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Review

Angiogenic approaches to meniscal healing

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ABSTRACT

Meniscal injuries commonly result in osteoarthritis causing long term morbidity, lifelong treatment, joint replacement and significant financial burden to the Canadian healthcare system. Injuries to the outer third of the meniscus often heal well due to adequate blood supply. Healing of injuries in the inner two thirds of the meniscus are often critically retarded due to a lack of blood flow necessitating partial meniscectomy in many instances. Localized angiogenesis in the inner meniscus has yet to be achieved despite a belief that vascularization of these lesions corresponds with meniscal healing. This review briefly summarizes the growth factors that have been assessed for a role in meniscal healing and points to a significant knowledge gap in our understanding of meniscal healing.

Contents

Introduction

The tibial menisci are a pair of semilunar fibrocartilaginous structures that are essential for health of the knee joint. The meniscus serves to improve load transmission, lubrication, congruity, proprioception and stability of the femoral-tibial joint [1]. Historically, the tibial meniscus was considered vestigial muscular remnants of which complete removal was often advocated [2,3]. In fact, as recently as 1970, Smille advocated complete meniscectomy for definitive diagnosis of suspected meniscal injuries. Such liberal resection of meniscal tissue has been recognised to result in long term morbidity in the form of

Abbreviations: ChM-1, chondromodulin-1; CTGF, connective tissue growth factor; ET-1, endothelin-1; HGF, hepatocyte growth factor; HUVEC, human umbilical vein endothelial cells; IGF-1, insulin-like growth factor-1; MFC, meniscal fibrochondrocytes; OA, osteoarthritis; PDGF, platelet derived growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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osteoarthritis (OA) [4,5]. Despite this, partial meniscectomy remains one of the most common orthopaedic surgeries as meniscal repair techniques are limited. Non-healing meniscal injuries are often debilitating and predispose the patient to lifelong pain and disability from OA. Currently OA places a significant burden on healthcare systems. OA affects 1 in 10 adults in Canada costing $4.4 billion annually [6]. The incidence of OA is expected to double over the next 10 years as our population ages [6].

Meniscal injuries are directly linked to development of OA. Such injuries rise significantly with increasing activity level and age [7–9] when compared to the general population [10]. Excellent healing of meniscal injuries occurs in the vascularized outer-third of the meniscus; however, tears located within the inner two-thirds heal poorly due to a paucity of tissue vascularization – Fig. 1 [11–13].

Several therapeutic approaches have been developed to repair avascular meniscal injuries. These approaches, however, require surgical intervention and are associated with a number of complications. Rasping [14–16], trephination [17,18], marrow stimulation [19–21], suture repair [22–24], synovial graft [25] and application of an autologous fibrin clot [22–24] are all reported to improve healing of lesions within the avascular zone. Despite improved healing with these techniques, little is known regarding the mechanism by which these processes stimulate repair. There is consensus that regardless of the intervention, improved meniscal healing is associated with ingrowth of vasculature to the area of damage within the avascular zone. This idea is not well supported in the literature as relatively few studies have assessed angiogenic approaches to stimulate healing in the avascular meniscus. As other strategies for meniscal healing have been reviewed in-depth else where [1], this review will focus on strategies that may improve angiogenesis, and hence healing of meniscal injuries in the avascular zone.

Literature reviewed

In December 2016, a literature review was performed using MEDLINE and EMBASE databases. Searches were limited to the English language and performed using the following keywords in combination using the "and" qualifier: tibial meniscus; knee injury; knee joint; avascular meniscus injury; meniscal fibrochondrocyte; VEGF; endothelial cell; angiogenesis; and angiogenic inhibitor. Search results were subjectively assessed to select papers evaluating interventions that may stimulate angiogenesis through *in vitro* analysis; *in vivo* animal studies; or clinical trials. A secondary search of works cited within these papers was performed manually using the database SCOPUS to evaluate all works cited to locate additional papers. In total 13 papers were found which met the search criteria (Fig. 2).

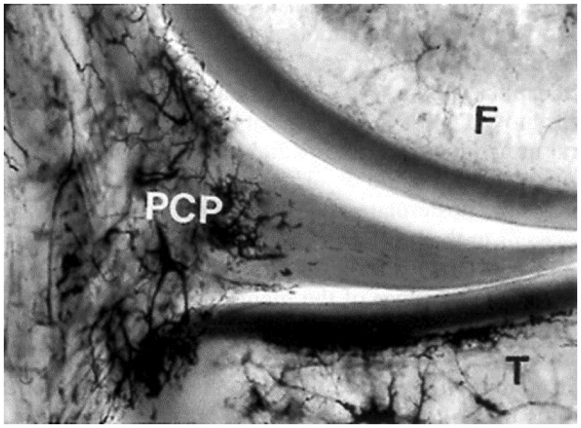

Fig. 1. The microvasculature of the meniscus. F = femur, T = tibia, PCP = perimeniscal capillary plexus. (Reproduced from Ref. 12).

Stimulation of angiogenesis

A variety of growth factors have been evaluated which play a role in meniscal healing. These factors predominantly focus on vascular endothelial growth factor (VEGF) production/supplementation; however, several other factors have been evaluated for their effect on improving healing of avascular meniscal injuries.

Vascular endothelial growth factor (VEGF)

VEGF is a selective endothelial cell mitogen that promotes angiogenesis and increases the permeability of the microvasculature to circulating macromolecules [26]. VEGF plays an important role in vascular growth within the musculoskeletal system [27] and is essential for the process of physiologic and pathologic vascular proliferation. Selective binding of VEGF occurs through two tyrosine kinase receptors [26] which are expressed on meniscus fibrochondrocytes (MFC) [28]. At least 12 isoforms of VEGF have been documented with both pro-angiogenic (VEGFa) and anti-angiogenic (VEGFb) effects [29]. Assuming different isoforms have different effects on meniscal angiogenesis, these multiple isoforms suggest a vast amount study required to fully evaluate the potential effects of VEGF supplementation on meniscal healing.

One *in vitro* study met the search criteria for this review evaluating the effects of VEGF supplementation on meniscal fibrochondrocytes (MFC) *in vitro*. Esparza et al. [30] assessed gene expression profiles of the vascular and avascular portions of the meniscus following supplementation with a variety of growth factors [30]. MFC originating from the vascular portion of the meniscus showed increased collagen II gene expression following supplementation with VEGF while MFC from the avascular portion showed increased collagen I gene expression following VEGF supplementation [30]. Interestingly, in the avascular zone insulin-like growth factor 1 (IGF-1) stimulated an 11-fold increase in VEGF and elevated levels of both collagen I and II gene expression as well [30]. With regards to potentially using exogenous VEGF to stimulate meniscal healing. This study provides support for exogenous supplementation assuming increased collagen II gene expression translates into increased type II collagen deposition in the inner meniscus. This study should, however, be followed up by documenting an increase in type II collagen within the inner meniscus. This apparent lack of evidence for *in vitro* growth factor supplementation may be due to the relatively short half-life of soluble growth factors and the relatively high doses and extended duration of treatment needed to utilize direct supplementation of VEGF as a stimulus for angiogenesis in avascular meniscal injuries.

Our search of the literature revealed seven *in-vivo* trials where VEGF was assessed as a potential therapeutic target for meniscal injuries (Table 1). Two observational studies report VEGF increased following creation of meniscal lesions in rabbits [31,32]. Despite an increase in endogenous VEGF; however, avascular meniscal lesions failed to heal in either study indicating endogenous VEGF is likely not sufficient to stimulate healing. Three studies evaluated VEGF as a therapeutic intervention *in vivo* following local administration. These studies report a lack of meniscal healing in treated animals [33–35]. Possible explanations for this lack of healing include: 1) therapeutic levels of VEGF were not achieved to stimulate healing, 2) VEGF isoforms exhibit tissue specific effects and specific isoforms or combinations needed to stimulate vascularization

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