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Editorial

Special Issue: Mechanics of Cells and Fibers☆

1. Introduction

Although cells have likely interacted with extracellular protein fibers since when our single-celled ancestors ruled the seas 600 million years ago [1], we modern and complex multicellular organisms have only recently begun to sort out how cell-fiber interactions drive mechanobiology. The vast majority of cell biology research has been conducted on cells that are cultured on flat, stiff, two-dimensional (2D) substrates, rather than in 3D and fibrous environments. This is surprising because the fibrous nature of animal tissues was appreciated by the early 1700′s [2]. In fact, it was rather over-appreciated, with fibers identified as the source of life in the "iatromechanical" models of that era, models that persisted in some quarters until Remak's demonstration that all life arises from cells in the mid 19th-century [2,3].. Fibers have been a focus of the field of tissue mechanics since the 1960s and 1970s [4]. However, studies of how cells, fibers, and their recursive interactions guide development and pathology are far more recent.

Research over the past two decades suggests major differences between 2D and 3D fibrillar environments, including unique cell-extracellular matrix (ECM) signaling and long distance cell-signaling [5,6]. Cells transduce these signals, adjust their fibrous environment, and respond to the new environment in a positive reinforcement loop that can lead to a new homeostasis or lead cells to leave their microenvironment and migrate elsewhere. Mechanical forces can reach the nucleus and affect gene expression and cell phenotype. The emerging field of mechanobiology seeks to understand and control the ways that mechanical forces and physical properties of cells and tissues influence biological processes (Fig. 1). For example, cells move through the interstitial matrix by manipulating ECM fibers, which can cause local rearrangement of the matrix [7], which further fuels the ability of cells to exert larger forces in a force feedforward loop [8]. Fibrous networks are shown to be key regulators of cell protrusions [9,10], migration [11–17], differentiation [18–21], nucleus shape [22–24], mitosis [25–27], and force exertion [28–31]. The changing physical properties of cells and the ECM are now known to intimately go hand-in-hand, with mechanics playing a precise and central role.

This special issue of *Acta Biomaterialia* brings together some of the most important breakthroughs in research on the mechanobiology of cells, fibers, and their interactions. The issue takes a critical look at four areas that have developed in just the last few years: the mechanics of collagen and fiber networks; the mechanics of development, remodeling, and wound healing; mechanotransduction by cells and nuclei; and the mechanics of migration, metastasis, and malignancy.

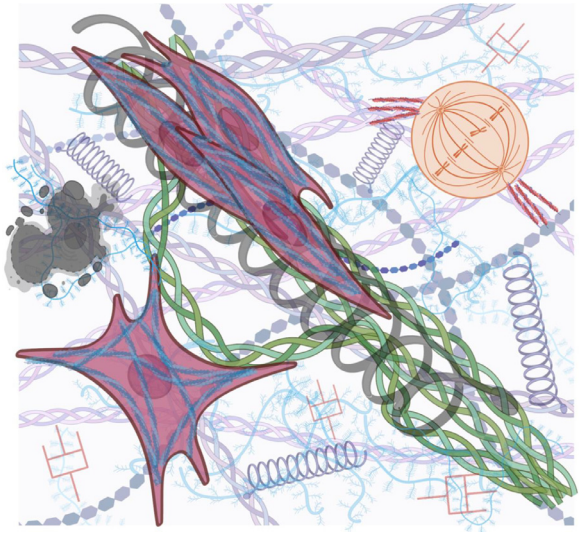

Fig. 1. Schematic illustrating the complexity of extracellular fibrous environment replete with cells, both composed of viscous and spring elements that collectively define the mechanics of cells and fibers in a feedforward loop.

2. The mechanics of collagen and fiber networks

The first area is the newly emerging understanding of the mechanics of collagen and fiber networks. As described in the modeling work of Barocas et al. [32], networks of fibers respond with behaviors that differ fundamentally from those of non-fibrous materials. Central to this is the emergence of a dominant network of fibers that carries a disproportionate share of mechanical load and determines how mechanical information crosses scales. Numerical simulation of these cross-scale phenomena has proven to be a longstanding challenge, with key issues being how to correctly capture a fibrous environment, how to combine discrete fiber phenomena with a continuum framework, and how, as in the case of aortic dissection studied by Barocas et al., these tissues come apart and lose their function.

Because of the strain stiffening phenomenon, with dominant fiber networks extending relatively long distances, boundary effects can travel distances that would horrify Saint Venant, and

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fibrous materials are notoriously difficult to characterize. The ability to interpret experiments such as simple indentation with an atomic force microscope (AFM) probe is a recent breakthrough, enabled by multiscale models of fiber networks. As described in the contribution from Picu and colleagues [33], fibrous materials have indentation moduli that are underestimated by the classic isotropic, linear elastic Hertz solution due to formation of a stiff, compact network beneath the indenter, with errors substantially higher when the indenter has a size on the same order of magnitude as the length of a fiber segment.

Another characteristic of protein networks that makes them challenging to characterize is that their unusual behavior at the macroscale can translate all the way down to the nanoscale. Such is the case of what is arguably the most important fibrous system in the body, that of type I collagen. As reviewed by Thurner and colleagues [34], measuring the mechanics of individual collagen fibrils in tension requires exquisite integration of modeling with testing apparatus such as AFM or microelectromechanical systems. The mechanics that emerges from such tests is decidedly non-linear. This nonlinearity is complicated by the interactions between mechanics and biochemistry in collagen, especially cleavage and fibril formation kinetics. Ruberti and colleagues [35] detail the role of mechanical force on development of collagenous tissues, via a mechanism known as mechanochemical force-structure causality. Through coupling between strain and collagen accumulation, collagen becomes increasingly stable in regions of higher tension, and hierarchical growth of collagen fibers is favored in places where they are most needed.

The resulting fibers are nonlinearly viscoelastic, as described by Chasiotis and co-workers [36]. The behavior of the fibers reaches the tissue level over timescales and spatial pathways that are defined by a variety of different hierarchical structures, and the viscoelastic behavior of individual fibers thus need not reflect the viscoelastic behavior of an entire tissue. Surprisingly, the work of the Chasiotis group shows that collagen nanofibrils display behavior that is of the same character as that of an entire tissue, and suggests that certain features of energy dissipation arising from intermolecular sliding at the nanoscale may arise through the different hierarchies present at the level of entire collagenous tissues. Recent breakthroughs enable the understanding of these observations through mechanistic models by Bouklas and colleagues, who describe such behavior through a viscoplastic constitutive model that tracks the interplay between inelasticity and viscoelastic dissipation in collagen fibers. The comprehensive model is now able to track this balance in collagen fibrils for monotonic and cyclic loading of all magnitudes [37].

With these basic building blocks in place, a number of additional issues can now begin to be addressed. A critical open issue in tissue biomechanics is how collagen fibers interact with other structurally important classes of fibers, especially elastin fibers. Common constitutive models, especially for vasculature, make the extreme assumption of affine deformation, with elastin deforming in parallel with all other tissue components. Lake and colleagues take an important step towards unraveling the true nature of collagen-elastin interaction through a series of integrated mechanical and structural studies of a range of tendons across species, with structure modulated via enzymatic degradation of elastin [38]. Results provide the deepest look yet into the structural contributions of elastin to tendon mechanics across species, and reveal a potential role of cross-fiber interaction in which elastin regulates mechanics by controlling collagen arrangement.

Fibrous tissues also evolve mechanical properties due to mesoscale interactions with cells and inclusions. Unraveling these represents another emerging frontier in mechanobiology, as described by Patteson and colleagues [39]. This work builds on emerging evidence that compressive properties of a broad range of tissues arise from lateral stretching of the fibrous network. This was elucidated in a model tissue system of fibrin networks with embedded, inert beads with the result that fluid flow associated with lateral flow affects the rate dependent responses of tissues, and that hindrance of network relaxation by the beads forms a newly identified source of network stiffening in compression.

Taken together, the collection of papers and review articles highlight a critical role for fibrous networks in mechanobiology. Fibers have long been known as building blocks that provide mechanical support and stiffness to tissues and organs, but only recently an appreciation of their deeper role in transmitting mechanical forces over long distances between cells and their surroundings, and to act as signaling platforms that influence cell behavior, migration, and differentiation has emerged. This collection highlights an emerging understanding of the mechanics of these networks and the critical roles they play in mechanobiology.

3. Mechanics of development, remodeling, and healing

The second section studies the physiological and pathophysiological implications of the continuous communication between cells, their neighbors, and their local and even distant ECM. Mechanosensation of signals from the cell's microenvironment are essential for healing and growth, and errors in mechanosensation can lead to significant pathology. Communication between cells and cell clusters is assisted by bands of aligned ECM proteins that interact recursively with cell populations, but also by direct cell-cell linkages. A longstanding question in mechanobiology is the degree to which mechanical strain and cell-cell contacts lead to the phenotypic changes associated with mechanotransduction. Billiar and co-workers apply a new system, with cells cultured on defined circular regions subjected to cyclic stress. They reveal that cell-cell communication leads to coordination in phenotypic transitions and signal transduction [40]. Changes in orientation and elongation of cells within aggregates occurs in multicellular bands and spreads to trigger global collective behavior, with a newly reported border zone effect in which the edges of bands present strong alignment and enhanced mechanical traction, but reduced proliferation. These highly contractile cells are more likely to undergo apoptosis and represent an activated phenotype that might seed emergent pathological behavior.

The fibers themselves can trigger pathological remodeling, with the archetypal example being attenuated wound-healing following the well-known stiffening of collagen through glycation in chronic hyperglycemia. However, collagen is only one element of the ECM, and is less relevant to tissue extensibility than elastin at the extremes of deformation. The effects of pathological concentrations of soluble factors on other fibers such as elastin represent an important unknown in mechanobiology, and the molecular dynamics (MD) simulations of Tarakonova and colleagues [41] provides critical new insight. Results reveal for the first time that elevated levels of calcium ions and glucose alter hydrogen bonding in elastin, and stiffen collagen. Beyond the obvious implications for hypercalcemia and hyperglycemia, findings show that multiple classes of fibers contribute to elastic changes in mechanobiological microenvironments and signaling associated with disease.

A more recent discovery is the many ways that ECM viscoelasticity affects the signaling networks that drive cell mechanosensing. A review by Kumar and co-workers [42] provides a much-needed critical look at the state of the art and open questions in this area. All fibrous biomaterials and their components exhibit a degree of viscoelasticity, as do the hydrogels of collagen, hyaluronic acid, and alginate that are critical to tissue and cellular engineering. At the core of cell responses is the Deborah number, the ratio of timescales for materials and timescales for cellular processes such as cytoskeletal remodeling and adhesion dynamics. Together,

these factors go a long way to ward explaining a range of cellular mechanosensing phenomena.

In addition to mechanics, cells sense and respond to the shapes of fibers and other features in their environment during development, remodeling, and healing. The contribution from Deshpande et al. [43] examines the shape-sensing phenomenon of contact guidance and explains it holistically through a statistical thermodynamics framework. In this framework, entropic and enthalpic factors mediated by biochemistry determine how or whether cells move. The results are surprisingly robust, with a perturbation-insensitive pathway towards stiff substrates emerging regardless of the factors that dominate the cell's effective free energy. Cell mechanosensing and substrate elasticity thereby combine to lead to the emergence of contact guidance.

Such structures enter development at multiple length scales, as characterized by Chen et al. [44], who report a new method of creating an artificial basement membrane and apply it to study the mechanobiology of epithelial morphogenesis and function. The basement membrane model they develop mimics several native basement membrane systems by combining a honeycomb-shaped electrospun layer of gelatin nanofibers with self-assembled collagen IV and laminin. The scaffold is a relatively thin structure with programmable plate-bending stiffness. This is exploited by Chen et al., to demonstrate how alveolar morphogenesis arises from a balance between epithelial contraction and basement membrane flexural rigidity.

Development of thicker tissues meets with a range of additional challenges. The first is providing for the metabolic needs of cells too far from the surface to have these needs met by diffusion. This is a major challenge in tissue engineering and a key limiting factor in the development of artificial organs and tissues. A substantial advance in this area is described by Levenberg and colleagues [45] who have developed a biodegradable macro-vessel "AngioTube" system for vascularization of thick, engineered tissues. The system uses micro-channel guides to promote both microchannel growth and sprouting of microvessels by endothelial cells and proves effective in a rat hindlimb model. The AngioTube system appears to be a powerful platform for both tissue engineering and the study of cells in relatively thick tissues.

A second challenge with the development of thicker tissues is quantifying cell behavior as development and remodeling occur. The state of the art has long been traction measurements that rely on idealizations of cell interactions with hydrogel systems and on linear models of 3D hydrogel behavior [46]. Validation has long been a key challenge. Sacks and colleagues report an important contribution to 3D, hydrogel-based traction force microscopy in an article on the 3D mechanics of aortic valve interstitial cells as the initially spherical cells develop protrusions [47]. Results show that a highly conserved contractile machinery drives cells of all shapes and elucidate key mechanisms controlling shape and contractility.

Expanding the library of such functional hydrogels for study of mechanobiology in 3D is a pressing need. As described in the review article by Arinzeh and colleagues [48], engineering of glycosaminoglycans is particularly critical because of their importance in cell signaling, proliferation, and differentiation, and in tissue development and repair. In addition to providing compressive stiffening and mechanical damping, Arinzeh and colleagues argue that engineered glycosaminoglycan hydrogels may serve to sequester growth factors and to endow fibrous ECM with mechanical properties that are currently difficult to attain.

Finally, an emerging and promising application of mechanobiology to healing is the use of mechanobiological stimuli to activate and prime the immune system. A critical review of this important and emerging area by Samavedi and colleagues details latest advances in electrospinning methods and fiber networks that show promise for controlling innate immune cell responses [49]. Samavedi and colleagues argue that, by leveraging matrix properties, matrix mechanics, surface functionalization, and advanced fabrication strategies, it may someday be possible to modulate between pro-inflammatory and pro-regenerative response in immune cells using electrospun, fibrous networks. Their critique highlights that the field still, however, has major hurdles to cross.

4. Mechanotransduction by cells and nuclei

One of the most vexing questions in the field of mechanobiology is how forces reach cells and nuclei to make lasting changes to function and phenotype. Even for cells in relatively simple loading states, these cellular responses and behaviors can be difficult to predict and interpret. In the case of compressed articular cartilage, as studied by Hung and colleagues [50], compressed chondrocytes near the surface can undergo cell death when subjected to physiologic loading conditions. The paper solves this mystery through use of finite element methods that predict how compression can attenuate nutrient flow, with a three order of magnitude reduction of hydraulic permeability after several hours of intermittent or continuous contact loading. The article reveals a fascinating example of (spoiler alert!) hydraulically driven mechanotransduction in which normal activities such as walking or standing can induce significant loss of intracellular fluid volume, potentially hindering metabolic activity and fluid transport properties, leading to cell death.

A key goal of tissue engineering is to manipulate these stresses in a way that instead drives a desired outcome. Such epigenetic factors involve multiple levels of mechanotransduction, with forces that reach the cell altering gene expression in the nucleus. Poh and colleagues critique our understanding of how 3D scaffold geometry affects cell and nuclear mechanics, with emphasis on the diversity of mechanotransduction pathways that can influence epigenetics [51]. Their review discusses the potential of using additive manufacturing for multi length-scale assembly of cells and multicellular tissues with desired functionalities, and points to critical challenges in recapitulating the cell's mechanical microenvironment and its dynamics. These dynamic epigenetic factors in 3D are recursive, with cell and ECM changes leading to modulation of one another. A review article by Boer and colleagues highlights the dynamic reciprocity ("loop of phenotype") between cells and ECM in tendon tissue during physiological homeostasis, and related loops of phenotype that can arise under pathological conditions[52]. A particularly interesting critique raised is that, although signaling between ECM and cells is known to occur at the tissue, cell and molecular levels, the integration of this for tenocytes is highly dependent on cell shape, and that biomaterials that aim for anabolic upregulation of ECM production may potentially be improved by accounting for causal linkages between tenocyte form and function.

Such linkages between form and function drive mechanosensing in bone development as well. As expounded upon by Kuo and colleagues [53], many signals in these cascades are mediated by focal adhesions that remodel in response to geometric cues in the cell microenvironment. These can adapt dynamically to direct intercellular tension towards the nucleus and thereby to regulate stem cell differentiation. This is demonstrated in a clever and impactful experiment in which stem cells patterned on square or round protein patches develop distinct patterns of radial actin bundles and myosin-IIA enriched transverse fibers. These modulate cytoskeletal tension, actin retrograde flow, and network architecture so as to upregulate tension in the nuclear envelope in cells on square patches, and downregulate it in cells on circular patches. The former cells show signs of osteogenesis, and the latter show signs of adipogenesis, providing evidence of a role for centripetal actin flow in regulating contractility and stem cell fate.

One of the central challenges in understanding the phenomena that drive mechanosensing by cells and nuclei is measuring the forces applied to them. The standard approach for estimating the traction stresses that a cell exerts on a substrate is to induce the cells to release the traction, then measure the displacements of fluorescent beads in the surface layer of the hydrogel and solve an inverse problem to estimate how hard the cells were originally pulling on the substrate. The technique is no longer particularly hard on graduate students, but is quite hard on cells because of the chemical disruption needed to release stresses. A significant advance in this class of technique is reported by Sniadecki and colleagues, who developed a technology to micropattern uniform arrays of opaque microscale markers on fluorescent substrates [54]. The method allows precise, high-throughput measurement of displacement fields without harming the cells because the regular reference configuration is known *a priori*. This is a highly promising new tool for prospectively tracking the mechanical responses of cells.

The connections between a cell and its neighbors and ECM not only determine the ways that a cell transduces force, but also the magnitude of the stresses it transduces. Quigley and colleagues demonstrate this in the astrocytic lamina in the optical nerve head, a structure that can become injured when overstretched in glaucoma [55]. In explanted mouse eye models, treatment with recombinant trypsin alters the mechanical fields and load transfer by the cells' basement membrane. These data show that cell-cell connections provide a significant contribution to the mechanics of the optic nerve head and provide a clear demonstration of ways in which cells can substantially modulate their mechanical environment through connectivity to that environment.

Understanding how these forces and stretches cause transitions in cells is a critical issue for mechanobiology. How do forces drive phenotypic changes in cells, and how do cells remember these? Wang and colleagues show a central role in this process for nuclear protein LAP2β [56]. LAP2β is responsible for transmission of contractile force from the nuclear lamina to chromatin inside the nucleus, and Wang et al. show for the first time that this is essential for nuclear mechanotransduction. The paper reports a critical result in mechanobiology, namely that chromatin itself must be stretched to promote mechanosensitive gene upregulation, and that LAP2β plays a critical role in this process.

How quickly can these changes occur? Although time constants for nuclear changes to cells are minutes to days [57–59], cells such as neurons are well known to change permanently over the course of milliseconds when subjected to rapid stress [60]. Neu and co-authors identify a series of mechanisms by which this might occur in a study that brings to bear remarkable imaging and high strain rate experiments on neurons [61]. Neu et al. examine the mechanics of neuronal nucleus and cytoskeleton response to impulsive loading representative of traumatic brain injury and discover loading-dependent changes to nuclear positioning and orientation, as well as F-actin puncta surrounding the nuclei associated with cytoskeletal depolymerization.

5. Mechanics of migration, metastasis, and malignancy

One of the most important motivations for studying cell-fiber interactions is identifying factors that make cells migrate and lead cancerous cells to metastasize. Material factors are key to this, as described in the review by Lim and colleagues [62]. Mechanosensation driven by the interplay between ECM biophysical cues and intracellular signaling drive these cellular decisions to metastasize, with factors such as fibrillar size and arrangement, crosslinking density, confinement, rigidity, topography, and non-linear mechanics affecting tumor cell behavior. How do each of these affect malignancies? In their thoughtful critique, the authors note that we still cannot answer that question, in part because of challenges in isolating these factors in well-defined, quantitative cell culture systems. The review covers and critiques a range of engineering approaches available to mimic the varying levels of complexity during tumorigenesis, and emphasize the need for a cell-instructive modular approach that accounts for interactions across cell types that promote metastatic invasion.

Amongst the many cell types that interact within the tumor microenvironment are cells of the immune system. These are amongst the most poorly understood actors in the tumor microenvironment, but potentially amongst the most important. M2 macrophages, immune cells that regulate inflammation and promote tissue repair, are often associated with tumor growth and progression, as they can secrete factors that promote cell growth and angiogenesis. A key question when designing treatments to eliminate the heterogeneous tumor cell population is how does the heterogeneity of the tumor cell population change with tumor development, including the stiffening associated with certain tumors? Reinhart-King and colleagues report a substantial advance in the science of how matrix mechanics drives the heterogeneity of the intratumor cell population [63]. Although the balance of stromal and cancer cells does not change, stiffening of the tumor microenvironment increases presence of tumor-promoting M2-like macrophages and promotes intercellular communication, establishing a role of mechanobiology in supporting tumor growth.

To understand how the fibrous nature of the ECM dictates migration speed and mode of these heterogeneous cell populations, Baker and colleagues interrogate the role of biophysical and biochemical cues from peritumoral stroma in tumor escape strategies [64]. Using electrospun fibers embedded within an amorphous hydrogel to create synthetic stroma, they discover independent roles of matrix fiber density and bulk hydrogel mechanics on cell migration. Attachment to ECM fibers promotes endothelial-to-mesenchymal transition, resistance to apoptosis, and invasive multicellular clusters, while soluble cues enhance single cell migration. Results highlight an interplay between ECM mechanics, ECM structure, and malignancy, and shed light on the mechanisms by which invasiveness determines malignancy and prognosis.

When cancer cells spread to other parts of the body, they typically invade together as attached groups of cells. Previous research has shown that when cancer cells are close to each other, they can push into soft materials more deeply than when they are spaced apart. Weihs and colleagues developed finite element models to interrogate the ability of well-spaced or adjacent cancerous cells to indent soft gels [65], and discovered a key role of the stiffness of the nucleus. When cells are close together, they can push more deeply into soft materials due to small increases in indentation depth. Additionally, they can interact in ways that enhance the force with which they invade due to additive, continuum mechanics-driven contributions. Findings suggest that cancer cells can invade collectively without directly interacting with each other, and reveal additive and synergistic mechanisms driving collective cancer-cell invasiveness.

Mechanical factors not only determine the outcome of disease, but also the outcome of treatment. A critical frontier is understanding how the fibrous environment of cells provides signaling and drug resistance to cancer. Zustiak and colleagues detail the use of gels of varying stiffness to test the efficacy of drugs in treatment of glioblastoma [66]. Cancer cells had higher and deeper infiltration in the soft compared to stiff gels. In hybrid scaffolds with both soft and stiff zones, minor infiltration was observed from soft to stiff regions, but not the other way around, contrary to other studies. Drug responsiveness was correlated with laminin expression in stiff hydrogels, indicating a role of stiffness in drug efficacy.

6. Outlook

The articles in this special issue point to a series of critical open questions that need to be addressed. Recursive interactions between cells and fibers govern development, healing, and a range of pathologies, but are in general poorly understood. At the level of fibrous networks, challenges that remain include accurately modeling fibrous environments, both experimentally and computationally, and characterizing both fibrous materials and the fibers themselves experimentally. Mesoscale interactions between fiber families and between fibers and cells continue to reveal new and unexpected material behaviors, and certainly deserve continued exploration.

The research agenda that emerges from the special issue also underscores a key need to understand the role of cell and fiber mechanobiology in physiological and pathophysiological processes. The role of cell communication, mechanical strain, and cell-cell contacts in phenotypic changes associated with mechanotransduction is not yet understood in the context of soluble factors, cell kinetics, and their effects on ECM proteins. The 3D culture systems that form the core of our understanding of cell-fiber interactions are not yet true 3D systems, and are instead limited by issues of nutrient distribution. Technologies for vascularization of idealized tissues continue to represent a pressing need.

Material factors in the fibrous environment are especially important in cancer cell behavior and cancer treatment. The interplay between ECM biophysical cues and intracellular signaling affects cellular decisions to metastasize, with factors such as fibrillar size and arrangement, crosslinking density, confinement, rigidity, topography, and non-linear mechanics affecting tumor cell behavior. The diverse cell populations, including immune cells, in the tumor microenvironment interact with tumor mechanics and structure to determine cancer cell migration and invasiveness, and to determine drug efficacy and resistance to cancer.

Finally, in the context of both physiological and pathophysiological development, understanding the mechanisms and kinetics of epigenetics remains a critical need. Breakthroughs reported in this special issue shed light on mechanisms at individual hierarchical scales within a tissue, but additional work is needed to link these across scales and identify druggable targets.

Progress in these areas is rapid, and it will be exciting for all of us to see what the next 600 million years of development add to the field.

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References

[1] N. King, The unicellular ancestry of animal development, Dev. Cell. 7 (2004) 313–325, doi:10.1016/J.DEVCEL.2004.08.010.
[2] H. Ishizuka, Fibre body": the concept of fibre in eighteenth-century medicine, c.1700-40, Med. Hist. 56 (2012) 562–584, doi:10.1017/MDH.2012.74.
[3] C. Hand, Cell theory : the Structure and Function of Cells, Cavendish Square, New York, 2018.
[4] Y. Lanir, Multi-scale Structural Modeling of Soft Tissues Mechanics and Mechanobiology, J. Elast. 129 (2017) 7–48, doi:10.1007/S10659-016-9607-0/METRICS.
[5] P. Friedl, E. Sahai, S. Weiss, K.M. Yamada, New dimensions in cell migration, Nat. Rev. Mol. Cell Biol. 13 (2012) 743–747, doi:10.1038/nrm3459.
[6] F. Alisafaei, X. Chen, T. Leahy, P.A. Janmey, V.B. Shenoy, Long-range mechanical signaling in biological systems, Soft Matter 17 (2021) 241–253, doi:10.1039/D0SM01442G.
[7] R. Malik, T. Luong, X. Cao, B. Han, N. Shah, J. Franco-Barraza, L. Han, V.B. Shenoy, P.I. Lelkes, E. Cukierman, Rigidity controls human desmoplastic matrix anisotropy to enable pancreatic cancer cell spread via extracellular signal-regulated kinase 2, Matrix Biol 81 (2019) 50–69, doi:10.1016/j.matbio.2018.11.001.
[8] A. Padhi, K. Singh, J. Franco-Barraza, D.J. Marston, E. Cukierman, K.M. Hahn, R.K. Kapania, A.S. Nain, Force-exerting perpendicular lateral protrusions in fibroblastic cell contraction, Commun. Biol. 3 (2020) 390, doi:10.1038/s42003-020-01117-7.
[9] D. Shakiba, F. Alisafaei, A. Savadipour, R.A. Rowe, Z. Liu, K.M. Pryse, V.B. Shenoy, E.L. Elson, G.M. Genin, The Balance between Actomyosin Contractility and Microtubule Polymerization Regulates Hierarchical Protrusions That Govern Efficient Fibroblast-Collagen Interactions, ACS Nano 14 (2020) 7868–7879, doi:10.1021/acsnano.9b09941.
[10] B. Koons, P. Sharma, Z. Ye, A. Mukherjee, M.H. Lee, D. Wirtz, B. Behkam, A.S. Nain, Cancer Protrusions on a Tightrope: nanofiber Curvature Contrast Quantitates Single Protrusion Dynamics, ACS Nano 11 (2017) 12037–12048, doi:10.1021/acsnano.7b04567.
[11] T. a Ulrich, E.M. de Juan Pardo, S. Kumar, E.M. de J. Pardo, The mechanical rigidity of the extracellular matrix regulates the structure, motility, and proliferation of glioma cells, Cancer Res 69 (2009) 4167–4174, doi:10.1158/0008-5472.CAN-08-4859.
[12] C.T. Mierke, Viscoelasticity acts as a marker for tumor extracellular matrix characteristics, Front. Cell Dev. Biol. 9 (2021), doi:10.3389/FCELL.2021.785138/FULL.
[13] J. Singh, A. Pagulayan, B.A. Camley, A.S. Nain, Rules of contact inhibition of locomotion for cells on suspended nanofibers, Proc. Natl. Acad. Sci 118 (2021) e2011815118, doi:10.1073/pnas.2011815118.
[14] S. Meehan, A.S. Nain, Role of suspended fiber structural stiffness and curvature on single-cell migration, nucleus shape, and focal-adhesion-cluster length, Biophys. J. 107 (2014) 2604–2611, doi:10.1016/j.bpj.2014.09.045.
[15] P. Keely, A. Nain, Capturing relevant extracellular matrices for investigating cell migration, F1000Res 4 (2015), doi:10.12688/f1000research.6623.1.
[16] A. Jana, I. Nookaew, J. Singh, B. Behkam, A.T. Franco, A.S. Nain, Crosshatch nanofiber networks of tunable interfiber spacing induce plasticity in cell migration and cytoskeletal response, FASEB J. 33 (2019) 10618–10632, doi:10.1096/fj.201900131R.
[17] S. Even-Ram, K.M. Yamada, Cell migration in 3D matrix, Curr. Opin. Cell Biol. 17 (2005) 524–532, doi:10.1016/j.ceb.2005.08.015.
[18] B.R. Seo, X. Chen, L. Ling, Y.H. Song, A.A. Shimpi, S. Choi, J. Gonzalez, J. Sapudom, K. Wang, R.C.A. Eguiluz, D. Gourdon, V.B. Shenoy, C. Fischbach, Collagen microarchitecture mechanically controls myofibroblast differentiation, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 11387–11398, doi:10.1073/PNAS.1919394117/SUPPL_FILE/PNAS.1919394117.SAPP.PDF.
[19] J. Eyckmans, T. Boudou, X. Yu, C.S. Chen, A hitchhiker's guide to mechanobiology, Dev. Cell. 21 (2011) 35–47 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3155761&tool=pmcentrez&rendertype=abstract. (accessed July 14, 2012).
[20] E.D.F. Ker, A.S. Nain, L.E. Weiss, J. Wang, J. Suhan, C.H. Amon, P.G. Campbell, Bioprinting of growth factors onto aligned sub-micron fibrous scaffolds for simultaneous control of cell differentiation and alignment, Biomaterials 32 (2011), doi:10.1016/j.biomaterials.2011.07.025.
[21] Y. Xu, G. Shi, J. Tang, R. Cheng, X. Shen, Y. Gu, L. Wu, K. Xi, Y. Zhao, W. Cui, L. Chen, ECM-inspired micro/nanofibers for modulating cell function and tissue generation, Sci. Adv. 6 (2020), doi:10.1126/SCIADV.ABC2036/SUPPL_FILE/ABC2036_SM.PDF.
[22] A. Jana, A. Tran, A. Gill, A. Kiepas, R.K. Kapania, K. Konstantopoulos, A.S. Nain, A. Jana, A. Gill, A.S. Nain, A. Tran, A. Kiepas, K. Konstantopoulos, R.K. Kapania Kevin T, Sculpting Rupture-Free Nuclear Shapes in Fibrous Environments, Adv. Sci. 9 (2022) 2203011, doi:10.1002/ADVS.202203011.
[23] K. Wolf, M. te Lindert, M. Krause, S. Alexander, J. te Riet, A.L. Willis, R.M. Hoffman, C.G. Figdor, S.J. Weiss, P. Friedl, Physical limits of cell migration: control by ECM space and nuclear deformation and tuning by proteolysis and traction force, J. Cell Biol. 201 (2013) 1069–1084, doi:10.1083/jcb.201210152.

[24] R.J. Petrie, H. Koo, K.M. Yamada, Generation of compartmentalized pressure by a nuclear piston governs cell motility in a 3D matrix, Science 345 (2014) 1062–1065, doi:10.1126/SCIENCE.1256965/SUPPL_FILE/PETRIE.SM.PDF.
[25] A. Lesman, J. Notbohm, D.A. Tirrell, G. Ravichandran, Contractile forces regulate cell division in three-dimensional environments, J. Cell Biol. 205 (2014) 155–162, doi:10.1083/jcb.201309029.
[26] S. Nam, O. Chaudhuri, Mitotic cells generate protrusive extracellular forces to divide in three-dimensional microenvironments, Nat. Phys. 14 (2018) 621–628, doi:10.1038/s41567-018-0092-1.
[27] A. Jana, A. Sarkar, H. Zhang, A. Agashe, J. Wang, R. Paul, N.S. Gov, J.G. DeLuca, A.S. Nain, Mitotic outcomes and errors in fibrous environments, Proc. Natl. Acad. Sci. 120 (2023) e2120536120, doi:10.1073/PNAS.2120536120.
[28] S.A. Maskarinec, C. Franck, D.A. Tirrell, G. Ravichandran, Quantifying cellular traction forces in three dimensions, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 22108–22113 http://www.pnas.org/cgi/content/abstract/106/52/22108. (Accessed 22 July 2012).
[29] D.E. Ingber, N. Wang, D. Stamenović, Tensegrity, cellular biophysics, and the mechanics of living systems, Rep. Prog. Phys. 77 (2014) 046603, doi:10.1088/0034-4885/77/4/046603.
[30] J. Steinwachs, C. Metzner, K. Skodzek, N. Lang, I. Thievessen, C. Mark, S. Münster, K.E. Aifantis, B. Fabry, Three-dimensional force microscopy of cells in biopolymer networks, Nat. Methods. 13 (2016) 171–176, doi:10.1038/nmeth.3685.
[31] K. Sheets, J. Wang, W. Zhao, R. Kapania, A.S. Nain, Nanonet force microscopy for measuring cell forces, Biophys. J. 111 (2016) 197–207, doi:10.1016/j.bpj.2016.05.031.
[32] E. Gacek, R.R. Mahutga, V.H. Barocas, Hybrid discrete-continuum multiscale model of tissue growth and remodeling, Acta Biomater. 163 (2023) 7–24, doi:10.1016/J.ACTBIO.2022.09.040.
[33] J. Merson, N. Parvez, R.C. Picu, Probing soft fibrous materials by indentation, Acta Biomater. 163 (2023) 25–34, doi:10.1016/J.ACTBIO.2022.03.053.
[34] O.G. Andriotis, M. Nalbach, P.J. Thurner, Mechanics of isolated individual collagen fibrils, Acta Biomater. 163 (2023) 35–49, doi:10.1016/J.ACTBIO.2022.12.008.
[35] S.M. Siadat, J.W. Ruberti, Mechanochemistry of collagen, Acta Biomater. 163 (2023) 60–62, doi:10.1016/J.ACTBIO.2023.01.025.
[36] F. Yang, D. Das, K. Karunakaran, G.M. Genin, S. Thomopoulos, I. Chasiotis, Nonlinear time-dependent mechanical behavior of mammalian collagen fibrils, Acta Biomater. 163 (2023) 63–77, doi:10.1016/J.ACTBIO.2022.03.005.
[37] F.F. Fontenele, N. Bouklas, Understanding the inelastic response of collagen fibrils: a viscoelastic-plastic constitutive model, Acta Biomater. 163 (2023) 78–90, doi:10.1016/J.ACTBIO.2022.07.011.
[38] J.D. Eekhoff, J.A. Abraham, H.R. Schott, L.F. Solon, G.E. Ulloa, J.A. Zellers, P.C. Cannon, S.P. Lake, Fascicular elastin within tendon contributes to the magnitude and modulus gradient of the elastic stress response across tendon type and species, Acta Biomater. 163 (2023) 91–105, doi:10.1016/J.ACTBIO.2022.03.025.
[39] B. Carroll, M.T.H. Thanh, A.E. Patteson, Dynamic remodeling of fiber networks with stiff inclusions under compressive loading, Acta Biomater. 163 (2023) 106–116, doi:10.1016/J.ACTBIO.2022.09.063.
[40] M. Jebeli, S.K. Lopez, Z.E. Goldblatt, D. McCollum, S. Mana-Capelli, Q. Wen, K. Billiar, Multicellular aligned bands disrupt global collective cell behavior, Acta Biomater. 163 (2023) 117–130, doi:10.1016/J.ACTBIO.2022.10.041.
[41] C. Yang, A.S. Weiss, A. Tarakanova, Changes in elastin structure and extensibility induced by hypercalcemia and hyperglycemia, Acta Biomater. 163 (2023) 131–145, doi:10.1016/J.ACTBIO.2022.03.041.
[42] E.M. Carvalho, S. Kumar, Lose the stress: viscoelastic materials for cell engineering, Acta Biomater. 163 (2023) 146–157, doi:10.1016/J.ACTBIO.2022.03.058.
[43] A. Ippolito, V.S. Deshpande, Contact guidance via heterogeneity of substrate elasticity, Acta Biomater. 163 (2023) 158–169, doi:10.1016/J.ACTBIO.2021.11.024.
[44] E. Rofaani, Y. He, J. Peng, Y. Chen, Epithelial folding of alveolar cells derived from human induced pluripotent stem cells on artificial basement membrane, Acta Biomater. 163 (2023) 170–181, doi:10.1016/J.ACTBIO.2022.03.022.
[45] B. Zohar, L. Debbi, M. Machour, N. Nachum, I. Redenski, M. Epshtein, N. Korin, S. Levenberg, A micro-channel array in a tissue engineered vessel graft guides vascular morphogenesis for anastomosis with self-assembled vascular networks, Acta Biomater. 163 (2023) 182–193, doi:10.1016/J.ACTBIO.2022.05.026.
[46] W.R. Legant, J.S. Miller, B.L. Blakely, D.M. Cohen, G.M. Genin, C.S. Chen, Measurement of mechanical tractions exerted by cells in three-dimensional matrices, Nat. Methods. 7 (2010) 969–971, doi:10.1038/nmeth.1531.
[47] A. Khang, Q. Nguyen, X. Feng, D.P. Howsmon, M.S. Sacks, Three-dimensional analysis of hydrogel-imbedded aortic valve interstitial cell shape and its relation to contractile behavior, Acta Biomater. 163 (2023) 194–209, doi:10.1016/J.ACTBIO.2022.01.039.
[48] R. Menezes, R. Vincent, L. Osorno, P. Hu, T.L. Arinzeh, Biomaterials and tissue engineering approaches using glycosaminoglycans for tissue repair: lessons learned from the native extracellular matrix, Acta Biomater. 163 (2023) 210–227, doi:10.1016/J.ACTBIO.2022.09.064.
[49] D. Venugopal, S. Vishwakarma, I. Kaur, S. Samavedi, Electrospun fiber-based strategies for controlling early innate immune cell responses: towards immunomodulatory mesh designs that facilitate robust tissue repair, Acta Biomater. 163 (2023) 228–247, doi:10.1016/J.ACTBIO.2022.06.004.
[50] K.R. Kroupa, L.R. Gangi, B.K. Zimmerman, C.T. Hung, G.A. Ateshian, Superficial zone chondrocytes can get compacted under physiological loading: a multiscale finite element analysis, Acta Biomater. 163 (2023) 248–258, doi:10.1016/J.ACTBIO.2022.10.013.
[51] P. Han, G.A. Gomez, G.N. Duda, S. Ivanovski, P.S.P. Poh, Scaffold geometry modulation of mechanotransduction and its influence on epigenetics, Acta Biomater. 163 (2023) 259–274, doi:10.1016/J.ACTBIO.2022.01.020.
[52] A. Dede Eren, S. Vermeulen, T.C. Schmitz, J. Foolen, J. de Boer, The loop of phenotype: dynamic reciprocity links tenocyte morphology to tendon tissue homeostasis, Acta Biomater. 163 (2023) 275–286, doi:10.1016/J.ACTBIO.2022.05.019.
[53] M.C. Wu, H.W. Yu, Y.Q. Chen, M.H. Ou, R. Serrano, G.L. Huang, Y.K. Wang, K. hui Lin, Y.J. Fan, C.C. Wu, J.C. del Álamo, A. Chiou, S. Chien, J.C. Kuo, Early committed polarization of intracellular tension in response to cell shape determines the osteogenic differentiation of mesenchymal stromal cells, Acta Biomater. 163 (2023) 287–301, doi:10.1016/J.ACTBIO.2022.10.052.
[54] K.M. Beussman, M.Y. Mollica, A. Leonard, J. Miles, J. Hocter, Z. Song, M. Stolla, S.J. Han, A. Emery, W.E. Thomas, N.J. Sniadecki, Black dots: high-yield traction force microscopy reveals structural factors contributing to platelet forces, Acta Biomater. 163 (2023) 302–311, doi:10.1016/J.ACTBIO.2021.11.013.
[55] A. Korneva, E.C. Kimball, S. Quillen, J.L. Jefferys, M. Nawathe, Y.T.T. Ling, T.D. Nguyen, H.A. Quigley, Mechanical strain in the mouse astrocytic lamina increases after exposure to recombinant trypsin, Acta Biomater. 163 (2023) 312–325, doi:10.1016/J.ACTBIO.2022.02.023.
[56] J. Sun, J. Chen, K. Amar, Y. Wu, M. Jiang, N. Wang, LAP2β transmits force to upregulate genes via chromatin domain stretching but not compression, Acta Biomater. 163 (2023) 326–338, doi:10.1016/J.ACTBIO.2021.10.029.
[57] W. Liu, A. Padhi, X. Zhang, J. Narendran, M.A. Anastasio, A.S. Nain, J. Irudayaraj, Dynamic Heterochromatin States in Anisotropic Nuclei of Cells on Aligned Nanofibers, ACS Nano 16 (2022) 10754–10767, doi:10.1021/ACSNANO.2C02660.
[58] F. Rashid, W. Liu, Q. Wang, B. Ji, J. Irudayaraj, N. Wang, Mechanomemory in protein diffusivity of chromatin and nucleoplasm after force cessation, Proc. Natl. Acad. Sci. U. S. A. 120 (2023) e2221432120, doi:10.1073/PNAS.2221432120/SUPPL_FILE/PNAS.2221432120.SAPP.PDF.
[59] C. Zhang, H. Zhu, X. Ren, B. Gao, B. Cheng, S. Liu, B. Sha, Z. Li, Z. Zhang, Y. Lv, H. Wang, H. Guo, T.J. Lu, F. Xu, G.M. Genin, M. Lin, Mechanics-driven nuclear localization of YAP can be reversed by N-cadherin ligation in mesenchymal stem cells, Nat. Commun. 121 (12) (2021) 1–13 2021, doi:10.1038/s41467-021-26454-x.
[60] S. Ji, Biomechanical Modeling of Traumatic Brain Injury, Encycl. Comput. Neurosci. (2022) 460–463, doi:10.1007/978-1-0716-1006-0_100668.
[61] S.E. Schneider, A.K. Scott, B. Seelbinder, C. Van Den Elzen, R.L. Wilson, E.Y. Miller, Q.I. Beato, S. Ghosh, J.E. Barthold, J. Bilyeu, N.C. Emery, D.M. Pierce, C.P. Neu, Dynamic biophysical responses of neuronal cell nuclei and cytoskeletal structure following high impulse loading, Acta Biomater. 163 (2023) 339–350, doi:10.1016/J.ACTBIO.2022.07.002.
[62] J. Vasudevan, K. Jiang, J.G. Fernandez, C.T. Lim, Extracellular matrix mechanobiology in cancer cell migration, Acta Biomater. 163 (2023) 351–364, doi:10.1016/J.ACTBIO.2022.10.016.
[63] P.V. Taufalele, W. Wang, A.J. Simmons, A.N. Southard-Smith, B. Chen, J.D. Greenlee, M.R. King, K.S. Lau, D.C. Hassane, F. Bordeleau, C.A. Reinhart-King, Matrix stiffness enhances cancer-macrophage interactions and M2-like macrophage accumulation in the breast tumor microenvironment, Acta Biomater. 163 (2023) 365–377, doi:10.1016/J.ACTBIO.2022.04.031.
[64] H.L. Hiraki, D.L. Matera, W.Y. Wang, E.S. Prabhu, Z. Zhang, F. Midekssa, A.E. Argento, J.M. Buschhaus, B.A. Humphries, G.D. Luker, A. Pena-Francesch, B.M. Baker, Fiber density and matrix stiffness modulate distinct cell migration modes in a 3D stroma mimetic composite hydrogel, Acta Biomater. 163 (2023) 378–391, doi:10.1016/J.ACTBIO.2022.09.043.
[65] M. Tulchinsky, D. Weihs, Computational modeling reveals a vital role for proximity-driven additive and synergistic cell-cell interactions in increasing cancer invasiveness, Acta Biomater. 163 (2023) 392–399, doi:10.1016/J.ACTBIO.2022.03.048.
[66] J. Bruns, T. Egan, P. Mercier, S.P. Zustiak, Glioblastoma spheroid growth and chemotherapeutic responses in single and dual-stiffness hydrogels, Acta Biomater. 163 (2023) 400–414, doi:10.1016/J.ACTBIO.2022.05.048.