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*Review Article*

# Biological Strategies to Enhance Healing of the Avascular Area of the Meniscus

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Meniscal injuries in the vascularized peripheral part of the meniscus have a better healing potential than tears in the central avascular zone because meniscal healing principally depends on its vascular supply. Several biological strategies have been proposed to enhance healing of the avascular area of the meniscus: abrasion therapy, fibrin clot, organ culture, cell therapy, and applications of growth factors. However, data are too heterogeneous to achieve definitive conclusions on the use of these techniques for routine management of meniscal lesions. Although most preclinical and clinical studies are very promising, they are still at an experimental stage. More prospective randomised controlled trials are needed to compare the different techniques for clinical results, applicability, and cost-effectiveness.

## 1. Introduction

The menisci of the knee are two semilunar fibrocartilaginous structures sitting between the joint surfaces of femoral condyles and the tibial plateau. Meniscal injuries are a common and important source of knee dysfunction. Repair should be considered depending on the type and location of the meniscal tear [1–3], as meniscal healing principally depends on the vascular supply of the zone that has been injured [4]. A rich network of arborizing vessels within the peripheral capsular and synovial attachments supplies vascularization to the menisci. This perimeniscal network provides radial branches to the meniscus. The outer third of the meniscus is vascularised, showing a good healing capacity. Given its abundant vascularization, this zone is also called "red-red zone." The remaining two-thirds of the meniscus, respectively called "red-white zone" and "white-white zone," have a scanty vascular supply and present a limited ability to heal spontaneously [4–7].

A meniscal lesion followed by disruption of the structure in the avascular zone impairs load distribution and initiates erosion of the adjacent articular surfaces, causing osteoarthritis (OA) [8–11]. The most common treatment for lesions of the avascular part of the meniscus is arthroscopic partial meniscectomy, which reduces symptoms but similarly predisposes patients to OA [12]. Studies have demonstrated that healing of the knee is inversely related to the amount of resected meniscal tissue [10, 11, 13, 14]. Meniscal repair techniques in the avascular zone are in continuous evolution.

This paper covers current knowledge on biological strategies for the stimulation of meniscal healing after repair.

## 2. Abrasion Therapy

Rasping of the damaged meniscus in the vascularized parameniscal synovium promotes an injury response and is one of the most simple and effective strategies to favour healing [3]. A small incision is performed to produce a vascular channel that redirects the blood flow from the vascular zone into the avascular one. Several studies showed a significant difference in healing between menisci treated

with abrasion therapy and control groups [15, 16]. The most common techniques of abrasion therapy are rasping or trephination, in which radially oriented channels are performed to encourage vascular and cellular migration from the peripheral vascular portion to the tear site [17–19]. Rasping increases the production of interleukin-I-alpha (IL-1-alpha), transforming-growth-factor-beta 1 (TGF-beta1), platelet-derived growth factor (PDGF), and proliferating cell nuclear antigen (PCNA). This protein network improves vascular induction and meniscal healing [20]. Nevertheless, trephination and rasping procedures may damage the normal meniscal structure by an additional full thickness-transverse tear, resulting in poor meniscal function.

## 3. Fibrin Clot

Fibrin is a fibrous protein produced in response to bleeding that plays an important role in blood clotting. Fibrin clots may be used topically or by injection as an haemostatic agent, binding to several adhesive proteins of different cells [21–33]. The fibrin clot technique acts as a chemotactic and mitogenic stimulus for reparative cells because of the presence of several growth factors [34–37]. The fibrin clot attaches to the exposed collagen caused by the tear and induces proliferation of fibrous connective tissue [38–44]. This stimulates the development of fibrocartilaginous tissue. The fibrin clot technique can be used in combination with abrasion therapy or with meniscal sutures [45–57]. Two studies in animal models showed that organized fibrous connective tissue developed into cartilaginous tissue after a period of 12–24 weeks [58, 59]. A potential disadvantage of the fibrin clot technique is the difficulty of keeping fibrin clots on the tear without immobilizing the operated leg [60].

## 4. Organ Culture

Organ culture is a useful model to assess the intrinsic healing potential of the meniscus excluding the influence of microvasculature and the synovium [61–63]. The effects of cultured meniscal explants in a rabbit model have been reported [63]. After gross evaluation, each meniscal explant underwent histological evaluation to study the relationship between the graft and recipient tissue. Application of this technique has demonstrated that meniscal tissue presents an intrinsic healing ability, which is greater in the peripheral zone of the meniscus than in the inner zone [63]. Regional differences in healing potential and extrinsic factors, such as blood supply, could explain good meniscal healing in the peripheral zone.

## 5. Cell Therapy

Human menisci are populated by different cell types, responding differently to various stimuli released from the matrix [64, 65]. Different cells have already been used in studies on meniscal healing: mesenchymal stem cells (MSCs) deriving from synovial or bone marrow, chondrocytes, and fibrochondrocytes. MSCs are pluripotent cells able to differentiate into specific therapeutic cell types (developmental plasticity) [66–68]. The effects of bioactive molecules, which are secreted by MSCs, determine a regenerative microenvironment that promotes healing of meniscal lesions [69, 70]. The combination of suturing and MSC treatment, combined or not with fibrin glue, seems to be the most effective treatment [71].

Zellner et al. [70] reported the efficacy of mesenchymal stem cells in the repair of meniscal defects in the avascular zone. Nonprecultured mesenchymal stem cells in hya-luronan-collagen composite matrices stimulated the development of completely integrated meniscus-like repair tissue in defects produced in the avascular zone of rabbit menisci [70].

Further studies confirm the production of abundant extracellular matrix around the cells, restoring a meniscal-like tissue in the avascular zone [70, 72–75]. These results are supported by early studies which demonstrated the efficacy of the association between growth factors and mesenchymal stem cells within scaffold implants to increase proteoglycans and/or collagen synthesis [70, 76]. Articular autologous and allogenic chondrocytes have also been used to induce repair in the avascular part of the meniscus [77, 78]. Peretti et al. described a porcine chondrocyte model where implantation of such cells was performed in the avascular part of the meniscus using an allogenic scaffold seeded with autologous chondrocytes. These chondrocytes were effective in promoting healing meniscal tears [77]. Fibrochondrocytes showed potential for initiating a reparative response in meniscal defects through the production of new extracellular matrix (ECM) [79, 80]. When seeded into a porous collagen scaffold, fibrochondrocytes harvested from the inner avascular part of the meniscus produce more glycosaminoglycans (GAGs) than fibrochondrocytes from a peripheral fibrous location [81, 82]. Although these findings are encouraging, the application of autologous fibrochondrocytes in meniscal tissue engineering is limited by the difficulty in harvesting a sufficient number of cells [83–93].

## 6. Growth Factors

Growth factors act as signalling molecules on target cells to stimulate the regeneration of damaged tissue [6]. Furthermore, they can induce the synthesis and inhibit degradation of ECM by a mechanism of downregulation of proteases [94]. Several studies in vitro and in vivo evaluated the effects of treatment with specific growth factors. Two categories of growth factors in consideration of their biochemical attributes are generally considered: anabolic and catabolic growth factors.

### *6.1. Anabolic Growth Factors*

*6.1.1. Fibroblast Growth Factor (FGF).* basic FGF was used to stimulate type II collagen and aggrecan mRNA production in cellular and tissue development [95, 96]. In an ovine experimental model, meniscal fibrochondrocytes responded to bFGF by proliferating and producing new extracellular

matrix [79]. Another FGF type, FGF-2, stimulates proliferation of the joint chondrocytes, mesenchymal stem cells, osteoblasts, and adipocytes. Furthermore, it maintains the ability of any cell types to differentiate [97, 98]. Moreover, a hyperexpression of FGF-2 and alpha-smooth muscle actin (alpha-SMA) through recombinant adeno-associated virus (rAAV) enhanced cell proliferation and increased survival rate compared with control groups. However, FGF did not significantly increase the synthesis of major extracellular matrix components or DNA contents [99].

*6.1.2. Transforming-Growth-Factor-Beta (TGF-Beta).* TGF-beta seems to have several regulatory activities, stimulating collagen and proteoglycan production to increase the attachment of the cells in repaired meniscal tissue. Nevertheless, it has no effect on cell proliferation [6, 100–103].

*6.1.3. Bone Morphogenetic Proteins (BMPs).* BMPs are a group of growth factors belonging to the TGF-$\beta$ superfamily playing an important role during embryogenesis and tissue repair in relation to their osteoinductive properties [104, 105]. BMP-2 acts as a stimulus in the differentiation of mesenchymal cells. It also presents a migratory effect in endothelial cells or smooth muscle cells, but rarely in chondrocytes [106]. BMP-7 regulates matrix homeostasis and inhibits the processes of degradation. BMP-7 acts with different chondrogenic agents and is more effective than BMP-2 in chondrogenic differentiation of MSCs in promoting meniscal healing [107].

*6.1.4. Insulin-Like-Growth-Factor-I (IGF-I).* This is considered the main anabolic growth factor for articular cartilage [108, 109]. Unlike TGF-beta I, IGF-I increases cell proliferation significantly but has no effect on the attachment [95]. Therefore, a mixture of growth factors in association with IGF-I could induce an extensive cellular response to mediate avascular meniscal healing [100].

*6.1.5. Vascular Endothelial Growth Factor (VEGF).* The induction of angiogenesis is important to stimulate healing of meniscal tears [110–122]. Vascular endothelial growth factor (VEGF) may promote better healing, stimulating angiogenesis to improve the healing capacities of meniscus tissue. In adults, VEGF expression is downregulated by endostatin, mostly in the avascular zone [123]. However, the local application of VEGF did not show an improvement of meniscal healing [124].

*6.1.6. Platelet-Derived Growth Factor-AB (PDGF-AB).* PDGF-AB plays an important role in the angiogenesis and cell development [125, 126]. The application of PDGF-AB in the peripheral part of the menisci showed a better healing response than the application in the central part [127]. However, this anabolic growth factor increased both cell proliferation and ECM formation in all zones of the meniscus, including the avascular zone [128].

*6.2. Catabolic Growth Factors*

*6.2.1. Endostatin.* Endostatin is an antiangiogenic factor expressed by fibrochondrocytes in the avascular zone of menisci. Endostatin concentrations were higher when fibrochondrocytes were in coculture with MSCs, suggesting that meniscal cell growth is inhibited by the proliferation of MSCs [7].

*6.2.2. Interleukin-I (IL-I).* This is a proinflammatory cytokine that stimulates the development of a local inflammatory reaction. Meniscal explants treated with IL-I have failed to show any signs of regeneration [129]. These findings suggest that relevant expression of IL-I in association with higher levels of tumor-necrosis-factor-alpha (TNF-alpha) inhibit meniscal repair [130].

## 7. Platelet Rich Plasma

Platelet-rich plasma (PRP) is an autologous substance rich in platelets that releases growth factors from both alpha and dense granules [131–150]. These growth factors have been associated with the initiation of a healing cascade leading to cellular chemotaxis, angiogenesis, collagen matrix synthesis, and cell proliferation [151]. Ishida et al. reported the effects of PRP on meniscal tissue regeneration, both in vitro and in vivo, in a rabbit model. In the in vitro study, monolayer meniscal cell cultures were prepared and proliferative behaviour, extracellular matrix (ECM) synthesis, and fibrocartilage-related messenger ribonucleic acid (mRNA) expressions were assessed in the presence of PRP. PRP stimulated DNA synthesis, ECM synthesis, and mRNA expression of biglycan and decorin [152–161]. In the in vivo study, full-thickness defects were produced in the avascular region of rabbit meniscus. Gelatin hydrogel (GH) was used to deliver PRP into the defects. At histology 12 weeks after surgery, significantly better meniscal repair was evident in animals that received PRP with GH than in the control groups [162].

In contrast, Zellner et al. evaluated several cell and biomaterial-based treatment options for repair of defects in the avascular zone of rabbit menisci by producing circular meniscal punch defects in the avascular zone of rabbit menisci. The defects were left empty or filled with hyaluronan-collagen composite matrices without cells loaded with platelet-rich plasma, autologous bone marrow, or autologous mesenchymal stem cells. Neither bone marrow nor platelet-rich plasma loaded in matrices induced improvement in meniscal healing [70].

## 8. Discussion

In the last few decades, many studies on meniscal healing have focused on methods to enhance the healing capacities of the meniscus after repair [163–178]. Abrasion of the torn meniscus and synovial tissue or the establishment of vascular channels to redirect blood flow into the avascular zone seems to be the preferred treatment [3, 15, 16]. However, the healing potential depends on the type and location of

the tear and its distance from the peripheral vascularised zone. The use of a fibrin clot can also be an effective technique to support a reparative response in the avascular zone of the meniscus [34, 35, 37]. Findings demonstrated that the rasping technique is more effective than fibrin clot application to improve meniscal healing [179]. Kobayashi et al. reported healing rates in the peripheral zone of the menisci in an on-organ culture model. Regional differences in healing potential and extrinsic factors, such as a blood supply, could explain the good meniscal healing potential in the peripheral zone [63].

Cell-based therapy for meniscal tears has significantly contributed to an increasing number of patients treated with repair techniques rather than meniscectomy. Different cell types have already been used in studies on meniscus healing: MSCs, articular chondrocytes and autologous fibrochondrocytes [70, 77, 81, 82]. Progenitor cells such as mesenchymal stem cells present the advantage of being easily expandable without losing their differentiation potential into a variety of mesenchymal tissues including bone, tendon, cartilage, muscle, ligament, fat, and marrow stroma [64, 66, 68]. The application of MSCs and their stimulation with growth factors in combination with a mechanically loadable scaffold have been proposed as the focus of future studies [135, 148].

Several studies reported the efficacy of mesenchymal stem cells in the repair of meniscal defects in the avascular zone, with production of abundant extracellular matrix around the cells and restoration of a meniscal-like tissue [70, 72–75]. Early studies demonstrated the efficacy of the association between growth factors and mesenchymal stem cells within scaffold implants to increase proteoglycan and/or collagen synthesis [180–196]. Therefore, the healing response of mesenchymal stem cells seems to produce additional repair qualities besides the delivery of growth factors [70, 76].

Many studies have shown the importance of growth factors in the treatment of meniscal tears of the avascular portion, but there is a very complex interplay among a variety of factors that influences healing processes. Growth factors that promote cell differentiation and chondrocytic proliferation include both anabolic growth factors (TGF-beta I, BMPs, IGF-I, FGF, VEGF, and PDGF-AB) and catabolic growth factors (endostatin, IL-1, and TNF-alpha). Anabolic growth factors could be of additional value in improving the healing of meniscal lesions [6, 79, 95–109, 123–128]. However, the application of growth factors remains very limited in clinical settings [6, 95]. Future research should focus on the use of tissue-engineered constructs in association with different growth factors [197–203]. A preparation rich in growth factors could produce better results than the use of isolated growth factors. Only a few studies to date have evaluated the effectiveness of a preparation of platelet-rich plasma (PRP), but there is some evidence that PRP can improve healing of the menisci [127, 128]. The release of growth factors from platelets has been associated with the initiation of a healing cascade leading to cellular chemotaxis, angiogenesis, collagen matrix synthesis, and cell proliferation [151, 162]. In contrast, a study in an animal model reported that application of PRP did not produce improvements in meniscal healing [70].

## 9. Conclusion

Patients with meniscal tears report pain and functional limitation of the knee joint. Partial meniscectomy is the most common treatment option, but it represents a predisposing factor for osteoarthritis [12]. To date only limited scientifically proven management modalities are available. A better understanding of meniscal healing mechanisms will allow specific treatment strategies to be developed. Although most preclinical and clinical studies are very promising, they are still at an experimental stage. Further prospective trials are necessary to compare the different techniques for efficacy, applicability, and cost-effectiveness in the management of lesions of the avascular region of the meniscus.

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