Systematic Review

Biological Augmentation and Tissue Engineering Approaches in Meniscus Surgery

Cathal J. Moran, M.D., F.R.C.S.(Orth), Alberto Busilacchi, M.D., Cassandra A. Lee, M.D., Kyriacos A. Athanasiou, Ph.D., and Peter C. Verdonk, M.D., Ph.D.

Purpose: The purpose of this review was to evaluate the role of biological augmentation and tissue engineering strategies in meniscus surgery. Although clinical (human), preclinical (animal), and in vitro tissue engineering studies are included here, we have placed additional focus on addressing preclinical and clinical studies reported during the 5-year period used in this review in a systematic fashion while also providing a summary review of some important in vitro tissue engineering findings in the field over the past decade. **Methods:** A search was performed on PubMed for original works published from 2009 to March 31, 2014 using the term "meniscus" with all the following terms: "scaffolds," "constructs," "cells," "growth factors," "implant," "tissue engineering," and "regenerative medicine." Inclusion criteria were the following: English-language articles and original clinical, preclinical (in vivo), and in vitro studies of tissue engineering and regenerative medicine application in knee meniscus lesions published from 2009 to March 31, 2014. **Results:** Three clinical studies and 18 preclinical studies were identified along with 68 tissue engineering in vitro studies. These reports show the increasing promise of biological augmentation and tissue engineering strategies in meniscus surgery. The role of stem cell and growth factor therapy appears to be particularly useful. A review of in vitro tissue engineering studies found a large number of scaffold types to be of promise for meniscus replacement. Limitations include a relatively low number of clinical or preclinical in vivo studies, in addition to the fact there is as yet no report in the literature of a tissue-engineered meniscus construct used clinically. Neither does the literature provide clarity on the optimal meniscus scaffold type or biological augmentation with which meniscus repair or replacement would be best addressed in the future. There is increasing focus on the role of mechanobiology and biomechanical and biochemical cues in this process, however, and it is hoped that this may lead to improvements in this strategy. **Conclusions:** There appears to be significant potential for biological augmentation and tissue engineering strategies in meniscus surgery to enhance options for repair and replacement. However, there are still relatively few clinical studies being reported in this regard. There is a strong need for improved translational activities and infrastructure to link the large amounts of in vitro and preclinical biological and tissue engineering data to clinical application. **Level of Evidence:** Level IV, systematic review of Level I-IV studies.

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The meniscus plays a key role in joint congruency, load distribution, enhanced stability, and assistance in lubrication and nutrition at the level of the knee.[1]

From Sports Surgery Clinic and Trinity College Dublin (C.J.M.), Dublin, Ireland; Antwerp Knee Centre, AC Monica Hospitals (P.C.V.), Antwerp, Belgium; Clinical Orthopaedics, Università Politecnica delle Marche (A.B.), Ancona, Italy; Departments of Orthopaedic Surgery & Biomedical Engineering, University of California (C.A.L., K.A.A.), Davis, California, U.S.A.

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Address correspondence to Cathal J. Moran, M.D., F.R.C.S.(Orth), Sports Surgery Clinic, Santry Demesne, Santry, Dublin 9, Ireland. E-mail: cathaljmoran@gmail.com

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Surgical intervention for the injured meniscus is driven by mechanical symptoms or pain (or both), with symptomatic relief being the primary concern of the patient. More than 1.5 million meniscus procedures are performed across the United States and Europe annually, most often partial meniscectomy for an irreparable lesion.[2] However, once the normal functions of the meniscus are impaired, chondroprotection is disrupted, and the risk of degenerative change and related morbidity is increased.[3] It follows that restoring normal meniscus form and function through repair or replacement may be in the interest of the long-term health of the knee.

Although it is now known that meniscus repair is the preferred option for patients with a meniscus lesion, there are many situations in which this is not possible—e.g., lesions affecting the inner third of the

meniscus, an area known to have a limited vascular supply and healing potential.[4] Degenerative tears of the meniscus are also unlikely to heal if repaired because of the pattern of the tear, the quality of the tissue, and the typically older patient profile with which they are most often associated. The preceding tear types are therefore usually an indication for meniscectomy. Furthermore, even when tears seem to have the ideal physical and biological characteristics for repair, we know that there remains a failure rate of up to 30%.[5] Although there are now increased data to support the use of synthetic and allograft meniscus replacement material in advanced cases of meniscus loss, even under appropriate indications these options are impaired by a lack of universal efficacy and limited availability.[6,7] For this reason, the consideration of biological augmentation and tissue engineering approaches to meniscus repair and replacement is important for surgeons and scientists alike.

Biological augmentation strategies attempt to overcome the inherent limitations in healing related to poor vascularity and heterogeneous cellularity by promoting chemotaxis, cellular proliferation, and matrix production at the repair site. Mechanical techniques traditionally used to stimulate healing by creating vascular access and stimulating cells, cytokines, and bone marrow cells in the vicinity of the repair are representative of early augmentation strategies. These techniques have been applied clinically over the years with varying clinical outcomes.[5,8] The provision of exogenous fibrin clot, growth factors, and cells from various sources to the meniscus repair site have also been previously noted in the literature.[9-12] Although the term "tissue engineering" has been applied to a multitude of biological strategies in previous literature, it correctly refers to the addition of cells or growth factors to a scaffold with the aim of host target tissue regeneration. This strategy may involve varying levels of focus on both ex vivo and in vivo meniscus tissue generation before and after implantation into the host. However, of critical importance is the understanding that current models of meniscus tissue engineering must also provide for the impact of mechanobiology (the effects of implant and tissue loading in the knee on cellular function and tissue formation).[13] This concept has grown in focus in recent years in the overall world of tissue engineering and regenerative medicine; it is of particular importance when considering musculoskeletal tissues. It may be of particular benefit to consider this in areas in which we have struggled in our efforts to make further advances toward the satisfactory surgical management of cartilage and meniscus lesions.

The aim of this article is to provide a review of the literature as it relates to original reports of biological augmentation and tissue engineering approaches in meniscus surgery. Because it is impossible to provide a comprehensive systematic overview of the entire literature in this field, which would cover all published reports of clinical (human), preclinical (animal), and in vitro studies, we have focused this review on studies reported in the past 5 years. The preceding period has also previously been addressed in this journal.[14] We place particular focus on addressing preclinical and clinical studies reported during this 5-year period in a systematic fashion while also providing a summary of some important in vitro tissue engineering findings in the field over this period. This approach serves to highlight the trends in the field, reveal the limited progress from in vitro investigations to clinical trials, and promote an understanding of the need for greater translational interaction to drive the process forward from here. The role of synthetic scaffolds used in isolation is not addressed in this article because it is dealt with in a separate focused review in this issue of *Arthroscopy*.

Methods

A search was performed on PubMed for original works published from 2009 to March 31, 2014 using the term "meniscus" with all the following terms: "scaffolds," "constructs," "cells," "growth factors," "implant," "tissue engineering," and "regenerative medicine" (Table 1). Inclusion criteria for the clinical and preclinical sections were the following: English-language articles and original clinical and preclinical (in vivo) studies of Tissue Engineering and Regenerative Medicine (TERM) application in knee meniscus lesions published from 2009 to March 31, 2014. To provide an up-to-date summary of some of the important in vitro data over time, the 5 years leading up to March 31, 2014 were also considered for the in vitro tissue engineering section, and some of the most important articles were chosen. All abstracts were evaluated. Only Level I to IV clinical studies were considered for the clinical section. When an article was included, the full-text article was reviewed, and reference lists and related electronic libraries were checked. All articles identified by these search terms were manually reviewed and discussed among us, and a decision was made regarding inclusion or exclusion.

Results

Clinical Studies 2009 to 2014

We identified 3 clinical articles relating to biological augmentation and tissue engineering approaches to meniscus repair or regeneration in the past 5 years (Table 2). Jang et al.[15] described a standardized arthroscopic technique to deliver additional autologous fibrin clot to inside-out sutures. This was reported to have a success rate of 95% (39 of 41 patients). This series included 41 meniscus tears (19 radial tears, 12 longitudinal tears in the red-white zone, 7 transverse

Table 1. Summary of the Data and Main Variables That Were Assessed During This Systematic Review

Search Terms:
Meniscus + one of the following terms:
Scaffolds, constructs, cells, growth factors, implant, tissue engineering, regenerative medicine
Criteria: English language original study
Type: Clinical or preclinical (Evidence Level I-IV for clinical articles)
Dates: 2009-March 31, 2014

tears, and 3 oblique tears). Ra et al. also investigated the efficacy of inside-out meniscus sutures in association with fibrin clot placed inside radial meniscus tears. At a mean of 30 ± 4 months postoperatively, the Lysholm score was noted to have improved from 65 ± 6 to 94 ± 3 and the International Knee Documentation Committee subjective knee score improved from 57 ± 7 to 92 ± 3. Second-look arthroscopy showed complete healing of the meniscus lesion in 6 of 7 cases. These data support previous studies that showed a benefit to using fibrin clot in meniscus surgery.[9,16,17] The delivery mechanism described by Jang et al. may provide a user-friendly technique for applying this strategy more frequently in the clinical setting.

In 2014, Vangsness et al.[18] reported on a randomized double-blind controlled study investigating the safety of intra-articular injection of human mesenchymal stem cells (MSCs) into the knee, the ability of MSCs to promote meniscus regeneration after partial meniscectomy, and the effects of MSCs on osteoarthritic changes in the knee. A total of 55 patients at 7 institutions underwent partial medial meniscectomy. A single superolateral knee injection was given within 7 to 10 days after meniscectomy. Patients were randomized to 1 of 3 treatment groups: group A, in which patients received an injection of 50×10^6 allogeneic MSCs; group B, in which patients received 150×10^6 allogeneic MSCs; and the control group, which received a sodium hyaluronate (hyaluronic acid/hyaluronan) vehicle control. Patients were followed to evaluate safety, meniscus regeneration, overall condition of the knee joint, and clinical outcomes at intervals over 2 years. Evaluations included sequential magnetic resonance imaging (MRI). No ectopic tissue formation or clinically important safety issues were identified. There was significantly increased meniscus volume (defined a priori as a 15% threshold) determined by quantitative MRI in 24% of patients in group A and in 6% of patients in group B at 12 months after meniscectomy ($P = .022$). No patients in the control group met the 15% threshold for increased meniscus volume. Based on visual analog scale assessments, patients with osteoarthritic changes who received MSCs experienced a significant reduction in pain compared with those who received the control vehicle.

Preclinical In Vivo Studies 2009 to 2014

We identified 18 preclinical in vivo studies relating to the biological augmentation and tissue engineering approaches to meniscus repair or regeneration published in the past 5 years (Table 3). These reports included both large animal models, such as goats, sheep, and swine, as well as smaller animal models, including rats, rabbits, and mice. The heterogeneity of experimental models testing the different treatments is also evident in Table 3. However, these reports do appear to provide promising data as to the potential benefit of biological treatments.

Regarding the potential benefits of augmenting meniscus repair with stem cells alone, in a "sandwich" model in nude mice Scotti et al.[27] showed that meniscus layers containing fibrochondrocytes in fibrin glue improved bonding and integration compared with acellular fibrin. Furthermore, the fibrin gel appeared to be a valid vehicle for cell migration and viability to promote fibrocartilaginous differentiation. In a rat model of meniscus defects, Horie et al.[28] not only reported the regenerative effects of synovial stem cells injected into the joint but also their differentiation to a meniscus lineage. This was shown through histologic data, immunostaining, and molecular analysis based on *LacZ* gene expression in transgenic mice. In a rabbit model, Horie et al.[29] injected synovial MSCs to stimulate the healing of a 1.5-mm–diameter defect in meniscus and noted a significantly improved regenerative response compared with their control of phosphate buffered saline alone. Ferris et al.[30] reported on a construct of meniscus layers and fibrin glue loaded with equine bone marrow stromal cells (BMSCs). They showed increased vascularization, thinner repair tissue, and better bonding with surrounding tissue when the construct with MSCs was compared with constructs without cells. Desando et al.[31] investigated the potential of adipose tissue–derived stem cells for meniscus repair, showing that these cells were able to improve healing of cartilage and meniscus defects in a rabbit osteoarthritis model. Finally, although all the studies mentioned point to the potential benefits of stem cell augmentation, in a meniscus pullout suture enhanced with human BMSCs versus simple sutures alone in a rabbit model, Hong et al.[32] did not show significantly increased healing in the group treated with suture and cells versus cells alone.

The role of growth factors has also been addressed in animal preclinical studies, both with and without cellular therapy or scaffold use. Zhang et al.[33] found that full-thickness meniscus tears in the avascular zone in a goat model showed enhanced repair when treated with human insulin-like growth factor 1 (hIGF-1)–meshed BMSCs in an injectable solution. Their study histologically and biochemically showed that the meniscus defect was completely filled at 16 weeks after

Table 2. Clinical Studies of Meniscal Repair With Biological Augmentation 2009-2014

Reference	Defect	Strategy	Cells	Control	Outcome Measure
Jang et al.[15] (2011)	41 meniscus tears (19 radial, 12 longitudinal in the red-white zone, 7 transverse, 3 oblique tears)	Inside-out sutures and fibrin clot	NA	NA	MRI and arthroscopic second look Average follow-up 8.3 mo
Ra et al.[19] (2013)	12 meniscal tears: 9 in the lateral meniscus and 3 in the medial meniscus	Inside-out sutures and fibrin clot	NA	NA	Lysholm and IKDC subjective scores at 2-yr follow-up: both significantly improved from 65 ± 6 and 57 ± 7 to 94 ± 3 and 92 ± 3, respectively
Vangsness et al.[18] (2014)	55 medial subtotal menisccectomies (> 50%)	Administration of A-MSCs injected in the knee 1 wk postoperatively	*Group A*: dose of 50×10^6 A-MSCs; *Group B*, 150×10^6 A-MSCs	Administration of one injection of hyaluronic acid	2-yr follow-up: MRI showed significant meniscus regeneration (15% threshold) in 24% of patients in group A and 6% in group B at 12 mo after meniscectomy No improvement in control group

A-MSCs, allogeneic mesenchymal stem cells; GF, growth factor; IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging; NA, not applicable.

treatment. He et al.[34] performed a study in rabbits using growth factors in fibrin glue. Their study found that connective tissue growth factor enhanced healing in defects of the avascular zone of the meniscus by stimulating the neosynthesis of both collagen types 1 and 2. Ionescu et al.[35] published a bovine study that evaluated the in vivo effect of basic fibroblast growth factor (bFGF) as a promitotic agent and transforming growth factor-β3 (TGF-β3) as a pro-matrix forming agent on meniscus repair and integration with synthetic meniscus scaffolding. In the short term, delivery of bFGF or sustained delivery of TGF-β3 increased both juvenile and adult tissue formation. In addition TGF-β3 stimulated an increase in proteoglycans in the longer term. Zellner et al.[36] carried out a study comparing different strategies to fix meniscus defects in the white zone in a rabbit model, comparing suture, fibrin matrix seeded and not seeded with BMSCs, platelet-rich plasma, and an untreated defect. They reported a significant healing rate when MSCs were used. Moriguchi et al.[37] developed an experimental tissue-engineered construct of synovial MSCs and ascorbic acid, showing significantly improved healing of 4-mm defects in the avascular zone of the meniscus after 6 months. Finally, Esparza et al.[38] assessed in vivo collagen gene expression by synovial meniscus cells after stimulation to vascular endothelial growth factor (VEGF), TGF-β, bFGF, and IGF. Data were reported for different areas of meniscus in vivo and showed that growth factors may exert different effects in different regions of the meniscus.

Biological Augmentation and Tissue Engineering Approaches In Vitro

Although there has been limited progression of scaffolds combined with cells or growth factors into preclinical studies, the in vitro tissue engineering literature is too vast to review all individual studies in a systematic manner here. However, some important findings and trends were noted. It has now been shown that various scaffolds (e.g., synthetic, extracellular matrix [ECM] constituent, tissue derived, and hydrogels) for meniscus tissue regeneration each have their own inherent advantages. Regarding their incorporation into meniscus substitutes, finite element models have shown that circumferential and axial/radial moduli are important determinants of the contact pressure distribution by the native meniscus and thus should ideally be matched in any replacement technology.[39] A significant advantage of synthetic scaffolds is the relative ease of manipulation of their biomechanical properties, whereas natural scaffolds may possess inherent advantages for cellular interaction. It has now also been shown that electrospun synthetic scaffolds (e.g., poly-E-caprolactone [PCL]) may provide an appropriate microarchitectural environment for meniscus cells. The nanofibers created

may provide an increased biomechanical advantage of the temporizing structure and of the regenerated meniscus by helping to organize and optimize the 3-dimensional (3D) orientation of ECM deposition in the circumferential direction while facilitating cellular infiltration through the scaffold's fibers.[40-42] At the same time, 3D woven PCL scaffolds have conferred increased biomechanical properties in a composite preparation with cartilage-derived matrix, obviating the need for growth factor augmentation, and may certainly be applied to meniscus restoration.[43,44] Gunja et al.[45-48] have conducted work using nonwoven poly-L-lactic acid scaffolds exploring the positive synergistic effects of bFGF and hypoxia, hydrostatic pressure, and TGF-ß and coculture (chondrocytes and meniscus cells) using in vitro models.

Ultimately, it is hoped that cellular infiltration and matrix deposition may restore some of the viscoelastic properties of meniscus tissue in which the fluid phase carries a significant amount of the load.[49] The biocompatibility and biomimetic properties of ECM constituent scaffolds have therefore led to their use in this situation despite their inferior biomechanical profiles. Balint et al.[50] reported the use of a collagen scaffold reinforced by a network of degradable tyrosine-derived polymer fibers that showed circumferential tensile strength stiffness and hoop stress behavior under compressive loading that mimics the normal meniscus. Hydrogels (natural or synthetic) are biochemically versatile and can be used as cell and growth factor delivery systems.[13] Although their biomechanical properties can be tailored somewhat by substrate concentration and composition, they often fall short of native meniscus properties. To overcome this problem, Holloway et al.[51] proposed a fiber-reinforced composite containing ultra-high-molecular-weight polyethylene fibers in a polyvinyl alcohol hydrogel and varied the composition and orientation of the fibers to mimic native meniscus properties for total meniscus replacement. On implantation in a dynamic cadaveric model, this construct was seen to restore contact mechanics to a level comparable to that of meniscus allograft transplantation.[52] Anatomically shaped alginate hydrogels have been fabricated using extracted geometries from MRI and microcomputed tomography and show improved biochemical and mechanical properties after seeding with fibrochondrocytes and supplementation with IGF-1.[53] Tissue-derived scaffolds under current investigation include small intestine submucosa (porcine) and silk scaffolds. The use of xenogeneic meniscus tissue is currently being investigated in animal models and may provide a solution for partial meniscus replacement. Indeed, processing of ovine meniscus tissue to improve porosity and interconnectivity as a xenogeneic meniscus scaffold has potential.[54]

There are growing data to show that the use of dynamic culture or fluid mixing can be optimized to modulate the spatial heterogeneity of engineered menisci as well as the correlated mechanical properties.[55-57] Compressive deformation or hydrostatic pressure has been shown to enhance the structure and function of engineered meniscus tissues.[58-60] Dynamic compression of constructs based on microchanneled scaffolds resulted in aligned cell layers and collagen fibers,[58] whereas hydrostatic pressure combined with TGF-β1 increased collagen and glycosaminoglycan deposition by meniscus cells, ultimately leading to enhanced compressive properties.[45] Cyclic tension specifically stimulated collagen type I mRNA expression and protein synthesis but had no effect on collagen type II, aggrecan, or osteocalcin mRNA levels, resulting in enhanced fibrochondrocyte-like differentiation of bone marrow–derived MSCs.[59] Combinatorial modes of mechanical stimulation, including tension-compression loading[60] or perfusion and cyclic compression,[61] were also reported to additively increase matrix production and tissue mechanical properties.

Another area of focus in tissue engineering of cartilage and the meniscus is the concept of scaffold-free self-assembly (Fig 1).[62] With this strategy, cells are seeded densely in nonadherent molds and manipulated to enhance cell-cell interactions, which initiates a process akin to a developmental one, allowing the formation of a matrix with adequate mechanical properties.[63] Cells naturally form a bioactive microenvironment that may increase the likelihood of integration with host tissue because of its biocompatibility. Growth factors such as bFGF, platelet-derived growth factor-AB, endothelial growth factor, and TGF-β have been shown to promote matrix synthesis as well as cellular proliferation and migration.[64-67] With exogenous agents such as chondroitinase ABC, self-assembled meniscus constructs have been shown to increase collagen content 196% per wet weight, 136% in compressive instantaneous modulus, 68% in compressive relaxation modulus, 600% in circumferential tensile modulus, and 500% in radial tensile modulus.[60] By increasing the circumferential and radial tensile modulus, anisotropy can be achieved. In addition, mechanical stimulation (hydrostatic pressure) has also been shown to improve mechanical properties.[68,69] Because the meniscus undergoes direct loading in vivo, these self-assembled constructs may provide a more physiological and biological implant in meniscus replacement.

Discussion

Meniscus repair and replacement is an area of growing investigation. Recent data from clinical, preclinical, and in vitro investigations have provided much support for the ongoing research in this field. However,

Table 3. Preclinical Studies of Biological Augmentation and Tissue Engineering in Meniscus Surgery 2009-2014

Reference	Animal	Defect/Model	Strategy	Cells	GF	Other	Control	Outcome Measure
Zhang et al.[33] (2009)	Goats	Full-thickness experimental defect anterior horn tear in white area	Injection of cell- loaded gel into the defect	Bone marrow mesenchymal stem cells transfected with *HIGF1* gene	NA	NA	3 control groups: cells without transfection, gel without cells, and defect left untreated	Histology, electron microscopy proteoglycan determination, MRI.
Scotti et al.[27] (2009)	Swine	Meniscal construct implanted in nude mice	Construct with cells in fibrin glue	Swine chondrocytes seeded on fibrin glue	NA	NA	Construct with acellular fibrin glue	Histology and Electron Microscopy
Horie et al.[28] (2009)	Lewis rat transgenic (Luc/LacZ)	Massive meniscal defect	Intra-articular cell injection	Rat synovium MSCs	NA	NA	NA	Electron microscopy, Histology, Real Time PCR
Zellner et al.[36] (2010)	New Zealand white rabbit	2-mm defect anterior lateral meniscus	Hyaluronan-collagen matrix with bone marrow or MSC	Autologous MSC (bone marrow)	NA	NA	Contralateral knee, scaffold alone	Gross, histology (integration, immunohistochemistry)
Hong et al.[32] (2011)	New Zealand white rabbits	Anterior horn defect	Transosseous pullout suture + cells	Human bone marrow mesenchymal stem cells	NA	Submeniscal cartilage defect	Simple pullout suture	Gross examination and histology
Riera et al.[20] (2011)	Swine	NA	Cell isolation and cultivation	Meniscal cells	IL-1 alpha, TNF-alpha, TGF-β1	NA	Cells in 10% serum without GF stimulation	Micro wound assay.
Horie et al.[29] (2012)	New Zealand white rabbit	Cylindrical meniscus defect	Intra-articular cell injection	Allogenic synovium MSCs in right knees	NA	NA	PBS + saline alone in left knees	Histology, fluorescence microscopy Immunohistochemistry
Ionescu et al.[35] (2012)	Bovine (juvenile and adult)	Cylindrical meniscus defect	Meniscus-to-meniscus construct + GFs	NA	Delivery of bFGF, TGF-β3 for 4 or 8 wk	Meniscus-to-scaffold construct + GFs	NA	Histology, Biochemical contents, Biomechanical tests.
Esparza et al.[38] (2012)	Merino sheep	Synovial vascularized area of meniscus	Cell incubation of GFs	NA	VEGF IGF TGF	NA	Avascular area of the meniscus	Col1, Col 2A, MMP-2 e MMP-13 expression
He et al.[26] (2012)	New Zealand white rabbits	3-mm defect in meniscus	Delivery of GF incorporated in fibrin glue	Fibrochondrocytes	Connective tissue growth factor	NA	NA	Immunofluorescence Col1, Col2, VEGF expression
Ferris et al.[30] (2012)	Horses	Placement of meniscal construct in nude mice	Construct + fibrin glue + cells	Bone marrow mesenchymal stem cells	NA	NA	Construct + fibrin without cells	Gross evaluation, H&E stain, SOFG stain
Kon et al.[21] (2012)	Bergamasca-Massese sheep	Subtotal medial meniscectomy	Cell-scaffold (hyaluronic acid HYAFF polycaprolactone)	Autologous articular chondrocytes			Acellular scaffold and empty defect/ meniscectomy	Gross, histology, OARSI cartilage OA grading system
Gu et al.[22] (2012)	Beagle dogs	Anterior horn medial meniscus	PLGA scaffold with autologous cells	Myoblasts cultured in chondrogenic media	NA		Acellular PLGA scaffold and empty defect	Gross, histology quality, immunohistochemistry

(continued)

Table 3. Continued

Reference	Animal	Defect/Model	Strategy	Cells	GF	Other	Control	Outcome Measure
Desando et al.[31] (2013)	New Zealand white rabbit	OA induced after ACL transection	Intra-articular cell injection	ASCs	NA	Role in Meniscal healing and anti-inflammatory role of cell administration	NA	Laverty's Score, Col1, Col2, MMP-1, MMP-3, TNF-alpha expression in cartilage, synovium and menisci.
Zellner et al.[36] (2013)	New Zealand white rabbit	4-mm meniscus defect	HA-Col matrix + PRP or cells	Bone marrow mesenchymal stem cells	PRP	NA	Suture with No. 5-0 thread	Gross examination, Histology, Biomechanical tests
Moriguchi et al.[23] (2013)	Swine	4-mm cylindrical defect	Construct of cells and ascorbic acid	Allogenic synovium MSCs	NA	NA	2 control groups: defect untreated and normal meniscus	Histology, Histomorphometry
Esposito et al.[24] (2013)	New Zealand white rabbit	Medial meniscus resection	PLDLA/PCL-T scaffold with allogeneic cells	Allogeneic fibrochondrocytes	NA	NA	Cell-free scaffolds *v* no implant	Gross, histology, histomorphometry
Hatsushika et al.[25] (2013)	Japanese white rabbits	Anterior horn Medial meniscus excision	Cell injection	Allogeneic Synovial MSCs	NA	NA	PBS	Histologic quantification, OARSI cartilage OA grading

ACL, anterior cruciate ligament; ASCs, adipose stem cells; bFGF, basic fibroblast growth factor; GF, growth factor; H&E, haematoxylin and eosin; HA-Col, hyaluronic acid-collagen; HYAFF, hyaluronic acid scaffold; IGF, insulin-like growth factor; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; NA, not applicable; PBS, phosphate-buffered saline; PCL-T, polycaprolactonetriol; PCR, polymerase chain reaction; PLDLA, poly-L/D-lactide; PLGA, poly (lactic-co-glycolic acid); PRP, platelet-rich plasma; SOFG, Safranin O-Fast Green; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

the reduction in the number of reports available in the literature as one moves from a search of in vitro to clinical studies reflects the immense difficulties that exist in the translational arena from laboratory investigation to clinical application. Safely taking advantage of the potential of such new treatment options that may be on the horizon is closely linked to the concept of translational research, the mechanisms by which we link science and surgery, the laboratory, and the patient.[70] As surgeons, our goal is ultimately to restore our patients to a state of natural form and function through our surgical interventions. In translational research, the relevant questions are raised at the bedside by clinicians and investigated in the laboratory and clinical research units before bringing a suitable form of intervention back to the bedside. It is critical that this process be applied in the context of meniscus surgery if we are to make progress in the field. This challenge is highlighted by the fact that the National Institutes of Health funded nearly $15 billion of basic science research in 2009.[71] Unfortunately, current statistics indicate that less than 25% of highly promising biomedical discoveries result in a published randomized clinical trial, and less than 10% are established in clinical practice within 20 years.[71] The trend in the data available for the techniques considered in this article suggests that approaches in biological augmentation and tissue engineering for meniscus repair are also being affected in this manner.

Although we have highlighted a large number of preclinical studies in this review, it is readily apparent that there is significant heterogeneity present in the studies reported. The need to identify appropriate translational models in regenerative repair is therefore of critical importance and worthy of particular consideration here. Arnoczky et al.,[72] Chu et al.,[73] and Sah and Ratcliffe[74] have previously addressed this issue separately regarding articular cartilage, the meniscus, and regenerative medicine in general, and readers are referred to these texts for comprehensive coverage of this important issue. Ultimately, there are many animal models that are used in meniscus and articular cartilage defect research. One can appreciate that various models offer distinct advantages and disadvantages for studying regenerative repair strategies. It is readily apparent that no one animal model reproduces all the features of the human injury condition regardless of the clinical condition being evaluated. All animals differ from humans regarding the biomechanical use of their joints. Large animal models such as the goat or the horse may more closely resemble the human than smaller animal models such as rodents or rabbits. However, it is usually not fiscally feasible or practical to conduct initial experiments in larger species. Also, because no animal is immunologically identical to the human, a possible adverse immunologic response to a regenerative medicine therapy in human patients may not be predicted

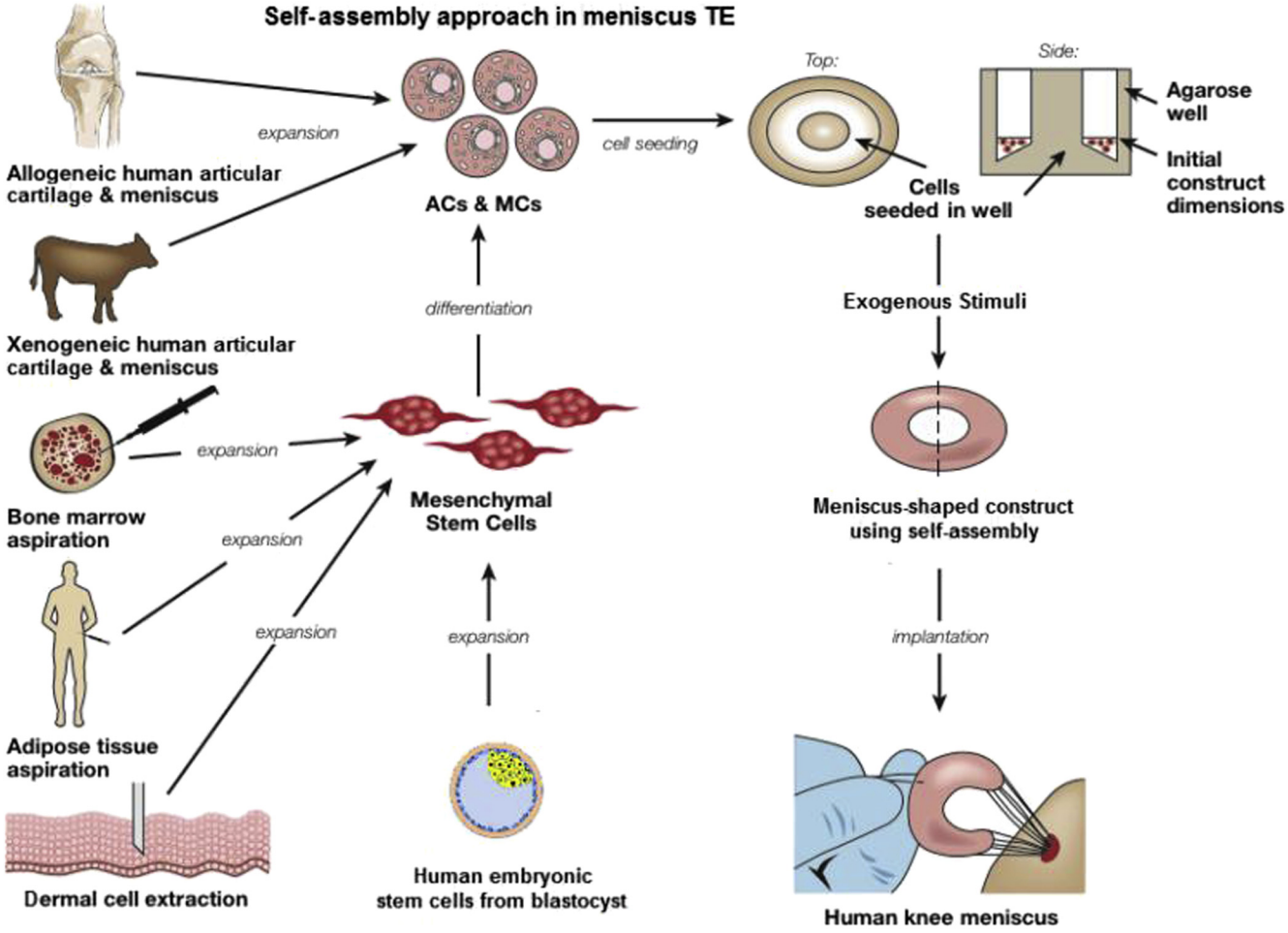

Fig 1. Strategy for self-assembly for meniscus tissue engineering. Reprinted with permission.[13]

from animal studies. Although a nonhuman primate shoulder, e.g., may offer more anatomic, biomechanical, and immunologic similarities to humans than do other animals, cost and management issues make use of this model impractical. Therefore, it is generally well accepted that a small animal model will be chosen for initial lines of investigation. However, final preclinical evaluation of a clinical strategy for a repair or reconstruction technique may require confirmation in a large animal model before trials in humans. Although scientists may play the leading role in selecting animal models for preclinical testing, it does not make sense for this process to be ignored by surgeons.

Ultimately, the design of a successful meniscus scaffold, while providing a degree of biomechanical stability in the short term, should incorporate features amenable to cellular infiltration at the meniscus tissue interface. These include consideration of pore size and interconnectivity while maintaining a near-native meniscus compression modulus to exert a profibrochondrogenic effect.[75] Mesenchymal stem cells, fibrochondrocytes, and chondrocytes have now all been successfully incorporated into cell-scaffold complexes and show promising results in both in vitro and in vivo studies. The overwhelming issue with the latter 2 cell types is availability. The use of autologous fibrochondrocytes/chondrocytes requires a 2-step operative process. Given the relative scarcity of these cells in the tissue, monolayer expansion is also required, which can result in downregulation of genes involved in matrix production.[76] Allogenic and xenogeneic cell sources have shown promise in animal models, and although they may overcome the discrepancy in supply and demand, they are fraught with translational issues.[77,78] MSCs, in contrast, have been successfully isolated from adipose tissue, muscle, and bone marrow and subsequently used in soft tissue engineering.[79] It is important to be aware that bone marrow aspirate, concentrated (bone marrow aspirate concentrate [BMAC]) or otherwise, does not equate to using a purified or cultured collection of MSCs. Although MSCs are present within the aspirate and concentrate, they are present in very low numbers and are only one of a number of cell types present. The possible advantage of BMAC, however, is that it may be of benefit for MSCs to remain among the other biological factors present in BMAC. Although

further work on point-of-care strategies such as BMAC is required, it may be that the next generation of genetically manipulated MSCs may further enhance the regenerative process by promoting growth factor production and directed cell differentiation.[80,81] As another cell type for discussion, synoviocytes have often been overlooked in meniscus regeneration and repair augmentation.[82] This is despite the fact that meniscus repair has been shown to be facilitated by fibroblasts from the surrounding synovium and joint capsule that are believed to undergo fibrocartilaginous metaplasia at the repair site.[83]

Cell chemotaxis, maintenance of cellular phenotype, and inducing matrix production are critical for the biological integration of a meniscus scaffold. The roles of biophysical and biochemical signaling are currently under review in this regard. Both the microarchitectural environment and biomechanical properties of a scaffold material act as biophysical cues for seeded and infiltrated cells.[13] In addition, the effect of mechanical loading on cellularized constructs, meniscus explants, and scaffoldless-assembly meniscus tissue is being investigated in an attempt to understand and use the resultant cellular responses; these may have a role in the maintenance of cell phenotype, matrix production, and overall improved vital role of cell phenotype maintenance and differentiation. Fibroblastic growth factor 2 has been shown to recover the monolayer expansion of meniscus cells, whereas TGF-ß1 has caused meniscus cells to take on a more chondrogenic phenotype.[13] As discussed, growth factor supplementation has shown improved cellular migration, proliferation, and matrix production, but important translational considerations include mode of delivery, localization of effect, and timing of growth factor release. The use of innovative imaging markers in future studies may prove efficacious in tracking cell migration and matrix production.

Regardless of the strategy applied, a key definition to be achieved in the field is the target level of functionality, which is required to support a superior clinical outcome. The unique anisotropic features of the meniscus may be nearly impossible to replicate or generate. Although ex vivo maturation is often mentioned, an increased level of maturation of engineered meniscus grafts would require not only more complex culture modalities but also likely longer culture durations, which in view of clinical translation would be reflected in higher manufacturing costs. The role of in vivo mechanobiology and the rehabilitation process is therefore likely to be of vital importance to making progress. In the translational process, surgeons must be aware of the need to identify a match between the properties of a meniscus graft and a suitable regimen of postoperative rehabilitation. This process may be assisted by the use of bioreactors applying regimens of forces and fluid dynamics mimicking those at the site of implantation. This offers the opportunity to investigate which structural and functional properties are sufficient to tolerate certain loading regimens that would be experienced by the graft on implantation or, alternatively, to help define which loading regimens are compatible for grafts of a defined functionality.[84] However, it is difficult for scientists or engineers to address this matter alone without clinical and rehabilitation input. If these areas of expertise can be matched appropriately, the introduction of bioreactor systems in the manufacture of cellular grafts can be exploited, not only to reach higher levels of tissue organization and mechanical functionality but also to reduce operator handling, automate processes, and ultimately standardize the quality of the product.[85]

Limitations

Limitations in this study relate to the relatively low number of articles evaluating the clinical and preclinical (animal model) investigation of meniscus tissue engineering. In addition, there is as of yet no report in the literature of a tissue-engineered meniscus construct used clinically. Neither does the literature provide clarity on the optimal meniscus scaffold type or the biological augmentation with which meniscus repair or replacement would be best addressed in the future. There needs to be an increased focus on this specialized field of orthopaedic surgery, with an improved level of communication across the clinician-scientist interface to ensure that we deliver improved treatment options going forward.

Conclusions

There appears to be significant potential for biological augmentation and tissue engineering strategies in meniscus surgery to enhance options in repair and replacement. However, there are still relatively few clinical studies being reported in this regard. There is a strong need for improved translational activities and infrastructure to link the large amounts of in vitro and preclinical biological and tissue engineering data to clinical application.

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