Chapter

Novel Approaches in Meniscal Repair Utilizing Mesenchymal Stem Cells, New Generation Bioscaffolds and Biological Adhesives as Cell Delivery Vehicles

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Abstract

Mesenchymal stem cells (MSCs) have been widely applied in the repair of the knee-joint menisci which have a limited ability to undergo spontaneous repair. The menisci stabilise the knee-joint and are weight-bearing structures subjected to considerable tensional and compressive forces during flexion-extension and torsional loading of the knee. Traumatic loading of the knee-joint menisci can generate a number of lesions in the inner avascular meniscal regions. These have a limited capability of intrinsic repair and predispose the underlying articular cartilages to premature osteoarthritis. A number of strategies have therefore been developed for meniscal repair employing MSCs, bioscaffolds, hydrogels, biological glue cell delivery systems and agents which promote cell proliferation/matrix synthesis. Meniscal implants have also been developed in combination with the above procedures. It is important that meniscal defects be repaired not only to maintain knee-joint stability but also to prevent further degenerative changes in other knee joint tissues. Degenerative menisci contribute degradative proteinases and inflammatory mediators to the total synovial degradative proteinase pool. Partial or total surgical removal of the menisci is not a solution since this leads to premature osteoarthritis. Meniscal integrity needs to be maintained or repair strategies implemented in a timely manner to maintain knee joint function.

Keywords: meniscal repair, mesenchymal stem cell, bioscaffolds, biological glues, meniscal implants/allografts

1. Introduction

1.1 Meniscal structure: function

The knee joint menisci provide joint stability during weight bearing, the curved superior meniscal surfaces provide congruity between the curved femoral condyle and flat tibial articular cartilages [1]. The menisci act as shock absorbers and protect

the weight bearing articular tissues from excessive point loading [2] transferring forces between the femoral and tibial joint surfaces, transmitting 50–90% of the total knee joint load during weight-bearing [3, 4]. The structural organisation of the meniscus is designed to withstand circumferential hoop stresses which are generated within the meniscal tissue to dissipate tensile stresses which are transferred along the circumferential meniscal collagen fibre networks counteracting the tendency of the menisci to be extruded peripherally when the knee joint is subjected to compressive loading [5]. Energy is absorbed into the collagen fibres by the dynamic expulsion of joint fluid from the aggrecan-hyaluronan macro-aggregate networks entrapped within the meniscal collagenous networks. The menisci are fibre reinforced structures stiffening and protecting them from damage by excessive deformation during compressive loading [6] (**Figure 1a** and **b**).

The contribution of intact menisci in knee load-bearing is emphasised from the increase in contact forces in the underlying articular cartilages of up to 350% following partial or total meniscectomy where as little as 16–34% of the intact meniscus may be removed [1, 3, 7]. Radial meniscal tears which extend to its periphery may result in significant contact forces being transmitted to the underlying articular cartilages which can damage these tissues [8].

Water (~70% wet weight) and collagen, (mainly type I, and lower amounts of type II, III and VI collagen constitute 60–70% of the meniscal dry weight) are major meniscal components [9–15]. Proteoglycans (aggrecan, decorin, biglycan, versican, fibromodulin, lumican, keratocan) and elastic microfibrillar glycoproteins are quantitatively minor meniscal extracellular matrix (ECM) components but convey essential functional properties [14–16]. The meniscus is a complex fibre-reinforced structure designed to withstand multidirectional tensional and compressive forces (**Figure 1a** and **b**). The outer third of the meniscus (red zone) is served by a fine capillary network. Defects in this region of the meniscus have the ability to undergo spontaneous repair however the inner two thirds of the meniscus (white zone) is avascular and has a limited ability to undergo repair (**Figure 2a**). The outer zone of the meniscus is a collagen rich fibrocartilaginous tissue while the inner zone contains higher proteoglycan levels and is cartilaginous (**Figure 2b**). Immunolocalisation of perlecan, HSPG2, a large modular HS multifunctional proteoglycan demonstrates a strong localisation pattern in this inner region. Perlecan is marker of chondrogenesis [17–20].

Supraphysiological overload of the menisci may generate defects in the inner meniscus diminishing its weight bearing capability and ability to resist tensional stresses and it becomes less able to dissipate such forces to prevent overloading of the underlying articular cartilage. A number of characteristic tears (bucket-handle, degenerate) occur in the inner meniscal region. Longitudinal and radial tears can also affect the outer meniscus (**Figure 2c**). This can also damage the underlying articular cartilages formerly protected by the menisci leading to degenerative changes and impacting on the knee's ability to act efficiently as an articulating weight bearing structure. Development of premature osteoarthritis (OA) may also result in such circumstances [21, 22]. Menisci in OA knees are also subject to ectopic focal depositions of calcium in cyst like structures (**Figure 2d**). Fibrillation of the inner meniscal region is also a common degenerative feature in OA. Meniscal cell clustering adjacent to such fibrillations is also common and may indicate endogenous adult stem cell activity in response to altered biomechanics/nutrition in this region. Cell clustering has also been observed adjacent to surface fibrillations in OA articular cartilage and adjacent to lesions in the annulus fibrosus of the degenerate intervertebral disc [23–29]. Such cell clustering may be indicative of an incomplete frustrated repair response by resident adult stem cells.

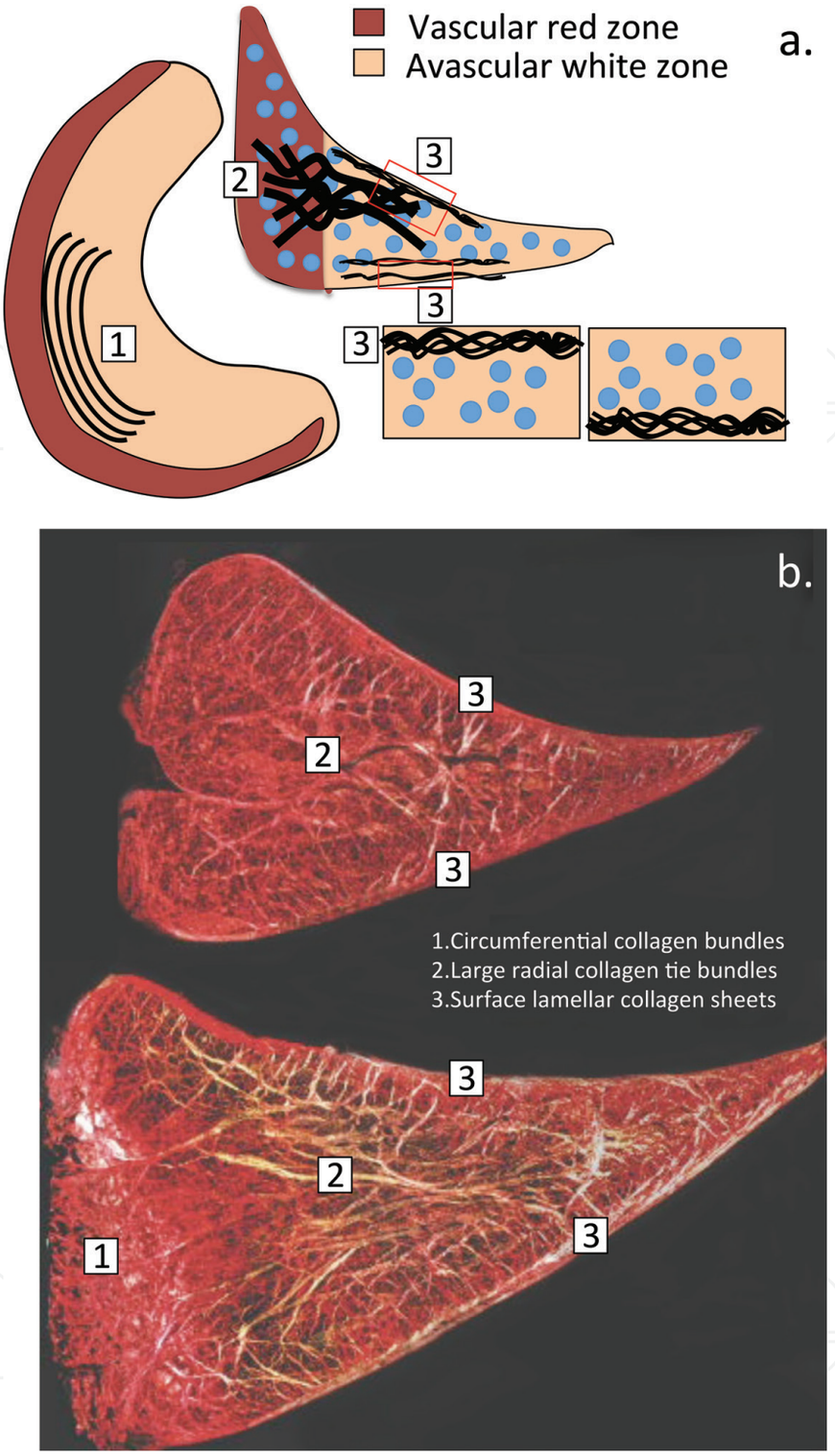

Figure 1.
Diagrammatic representation of the collagenous organisation in a meniscus. (i) The meniscus contains a complex arrangement of radial collagen fibre bundles in the outer meniscus, (ii) thick radial tie bundles internally as well as (iii) finer collagen fibre bundles of collagen in lamellar sheets in the inferior and superior meniscal surfaces. Notice that the inferior lamina is significantly thicker than the superior lamina. Vertical radial sections through 2 year old lateral and medial ovine menisci stained with picrosirius red and viewed under polarised light depicting collagen bundles which are highly refractile due to their ordered collagenous structure appearing as bright rod-like structures (b). Picrosirius red predominantly visualises the major fibrillar meniscal collagen, type I collagen. Methodology for Picrosirius red staining is as described earlier [78].

Many strategies have consequently been developed to effect meniscal repair using a number of cell types including mesenchymal stem cells (MSCs) sourced from a number of tissues (**Table 1**), and combinations of bioscaffolds, hydrogels,

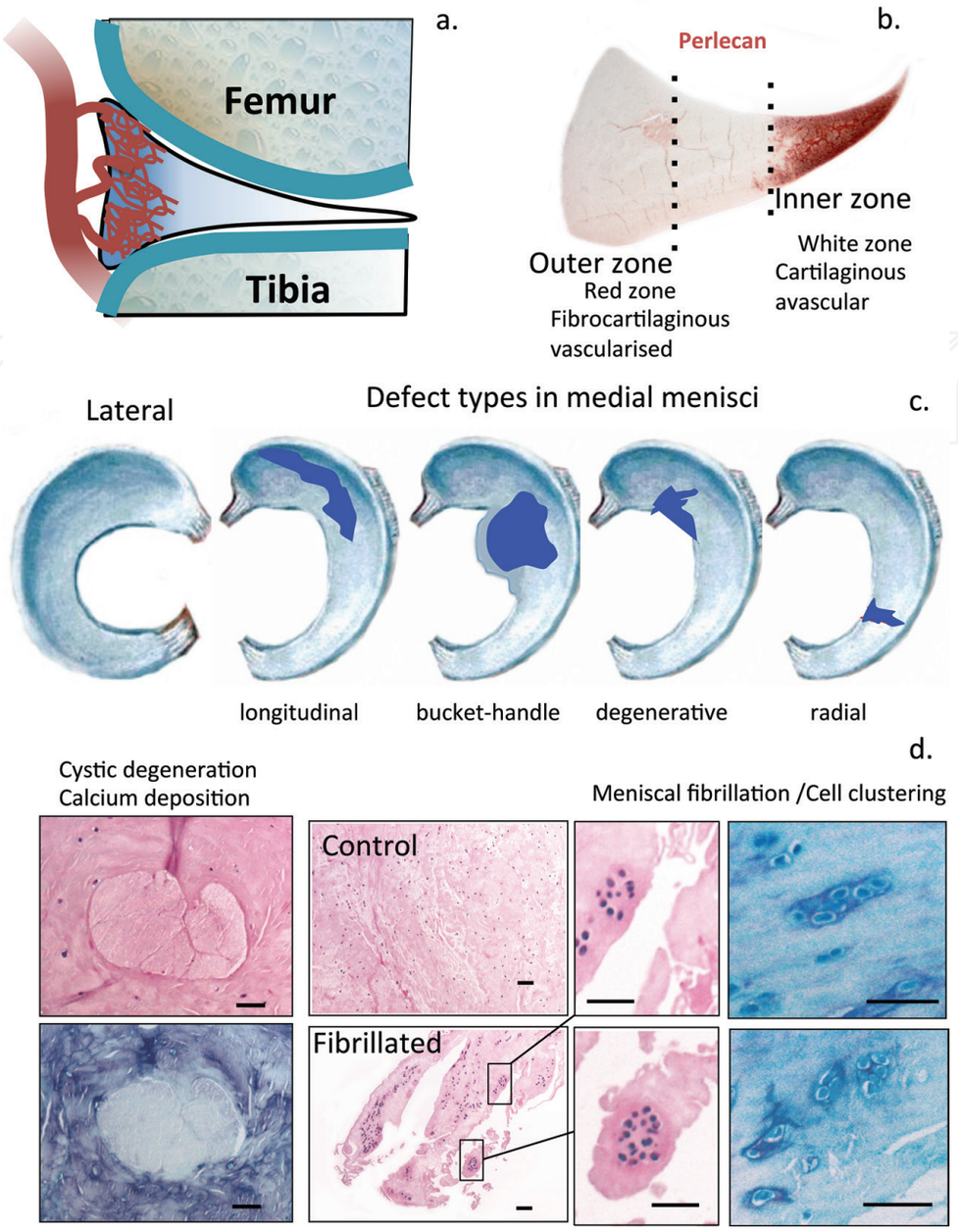

Figure 2.
Structural features evident in the normal and degenerate meniscus. Diagrammatic representation of the vascularisation of a vertically sectioned meniscus showing the extensive capillary network in the outer meniscal red zone and lack of a blood supply to the inner two thirds of the meniscus (a). The inner meniscus is a cartilage like tissue which is well delineated in a newborn meniscus by immunolocalisation of perlecan, HSPG2, a chondrogenic marker proteoglycan (b). Menisci are subject to a number of structural defects which are summarised diagrammatically (c). Histochemical visualisation (H & E) and toluidine blue staining, of some features of degenerate menisci (d). Focal deposition of small calcium deposits in a cyst like formation in the outer meniscus zone in a 53 year old human meniscus. Fibrillation of the inner meniscal zone and cell cluster formation. In the normal meniscus single cells are distributed throughout the meniscus with no clustering.

bioadhesive cell delivery systems and bioactive agents which stimulate the resident and exogenous cells applied for therapeutic purposes (**Tables 2** and **3**).

In-vitro experiments have shown that co-culture of bone marrow derived stromal stem cells with meniscal cells increases cell proliferation and matrix synthesis [30]. Type I and type II collagen and aggrecan mRNA expression were elevated and ECM protein levels increased (**Figure 3a** and **b**). Significantly, meniscal cells stimulated with FGF-2 or FGF-18 in 3D pellet culture also produced elevated levels of these ECM components (**Figure 3c** and **d**). MSCs are believed to act both through transfer of material directly to resident cell populations through cell-cell contact

MSC source	Lesion or study type	References
Intra-articular injection synovial MSCs	Avascular tear	[143]
Rabbit meniscal MSCs	Central meniscal defect	[155]
Synovium derived MSCs	Longitudinal tears and punch holes	[142, 144, 145]
Targeted intra-articularly delivered super-paramagnetic FeO labelled adipose MSCs	Massive lesions encompassing the avascular zone	[146]
Bone marrow, adipose, synovium, meniscus derived MSC delivery to tears in fibrin glue/gel/clot, scaffold	Literature Review of MSCs used in meniscal repair in multiple animal models	[44, 45]
Bone marrow and meniscal derived MSCs	In vitro cell culture	[148]
Blood vessel derived MSCs	Avascular tears	[151]
Bone marrow derived MSCs and fibrin glue	Closure of meniscal tears	[149]
Collagen membrane wrapped meniscal defects injected with MSCs	Tears in avascular zone	[156]
Co-cultured synovial stem cell-meniscal cell cultures	In-vitro demonstration of superior cell proliferation with co-culture compared to monoculture	[43]
Systematic review of the use of MSCs in meniscal repair	Promising results in human meniscal repair	[152]
Comparison of autologous MSCs and meniscal cells for meniscal repair	Rabbit meniscal model punch defect, successful repair of meniscal defects in OARSI grade 3.1 early OA tissues by both cell types	[46–48]
hMSCs delivery in a decellularized ECM to meniscal defects in a nude rat model	Delivery system appropriate for repair purposes	[158]
Review of hMSCs in human meniscal repair	Autologous adipose tissue-derived stem cells or culture-expanded bone marrow-derived stem cells were both suitable for meniscal repair	[153]
Prospective, open-label first-in-human safety clinical trial of hMSCs delivered in collagen scaffold in patients with an avascular meniscal tear	Repair of torn avascular meniscal cartilage by undifferentiated hMSCs harvested from iliac crest bone marrow biopsy. Significant clinical improvement over 2 years, no recurrence of meniscal tears	[157]
3D co-culture meniscal cell: equine MSCs in collagen type I tissue derived small intestinal ECM bioscaffold	Favourable in-vitro results obtained with cells of meniscal cellular morphology attained by MSCs and expression of type I, II collagen	[160]
Allogeneic adipose derived stem cells in scaffold free tissue engineered construct	Rabbit model using 1.5 mm circular defects in anterior horn of medial menisci filled with MSCs in bioscaffold gave positive results	[147]
A review of cell based approaches in meniscal repair	An assessment of mono and co-culture approaches with meniscal cells and MSCs in bioscaffolds and scaffold free approaches	[154]
3D MSC: meniscal fibrochondrocyte co-cultures for meniscal repair	Change in MSC morphology to a fibrochondrocytic phenotype is conducive to meniscal repair	[159]

Table 1.
Mesenchymal stem cell (MSC) sources used in therapeutic approaches for meniscal repair.

Method/polymer	Details of technique	References
Regen Menaflex™ collagen meniscal implant	Resorbable meniscal implant, however the FDA removed approval for device in 2013	[87]
Actifit synthetic meniscal substitute to stabilise knee	Post meniscectomy allogeneic implant with cell infiltration into implant from meniscal wall	[88]
Medial meniscus allograft transplantation (MAT) using a modified bone plug	Meniscal allograft harvested using an arthroscopic bone plug technique	[100]
Anatomically shaped polycarbonate-urethane meniscal implant	Artificial meniscal implant designed for the preservation of articular cartilage	[93]
Polycarbonate-urethane implant	Meniscal replacement	[91]
Thermoplastic polyurethane implant	Meniscal replacement	[98, 219]
Salt modified crosslinked PVA hydrogel meniscus cell implant	Meniscal shaped flexible implants for meniscal replacement	[95]
Polycaprolactone supplemented with slow release microbeads containing CTGF and TGF-β3	3D printed meniscus	[103, 106]
Interpenetrating network gels of poly(2-acrylamido-2-methylpropanesulfonate) and polyacrylamide	3D printed meniscal replacement	[104]

Table 2.
Meniscal allografts and implants used for meniscal repair and replacement.

Scaffolds	Lesion and study type	References
Myoblast loaded PLGA mesh scaffold	Avascular tears	[172]
HYADD4® HA hydrogel cell delivery	Radial-longitudinal tears	[173]
Electro spun type I collagen scaffolds and vascular/avascular region meniscal cells	Avascular meniscal tears	[174]
Radio opaque electro spun scaffold	Meniscal regrowth	[176]
Wrapping of meniscal defects with collagen membrane and injection of MSCs	Tears in avascular zone	[156]
Aligned electro spun nano fibrous scaffold	Radial tear	[178]
Collagen gel scaffold or HA hydrogel delivery of meniscal, synovial and adipose cells	Bucket handle tear	[177]
Type I collagen scaffold/ infrapatellar fat pad	Anterior 2 mm round holes	[179]
Chondrocyte + PLGA mesh scaffold + PRP	Chondrocytes evaluated	[180]
Meniscal cells in fibre reinforced collagen-GAG scaffold + PRP	Gene profiling study	[168]

Scaffolds	Lesion and study type	References
Juvenile meniscus fragments	Avascular tears	[181]
A review of biomaterials used in meniscal repair	An assessment of state of the art materials currently in use in meniscal repair	[197]
Tissue derived ECM scaffolds	Biological scaffolds derived from cell and tissue-derived ECM have shown great promise in tissue engineering maintaining the biological and biomechanical properties, structure, and function of the native meniscus	[198]
A comprehensive review of hydrogels used in meniscal repair	A number of hydrogels exhibiting high water regain provide a 3D microenvironment with variable topographical properties typical of meniscal tissue and useful platforms for cellular colonisation. Controlled delivery of bioactive molecules has been built into the design of some of these scaffolds to enhance repair processes	[200]
Decellularised, micronized ECM scaffolds for improved meniscal repair	Decellularised menisci cryoground into a powder was cytocompatible with meniscal fibrochondrocytes, synoviocytes. Cellular infiltration and proliferation demonstrated the ability of this scaffold to promote cellular survival, migration, and proliferation and meniscal repair	[198]
Rapidly dissociation of autologous meniscal cells enhances their healing properties	Bovine meniscal cells were isolated by rapid dissociation using collagenase and applied in a fibrin gel to a radial meniscal tear. This procedure enhanced the healing properties of the seeded cells inserted into the meniscal defect	[199]
Bioactive supplements added to scaffolds		
Multiple injection of leukoreduced PRP	ACL and meniscal repair	[165]
10% human serum, 5% PRP, 5% autologous plasma	Non-vascular meniscal lesions	[166]
Human chondrocyte-seeded PLGA scaffold + PRP	Testing of biocompatibility of bio scaffold in nude mice	[170, 197]
PRP plasma for anterior cruciate ligament and meniscal repair	A review of clinical and basic science strategies aimed at biological augmentation of the healing response	[120]
Platelet-rich plasma for open meniscal repair in young patients	Effective treatment of horizontal tears extending into the avascular zone	[171]
Platelet-rich fibrin for meniscal repair	PRP-fibrin promotes rabbit meniscus repair by meniscocyte Proliferation, migration, and ECM synthesis	[220]
Fibrin clot augmentation	Fibrin clot augments meniscal repair	[221]
Platelet rich fibrin clot	Repair of horizontal meniscal defects	[222]
Platelet rich plasma for meniscal repair	Prospective, randomized, double-blind, placebo-controlled study evaluating healing of unstable complete vertical bucket handle meniscal healing, of unstable, complete vertical meniscal tears (Bucket Handle)	[169]

Scaffolds	Lesion and study type	References
Administration of an EGF inhibitor in a customised collagen bio scaffold	Meniscal regeneration in a rabbit model	[223]
Administration of Simvastin in meniscal repair	Repair of avascular defects in a rabbit meniscal defect model	[224]
Overexpression of TGF-β via rAAV-mediated gene transfer	Healing of human meniscal lesions	[183]
rAAV overexpression of TGF-β	Complex meniscal tears	[183]
Transduced IGF-1 over-expressing meniscal cells	Avascular tears	[184]
Liposome gene transfer IGF-1 meniscal cells	Avascular tears	[185]
Chondrocyte, VEGF, BMP-7, matrigel, HA cultures	Inner avascular tears	[186]
Intra-articular injection of microRNA-210	Avascular tears	[187]
Fibrin-CTGF stimulates meniscal cell to repair inner zone meniscal defects	Avascular tears	[188]
Serum, HA, TGF-β3 supplemented scaffold directed repair of meniscal tears	Directed repair of meniscal tears	[182]
Non-viral gene transfer to meniscal cells and FGF-2 overexpressing meniscal cells	FGF-2 transduced meniscal cells in alginate beads	[190, 191]
VEGF stimulation of resident meniscal cells	Avascular tears	[194]
TGF-β1 induction of meniscal cell proliferation and migration to a meniscal defect	Micro wound assay system	[195]
OP-1 putty in punch biopsy meniscal holes	2 mm holes—inner meniscus	[196]
Gelatin hydrogel + FGF-2	Horizontal tears	[192]
HA-collagen composite + PRP	2 mm holes, implant	[47, 193]
Type I collagen scaffold and infrapatellar fat pad	Repair of 2mm meniscal defects	[179]
Intra-articular injection of micro RNA 210	Promotes angiogenesis and repair of avascular meniscal defects	[187]
Use of BMP-7 for meniscal repair	healing of circular defects in avascular region by OP-1 putty	[186]
VEGF, BMP-7, Matrigel™, hyaluronic acid, in vitro cultured chondrocytes for meniscal repair	Healing of defects in the inner two thirds of the meniscus	[186]
Electro spun gelatin/poly(lactic acid-co-glycolic acid) bilayered nanofiber scaffolds for meniscal repair	PLGA nanofibre reinforced scaffolds have useful properties and are compatible as a substrate for meniscal repair	[175]

Scaffolds	Lesion and study type	References
HYADD4 based hydrogel for meniscal repair	Intra-articular administration of HYADD4 hydrogel to human knees containing degenerative meniscal tears improved VAS pain clinical indices and improved knee functionality based on WOMAC scores	[173]
Electro spun collagen bio scaffolds for meniscal repair	Electro spun collagen type I scaffolds seeded with human meniscal cells placed in longitudinal avascular meniscal defects stimulated meniscal repair as assessed by histology, immunohistochemistry, mechanical testing, and MRI	[174]
Aligned electro spun nano fibrous scaffolds for meniscal repair	Repair of meniscal radial tears using aligned electro spun Nano fibrous scaffolds seeded with meniscal fibrochondrocytes	[178]
Non-viral gene transfer systems of possible application in meniscal repair	A comparison of 18 non-viral gene transfer systems to identify an efficient transfection system for primary cultures of juvenile and adult human meniscal fibrochondrocytes. Overexpression of FGF-2 following transfection with FGF-2 increased meniscal fibrochondrocyte proliferation but not GAG synthesis	[190, 191]
Bio adhesives		
Pre-treatment of meniscal surfaces with collagenase and TGF-β3 prior to use of bio adhesives for meniscal repair	Enzymatic pre-treatment improves effectiveness of bio adhesives	[225]
Biodegradable hyper-branched adhesives for meniscal repair	Sealing of meniscal tears	[211]
CS-bone marrow tissue adhesive	Novel bone marrow derived CS adhesive suitable for securing repair tissue interfaces	[214]
3D PGA-HA bio scaffold stabilized with fibrin	ECM repair by meniscal cells	[189]
New generation meniscal adhesives	Inner avascular lesions	[211]
Re-attachment of horizontal meniscal tears	Fibrin re-attachment	[215]
Mussel based bio adhesives	bio adhesives containing bactericidal and fundgicidal activity and improved wet strength for reattachment of surgical incisions	[216, 217]

Abbreviations: PRP, platelet rich plasma; rAAV, recombinant Adeno-Associated Virus; PGA, polyglycolic acid; HYADD4®, hyaluronan derivative; PLGA, polylactic-co-glycolic acid, CTGF, connective tissue growth factor; VEGF, vascular endothelial cell growth factor; OP-1, osteogenic protein-1; CS, chondroitin sulphate; FGF-2, fibroblast growth factor-2; TGF-β, transforming growth factor-β.

Table 3.
Meniscal repair using bio scaffolds, bioactive substances and bio adhesives.

and also by secretion of trophic factors which both stimulate tissue regenerative processes [31–42]. Co-cultures of synovial stem cells [43] and MSCs [44–48] with meniscal cells have been evaluated in a number of biomatrices for meniscal repair purposes (**Table 1**).

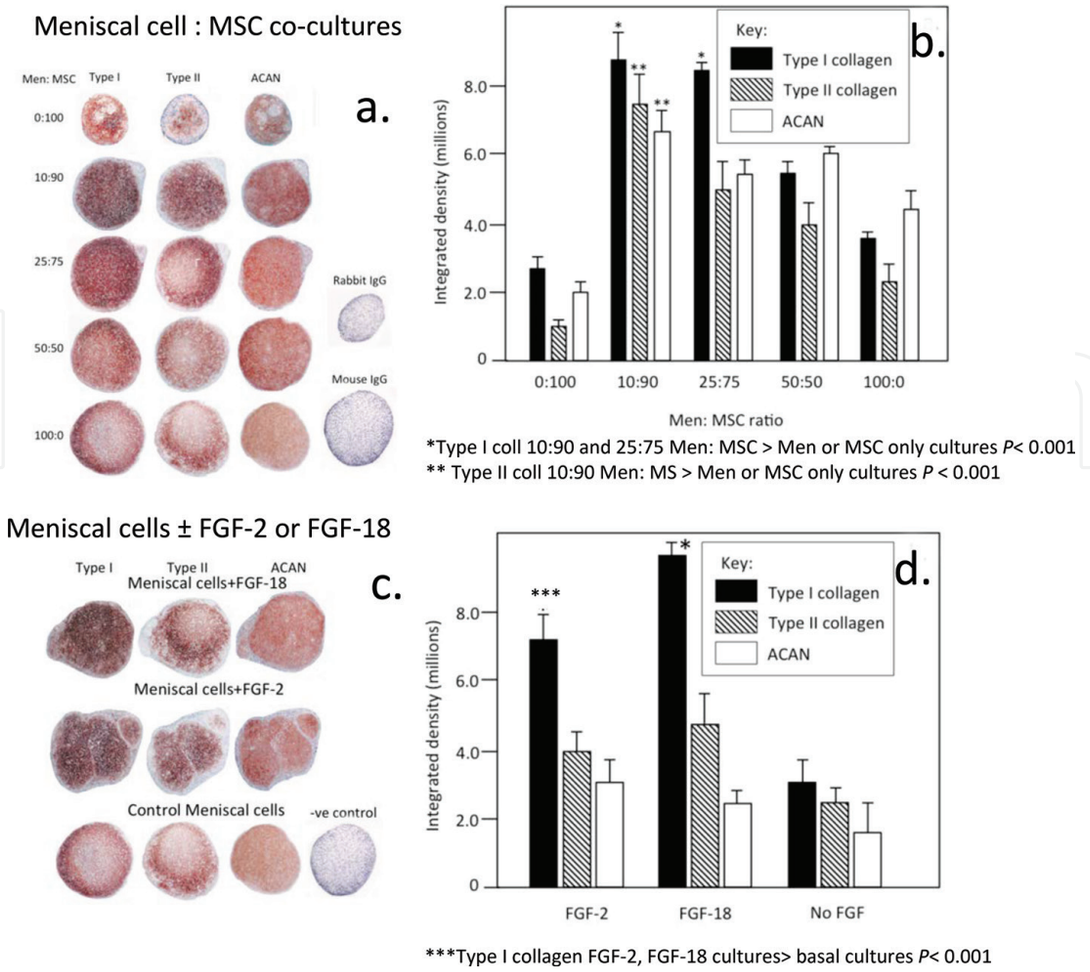

Figure 3.
Co-culture of meniscal cells and bone marrow derived mesenchymal stromal cells induces cell proliferation and ECM production and is recapitulated to some degree by treatment of meniscal cells with FGF-2 and FGF-18. Immunolocalisation of meniscal matrix components in micro-mass pellet culture. Immunolocalisation of type I collagen, type II collagen and aggrecan (ACAN) in meniscal-MSC micro-mass pellet co-cultures (a). Negative controls of pellets using rabbit IgG (MSC pellet) and mouse IgG (meniscal cell pellet) for immunolocalisation in the absence of primary antibody. Anti-type I collagen (clone I-8H5) and anti-type II collagen (clone II-4CII) were from MP Biomedicals, Ohio, USA. A rabbit polyclonal antibody (pAb) # 2194 to aggrecan G1 domain was a gift from Dr. J Mort Joint Diseases laboratory, Shriners, Hospital for Children, McGill University, Montreal, QC, Canada [218]. PAb 2194 was raised against a mixture of four aggrecan specific G1 peptide-ovalbumin conjugates including HDNSLSVSIPQPSGGC, RVLLGTSLTIPCYFIDPMHPVTTAPS, TEGRVRVNSAYQDKGGC and SSRYDAICYTG (single letter amino acid code). Morphometric image analysis of meniscal matrix components produced in pellet culture. Quantitation of type I and type II collagen and aggrecan immunolocalisation levels in meniscal: MSC co-cultures using Adobe Photoshop CS4 morphometric image analysis software as integrated pixel density. Mean values ± SD for 3 pellet sections is shown (b). Immunolocalisation of matrix components produced by meniscal cells in pellet cultures stimulated with FGF-2 and FGF-18. Immunolocalisation of Type I and Type II collagen and aggrecan (ACAN) in meniscal cell micromass pellet cultures stimulated with FGF-2 and FGF-18 (a–c) for 21 days (c). Morphometric image analysis of meniscal matrix components using Adobe Photoshop CS4 morphometric image analysis software (d).

2. Meniscus preserving therapies

2.1 Why it is important to preserve the knee joint meniscus? A historical perspective

The meniscus was historically considered a vestigial muscle remnant and little importance was attributed to this structure for knee joint function. Consequently, radical surgery and total removal of the meniscus were common surgical practice in the 1980s with serious long-term consequences for the meniscectomised knee. It should have been obvious from meniscectomy studies used to induce OA

experimentally in animals that surgical removal of the menisci from knee joints was not a benign procedure [49–74]. However it took time for these animal findings to be translated to human studies [59–61, 65, 67, 70, 72] and for these experimental findings to be fed through to human clinical practice and the importance of the meniscus in entirety in knee joint articulation, weight bearing and load distribution became established. Even so, publications were still appearing as late as 2016 emphasising the importance of the preservation of the knee joint menisci to ensure optimal knee joint function three decades after meniscal removal had been shown to induce degenerative changes in other knee joint tissues [75].

Currently, the consensus in the surgical treatment of meniscal tears is to preserve as much functional meniscal tissue as possible to preserve knee joint function [76].

The menisci play critical protective roles for the knee joint articular cartilages through shock absorption and load distribution and also have important roles to play in proprioception and balance [5]. The ESSKA (European Society for Sports Traumatology, Knee Surgery and Arthroscopy) MENISCUS CONSENSUS INITIATIVE was initiated in 2014 to find a European consensus on the treatment of meniscus pathologies [76].

Further studies in animals [73, 77–79] established a more direct contribution from meniscal degeneration to joint structures globally during degenerative conditions such as OA and RA. During the development of arthritic conditions in animals [73, 77, 79] and humans [80] tissue proteoglycans become fragmented through proteolytic degradation and this reduces the weight bearing and articulatory properties of the articular cartilages and menisci and may even impact on subchondral bone [80]. Matrix metalloproteases (MMPs), ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs)-4 and ADAMTS-5 produced by articular chondrocytes have a major impact on aggrecan and other cartilage proteoglycans reducing the weight bearing properties of the knee joint articular cartilages. The increase in synovial degradative protease pool during OA and RA was previously attributed to the articular chondrocytes which respond to inflammatory cytokines in the arthritic joint by producing these degradative proteases. Recent in-vitro studies have however now shown that meniscal fibrochondrocytes also potently respond to interleukin-1 and tumour necrosis factor-α by producing significant levels of MMPs (MMP-1, 2, 3, 9, 13), ADAMTS-4 and ADAMTS-5 and are a major cellular source of these components in the total global degradative enzyme pool present in synovial fluid [81–83]. Meniscal cells actually produce higher levels of these degradative components than articular chondrocytes, thus represent a previously unidentified therapeutic target in the treatment of OA and RA.

2.2 Meniscal implants

Partial or total meniscal replacement by collagen or synthetic allografts following meniscectomy have yielded mixed results (**Table 2**) [84, 85]. Implants fall into two categories, (i) porous, resorbable implants which stimulate tissue regeneration and (ii) solid, non-resorbable implants which physically replace the meniscus [86]. The Regen Menaflex™ collagen total meniscal implant (CMI®, Ivy Sports Medicine) is a resorbable implant. A review of the CMI® by Hansen et al. in a 10 year follow up confirmed good clinical outcomes, solid integration of the CMI® with host tissue and it was concluded that the CMI® held promise for meniscal repair [87]. After a protracted series of re-reviews of experimental data, technical issues and protocols the FDA rescinded approval for the Menaflex® device in 2013. The Actifit® polymeric polyurethane partial implant (ORTEQ Sports Medicine) is a honeycomb scaffold that enables blood-flow through it providing a route for cellular in-growth as the body's natural healing process takes place. Once the damaged section of the

meniscus surgically removed the implant is attached to an area of the remaining meniscus with a good blood supply [86]. This has improved knee joint function and reduced knee pain in patients for up to 5 years after implantation and a stable cartilage profile was achieved in 46.7% of patients but a relatively high failure rate was also reported [88–90].

An artificial Polycarbonate-urethane implant has been developed for replacement of the medial meniscus [91–93]. NUsurface® have developed a polyethylene reinforced polycarbonate urethane total meniscal implant, approved for use in Europe since 2008 and in Israel since 2011 [94]. The safety and long-term performance of the NUsurface implant is currently under evaluation in SUN (Safety Using NUsurface®) and VENUS (Verifying the Effectiveness of the NUsurface® System) clinical trials in the USA.

Salt modified cross-linked PVA based hydrogels seeded with meniscal cells have been evaluated for meniscal repair [95] as have polyglycolic acid implants seeded with chondrocytes [96] and (poly-(3-hydroxybutyrate-co-3-hydroxyvalerate) meniscal implants seeded with fibrochondrocytes [97].

Biodegradable thermoplastic polyurethane Estane® polymer (Lubrizol Corp, USA) porous implants have been evaluated in dogs as a meniscal replacement [98]. Colonisation of the implant by resident meniscal synovial cells from the peripheral attachments, laying down of matrix components within the implant and the biointegration of the implant to the peripheral meniscal attachment tissues were evaluated 3–6 month post implantation. This demonstrated that the implant filled completely with meniscal tissue as demonstrated by toluidine blue staining for proteoglycan, and for type II collagen and I by immunolocalisations using specific collagen antibodies. Histological evaluation of the tibia and femoral articular cartilages confirmed these tissues did not degenerate in the experimental period employed for this study.

A number of critical reviews on the performance of meniscal implants [86, 87, 99–101] generally acknowledge that despite initial promising findings long-term and randomised controlled studies still need to be undertaken to confirm implant performance and reliability for meniscal repair and that the development of a meniscal replacement tissue of comparable performance to native tissue has yet to be achieved.

2.3 3D printing of knee joint menisci

Polycaprolactone has been used as a scaffolding material to form an exact meniscal replica using a 3D printer [102–105]. MRI scans of the meniscus are converted into a 3D image, data from this image is then used to drive a 3D printer, which produces a scaffold in the exact shape of the meniscus, down to a resolution of 10 μm. Differential release of CTGF and TGF-β3 to drive formation initially of the outer collagenous meniscal region then the more cartilaginous inner meniscus is achieved by slow release microspheres containing CTGF and TGF-β3 in the printed meniscus. These attract meniscal progenitor cells into the scaffold which lay down tissue gradients to form the collagenous outer and cartilaginous inner regions of the meniscus. In sheep this takes between 4 and 6 weeks to achieve meniscal replacement and the scaffolding material then slowly redissolves to be eliminated by normal resorptive processes.

Interpenetrating networks of poly(2-acrylamido-2-methylpropanesulfonate) and polyacrylamide can be prepared by varying the ratio of polyacrylamide to cross-linker, to yield a gel with compression strength and elastic modulus of 61.9 and 0.44 MPa. This gel has maximum compressive and tensile strengths of 93.5 and 1.4 MPa respectively. This can be used in a 3D printer to prepare replacement

menisci from a patients X-ray computed tomography image of a meniscus [104]. Slow release of CTGF and TGF-β3 from a 3D printed meniscus stimulated endogenous stem/progenitor cells to undertake meniscal regeneration [106].

3. Meniscus regenerative therapies

3.1 Therapeutic use of mesenchymal stem cells in tissue repair

Mesenchymal stem cells (MSCs) have been the subject of intense investigation since their discovery in the 1960s due to their remarkable efficacy in tissue repair. MSCs were originally considered to migrate into sites of injury, where they engrafted, and differentiated into functional cells, resulting in regeneration of damaged or diseased connective tissue [107]. Findings from several hundred animal studies and many human clinical trials have challenged this mode of action. MSCs certainly exhibit a remarkable ability to repair diseased tissues, but it has become increasingly apparent that they do not engraft in enough numbers or for sufficient durations in tissue defects to provide tissue repair and clinical benefit directly. Additional modes of action for MSCs have therefore been proposed based on their ability to enhance resident cell viability and/or proliferation, reduce cell apoptosis [108, 109], and, in some cases, modulate immune responses [110–114]. These are due to paracrine effects due to secreted growth factors, cytokines, and hormones by the MSCs and cell-cell interactions mediated through communicating nanotubes, which convey extracellular vesicles containing reparative peptides/proteins, mRNA, and microRNAs [107]. Caplan (2017) has proposed that stem cells should be renamed *Medicinal Signalling Cells* to more accurately reflect how they home in on injured or diseased tissue sites secreting bioactive factors with immunomodulatory and trophic properties which direct the resident cells to undertake the tissue repair process, this may happen long after the MSCs have disappeared from the defect site [115].

MSCs have gained popularity for tissue repair with good reason [32, 116], and several applications have been developed for their use in the repair of connective tissues including the meniscus [117–125].

3.1.1 How do MSCs effect tissue repair?

Despite their widespread use in therapeutic applications the precise mode of action of MSCs remains elusive [126–130]. MSCs undergo engraftment in a defect site and differentiate to an appropriate cell lineage conducive to tissue repair [131] where they act as in-situ reservoirs of trophic factors [132] which direct resident cell populations to effect tissue repair [33, 40, 133–135]. It is un-resolved whether cell-cell contact is essential for MSC action in tissue repair [33, 117, 131]. The pluripotency of MSCs facilitates the differentiation of the engrafted cells to effect tissue repair [33, 133]. However, some evidence shows that only a small proportion of the MSCs actually integrate and survive in the host tissues and the predominant mechanism by which MSCs participate in tissue repair appears to reside in their paracrine activity through the production of a multitude of growth factors and cytokines [33, 132]. Lipid micro vesicles released by MSCs have also been shown to be an important means of cellular communication and occurs alongside the mediators secreted by the MSCs. Nano vesicles/exosomes transfer proteins, lipids and small RNAs to neighbouring cells, and through these mediate a variety of biological responses in addition to those mediated by soluble trophic factors supplied by the MSCs [35, 136, 137].

3.2 Use of MSCs and chondrocytes for meniscal repair

The use of meniscal, chondrocytes or MSCs [138] in tissue engineering [139] using synthetic and biological scaffolds [101] containing bioactive factors [140] hold promise in the repair of the meniscus. Direct intra-synovial injections of MSCs have also been employed and meniscal regeneration and resolution of pain recorded [135, 141]. MSCs sourced from a number of tissues including synovial tissues [142–145], adipose [146, 147], bone marrow [45, 148–150] and blood vessels [151] have been applied in a number of applications to promote meniscal repair [44–48, 152–158] (**Table 1**). Co-cultures of meniscal cells and MSCs have also been examined in meniscal repair strategies [43, 159, 160]. Furthermore, a diverse range of bio scaffolds have been developed containing CS have been developed to promote MSC differentiation in-vivo for varied applications in repair biology [161] (**Table 3**). These scaffolds are also appropriate for strategies aimed at meniscal repair but have yet to be applied in this area.

3.3 Co-culture of MSCs/meniscal cells and in-vitro stimulation with FGF-2/FGF-18

MSCs hold tremendous promise in regenerative medicine however their mode of action remains to be precisely established. Direct cell-cell transfer of stem cell material to resident cells has been shown to promote tissue repair processes, while soluble trophic factors secreted by the stem cells can also stimulate repair. In order to examine these possibilities further in the meniscus, bone marrow MSCs and meniscal cells have been co-cultured in micro-mass pellet cultures (**Figure 3a** and **b**). The influence of FGF-2 and FGF-18 on meniscal pellet cultures have also been assessed to mimic the action of soluble trophic factors (**Figure 3c** and **d**). Immunolocalisation of the extracellular matrix (ECM) components type I and II collagen and aggrecan (ACAN) have been used to assess the response of the meniscal cells to these treatments. Meniscal cell proliferation is significantly elevated by MSC co-culture, and deposition of type I collagen and type II collagen and ACAN elevated. FGF-2 and FGF-18 also increase these ECM components in pellet culture. Cross-talk between meniscal cells and MSCs (and FGF-2 and FGF-18 to a lesser extent) thus positively influence cell proliferation and matrix production conducive to tissue replenishment and repair which would be expected to be re-capitulated in-vivo upon administration of stem cells to meniscal defects. Thus direct cell-cell contact and soluble trophic factors both stimulate meniscal repair processes.

3.4 Bioscaffolds, bioactive substances and bioadhesives and meniscal repair

The outer and inner meniscus have widely differing repair capability correlating with their relative blood supply [162, 163] (**Figure 1a**). The inner meniscus has the poorest blood supply and consequently the weakest repair response. Many strategies have focussed on the development of measures to improve repair of the inner meniscus and they fall into three broad categories: (i) mesenchymal stem cells administered by direct intra-articular injection; (ii) bioscaffold, hydrogel or bioadhesive cell delivery vehicles for the delivery of chondrocytes, meniscal cells or MSCs into meniscal defects; and (iii) meniscal implants and allografts for total or partial meniscal replacement. These procedures are often undertaken with bioactive substances in the scaffold, hydrogel or bioadhesive delivery system which stimulate repair processes in therapeutic and resident cell populations (**Table 3**). An alternative approach is the co-culture of MSCs with chondrocytes or meniscal cells to pre-condition these or expand cell numbers prior to their incorporation

into bioscaffolds, hydrogels or bioadhesives prior to administration to the meniscal defect [159, 164] (**Figure 3a** and **b**). Platelet rich plasma or platelet rich fibrin clots have been used to enhance meniscal repair in bioscaffolds [120, 165–171].

Myoblast loaded PLGA scaffolds have been evaluated for the repair of inner meniscal defects [172]. A derivatised HA, HYADD4® hydrogel cell delivery system has been used for the repair of radial-longitudinal tears in a randomised controlled study [173]. Electrospun type I collagen and gelatin-PLGA bilayered nanofibre reinforced scaffolds seeded with meniscal cells isolated from outer and inner regions have been used in the repair of lesions in the inner meniscus [174, 175] and radio-opaque collagen scaffolds have been used in order to observe the action of therapeutic cells including MSCs on meniscal repair [176]. Meniscal defects wrapped in collagen membranes prior to injection of autologous chondrocytes for repair have been evaluated for the repair of the avascular meniscus [156]. Collagen gel scaffolds containing meniscal, synovial and adipose stem cells have been employed for meniscal repair [177] or in electrospun nanofibrous scaffolds [178]. The use of a type I collagen scaffold and infrapatellar fat pad for meniscal repair has been evaluated in rabbits [179]. PLGA mesh and fibre reinforced collagen-GAG scaffolds seeded with chondrocytes [180] or meniscal cells [168] supplemented with PRP have been evaluated for meniscal repair. Minced juvenile menisci sandwiched with meniscal explants from inner meniscal regions have been evaluated for their reparative potential on tears of the inner meniscal regions [181]. A number of bioactive factors have been evaluated for their reparative properties on meniscal defects. These include multiple injections of leuko-reduced PRP [165], 10% human serum, 5% PRP, 5% autologous plasma [182]. Over expression of TGF-β induced by a rAAV vector, stimulated matrix production and cell proliferation in human meniscal explants consistent with active repair [183]. IGF-I over-expressing meniscal cells induced by transfection of the hIGF-I gene [184] or by liposome Fugene 6 transfer of hIGF-I, stimulated ECM production, proliferation and differentiation of cultured meniscal cells and explants from the inner meniscus [185]. VEGF, BMP-7 and HA stimulated chondrocytes have been implanted into meniscal defects to undertake repair in-vitro [186]. Intra-articular injection of microRNA 210 stimulated mitochondrial activity and angiogenesis promoting repair of avascular meniscal defects by upregulation of anabolic matrix genes by resident meniscal cells, VEGF and FGF-2 production [187]. Fibrin-CTGF administration into avascular defects stimulated repair by the resident meniscal cells [188] as did HA, TGF-β3, platelet concentrates and serum supplemented scaffolds [166, 182, 189]. FGF-2 over-expressing meniscal cells [190, 191] and gelatin-FGF-2 scaffolds [192] also stimulated repair of inner meniscal defects. HA-collagen-PRP composites [47, 193], VEGF [194], TGF-β1 [195] and OP-1 [196] also stimulated meniscal cells and MSCs to undertake repair of inner meniscal defects or punch biopsy wounds in menisci. The bioscaffolds used in meniscal repair or regenerative strategies have been extensively reviewed [197–200].

3.5 Bioadhesives and meniscal repair

First generation fibrin sealant/glue formulations (Tisseel® (Baxter International Inc.), Tissucol® (Baxter Healthcare SA), Beriplast® (CSL Behring GmbH), Hemaseel® (Haemacure Corp)) were originally based on bovine fibrinogen, thrombin and aprotinin isolated from pooled bovine donors. With the discovery of bovine spongiform encephalitis and the technical difficulty of removing prions from bovine protein products, second generation fibrin glues were developed using human proteins and in-house methodologies for the isolation of autologous platelet plasma. Vitagel® (Orthovita Inc.)/Costasis® (Angiotech Pharmaceuticals Inc.) is a fibrin sealant variant containing bovine collagen and thrombin and human

plasma. To minimise transmission of viral components, second generation fibrin sealants/glues utilise heat-treated human fibrinogen, autologous platelet plasma and virally incapacitated human thrombin. Autologous fibrin sealants based on platelet rich plasma (PRP), or platelet poor plasma (PPP) with added calcium and thrombin, produce a platelet gel which promotes haemostasis and wound healing aided by the release of platelet growth factors (especially TGF-β1 and TGF-β2) and cytokines. Autologous fibrin sealants suffer inconsistency due to variation in patient plasma protein profiles. Commercial FDA approved second generation fibrin sealants such as Quixil® (OMRIX Biopharmaceuticals SA)/Crosseal™ (OMRIX Biopharmaceuticals) have controlled levels of fibrinogen and thrombin with aprotinin replaced by the anti-fibrinolytic, tranexamic acid. Concerns over the use of tranexamic acid subsequently led to it being dropped from the formulation in the product Evicel® (Ethicon HCP). Formulations of fibrin sealants/glues have been developed as aerosol administered foams and collagen films based on equine collagen and combinations of animal (Tachocomb® (Baxter Healthcare Corp)) and human fibrinogen/thrombin (Tachocomb H®, TachoSil® (Baxter Healthcare Corp)). While fibrin sealants/glues were originally developed to minimise surgical blood loss and to aid in wound repair they have now been applied as autologous cell delivery vehicles for osteochondral repair in autologous chondrocyte implantation (ACI) whereby chondrocyte numbers are expanded in-vitro then loaded into cartilage defects and are contained within this site using a periosteal or collagen membrane sutured over the defect site and sealed along its margins using fibrin sealants/glues. This technique was subsequently modified using the matrix assisted chondrocyte implantation (MACI) procedure where chondrocytes seeded into a matrix material were placed into the chondral defect and sealed in place with fibrin sealant/glue obviating the use of sutures. A modification of this procedure (fibrin ACI) where fibrin sealants were used as scaffolds for cell delivery has also been developed. The fibrin ACI methodology has been applied to the repair of meniscal tears [201–203] using a number of bioactive supplements to improve cell proliferation and matrix synthesis to promote meniscal repair.

An interesting novel bio-glue has been discovered in the Australian frog genus *Notaden bennetti*. During the mating season the female frog expresses an adhesive exudate from the dorsal skin which ensures sexual union with the male for an extended period to ensure effective fertilisation. This exudate has been harvested from frog skin by electro-stimulation and characterised. Examination of the toxicity and biocompatibility of this biological glue [204], its molecular composition and mechanism of action [205] has shown that this protein based adhesive [206] is non-immunogenic, biocompatible, displays elastomeric properties similar to elastin and the strength of its adhesive properties is several fold that of fibrin glue. This frog glue has been used in combination with suturing of infraspinatus tendon to the bone interface in rotator cuff operations and significantly increased the strength of these attachments [207]. The frog glue also outperformed fibrin glue for the re-attachment of the cut surfaces of a longitudinal bucket handle meniscal tear in an in-vitro comparison [208, 209]. Marine sources of biological glues from the New Zealand green lipped mussel and barnacle are known and have appropriate strong adhesive properties for orthopaedic applications, these await commercialisation [210–213].

CS-bone marrow tissue adhesive [214], fibrin stabilised PGA scaffolds [189] have both found application in meniscal repair. New generation bio-glues has been used as cell delivery vehicles and as bioadhesives in meniscal repair [210, 211] and in the re-attachment of horizontal meniscal defects [215]. Mussel based bioadhesives containing antibiotics and fungicides with improved wet strength properties for use in the closure of surgical incisions have even been developed [216, 217].

4. Conclusions

i. Direct MSC-meniscal cell contact and soluble trophic factors both stimulate meniscal repair processes by the resident meniscal cell populations.

ii. The bioscaffolds, hydrogel and bioadhesive cell delivery described in this review provide not only protective matrices for MSC and other administered cells but provide a matrix for attachment of migrating cells at the defect site and physical stabilisation of the defect site to prevent further damage while the repair process ensues. MSCs have impressive therapeutic credentials.

iii. Bioscaffolds and cell delivery systems have undergone significant advances in the last few years facilitating the localisation of MSCs in tissues for reparative purposes, and hold considerable therapeutic promise in the treatment of problematic lesions in the inner meniscus zone.

iv. Many biomaterials have been examined in the quest for potential meniscal implants but none have displayed as efficient properties as the native menisci of the human knee.

v. Clinical trials of partial/total replacement menisci are enrolled and their results are eagerly awaited. Despite promising results, scaffold and implant properties still need optimisation.

vi. Advanced degeneration of menisci and mechanical damage result in a significant loss of meniscal tissue and there is a clear need for a replacement material either for a portion of the meniscus or the meniscus in entirety.

vii. Significant in-roads have been made in the development of new biopolymers for use in 3D printing and slow release biofactors which direct meniscal regeneration.

viii. Developments in bioadhesive design offers improved adhesive properties for surgical applications. These can also be used as cell delivery vehicles to promote meniscal regeneration.

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