the joint function of the patients. Numerous surgical procedures for treating focal cartilage defects have been developed. These surgical treatments are classified as palliation (e.g. fixation, metallic spacing devices, chondroplasty, and debridement), repair (e.g. drilling and microfracture (MFX)), or restoration (e.g. osteochondral autograft or allograft transplantation, autologous/allogeneic chondrocyte implantation (ACI), and even osteotomies).[9]

One of the biggest problems in the field of orthopaedics is still how to get joint cartilage to grow back. The problem is that it doesn't have many blood vessels, which makes it hard for stem cells to get in and make repairs. Undifferentiated mesenchymal stem / stromal cells (MSCs) from the bone marrow start the repair process for toosteochondral damage that also affects the subchondral bone. However, the resulting tissue is fibrocartilage, which is not a good replacement for hyaline articular cartilage. Also, the damaged joint's active inflammatory environment has an effect on its ability to heal.[5,13]

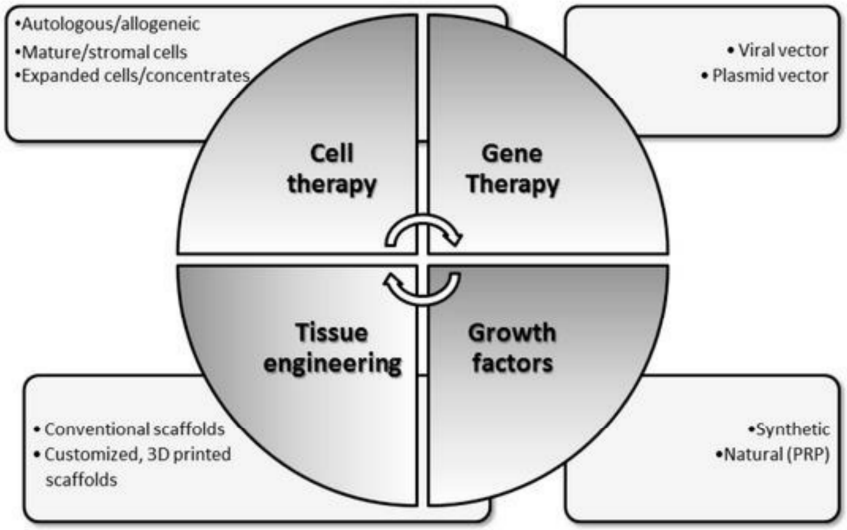

Figure 6. Graphic showing regenerative medicine

The osteochondral grafting regeneration method involves replacing the damaged osteochondral area with cartilage and bone from the same person (mosaicoplasty) or a different person (allograft transplantation). The method could cause problems if the donor site gets sick and the graft doesn't work, or if the allogeneic procedure can spread disease and the cells don't live long enough. The majority of the most recently established techniques for regeneration make use of a number of technologies that, when combined, lead to the development of a variety of therapeutic solutions and methodologies: technology such as cell treatment, tissue engineering, and gene therapy.[13]

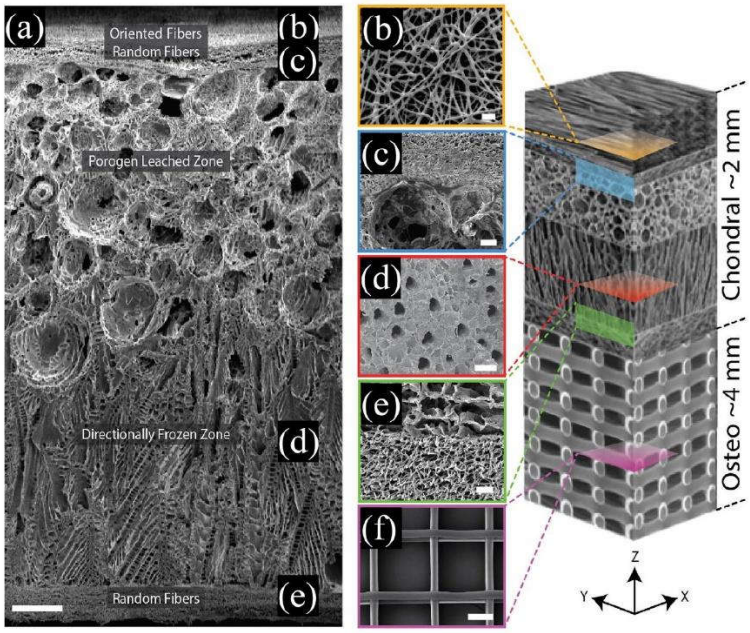

Figure 7. A zonal microstructured scaffold mimics the structure of AC and subchondral bone to repairing osteochondral defects: (a) cross-section of the complete scaffold showing each unique zone, (b) partially fused poly-ε-caprolactone (PCL) fibers used to adhere the electrospun mat to the underlying foam using residual solvent (top-down image), (c) a cross-sectional view of the porogen-electrospun interface, (d) vertical channels through the directionally frozen foam (top-down image), (e) a cross-sectional view of the directionally frozen-electrospun interface, and (f) melt-electrowritten osteo component (top-down image). The osteo component consisted of 20 µm diameter fibers stacked at 200 µm intervals in a 90-degree lay-down pattern. Figure at right is a conceptual schematic of the zonal microstructured osteochondral scaffold, features are not proportionally represented[9]

A cell therapy is a clinical treatment that involves the injection, transplantation, or implantation of ex vivo-manipulated cells. Cell administrations can be single or multiple, local or systemic.[14] Cell sources may be autologous to avoid immune response problems and disease transmission, or allogeneic (from living or deceased donors) to eradicate donor-site morbidity and maximise availability. Cells may or may not be expanded in culture (concentrates). The selection of a cell population that enables cartilage regeneration most effectively remains a challenge.[13]

Specifically, an optimal cell component should be: viable; accessible; non-immunogenic; non-tumorigenic; phenotypically stable; and responsive to bioactive factors. Tissue engineering's emergence has inspired optimism in the scientific and medical communities, and its principles have been applied to the treatment of cartilage lesions. It depends on the use of scaffolds that not only serve as a template for cell attachment, but are also designed to replicate cartilage ECM structure as closely as possible in order to provide the optimal environment for cell growth and chondrogenic differentiation.[13]

In addition, they permit a more stable spatial distribution of cells, thereby preventing their dispersion in the articular space. Scaffolds may vary in origin, composition, structure, and status, but they must be able to support implantable cells while preserving their phenotype and attempt to replicate cartilage ECM. Moreover, they must be biocompatible, biodegradable, non-immunogenic, bio-mimetic in order to induce chondrogenic differentiation and ECM production, architecturally structured to permit cell colonisation and nutrient exchange, and possessing mechanical properties to support tissue growth under native mechanical loads.[13]

Some therapeutic solutions have been devised in this direction; both cell therapy and tissue engineering can be made more effective through the use of growth factors known to enhance the regeneration process. There has been an increase in OA genomic research in recent years. It is becoming evident that numerous alleles, each with a modest effect size, contribute to the disease's risk, development, and progression. The multifactorial aetiology and localised nature of OA make it an ideal gene therapy candidate.[15]

Gene therapy is the process of introducing genomic material (trans-gene) into specified target cells to treat human diseases by correcting an existing abnormality or providing a new function. A carrier, known as an expression vector, is genetically modified to transport the gene into the cells. Non-viral and viral vectors are the two primary types of vectors.[16] Typically, non-viral vectors are plasmids that can be transmitted to recipient cells through physical or chemical means. Adenoviruses, recombinant adeno-associated viral (rAAV), retroviruses, and baculoviruses are viral vectors. Non-viral methods are safe, simple, and cost-effective, but their delivery efficiency is inferior to that of viral vectors.[17]

CONCLUSION

By using cell and gene therapy and tissue engineering, regenerative medicine has become one of the most interesting areas of biotechnology. This has given researchers, doctors, and patients a lot of hope. The main goal of improvements in this field is to heal damaged tissue, not to replace it with an outside device. This means that grafts and artificial prostheses may not be needed in the future.

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