SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Current advances in the development of meniscus tissue engineering: narrative review

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ABSTRACT

Introduction: The meniscus plays an important role in maintaining homeostasis to facilitate the normal function of the knee joint. It is one of the most commonly injured areas of the knee joint. Meniscal-related injuries can lead to significantly decreased athletic ability, and their incidence has increased yearly. It has been found that most meniscal injuries are irreparable, and meniscectomy can increase the predisposition to knee osteoarthritis. Tissue engineering technology on meniscus repairing and transplantation has received widespread attention recently. This review aimed to analyse the scientific literature regarding the potential applications of tissue engineering on meniscus repairing and transplantation procedures.

Method and Materials: The electronic search was carried out using PubMed/MEDLINE®databases with the keywords "tissue engineering AND meniscus" spanning the period of publications from Jan 1980 until Dec 2022.

Results: The literature search identified 405 references in PubMed/MEDLINE, and 179 were selected following the eligibility requirements. The research analysis showed that the existing meniscal tissue engineering studies used a wide variety of seed cells, cytokines, bioactive materials and 3D structures. Each showed distinct advantages and disadvantages in terms of biocompatibility, degradability, mechanical strength, porosity, and etc. It was noted that 3D printing technology is promising for tissue engineering meniscus research. In addition, the optimal use of compression and hydrostatic pressure to markedly improve the functional properties of tissue-engineering meniscal can serve as an useful strategy.

Conclusion: This review analysed the different approaches employed for meniscus tissue engineering and regeneration. Meniscal tissue engineering still faces several major challenges in terms of seed cells, choice of materials and 3D printing strategies, which should be effectively overcome to harness the full potential of this technology.

KEYWORDS:
Stem cells; biomaterials; tissue engineering; meniscus

INTRODUCTION

The meniscus is a critical component of the knee joint that absorbs oscillation. It conducts load and increases the stability of the knee joint, in addition to lubricating the joint and preventing degeneration of the articular cartilage, which is of considerable importance in ensuring the normal function of the knee joint.[1] The principal components of the meniscus are water (72%), collagen (22%) collagen and glycosaminoglycans (GAGs) (0.8%). The fibres and fascicles in the meniscus are distributed in various arrangements, depending on the location of the tissue.[2] The inner component of the meniscus is composed of small and irregular radial collagen fibrils with a structure similar to that of hyaline cartilage.[3] Conversely, the outer region is composed of organised interweaved collagen fibrils, fibres and fascicles with a circumferential orientation.[3]

The ability of the meniscus to regenerate following an injury is minimal due to the nature of the blood supply. Clinical management depends on multiple factors, especially age, concurrent chondral injury and the time between injury and surgery.[4] Surgical treatment options include meniscal sutures, partial or complete meniscectomy and meniscal allograft transplantation. Meniscectomy and debridement are more traditional, earlier and widely used interventions. However, this induces functional loss after resection and abnormal weight distribution, causing patients to suffer from osteoarthritis (OA) at an early age.[4] Meniscal allograft transplantation of the damaged meniscus has been reasonably successful and has proven safe. However, the poor durability of allografts gives rise to a high reoperation rate.[5] Hence, using biomaterial scaffold meniscus may be advantageous compared to meniscal allograft transplantation.

However, progress in strategies to replace the function of this structure has lagged behind other tissue engineering endeavours.[6] Notably, the principal problems in meniscus

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tissue engineering include the complexity of the three-dimensional (3D) structure with individualised size characteristics, the high compressive and tensile requirements and the inadequacy of the blood supply. There is emerging evidence of the capability and efficacy of tissue engineering, especially with the use of stem cell technology and different clinical adjuvants, e.g., cytokines and newer biomaterials, that will be outlined in this review.

MATERIALS AND METHODS

The electronic search was carried out using PubMed/MEDLINE®databases with the keywords "tissue engineering AND meniscus" spanning the period of publications from Jan 1980 until Dec 2022.

RESULTS

The literature search identified 405 references in PubMed/MEDLINE, and 179 were selected following the eligibility requirements. The research analysis showed that the existing meniscal tissue engineering studies used a wide variety of seed cells, cytokines, bioactive materials and 3D structures. Each showed distinct advantages and disadvantages in terms of biocompatibility, degradability, mechanical strength, porosity, and etc. It was noted that 3D printing technology is promising for tissue engineering meniscus research. In addition, the optimal use of compression and hydrostatic pressure to markedly improve the functional properties of tissue engineering meniscal can serve as a useful strategy.

The traditional aim of meniscus healing is the preservation and repair of the original meniscus as far as possible. With the advent of novel technologies and materials, researchers have utilised tissue engineering techniques to repair an injured meniscus or even reconstruct the entire meniscus, providing alternatives for patients who require the removal of the whole meniscus. Seed cells, scaffold materials and growth factors are the three essential factors in tissue engineering.[7]

Seed Cells for Meniscus Tissue Engineering

The ideal seed cells should be available from abundant sources, be easy to harvest, proliferate and induce to undergo differentiation, secrete sufficient extracellular matrix (ECM) and have a stable phenotype. The development of stem cell therapies has provided a novel direction for meniscal injury repair because they display all these characteristics.[3,7]

The meniscus has variations in fibre anisotropy, regionally different cells and various ECM components.[1,3] Meniscal cells are broadly classified into three varieties, including fibroblast-like cells, superficial zone cells and meniscus fibrochondrocytes (MFCs) (Figure 1).[8] Fibroblast-like cells, principally located in the most lateral 1/3 of the meniscus, exhibit elongated cellular morphological characteristics and are encapsulated in a fibre network composed of collagen type I (COL I).[9] Superficial zone cells are characterised as $CD34^{+}$, $CD31^{-}$ and SMA^{+} and are located in the superficial surface of the meniscus, displaying a flattened, fusiform morphology without cell extensions. Several reports suggested that the superficial zone cells are potential progenitor cells with therapeutic and regenerative properties.[1,3,7] However, no studies have been published on the application of meniscus surface cells for stem cell therapy or meniscal tissue engineering. MFCs predominantly located in the 2/3 of the most medial meniscus. They are morphologically round and often surrounded by a network of fibres woven by COL I and COL II (at a ratio of 2:3).[1,9] As self-seeded cells repair meniscal injuries, MFCs can be obtained through minimally invasive surgery through rapid expansion *in vitro*, generating a fibrocartilagenous matrix. Typically, the most common source of MFCs is a badly injured meniscus or the lateral side of a meniscus, in numbers that can satisfy the needs of the majority of patients after propagation. However, propagated MFCs always display dedifferentiation, and the capacity to generate cartilaginous ECM decreases with age.[1,9] The addition of fibroblast growth factor (FGF) could potentially solve this problem by inhibiting cellular dedifferentiation and promoting the secretion of the ECM.[2]

BMSCs（Bone marrow mesenchymal stem cells）possess the potential to differentiate into osteoblasts and chondrocytes and have high expansion capability *in vitro* with low immunogenicity. Therefore, BMSCs have commonly been used as seed cells in meniscal tissue engineering research.[10,11] In a study with scaffolds fabricated with collagen type I that compared the potential to engineer meniscus-like tissue using BMSCs and MFCs, the BMSCs expressed higher levels of COL2A1, ACAN, COL10A1 and GAG content than MFCs.[10] BMSCs may directly participate in tissue repair or indirectly induce the repair response in the host via the paracrine pathway.[11] BMSCs injection also showed graft versus host disease inhibition because of the significant effect of modulating the immune response and reduced impediment to immune rejection of allografts.[12] BMSCs injection also enhanced the prognosis of meniscal allograft transplantation. Struijk et al.[13] injected doses of BMSCs (>0.1 million) in meniscus allograft tissue, and the results showed prominent cell proliferation and migration in 14 days and ideal cell survival in 28 days. Attachment of BMSC to the scaffold material facilitates the fixation of BMSC at the site of the meniscus injury and results in a better repair. Whitehouse et al.[14] implanted autologous bone marrow MSCs (Mesenchymal Stem Cells) seeded into collagen-coated scaffolds into non-vascular meniscal injuries in a clinical trial of five patients. After 24 months of follow-up, the symptoms of injury in those patients were significantly improved. Symptoms were entirely relieved in three patients, while the symptoms did not improve in the other two patients 15 months after transplantation, who required meniscal resection. No adverse reaction was observed in these patients, confirming the potential of BMSCs to repair meniscal injury. The technique of BMSCs therapy for meniscal injuries needs to be combined with biomaterials to have better results. However, *in vivo* studies on BMSC biomaterials are generally performed in animal models. Many of these animal models (small animals) have knee joints that differ significantly from those of humans. More clinical studies are needed to obtain more reliable data and establish a more comprehensive understanding.

From the results of gene similarity analysis, gene expression in SMSCs is closer to meniscal cells than to bone BMSCs.[15]

Table I: Application of growth factor in meniscus tissue engineering.11,20, 22

Growth factor	Cell types	In vitro/ In vivo	Biomaterials/scaffold/explants	Delivery systems	Effects
TGF-β1	Rabbit meniscus cells	In vivo	Poly-L-lactic acid (PLLA)	Not available	Increased collagen and GAG
TGF-β1	Rabbit mesenchymal stem cells	In vivo	Situ crosslinked hydrogel	Not available	Stimulated cell differentiation
TGF-β3	Human bone marrow mesenchymal stem cells (hBMSCs)	In vitro	Meniscus-derived matrix (MDM)	Not available	Enhanced production of proteoglycans
TGF-β3	Cow meniscus cells	In vitro	Meniscus tissue block	Three-armed TMPE-(TMC2-HDI)3 adhesive and hyper-branched CA-4PEG-(TMC2)2-HDI adhesive	Enhanced cell proliferation
TGF-β3, bFGF	Bovine meniscus cells	In vitro	Electrospun produced by poly (ε-caprolactone) (PCL) and N, N-dimethylformamide (DMF) scaffolds	Not available	TGF-β3 increased proteoglycan content in the explants
TGF-β3, CTGF	Synovial MSCs	In vitro	CTGF-loaded fibrin glue mixed with TGFβ3-encapsulated polylactide glycolide acid (PLGA) microspheres	Not available	Induced recruitment and step-wise differentiation of synovial mesenchymal stem/progenitor cells
TGF-β3	Tonsil-derived MSCs	In vitro	Riboflavin-induced photo cross-linked collagen-hyaluronic acid å(COL-RF-HA) hydrogels	Not available	Stimulated the expression of COL2, SOX9, ACAN, COL1 and production of ECM
TGF-β3, CTGF	Without cells	In vivo	3D printing PCL scaffold	PLGA microspheres	No adverse response
TGF-β3, CTGF	MSCs	In vitro	Meniscus explant model	PLGA microspheres	High CTGF dose and slow TGFβ3 release were most effective for integrated healing of avascular meniscus
TGF-β, Matrilin-3	Adipose-derived mesenchymal stromal cells	In vitro	Not Available	Methacrylated hyaluron (MAHA)	Increased expression of the chondrogenic marker, and decreased the mRNA marker for hypertrophy and protein expression
TGF-β1, chondroitinase-ABC (C-ABC)	Articular chondrocytes and meniscus cells from calves	In vitro	Agarose	Not Available	Increased compressive modulus
TGF-β	Meniscus fibrochondrocytes	In vitro	Polyurethane (PU)	Not Available	Enhanced cell proliferation and ECM production
TGF-β	Meniscus cells	In vitro and vivo	Silk fibroin sponge	Platelet-rich gel (PRG)	Enhanced in vitro cytocompatibility, and in vivo cell infiltration
TGF-β3, CTGF	Meniscus fibrochondrocyte-like cells and MSCs	In vitro and vivo	3D printing PCL scaffold	PLA/PGA	Enhanced cell proliferation, ECM production and mechanical properties
SDF-1	Human cartilage mesenchymal progenitor cells (C-PCs)	In vitro	Hydroxypropyl cellulose (HPC)	Not Available	Enhanced cell migration
IGF-1	Bovine meniscal fibrochondrocytes	In vivo	Alginate cross-linked with calcium sulfate	Not Available	Improved mechanical and biochemical properties, increased glycosaminoglycan (GAG) and collagen
Platelet-derived growth factor (PDGF-BB)	Meniscal and synovial cells	In vitro	Electrospun nanofibers	Not Available	Increased cell viability, proliferation and infiltration, upregulated key genes OF ECM
PDGF-AB, PDGF-BB, IGF-I, TGF-β1	Ovine meniscal chondrocyte (OMC)	In vitro	Polyglycolic acid (PGA)	Not Available	Increased collagen type I, and decreased collagen type II production

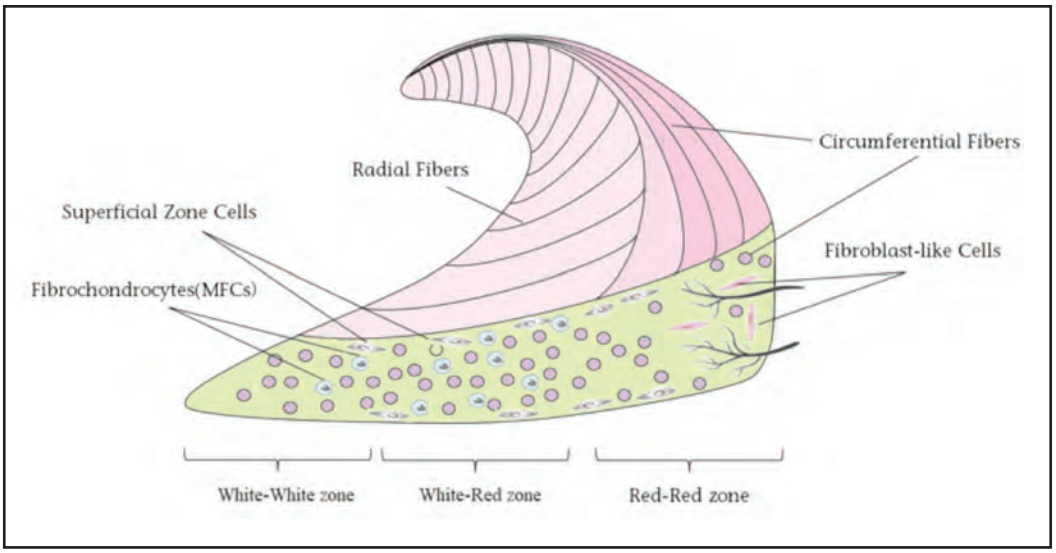

Fig. 1: Structure of the meniscus

SMSCs possess more significant potential to form colonies and can migrate to the site of defects in the meniscus; SMSCs have gradually become a focus of research attention in tissue engineering. In vivo studies in pigs and mice have shown that SMSCs, when injected into a defect, promote the proliferation and differentiation of native meniscus chondrocytes to self-repair.[16]

Adipose tissues are widely distributed throughout the human body and can harvest easily. They are widely used in a variety of fields in regenerative medicine. The application of ADSCs (Adipose tissue-derived stem cells) in meniscus repair must also attach to the scaffold material. A study in a rabbit model demonstrated that sheets of ADSCs promote meniscus regeneration, but the collagen component of the ADSCs sheet-treated tissue differs depending on the defect site.[17] Nevertheless, several reports suggest that ADSCs produce factors that inhibit chondrocyte proliferation and stimulate chondrocyte apoptosis, while other research shows ADSCs exhibiting tumour-enhancement properties.[18] In addition, several researchers report that ADSCs isolated from different anatomical sites and from donors of different genders and ages display variable differentiation potential.[19] The study of ADSCs in meniscus repair is limited to animal experiments.

A majority of research efforts have focussed on developing novel methods, including gene editing and culture techniques in recent years, on improving the efficiency of seed cells in regenerating meniscus tissue.[20] Cytokines play a significant role in cell proliferation, migration and differentiation, and related genes are often used as editing targets for meniscus tissue engineering seed cells. Frequently used target genes in meniscus tissue engineering include FGF-2, TGF-β, insulin-like growth factor I (IGF-I), tumour necrosis factor-α (TNF-α) hepatocyte growth factor (HGF) and activin receptor-like kinases 5 (Alk5)[21,22] and serve different functions to promote meniscal tissue repair (Table I). Noteworthy, *in vitro* gene editing studies have aimed to determine the precise control mechanism of gene expression that promotes the release of cytokines.[22]

- Promote proliferation: TGF-β, FGF-2, IGF-I, platelet-derived growth factor (PDGF), CTGF, calcitonin gene-related peptide (CRGF);
- Modulate cell migration: TGF-β, stromal cell-derived factor 1(SDF-1), Chondroitinase ABC;
- Stimulate anabolic pathways: TGF-β, FGF-2, IGF-I, PDGF, hepatocyte growth factor (HGF), bone morphogenetic protein-7 (BMP-7);
- Modulate cell differentiation: TGF-β, FGF-2, bone morphogenetic protein-2(BMP-2), cartilage-derived morphogenetic protein (CDMP-2);
- Inflammatory response and catabolic/catabolism pathways: TGF-β, Interleukin (IL)-1, matrix metalloproteinases (MMP) family, TNF-α.

Biomaterials for Meniscus Tissue Engineering

Tissue engineering of the meniscus should be capable of supporting axial impact, rotational forces and shear forces in the knee joint. Biomaterials should provide a microenvironment conducive to cell adhesion, proliferation and matrix synthesis. The meniscus scaffolds should process suitable pore size and porosity, excellent biocompatibility and ideal biodegradability.

Tissue engineering materials used to generate a meniscus includes two types: natural biomaterials and synthetic materials.[23] Natural biomaterials include decellularised meniscus, collagen, hyaluronic acid (HA), chitosan, gelatin and bacterial cellulose. Synthetic materials include polyglycolic and polylacticcolic acids.

The ECM of the meniscus has a complicated 3D structure that supports the morphology, behaviours and function of cells, such as migration, proliferation, secretion and differentiation.[24] The internal microenvironment of the artificial meniscus tissue engineering scaffold should be similar to natural ECM to provide biocompatibility and degradability.[25] The meniscus is predominantly composed of collagen and proteoglycans. Natural biomaterials have similar components making biological compatibility and

biochemical active. Thereby promoting the regeneration of meniscus tissue[26] based on the monomer units and structure, most natural biomaterials are categorised as protein/polypeptides (e.g., collagen, gelatin, silk) or polysaccharides (e.g., HA, alginate, agarose, GAGs, chitin, chitosan). Proven commercial products that are natural biomaterials have been used in the clinic. CMI® is an FDA-approved cell-free scaffold derived from bovine Achilles tendon collagen. At 1-year follow-up after transplantation in acute/chronic meniscus injury patients, CMI® showed acceptable biocompatibility and was able to consolidate to the host meniscus.[27] At 10-year follow-up, all of the 25 patients reported pain relief and improved function and most patients did not experience degenerative disease of the knee joint.[28] Natural biological materials are suitable for the growth, development and metabolism of seed cells. However, natural biological materials have some limitations, e.g., collagen lacks flexibility, has low tensile strength, has poor initial stability and degrades quickly. HA and alginate lack anti-pressure ability, unable to adapt to changes in gravity and are slowly degraded.[20] All these limitations warrant consideration for synthetic materials for meniscus tissue engineering.

Synthetic materials are organic polymers with several advantages, including strong mechanical properties and ease of production. These characteristics allow the materials to adapt to the needs of different tissues by adjusting the molecular weight and relative proportions of the components so they can be widely used to produce scaffolds in meniscus tissue engineering.[29] Synthetic materials commonly used in meniscus tissue engineering include polyglycolic acid (PGA), polylactic acid (PLA), polylactide glycolide acid (PLGA), polycaprolactone (PCL), polyurethane (PU), polyvinyl alcohol (PVA) and new nanomaterials.[2,3] Typically, scaffolds that consist of more than two kinds of composite materials are called composite scaffolds, such as PGA/PLGA and HA/PCL. These materials are biocompatible and have good mechanical strength. Notably, the degradation rates of these materials can be controlled by changing the proportion of polymers, molecular weight and crystallinity. Synthetic materials can be produced under controlled conditions to obtain predictable mechanical and physical characteristics such as strength, degradation rates, porosity and Young's modulus. Natural biomaterials have been used in commercial products in the clinic. Actifit® (Orteq Sports Medicine, London, UK) is an improved PU scaffold consisting of 20% PU and 80% of PCL. Actifit® has been approved for use in Europe.[36] In a clinical study, patients showed improved mobility with cartilage tissue growth into the scaffold.[30] At a follow-up of 5 years, MRI showed that the Actifit® meniscal implant had an intermediate signal and was reduced size in all patients. These data indicate that Actifit® still has limitations as it deforms and undergoes atrophy following long-term use.[31] NUSurface® is a cell-free anisotropic synthetic biomaterial comprising polycarbonate urethane (PCU).[30] At a follow-up of 2 years', patients reported pain relief and had a lower rate of knee reconstructive procedures compared to the control group.[32] However, larger prospective trials are required to validate these findings. Compared to natural biomaterials, synthetic materials can lack surface cell adhesion sites on the surface and can be less biocompatible. Researchers have combined synthetic and natural materials to solve these problems to produce meniscal tissue engineering materials. Natural biomaterial hydrogels have been shown to have good histocompatibility and absorption properties and have been applied in repairing knee cartilage and the meniscus by injection treatments.[20] Chen et al.[33] injected a hydrogel produced by decellularised meniscus ECM into a 3D-printed PCL scaffold which was implanted into the knee of a New Zealand rabbit undergoing total medial meniscectomy. Six months after implantation, the meniscus was regenerated and had a similar microstructure, biochemical composition and biomechanical properties to the natural meniscus.

Natural biomaterials can also be combined with synthetic materials for 3D-printed tissue-engineered scaffold structures. Cengiz et al.[34] blended PCL with silk fibroin (SF) and entrapped it in a 3D-printed cage scaffold. Human meniscocytes and ADSCs have shown satisfactory cell adhesion, metabolic activity and proliferation on scaffolds after being seeded in vitro. The scaffold was shown to have ideal biomechanical properties after subcutaneous implantation in nude mice. Combining natural and synthetic polymers (bioartificial combination) is a multipurpose method to design more successful biomaterials that enhance physical and biological features, such as biocompatibility.[35] They have been combined to take advantage of their favourable properties to overcome the disadvantages of each particular type of material.

Advancements in Biomaterial Techniques of Meniscus Tissue Engineering

Cytokines can guide cell proliferation, migration and differentiation through biochemical signals and have been widely used in vitro. Cytokines commonly used in meniscal tissue engineering and cell therapy include TGF-β, FGF-2, IGF-I and Chondroitinase ABC.[26,36] In vitro and signalling pathway studies have found that many other cytokines have potential roles in meniscus repair. Cytokines are sensitive to variations in temperature, pH and other factors within the microenvironment.[20] They are also prone to denaturation, inactivation and decomposition. Therefore, strategies to maintain the activity of cytokines and obtain controlled and sustained release need to be developed to optimise tissue engineering meniscus technologies. The biomaterial's molecular weight, solubility, surface charge and degradation rate are key factors that determine the rate of cytokine release.[22] Current biomaterials for tissue engineering delivery and the loading of cytokines or other active substances include hydrogels, acellular matrices and composite scaffolds (PCL, PLGA, agarose). These materials have strong biocompatibility but are suboptimal in terms of mechanical strength, degradation rate and cytokine-controlled release. Research is being conducted to develop 3D printing technology in meniscus tissue engineering.[22,34]

Meniscal tissue engineering has high requirements on the mechanical structure, molecular weight, porosity, fibre anisotropy, degradation rate, surface roughness, stiffness, hydrophilic/hydrophobic ratio and surface charge of biomaterials.[20] In recent years, the design of tissue engineering meniscus trying to mimic the microstructure and

chemical properties of human meniscus.. Currently, physical and chemical methods are used for meniscus tissue engineering (e.g., freeze-frying, melt moulding, solvent casting, particulate leaching and gas foaming) that provide an ideal microenvironment for cell culture in which the degradation rate is controllable to a certain extent.[37] However, pore size, porosity and surface charge are difficult to control. Electrospinning can be used to produce nanoscale fibres that mimic collagen. However, this technique has many limitations relating to porosity and precise microstructural control.[38] Moreover, the composition, structure and cell types of the inner and outer regions of the meniscus are significantly different.[37,38] This is difficult to recreate in a single material preparation and scaffold construction method using a single cell type.

Recently, 3D bioprinting has attracted significant research attention. 3D bioprinting is an automated, organisation friendly manufacturing method that accurately simulates the microscopic columns of a target tissue enabling the precise construction of tissue blocks with specific shapes and structures.[25] Commonly used bioprinting techniques for meniscus tissue engineering include direct ink writing, fused deposition modelling (FDM) and extrusion-based bioprinting.[37,39] High extrusion temperatures result in FDM technology producing materials with poor surface quality and difficulties combining biopolymers.[39] Extrusion bioprinting techniques are the most commonly used techniques in meniscus tissue engineering. Recently, this technique has been employed to produce structures with high yields and structural integrity for easy modification. Zhang et al.[40] printed meniscus-shaped scaffolds with PCL using the melt deposition technique and transplanted the scaffolds into New Zealand white rabbits after seeding BMSCs. The regeneration and mechanical properties of the implanted tissues were assessed, and rough and microscopic observations assessed the degeneration of the articular cartilage at 12 and 24 weeks after surgery. The study showed that the 3D-printed scaffolds seeded with MSCs promoted fibrocartilage tissue regeneration and increased the mechanical strength of the tissue. This approach may provide a functional replacement of the meniscus to reduce postoperative damage to knee cartilage.

Meniscus scaffold should show high mechanical strength to hold the weight, good porosity to satisfy cell colonisation requirements and excellent biocompatibility to prevent cytotoxicity. Still, only some types of biomaterials meet all these requirements.[39] Researchers print polymeric as the backbone and fill it with biological materials combined with growth factors to promote cell proliferation and the matrix-forming phenotype of the cells to build an adjustable scaffold to solve this challenge. Chen et al.[33] produced synthetic 3D-printed conditioned scaffolds by PCL and hydrogel derived from meniscus extracellular matrix to reproduce native ECM-like environments. The scaffold yielded outstanding biomechanical strength that was close to those of the native meniscus. They implanted the MFCs-loaded scaffold into the knee joints of New Zealand rabbits. They found that the cell-loaded scaffold exhibited better physical appearance and ability of cartilage protection than the acellular scaffold.

CONCLUSION

To summarise the type of seed cells and biomaterials that are used in meniscus tissue engineering, we reviewed all the existing literature in this field and discussed the unique characteristics of each of them. Insufficiency in current meniscal repair techniques to halt the development and progression of the disease has accelerated the development of tissue engineering strategies. The goal of meniscus tissue engineering is to create new tissue that is similar to meniscus tissue in vivo and suitable for cell proliferation or differentiation, readily integrates into surrounding native tissues and ensures positive outcomes regardless of biological variability and the age of the patient. A big leap in research progress in the field of stem cell sources, biomaterials and the application of stimuli methods to develop tissue engineering techniques for meniscus repairing can be observed to produce therapeutic strategies with lasting effects for meniscus injury. The biomechanical properties of the existing tissue-engineered meniscus still need to be improved. Numerous clinical trials of stem cell-based tissue engineering meniscus have been carried out.

The complex mechanics of the knee joint and the lack of blood supply to the meniscus make 3D-printed meniscus with stem cells the best choice for tissue engineering scaffolds. The bio-ink should possess the characteristic of ideal printability, proper mechanical strength and a mild curing process for cell protection. Single material can only meet these requirements in the studies so far. Part of the researchers choose materials of high mechanical strength as bio-ink to print the backbone of the meniscus and use materials with high biocompatibility to fill the void, exploring a promising technological route. Still, finding the ideal type of biomaterials, the most suitable growth factor and the ideal additive manufacturing method pose enormous challenges.

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