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SYMPOSIUM: CLINICALLY RELEVANT STRATEGIES FOR TREATING CARTILAGE AND MENISCAL PATHOLOGY

Cell-based Meniscal Tissue Engineering: A Case for Synoviocytes

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Abstract

Background Avascular meniscal injuries are largely incapable of healing; the most common treatment remains partial meniscectomy despite the risk of subsequent osteoarthritis. Meniscal responses to injury are partially mediated through synovial activity and strategies have been investigated to encourage healing through stimulating or transplanting adjacent synovial lining. However, with their potential for chondrogenesis, synovial fibroblast-like stem cells hold promise for meniscal cartilage tissue engineering.

Questions/purposes Thus, specific purposes of this review were to (1) examine how the synovial intima and synoviomeniscal junction affect current meniscal treatment modalities; and (2) examine the components of tissue engineering (cells, scaffolds, bioactive agents, and bioreactors) in the specific context of how cells of synovial origin may be used for meniscal healing or regeneration.

Methods An online bibliographic search through PubMed was performed in March 2010. Studies were subjectively evaluated and reviewed if they addressed the question posed. Fifty-four resources were initially retrieved, which offered information on the chondrogenic potential of synovial-based cells that could prove valuable for meniscal fibrocartilage engineering.

Results Based on the positive effects of adjoining synovium on meniscal healing as used in some current treatment modalities, the chondrogenic potential of fibroblast-like stem cells of synovial origin make this cell source a promising candidate for cell-based tissue engineering strategies.

Conclusions The abundance of autologous synovial lining, its ability to regenerate, and the potential of synovial-derived stem cells to produce a wide spectrum of chondral matrix components make it an ideal candidate for future meniscal engineering investigations.

Introduction

The integral roles the menisci provide to maintaining appropriate function of the knee are well documented in the literature and include load transmission [1], stability and alleviation of tibiofemoral joint incongruity [54, 81], shock absorption [91], joint lubrication [17], and proprioception [98]. Injury to the menisci can therefore be exceptionally debilitating. In 1999, it was estimated that more than 636,000 knee arthroscopic procedures were completed in the United States with the majority of these cases being related to conditions of the meniscus [69]. Treatment decisions and techniques for meniscal tears have been the object of increasing investigation over the last four decades.

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For years, most meniscal injuries were treated through aggressive meniscectomies. It is now accepted that preservation of functional meniscal tissue is critical to maintaining normal knee function, yet current treatment strategies are fairly limited and largely based on the extent and location of the injury within the meniscus. One of the most important advancements in knowledge of the healing potential of the meniscus was the elucidation of the tissue's vascular supply by King [49]. This work suggested meniscal tears would not heal unless they communicated with the blood supply, which arises from the perimeniscal capillary plexus and is restricted to the periphery of the tissue [49]. Further defining the healing potential of different types and locations of meniscal pathology, however, was largely ignored because of the perceived questionable importance of the tissue to the knee. Meniscal injuries were usually treated by total meniscectomy, which was supported by the observation that in many cases, the body would mount a regenerative response to form new meniscal-like tissue containing chondrocyte-like cells [5, 20, 24, 47]. Interestingly, for the formation of this tissue to occur in a more complete fashion, it was determined that the meniscectomy must not interfere with the adjacent synovial lining, thus suggesting an important modulatory role synoviocytes have on meniscal adaptation [4, 47]. Based on these initial observations of the importance of the synoviomeniscal relationship, the objective of this article was to examine the potential use of synovial-based cells as a key element toward the engineering of meniscal-like fibrocartilage tissue.

Thus, specific purposes of this review were to (1) examine how the synovial intima and synoviomeniscal junction affect current meniscal treatment modalities; and (2) examine the components of tissue engineering (cells, scaffolds, bioactive agents, and bioreactors) in the specific context of how cells of synovial origin may be used for meniscal healing or regeneration. The basic question for this investigation was: What evidence exists that supports or refutes the use of synovial lining or synovial-based cells for meniscal tissue engineering?

Search Strategy and Criteria

An online bibliographic search through PubMed was completed during March 2010 using the terms "synoviocytes," "synovium," "stem cells," "cartilage," "fibrocartilage," "meniscus," "meniscectomy," and "tissue engineering" in various combinations using the "AND" Boolean operator. The resulting studies were subjectively reviewed for their ability to address the study purposes. Furthermore, works referenced by the resulting body of retrieved manuscripts were examined to expand the search for relevant papers. Fifty-four studies resulted from this search, which were then supplemented by other referenced peer-reviewed papers, proceedings, textbook chapters, and other communications to address both (1) the justification of examining the effect of synovial physiological responses to meniscal injury based on current meniscal treatment modalities; and (2) investigations examining the use of cells of synovial origin for cartilage and meniscal engineering.

Current Meniscal Treatment Modalities

Despite the well-known importance of meniscal function, partial meniscectomy is one of the most frequently performed orthopaedic procedures today [77]. When considering why meniscectomy remains so popular, one can refer to those reports that indicate relatively little clinical impact of the technique long term, especially if partial meniscectomy is completed versus total meniscectomy [2]. Such studies that demonstrate favorable postoperative outcome after meniscectomy also relate that not all meniscectomies are "created equal" and that much variation exists in outcome depending on a number of factors. Thus, a large body of work has been dedicated to discerning the deleterious effects of meniscectomy on knee function and subsequent osteoarthritis specific to certain variables. The amount of tissue resected [13, 38], the location of the meniscal damage requiring resection [39], sidedness of meniscal injury [59], mechanical axis alignment of the knee [19], presence of pre-existing osteoarthritis [75], and status of the ACL [78] all negatively affect patient outcome after meniscectomy.

With the large number of factors potentially attenuating a positive outcome after meniscectomy, recommendations to promote the development of novel treatment strategies with respect to repair and healing augmentation have been suggested [2]. Such attempts have been based on the observed direct relationship between healing potential of meniscal tears and their proximity to both vascular and synovial sources [7, 15, 37, 47]. Specifically, tears in the peripheral, vascularized (red-red) zone of the meniscus can undergo a healing response mediated initially through the formation of a fibrin clot [7, 15, 37, 47]. Over time, the fibrin clot develops into a fibrovascular scar in such fashion that newly formed tissue anneals to the surrounding meniscal tissue as it undergoes fibrochondroid modulation [7, 15, 37]. Researchers examining this response speculated that the cells involved in the process included fibroblasts, synoviocytes, and mesenchymal stem cells [7, 15, 37, 47].

The purely avascular (white-white) meniscal injuries still, however, pose a major challenge. Whereas partial and total meniscectomies remain an option for extensive, highly debilitating avascular injuries, one treatment

alternative is meniscal replacement with allografts. Animal models have demonstrated the ability of transplanted menisci to attach to the host peripheral tissue through the formation of a fibrovascular scar and revascularization as the tissue is repopulated by host-derived cells [8, 14]. In examining the biologic response to meniscal allografts, histopathologic studies have substantiated initial claims made by Arnoczky [6] that the grafts are likely repopulated by cells of synovial origin [71]. For less extensive avascular injuries, alternatives to meniscal replacement or removal include a variety of methods to stimulate or augment healing and include rasping and trephination, which are both dependent on the synoviomeniscal junction. Meniscal rasping involves roughening of the femoral surface of the meniscus around the tear abaxially to encourage the formation of a fibrovascular response to migrate from the peripheral synovial lining into the tear. Examined clinically, meniscal rasping of tears in the red-red, red-white, and white zones without concurrent suture repair had a success rate of 71% [88]. Trephination involves the formation of minimally invasive vascular access channels through the creation of multiple partial-thickness penetrations between an avascular tear and the meniscal periphery during the surgical repair of a lesion [96, 97]. Studies examining this technique in animal models have reported higher healing responses with their use [97]. When trephination with suture repair was compared with suture repair alone in a clinical prospective study of the treatment of stable avascular meniscal injuries, the addition of trephination reduced the risk of retearing [96]. Other reports, however, document the deformation and subsequent closure of trephination holes resulting from meniscal viscoelasticity resulting in inconsistent neovascularization [40]. Recently, synthetic conduits implanted within fashioned trephinations were assessed in both animal and in vitro models, which demonstrated optimized maintenance of the channel diameter, thus facilitating neovascularization and conduction of synoviocytes more optimally than with the presence of a trephine alone [18, 33].

These data highlight the potentially vital roles that blood supply and access to resident synovial cells may play in any modality aimed at treatment of avascular meniscal defects. Further expounding on this strategy is the reportedly successful technique of advancement of vascularized synovial pedicle flaps into avascular meniscal defects [35, 48]. Despite the fragility of the tissue noted in animal models [35], a small case series demonstrated the potential use of the procedure [48]. Despite the presence of both neovascularization and neocellularization resulting from rasping and synovial advancement flaps, the cellular component of both techniques may be more important than the vascular [45, 64, 79]. In vivo and in vitro experiments show that free synovial autografts placed into avascular meniscal injuries can promote healing through cell proliferation and collagen production without the need for a vascular supply [45, 64, 79]. The use of autogenous fibrin clots to induce healing of avascular meniscal defects also lends support to this theory [9, 11, 30, 41, 42, 57, 70, 76, 89, 92]. Arnoczky and associates demonstrated the avascular meniscal defects filled with autogenous blood clots healed first through a proliferation of fibrous connective tissue that later modulated into fibrocartilaginous tissue [9]. The clot likely served two purposes in acting as chemotactic and mitogenic stimuli for local reparative cells as well as serving as a scaffold on which the new tissue could develop [9]. Although the source and type of cells participating in the repair were not determined, it was postulated that they were predominantly of meniscal and synovial origin [9]. Because fibrin is the most natural scaffold to guide new tissue formation, these attempts at meniscal healing using the direct implantation of bioactive clots into meniscal defects represent the first successes in using modern principles of tissue engineering to facilitate meniscal regeneration.

Tissue Engineering

Tissue engineering is the well-established discipline focused on either the de novo creation or recapitulated development of any tissue used to replace those structures lost by disease processes. Meniscal tissue engineering can use any combination of cells, scaffolds, bioactive factors, and bioreactors to meet this goal. Although there are a large number of different strategies that surgeons and researchers are investigating to develop meniscal-like tissue, for the purposes of this review, the authors have elected to specifically focus on the potential roles that synovial-derived cells may play in meniscal engineering.

Synovial-based Cells

Although some meniscal engineering techniques are acellular and entirely scaffold-based, many researchers believe that the use of an appropriate cell source is paramount to the formation of functional meniscal-like fibrocartilaginous tissue. The type of cell to be used is debatable but is often dictated by how the specific strategy seeks to ultimately achieve the most optimal tissue. For example, if creation of mature tissue is the goal, then committed cell lines such as meniscofibrochondroctyes are used, whereas for purposes of recapitulating the embryologic development of the tissue, progenitor cells may likely be more beneficial [5]. Thus, most meniscal cell-based engineering techniques use

one of three cell types: the meniscofibrochondrocyte, the mesenchymal stem cell, or the pluripotential fibroblast [5]. With respect to the synovial lining, the latter two cell lineages are both residents, are intimately related, and have become the focus of much investigation for cartilage engineering purposes.

The synovial membrane is divided into the synovial subintima and the intima, which is one to four cell layers thick [21]. The intima forms microvilli and larger alar folds and produces the synovial fluid that is crucial for nutrient delivery to the intra-articular structures, including molecular lubricants such as lubricin and hyaluronan that are essential to normal, low-friction joint movement [10, 25–27, 36, 55, 82, 83, 93]. The subintima, or lamina propria, is a loose areolar connective tissue that contains glycosaminoglycans (chondroitin-4-sulfate and chondroitin-6-sulfate) and fibrils of Type I, III, V, and VI collagen and serves as the supportive stroma for the synovial intima [25–27, 36, 55]. The synovial intima contains several cell types: the Type A synoviocyte, a type of tissue macrophage, which has phagocytic functions and mediates inflammation, and Type B cells, which are fibroblast-like and perform secretory functions [25, 26, 52]. Like other adult mesenchymal tissues, synovial lining also contains progenitor stem cells, which can undergo terminal differentiation into numerous different tissue types, including cartilage if exposed to the appropriate stimuli [22, 23, 62, 90]. This differentiation is believed to occur during chondrogenic metaplasia seen pathologically with the clinical disorder synovial chondromatosis [58]. The synovial cells of greatest potential use to musculoskeletal applications, and more specifically cartilage-based tissue engineering purposes, are the fibroblast-like synoviocyte and synovial-derived mesenchymal stem cell (SMSC) populations. De Bari and colleagues first isolated SMSC from human synovial lining through a selective adherence monolayer culturing process (thus allowing nonadherent Type A cells to be eliminated with media changes) and further determined that the adherent cells possessed multilineage potential that was stable up to 10 passages [23]. Obvious interest developed to more specifically characterize these cells; however, early attempts to further distinguish fibroblast-like or Type B synoviocytes from SMCSs did not result in clearly distinctive characteristics. Vandenabeele et al. determined that similar to synovial fibroblasts, the SMSCs also originate from the synovial lining and possess a phenotype highly similar to the Type B synoviocyte [90]. Despite the original theory that De Bari's culturing technique resulted in homogenous population of cells, later work suggested that synovial-derived adherent cell populations were far more heterogeneous than progenitor cells isolated from other sources such as bone marrow and that a more elaborate method of isolating MSCs from synovial lining was required [46]. Expanding on this was the study by Bilgen et al., which showed that selecting synovial fibroblasts from a mixed population of synoviocytes by way of CD-14-negative isolation resulted in a chondrogenically enhanced, more homogenous progenitor cell population [12]. Regardless, despite obtaining more heterogenic populations using the culturing techniques described by De Bari, human SMSCs have still demonstrated the greatest capacity for chondrogenesis when compared with MSCs isolated from bone marrow, periosteum, skeletal muscle, and adipose tissue [72] (Table 1).

Recently the ideal cell source for cell-based meniscal engineering was defined by Hoben and Athanasiou as being (1) autologous; (2) acquired in a minimally invasive fashion; (3) abundant; (4) capable of in vitro expansion; and (5) able to produce robust fibrocartilaginous matrix [43]. Addressing these criteria, the naturally abundant synovial tissue is capable of rapid regeneration postsurgical synovectomy [65] and is readily harvested in a minimally invasive fashion through arthroscopy [87]. Furthermore, when compared with MSC from bone marrow, periosteum, adipose, and muscle tissue, cultures of synovial-derived MSCs result in colony numbers that are 100-fold higher than the other cell types [95]. With respect to expansion potential, the SMSCs exhibit the highest colony-forming

Table 1. Comparison of engineering properties of bone mesenchymal stem cells and synovial derived mesenchymal stem cells

Reference	Cell origin	Yield (colony number/nucleated cell number)	Expansion/ proliferation	Chondrogenesis	Chondrogenesis regimen studied
Sakaguchi et al., 2005 [72]	Human	SMSC	SMSC = BMSC	SMSC	TGF-β3, BMP-2, dexamethasone, ITS
Shirasawa et al., 2006 [80]	Human	NA	SMSC = BMSC	SMSC	TGF-β, BMP-2, dexamethasone, ITS
Yoshimura et al., 2007 [95]	Rodent	SMSC	SMSC	SMSC	TGF-β3, BMP-2, dexamethasone, ITS
Koga et al., 2008 [51]	Rabbit	NA	SMSC	SMSC = BMSC	TGF-β3, BMP-2, dexamethasone, ITS

Review of those studies that completed a comparative analysis of culturing responses of both BMSC and SMSC to be used for chondral engineering purposes. For yield, expansion, and chondrogenesis, the acronym of the cell line that proved superior is listed unless it was not assessed (NA) or the two cell lines were equivalent in that assessment; BMSC = bone marrow mesenchymal stem cells; SMSC = synovial-derived mesenchymal stem cells; NA = not assessed; TGF-β = transforming growth factor beta; BMP = bone morphogenic protein; ITS = insulin, transferring, and selenium.

efficiency, fold increase, and growth kinetics [95]. Another potential hurdle to overcome with the use of any cell type harvested from the same joint that possesses a damaged meniscus is the impact of the subsequent osteoarthritis on those cells' chondrogenic capabilities. However, it has recently been confirmed that SMSCs obtained from human patients with end-stage knee osteoarthritis express typical combinations of mesenchymal progenitor surface markers and retain the potential for chondrogenic differentiation [29]. Hoben's final "ideal cell" criteria regarding the ability to produce robust fibrocartilaginous matrix is simultaneously challenging and yet ill-defined [43]. The vast majority of engineering investigations regarding synoviocytes have been directed toward the formation of hyaline-like cartilage for articular surface applications. Chondrogenesis, in this sense, can be defined by the production of sulfated proteoglycans, collagen II, and aggrecan. However, meniscal architecture possesses regional heterogeneity of extracellular matrix (ECM) constituents that result in the deeper and more axial (inner) zones of the meniscus having higher concentrations of these hyaline-like elements, whereas the meniscal surface and abaxial portions show more classic fibrocartilage architecture and composition [61]. By some estimations, 60% of the inner third of the meniscus is comprised of Type II collagen with five to six times the glycosaminoglycan compared with the outer third [16, 61]. Thus, the ideal cell type for meniscal engineering (if only one is to be used) should have the capacity for a spectrum of chondrogenic potential ranging from hyaline-like cartilage to fibrocartilage tissue production. It is now understood, however, that nonstimulated fibroblast-like SMSCs constitutively produce collagen Type I predominantly over collagen Type II [34, 66]. However, with appropriate culture conditions, synoviocytes can switch the ratio of collagen production to favor Type II relative to Type I, thus suggesting versatility of SMSCs in the development of a tissue with chondral heterogeneity in response to various stimuli [66].

Scaffolds

Once a cell type is selected, a second component to tissue engineering of musculoskeletal tissues is the potential use of a scaffold that can serve the dual purposes of providing instant structure on which the new tissue may develop as well as to act as a method of delivery for the cells. Scaffolds may further be defined as "smart scaffolds" if they carry with them some type of signal that can direct appropriate tissue formation either from the implanted cell type or from the surrounding resident cellular population. With respect to the delivery of synoviocytes for cartilage (hyaline or fibrocartilage) engineering, a number of different systems have been investigated including hydrogels (alginate [53, 66] collagen [51, 63, 94], and gellan [28]), pellet cultures [63, 80], micromasses [3, 66], small intestinal submucosa (SIS) [84], hyaluronan-based scaffolds (Hyaff-11®; FAB, Abano Terme, Padova, Italy) [56], polyglycolic acid (PGA) [67, 74], PGA/poly (L) lactic acid (PLLA) combinations [34], and scaffold-free cell infusions [44, 60]. With relatively few studies directly comparing delivery methods, elucidating an optimal carrier or scaffold from the literature alone is difficult. Not surprisingly, with three-dimensional culturing systems, SMSCs become more chondrogenic both in appearance and in production of extracellular matrix constituents versus using two-dimensional systems [66]. The earliest demonstration of this was from the examination of synovial cell pellet culture systems [56, 72, 80]. However, the surgical applicability of small spheroid pellets is somewhat limited for many large chondral applications. Hence, for articular cartilage, recent developments of a variety of hydrogel carriers that can suspend synoviocytes in three dimensions while filling discrete chondral defects have been investigated [28, 51, 53, 63, 66, 94]. For meniscal applications, however, the need for tissue regeneration frequently resides in the avascular portion of the tissue, which may not exist as a singular defect with complete borders, thus posing a highly unstable and challenging environment for the surgical implantation of an engineered structure. To date, this has resulted in two different strategies for cell-based meniscal engineering using synoviocytes: a scaffold-free approach in which free cells are infused directly into the joint to hopefully reside on the edges of the damaged meniscus to guide a regenerative response [44, 60] or a more highly engineered approach in which a physical tissue is formed before implantation. Investigations examining joint infusion with SMSCs have attempted to mimic and optimize what the authors speculate occurs during naturally occurring meniscal injury: the extrication of SMSCs from the synovial intima into the joint fluid with ultimate adherence onto and modulation of the damaged meniscus. The findings of this work were promising in that the injected synoviocytes appeared to promote meniscal regeneration in an anterior horn meniscectomy model [44]. The latter approach of forming a synoviocyte-based engineered tissue has been attempted with seeding cells on a surgically implantable scaffold [34, 84] or, conversely, not using a scaffold at all but rather culturing a highly cellular tissue-like micromass for subsequent implantation [86]. The attempts to develop cell-seeded scaffolds to form a tissue-like construct have produced mixed results. Whereas PGA/PLLA combination scaffolds yielded poor results for meniscal application in one study [34], others have demonstrated excellent hyaline-like chondrogenesis using

nonwoven PGA scaffolds [67, 74]. The difference in study outcomes may be attributable to differing biochemical stimulation, however [34]. Interestingly, coculturing of SMSCs and meniscal fibrochondrocytes on SIS has resulted in tissue constructs with higher cell survival and chondrogenic differentiation exhibiting more robust ECM production than techniques using synovial cells alone [84]. This finding further demonstrates the potential advantages of using more elaborate cell-seeding protocols for in vitro tissue engineering strategies [84]. The aforementioned alternative to the use of a scaffold to engineer a synovial-based implantable tissue is through a scaffold-free approach. Although scaffold-free, SMSC-cultured micromasses have been developed and assessed in vivo with potentially promising results with respect to fibrocartilage regeneration, the meniscal defects tested were very stable; thus, the clinical relevance of this modality has yet to be validated [86]. These studies have clearly shown that despite the term "fibrochondrogenesis" still being incompletely defined, the impact of the cell delivery system, or scaffold, can greatly affect the SMSC's phenotype and will thus ultimately play an important role in affecting which type of chondral tissue will be developed along the spectrum of hyaline cartilage to fibrocartilage depending on which portions of the meniscus are to be engineered. However, the scaffold must work in concert with chondrogenic bioactive agents, which are likely the most powerful determinant of chondromodulation of synovial-based cells.

Bioactive Agents

Chondrogenesis of synoviocytes has been extensively investigated through the application of a number of different cytokines and hormones. Whereas no single cocktail of factors will likely ever be a panacea for optimizing chondromodulation of synoviocytes, several growth factors and other bioactive agents have now emerged as very efficacious candidates. However, the timing, dosing, and combination of the various elements that result in the optimal formula have yet to be definitively determined. The following list is hardly exhaustive but rather represents those factors that carry potentially the most promise with respect to future meniscal engineering attempts using the synoviocyte.

Transforming Growth Factor

Members of the transforming growth factor-beta (TGF-β) superfamily are well important mediators of chondrogenic differentiation in a number of MSC lines. After TGF binds to cell-surface receptors, various intracellular kinase pathways become activated until ultimately, transcription factors such as SOX-9 are turned on and induce the expression of chondrogenic genes. In this fashion, several reports indicate that the TGF-β1 isoform is an essential component of media additives to prompt the induction of synovial chondrogenesis [12, 28]. Insulin-like growth factor (IGF) has been assessed as a potential factor to further boost the performance of the TGF-β isoform with conflicting data. Where Sakimura et al. [74] has found a combination of the two growth factors results in higher production of glycosaminoglycans from SMSCs cultured on PGA, Bilgen et al. [12] found no such advantage. Also frequently investigated is the use of the isoform TGF-β3, which, in combination with other factors, is a powerful chondrogenic stimulus; a large body of work has now started to use a cocktail of TGF-β3 with bone morphogenic proteins (BMPs) and the synthetic glucocorticoid dexamethasone to consistently promote synovial-based chondroid matrix production [50, 72, 80, 94].

Bone Morphogenic Protein

As previously discussed, numerous studies have demonstrated that the BMPs (within the TGF superfamily) are potentially potent morphogens. Thus, they have been frequently used with TGF-β1 and TGF-β3 for the directed chondrogenic transformation of synovial cells. However, relatively few studies have specifically compared the efficacy of the various TGF-β and BMP isoforms with respect to chondrogenic potential. Examining synovial cells seeded three-dimensionally in alginate discs, Kurth and colleagues determined that both BMP-2 and BMP-7 induced chondrogenic differentiation of human synovial MSCs in a dose-dependent manner more potently than TGF-β1 [53]. However, the production of chondral ECM and genetic signaling for aggrecan and Type II collagen were suppressed if either fetal bovine serum (FBS) or dexamethasone were added into the culture media [53]. From these results, the authors concluded that FBS contains biologically active agents that interfere with BMP-associated chondrogenic transformation of synovial cells. Recently, Fan et al. compared the effects of two TGF-β isoforms to BMP-2 with respect to SMSC chondrogenesis in gellan hydrogels and, contrary to Kurth, found BMP-2 growth factor was an inferior chondral morphogen compared with TGF-β1 and β3 [28]. However, the initial cell growth media used by those investigators contained 10% FBS, the BMP-2 concentration used was lower, and the chondrogenic media they used contained dexamethasone [28]. Despite the controversy surrounding the concomitant use of the glucocorticoid dexamethasone

and BMPs, numerous recent attempts to use SMSCs for articular cartilage engineering have used the combination of BMP-2, TGF-β3, and dexamethasone as a chondrogenic media in which to immerse three-dimensionally cultured synoviocytes, whether in pellets or collagen gels, all with promising results [50, 63, 80, 94]. Because most of these strategies are geared toward the production of a hyaline-like articular cartilage, typical outcome measures include signaling or production of collagen Type II, aggrecan, and the activation of SOX-9. What remains to be determined is if this same matrix production will work for meniscal engineering. However, at least one study suggests that for axial, avascular meniscal engineering, the formation of a more hyaline-like tissue is desirable [84].

Platelet-derived Growth Factor

Recently, optimal culture conditions have been researched for SMSCs, specifically with respect to which type of serum media additives may promote both rapid cellular proliferation and chondral differentiation. As previously mentioned, FBS may downregulate the production of chondroid ECM components. Thus, several studies have been conducted to investigate the use of autologous serum for the expansion and differentiation of SMSCs. Tateishi and colleagues determined that culturing human SMSCs in human serum resulted in more rapid cellular proliferation but showed no difference in altering chondrogenic potential when compared with FBS [85].

These findings were further substantiated by Nimura et al. who similarly determined that autologous serum enhances SMSC expansion but not in vivo chondrogenic transformation [63]. Interestingly, these researchers also found the mechanism by which the upregulated proliferation occurs is through platelet-derived growth factor (PDGF) for which the α-receptor expression in synovial-derived MSC far surpasses bone marrow MSC [63]. PDGF is a known mitogenic and chemotactic stimulus and is present in high concentrations within fibrin clots, the most natural scaffold for wound healing, and thus is a powerful mediator for fibroblast recruitment and proliferation. This fact, paired with the relatively higher expression of PDGF receptor in SMSC when compared with other MSCs, lends support for SMSC treatment with either autologous serum or PDGF in the early phase of SMSC culturing to accelerate proliferation. This finding may also offer an additional explanation for the positive healing influence that vascular access can have on meniscal injuries, because the two major isoforms of PDGF in human serum (AB and AA) will maximally stimulate the variety of PDGF receptor α (both α/α homodimers and α/β heterodimers) that are present on the SMSCs.

Insulin and Insulin-like Growth Factor

The polypeptide IGF has also been investigated with respect to its chondrogenic and proliferative potential on SMSCs with mixed results. Kurth documented no effect of IGF-1 alone to promote the increased mRNA signaling for aggrecan or Type II collagen in SMSCs [53]. Likewise, Bilgen and colleagues were not able to demonstrate either an increase in synoviocyte proliferation nor glycosaminoglycan production in response to the growth factor [12]. However, when used in concert with TGF-β, IGF-1 increases glycosaminoglycan production and signaling for Type II collagen and aggrecan when the treated synoviocytes were seeded either on PGA [34, 74] or SIS scaffolds [84]. Interactions of TGF-β1 and IGF-1 on cultured chondrocytes have been well documented and despite TGF-β causing decreases in cellular IGF-1 production, increases in IGF-1 binding sites, and downregulation of IGF-1-induced receptor autophosphorylation, both insulin and IGF-1 are crucial in TGF-β-mediated re-expression of aggrecan and Type II collagen [68]. The IGFs are obviously so named because of their high sequence similarity to the hormone insulin. Insulin is now commonly used as a component of a chondrogenic media additive (insulin-transferrin-selenium [ITS]) at high levels to maintain the chondrogenesis of synoviocytes. However, based on the results of Pei et al., such supraphysiological concentrations of insulin may also result in the nonspecific stimulation of IGF-1 receptors, thus attenuating the effects of IGF-1 when used alone [68]. From these studies, it may be deduced that if ITS is to be used as a chondrogenic media additive, then IGF-1 should only be used in combination with TGF-β because the effects of its independent use are likely to be negligible.

Bioreactors

The remaining step to be considered in meniscal cartilage engineering is the application of biomechanical stimuli. Bioreactors exist as environments in which mechanical load and bioactive agents can be applied to a newly developing tissue and can either be in vivo or in vitro in nature. Whereas in vivo bioreactors include the implantation of engineered constructs into the body either remotely or at the site of ultimate application, in vitro bioreactors come in a variety of designs for the purposes of applying specific forces to the construct in very controlled ways before surgical implantation. Whereas studies examining the mechanical stimulation of chondral progenitor cells have indicated that mechanotransduction is an important component to the maintenance of chondrogenic phenotype and matrix production, the mechanical

responsiveness of stem cells of synovial origin specifically are greatly lacking. Using the knee as an in vivo bioreactor, these authors demonstrated that the insertion of acellular disks of SIS freely within a synovial joint results in fibrochondrogenesis of the disks and speculated that this occurs through a process of synoviocyte extrication and dynamic mechanical stimulation [31]. Because the exact contributing elements were not elucidated, attempts were made to recreate the phenomenon using synovial fibroblasts seeded on a variety of collagen-based scaffolds and dynamically compressed in an in vitro bioreactor [32]. Despite the ability of the synoviocytes to migrate within the SIS scaffolds and produce small amounts of collagen, chondrogenic transformation of the cell-seeded scaffolds was not observed in response to the mechanical stimulus [32]. However, the mechanoresponsiveness of synovial fibroblasts cultured in monolayer has recently been demonstrated through their chondrogenic differentiation in response to intermittent hydrostatic pressure [73]. Expression of proteoglycan, collagen Type II, and SOX-9 mRNA was upregulated and production of SOX-9 protein and GAG was increased in response to the mechanical stimulation through a c-Jun N-terminal kinase pathway [73]. Despite synoviocytes demonstrating chondrogenesis in response to dynamic hydrostatic pressure application, it is possible that the fibroblast-like SMSCs need to be primed to produce robust chondral ECM before the application of more clinically relevant mechanical loads for meniscal tissue such as dynamic compressive and tensile forces.

Discussion

The objective of this review was to provide evidence from the existing literature, as retrieved from an online bibliographic search, that addressed two specific purposes: (1) providing justification for the further examination of synovial lining as a tissue source of cells for meniscal healing and regeneration based on current meniscal treatment modalities; and (2) review that research that has examined how synovial cells have been studied with specific context to the main components of meniscal tissue engineering.

A number of limitations exist with respect to how this review was executed. First, this work does not, nor was intended, to represent a thorough meta-analysis of the topic at hand. As such, the referenced works were not categorized with respect to their evidence class, and thus each was awarded equal value. Second, only a single online search engine was used to retrieve studies (PubMed). The resulting body of evidence was supplemented by other referenced works not obtained through the initial online search from both the works cited by the retrieved papers and also those that the authors were aware of through their work in the field. Third, specific exclusion criteria for retrieved studies were not used, but rather all studies were examined subjectively with respect to how well they addressed the study question and included if, in the opinion of main author (DBF), they were deemed useful for the development of future cell-based meniscal tissue engineering strategies. With full consideration of the limitations of this review, existing evidence still indicates that fibroblast-like stem cells of synovial origin show promise for meniscal tissue engineering applications.

Our first purpose was to demonstrate how the synoviomeniscal relationship impacts current meniscal treatment strategies as justification for the continued examination of this cell source for novel treatment development. In so doing, it was determined that synoviocytes are natural modulators of the injured meniscus and that several current treatment modalities for meniscal tears use resident synovial lining or synoviocytes. These include synovial advancement flaps, synoviomeniscal rasping, and the implantation of cellular-vascular access channels and conduits from the abaxial synovial perimeniscal capillary plexus to the location of the meniscal tear. Additional studies have demonstrated the importance of synovial cells in modulating responses to meniscectomies and populating allografts.

This evidence has supported the movement to investigate the role of synovial-based cells as the key cellular element for meniscal tissue engineering strategies, which was reviewed and summarized for the second purpose of this study. Synoviocytes carry the potential to be primed in the synovial environment to exhibit chondroprogenitor behavior and these responses have been recreated both in vitro and in vivo with the use of a variety of scaffolds, bioactive factors, and now mechanical stimulus. The specific combinations and types of stimuli have yet to be determined to optimize the fibrochondral transformation of cell-seeded constructs, however. Of particular challenge will be the continued investigation of the most appropriate regimen and method of mechanostimulation of the fibroblast-like synoviocyte. Furthermore, the ideal type of matrix produced with respect to collagen Types I or II has yet to be defined for meniscal application. Despite these challenges, autologous synovial lining is available in abundance and can regenerate quickly after harvest with robust resident stem cell populations possessing chondroprogenitor potential. Thus, the potential of the synovial-derived stem cells to proliferate rapidly and then produce a wide spectrum of chondral matrix components from fibrocartilage to hyaline cartilage makes it an ideal candidate for future meniscal engineering investigations.

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