

**Table 1. Patient information**

Serial no.	Age	Sex	Clinical Diagnosis	NAS Score
1	61	Female	Healthy	0
2	56	Male	Healthy	0
3	40	Male	NASH/Diabetes	6
4	58	Female	NASH/Diabetes	5
5	51	Male	NASH	6
6	38	Female	NASH/Diabetes	2
7	50	Male	Healthy	0
8	70	Male	NASH/Diabetes	3
9	47	Female	Healthy	0
10	52	Female	NASH	4
11	66	Male	NASH	3
12	58	Male	NASH	3
13	66	Male	NASH/Diabetes	4
14	59	Female	NASH/Diabetes	5

**Table 2. List of antibodies used for various applications**

	<b>Manufacturer/ Cat #</b>	<b>Application/ Concentration</b>
<b>Primary Antibodies</b>		
c-Myc	Santa Cruz , #sc-40	IHC, 1:200
Glutathione Synthase (GS)	Santa Cruz, #sc-74430	IHC, 1:200
Cortactin	Abcam, #ab33333	IF, 1:200
Ki67	Abcam, #ab15580	IF, 1:200
Tensin 1 (TNS1)	Sigma-Aldrich, #SAB4200283	IF, 1:200; WB, 1:1000; PLA, 1:
YAP	Cell Signaling Technology, #4912S	IF, 1:200; WB, 1:1000
Vinculin	Abcam, #ab129002	WB, 1:10,000
Integrin $\beta$ 1 (Itgb1)	Abcam, #ab24693	PLA, 1:100
<b>Secondary Antibodies</b>		
HRP Goat $\alpha$ -Rabbit	Abcam, #ab6721	WB, 1:5000
Alexa Fluor 488 Chicken $\alpha$ -Rabbit	Invitrogen, #A21441	IF, 1:500
Alexa Fluor 555 Goat $\alpha$ -Mouse	Invitrogen, #A21422	IF, 1:500
Alexa Fluor 555 Donkey $\alpha$ -Rabbit	Invitrogen, #A31572	IF, 1:500
Biotinylated Goat $\alpha$ -Mouse	Vector Lab, #BA-9200	IHC, 1:500

**Table 3. List of sequence of primers for qPCR.**

<b>mRNA</b>	<b>Primer Sequence</b>
<b>Human <i>ARBP</i></b>	Forward: 5'- GAAACTCTGCATTCTCGCTTC-3' Reverse: 5'- GGTGTAATCCGTCTCCACAG-3'
<b>Human <i>CTGF</i></b>	Forward: 5'- GACGAGCCCAAGGACCAAAC -3' Reverse: 5'- TCATAGTTGGGTCTGGGCCA-3'
<b>Human <i>Ki67</i></b>	Forward: 5'- TCCTTTGGTGGGCACCTAAGACCTG-3' Reverse: 5'- TGATGGTTGAGGTCGTTCCCTTGATG-3'
<b>Human <i>TNSI</i></b>	Forward: 5'- GTACGTCACAGAGAGGATCATCG -3' Reverse: 5'-GCAGGTAGTTGCCTCCATGTT -3'

**Table 4. List of parameters employed in the computational model.**

<b>Symbol</b>	<b>Definition</b>	<b>Value</b>
$r_{0,f}$	Equilibrium length of fibril segments	$5.0 \times 10^{-7}$ [m]
$r_{c,f}$	Diameter of fibril segments	$2.0 \times 10^{-8}$ [m]
$\theta_{0,f}$	Bending angle formed by adjacent fibril segments	0 [rad]
$\kappa_{s,f}$	Extensional stiffness of fibrils	$1.59 \times 10^{-2}$ [N/m]
$\kappa_{b,f}$	Bending stiffness of fibrils	$1.67 \times 10^{-19}$ [N·m]
$r_{0,bu}$	Equilibrium length of a bundler arm	$2.0 \times 10^{-8}$ [m]
$r_{c,bu}$	Diameter of a bundler arm	$2.0 \times 10^{-8}$ [m]
$\theta_{0,bu,1}$	Bending angle formed by two bundler arms	0 [rad]
$\theta_{0,bu,2}$	Bending angle formed by mother and daughter fibrils	0-30 [deg]
$\kappa_{s,bu}$	Extensional stiffness of cross-linkers	$2.0 \times 10^{-3}$ [N/m]
$\kappa_{b,bu,1}$	Bending stiffness 1 of cross-linkers	$1.04 \times 10^{-18}$ [N·m]
$\kappa_{b,bu,2}$	Bending stiffness 2 of cross-linkers	$1.04 \times 10^{-18}$ [N·m]
$r_{0,xl}$	Equilibrium length of a cross-linker arm	$2.0 \times 10^{-8}$ [m]
$r_{c,xl}$	Diameter of a cross-linker arm	$2.0 \times 10^{-8}$ [m]
$\theta_{0,xl}$	Bending angle formed by two cross-linker arms	0 [rad]
$\kappa_{s,xl}$	Extensional stiffness of cross-linkers	$2.0 \times 10^{-3}$ [N/m]
$\kappa_{b,xl}$	Bending stiffness of cross-linkers	$1.04 \times 10^{-17}$ [N·m]
$\kappa_r$	Strength of repulsive force	$1.69 \times 10^{-3}$ [N/m]
$k_{+,xl}$	Binding rate of cross-linkers	$1 \times 10^2$ [ $\mu\text{M}^{-1}\text{s}^{-1}$ ]
$k_{-,xl}^0$	Zero-force unbinding rate constant of cross-linkers	$1 \times 10^{-6}$ [ $\text{s}^{-1}$ ]
$x_{-,xl}$	Force sensitivity of cross-linker unbinding	$4.0 \times 10^{-10}$ [m]
$\langle L_f \rangle$	Average length of fibers	3 or 5 [ $\mu\text{m}$ ]
$C_f$	Fiber density	16.96 [fibril/ $\mu\text{m}^3$ ]
$C_{bu}$	Bundler density	1.68 [bundler/ $\mu\text{m}^3$ ]
$C_{xl}$	Cross-linking density	120 [cross-linker/ $\mu\text{m}^3$ ]
$\gamma$	Shear strain	0.2 (= 20 %)
$\Delta t$	Time step	$4.91 \times 10^{-5}$ [s]
$\mu$	Viscosity of medium	8.6 [Pa·s]
$k_B T$	Thermal energy	$4.142 \times 10^{-21}$ [J]

## SUPPLEMENTARY TEXT

### Brownian dynamics based on the Langevin equation

The displacements of the cylindrical elements at each step are governed by the Langevin equation with negligence of inertia:

$$\mathbf{F}_i - \zeta_i \frac{d\mathbf{r}_i}{dt} + \mathbf{F}_i^T = 0 \quad (\text{S1})$$

where  $\mathbf{r}_i$  indicates the position of the  $i$ th element,  $\zeta_i$  is a drag coefficient,  $\mathbf{F}_i$  is a deterministic force, and  $t$  is time. The stochastic force  $\mathbf{F}_i^T$  satisfies the fluctuation-dissipation theorem <sup>1</sup>:

$$\langle \mathbf{F}_i^T(t) \mathbf{F}_j^T(t) \rangle = \frac{2k_B T \zeta_i \delta_{ij}}{\Delta t} \boldsymbol{\delta} \quad (\text{S2})$$

where  $\delta_{ij}$  is the Kronecker delta,  $\boldsymbol{\delta}$  is a second-order tensor, and  $\Delta t$  is a time step.

The drag coefficients are calculated using an approximated form for a cylindrical object <sup>2</sup>:

$$\zeta_i = 3\pi\mu r_{c,i} \frac{3 + 2r_{0,i} / r_{c,i}}{5} \quad (\text{S3})$$

where  $\mu$  is the viscosity of a surrounding medium, and  $r_{0,i}$  and  $r_{c,i}$  are the length and diameter of an element, respectively. To update the positions of all cylindrical elements at each time step, we use the Euler integration scheme:

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \frac{d\mathbf{r}_i}{dt} \Delta t = \mathbf{r}_i(t) + \frac{1}{\zeta_i} (\mathbf{F}_i + \mathbf{F}_i^T) \Delta t \quad (\text{S4})$$

### Deterministic forces

Deterministic forces include extensional and bending forces that maintain equilibrium lengths and equilibrium angles as well as repulsive forces accounting for volume-exclusion effects between cylindrical elements that represent fibrils. Extensional and bending forces for fibrils, bundlers, and cross-linkers originate from harmonic potentials:

$$U_s = \frac{1}{2} \kappa_s (r - r_0)^2 \quad (\text{S5})$$

$$U_b = \frac{1}{2} \kappa_b (\theta - \theta_0)^2 \quad (\text{S6})$$

where  $\kappa_s$  and  $\kappa_b$  are extensional and bending stiffnesses,  $r$  and  $r_0$  are the instantaneous and equilibrium lengths of cylindrical elements, and  $\theta$  and  $\theta_0$  are instantaneous and equilibrium angles formed by interconnected elements.

### **Simplified geometry and mechanics of matrix elements**

Fibrils are comprised of serially connected cylindrical segments. The equilibrium length of fibril elements ( $r_{0,f} = 0.5 \mu\text{m}$ ) and an equilibrium angle formed by two adjacent fibril elements ( $\theta_{0,f} = 0 \text{ rad}$ ) are maintained by extensional ( $\kappa_{s,f}$ ) and bending stiffnesses ( $\kappa_{b,f}$ ) of fibrils, respectively. The value of  $\kappa_{b,f}$  used in the model corresponds to the persistence length of  $\sim 20 \mu\text{m}$ . Bundlers consist of two cylindrical arm segments. The equilibrium length of a bundler arm ( $r_{0,bu} = 20 \text{ nm}$ ) is maintained by extensional stiffness ( $\kappa_{s,bu}$ ). An equilibrium angle between two arms of each bundler ( $\theta_{0,bu,1} = 0 \text{ rad}$ ) is maintained by bending stiffness ( $\kappa_{b,bu,1}$ ). An equilibrium angle between two fibrils connected by bundlers ( $\theta_{0,bu,2}$ ) is maintained by additional bending stiffness ( $\kappa_{b,bu,2}$ ). Cross-linkers also consist of two cylindrical arm segments. The equilibrium length of a cross-linker arm ( $r_{0,xl} = 20 \text{ nm}$ ) is maintained by extensional stiffness ( $\kappa_{s,xl}$ ), and an equilibrium angle

formed by two arms of each cross-linker ( $\theta_{xl} = 0$  rad) is maintained by bending stiffness ( $\kappa_{b,xl}$ ). Forces exerted on fibril elements by bundlers or cross-linkers are distributed onto two nodes located at the ends of the fibril element.

Repulsive forces between fibrils prevent the fibrils from passing through each other. A minimum distance between two cylindrical elements,  $r_i$ , is computed, and the repulsive force originates from the following harmonic potential ( $U_{r,f}$ ):

$$U_{r,f} = \begin{cases} \frac{1}{2} \kappa_{r,f} (r_i - r_{0,r})^2 & \text{if } r_i < r_{0,r} \\ 0 & \text{if } r_i \geq r_{0,r} \end{cases} \quad (S7)$$

where  $\kappa_{r,f}$  is the strength of repulsive force, and  $r_{0,r}$  is a critical distance.

### **Dynamics of fibrils, bundlers, and cross-linkers**

Nucleation of seed fibrils takes place via appearance of one cylindrical segment. It is quickly elongated in one direction up to either 3  $\mu\text{m}$  or 5  $\mu\text{m}$  via addition of segments. Depolymerization of fibrils is not considered.

Arms of bundlers irreversibly bind to binding sites located every 50 nm on fibril elements. One of the bundler arms rapidly binds to the end or mid of fibrils at a rate. Then, a daughter fibril is instantaneously nucleated on the other arm via appearance of one segment with a given angle relative to the mother fibril, followed by elongation of the daughter fibril up to 3  $\mu\text{m}$  or 5  $\mu\text{m}$ . The length of long bundles is controlled by limiting part of mother fibrils where bundlers can bind. For example, longer bundles are formed if a bundler can bind to any part of mother fibrils. By contrast, shorter bundles are formed if a bundler can bind only to either the end of mother fibrils or part close to the end. The angle between mother and daughter

fibrils determines a bundle shape. If the angle is zero, fibrils in bundles are parallel to each other, leading to formation of tight bundles, whereas larger angles result in loose bundles with splaying fibrils.

Arms of cross-linkers also bind to binding sites located every 50 nm on fibril elements at a rate,  $k_{+,xl}$ , without preference of contact angle. Cross-linker arms also unbind from fibers at a force-dependent rate,  $k_{-,xl}$ , determined by Bell's law <sup>45</sup>:

$$k_{-,xl} = \begin{cases} k_{-,xl}^0 \exp\left(\frac{F_{s,xl}x_{-,xl}}{k_B T}\right) & \text{if } r \geq r_{0,xl} \\ k_{-,xl}^0 & \text{if } r < r_{0,xl} \end{cases} \quad (S8)$$

Where  $k_{-,xl}^0$  is a zero-force unbinding rate constant,  $x_{-,xl}$  represents sensitivity to the magnitude of an applied spring force ( $F_{s,xl}$ ),  $r_{0,xl}$  is the equilibrium length of a cross-linker element, and  $k_B T$  is thermal energy. The values of  $k_{-,xl}^0$  ( $= 10^{-6} \text{ s}^{-1}$ ) and  $x_{-,xl}$  ( $= 4.0 \times 10^{-10} \text{ m}$ ) are determined by benchmarking *in-vitro* experimental results as shown in our previous study <sup>46</sup>.

## Matrix assembly and bulk rheology

The computational domain is rectangular with  $20 \times 20 \times 5 \text{ }\mu\text{m}$  in x, y, and z directions. A periodic boundary condition exists only in x and z directions. First, fibrils are assembled with or without bundlers. Some of the fibrils are permanently bound to two boundaries normal to the y direction (i.e., +y boundary located at  $y = 20 \text{ }\mu\text{m}$  and -y boundary located at  $y = 0 \text{ }\mu\text{m}$ ) during the formation of individual fibrils or bundles. After completion of fibril/bundle assembly, a large number of cross-linkers are added to connect fibrils or bundles into a matrix. Then, 20% shear strain is applied to the +y boundary in the +x direction to mimic bulk rheology, whereas the -y boundary is fixed. After reaching the 20% strain, the strain is held at a constant level to measure stress relaxation. Stress at each time point is calculated by summing all forces acting on the +y boundary in the x direction and then dividing the sum by the area of the boundary.