Fibronectin matrix polymerization increases tensile strength of model tissue

Candace D. Gildner, Amy L. Lerner, and Denise C. Hocking

1Department of Biomedical Engineering and 2Department of Pharmacology and Physiology, University of Rochester Medical Center, Rochester, New York 14642

Submitted 10 September 2003; accepted in final form 26 February 2004

Fibronectin matrix polymerization increases tensile strength of model tissue. Am J Physiol Heart Circ Physiol 287: H46–H53, 2004. First published March 4, 2004; 10.1152/ajpheart.00859.2003.—The composition and organization of the extracellular matrix (ECM) contribute to the mechanical properties of tissues. The polymerization of fibronectin into the ECM increases actin organization and regulates the composition of the ECM. In this study, we examined the ability of cell-dependent fibronectin matrix polymerization to affect the tensile properties of an established tissue model. Our data indicate that fibronectin polymerization increases the ultimate strength and toughness, but not the stiffness, of collagen biogels. A fragment of fibronectin that stimulates mechanical tension generation by cells, but is not incorporated into ECM fibrils, did not increase the tensile properties, suggesting that changes in actin organization in the absence of fibronectin fibril formation are not sufficient to increase tensile strength. The actin cytoskeleton was needed to initiate the fibronectin-induced increases in the mechanical properties. However, once fibronectin-treated collagen biogels were fully contracted, the actin cytoskeleton no longer contributed to the tensile strength. These data indicate that fibronectin polymerization plays a significant role in determining the mechanical strength of collagen biogels and suggest a novel mechanism by which fibronectin can be used to enhance the mechanical performance of artificial tissue constructs.

Tissue engineering; extracellular matrix; mechanical properties

Tissue engineering is a potentially revolutionary approach for replacing or regenerating diseased or destroyed organs and tissues. Most organs and tissues in the body are subjected to mechanical stresses and strains. Thus one of the challenges that face tissue engineering involves identifying and optimizing the critical structural and mechanical factors that contribute to the mechanical properties of load-bearing tissues. In blood vessels, for example, the mechanical properties that are essential for proper functioning include tensile stiffness, elasticity, and compressibility (28). These mechanical properties are mediated, in part, by components of the extracellular matrix (ECM) (28). How individual ECM molecules contribute specifically to the mechanical properties of tissues is incompletely understood. For tissue engineering, tailoring the composition and organization of the ECM to selectively attain the appropriate mechanical properties for a given tissue will likely serve as a critical approach to linking structure with function.

Fibronectins are high-molecular-mass glycoproteins that circulate in a soluble form in the plasma and are also found in an insoluble form that localizes to the ECM (21). Soluble fibronectin is polymerized into ECM fibrils through a tightly regulated, cell-mediated process (21). Fibronectin fibril formation is not spontaneous but instead requires coordinated events involving integrin receptors and the actin cytoskeleton (21). The active assembly of fibronectin into the ECM controls the subsequent deposition, organization, and retention of several other ECM molecules, including collagen I (25, 31, 34). Fibronectin polymerization increases cytoskeletal organization and mechanical tension generation by cells (17). Furthermore, fibronectin induces the contraction of cell-embedded collagen biogels (12) by a mechanism that requires fibronectin polymerization (17). Both the actin cytoskeleton and the ECM contribute quantitatively to the mechanical properties of artificial tissues (35). Thus we hypothesized that fibronectin matrix polymerization plays a pivotal role in determining the mechanical strength of tissues.

As the primary structural protein of vertebrates, collagen has numerous advantages as a biomaterial, including low toxicity and antigenicity, biodegradability, and high abundance (20). Collagen-based implants have been successfully used as skin replacements (20) and are being tested for their use in tissue-engineered vascular grafts and heart valves (28). In this study, we utilized an established, collagen-based tissue model in which neutralized type I collagen is seeded with fibroblasts and then allowed to polymerize and contract in ring-shaped structures (3, 7). Uniaxial tensile testing was used to determine how the cell-mediated formation of ECM fibronectin fibrils contributes to the mechanical properties of these artificial tissue constructs. Our results demonstrate that fibronectin matrix polymerization stimulates a rapid and significant increase in the ultimate strength and toughness, but not the stiffness, of collagen biogels.

Materials and Methods

Materials. Reagents were obtained from Sigma (St. Louis, MO) unless otherwise specified. Tissue culture materials were purchased from Corning/Costar (Cambridge, MA). Human plasma fibronectin was isolated as described (22). The construction and purification of the recombinant fibronectin fragment, glutathione-S-transferase (GST)/III-1H8–10, has been described (16). Human fibrinogen, depleted of fibronectin, was a gift from Dr. Patricia J. Simpson-Haidaris (University of Rochester; Rochester, NY) (25). Laminin was from BD Biosciences (Bedford, MA). Type I rat tail collagen was from Upstate Biotechnology (Lake Placid, NY). Cytochalasin D (CytoD) was from Calbiochem (San Diego, CA). The anti-fibronectin monoclonal antibody (mAb) 9D2 (8) was provided by Dr. Deane Mosher (University of Wisconsin, Madison, WI).

Cell culture. Mouse embryonic fibronectin-null myofibroblasts (32) were a gift from Dr. Jane Sottile (University of Rochester). Fibronectin-null cells do not produce endogenous fibronectin but are able to polymerize exogenously added fibronectin into the ECM (32).

Acknowledgments

This research was supported by National Institutes of Health Grants HL63561, HL70852, and HL70844.

Address for reprint requests and other correspondence: D. C. Hocking, Dept. of Biomedical Engineering and Dept. of Pharmacology and Physiology, Univ. of Rochester Medical Center, 601 Elmwood Ave., PO Box 711, Rochester, NY 14642 (E-mail: denise_hocking@urmc.rochester.edu).
Cells were cultured on collagen type I-coated dishes and grown in a 1:1 mixture of AimV (Invitrogen; Carlsbad, CA) and Cellgro (Mediatech; Herndon, VA) (32). These media do not require serum supplementation. Thus no exogenous source of fibronectin is present during routine culture.

Cell-embedded collagen biogels. Cell-embedded collagen gels were prepared as previously described (17) to obtain a final collagen concentration of 0.8 mg/ml. Fibronectin-null cells were added to the neutralized type I collagen solutions at 2 × 10^5 cells/ml. Fibronectin (10–80 nM), GST/III-H,8–10 (250 nM), laminin (40 nM), fibrinogen (40 nM), or an equal volume of PBS was added to the collagen/cell solution. For tensile testing, collagen biogels were formed into ring-shaped structures by pipetting 3 ml of the collagen/cell mixture containing cell solution. For tensile testing, collagen biogels were formed into ring-shaped structures by pipetting 3 ml of the collagen/cell mixture containing cell solution.

To inhibit fibronectin matrix polymerization, fibronectin was pre-treated with either the fibronectin-specific mAb, 9D2 (25 μg/ml) (8), or nonimmune mouse IgG (25 μg/ml) for 30 min before its addition to the cell/collagen solution. In other experiments, CytoD was solubilized in DMSO and added to the collagen/cell mixture either before collagen biogel polymerization (2 μM) or to the media of contracted collagen biogels (10 μM) 2 h after mechanical testing (26, 35). These concentrations of CytoD have previously been shown to inhibit actin polymerization (26, 36). Control biogels received an equal volume of DMSO.

Mechanical testing. Uniaxial tension tests were performed on contracted collagen rings using a Q-Test 5 electromechanical testing machine (MTS Systems; Eden Prairie, MN). Collagen biogels were looped over 6.4-mm nylon grips precoated with 2% BSA and hydrated by placing a cheesecloth wetted with DMEM/HEPES (Invitrogen) at the top of the biogel. A representative biogel at the start of mechanical testing is shown in Fig. 1. Collagen biogels were pulled to failure at a constant speed of 1 mm/min for an initial strain rate of 2–3%. Front- and side-view images of the collagen biogels were taken at the beginning and end of each experiment with the use of a digital camera (model DC 290, Eastman Kodak; Rochester, NY). The average initial cross-sectional diameter of each leg of the collagen biogel and its length were measured with ImagePro Plus software (Media Cybernetics; Silver Spring, MD). The load was recorded as a function of the distance stretched and was measured to the nearest thousandth of a Newton with the use of a 5 N load cell (MTS Systems). The baseline noise of the load cell was determined in the absence of sample (~0.002 N) and was subtracted from the loads subsequently recorded for each collagen biogel. The initial length of the gel was then defined as the initial recorded length plus the distance the crosshead traveled until a load of >0.001 N was obtained. The initial volumes of the collagen biogels were calculated by multiplying the cross-sectional area of the biogels by their length. The grip region was defined as the material resting on the grip plus the material 1 cm above and below the center of each grip. At failure, this accounted for ~40% of the total length of the collagen biogel. Failure occurred within the grip region 48% of the time, indicating a minimal stress concentration at the grips.

Engineering analysis. The engineering stress (σ) and strain (ε) were calculated using the initial cross-sectional area and length of the collagen biogel, respectively (6). Fung (11) defined the instantaneous tensile modulus for soft biological tissue as a linear function of the stress. Stress is defined as

\[ \sigma = A(e^{B} - 1) \]  

where A and B are material constants. A and B were determined by performing a nonlinear regression using Mathematica 4.2 (Wolfram Research; Champaign, IL), which fit the experimental stress-strain data to Eq. 1 (+FN, n = 20; +PBS, n = 19). Data were fit with a 95% confidence level. The ultimate strength was defined as the maximum stress a biogel could withstand before failure. The toughness of each curve was defined as the area under the curve before the ultimate stress (6) and was calculated using the trapezoidal rule (n = 380). Studies (not shown) indicated that the tensile mechanical properties were independent of evaluated mechanical testing speeds (0.5, 0.75, and 1 mm/min).

Circumferential residual stress was determined by measuring the “opening angle” of radially cut collagen biogels, as described (24). Briefly, collagen biogel rings were photographed before and 15 min after a single radial cut was made in the ring. The angle of displacement was defined as the angle created between the two endpoints and the middle of the gel’s circumference and was determined using ImagePro Plus software. The angle of displacement was negligible for both fibronectin-treated (n = 5) and PBS-treated (n = 5) gels, indicating that residual stresses had not developed.

Statistical analysis. Mechanical properties are reported as means ± SE and were determined from at least two independent experiments performed in either duplicate or triplicate. One-way ANOVA, followed by Tukey’s test, were performed on the data (Prizm Software, GraphPad; San Diego, CA). Changes were considered significant for P values <0.05.
RESULTS

Fibronectin enhances tensile mechanical properties of cell-embedded collagen biogels. We previously demonstrated that fibronectin matrix polymerization increases collagen biogel contraction (17) and is required for the organization of ECM collagen fibrils (31). Other studies have demonstrated that the tensile properties of cell-embedded collagen lattices are influenced by both biogel contraction and collagen fibril alignment (18, 35). To determine the effect of fibronectin on the tensile mechanical properties of collagen biogels, fibronectin-null myofibroblasts were embedded in type I collagen. The fibronectin-null background provides an ideal system for determining the mechanical properties in the complete absence of fibronectin and for distinguishing the effects of soluble versus ECM fibronectin (16, 17, 31, 32). Cell-populated collagen gels were allowed to contract freely in the absence and presence of increasing concentrations of fibronectin and then subjected to uniaxial tension testing. Representative stress-strain curves are shown in Fig. 2A. Both PBS- and fibronectin-treated biogels were characterized by an exponential increase in their stress as a function of strain (Fig. 2A).

In the absence of fibronectin, the average ultimate strength and toughness were 4.7 ± 1.2 kPa and 0.36 ± 0.09 kJ/m^3 (Fig. 2, B and C), respectively. The addition of fibronectin to collagen biogels induced a significant dose-dependent increase in the ultimate strength (Fig. 2B) and toughness (Fig. 2C) of these biogels. At a fibronectin concentration of 80 nM (40 μg/ml), the ultimate strength was increased ~5-fold to 25.7 ± 1.6 kPa and the toughness was increased ~13-fold to 4.6 ± 0.6 kJ/m^3. A similar relationship was observed with the ultimate strain, which increased from 0.17 + 0.02 in the absence to fibronectin to 0.48 + 0.04 when 80 nM fibronectin was added to the collagen biogels. These data indicate that fibronectin increases the stress that collagen biogels can withstand and the energy that these biogels can absorb before failure.

The modulus of a material is typically defined as the slope of the linear portion of the stress-strain curve. However, in these experiments, the instantaneous modulus was calculated to account for the nonlinear, exponential character of the experimental stress-strain curves (11). The average values for the material constants A and B described in Eq. 1 of PBS- and fibronectin-treated biogels were not significantly different (A, 17.54 vs. 6.32 kPa; B, 4.19 vs. 4.18, respectively). In addition, the initial moduli (the modulus at a state of zero stress) of control and fibronectin-treated collagen biogels were similar (Fig. 3B). Likewise, the addition of fibronectin to collagen biogels did not affect the rate at which the modulus increased as a function of the stress (Fig. 3B). These data indicate that fibronectin does not increase the stiffness of collagen biogels.

To determine whether the increase in the mechanical properties of collagen biogels was specific for fibronectin, cell-embedded collagen gels were treated with an equal molar concentration of either fibrinogen or laminin. As shown in Fig. 4, the ultimate strength and toughness of fibrinogen- and laminin-treated collagen biogels were similar to that of PBS-treated biogels. These data indicate that the ability of fibronectin to increase the tensile mechanical properties of collagen biogels is not a general property of ECM proteins.

Fig. 2. Fibronectin increases the mechanical properties of collagen biogels. Cell-embedded collagen gels were prepared in the absence and presence of increasing concentrations of fibronectin. Biogels were pulled to failure at a constant speed of 1 mm/min. A: representative stress-strain curves for biogels treated with 40 nM fibronectin (–) or an equal volume of PBS (○). The ultimate strength (B) and toughness (C) are shown as a function of fibronectin concentration. *P < 0.001 and #P < 0.05 vs. PBS.
Fibronectin polymerization is essential for fibronectin-induced changes in tensile mechanical properties. Plasma- or tissue-derived soluble fibronectin is assembled into ECM fibrils on the cell surface through a dynamic, cell-mediated process (21). We previously demonstrated that the fibronectin-induced increase in cell contractility requires the polymerization of fibronectin into the ECM (17). To determine whether the fibronectin-mediated increases in the ultimate strength and toughness of collagen biogels similarly require the formation of ECM fibronectin fibrils, fibronectin polymerization was inhibited with the anti-fibronectin mAb 9D2. The 9D2 mAb has been shown to inhibit fibronectin polymerization in a variety of cell types, including dermal fibroblasts (8), aortic smooth muscle cells (31), microvascular endothelial cells (31), and fibronectin-null cells (32). Treatment with 9D2 mAb does not inhibit cell adhesion to fibronectin (15) nor does it block the initial association of fibronectin to the surface of adherent cells (8). Furthermore, we (17) have previously shown that the 9D2 mAb blocks the formation of fibronectin multimers in collagen biogels. As shown in Fig. 5, the addition of 9D2 mAb to fibronectin-treated collagen biogels resulted in a significant inhibition of the fibronectin-induced increases in the ultimate strength and the toughness of collagen biogels compared with nonimmune IgG-treated controls. These data indicate that fibronectin increases the mechanical properties of collagen biogels by a mechanism that requires the assembly of fibronectin into ECM fibrils.

Fibronectin matrix mimetic GST/III-1H,8–10 does not enhance mechanical properties of cell-embedded collagen biogels. We have engineered a recombinant fibronectin construct, GST/III-1H,8–10, which has functional properties similar to ECM fibronectin but does not become assembled into ECM fibrils (16). GST/III-1H,8–10 binds to both integrins and heparan sulfate proteoglycans and promotes collagen biogel contraction (16) as well as cell migration (15). To determine
whether the increase in mechanical properties induced by ECM fibronectin was mimicked by GST/III-1H,8–10, collagen biogels were treated with saturating concentrations of GST/III-1H,8–10. As shown in Fig. 6, neither the ultimate strength (Fig. 6A) nor toughness (Fig. 6B) of collagen biogels treated with GST/III-1H,8–10 were significantly different from control biogels. Collagen biogels treated with GST/III-1H,8–10 had a significantly smaller volume than biogels treated with PBS (Fig. 6C), indicating that GST/III-1H,8–10-treated biogels were more contracted than controls. These data indicate that treatment of collagen biogels with a recombinant fragment of fibronectin that stimulates collagen biogel contraction but is not incorporated into ECM fibrils is not sufficient to increase the mechanical properties of collagen biogels.

**Role of actin cytoskeleton in determining mechanical properties of cell-embedded collagen biogels.** The actin cytoskeleton can contribute to the mechanical properties of cell-embedded collagen biogels (35) and is required for cell-mediated fibronectin polymerization (36). To determine whether the actin cytoskeleton is essential for the initiation of fibronectin-induced changes in the mechanical properties of collagen biogels, fibronectin was added to the collagen/cell solution in the absence and presence of CytoD. Biogels were allowed to contract for 20 h and mechanical testing was performed. The addition of CytoD to collagen biogels at the same time fibronectin was added prevented the fibronectin-induced increases in the ultimate strength and toughness of collagen biogels (Fig. 7A), indicating that the actin cytoskeleton is required to initiate the fibronectin-induced increase in the tensile strength.

To determine whether an intact actin cytoskeleton is necessary to maintain the level of collagen biogel contraction induced by ECM fibronectin, assays were performed in which collagen biogels were allowed to contract in the absence and presence of fibronectin for increasing amounts of time. Two hours before measurement of collagen gel contraction, the actin cytoskeleton was disrupted by the addition of CytoD to the media. As shown in Fig. 7B, fibronectin-induced collagen biogel contraction was partially reversible up to 8 h after the initial formation of the collagen biogels. Similar effects of CytoD on collagen biogel reexpansion have been previously reported (14). However, after 10 h of fibronectin treatment, the extent of biogel contraction was not altered by the disruption of the actin cytoskeleton. The extent of contraction that occurred in response to fibronectin between 6 and 10 h was similar (Fig. 7B), providing evidence that the inability of CytoD to reverse contraction at later time points was not due either to an inability of the CytoD to diffuse into the gel by 2 h or to differences in the degree of collagen gel contraction. These data indicate that the actin cytoskeleton is not required to maintain the fully contracted state of fibronectin-treated collagen biogels.

To next determine the relative contributions of the ECM and the actin cytoskeleton to the mechanical properties of fully contracted collagen biogels, fibronectin-treated biogels were allowed to contract for 20 h. The actin cytoskeleton was then disrupted by treatment with CytoD for an additional 2 h. As
shown in Fig. 7C, treatment of fully contracted, fibronectin-treated biogels with CytoD did not affect the fibronectin-induced increases in the ultimate strength and toughness. These data suggest that the tensile strength of contracted, fibronectin-treated collagen biogels is determined primarily by the ECM and not the cells.

**DISCUSSION**

In the present study, we have shown that the addition of relatively small quantities of fibronectin (5–40 μg/ml) to biogels containing 0.8 mg/ml collagen type I results in up to a 5-fold increase in the tensile ultimate strength and a 13-fold increase in the toughness of this tissue model. Blocking fibronectin matrix polymerization inhibited the fibronectin-induced increases in the ultimate strength and toughness of collagen biogels, indicating that the formation of insoluble ECM fibronectin fibrils is essential to the development of mechanical strength. The 9D2 mAb does not block either cell adhesion to fibronectin (15) or the initial association of fibronectin to cell surfaces (8). In addition, the integrin-binding fragment of fibronectin, GST/III-1H,8–10, stimulated collagen biogel contraction but did not enhance the mechanical properties of these gels. These data indicate that neither contraction alone nor integrin-mediated adhesion to fibronectin is sufficient to increase the mechanical properties of collagen-based tissue constructs. Importantly, these data provide evidence that the cell-directed organization of the ECM, and not simply the ECM components, governs the mechanical properties of tissues.

ECM fibronectin controls cytoskeletal organization, in part, through intracellular signals that are initiated after the exposure of a neoepitope within fibronectin’s III-1 module during matrix polymerization (16). A recombinant fibronectin construct that contains both the matricryptic, heparin-binding fragment of III-1 and the integrin-binding III8–10 modules (GST/III-1H,8–10) mimics the effect of ECM fibronectin on collagen biogel contraction (16). In the present study, addition of GST/III-1H,8–10 to cell-embedded collagen gels promoted biogel contraction, but did not increase the mechanical strength of these gels. Unlike intact fibronectin, GST/III-1H,8–10 does not become incorporated into ECM fibrils and does not promote the co-polymerization of collagen into the ECM (D. C. Hocking and J. Sottile, unpublished observations). These data indicate that intracellular signals triggered in response to GST/III-1H,8–10, which promote actin reorganization and collagen biogel contraction, are not sufficient to increase the mechanical strength of collagen biogels.

In the present study, the actin cytoskeleton was required to initiate the fibronectin-induced increases in the mechanical strength of collagen biogels. A functional actin cytoskeleton is essential for cell-mediated fibronectin matrix polymerization (36). Thus the actin cytoskeleton likely contributes to the development of mechanical strength by promoting the polymerization of a fibronectin matrix. In a study by Wakatsuki et al. (35), contracted collagen biogels were treated with CytoD and then mechanically tested to distinguish the contribution of the “active,” or cellular components, from that of the “passive,” ECM components. Their data demonstrated that both the
cells and the ECM contributed to the tensile mechanical properties of their collagen biogels. In our study, the tensile strength of full-contracted fibronectin-treated collagen biogels was maintained after treatment with CytoD, suggesting that under our culture conditions, the ECM was the primary contributor to the tensile strength of the biogel. Taken together, these data suggest that under different physiological and/or pathological conditions, the relative contribution of the cells and the ECM to the tensile mechanical properties of tissues may vary. Furthermore, these studies raise the possibility that during abnormal vasculature remodeling, as occurs in such diseases as atherosclerosis, hypertension, and restenosis (21), differences in the extent or organization of the fibronectin ECM may have a significant affect on the tensile properties of native blood vessels.

When embedded in a collagen gel, cells organize and contract the surrounding collagen fibrils (2, 4, 33). The mechanical properties of cell-populated collagen gels are influenced by both cell contraction as well as collagen fibril alignment (18, 35). The association of fibronectin and collagen in the ECM of tissues is well documented (19). In addition, binding interactions between fibronectin and individual type I collagen fibrils have been demonstrated in vitro (9, 10). Fibronectin matrix polymerization is required for the deposition of collagen fibrils in the ECM (31, 34). Moreover, fibronectin-collagen interactions are necessary for collagen biogel contraction in response to fibronectin (17). Taken together, these data suggest that the fibronectin-mediated increase in collagen gel tensile strength may involve the interaction of fibronectin with collagen fibrils in the ECM. Interestingly, the fibronectin-induced increase in tensile strength occurs in the absence of a change in stiffness, implying that the collagen fibers were able to extend further and absorb more energy before failure. These data suggest the possibility that fibronectin may protect the biogels from failure by interacting with the collagen and altering the microstructure of the collagen fibrils (29). The increased failure strain observed in our system could occur through several mechanisms including changes in the extent of intrafibrillar cross-links or hydrophobic interactions or alterations in the organizational structure of the collagen bundles (29).

The tensile mechanical properties of soft tissues may change if the material is repeatedly strained to a point below the failure threshold (35). The differences that have been observed after the first stretch cycle have been attributed to a remodeling of the ECM material (35). In the present study, our focus was to determine how the cell-dependent organization of the fibronectin ECM contributes to the tensile properties. Because preconditioning with mechanical strain may have remodeled this ECM and thus introduced an additional variable, our studies were performed on gels that were pulled directly to failure. Future studies will determine whether the tensile properties of fibronectin-treated collagen biogels are altered by cyclic strain.

To function as replacements for load-bearing tissues, collagen-based tissue constructs must be able to withstand in vivo mechanical forces and deformations. The tensile ultimate strength and toughness of intact blood vessels is 1–2 MPa (23) and 1–2.5 kJm$^{-2}$ (27), respectively. Currently, the mechanical strength of most collagen-based constructs is well below these values. In the absence of fibronectin, the average ultimate strength of cell-embedded collagen gels was $\sim$5 kPa, which is similar to previously reported values (29, 30). In previous studies, subjected collagen biogels to cyclical strain for either 4 or 8 days increased the ultimate strength to 17 and 58 kPa, respectively (30). By allowing collagen biogels to contract around a central mandrel for 36 h, the ultimate strength was increased by 6.5-fold to 0.7 kPa (1), whereas glycation of ECM proteins increased the ultimate strength by 2-fold after 70 days to 40 kPa (13). In our studies, the addition of 80 nM fibronectin to collagen biogels for 20 h induced a 5-fold increase in the ultimate strength to 25.7 kPa. Thus, by comparison, ECM fibronectin stimulates a rapid and significant increase in the mechanical properties of cell-embedded tissue constructs.

In summary, we have shown that fibronectin increases both the ultimate strength and toughness of cell-embedded collagen gels in a manner that is dependent on the cell-mediated assembly of a fibronectin matrix. Emerging evidence indicates that ECM fibronectin plays a unique role in regulating cell processes that are essential for tissue remodeling, including cytoskeletal tension generation (17), ECM deposition and organization (31), as well as cell growth (32) and migration (15). As such, optimizing the mechanical and biological properties of artificial tissues by incorporating the organization and essential characteristics of ECM fibronectin into the design of these constructs will likely enhance not only biological function, but will also improve the performance of these tissues after implantation (5).

GRANTS

This work was supported by National Institutes of Health Grants EB-00986 and HL-64074.

REFERENCES


