

Articular Cartilage Regeneration: An Update of Possible Treatment Approaches

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Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: February 24, 2017

Revised: April 25, 2017

Accepted: April 27 2017

Published online: August 28, 2017

ABSTRACT

BACKGROUND: Osteoarthritis, a widespread chronically disabling disorder primarily affecting articular cartilage is said to be irreversible. Researchers have however, been examining processes and methods of promoting articular cartilage repair for some time.

QUESTIONS: Can a case be made for the possibility of restoring osteoarthritic cartilage? How advanced is this undertaking? What barriers exist in translating basic studies in the clinical realm? What physical modalities are deemed efficacious in promoting cartilage structure?

METHODS: All relevant publications detailing articular cartilage

repair themes in the leading databases were examined. Specific emphasis was placed on a broad array of efforts and observations concerning articular cartilage and its repair. Articles of historic significance and more current strategies designed to foster cartilage repair were focused on, and reported in narrative form. Ideas extracted from the voluminous literature were those that answered one or more of the key questions driving this research.

RESULTS: Numerous attempts have been made over time to foster cartilage repair, using a variety of approaches such as creating artificial cartilage, and transplanting stem cells into damaged cartilage to promote repair. Most current strategies are forged in laboratories and do not always account for the complex disease process, and the importance mechanical and inflammatory determinants play in the disease. However, manipulating biophysical, and biomechanical stimuli favorably is likely to hold promise for attenuating destruction of/or for fostering cartilage viability and repair, even in the presence of adverse osteoarthritic cartilage tissue changes.

CONCLUSION: More work is needed to examine the key upstream determinants leading to articular cartilage destruction, and to enhancing the viability of the tissue. Employing carefully construed therapeutic strategies known to impact articular cartilage homeostasis safely and effectively can potentially preserve chondrocyte homeostasis, either alone or in conjunction with new technologies.

Key words: Articular cartilage, Chondrocyte, Osteoarthritis, Regeneration, Repair, Stem cells

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Marks R. Articular Cartilage Regeneration: An Update of Possible Treatment Approaches. *International Journal of Orthopaedics* 2017; 4(4): 770-778 Available from: URL: <http://www.ghrnet.org/index.php/ijo/article/view/2010>

INTRODUCTION

A commonplace view, still widely held today, is that osteoarthritis, a chronic disease affecting the articular cartilage lining of freely moving joints is irreversible, and once it ensues, its destruction is progressive and inevitable. This is surprising given quite a robust literature revealing articular cartilage may be amenable to selected

degrees of repair under certain conditions, and that articular cartilage cells or chondrocytes do attempt to mount a reparative process when injured in some way. Moreover, other joint structures implicated in osteoarthritis that are amenable to repair, such as bone, may impact articular cartilage reparative processes quite favorably, and episodes of spontaneous articular cartilage repair are not unknown.

However, in light of the limited capacity for mature cartilage cells to divide, and the fact that cartilage has no direct vascular supply, the view that cartilage repair is unlikely to ensue without some form of cell-based intervention or stimulus is widespread. Moreover, the quality of any reparative tissue is often less than desired to offset further osteoarthritic joint damage. To allay the pain and dysfunction associated with articular cartilage damage, many researchers of late have sought and are seeking mechanisms to either promote more optimal repair of the damaged articular cartilage through artificial strategies, using a variety of physicochemical and biomechanical stimuli, or opportunities to replace the damaged tissue with a viable substitute^[1].

Related questions arising in this sphere are consequently - what strategies are potentially suitable for fostering articular cartilage repair or aiding in an intrinsic reparative process? Will the artificial production of articular cartilage resemble normally structured hyaline cartilage, a composite of articular chondrocyte cells or chondrocytes and a complex intercellular matrix of collagen and proteoglycan derivatives and other elements? And under what conditions will a reparative process take place or be prevented?

METHODS

To provide some insight into these and related questions, a specific search on Web of Science that covers five databases, as well as PubMed was undertaken for time periods between 1925-2017, with a focus on years 2013-2017 up to and including April 15, 2017. These data were categorized as representing either historic data or contemporary data and the former were only briefly discussed in order to provide a context for the more current work in this realm. Key words used were *articular cartilage repair and osteoarthritis*, *articular cartilage regeneration*, *cartilage repair*, *articular cartilage regeneration and physical therapy*, and *articular cartilage repair and pulsed electromagnetic fields*, a physical modality showing promise for fostering cartilage repair.

Articles alluding to osteoarthritis pathology, and articular cartilage physiology were also sought in an effort to provide a well-rounded picture of the continuing discourse in this field of endeavor.

Osteoarthritis is a prevalent highly disabling disease affecting older as well as younger adults. In the absence of any successful targeted therapy that would attenuate or foster reversal of the osteoarthritic process^[1], the topic of articular cartilage repair is currently of great interest with more than 5,500 citations regarding this topic in recent years.

In this respect, the present paper was designed to simply offer a brief snapshot of some relevant past and present research that has examined the topic of articular cartilage, believed to be the tissue most damaged in painful disabling osteoarthritis, in terms of its regenerative capacity.

RESULTS

The literature search revealed many related works, mostly dealing with the cellular aspects of cartilage repair^[1,2], factors influencing cartilage biomechanics and chemistry^[1], magnetic stimulation and cartilage tissue engineering^[1,3] and preservation^[4]. Other topics

reported include the role of cyclic compression and chondrocyte function^[1], cartilage engineering^[5], factors influencing articular cartilage and its micro environment, and stem-cell-based articular cartilage repair strategies^[6,7]. Others are the application of autologous chondrocyte implantation procedures^[8], and orthopedic surgical options for joint cartilage repair^[9].

Among current articles published in the last five years, at least 20 reviewed the topic in general, or different aspects of the cartilage repair topic in narrative, systematic, or metanalytic forms. Among the scientific papers, discussed were animal models, human explants, clinical studies, preclinical studies, and a wide variety of reparative strategies and perspectives, rather than any focused perspective.

Specific findings

Early observations

Many current authors recount the longstanding belief that cartilage damage is irreversible^[10,11], even though research extending back as far as the 1920s^[12,13] demonstrated the potential for articular cartilage lesions to undergo repair. Although the repair process did not produce hyaline cartilage, sources for repair including mesenchymal tissue of synovial origin, and of subarticular origin were evidenced^[14]. Others found that cartilage defects sufficiently small and located solely in the cartilage superficial and intermediate zones were able to heal consequent to their increased proliferation and synthesis of matrix^[15-17]. In related work, and contrary to established beliefs, long term organ cultures of mature adult chondrocytes damaged chemically were able to mount an active regenerative phase of matrix repair^[16].

In addition, in 1958, Urist^[18] found varying degrees of articular cartilage repair in post arthroplasty cases examined at 18 months to two years, including observations of hyaline cartilage. Similarly, 8/14 cases followed post osteotomy for medial knee osteoarthritis, were found to exhibit cartilage regeneration verified by arthroscopy and cartilage punch biopsy. Later Salter *et al*^[19] noted that full thickness defects healed more rapidly and completely if subjected to intermittent active motion, as did Burr *et al*^[20] using an animal model exposed to intermittent muscle contractions of the thigh.

Along with surgical osteotomy that can offset cartilage deterioration and occasionally promote its healing^[21], Bland^[22] who reviewed the status of knowledge at that time concluded that the process or sequence of events resulting in osteoarthritis is subject to arrest and possibly spontaneous reversal if initiated at an early disease stage. Turnquist *et al*^[23] on the other hand, found there was complete reversibility of joint degeneration in monkeys if they underwent a period of immobilization, followed by period of gradual activity, as did Tammi *et al*^[24].

Other results revealed chondrocytes were able to mount selected aspects of repair in the context of cell cultures^[25], and could respond metabolically to selected mechanical stimuli^[26]. Others showed articular defects of old chickens could regenerate using embryonic chick chondrocyte implants^[27], and that low frequency pulsed electromagnetic fields had a biological modifying effect on cartilage chondrocyte activity, as did certain hormones, medications, enzymes, and insulin. At around the same time, efforts to regenerate cartilage from chondrocytes cultured on variously shaped polymer scaffolds showed an initial rapid cell growth was possible followed by a slower growth period involving matrix product formation^[28]. Other approaches are well described by Anz *et al*^[29] and include but are not limited to: (a) Non-operative treatment with “proliferative” or sclerosing agents; (b) Surgical treatment or debridement of the osteoarthritic joint; (c) Prolotherapy of injecting a sugar solution

into injured tissue; (d) Closely spaced multiple drilling of arthritic articular cartilage defects; (e) Microfracture of bone.

Although findings were variable, those described above and others^[30-32], tended to indicate the chondrocyte was not an effete cell, and that following damage to mammalian joint surfaces^[33], repair tissue might be generated, and at times, this might resemble hyaline cartilage under favorable conditions^[16]. Indeed, after undertaking a very careful review of articular cartilage repair process literature in 1998, Newman^[15] stated that the centuries-long belief that articular cartilage was unable to heal seemed highly dubious and about to fall.

Contemporary observations

Among the voluminous array of studies and data that have prevailed over the last three decades in the context of articular cartilage repair, as outlined in a report by Carlos-Rodriguez-Merchan^[2] most have focused on the use of cartilage therapy to improve the opportunities for repair of focal articular cartilage lesions, rather than conservative efforts to promote natural healing directly. No broad theory seemed to guide the research however, and among the 44 reports reviewed by Merchan^[2] an array of studies dating from 2006-2012 revealed a wide variety of diverse reparative approaches were used over this time period. These involved various attempts at articular cartilage repair using gene-activated matrices, autologous implantation of chondrocytes, meaning the use of chondrocytes taken from the host, biological approaches, stem cell implants, and various chondroprotection strategies, and models, experimental methods, time frames, outcome measures, and related methodologies that were truly not comparable in this body of research.

Nonetheless, none achieved the desired result, and among the key factors found to influence the reported outcomes were: the method employed to enhance repair, the site in question, and the age of the candidate or animal. While no definitive approach was deemed superior to any other, most relied solely on some form of implantation, even though careful attention to mechanisms of joint usage, along with the importance of inflammation control, and acknowledging the cause and extent of the condition, may be crucial outcome determinants^[15,16]. Mediated by multiple pathological mechanisms, including extracellular degradation, impaired formation of new matrix, and abnormal activation of cartilage cells^[34], other current approaches advocated for advancing cartilage repair put forth included the use of viscosupplementation, neuroceuticals, nanoengineered biomaterials^[35,36], various growth factors^[37], microfracture surgery whereby holes were drilled in the subchondral bone to promote small defect healing^[6], and low intensity ultrasound^[38], but again none achieved the desired result.

Newer surgical approaches designed to restructure or emulate the complex architecture of articular cartilage have since emerged. These generally attempt to employ scaffolds constituted by a variety of synthetic materials^[6], single stage cell implants, gene therapy and stem cell implantation^[11], and implants of presumably healthy chondrocytes from non-load bearing joint sites^[6]. Other more passive possible approaches include the application of targeted cartilage matrix degradation and bone remodeling strategies, the targeting of any prevailing inflammation, dysfunctional skeletal muscle, adipose tissue and the inflammatory environment caused by adipose tissue^[39], and platelet promoted cartilage repair^[40].

Also discussed in efforts to maximize repair of articular tissue that resembles hyaline rather than fibrocartilage is the utilization of tissue-engineered nasal chondrocytes^[41] and extracellular matrices that act as a natural scaffold and promote cell attachment, while maintaining a stem cell niche^[6]. As well, the use of osteoarthritis-derived

chondrocytes as a potential source of multipotent progenitor cells rather than autologous chondrocyte implantation^[34,41,42], which is not able to fully restore functional hyaline cartilage^[1] has been advocated. In addition, resurfacing damaged articular cartilage using tyramine-substituted sodium hyaluronate and riboflavin^[43] has been proposed, along with the use of growth factors^[1].

More novel current ideas involve using microRNAs as possible targets for articular cartilage engineering^[44] along with mesenchymal stromal cell-based therapy using stem cells extracted from bone marrow, adipose tissue, or other sources^[45]. The use of human embryonic stem cells treated with bone morphogenetic protein 2 and Wingless-Type MMTV Integration Site Family, Member 5A (Wnt5a)^[46], along with vitrified-thawed chondrocyte sheets^[47], are additional potentially useful strategies.

In addition, among various physical modalities that have been applied to foster articular cartilage repair, pulsed electromagnetic fields, have been found to have unique effects on articular cartilage tissues^[1] and appear beneficial in fostering the differentiation of human mesenchymal cells into chondrogenic cells, as well as for reducing inflammation and impacting bone health in a positive manner^[3]. Employed therapeutically as magnetic nanoparticles, these fields may also have the potential to foster better extrinsic control over tissue engineered structures in the context of cartilage regeneration strategies^[48]. Other potential strategies identified as promising in the literature are efforts to identify cartilage regeneration promoting genes, increased efforts to explore the relationship between cartilage healing and protection from osteoarthritis after trauma, and modulation of inflammation by drugs, and/or Wnt pathway activators and inhibitors thought to be implicated in the context of cartilage repair^[49]. See Table 1 for selected examples of the diverse approaches reported in the current literature, including ultrasound therapy, laser therapy, electrical muscle stimulation, exercise, passive motion, and microcurrent stimulation that all appear promising.

As recounted above there is thus no shortage of research efforts directed towards trying to emulate or mimic the original articular cartilage structure and function in cases where degeneration has ensued, as well as attempts to stimulate intrinsic repair. Yet, more often than not, almost all such attempts to manipulate or produce artificial cartilage exogenously have failed to generate durable articular cartilage^[50], with properties similar to hyaline cartilage^[1], with no singular method yet being shown to be superior to any other in the clinical realm. This may be because numerous factors must clearly be considered and in place in efforts to foster functional articular cartilage regeneration processes. These factors include, but are not limited to the nature of the tissue microenvironment^[1], intradonor variability of autologous articular chondrocytes, problems of cell retention at the implantation site^[27], formation of fibrocartilage or portions of cartilage located in fibrous tissue^[27], and effects of the reparative strategy on subchondral bone, implicated in the osteoarthritic disease process^[41].

Other factors are the limitations associated with the development of biocompatible scaffolds that can foster stem cell growth, plus the use of growth factors that can enhance chondrogenesis^[1], which must match the native tissue structurally and functionally^[41].

The structural and mechanical complexity of articular cartilage^[1] can also hamper the desired differentiation of chondrocytes and their ability to maintain or produce an optimally durable cartilage matrix structure and function^[7], as well as efforts to prevent cell death at the defect margins when the constructs are placed into the host tissue^[1]. Other influential factors are initial seeding density^[28,52], location-specific differences in natural healing responses of chondral injuries,

and donor age when employing autologous chondrocyte implants^[52]. Others are the use of invasive procedures required to extract mesenchymal bone derived stem cells^[34], defect size^[1,52], other injury characteristics^[9], and those problems associated with autologous chondrocyte implantation outlined by Oda *et al*^[42].

Other mediating or moderating factors that may affect both articular cartilage repair as well as efforts to stimulate damaged cartilage in the *in vivo* situation include the extent of prevailing intermittent compressive forces^[28], and influential factors specifically associated with applying growth factors to regulate chondrocyte proliferation, including undesired side-effects such as inflammation and osteophyte formation, unwanted osteogenic differentiation, the short half-life of these factors, and the high costs involved in producing and maintaining these products. The use of growth factors in combination with scaffolds or decellularized extracellular cartilage matrices, although a potentially useful mechanism for mimicking the structure and biology of articular cartilage, is also potentially problematic since not every element of native healthy cartilage is optimally represented in the synthetic microenvironment^[1].

According to Lee *et al*^[53] the initiation of chondrocyte self-assembly, which has emerged as a robust scaffold-free engineering methodology still requires an intact cytoskeletal network, and the conditions for the formation and maintenance of biologically and functionally appropriate tissue *in vitro* must be pre determined^[28]. Repair of articular cartilage also requires a sufficient number of chondrocytes to replace the defect^[54]. In this respect Duan *et al*^[55]

found a composite based on a novel biphasic scaffold combined with bone marrow stem cells showed a high potential to repair large osteochondral defects in a canine model, as did Yoon *et al*^[58] when applying a biphasic scaffold loaded with a combination of a chemokine and bone marrow concentrate to foster tissue regeneration in knee articular cartilage of beagles with cylindrical osteochondral defects, but this was not tested in patients with an osteoarthritic condition. Alternately, the beneficial use of scaffold free transplantation of chondrocytes has also been discussed, but its application remains to be demonstrated^[59]. Studies that have examined physical modalities including exercise in the context of fostering regeneration of articular cartilage explants, cell transplantation therapy, chondrogenesis of mesenchymal stem cells, or damaged cartilage in a variety of animal models, or *in vitro* situations, may not replicate the human situation at all well, and may be conflicting or show that bone rather than cartilage is the tissue benefited. In the more positive study by Zati *et al*^[92] who examined treatment of cartilage defects by Nd: YAG laser, patients who benefited were young, and had moderate, rather than severe cartilage damage.

DISCUSSION

For over a century researchers and scholars have carefully examined and discussed and debated the potential for articular cartilage to heal in cases where the tissue is damaged or destroyed. The importance of

Table 1 Diverse promising cartilage repair strategies published in the last 5 years [*=physiotherapeutic type strategies].

Research Group	Cartilage Repair Approach
Almeida <i>et al</i> [69]	Anisotropic shaped-memory alginate scaffolds with either Type I or II collagen
Bonasia <i>et al</i> [67]	Autologous adult, allogenic juvenile, and combined juvenile-adult cartilage fragments
*Boopalan <i>et al</i> [47]	Pulsed electromagnetic fields
Broguiere <i>et al</i> [70]	Factor XIII cross-linked hyaluronan hydrogels
Chang <i>et al</i> [102]	Cell free porous poly graft implants plus early loading exercise
Corradetti <i>et al</i> [73]	Chondroiten sulphate immobilized on a biometric scaffold
Choi <i>et al</i> [72]	Small molecule with sulfonamide
Chen <i>et al</i> [71]	Superabsorbant 3D scaffold based electrospun nanofibers
Donnelly <i>et al</i> [42]	Photo cross linked tyramine-substituted hyaliuronate hydrogels with tunable mecjanical properties
Driesen <i>et al</i> [54]	Chondrocyte cellular reprogramming
Embree <i>et al</i> [76]	Use of fibrocartilage stem cells
Gupta <i>et al</i> [76]	Adult human bone marrow-derived cultured, pooled, allogenic mesenchymal stromal cells
Karlsen <i>et al</i> [77]	Forced expression of micro-RNA 40
*Kwon <i>et al</i> [78]	Electrical stimulation
Latief <i>et al</i> [79]	Adipose stem cells differentiated chondrocytes
Maruki <i>et al</i> [80]	Collagen vitrigel incorporating TGF-B1-cell free method
Meng <i>et al</i> . [81]	Peritoneum derived a cellular matrix combined microracture
Nam <i>et al</i> [82]	Cord blood derived pluripotent stem cells
Park <i>et al</i> [83]	Allogeneic mesenchymal stem cells and hyaluronate gel
Pot <i>et al</i> [84]	Implantation of a cellular biomaterials after bone marrow stimulation
Ramakrishnan <i>et al</i> [85]	Injectable and 3D bioprinted polysaccharide hydrogels
Ruta <i>et al</i> [8]	Bone marrow stimulation, whole-tissue transplantation, and cell-based surgical strategies
Sakata <i>et al</i> [86]	Platelet rich plasma injections
Sartori <i>et al</i> [87]	Bi-layered scaffold and 'bioinspired' approach
Shi <i>et al</i> [88]	Adipose-derived stem cells co cultured with chondrocytes
*Wiegant <i>et al</i> [89]	Joint distraction
Vega <i>et al</i> [90]	Hydrogels as a promising scaffold for cartilage engineering
*Tan <i>et al</i> [4]	Ultrasound
Yamaguchi <i>et al</i> [90]	Mesenchymal stromal cell injection combined with pulsed ultrasound
*Zati <i>et al</i> [92]	Nd: YAG Laser Therapy

this issue, which stems from the widespread disability associated with the joint disease known as osteoarthritis, wherein articular cartilage pathology is a key component, remains, however, despite voluminous efforts over the past three decades to ameliorate this disabling disease via extrinsic and intrinsic cartilage repair strategies. However, even if one accepts articular cartilage has some reparative potential, this remains generally less than desirable, and is only partially assisted by past and current efforts to test and develop strategies to repair or regenerate the synovial joint surface if it is destroyed in some way.

This challenge is basically no simple task, given the complex processes involved in cartilage homeostasis, and maintenance, as outlined very briefly in this summary review. As shown in Table 1, many interesting options thus continue to emerge in the current literature. Popular approaches include - but are not limited to- gene therapy, hyalinization of repair tissue using growth factors, the use of stem cells, scaffold-free cartilage-like cell sheets, osteochondral allografts, and pulsed electromagnetic fields^[2,3,8,11,54,59,60]. None are superior however, none have been shown to have long term benefits in the context of large cartilage defects, and some have only been examined in animal models, selected joints, osteoarthritic conditions with artificially created defects that may not emulate the natural disease process, or in a variety of explants in the laboratory.

Moreover, in light of what we know about articular cartilage physiology, its shock-absorbent and lubricating property^[85], and its dependence on loading for nutrition and lubrication, plus the fact that this tissue is not uniquely involved in the pathogenesis of osteoarthritic joint disease, nor is it a structurally homogenous tissue unit, it is possible no singular extrinsically manufactured approach alone can achieve the desired result, no matter how sophisticated. In addition, without careful simulations of the osteoarthritic environment, where chondrocyte assemblies may be selectively or collectively disrupted, and proinflammatory mediators and infiltrating cell populations may induce chronic inflammation^[73], efforts to fully restore damaged articular surfaces and its structure, may still fail, unless these are carefully construed^[56]. Indeed, in recognition of the multiple biochemical and physiological processes within and surrounding articular cartilage in both healthy and osteoarthritic joints, the importance of understanding the role of inflammation in this disease, plus differences in disease origin, and impact of aging on all these processes renders the challenges in this realm highly complex.

Other limitations of current repair interventions for articular cartilage regeneration include the challenges in applying various scaffolds, including their controllability, actuation, and response properties^[1,48]. The stage of the disease, the health status of the candidate, the nature, location, and extent of the defect, plus the choice of cell or cell fragment mix, as well as differentiation medium and scaffold stimuli^[87] used for repair^[56] are also other highly salient issues that have not adequately simulated in any laboratory to date, despite new developments that are being investigated^[87]. As well, the persistent belief in a limited natural capacity for articular cartilage regeneration^[9], despite early observations from a variety of laboratories to the contrary, in addition to the paucity of case studies and clinical data, is another potentially insurmountable barrier for the current patient.

Alternately, more advanced efforts to examine the most appropriate stem cell transplant methods that can be applied in conjunction with carefully designed environmental regulation strategies and that map the configuration of any defect may prove helpful^[1], as may the use of tailored injectable hydrogels designed to promote long-term functionality and hyaline cartilage construction^[85]. Follow up

analyses that examine the structural, and mechanical properties of the transplanted tissue using objective approaches, including weight bearing radiographs, serum biomarkers^[56], nano-engineered biomaterials proposed to mimic tissue interfaces^[35], and examining whether osteoarthritic like processes resurface or not – along with an examination of the functional longevity of a graft over an extended time periods would also be more helpful than not in all likelihood^[56].

Finally, re examining earlier observations of spontaneous joint space recovery^[61], and others strategies that produce good to excellent clinical results, such as arthroplasty surgery^[18], osteotomy, tenotomy^[62], free periosteal grafts^[63], drilling of the subchondral bone plate, carbon fiber plugs, perichondral grafting, and electrical, and magnetic interventions^[57,60] and comparing these results to current and future tissue regeneration and implant efforts may permit a more comprehensive set of clinical opportunities for the patient. Ensuring that joint loading is carried out incrementally, inflammation is controlled, and practicing standard joint protection strategies before and after any surgical repair attempt is strongly indicated as well.

SUMMARY

For many years, it was assumed articular cartilage, a key source of pathology in adults with osteoarthritis, could not regenerate or undergo repair. While this does not occur readily, or spontaneously^[37], careful observation demonstrates that this premise is not consistently valid, and that the site of injury, as well as the magnitude of injury, may be critical^[66].

Indeed, a large body of related research shows long-term, as well as effective short-term strategies can clearly foster cartilage repair^[2], including the use of cartilage from alternative sources, and growth factors^[2]. As well, the application of appropriately timed biophysical stimuli when engineering neocartilage^[7], and one less well studied related topic, examining upstream factors that can be harnessed to protect articular cartilage may help to avert progressive cartilage deterioration and degradation, and/or to produce functional cartilage. As well, the possible use of multiple, rather than single therapeutic strategies to attenuate the disease process^[15], including joint protection efforts in the face of attempts to stimulate neocartilage might prove especially helpful, as might careful mechanical or electrical stimulation of the affected osteoarthritic joint or both^[102-112].

Most problematic though is that despite the highly complex interaction of mechanical, biological, chemical, and physiological processes that impact osteoarthritic articular cartilage structure, and that involve bone, and several structural changes in the extracellular matrix, most current molecular oriented research efforts along with those in animal models do not consider the interaction of these factors in the context of their cartilage regenerative efforts. Signaling cascades involved in limb patterning that may play a role in cartilage repair also remain to be elucidated, as do the role of stem cells and mature chondrocytes in osteoarthritis progression^[93]. Consequently, no matter how sophisticated the current tissue engineering strategies and others may be, without careful consideration of the individual and collective influence of joint biomechanics, biological and biomechanical cartilage cellular and intracellular transduction pathways, and extent and severity of any lesion, as well as its cause, it seems reasonable to propose that no single uni-dimensional approach, no matter how sophisticated, is likely to yield any desired long-term effect to restore authentic articular cartilage in its optimal architectural, biomechanical and biochemical form^[1,11,56].

As outlined by Fitzgerald^[49], adult articular cartilage has a poor capacity to undergo intrinsic repair, and despite an array of potential

strategies developed to hasten intrinsic cartilage repair, strategies for fostering repair of large cartilage defects remain unsatisfactory. To restore cartilage with the same resistance to biomechanical loading as authentic articular cartilage that does not degrade over time, possible approaches applied in light of the complex osteoarthritic process that involves enzymatic degradation, pain, joint swelling, cartilage fragmentation, or softening, are care to protect an osteoarthritic joint from excess impact, while not favoring complete immobilization. Others are, eliminating or reducing any obvious structural deformities, maximizing muscle and joint function, careful placement of any implants, and in recognition of the structure of the diseased tissue, possible enzymatic control to reduce immunogenic responses^[64]. The use of weight-bearing activities that match the repair tissue biomechanical properties^[65], pulsed electromagnetic fields and other remedies to quell pain, and joint swelling, in addition to harnessing the multilineage differentiation capacity of osteoarthritis multipotent progenitor cells^[42], or mixing adult and juvenile cartilage fragments^[67] and introducing early exercise loading following graft implantation^[102], laser therapy^[104-108], may also favor the initiation of desirable chondrocyte reparative processes.

Highly promising too are the application of relevant magnetic stimuli that can affect calcium signaling and mechano transduction positively^[1], along with efforts to limit excess damage in those with diminished joint sensitivity, excess joint effusion, and unstable joints. Bio-imaging to monitor stem cell to chondrocyte differentiation processes^[65], the use of magnetic nanoparticles^[48], exercise^[102-104], and regenerative therapies that are carefully staged and of sufficient intensity and duration and tailored for each product may also help to foster maximal results^[68].

Future directives that may be especially helpful are:

1. Developing a better understanding of load-induced biophysical changes and trigger mechanisms as this impacts early osteoarthritis damage, and how biomechanical stimuli can be harnessed to promote chondrocyte cell function remain highly relevant issues in the context of articular cartilage regeneration, restoration, or repair efforts^[1,56].
2. Exploring how to integrate stem cell biology, mechanobiology, and chip technology^[5].
3. Strategies to mimic the structural and bioactive conditions of articular cartilage using growth factors and biocompatible scaffolding may further enhance the pursuit of regenerative therapies in the field^[1,93], as may implantation of acellular biomaterials^[84], co culturing chondrocytes with stromal vascular fraction cells of adipose tissue rather than with autologous chondrocytes^[92], employing muscle derived stem cells^[95], intra-articular injections of autologous expanded bone marrow^[96], use of a pyrolytic carbon implant for reconstruction of a focal cartilage defect^[97], platelet activated serum and plasma^[98,99] and Interleuken-8 and bone marrow concentrate to upregulate chondrogenic transcription^[100].
4. Efforts to examine and integrate promising physical modalities into the cartilage repair paradigm, such as laser light applications, ultrasound, pulsed electromagnetic fields, electrical stimulation, active and passive exercises^[102-115].

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