Current Concepts in Meniscus Tissue Engineering

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Abstract: After partial or total meniscus resection, cartilage degeneration can be observed in many knee joints, frequently culminating in osteoarthritic changes. Therefore, a meniscus preserving therapy should be performed whenever possible. However, despite improved surgical techniques and new treatment strategies, meniscal tissue resection cannot always be avoided. Currently, only few treatment options are available after total meniscectomy, a dissatisfying situation considering that many patients presenting with meniscal injuries are young patients. Transplantation of allogenous menisci has been valuable only in particular cases and does not seem to prevent degenerative changes in the affected knee joint. Because of the unsatisfactory clinical progression after resection of meniscal tissue, new tissue engineering concepts are eagerly sought after. A first step towards a meniscus replacement therapy has been achieved with the development of a collagen meniscus implant (CMI), which has recently been approved for clinical application in Europe. This review will give a short overview about actual meniscus replacement therapies. Current experimental research concepts for meniscus tissue engineering and new perspectives for clinical treatment strategies will also be presented. Additionally, we will report about successful experimental application of new scaffolds and scaffolding materials, the use of different cell types and gene therapy approaches.

Keywords: Collagen meniscus implant, tissue engineering, meniscus defect, scaffold material, progenitor cells, gene therapy.

INTRODUCTION

The menisci are of great importance in normal knee function. They adapt the round surface of the femoral condyle to the more planar surface of the tibial plateau, providing load bearing and load distribution, shock absorption, stability and lubrification within the joint [1-3]. Mechanical overstraining or extreme sportive exposure may lead to traumatic meniscus injuries, but also degenerative changes with a subsequent loss of functional characteristics of the tissue may result in meniscus tears. In Germany, about 300.000 surgical interventions are carried out each year to treat meniscus injuries. If left untreated, such injuries may result in chronic inflammatory processes, cartilage damage and finally osteoarthritis in the knee joint, which mostly implies a drastic reduction of life quality because of pain and restriction of movement.

Looking at the histology, the meniscus does not have a unique structure, it is rather a quite heterogeneous tissue with different composites in various areas, and e.g., the posterior and anterior horns are clearly different from the middle part concerning stiffness, permeability, cell population, interstitial substance and arrangement of connective fibers [4, 5]. In principle, the sickle shaped meniscus can be divided into three zones, the red zone, the red-white zone and the white zone. The white zone has no blood supply and consists mainly of fibrocartilage tissue with chondroid cells, some chondroid interstitial substance and parallel circumferentially oriented fascicles of connective fibers. The nutrition of this tissue occurs by diffusion only. The outer edge of the meniscus (red zone) resembles more a connective tissue with cross bundles of connective fibers, fibrocytes and blood vessels [5]. The intermediate red-white zone is poor in blood vessels and nutrition is supplied by both, blood vessels and diffusion from synovial fluid. Concerning the morphology there is no uniform population of meniscus cells [6]. The predominantly meniscus collagen is type I (> 90%) [7, 8] with only small amounts of type II, III, V and VI [4, 9, 10]. Lesions within the vascular zone can heal spontaneously [11] but because of the described lack of blood supply tears in the inner zone of the meniscus have a very limited healing capacity [12]. However, if degenerative changes of the meniscus are present, a meniscus preserving therapy often results in pain and limited function of the knee caused by non-healing or re-rupture. Partial or total meniscal resection can be necessary. Keeping the negative long term results after meniscectomy in mind a high need for treatment strategies to regenerate meniscal tissue exists.

TREATMENT STRATEGIES

Until the past two or three decades it was assumed that the menisci were only functionless remains of leg muscles with none or inferior importance for the knee joint, an assumption that resulted in total meniscectomy as a routine treatment of meniscus defects until as recently as the 1970s [13]. However, nowadays there is no doubt that this procedure predisposes for the development of degenerative joint disease [14-18]. Therefore, the primary aim of treatment of meniscus injuries is now the preservation of the native tissue. Whenever possible, meniscal tears are repaired, mainly sutured [19] or stuck together with bioabsorbable fixation devices [20]. The use of fibrin sealant is inferior to suture but can be used in conjunction with suture for better results [21-23]. Further treatment options are abrasion therapy [24] or induced vascularization [25]. Repaired tears in the outer peripheral, vascularized zone can heal well, whereas ruptures in the inner, avascular area of the meniscus have nearly no

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healing capacity even when surgically repaired [26]. Such injuries are commonly treated by resection of the damaged tissue, e.g. partial or total meniscectomy. As such a treatment inevitably leads to alterations in the biomechanical characteristics of the knee joint [27] with the potential risk of initiating degenerative processes, a high need exists for suitable substitutes replacing the excised tissue. A lot of research has been done and is still carried out in search for the proper approach, focusing currently on tissue engineering concepts for the development of artificial meniscus implants. This complex tissue engineering field comprises several independent research topics like, for example, materials research, cell biology, cell culture systems and environmental stimuli *via* growth factor application or mechanical strain. At present the best results in treatment of a subtotal loss of the medial meniscus seem to be obtainable by using a resorbable collagen type I meniscal implant (CMI). The CMI was developed by Stone, Steadman and Rodkey [28]. This scaffold consists of purified type I collagen isolated from bovine Achilles tendon, molded into a circumferential orientation [28]. The use of the CMI for replacement of both the medial and lateral meniscus is licensed in Germany since 2006 [29]. As the initial mechanical properties of the collagen I-glycosaminoglycan (GAG) scaffold are inferior to the native meniscus tissue [30], a contraindication for the CMI implantation is a complete loss of the meniscus, as the scaffold has to be sutured to the intact peripheral rim of this tissue [29]. Clinical studies demonstrated that patients receiving a CMI had better clinical outcomes than their preoperative status [31, 32]. Steadman [31] reports that on arthroscopic observations at a mean follow-up of 5,8 years the newly grown tissue appeared meniscus-like, whereas Zaffagnini [32] describes the aspect of the implants after a final observation at a mean follow-up of 6,8 years as mostly abnormal, although patients improved concerning pain and physical activity. Both studies report a functioning of the implant without negative effects or complications related to the device for the entire follow-up period. However, it is not completely clear yet, whether the CMI is able to prevent osteoarthritis in the long term.

Pre-seeding of the CMI with autologous fibrochondrocytes seems to improve the macroscopic and histologic performance of the implant. In an animal study, enhanced vascularisation, accelerated scaffold re-modelling, a higher content of extracellular matrix and lower cell number was observed in pre-seeded menisci in comparison with non-seeded controls [33]. However, further studies are needed to prove if such a cell-seeding procedure is feasible for human applications.

Indications for the insertion of the CMI are restricted and a great disadvantage is the necessary prerequisite of an intact peripheral meniscus rim. In cases of a completely destroyed meniscus the CMI cannot be used. In such settings a meniscus allograft transplantation might be an option. *Via* allograft transplantation pain relief and functional improvement has reliably been achieved at short- and medium-term follow-up [34]. Although this procedure seems to be the treatment of choice in symptomatic, meniscus-deficient patients, the effectiveness of meniscal allograft transplantation regarding protection of articular cartilage and prevention of osteoarthritis is still a matter of debate [35-37]. Critical issues associated with allograft transplantation are the question of graft processing and conservation, optimal timing of the procedure, risk of immune rejection and disease transmission, graft size and graft attachment to the tibial plate [38].

Natural and Synthetic Scaffold Materials

In search for the optimal scaffold material for replacement of damaged meniscus, different natural tissues like small intestinal submucosa (SIS) [39-41] perichondral [42] and periosteal [13] tissues have been studied. All come along with their specific disadvantages like poor initial mechanical properties, inappropriate pore size or tendency to differentiate into bone [13]. Other natural scaffold materials tested are fibrin [43, 44], chitosan-alginate-hyaluronate complexes [45] and collagen II-GAG [46].

Next to natural tissues or natural materials numerous synthetic scaffolds are under investigation *in vitro* and *in vivo*. Synthetic scaffolds comprise Teflon-nets [47, 48], poly(L-lactide) (PLLA)-epsilon-caprolactone [49], polyglycolic acid (PGA) and poly(D,L-lactide-coglycolide) (PLGA) [50, 51], poly-urethane (PU) [52], carbon fibers [53], butandiisocyanate-foams [54, 55] and various others. Kobayashi *et al*. [56] studied an artificial meniscus composed of a high water content polyvinyl alcohol-hydrogel (PVA-H) in a rabbit animal experiment. Good results concerning the articular cartilage state of knee joints implanted with PVA-H meniscus could be reported after 1,5 years, whereas osteoarthritic changes progressed in meniscectomized knee joints [56]. In an ectopic rat animal study, different biodegradable polyurethane scaffolds like estane and polycaprolactone-polyurethane (PCLPU) were tested, demonstrating higher tissue ingrowth rates for PCLPU [57]. However, development of cartilage-like tissue with a matrix rich in collagen type II and proteoglycans has been shown for estane scaffolds in a meniscectomized dog model [58]. Many natural and synthetic materials have already been studied as potential substitutes for meniscus tissue, but none has been completely satisfactory. It remains a challenging task to find and develop the perfect meniscus substitute. The ideal scaffold would be designed as a temporary supporting device inducing and conducting cell growth, providing appropriate biomechanical characteristics, biocompatible degradation products and a degradation rate suitable to the speed with which new matrix is synthesized and new functional tissue develops.

Cell Seeding

In order to improve implant ingrowth and primary biomechanical stability, scaffolds can be used in combination with cells, resulting in a living bioactive composite. Which cells are to be used is another comprehensive field of research, currently focusing on differentiated adult cells of various tissues. Most commonly used are meniscal fibrochondrocytes (MFC) as the most obvious cell source would be the injured meniscal tissue or the contralateral meniscus. MFC have been studied intensively in various animal models. They have been examined in combination with natural scaffolds like collagen I [33, 46], collagen II [46], fibrin [43] and agarose [59] or synthetic scaffolds like PGA [50, 60-62] or PCL [26] or just recently in a scaffold-less co-culture approach in combination with cartilage chondrocytes [63, 64]. However, the use of MFCs for tissue engineering concepts might be suboptimal because of the quantity of cells needed

in such approaches. Only a small amount of meniscal tissue can be harvested, which in addition is a tissue poor in cells. Furthermore, the harvest requires an invasive procedure. Therefore, chondrocytes of other adult cartilaginous tissues like articular [45, 65-67], auricular [68] and nasal cartilage [69-71] have been tested in combination with different scaffold materials. These chondrocytes are more abundant in comparison to meniscal fibrochondrocytes and easier to obtain. Following such considerations, dermal fibroblasts [72-75] and synovial cells [76] could be other possible cell sources.

When cells come into play one has to think about cell culture conditions which should prevent loss of inherent desirable cell characteristics or induce cells to differentiate into the desired phenotype. For the induction of differentiation or proliferation several growth factors like insulin-like growth factor (IGF), bone morphogenetic protein 2 (BMP-2), platelet derived growth factor (PDGF), transforming growth factor ß (TGF-ß), hepatocyte growth factor (HGF), interleukine 1 (IL-1), epidermal growth factor (EGF) and fibroblast growth factor (FGF) and many others have been studied, applied either alone or in various combinations [12, 62, 77, 78]. It would go too far beyond the topic of this review to list all the growth factors studied in this tissue engineering context and to detail known function(s) and effects. Only some will be briefly characterized. For example, IGF is known as a main anabolic growth factor of cartilage, playing a pivotal role in cartilage homeostasis, balancing proteoglycan synthesis and breakdown [77]. It also induces meniscal cell migration [78]. Members of the BMP family are implicated in various functions; they are commonly involved in regulation of cell proliferation and differentiation, inducing bone, cartilage, ligament and tendon formation [79]; they were shown to induce meniscal cell migration [78]. PDGF is well known as a potent mitogenic and chemotactic factor for cells originating from the mesenchymal lineage [77]; it also stimulates meniscal chondrocyte proliferation [80]. TGF-ß is a multifunctional peptide with regulatory tasks and it stands for a prototypical member of a large family of cytokines. It is involved in many aspects of cellular function, i. e. cellular proliferation, differentiation, migration, adhesion, apoptosis and immune responses, to mention the most common ones [81,82]. TGF-ß is reported to have stimulating effects on proteoglycan production by meniscus cells *in vitro* [83, 84]. Bhargava *et al.* [78] tested the influence of growth factors on meniscus cells isolated from the different meniscus' zones (white-white zone, red-white zone and red-red zone). They observed an increase in the migration of cells derived from all three zones when stimulated by HGF, whereas IL-1 stimulated migration only of cells from the outer meniscal zone. EGF was less effective in stimulating cell migration and did so only on cells of the inner and outer zone. Last but not least, FGF has been reported to have a proliferative effect on meniscal fibrochondrocytes [61, 85].

Still another way to promote a desirable development of cellular characteristics is the application of mechanical stimuli [67, 76].

Progenitor Cells in Meniscal Tissue Engineering

Adult bone marrow is known to contain multipotent progenitor cells, commonly described as mesenchymal stem cells (MSC) [86-89]. This cell type has been highly investigated in the last two decades as those cells hold great promise for various tissue engineering treatment concepts; however, no human MSC-based tissue engineering technology is currently clinically available [90]. MSCs can be easily harvested from bone marrow or marrow aspirates, isolated and culture expanded. With their great proliferative capacity and the potential to differentiate into cell types of specific mesenchymal tissues like muscle, tendon, bone and cartilage [89], they soon became potential candidate cells for meniscal tissue engineering approaches. A basic work done by Ishimura *et al.* in 1997 [91] evaluated the healing-promoting properties of bone marrow containing pluripotent stroma stem cells, applied in combination with fibrin glue into full-thickness defects in the avascular area of the medial meniscus in a rabbit model. The histological study showed earlier mature healing in the group where bone marrow containing fibrin glue was used. Similar positive results promoting the direct application of bone marrow aspirates to meniscal tears were obtained by Abdel-Hamid in a dog model [92]. Izuta *et al.* [93] used isolated and *in vitro* expanded MSCs in combination with fibrin glue to treat meniscal defects of Sprague-Dawley rats in an *in vitro* organ culture model. The production of abundant toluidine staining extracellular matrix, which contributed to meniscal healing by the proliferating transplanted cells, could be observed and it was suggested that MSC transplantation might be a promising clinical strategy for the treatment of meniscal tears in the avascular zone. This report is supported by an *in vivo* study conducted by Murphy and coworkers in 2003 [94]. They injected monolayer-expanded MSCs together with sodium hyaluronan into caprine knee joints which had undergone complete excision of the medial meniscus. Their results promote the local delivery of MSCs to injured joints, as regeneration of meniscal tissue was stimulated: A hyaline tissue with a dense type I collagen containing network surrounding cells with fibroblastic morphology could be observed in the knees treated with MSCs. At the same time point no such tissue could be seen in control animals. Further, the progressive destruction of articular cartilage has been retarded in their study.

A further approach is the combination of MSCs with a scaffold material. Walsh *et al.* [13] used a collagen type I sponge to treat a partial defect in the medial meniscus of rabbit. MSCs were previously allowed to attach to the sponge. These cells were observed to augment the repair process to include fibrocartilage histologically similar to normal meniscus, but results were not satisfactory concerning restoration of biomechanical function of the meniscus and prevention of degenerative changes. There are reports testing PCL scaffolds in combination with MSCs, focusing on the influence and importance of nanofiber alignment. In cell culture, MSCs organize their actin filaments according to the prevailing nanofiber orientation [95]. Baker *et al.* [26] tested the effect of nanofiber alignment on the maturation of cell-seeded meniscus constructs, comparing behaviour and matrix production of MSCs and MFCs on non-aligned or fiber-aligned nanofibrous scaffolds. Mechanical properties of scaffolds increased more for the aligned ones, independent of the cells used for seeding. MSC-constructs yielded more extracellular matrix, i.e. an increase in Glycosaminoglycan-content and total collagen, thereby confirming that MSCs

could serve as an alternative to the use of MFC in meniscus tissue engineering [26].

Gene Therapy

The possibility of exploiting the principles of gene therapy for healing of the meniscus has to be mentioned. Mesenchymal stem cells and meniscal fibrochondrocytes can be easily transduced with adenoviral vectors and levels of transgene expression are high, although declining with time [96]. Marker genes have previously been successfully delivered to meniscal allografts [97] and to meniscal lesions in *ex vivo* and *in vivo* approaches [98]. Steinert *et al*. [96] used a cell-based gene-delivery method, expressing the TGF-ß transgene in MSCs and MFC, seeding collagen type I-glycosaminoglycan matrices with these cells. After *in vitro* culture, scaffolds were transplanted into tears of menisci in an *in vitro* model of meniscal healing. The TGF-ß transgene expression led to an increase in cellularity and enhanced the deposition of proteoglycans and collagen type II, indicating that TGF-ß cDNA delivery may affect cell-based meniscus repair approaches *in vivo* [96]. However, risks like ectopic target gene expression and immunogenicity of adenoviral vectors have to be addressed and render such gene therapy approaches currently impractical for clinical application.

CONCLUSION

Partial or total meniscectomy results in a high rate of osteoarthritis. Therefore, an increasing amount of research is done in the field of meniscus tissue engineering. Many different experimental approaches are pursued, comprising research concerning scaffold materials, potential cell sources and stimulation of desired cellular differentiation. Because of the ease of accessibility and harvest, mesenchymal stem cells are potential candidates for cell based therapies. Although there is only few data about the use of MSCs for meniscal repair [12, 13, 26, 93, 94, 99, 100] so far, a potential suitability and applicability of MSCs as a cell source for meniscus tissue engineering repair approaches can be concluded. However, it is still questionable whether modern tissue engineering will be able to totally regenerate the anatomical and functional structure of the normal meniscus. This will be the challenge of basic research in the next decades.

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