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Review Article

Advances in biomechanical and biochemical engineering methods to stimulate meniscus tissue

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Abstract: Meniscal injuries can cause cartilage degeneration, which usually leads to the development of osteoarthritis (OA) and results in progressive destruction of the knee joint. Therefore, it is important to identify methods to stop or slow the development of OA after the onset of meniscal defects. The current surgical techniques for meniscal injuries are insufficient to prevent the progression of knee OA, which has accelerated the development of alternative tissue engineering strategies. Much progress has been made in the use of biomechanical and biochemical stimuli in the past decades to engineer neotissue akin to native meniscus. In this review, we focus on the current progress in biomechanical and biochemical stimuli-based strategies applied to meniscal tissue engineering, and explore how these factors influence meniscal regeneration. By understanding the functional mechanism that can stimulate regeneration in the meniscus, we hope that this review will provide a theoretical basis and strategies for meniscus tissue engineering.

Keywords: Meniscus, tissue engineering, biomechanical stimuli, biochemical stimuli

Introduction

The menisci are two semicircular fibrocartilaginous structures in the knee joint. They have many important functions for the knee, such as absorbing shock, transmitting stress and stabilizing the knee joint [1]. Population-based data suggest that the prevalence of a meniscal tear or meniscal destruction ranges from 19% among 50 to 59 years of age to 56% among 70 to 90 years of age in the general population [2]. With the rapid rise in aging populations worldwide, the incidence of meniscal injuries may further increase. Previous clinical or zoological studies have found that if meniscal injury is not treated, it may lead to aggravation of clinical symptoms, osteoarthritis (OA), and even disability [3]. The annual cost of meniscal disease in the United States is estimated between $500 million and $5 billion [4].

Clinical treatment strategies for meniscal injuries have changed with surgeons' understanding of the anatomic structure and function of the meniscus. In the past 60 years, because 2/3 of the meniscus lacks blood vessels, it was considered difficult to heal it after meniscal injury. Therefore, the meniscus is often completely removed after injury, that is, total meniscectomy [5]. However, after total meniscectomy, the average stress on the knee cartilage will increase by 3 times, and peak stress will increase exponentially [3]. Clinical studies have shown that this accelerates the degeneration of knee cartilage and gradually leads to OA [3]. Later studies showed that in addition to the torn part that needs to be removed, the remaining intact part needs to be preserved to maintain the function of the meniscus [6, 7]. However, even with partial meniscectomy, cartilage damage, osteophyte formation, and early degeneration of the knee joint can still occur [8]. Therefore, the current treatment strategy is to preserve as much meniscal tissue as possible. However, there are still many patients with complex meniscal injuries that are difficult to

suture and heal, and eventually require a total meniscectomy. Montgomery et al. reported that among patients undergoing meniscal surgeries, 96% of patients undergo meniscectomy, with only 4% undergoing meniscal repair [9]. For patients with total meniscectomy, allogeneic meniscus graft is often recommended. However, an allograft also has obvious disadvantages, such as limited supply, immune rejection, and disease transmission [10].

The current surgical techniques for meniscal injuries are insufficient to halt the development and progression of OA, thus stimulating the need for alternative tissue engineering strategies. To engineer neotissue akin to native meniscus, many advances have been achieved by using biomechanical and biochemical stimuli in the past decades. In this review, we focus on current progress in biomechanical and biochemical stimuli-based strategies used in meniscus tissue engineering, and explore how these factors influence meniscal regeneration. By explaining the functional mechanisms that can stimulate regeneration in the meniscus, this review will provide a theoretical basis for strategies for meniscus tissue engineering.

Meniscus anatomy and functional properties

The menisci are located between the femur and tibia, and can be divided into a C-shaped medial meniscus and an O-shaped lateral meniscus (**Figure 1**). The meniscus has a high water content (72% water), with the remaining 28% composed of organic matter, including extracellular matrix (ECM) and cells [11]. In the ECM, collagen makes up the vast majority, followed by glycosaminoglycan (GAG), DNA, glycoproteins, and elastin [11]. The content of these substances changes with age and physiologic environment [12]. The collagen content of the meniscus increases with weight bearing and joint movement until the age of 30, and stabilizes until starting to decrease around the age of 80 [12]. According to the distribution of blood vessels and nerves, the meniscus can be divided into 3 areas, namely the outer, intermediate, and inner areas [13]. The outer area of the meniscus, which is usually called the red-red area, is rich in blood vessels and nerves, and has the ability to heal. This area contains a large amount of type I collagen fibers, which make up 90% of its composition by dry weight, with other collagens constituting less than 1% [14]. The cells in this area are mainly elongated fibroblast-like cells, surrounded by abundant collagen type I [15]. The inner area of the meniscus, which is called the white-white area, lacks blood vessels and nerves. Once damaged, this inner area is difficult to heal. Unlike the outer area, the inner area contains relatively fewer collagen fibers, and is slightly less than 70% of the dry weight, of which 40% is collagen type I and 60% is collagen type II [14]. The cells in this area are mainly chondrocytes [15]. Regional variation of glycosaminoglycans (GAGs) has also been found, with a relatively higher proportion of proteoglycans in the inner two-thirds than in the outer one-third [16] (**Figure 2A**). The main function of GAG is to absorb water, which enables the meniscus to withstand compression [17]. The orientation and structure of collagen also differ between the meniscal surface layer and deeper tissue [18, 19]. The orientation of collagen fibers in the deep tissue is mainly in the circumferential direction. The collagen fibers covering the surface of the meniscus tissue are randomly oriented and have a network structure. The radial binding fibers are arborized from the outer area of the meniscus to the inner tip [20]. The presence of bonding fibers can affect the tensile modulus of the meniscus.

The meniscus can withstand various forces, such as compression, tension, and shear. It also plays an important role in the loadbearing, shock absorption, load transmission, and nutrition of articular cartilage [21-23]. As the meniscus is wedge-shaped, it fits well between the flat tibial plateau and the curved femoral condyle in articulation [24, 25]. In daily activities, the axial force between the tibia and femur compress the meniscus. The horn attachment and the wedge shape of the meniscus help convert vertical compressive forces into horizontal hoop stresses (**Figure 2B**). If the meniscus deforms radially under compression, a shear force is generated between the collagen fibers of the meniscus [1, 26]. Due to the specialized structure, the meniscus sustains axial compression with an aggregate modulus of 100-150 kPa [27]. The tensile modulus varies between the circumferential and radial directions, which is approximately 100-300 MPa circumferentially and 10-fold lower than this radi-

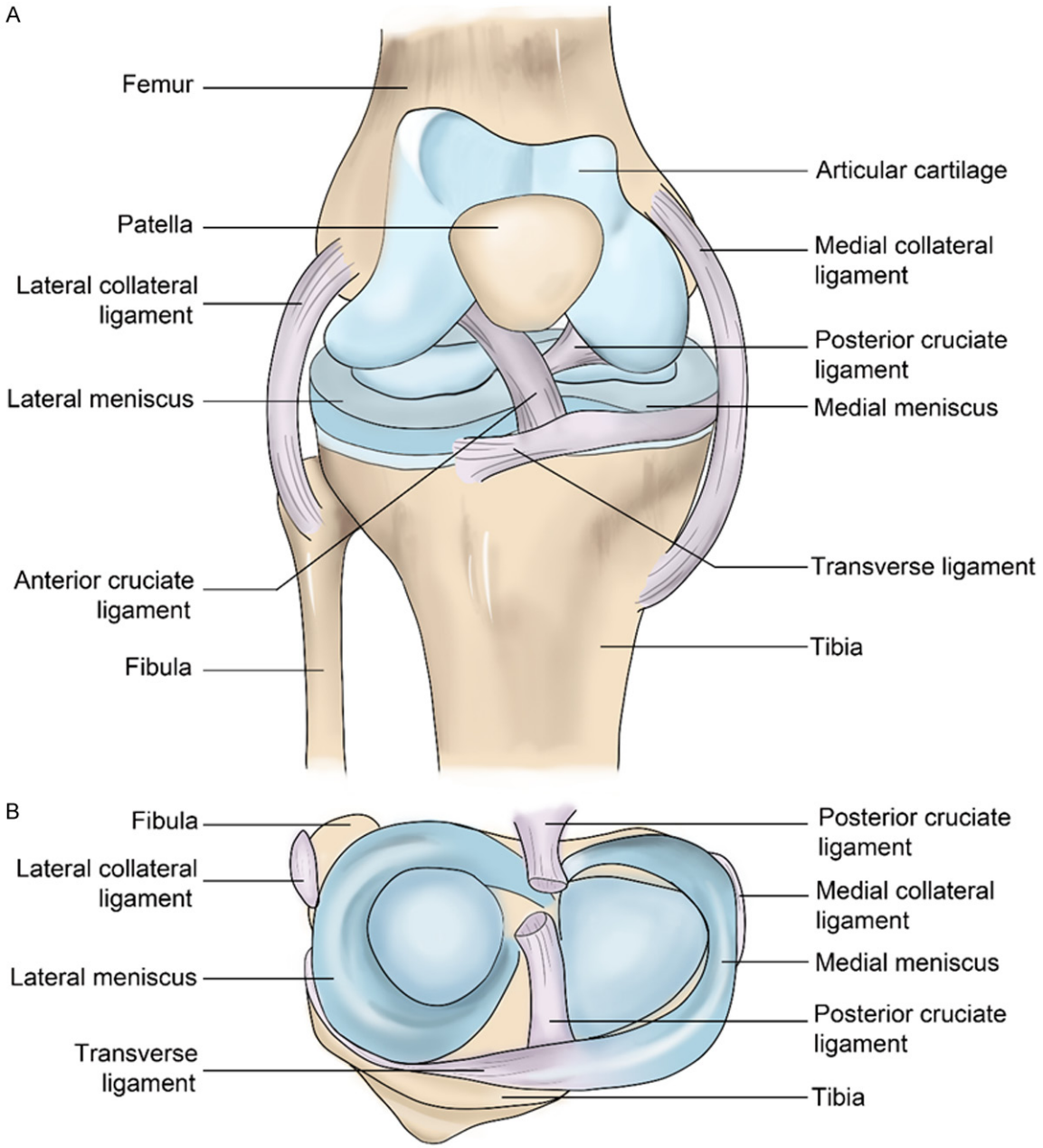

Figure 1. The knee joint, depicting meniscus and major ligaments. A. Anterior view. B. Superior view of the tibial plateau.

ally [28]. The shear modulus of the meniscus is approximately 120 kPa [28].

Biomechanical stimuli for meniscus tissue engineering

Mechanical stimulation has an important influence on the development, homeostasis, and degeneration of weight-bearing tissues. Studies have demonstrated the important role of physical movement in the formation of embryonic cartilage. When chick embryos undergo paralysis, chondrogenesis of progenitor cells can be inhibited at the quadratojugal hook [29, 30]. Moreover, immobilization of chick embryos can inhibit the formation of articular joint cavity during limb development, reducing the hyaluronan content in articular surfaces, and the meniscus is also absent in immobilized animals [31, 32]. Overall, these studies indicate that the trans-

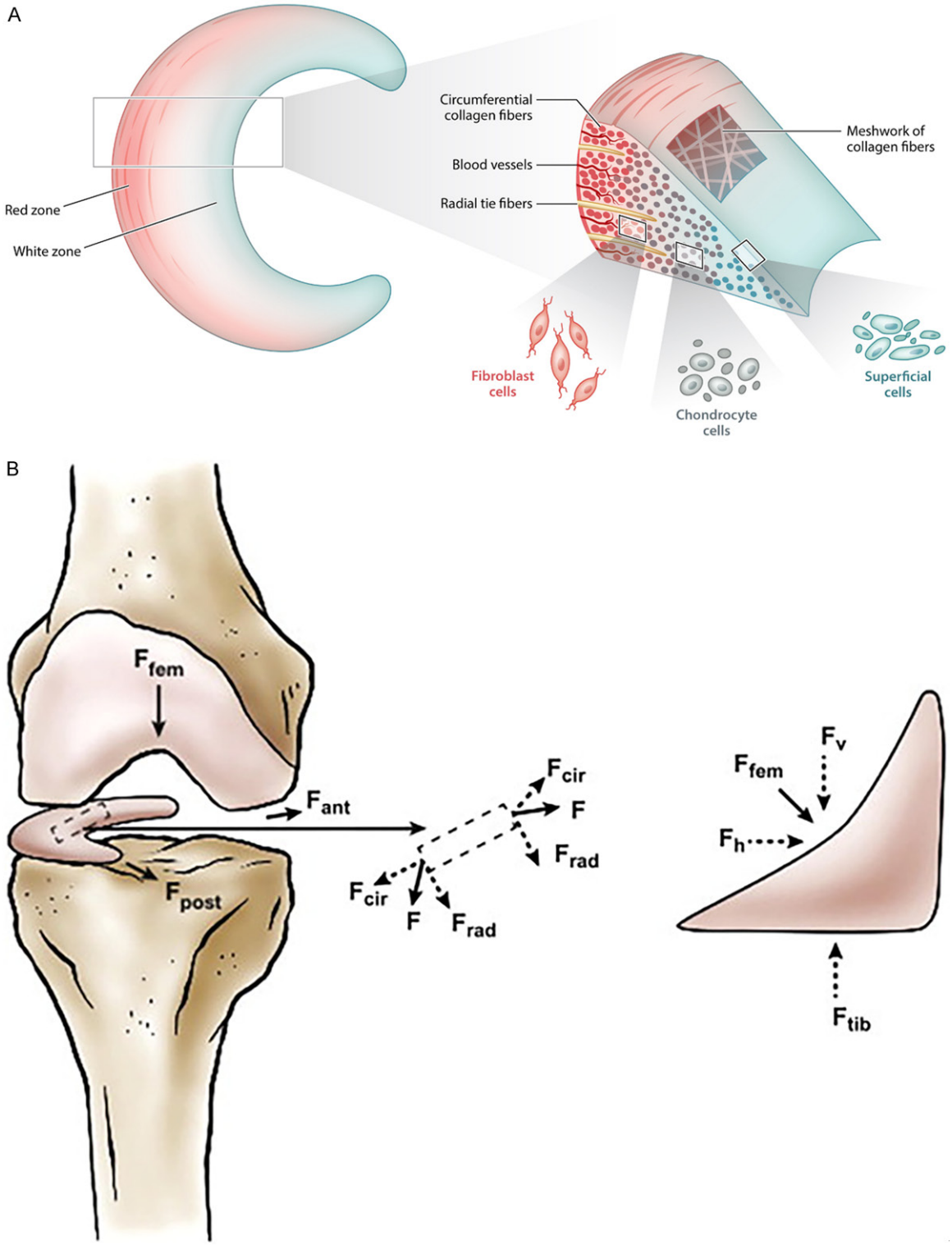

Figure 2. A. The internal structure of the meniscus depicting variation in collagen orientation, vascularization, and cell population. Reproduced with permission [13]. *Copyright, 2019 Annual Reviews*. B. The transduction of force upon and throughout the knee meniscus. Free body diagram of the forces acting on the knee lateral meniscus during loading. During everyday activity, the menisci are compressed by the downward force of the femur. Since the meniscus is a wedge, the femoral force is enacted at an angle, and thus a vertical component exists which is countered by the upward force of the tibia. Additionally, a horizontal component of the femoral force exists, which is exerted radially outward on each meniscus. This horizontal force is in turn countered by the anchoring force of the

attachments at the posterior and anterior horns of the meniscus. Additionally, as this compression occurs, circumferential stress is created along the meniscus. Therefore, the menisci function by converting compressive loads to circumferential tensile loads. Reproduced with the permission [14]. *Copyright 2011, Elsevier*.

Table 1. Effect of biomechanical stimuli for meniscal tissue engineering

Biomechanical stimulus	Effects	Culture conditions
Hydrostatic pressure	Chondrogenic differentiation of stem cells ↑	Monolayer [44, 50, 52]
		Scaffold [45, 47, 49, 53]
		Explant [48]
	Collagen synthesis ↑	Monolayer [40]
	Proteoglycan/GAG synthesis ↑	Monolayer [40]
		Explant [36-39]
	Matrix metalloproteases expression ↓	Explant [41, 42]
Direct compression stimulation	Chondrogenic differentiation of stem cells ↑	Scaffold [65-71]
	Collagen synthesis ↑	Scaffold [56, 116]
		Explant [57, 58]
	Proteoglycan/GAG synthesis ↑	Scaffold [60, 61, 116]
		Explant [58]
	NO release ↓	Explant [63]
Tension stimulation	Chondrogenic differentiation of stem cells ↑	Monolayer [81]
		Scaffold [75, 76]
	Collagen synthesis ↑	Explant [73]
		Scaffold [75, 76]
	Proteoglycan/GAG synthesis ↑	Explant [73]
		Scaffold [74, 75]
	Matrix metalloproteases expression ↓	Explant [77]
	NO and PGE2 release ↓	Monolayer [77, 78]
	NO and PGE2 release ↑	Monolayer [79, 80]

duction of biomechanical stimulation to molecular signals may regulate cell differentiation and maturation, highlighting the important role of mechanical stimulation in meniscal development, growth, and health. In this review, we focus on three common biomechanical stimuli in meniscus tissue engineering, namely, hydrostatic pressure, direct compressive loading, and tension stimulation (**Table 1**).

Hydrostatic pressure

Under hydrostatic pressure, cells and tissues experience uniform and normal compression on all surfaces. Hydrostatic pressure is one of the major forms of mechanical stimulation, as it is resisted by the meniscus during every joint movement [33]. Similar to cartilage, meniscus experiences 3-10 MPa of hydrostatic pressure [34]. Under hydrostatic pressure condition, changes in the intracellular osmotic composition may affect gene expression and further influence the biomechanical properties of the meniscus [35].

Studies have shown enhanced extracellular matrix formation in chondrocytes under hydrostatic pressure condition. For example, a 1.3-fold increase in GAG was found in chondrocytes exposed to hydrostatic pressure compared with static controls [36]. Chondrocytes stimulated with hydrostatic pressure show a significant increase of 64% more GAG [37]. In tissues derived from juvenile chondrocytes, GAG content was significantly increased when hydrostatic pressures were between 7 and 10 MPa [36, 38, 39]. When exposing chondrocytes in a monolayer to 10 MPa hydrostatic pressure for 4 h, GAG synthesis was enhanced to 65% under intermittent pressure and 32% under constant pressure, and collagen type II was also increased in response to both intermittent and constant pressure [40].

Hydrostatic pressure may also reduce catabolic gene expression on the meniscus. A study showed that hydrostatic pressure led to the downregulation of matrix metalloproteinase (MMP)-1 and MMP-13 mRNA expression, whereas cyclic hydrostatic pressure resulted in significantly enhanced expression of tissue inhibitors of metalloproteinases (TIMPs) and collagen type I mRNA [41]. Similarly, another study demonstrated that hydrostatic pressure could reduce the upregulation of catabolic genes, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and MMPs, which increase in the absence of in vivo mechanical loading [42]. Furthermore, the expression of proteoglycan core protein was increased under physiologic levels of hydrostatic pressure (1 or 5 MPa), whereas hydrostatic pressure at excessively high levels (10 or 50 MPa) reduced the expression of proteoglycan core protein and induced interleukin-6 (IL6) and tumor necrosis factor-α (TNF-α) expression [43].

Many studies have shown the importance of hydrostatic pressure for the chondrogenic differentiation of mesenchymal stem cells (MSCs). In the study by Angele et al., when hydrostatic pressure was applied to MSCs, there was an increase in GAG and collagen matrix synthesis at days 14 and 28 [44]. In the study by Correia et al., under physiologic hydrostatic pressure, greater matrix deposition and chondrogenic differentiation were found for human adipose stem cells encapsulated in gellan gum hydrogels, with increased gene expression of SOX-9, collagen type II, and aggrecan [45]. Moreover, MSCs under cyclic hydrostatic compression resulted in increased type II collagen and aggrecan gene expression [46]. Other studies found similar results, in which applying hydrostatic pressure for 14 or 21 days enhanced chondrogenic (ACAN, COL1A1, COL2A1 and SOX9) gene expression in MSCs [47-53].

By combining hydrostatic pressure and growth factor stimuli, the mechanical properties of the regenerated meniscus can be increased. In the study by Gunja et al., with the combination of hydrostatic pressure and transforming growth factor (TGF)-β1 stimuli, additive increases in collagen and GAG deposition as well as a synergistic increase in compressive properties were observed in meniscal cell-seeded poly-l-lactic acid (PLLA) constructs [54]. Similarly, another study by Elder et al. found that static hydrostatic pressure at 10 MPa resulted in 92% increases in Young's modulus, with corresponding increases in collagen content, and 96% increases in aggregate modulus, with corresponding increases in GAG content [39]. Moreover, the combination of 10 MPa static hydrostatic pressure and TGF-β1 demonstrated an 85% increase in GAG/wet weight, a 164% increase in aggregate modulus, a 173% increase in collagen/wet weight, and a 231% increase in Young's modulus when compared with the control [39].

Direct compression stimulation

During daily activity, the axial force between the femur and tibia compresses the meniscus. Previous studies have shown that the meniscus underwent axial compression with an aggregate modulus of 100-150 kPa [27]. Compressive loading is thought to facilitate the exchange of nutrients and waste in the transport-limited zone of the meniscus [55].

Numerous studies demonstrate that matrix synthesis is increased by dynamic compression stimulation. With a compressive stimulation of 0.5 kPa, the collagen content of chondrocytes was increased to 1.5-fold compared with free-swelling controls [56]. Similarly, when chondrocytes were cultured under passive compressive loading at 5 kPa, the collagen content was increased by 61% [57]. This study also found that constructs under high compressive loading tend to have lower collagen content, indicating that excessive compressive load can cause ECM protein degeneration [57]. When exposing fibrocartilaginous neotissues from the meniscus under 0.1 N compressive stress, a 27% increase in collagen content and 67% increase in GAG synthesis were obtained [58]. In chondrocyte-seeded agarose gels, the GAG content was also found to be increased by 60% under dynamic compressive stimulation [59, 60]. Additionally, under monolayer condition, chondrocytes stimulated with 20% dynamic compressive strain resulted in a 45% increase in GAG synthesis [61].

Direct compressive loading has been shown to influence the anabolic and catabolic activities of meniscal cells. For example, compared to no dynamic loading, 10% compressive strain could

cause the upregulation of COX-2, Aggrecan, and ADAMTS5 gene expression in meniscal cells [62]. However, 20% dynamic compressive strains led to an upregulation of MMPs and ADAMTS4 compared to no dynamic loading [62]. Similarly, another study showed that iNOS and IL-1 gene expression, as well as nitric oxide (NO) release, were enhanced under 20% compressive strain. However, a physiologic compressive strain of 10% would reduce NO release compared to pathologic unloading (0% compressive strain) [63]. McHenry et al. demonstrated that 20% compressive strain, in which the strain and stress correspond to partial meniscectomy, result in the greatest proteoglycan breakdown [64]. These results indicate that a physiologic compressive strain of 10% may result in anabolic activity, whereas a 20% compressive strain is associated with catabolic activity.

Several studies have shown that direct compressive loading plays a crucial role in the chondrogenic differentiation of MSCs. In the study by Bian et al., after 70 days of culture of human MSCs in hyaluronic acid hydrogel constructs, dynamic compressive loading increased collagen and GAG contents, and enhanced the mechanical properties [65]. In another study by Huang, after being subjected to a 10% compressive strain at a frequency of 1 Hz for 4 hours a day, compressive loading significantly enhanced the expression of chondrogenic markers (aggrecan and collagen II) at 3, 7 and 14 days for MSCs in agarose cultures [66]. Similar results were obtained by other studies, whereby chondrogenic genes were increased by applying dynamic compressive loading for 14 or 28 days [67-71].

By simultaneously applying dynamic compressive stimulation and growth factors, it becomes possible to develop anisotropic reconstruction for the meniscus. In the study by Zhang et al., two types of stimuli were simultaneously used: TGF-β3 and connective tissue growth factor (CTGF) for 4 weeks (biochemical stimulation) followed by dynamic 10% compressive strain for 2 weeks (biomechanical stimulation). With the combination of biochemical and biomechanical stimuli, higher collagen I content was observed in the outer area, while higher GAG and collagen II contents were observed in the inner area, reminiscent of the structure of a native meniscus (**Figure 3**). Moreover, under the double stimuli, the inner area of the regenerated meniscus exhibited an upregulation of chondrogenic genes (COL2A1, ACAN, and SOX9), while the outer area exhibited an upregulation of fibrogenic genes (COL1A1, FN1, and TNC), which suggests zone-specific mRNA phenotypes [72].

Tension stimulation

By pulling the tissue outward along the edges, a tensile force is generated in engineered tissues. In the meniscus, the wedge shape and the horn attachments help convert the vertical forces to horizontal hoop stresses [14]. According to previous studies, the tensile modulus of the meniscus is 100-300 MPa circumferentially and 10-fold lower radially [28].

In the study by Lee et al., uniaxial tensile loading increased matrix formation in chondrocytes explant by 33% [73]. In fibrin hydrogel constructs, oscillatory tensile loading also led to an increase of 20.6% in GAG synthesis for chondrocytes [74]. By applying tensile stimulation to fibrocartilage constructs, increased collagen I mRNA expression as well as increased GAG and collagen contents were obtained [75]. Similarly, in the study by Baker et al., dynamic tensile loading resulted in increased expression of fibrous genes, enhanced collagen deposition, and an increased tensile modulus for MSC-laden nanofibrous constructs [76].

Tensile loading could also influence catabolic activity on the meniscus. In the study by Agarwal et al., cyclic tensile strain reduced the catabolic effects of IL-1β on fibrochondrocytes by inhibiting MMP-1, COX-2, and iNOS mRNA expression and MMP-1, prostaglandin E2 (PGE2), and NO release. Cyclic tensile strain also counteracted rHuIL-1β-induced suppression of proteoglycan synthesis [77]. Similarly, in the study by Gassner et al., cyclic tensile strain was directly attributed to the inhibition of iNOS mRNA expression and protein synthesis in chondrocytes. Furthermore, the inhibition of iNOS induction by cyclic tensile strain is paralleled by abrogation of IL-1β-induced downregulation of proteoglycan synthesis [78]. However, conflicting results were obtained by other studies, whereby tensile stimulation increased the release of PGE2 and NO [79, 80].

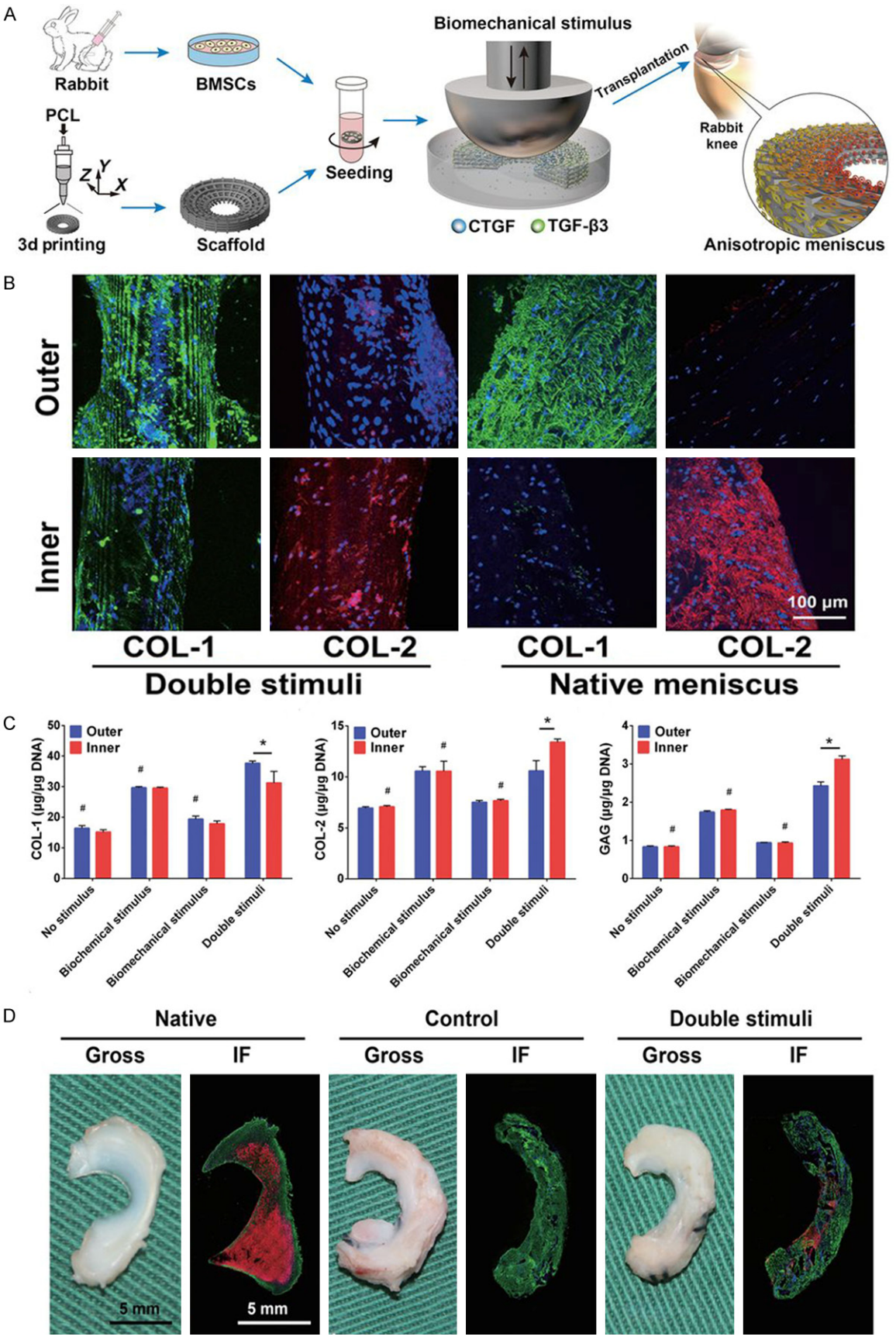
A
Rabbit
BMSCs
PCL
3d printing
Scaffold
Seeding
Biomechanical stimulus
CTGF
TGF-β3
Transplantation
Rabbit knee
Anisotropic meniscus
B
Outer
Inner
100 μm
COL-1
COL-2
COL-1
COL-2
Double stimuli
Native meniscus
C
COL-1 (μg/μg DNA)
COL-2 (μg/μg DNA)
GAG (μg/μg DNA)
Outer
Inner
No stimulus
Biochemical stimulus
Biomechanical stimulus
Double stimuli
D
Native
Control
Double stimuli
Gross
IF
5 mm

Figure 3. Reconstruction of functional anisotropic meniscus by combining biomechanical and biochemical stimuli. A. Flowchart of stem cell-based strategies for construction of a tissue-engineered meniscus with anisotropic structures. BMSCs, bone marrow-derived stem cells. B. Zonal fibrochondrocyte differentiation of MSCs in 3D PCL scaffolds in the double-stimuli versus native meniscus (green, COL-1; red, COL-2). C. COL-1, COL-2, and GAG contents in the inner and outer regions of each study group. *P<0.05 between the inner region and outer region in the same group; #P<0.05 between the double-stimuli group and other groups in the same region. D. Gross view and low-magnification immunofluorescence (IF) images of native or regenerated menisci at 24 weeks after in vivo implantation in rabbit knees. Green, COL-1; red, COL-2. Reproduced with permission [72]. *Copyright 2019, Science*.

Several studies have used tension stimulation as a strategy for chondrogenic differentiation of MSCs. For example, in MSC-laden precultured constructs, tensile loading had a significant influence on the synthesis of ECM and expression of ECM-related genes [76]. Compared to nonloaded controls, four weeks of tensile stimulation led to a twofold enhancement in collagen I synthesis [76]. In another study, 24 h of dynamic tensile strain increased the synthesis of proteoglycan in MSC-seeded fibrin constructs [75]. Moreover, one week of dynamic tensile strain significantly enhanced the collagen and GAG contents in the constructs [75]. Tension stimulation has been shown to preferentially promote fibrogenesis (collagen I, versican) over chondrogenesis (collagen II, Sox9, aggrecan) in adipose-derived stromal cells [81].

Biochemical stimuli for meniscal tissue engineering

There are already a number of biochemical stimuli used for meniscus tissue engineering (**Table 2**). Commonly used biochemical stimuli include growth factors, such as TGF-βs, bone morphogenetic proteins (BMPs), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and hepatocyte growth factor (HGF); small bioactive molecules such as E7 peptide, kartogenin (KGN), and Y-27632; biophysical factors such as chondroitinase ABC (C-ABC), lysyl oxidase-like 2 (LOXL2); oxygen tension; and gene therapy.

Growth factors

Among numerous biochemical stimuli, growth factors are the most commonly used in meniscal tissue engineering (**Table 2**). A large number of growth factors, including the TGFβ family, EGF, PDGFs, and FGFs have shown efficacy for promoting ECM synthesis in meniscal regeneration [14, 82]. Compared with the untreated meniscal construct, the addition of FGF2 and TGFβ1 increased collagen production by 60% and 144%, respectively [83]. Moreover, TGFβ1 could also promote the synthesis of GAG [83]. In the study by Bhargava et al., when BMP-2, HGF, and PDGF were applied to meniscal cells from different areas, a 2-3 fold enhancement in DNA production was observed [84]. In addition, cells in different meniscal areas have different responses to growth factors. For example, HGF has a higher influence on cells in the inner area, while BMP-2 has a higher influence on cells in the central area of the meniscus [84]. The influence of growth factors on the migration of meniscal cells was also studied. EGF increased the migration of cells from the inner and outer areas of the meniscus, IGF-1 increased the migration of cells from the inner and central areas of the meniscus, BMP-2 increased the migration of cells from the central area of the meniscus, and PDGF-AB and HGF enhanced the migration of cells from all meniscal areas [84]. By combining different growth factors, engineered meniscus could exhibit zone-specific matrix. In the study by Lee et al., by spatially delivering CTGF and TGFβ3 from a 3D-printed meniscus scaffold [85], inhomogeneous mechanical properties as well as zone-specific matrix phenotypes were developed by endogenous cells, with collagen II in the inner area, and collagen I in the outer area in the regenerated meniscus, which was reminiscent of the structure of a native meniscus [85] (**Figure 4**).

Small bioactive molecules

Many studies have shown encouraging results for small bioactive molecules such as E7 peptides, KGN, Y-27632, and aptamers in meniscus and cartilage tissue engineering (**Table 2**). For example, in the study by Yan et al., hyaluronic acid hydrogel with KGN-loaded PLGA nanoparticles showed improved biomechanical properties and more hyaline-like cartilage in terms of ECM, cartilage lacunae, and type II col-

Table 2. Effect of growth factors, small bioactive molecules, biophysical factors, and low oxygen tension for meniscal tissue engineering

Biochemical stimulus	Effects	Culture conditions
Growth factors		
TGF-β1	Chondrogenic differentiation of stem cells and proliferation ↑	Monolayer [117, 118]
		Scaffold [119]
	Collagen synthesis ↑	Monolayer [120, 121]
		Scaffold [54, 83, 101, 122]
		Scaffoldless [100]
		Explant [123]
	Proteoglycan/GAG synthesis ↑	Monolayer [120, 121]
		Scaffold [54, 124, 125]
		Scaffoldless [83]
		Explant [123, 124]
	Matrix metalloproteases expression ↓	Monolayer [126]
		Explant [127]
TGF-β3	Chondrogenic differentiation of stem cells and proliferation ↑	Scaffold [128-130]
	Collagen synthesis ↑	Scaffold [129-131]
		Monolayer [132]
	Proteoglycan/GAG synthesis ↑	Scaffold [130, 131, 133, 134]
BMP-2	Chondrogenic differentiation of stem cells and proliferation ↑	Monolayer [135]
		Scaffold [136]
	Chondrocytes migration ↑	Explant [137]
BMP-7	Collagen synthesis ↑	Monolayer [138, 139]
		Explant [140]
	Matrix metalloproteases expression ↓	Monolayer [138, 139]
b-FGF	Proliferation ↑	Monolayer [141-143]
		Scaffold [106, 144, 145]
	Collagen synthesis ↑	Monolayer [142, 146]
		Scaffold [147]
	Proteoglycan/GAG synthesis ↑	Monolayer [146, 148]
		Scaffold [106]
		Explant [149]
IGF-1	Chondrogenic differentiation of stem cells and proliferation ↑	Monolayer [122, 124, 150, 151]
		Scaffold [83, 152]
	Cell migration ↑	Explant [84]
	Collagen synthesis ↑	Monolayer [121]
		Scaffold [122, 153, 154]
	Proteoglycan/GAG synthesis ↑	Scaffold [153]
		Explant [123]
PDGF	Chondrogenic differentiation of stem cells and proliferation ↑	Monolayer [142, 155, 156]
		Scaffold [157]
		Explant [157]
	Cell migration ↑	Monolayer [84]
		Scaffold [157]
		Explant [157]
	Collagen synthesis ↑	Monolayer [142]
	Proteoglycan/GAG synthesis ↑	Monolayer [148]
HGF	Proliferation ↑	Monolayer [84]
		Scaffold [157]
	Cell migration ↑	Monolayer [84]
		Scaffold [157]

		Explant [157]
	Collagen synthesis ↑	Scaffold [157]
EGF	Proliferation ↑	Monolayer [142]
	Collagen synthesis ↑	Monolayer [142]
Small bioactive molecules		
KGN	Chondrogenic differentiation of stem cells and proliferation ↑	Explant [87]
		Scaffold [158, 159]
	Collagen synthesis ↑	Explant [87]
		Scaffold [158]
	Proteoglycan/GAG synthesis ↑	Scaffold [159]
E7 peptide	Cell migration ↑	Scaffold [160-162]
Y27632	Dedifferentiation of chondrocytes ↓	Monolayer [91]
	Collagen synthesis ↑	Monolayer [163]
Biophysical factors		
C-ABC	Collagen synthesis ↑	Explant [97, 99, 164]
LOXL2	Collagen synthesis ↑	Explant [164]
Low oxygen tension	Chondrogenic differentiation of stem cells ↑	Monolayer [104]
		Scaffold [165]
	Collagen synthesis ↑	Scaffold [105, 165]
		Monolayer [165, 166]
	Proteoglycan/GAG synthesis ↑	Scaffold [105, 165]
		Monolayer [165, 166]

lagen when compared with hyaluronic acid hydrogel alone [86]. In the study by Huang et al., KGN had direct effects on the chondrogenic differentiation of tendon stem cells in vivo and in vitro [87]. Moreover, a KGN-treated tendon graft could promote the formation of meniscus-like tissue in vivo [87]. By using small bioactive molecules to recruit MSCs, the effect of meniscus and cartilage tissue regeneration could be enhanced. For example, when using the E7 peptide, cartilage regeneration was enhanced by the specific homing of endogenous stem cells [88]. By applying a synovium-derived MSC-specific affinity peptide, meniscal repair was further reinforced by recruiting and retaining endogenous stem cells [89]. Moreover, osteochondral regeneration was enhanced with an aptamer-loaded scaffold, which could also specifically recognize and recruit MSCs [90]. Rho-kinase inhibitors such as Y-27632 also promote the chondrogenic differentiation of MSCs and inhibit the dedifferentiation of chondrocytes [91, 92].

Biophysical factors

As a biophysical agent, C-ABC affects meniscal and cartilage regeneration by removing dermatan sulfate and chondroitin from proteoglycan chains while leaving collagen intact [93, 94]. This process was studied previously for cartilage integration because it was thought to be able to target cartilage integration hindrances [95, 96]. For example, engineered cartilage treated with C-ABC could lead to increased compressive stiffness and tensile properties, as well as recovery of GAG content after 2-4 weeks of culture compared to untreated groups [97-99]. The efficacy of C-ABC on engineered cartilage promotes its application in engineering meniscal tissue. Along these lines, self-assembled meniscal constructs treated with C-ABC exhibited a 2-3 fold enhancement in tensile modulus compared with untreated groups [100]. Furthermore, application of both TGF-β1 and C-ABC resulted in significant increases in both the collagen density and fiber diameter by 32% and 15%, respectively, as well as in the ultimate tensile strength and Young's modulus of the engineered fibrocartilage [101] (**Table 2**).

Oxygen tension

Since the inner area of the meniscus lacks blood supply and has a hypoxic environment, studies have attempted to mimic this environment to restore a differentiated phenotype (**Table 2**). The primary key factor mediating the hypoxic response of meniscal cells is hypoxia-inducible factor-1α (HIF-1α), which regulates

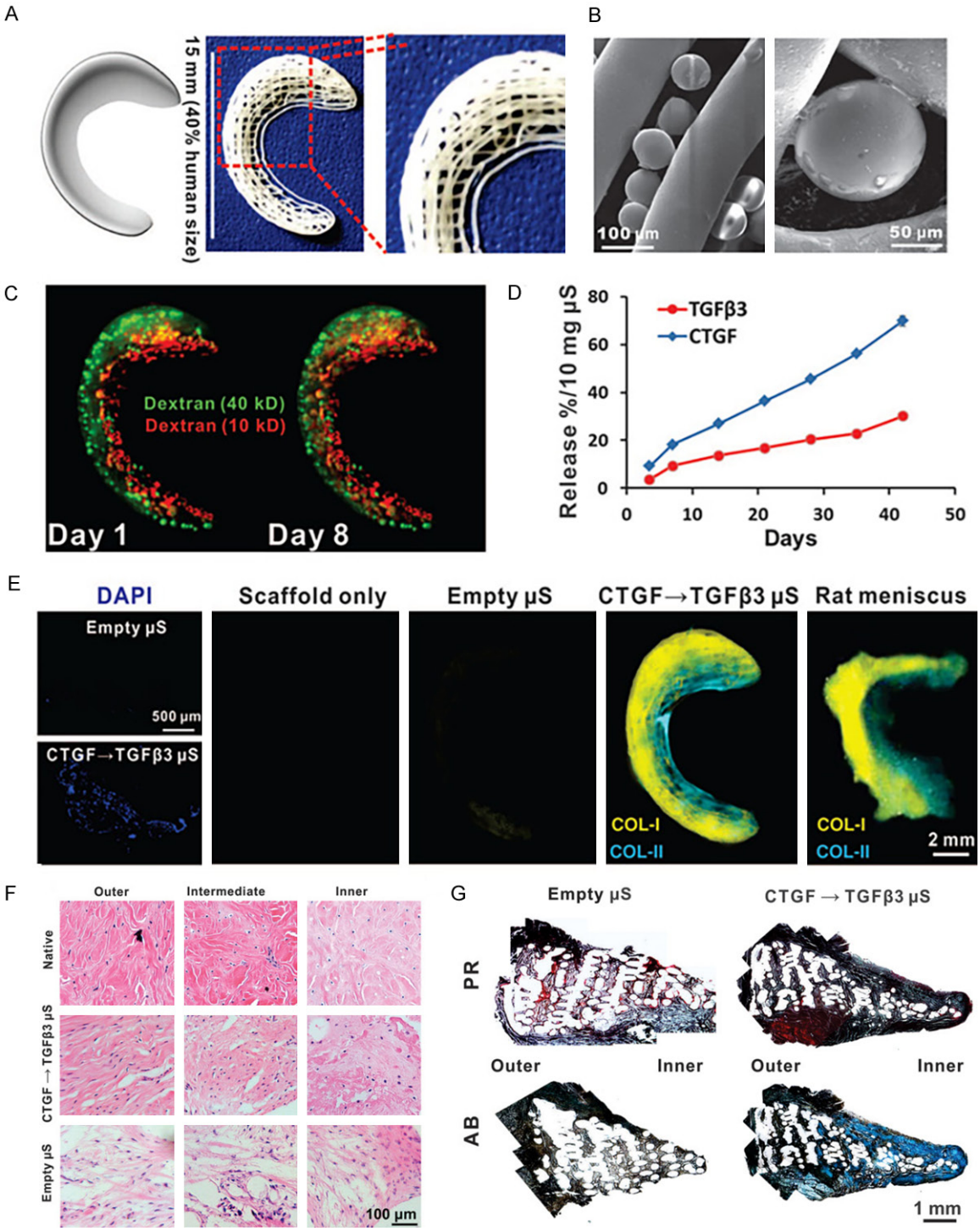

Figure 4. Spatiotemporally released rhCTGF and rhTGFβ3 induced fibrocartilage-like matrix formation in 3D-printed porous scaffolds. A. Anatomic reconstruction of human meniscus. Human meniscus scaffolds were 3D-printed with layer-by-layer deposition of PCL fibers (100-μm diameter), forming 100- to 200-μm channels. B. Poly(lactic-co-glycolic acid) (PLGA) micro-spheres (μS) encapsulating rhCTGF and rhTGFβ3 were in physical contact with PCL microfibers. C. Fluorescent dextrans simulating CTGF (green, 40 kD) and TGFβ3 (red, 10 kD) were delivered into the outer and inner zones, respectively, of human meniscus scaffolds to show scaffold loading. Distribution of dextrans was maintained from day 1 today 8. D. rhCTGF and rhTGFβ3 release from the PCL scaffolds over time in vitro. E. When the scaffolds were incubated atop human synovium MSC monolayers for 6 weeks, spatiotemporally delivered rhCTGF and rhTGFβ3 induced cells to form zone-specific collagen type I and II matrices, similar to the native rat meniscus. F.

Outer, intermediate, and inner zone phenotypes of cells populating the regenerated meniscus (H&E staining) after 12 weeks in vivo. G. Low-magnification images of retrieved meniscus grafts with spatiotemporal delivery of rhCTGF and rhTGFβ3 in comparison to empty μS after 12-week in vivo implantation. AB: alcian blue; PR: picrosirius red. Reproduced with permission [85]. *Copyright 2014, Science*.

Table 3. Effect of gene therapy for meniscal tissue engineering

Type of gene	Cells	Vector	Effects
TGF-β	Meniscal cells	RV	Matrix synthesis ↑ [113]
	Meniscal and MSCs	AdV	Cell proliferation and matrix synthesis ↑ [112]
	Meniscal cells	rAAV	Cell proliferation and matrix synthesis ↑ [110]
b-FGF	Meniscal and MSCs	rAAV	Cell proliferation ↑ [109, 167]
	Meniscal cells	NV	Cell proliferation ↑ [110]
IGF-1	Meniscal cells	NV	Cell proliferation ↑ [111]
HGF	Meniscal cells	AdV	Meniscal vascularization ↑ [115]

oxygen homeostasis and may play an important role in determining the phenotype of meniscal cells [102]. A study has shown that under hypoxic conditions, increased proteoglycan and type II collagen production could be observed in meniscal fibrochondrocytes [103]. Hypoxia also promotes chondrocytic differentiation and cartilage matrix synthesis in pluripotent mesenchymal cells [104]. In addition, the synthesis of GAG and collagen II are significantly enhanced in MSC-laden hydrogels under hypoxic culture [105]. By combining bFGF and hypoxia, a study has observed a significant increase in the ability of meniscal cells to synthesize GAG and improvement in the compressive properties of regenerated meniscal constructs [106].

Gene therapy

Gene therapy is an alternative method to augment tissue engineering by transferring genes to the repair sites [107]. Gene therapy promotes tissue regeneration by enabling the sustained, regulated, and local expression of gene products. Unlike growth factors developed in bioreactors and needed for storage, gene products are nascent proteins released through posttranslational modifications [108]. For meniscal tissue engineering, various pathways have been targeted to improve the repair effect via gene transfer (**Table 3**). For example, improvement of proliferative activities in MSCs and meniscal cells has been observed by gene transfer of FGF-2 [109, 110], TGF-β [110], and IGF-1 [111] for up to 21 days using nonviral (NV), adenoviral (AdV), and recombinant adeno-associated virus (rAAV) vectors in vitro. It has also been shown that by gene transfer of TGF-β [112-114] for up to 21 days using AdV, retroviral (RV), and rAAV vectors, anabolic processes of MSCs and meniscal cells were enhanced. In vivo, gene therapies have been developed through transplanting meniscal cells modified by HGF AdV with a PGA scaffold in a mouse model [115] or through MSCs modified by IGF-I RV with an alginate scaffold in goat meniscal injuries [111], resulting in an improved repair effect for up to 16 weeks.

Conclusion

The current surgical treatment for meniscal injuries is insufficient to prevent the progression of OA, thus accelerating the development of alternative tissue engineering strategies. Although many advances in meniscal tissue engineering have been made by using biomechanical and biochemical stimuli to regenerate neotissue akin to native meniscus, there are still many problems to be solved in the future. For biochemical stimuli, further research is needed to study the effect of small bioactive molecules on meniscal tissue engineering. In addition, the spatiotemporal specificity of meniscal regeneration might be considered when designing growth factor application strategies. It is also important to develop a sequential release model of multiple growth factors that can simulate cell proliferation, differentiation, and tissue remodeling for regenerated meniscus. Hypoxia may be combined with growth factors to enhance the repair effect and develop anisotropic reconstruction for regener-

ated meniscus. The safety and effect of gene therapy need further verification in the future. For biomechanical stimuli, more work is needed to determine an optimal regimen because the effects of biomechanical stimuli on meniscal constructs vary depending on the type, time, magnitude, and frequency of the applied load. The combination of biomechanical stimuli and biochemical stimuli may be an alternative way to develop structural and functional anisotropy in an engineered meniscus.

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Disclosure of conflict of interest

None.

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