Regenerative Rehabilitation
Special Series

Mechanotransduction: Relevance to Physical Therapist Practice—Understanding Our Ability to Affect Genetic Expression Through Mechanical Forces

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Mechanotransduction, the mechanism by which mechanical perturbation influences genetic expression and cellular behavior, is an area of molecular biology undergoing rapid exploration and discovery. Cells are sensitive to forces such as shear, tension, and compression, and they respond accordingly through cellular proliferation, migration, tissue repair, altered metabolism, and even stem cell differentiation and maturation. The study of how cells sense and respond to mechanical stimulation is under robust expansion, with new scientific methods and technologies at our disposal. The application of these technologies to physical therapist practice may hold answers to some of our age-old questions while creating new avenues for our profession to optimize movement for societal health. Embracing this science as foundational to our profession will allow us to be valuable scientific collaborators with distinctive knowledge of the effects of loading. These partnerships will be key to augmenting the clinical utility of emerging therapies such as regenerative medicine, tissue engineering, and gene therapy. Collaboration with other scientific disciplines in these endeavors, along with the inclusion and application of these discoveries in our academic programs, will enhance the understanding of the impact of our practice on biologic and genetic processes. A basic understanding of mechanotransduction and its relevance to physical therapist practice is warranted to begin the conversation.

In the Tenth Mary McMillan Lecture in 1975, Helen Hislop shared with us her not-so-impossible dream that physical therapy would achieve greatness as a profession.[1] She declared our vulnerabilities as being relatively defenseless against modern science and the lack of a clear identity. Hislop claimed these vulnerabilities would leave us "open to attacks against [our] inadequacies—attacks from medicine, attacks from government, challenges from fiscal agencies, and questions from the consuming public."[1(p1070)] Yet, she laid out a dream that our profession would overcome these vulnerabilities to fulfill our potential through scientific rigor and excellence in practice.[1] Significant opportunities in science and practice are at our doorstep to fully realize the dream she shared 40 years ago.

As physical therapists, we are educated and qualified to analyze, diagnose, and provide interventions to address the human movement system. We are clinically oriented to movement impairments and the interventions necessary to correct them. This systems-level inclination, along with an underrepresentation of molecular science in our academic preparation, often causes us to overlook the cellular and molecular biology influenced by our movement-related interventions. The forces we use in our practice, either through exercise prescription or direct manual application, create specific molecular and cellular responses.[2–4] Harnessing an understanding of these adaptive cellular responses to specific physical forces will lead to therapeutic reasoning and modification of our practice according to the biologic response to our interventions.

Just as pharmaceuticals chemically influence cellular behavior, mechanical loading influences cellular behavior through a mechanism termed "mechanotransduction." Mechanical forces at the cellular level influence signal transduction, genetic transcription, and protein translation.[5–7] Specificity of the interaction can either up- or down-regulate these cellular responses.[5,7] The correct dosage of mechanical stimuli applied during the correct phase of healing may have a profound impact on our therapeutic outcomes and begs for our involvement in basic science exploration and collaboration with other disciplines involved in areas such as tissue engineering, stem cell transplantation, molecular biology, and genetics. With an enhanced awareness of how these basic sciences directly translate to our clinical application, perhaps we can add to our understanding of therapeutic dosing while contributing to improved clinical outcomes of these novel therapeutic approaches. We hope that this perspective article will move the conversation forward through a simplistic approach to molecular biology, genetic expression, and the cellular responses influenced by mechanical perturbation.

For decades, we have been encouraged by leaders in our field to embrace basic science and to claim the human movement system.[1,8] The House of Delegates of the American Physical Therapy Association recently adopted a new vision for the profession: that we would transform society by optimizing movement to improve the human experience.[9] With mechanotransduction added to our foundational sciences and movement as our identity, we will promote these ideals toward a combined reality. A good place to start is within our academic programs. Khan and Scott[3] convened informal international focus groups and determined that mechanotransduction was not being taught as an important biological principle in physical therapy programs. They considered this a major failing of education because of the current public health problems associated with physical inactivity:

> To highlight the crucial role of mechanotransduction in underpinning musculoskeletal rehabilitation, we propose to reintroduce the term "mechanotherapy" for those many situations where therapeutic exercise is prescribed to promote the repair or remodeling of injured tissue. Mechanotherapy was first defined in 1890 as "the employment of mechanical means for the cure of disease" (*Oxford English Dictionary*). We would update this to "the employment of mechanotransduction for the stimulation of tissue repair and remodeling." This distinction highlights the cellular basis for exercise prescription for tissue healing and also recognizes that injured and healthy tissues may respond differently to mechanical load.[3(p248)]

Beyond Khan and Scott's imploring our profession's investment and inclusion, going so far as to reintroduce it as "mechanotherapy," others are identifying mechanobiology as a new era in medicine, ripe for innovative interventions with enormous potential to overcome many diseases.[10] The profession of physical therapy is poised to contribute our clinical relevance to these discoveries as we engage in the science and conversation.

This perspective article can be considered a beckoning call to connect with a science most fundamental to our practice. Students should come into our professional programs with undergraduate preparation in basic sciences, and our professional education could better link our clinical management to the molecular, genetic, and cellular responses associated with mechanobiology and mechanotransduction. The addition of genetics as a required foundational science to the 2016 *Standards and Required Elements for Accreditation of Physical Therapist Education Programs*[11] is a great beginning for this transition. Additionally, and as was discussed in the Physical Therapy and Society Summit (PASS) in 2009, "meeting this challenge will require spending far less time learning activities such as range of motion and muscle testing and more time assimilating advances in genomics, molecular science, and technologies. Comprehension of the latter underscores the physical therapy profession's ability to be in the forefront of advances in the evaluation and treatment of consumers with movement impairments and thus full participants in the post–PASS care delivery paradigm."[12(p1560)]

Our involvement as primary and collaborative investigators in these scientific endeavors will bring answers to our age-old questions about therapeutic dosing of our mechanical interventions: "Which types of forces are most effective?" and "When is it best to apply forces during the phases of healing, and which dose is optimal?" In order to answer these ques-

tions, we should no longer tolerate speculation, as our value to and contract with society is confirmed. As Hislop asserted, "Physical therapy has yet to document its own conviction about its value to total health care and to demonstrate its commitment to develop, teach, and apply its scientific principles as effectively as possible."[1(p1070)] Discovery, technology, and innovation are at our fingertips to use molecular and genetic techniques to answer long-standing questions about our effectiveness. We need only to "take the next step" because "our destiny is now."[13]

Mechanotransduction: Defined

Mechanotransduction, by definition, is the mechanism by which cells convert mechanical stimuli into cellular responses to a variety of mechanical loads.[3,14] The molecular mechanisms of cellular mechanosensitivity and mechanoresponsiveness have been studied for more than 30 years and, as molecular and genetic science have evolved, so has our understanding.[6] New tools such as high-resolution microscopy, atomic force microscopy, 3-dimensional cell culture, cyclic loading mechanisms, gene chip analysis, molecular manipulation, nanotechnology, and computer modeling provide ample technologies to lend to additional discovery.[15–17]

Cells Known to Be Influenced by Mechanotransduction

One of the most familiar and long-standing examples of mechanotransduction occurs at the hair cells of the inner ear, which convert sound waves to an action potential along the acoustic nerve.[18] The mechanical stimulation of a sound wave creates tension on linker proteins tethered between the bending stereocilia of the hair bundles, opening and closing transduction channels on the surface of the cells. Channel opening precipitates an influx of ions and membrane depolarization, which ultimately results in neurotransmitter release.[18]

Many cell types have been identified to sense and respond to mechanical stimuli: osteocytes,[19] chondrocytes,[20,21] fibroblasts,[5,22] keratinocytes,[23] and even stem cells,[24,25] to name a few. Mounting evidence points to the primary cilium of most cell types to be mechanosensitive and responsive, leading some authors to believe it to be a universal cellular mechanosensor of sorts.[26–28] However, known mechanisms of cellular sensing and responsiveness to mechanical loads have been well-established and include cell-cell, cell-matrix, and cell-lumen interactions, which are mediated through cell surface receptors, integrins, adhesion complexes, and stretch-activated ion channels.[6,14,29]

Molecular Biology

A brief review of cellular and molecular biology is in order for a clear understanding of mechanotransduction and its resultant cellular responses. Many of us took our undergraduate biology courses during an era predating contemporary science, when the cell was understood to contain a viscous cytoplasm surrounded by a membrane with a nucleus and other organelles inside, the functions of which were poorly elucidated. Our current understanding is that living cells have their own cytoskeleton, an internal molecular framework that can sense, generate, and respond to forces applied across the membrane.[30–32] Cells also have machinery to sense and respond to the relative stiffness of the ECM.[33] Now we know that cells are dynamic and can deform, migrate, proliferate, or act on their surroundings according to the cues they receive from their environment, regardless of whether chemical or mechanical.[15]

Receptors of Mechanical Stimuli

All eukaryotic cells are covered by a cell membrane, consisting of a lipid bilayer, which has proteins either associated with or embedded in its surface, along with lipid rafts that carry molecules and proteins along the cell surface.[6] Many of the proteins at the cell surface are called "receptors" because they receive signals either from inside or outside the cell and transmit the signal across the membrane for functional purposes. Both biochemical and mechanical signals operate through these receptors to affect cell behavior through downstream cytosolic interaction of effector proteins and transcription factors.[5]

Receptors known to be mechanosensitive include stretch-activated ion channels, integrins, growth factor receptors, and G-protein-coupled receptors[34] (Fig. 1). Integrins are transmembrane receptors with 2 subunits, α (alpha) and β (beta), which have distinct regulatory and signal-transducing functions, respectively. Both subunits contribute to connecting the cell to specific ECM proteins through transmembrane associations with the cytoskeleton. Integrin activation for matrix binding and signaling is multifaceted and may include allosteric interactions, clustering to form signaling complexes, or cytoskeletal tensioning through integrin-mediated attachments.[35] These attachments may form focal adhesion complexes (Fig. 2) between cells and matrix or create cell-cell interactions, serving critical roles in transmission of forces across the cell membrane and cellular sensing of matrix stiffness.[36] These contacts influence cell behavior, including adhesion, migration, shape, proliferation, stem cell differentiation, intracellular signal transduction, and matrix turnover.[37–41]

Stretch-activated ion channels are transmembrane proteins that create pores in the cell membrane large enough to pass calcium and other cations when open. Mechanically induced membrane tension is capable of opening the channels to allow an influx of efflux of ions, depending on the concentration gradient across the cell membrane. Ionic balance is important to many cellular functions and contributes to the tightly regulated electric potential of the cell membrane. Intracellular calcium concentrations regulate intracellular signaling, actin polymerization, cytoskeletal remodeling, and cell motility.[6,42]

G-protein-coupled receptors (GPCRs) are large proteins with 7 transmembrane domains. The extracellular portion binds many effector proteins and molecules, such as growth factors, inflammatory cytokines, neuropeptides, and hormones, creating a conformational change in the protein's structure. Once activated, the cytosolic portion interacts

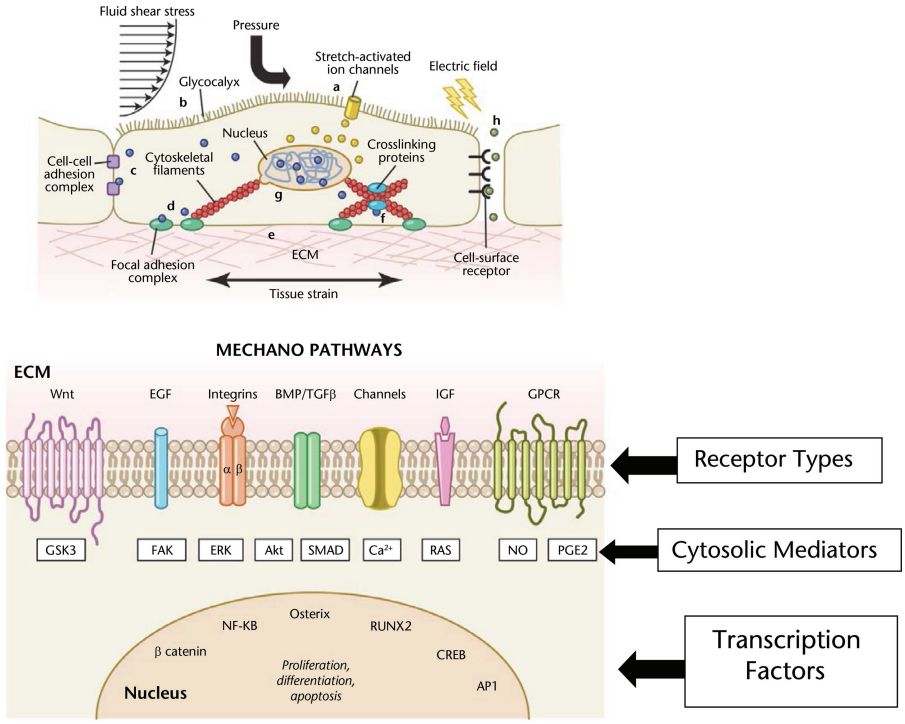

Figure 1.
Mechanosensing cell membrane receptors are responsive to tissue deformation. (Top) Mechanical forces are sensed and transduced at cell-cell, cell-matrix, and cell-lumen interfaces through adhesion complexes, stretch-activated ion channels, or cell surface receptors. The letters "a" through "h" represent the various methods cells use to sense mechanical stimuli: a=stretch activated ion channels open to allow influx or efflux of ions; b=cilia or glycocalyx on the cell surface sense fluid shear or compression; c and d=cell contacts with adjacent cells or ECM allows cells to sense and respond to their local physical environment; e=extracellular proteins within the ECM exert forces on the cell; f=intracellular strain from cytoskeletal components transmits and senses forces across the cell membrane; g=cytoskeletal components adhere to the nuclear envelope to sense cell deformation and alter transcriptional events; and h=intracellular compression affects receptor binding events at the cell surface. (Bottom) Cell surface receptors known to be mechanosensitive include growth factor receptors, integrins, stretch-activated ion channels, and GPCRs. Once stimulated, receptors activate intracellular cytosolic mediators (represented in boxes) to initiate signaling cascades. These cascades may result in nuclear translocation of transcription factors (eg, NFKB), which influence genetic regulation and cell behavior. ECM=extracellular matrix; Wnt=wingless-type signaling pathway; EGF=epidermal growth factor; BMP=bone morphogenic protein; TGFβ=transforming growth factor beta; IGF=insulin growth factor; GPCR=G-protein-coupled receptor; GSK3=glycogen synthase kinase 3; FAK=focal adhesion kinase; ERK=extracellular signal regulated kinase; Akt=protein kinase B; SMAD=a family of signal transduction proteins that respond to TFGβ; Ca^{2+}=calcium; RAS=a family of signal transduction, proteins originally identified and named for rat sarcoma cells; NO=nitrous oxide; PGE2=prostaglandin E2; NF-KB= nuclear factor kappa B; RUNX2=runt-related transcription factor 2; CREB=cyclic AMP response element binding protein; AP1=activator protein 1. Reprinted by permission of Macmillan Publishers Ltd, Nature Publishing Group, from: Bonnet N, Ferrari SL, Exercise and the skeleton: how it works and what it really does. *IBMS Bonekey*. 2010;7:7. Copyright 2010.

with intracellular G-proteins to affect the signaling cascade according to the specificity of the signal. These receptors also may be activated by mechanical loads across the cell surface, which initiate secondary messenger cascades within the cell.[34,40]

Growth factor receptors are activated by binding extracellular growth factors, which, in turn, activate several receptor-mediated second messenger pathways inside the cell. Growth factor receptors associate with other mechanosensing receptors in the cell membrane and have been found to create additive or complementary signaling effects.[24,43]

Cell-cell interactions also create a mechanical influence on neighboring cells through cell adhesion molecules (CAMs). These CAMs include transmembrane proteins, such as integrins, cadherins, selectins, and connexins, which bind cells together for structural and functional purposes. Adherens junctions between cells closely resemble the cell-matrix focal adhesion complexes, with dynamic links to the actin cytoskeleton that are responsive to mechanical tension.[44]

Membrane receptors interact with each other to create cross talk among intracellular signaling cascades, influence cytoskeletal structure and function, and either regulate or act in synergy with other transduction events.[5,24,40,43] Mechanical and chemical signal transduction mechanisms stimulate the same intracellular signaling pathways, and neither works in isolation of the other; more

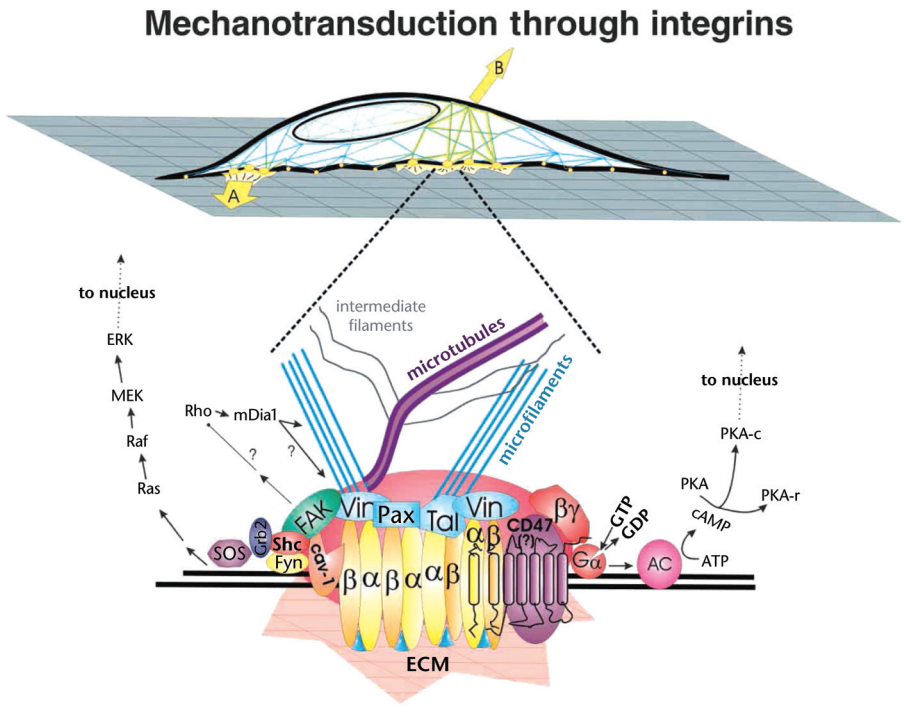

Figure 2.
Focal adhesion complex: a cell matrix binding complex mediated by integrins. A schematic diagram of how forces applied via the ECM (A) or directly to the cell surface (B) travel to integrin-anchored focal adhesions through matrix attachments or cytoskeletal filaments, respectively. Internally generated tension and forces transmitted via cell-cell contact similarly reach focal adhesions through the cytoskeleton. ECM=extracellular matrix; ERK=extracellular signal-regulated kinase, MEK=mitogen activated kinase, Raf and Ras=signaling proteins originally identified in rapidly accelerating fibrosarcoma cells, SOS=Son of Sevenless protein, Grb2=growth factor receptor-bound protein 2, Shc=SH-2 containing adapter protein, FAK=focal adhesion kinase, cav-1=caveolin-1, Vin=vinculin, Pax=paxillin, Tal=talin, GTP/GDP=guanosine tri- and di-phosphate, PK=protein kinase, cAMP=cyclic adenosine monophosphate, ATP=adenosine triphosphate, AC=adenylyl cyclase. Republished with permission of Company of Biologists Ltd from: Ingber DE. Tensegrity II: how structural networks influence cellular information processing networks. *J Cell Sci.* 2003;116:8; permission conveyed through Copyright Clearance Center Inc.

likely, there are synergistic and competing effects to either up- or down-regulate genetic influence.[5,24,36,43] In addition, mechanical forces transmitted through the cytoskeleton influence the nuclear membrane through its interconnectivity with cytoskeletal filaments.[7] Control of cell fate between growth, differentiation, and cell death has been attributed to nuclear mechanics regulated by these connections.[45]

Downstream Cellular Effects of Mechanical Stimulation

Transduction

Signal transduction across the cell membrane is just the first step in a multistep process. The next step involves multiple potential cytosolic mediators, called "signaling cascades," which transmit the signal from the cell surface to the effector end point, regardless of whether that is an organelle, a cytosolic function, or the translocation of transcription factors into the nucleus for genetic regulation.

Transcription

If the signal activates transcription factors, these proteins are translocated across the nuclear envelope to influence genetic expression. Transcription is the enzymatic process by which DNA is unwound and a specific segment of DNA, a gene, is copied to messenger RNA (mRNA) with precise nucleotide matching. The mRNA is packaged and then exits through nuclear pores back into the cytosol, where it will be translated into a protein.

In addition to activation of transcription factors, mechanical forces have been found to directly alter the transport of transcription factors and calcium across the nuclear envelope and nuclear ion channels, respectively.[7,46] Thus, mechanical loads influence transcription indirectly through the receptor-activated signaling cascades or directly through altering nuclear membrane transport.

Translation

Once in the cytosol, mRNA is bound by ribosomes for message decoding. The mRNA sequence, previously read from the gene during transcription, contains codons, which are strips of 3 nucleotides matched to specific amino acids. Transfer RNA (tRNA) facilitates the matching process from mRNA to amino acids, which are then sequentially linked to form proteins. Once translated, proteins are sorted and targeted according to their sequence and intended function to reach their correct destination within

the cell or to be released from the cell via the secretory pathway. Through the posttranslational process, proteins are modified, folded, and packaged for transport through the endoplasmic reticulum to the Golgi vesicles and Golgi cisternae to secretory and transport vesicles. Protein folding and modifications lend regulatory control and functionality to each protein, and these alterations are dictated by the protein sequence as transcribed and translated. Proteins are the chief actors in cell behavior, and their amino acid sequence and conformation provide for functional specificity. This entire molecular process, from transduction, transcription, and translation to protein transport, is tightly regulated, yet responsive to mechanical perturbation.

Role of the Extracellular Matrix

Integrity and stiffness of the ECM play significant roles in force transmission and mechanosensitivity.[27,33,41,47,48] Cells test the rigidity of their surrounding matrix by pulling through their focal adhesions (Fig. 2), which are concentrated integrin connections between the ECM and cytoskeleton.[33,35,38,41,48] Tissue rigidity guides many cellular responses, including cellular migration, proliferation, and even differentiation of stem cells, during embryonic development, organogenesis, or tissue regeneration.[7,24,33,48] Native cells prefer their native substrate, so specificity of the environmental construct guides cellular behavior.[33] Injury to the ECM provides mechanical cues for cells to reshape their environment through the assembly and production of native matrix proteins.[33,41,49]

Load Responsiveness

The term "tensegrity" was coined by the architect and engineer, R. Buckminster Fuller, in 1961 to describe the tensional integrity of geodesic structures, which consist of internal components under compressive loads within a system of external tension. Donald E. Ingber, a Harvard biologist and bioengineer, later applied the term to biologic systems to describe the molecular framework sustaining the hierarchical structure of systems from cell, to tissue, to organ, and finally to organism-level interactions.[30,31] Organs and tissues are organized as prestressed structural hierarchies, which lend themselves to immediate mechanical responsiveness.[14,30,31] Mechanical coupling of cells to the ECM through membrane-associated proteins allows them to sense and respond to either ECM distortions or changes in matrix stiffness; perturbations of this structural architecture regulate biologic responses.[14,30,31,50–52]

Structural prestress and mechanical responsiveness of tissues and cells to loading lend relevance of mechanobiology to physical therapist practice in that forces regulate and influence biochemistry, genetic expression, tissue integrity in homeostasis, and developmental and repair processes.[50] Many otherwise unrelated disease processes share abnormal mechanotransduction, as the etiology or clinical presentation and molecules that mediate mechanotransduction present therapeutic targets for amelioration of these diseases.[50] Physical therapists use mechanical forces to influence tissue repair and may readily utilize these tools within their scope of practice to affect mechanotransductive-related diseases.

Load Specificity

Mechanical forces, such as tension, compression, and shear, are sensed and transmitted at cell-cell, cell-matrix, and cell-lumen interfaces, (Fig. 1) creating responses that can either strengthen the complexes that bear the load or change the distribution of receptors to mitigate the load.[38] In this way, cells can immediately mount a specific response to either up- or down-regulate transcriptional responses to the load.[36] Just as native cells prefer their native substrate, each cell type responds differentially to the variety of forces to which the cells are exposed.[2,22,23,53–65] Cells also respond differentially to the magnitude, duration, and frequency of the load applied.[22,29,33,53] In addition, most transcriptional responses to loads are mediated through secondary messenger cascades and may create lasting biologic effects.[5,29] Following are examples of load and tissue specificity, which are but an introduction to the broad impact of mechanobiology to health and disease across the many areas in which physical therapists practice.

Shear and Endothelial Cells

Endothelial cells line blood vessels and are constantly exposed to the stresses of the cardiovascular system, namely the fluid shear stress of blood flow and the pulsatile pressures and cyclic mechanical strain from the beating heart and volume pressures. Fluid shear stresses are required for the transcriptional activation of genes necessary to produce proteins critical to vascular homeostasis, platelet-derived growth factor B, nitric oxide synthase 3, and platelet endothelial cell adhesion molecule 1.[66–68] Shear stress also regulates the binding of transcription factors to the promoter region of these genes.[56] Fluid shear stress is necessary for endothelial survival and integrity.[7] Deregulation of these transcriptional relationships has been found to contribute to atherosclerosis and resultant turbulent flow, which feeds forward to create additional atherosclerosis.[56]

Tension and Lung Tissue

The application of tension to lung epithelial cells activates transcription factors NFkB and serum response factor during embryonic development. These transcription factors regulate maturation and morphogenesis of lung branching, along with myogenesis of smooth muscle necessary for bronchial development.[65,69] At birth, the transition to breathing air creates changes in force distribution across lung tissue and results in the formation and maturation of alveolar structures.[70,71] Asthma and ventilator-induced lung injuries, both of which are related to excessive tensile loads, are associated with deregulation of the transcription factor NFkB and resultant detrimental structural and physiologic changes.[72,73] Matrix alterations in response to mechanical cues have recently been associated with the pathogenesis of chronic, fibrotic lung diseases such as idiopathic pulmonary fibrosis.[74,75] Rigidity of the ECM of the lung due to scarring is related to mechanoinductive events that exacerbate matrix stiffness, ultimately leading to decreased lung compliance and emphysema; a better understanding of the role of matrix mechanics in cell-matrix interactions will be a critical factor in regenerative

approaches to engineer functional lung tissue.[75]

Compression, Distraction, and Bone

In 1892, Julius Wolff was the first person to propose that bone changes its internal architecture according to the forces placed upon it.[76] Now, we know that osteocytes, housed in the lacunae of the Haversian system, are the bone cells primarily sensitive and responsive to mechanotransduction.[19,54,58,61] Because of the rigid matrix of cortical bone, osteocytes are stress shielded from compressive loads and instead respond to fluid shear stress induced through the lacuna-canalicular network in response to compression.[54] Osteocytes project long, slender cell processes through this porous canalicular network to connect to other osteocytes via gap junctions. Interstitial fluid flow induces osteocyte transcription and translation of proteins responsible for bone integrity, and low fluid flow is associated with osteoporosis.[19,54,77,78] Osteocytes are responsible for bone matrix homeostasis and appear to orchestrate selective recruitment of either osteoblasts in high-load situations or osteoclasts in low-load situations to regulate bone remodeling for the restoration of steady state.[7,19,54,58]

Distraction osteogenesis is a technique that utilizes tensile forces to grow new bone in fracture repair.[79,80] Osteoblasts exposed to tension have been shown to up-regulate osteopontin and several bone morphogenic proteins.[80] In addition, emerging evidence reveals bone marrow-derived mesenchymal stem cells, progenitors for both osteoblasts and adipocytes, may respond to high-frequency, low-intensity loading exercise by differentiating toward osteogenesis, tipping the balance from fat storage to bone deposition.[78,81–83]

Multiple Forces and Cartilage

Like osteocytes, chondrocytes are encapsulated in a complex matrix structure that provides stress shielding. Each chondrocyte is housed in a chondron, a thin pericellular matrix (PCM) within the ECM of articular cartilage. The PCM transmits forces between the ECM and chondrocyte, and the chondron is considered to be the mechanical unit of cartilage.[20] The articular chondrocyte lives in a dynamic environment with a multitude of forces: shear stress, osmotic pressure, compression, tension, and hydrostatic pressure, all of which specifically regulate genetic responses during physiologic joint loading.[20,84]

Dynamic, cyclic compression and hydrostatic pressure have been shown to up-regulate the transcription and translation of ECM proteins aggrecan and type II collagen, whereas static compression down-regulates both.[55,85] In addition, shear stress elicits more transcription and translation of the ECM proteins proteoglycan and collagen in bovine chondrocytes than compressive loading,[62] whereas excessive compression deregulates NFkB, leading to arthritic changes.[86]

The contrasting orientation of the primary cilia on chondrocytes in articular cartilage compared with those in epiphyseal cartilage lends to the possibility of directional mechanical cues for proliferation and directional production of ECM in response to compression.[28,87] Taken together, chondrocytes are subjected to many mechanical loads in health and disease and are able to specifically respond to distinct mechanical stimuli to regulate metabolism and matrix production.[20,21,27,28]

Tension and Skeletal Muscle

It has long been understood that tension through resistive exercise results in muscle hypertrophy, whereas disuse results in atrophy. Many of the underlying molecular mechanisms are beginning to point to mechanotransduction as pivotal in the regulation of protein synthesis, calcium balance, contractility, and muscle mass.[88–93] Each muscle cell or myofiber is packed with myofibrils that extend the length of the cell and contain contractile units (ie, sarcomeres) oriented end to end along their length. Z-discs demarcate each sarcomere and are important to mechanical stability, but they also are composed of many proteins important to mechanotransduction and protein turnover within muscle, whereas their deficiency is related to many human diseases.[91] In addition, there is evidence to suggest that myofibers are capable of differentiating between chronic longitudinal tension, producing growth in length through sarcomere deposition in series, and chronic functional or resistive overload, which produces cross-sectional hypertrophy.[89,94] As these mechanisms are further elucidated, there is an obvious need for precision in the type, frequency, and duration of loading to create the desired effect on muscle.

Tension and Tendon

Tenocytes (tendon fibroblasts), the primary cell type in tendon, are embedded in densely packed parallel bundles of mostly type I collagen. As tendons are placed under tension, the tenocyte experiences compression and shear forces through its links to the collagen bundles and tension in the direction of the tensile load.[95] The tenocyte is mechanosensitive, with specific transcriptional responses to underloading, physiologic loading, and overloading.[53,60,96] Underloading decreases the expression of several ECM proteins, including collagen, aggrecan, decorin, and fibronectin,[60] whereas overloading produces an increased expression of proinflammatory cytokines, such as prostaglandin[96] and matrix metalloproteinases.[97] Physiologic loading creates matrix homeostasis with tenocyte proliferation and matrix production according to the load.[53,60,95–97] Investigators have identified that frequency, duration, and magnitude of the load creates differential anabolic and catabolic cellular responses, concluding that specific ranges of mechanical loads are required for tissue homeostasis and repair.[53,60,95–97]

Tension and Skin

Studies of wound healing have provided clues to the effects of mechanotransduction through the use of compression to minimize fibrotic scarring and negative pressure wound therapy to accelerate closure. Most major cell types found in skin have been identified as mechanoresponsive, but the fibroblast is the most studied.[23] Fibroblasts respond to tension by proliferating and through increased expression of collagen, α-smooth muscle actin, and cytokines.[57,64,98,99] Expression

of α-smooth muscle actin is a critical step in wound contraction,[32] but if deregulated through excessive tension or excessive TGF-β production, it may result in hypertrophic scar formation.[100] Compression therapy has been utilized for more than 25 years to mechanically offload burn scars to prevent hypertrophic scarring.[63] In addition to fibroblasts, keratinocytes use mechanosensing to tug on the ECM before migrating across the wound bed; indicating an ability to determine whether the matrix is ready for closure.[101,102]

Importance of Physiologic Loads to Tissue Integrity in Health and Use of Precise Loads in Repair

Physical therapists understand the importance of tissue integrity to overall health and function. When the Physical Stress Theory was presented by Mueller and Maluf in 2002,[103] we became more aware of the detrimental effects of both underloading and overloading of tissues. Our profession has a general appreciation for tissue response to loading, and we use these biologic concepts in progressing the intensity of our interventions over time to build tissue capacity. However, as we continue to explore clinical questions related to dosing, we do not have the answers we need to precisely load healing tissue with the exact frequency, duration, magnitude, and types of loads to extract the optimal outcome.[104–106] Our clues to dosing are based on the patient's response to our intervention, regardless of whether inflamed or not. Through mechanobiology, we know that excessive loading of many tissues increases the genetic up-regulation of proinflammatory mediators and enzymes.[7] However, we do not know the ideal dosing of mechanical loads, nor when best to use them during the repair process to produce the optimal effects of matrix deposition, alignment, and tissue integrity.[104–106] Given the advances in technology, the fields of mechanobiology and regenerative medicine are ripe for future research, to include clinical implications of force specificity and load dosing to optimize resource utilization over time and improve clinical outcomes associated with new and old therapeutic interventions.

Conclusions

Mechanobiology, as a scientific field, has become established, with solid evidence and techniques, and thus presents exciting times ahead, with much to be discovered about its relevance in health, disease, and therapeutic intervention, including tissue engineering and regenerative medicine.[7,29] Physical therapists have opportunities to embrace and contribute to this evolving science in order to determine the genetic and biological effects that may enhance our current interventions. In addition, we have the clinical expertise to contribute as collaborators in innovative approaches that combine mechanical loading with other biologic interventions such as gene therapy, biologic tissue engineering, and regenerative medicine for synergistic effects that could optimize any associated outcome.[107]

Physical therapists have used molecular biology in our interventions since the inception of our practice, and over the last few decades, we have enhanced the credibility of our practice through outcomes research. Now that there is an evolving basic science to explain the mechanistic underpinnings of our practice, our participation could help determine optimal dosing and precision in our exercise prescription and mechanical loading. By optimizing the time we have with the consumer, this science could result in greater satisfaction, better outcomes, and enhanced value. Our distinct contribution to society is that which optimizes human movement with minimal risk. Perhaps mechanobiology is one of the keys to unlocking this professional potential and fully realize Dr Hislop's dream.

Dr Dunn provided concept/idea/project design. Both authors provided writing. Dr Olmedo provided consultation (including review of manuscript before submission).

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