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Articular Cartilage Repair: Where We Have Been, Where We Are Now, and Where We Are Headed

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Abstract

This review traces the genealogy of the field of articular cartilage repair from its earliest attempts to its present day vast proliferation of research advances. Prior to the 1980s there was only sporadic efforts to regenerate articular cartilage as it was considered to be incapable of regeneration based on historical dogma. The first flurry of reports documented the use of various cell types ultimately leading to the first successful demonstration of autologous chondrocyte transplantation which was later translated to clinical use and has resulted in the revised axiom that cartilage regeneration is possible. The current field of cartilage repair is multifaceted and some of the 1980s' vintage concepts have been revisited with state of the art technology now available. The future of the field is now poised to undertake the repair of whole cartilage surfaces beyond focal defects and an appreciation for integrated whole joint health to restore cartilage homeostasis.

Keywords

chondrocytes, cells, articular cartilage, tissue, osteoarthritis, diagnosis

Introduction

Lesions in articular cartilage are difficult to treat and cause considerable musculoskeletal morbidity, with significant economic and social implications. It is generally well accepted that such lesions eventually result in osteoarthritis (OA). OA has a significant impact on human health, particularly in populations who are at higher risk for cartilage trauma over the course of their lifetimes. These include patients who have sustained sports injuries, have biomechanical aberrations, or repetitive micro trauma to their joints. Although cartilage has a relatively simple structure compared with other tissues, cartilaginous injuries can be extremely unforgiving. The limited blood supply in cartilage is thought to be responsible for the inadequate repair post-injury. A substantial fraction (~12%) of the overall burden of OA arises secondary to joint trauma, where the risk of posttraumatic OA (PTOA) ranges from 20% to 50%.[1,2] Currently, 9% of the U.S. population aged 30 years and older has OA of the hip or knee, costing an estimated $28.6 billion dollars with >400,000 primary knee replacements currently being performed each year in the United States alone.[3] Thus, methods for successful cartilage repair still remain a largely unmet clinical need.

Cartilage Repair: The Pre-Autologous Chondrocyte Transplantation Era

The well-referenced 1743 quote from the British anatomist Hunter in which he states "Cartilage injury is a troublesome thing and once injured is seldom repaired" was the general axiom for thinking about cartilage repair for the next 200 years. Despite such negativity, there were pioneers such as William Green, MD,[4] who performed seminal experiments investigating the reparative potential of autologus and homologous chondrocyte transplantation in the 1970s. He used decalcified bone as a type of scaffold for cell transplantation. He was also the first to use the rabbit as a model to study cartilage repair. Although his success was hampered by the technology of the times, his work was a cornerstone for the future of cartilage repair as well as a pioneer in what was to become the field of tissue

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engineering. Later, his colleagues George Bentley and Robert Greer[5] experimented with epihyseal and articular chondrocyte allografts in rabbits.

By the early 1980s, the concept of healing cartilage with predominantly hyaline tissue was still largely considered a myth. Popular procedures at the time included Pirdie drilling and abrasion arthroplasty, which resulted in largely fibrous to fibrocartilaginous tissue. Based on the combined works of Green, Bentley, and Sokoloff,[6] a multidisciplinary group of orthopedic researchers at the Hospital for Joint Diseases in New York City, hypothesized that hyaline cartilage repair could be achieved by a cell-based approach to the problem. This began a collaboration to try and develop a new method for achieving the goal of hyaline cartilage repair. The clinical motivation for pursuing this project were patients who had sustained cartilage injury but were still deemed too young for total joint arthroplasty and which resulted in pain and disability for young active individuals. The concept of a cell-based strategy was explored and determined to be a viable option. After several experiments it was concluded that articular chondrocytes exhibited several intrinsic properties of the tissue that were deemed key to repair.

First, they were already programmed to synthesize type II collagen and aggrecan. The clinical strategy was developed to first obtain a biopsy of cartilage, which would then be used to isolate free chondrocytes and expanded in culture followed by a second transplant procedure. Based on earlier work by Benya and Shaffer,[7] it was hypothesized that chondrocyte phenotype was plastic and a limited culture time in monolayer 2-dimensional culture could then be reestablished by return to a 3-dimensional environment. Optimizing cell delivery and a technique for maintaining the chondrocytes within a defect was problematic as suitable biomaterial membranes were scarce at that time. The decision to use periosteum was based on its anatomical proximity to the surgical site as well as its historical use in many orthopedic applications such as interpositional arthroplasty procedures. The first results of rabbit experiments were decidedly superior then expectations and the realization that a new chapter in orthopedic research had been opened. The first report of the technique were presented at the annual meeting of the Orthopaedic Research Society in 1985 by Lars Peterson, MD, and were promptly met with skepticism as the promising results were in conflict with current thinking as well as more than 200 years of dogma. This was followed up by 2 seminal publications, 1 in the *Journal of Orthopedic Research* in 1989 received significant attention.[8] The other published in the *Anatomical Record*[9] as part of the first author's (DAG) thesis. The procedure is now known as autologous chondrocyte implantation (ACI).

The first reports studied chondral defects made in the patella of rabbits and did not violate the subchondral plate thus avoiding bleeding and the repair mechanism intrinsic to other previous surgical procedures.[8] The results demonstrated nearly complete regeneration of the cartilage defects with a tissue that was blindly classified as hyaline cartilage. The fate of the transplanted cells was followed by autoradiography but only a small fraction, 10% to 15% of the cells could be localized within the defect. The mechanism of cartilage regeneration was postulated to be either the result of the transplanted cells, however, the radiolabel was serially diluted to be nondetectable, or that the cells induced an endogenous repair response. Further recent studies with better cell tracking methodology have determined that these cells do persist and function in establishing new hyaline cartilage.

In spite of initial skepticism, Lars Peterson, MD, then conducted the first human clinical trials using the exact same protocols developed for the preclinical studies back in his native Sweden.[10]

The ACI technique has been proven to be a successful treatment modality for treatment of cartilage lesions and which has resulted in long-term clinical success without the need for total joint arthroplasty. The use of periosteum as a covering membrane has been the principal source of morbidity because of its capability of being stimulated to undergo hyperplasia when removed from its anatomical location. Significant research has subsequently been performed to find alternative nonreactive membranes to replace periosteum as a cover. Further investigation has characterized the importance of maintaining the chondrocyte phenotype and applying principles of big pharma to the performance of cells.[11] Certifying that chondrocytes are expressing a gene profile consistent with a hyaline phenotype demonstrated superior structural repair in a prospective randomized clinical trial comparing ACI versus microfracture.[12]

Where We Are Now

The 1980s-1090s period was a productive time for cartilage research. Several concepts developed during this period laid the foundation for technologies in current use today. The use of immature, neonatal chondrocytes for cartilage repair was based on the higher metabolic rates of these cells compared to those of adult. These were shown to be capable of excellent repair in an avian model by Itay et al.[13] Although not developed further at that time the use of young cartilage has recently been adapted by Zimmer (Warsaw, IN) as their product DeNovo-NT and has been used clinically in the United States to treat more than 3,000 patients. The product consists of minimally manipulated cartilage tissue harvested young donors that is placed within a cartilage defect and held in place by fibrin glue. The mechanism of action is unclear but it is likely that the cells within the transplanted tissue are able to migrate out and contribute to the repair tissue observed.

The archetypes of plug-type scaffolds for arthroscopic delivery were initially fabricated of carbon fiber by Dunlop Corp in Birmingham, United Kingdom, and investigated in clinical trials by McMinn, Coutts, and Amiel studied cartilage repair using the bioabsorbable scaffold material poly-L-lactic acid with the addition of perichondrial derived chondrocytes.[14] The descendants of this research include the currently available True-Fit plug (Smith & Nephew, Andover, MA) along with other similar collagen based plugs like the Chondromimetic product (formerly Tigenix) and being developed by Kensey-Nash (Exton, PA).

Work done by Kandel et al,[15] growing chondrocytes on a suspended membrane culture system, thus allowing nutrient diffusion in 2 planes resulted in reformation of cartilage tissue with enhanced matrix deposition and multiple cell layers in thickness. The membrane could then be used as a delivery system to transplant the neocartilage construct.[17] This innovative approach is the basis for matrix-assisted chondrocyte implantation (MACI), currently in clinical trials in the European Union.

The prototype for a tissue engineered strategy was developed by using vicryl suture (polylactic glycolide) formed into a rudimentary nonwoven scaffold and seeded with chondrocytes.[16]

This study demonstrated that chondrocytes could generate cartilage tissue de novo as the scaffold degraded leaving only the cells and their synthesized extracellular matrix. The field of tissue engineering has seen a prolific amount of activity with respect to cell types explored (chondrocytes, stem cells; marrow, muscle, adipose, synovial, embryonic, induced pluripotent stem cells) and scaffold fabrication.

While the putative mechanisms for joint degeneration from cartilage defects leading to PTOA occur at the molecular, cellular, and tissue level, current treatments for PTOA are primarily surgical.[17-19] Several procedures are in wide use today such as microfracture, osteochondral autograft transfer system, mosaicplasty, and ACI, and MACI have been devised to relieve pain, restore function, and delay or halt the progression of focal cartilaginous defects.[17-19,22,23] Each of these methods has its own characteristic advantages and limitations.[8,22-25] Microfracture involves the piercing of the subchondral bone to allow marrow and its host stem cells to colonize the wound bed, promoting cartilage formation that is more fibrous than hyaline in quality. Osteochondral allografting involves the transfer of bone–cartilage units from "healthy" regions to damaged regions and rapidly restores load-bearing capacity and cartilage structure; however, limitations arise because of donor site morbidity, lack of healthy donor tissue, and insufficient integration. ACI (injection of chondrocytes in suspension under a periosteal flap) has shown promise in small defects in non- and low load-bearing sites; however, it employs adult human chondrocytes from potentially OA cartilage, which possess a limited capacity to form a hyaline rich tissue. In MACI, a scaffold cut to the shape and size of the defect is seeded with autologous chondrocytes and secured in the defect using a fibrin glue.[26,27] New techniques involving tissue engineering use cells in combination with scaffolds to regenerate a cartilage plug *in vitro* for implantation into the joint.[28]

Procedures such as platelet-rich plasma[29] and bone marrow aspirate concentrate[30] use a patient's autologous blood or bone marrow in a perioperative setting to deliver stem cells locally in cartilage defects. Other biological-based treatments such as Orthokine or interleukin receptor antagonist[31] have also been isolated from each patient's blood and delivered locally into the joint. These technologies are highly cost-effective relative to cell-based repair strategies and are readily available for adaption to clinical setting. However, clinical studies and independent trials have yielded largely mixed outcomes and will likely remain so until well-designed prospective randomized clinical trials are conducted and demonstrate efficacy.

Cartilage Repair: Where We Are Headed and the Future of Cartilage Repair

The field of tissue engineering has largely been supplanted by the emergence of regenerative medicine. Regenerative medicine is defined as the "process of replacing or regenerating human cells, tissues, or organs to restore or establish normal function." It was first coined by William Haseltine, the founder of Human Genome Sciences and cartilage repair is highly attractive for implementing regenerative strategies.

The Need for Early Intervention in Cartilage Repair

There is a new paradigm emerging suggesting the need to treat the whole joint as an organ system and not just the cartilage defect. The early phase of inflammation post joint trauma triggers a cascade of catabolic changes in cartilage, synovial tissue, and underlying bone. Whereas acute inflammation can be part of the normal healing process, chronic inflammation in PTOA is associated with a positive feedback cycle that augments the destructive and degenerative pathways mediated by matrix-degrading enzymes, primarily matrix metalloproteinases (MMPs). The use of an MMP inhibitor as an early intervention shortly after the incidence of injury is attractive because it may be deployed outside of a surgical unit, where oral administration may be preferred. Specifically inhibiting MMPs, target the pathophysiologic enzymes responsible for extracellular matrix breakdown, without inhibiting the other mediators of normal inflammatory responses, associated with physiological healing. MMP

inhibition can reduce or potentially delay the onset of PTOA, thus decreasing the need for more invasive procedure such as total joint replacement. Moreover, MMP interventions early in the acute post-traumatic period can significantly improve the therapeutic outcomes of treatments administered later during surgical repair, by reducing the severity of the disease. MMP inhibition is also expected to reduce the production of fibrous cartilage (inferior quality "scar-like" tissue) in favor of improved production of hyaline (type II collagen rich) cartilage with mechanical properties significantly improved over existing repair techniques. Studies using an equine model that delivered both interleukin-1 receptor antagonist protein and insulin-like growth factor-1 demonstrated significant improvement in cartilage repair as a result of interleukin-1 inhibition.[32]

Successful Large Defect Resurfacing

Recent investigations have demonstrated proof of principle achievement of the ability to resurface large defect surfaces and in some cases whole joint surfaces by "*in situ* tissue engineering." This approach seeks to recruit the endogenous stem populations from both the bone marrow and synovial compartments via chemoattraction to an implanted scaffold impregnated with a homing factor such as transforming growth factor-β3.[33] Other approaches[34] have demonstrated success using 3-dimensional composite woven polycaprolactone scaffolds vacuum infiltrated with gel containing cells. Such innovative designs are able to bear the high shear forces and loads encountered in a typical joint.[35] The future is now set for the age of biological whole joint resurfacing.

Summary

The history of cartilage repair undergone significant evolution over the past 40 years. Discoveries made more than 30 years ago are seeing rebirth as newer technologies have been developed to overcome some the problems associated with the era in which they were first proposed. Effective and comprehensive treatment of all phases of injury is essential to address the initial structural joint injury as well as the inflammatory and destructive processes that follow and can result in more diffuse joint pathology. Acute, subacute, and chronic surgical resurfacing of larger or multifocal symptomatic hyaline tissue traumatic defects and associated osteochondral defects is essential. Although current marrow stimulation (microfracture) and autogenous osteochondral transplantation techniques have been available, these methods have had less effective application in treating larger sizes defects (>2 cm^2). Use of volume stable scaffolds coated to chemotactically enhance mesenchymal stem cell recruitment to the repair construct is an attractive option. The concurrent use of biochemical catabolic inhibitors that can reduce degradative inflammatory mechanisms that can biologically expedite recovery and improve the quality of structural repair is a promising strategy as there are few surgical techniques that result in superior and durable clinical outcomes in young active patients.

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Ethical Approval

This study was approved by our institutional review board.

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