Mechanobiology and Diseases of Mechanotransduction

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FROM ABSTRACT

The current focus of medicine on molecular genetics ignores the physical basis of disease even though many of the problems that lead to pain and morbidity, and bring patients to the doctor's office, result from changes in tissue structure or mechanics.

The main goal of this article is therefore to help integrate mechanics into our understanding of the molecular basis of disease.

This article first reviews the key roles that physical forces, extracellular matrix and cell structure play in the control of normal development, as well as in the maintenance of tissue form and function.

Recent insights into cellular mechanotransduction--the molecular mechanism by which cells sense and respond to mechanical stress--also are described. Re-evaluation of human pathophysiology in this context reveals that a wide range of diseases included within virtually all fields of medicine and surgery share a common feature: their etiology or clinical presentation results from abnormal mechanotransduction.

This process may be altered by changes in cell mechanics, variations in extracellular matrix structure, or by deregulation of the molecular mechanisms by which cells sense mechanical signals and convert them into a chemical or electrical response.

Molecules that mediate mechanotransduction, including extracellular matrix molecules, transmembrane integrin receptors, cytoskeletal structures and associated signal transduction components, may therefore represent targets for therapeutic intervention in a variety of diseases.

KEY MESSAGES FROM AUTHOR

1) “Mechanical forces are critical regulators of cellular biochemistry and gene expression as well as tissue development.”

2) “Mechanotransduction -- the process by which cells sense and respond to mechanical signals -- is mediated by extracellular matrix, transmembrane integrin receptors, cytoskeletal structures and associated signaling molecules.”

3) "Many ostensibly unrelated diseases share the common feature that their etiology or clinical presentation results from abnormal mechano-transduction."

4) "Mechanotransduction may be altered through changes in cell mechanics, extracellular matrix structure or by deregulation of the molecular mechanisms by which cells sense mechanical signals or convert them into a chemical response."

5) "Molecules that mediate mechanotransduction may represent future targets for therapeutic intervention in a variety of diseases."

THIS AUTHOR ALSO NOTES:

"There is a huge disconnect between 'genome-age' technologies and the reality of how diseases manifest themselves. From the time the first human looked, listened and felt for what is wrong with a sick friend, caregivers have recognized the undeniable *physical* basis of disease." **[Key Point]**

"In the current genome euphoria, there appears to be no place for 'physicality'. This is especially worrisome given that abnormal cell and tissue responses to mechanical stress contribute to the etiology and clinical presentation of many important diseases, including asthma, osteoporosis, atherosclerosis, diabetes, stroke and heart failure."

There is a "strong mechanical basis for many generalized medical disabilities, such as lower back pain and irritable bowel syndrome, which are responsible for a major share of healthcare costs world-wide."

Physical interventions can influence cell and tissue function.

"Altered cell or tissue mechanics may contribute to disease development." **[Very Important]**

"In biology and medicine, we tend to focus on the importance of genes and chemical factors for control of tissue physiology and the development of disease, whereas we commonly ignore physical factors. This is interesting because it was common knowledge at the turn of the last century that mechanical forces are critical regulators in biology." **[Key Point]**

Because of the recent advances in the molecular basis of disease, there has been a loss of interest in mechanics. **[Important]**

Mechanical forces are important for the development and function of the heart and lung, the growth of skin and muscle, the maintenance of cartilage and bone, and the etiology of many debilitating diseases.

The basic mechanisms of sensation and autonomic control, including hearing, balance, touch, and peristalsis have mechanical explanations.

"Mechanical forces serve as important regulators at the cell and molecular levels, and they are equally potent as chemical cues."

"Cell-generated tensional forces have been shown to regulate diverse functions, ranging from chromosome movements and cell proliferation to tissue morphogenesis, in addition to cell contractility and motility."

Tissues are composed of groups of living cells held together by an extracellular matrix (ECM) comprised of a network of collagens, glycoproteins, and proteoglycans.

"Each cell contains a surface membrane, intracellular organelles, a nucleus, and a filamentous cytoskeleton that connects all these elements and is permeated by a viscous cytosol." **["Filamentous Cytoskeleton"]**

Because our bodies are complex hierarchical structures, "mechanical deformation of whole tissues results in coordinated structural rearrangements on many different size scales."

In any three-dimensional structure, mechanical loads will be transmitted across structural elements that are physically interconnected.

"Forces that are applied to the entire organism (e.g., due to gravity or movement) or to individual tissues would be distributed to individual cells via their adhesions to the ECM support scaffolds (basement membranes, interstitial matrix, cartilage, bone) that link cells and tissues throughout the body."

ECM mediates mechanical energy transfer to sensory cells within muscle stretch receptors.

If the ECM is less flexible, then stresses will be transmitted to and through the cell. **[Very Important]**

The ECM plays a role of mechanoregulation in all solid tissues by distributing stresses throughout tissues and focus these forces on sites of cell-ECM adhesion.

Cells adhere to ECM through the binding of cell surface receptors known as 'integrins'.

Integrins provide a preferred site for mechanical signal transfer across the cell surface.

Integrins appear to function as cell surface 'mechanoreceptors' in that they are among the first molecules to sense a mechanical stress applied at the cell surface, and they transmit this signal across the plasma membrane and to the cytoskeleton.

Living cells contain a cytoskeleton.

The cytoskeleton is not simply a passive gel because all cells generate tensional forces through actomyosin filament sliding in their cytoskeleton.

"This type of force balance is a hallmark of an architectural system known as 'tensegrity'." **[Tensegrenous Matrix]**

The viscoelastic behavior of living cells results from collective mechanical interactions within the tensed molecular cytoskeleton.

Cytoskeletal forces are transmitted to transport organelles (e.g., mitochondria, synaptic vesicles) in the cytoplasm, and to chromosomes during mitosis.

Changes that alter the cytoskeletal force balance and modulate cell shape "also control complex cell behaviors that are critical for development and tissue homeostasis." **[Important]**

"Cell growth, differentiation, polarity, motility, contractility and programmed cell death, all can be influenced by physical distortion of cells through their ECM adhesions." **[Important]**

Altering tissue stress alters the function of chondrocytes, hepatocytes, mammary epithelium, retinal epithelium, capillary endothelium, and fibro-blasts.

Direct application of tensional forces to endothelial cells promotes capillary outgrowth and "nerve cells respond to tensional forces exerted on their surfaces by extending nerve processes in the direction of the applied stress." **[Important]**

"The physicality of the ECM substrate and degree of cell distortion govern cell behavior regardless of the presence of hormones, cytokines or other soluble regulatory factors."

"Regional changes in ECM structure and associated changes in cytoskeletal mechanics similarly contribute to control of angiogenesis that is required for wound healing as well as tumor progression." **[Important]**

"In fact, cell-generated tensional forces appear to play a central role in the development of virtually all living tissues and organs, even in neural tissues, such as retina and brain."

"In vitro and in vivo studies confirm that mechanical forces directly regulate the shape and function of essentially all cell types."

Any external mechanical stimulus that impinges on an adherent cell is imposed on a pre-existing force balance, which can govern the ‘response’ to the mechanical ‘stimulus’.

“A tug on the ECM will be felt by the cell through its focal adhesions and hence, through its transmembrane integrin receptors that link to the cytoskeleton.”

“When the shape of a molecule is altered, its biophysical properties change, and hence biochemistry (e.g., chemical reaction rates) will be altered.” **[Important]** “This is important because many of the enzymes and substrates that mediate cellular metabolism (e.g., protein synthesis, glycolysis, RNA processing, DNA replication) are physically immobilized on the cytoskeleton and nuclear matrix (nucleoskeleton).”

Local changes in biochemical signal transduction are produced when external forces are applied to integrins.

“Mechanical stress application to integrins also stimulates rapid (within 10 msec) calcium influx in the neuromuscular synapse, recruits the protein synthetic machinery to the site of force application, and activates cAMP signaling within the focal adhesion which eventually leads to stress-induced changes in gene transcription.”

“All cells also contain ‘stress-sensitive’ (mechanically-gated) ion channels that either increase or decrease ion influx when their membranes are mechanically stressed.”

“The global shape of the cell dictates its behavior (e.g., growth versus differentiation or apoptosis), and these effects are mediated through tension-dependent changes in cytoskeletal structure and mechanics.” **[Important]**

“These new insights into mechanobiology suggest that many ostensibly unrelated diseases may share a common dependence on abnormal mechanotransduction for their development or clinical presentation.”

“Mechanotransduction may be altered through changes in cell mechanics, ECM structure or by deregulation of the molecular mechanisms by which cells sense mechanical signals or convert them into a chemical response.”

“Local changes in tissue structure also may explain why genetic diseases, including cancer, often present focally.”

“Understanding of the relation between structure and function in living tissues and of fundamental mechanisms of cellular mechanotransduction may therefore lead to entirely new modes of therapeutic intervention.”

"The therapeutic value of physical therapy, massage, and muscle stimulation is also well known."

CONCLUSION

"The current focus in medicine is on the genetic basis of disease. However, it is not necessary to correct the underlying genetic defect in order to treat clinically relevant symptoms or relieve the pain and morbidity of disease. Moreover, most of the clinical problems that bring a patient to the doctor's office result from changes in tissue structure and mechanics. Although these physical alterations have been commonly viewed as the end-result of the disease process, recent advances in mechanobiology suggest that abnormal cell and tissue responses to mechanical stress may actively contribute to the development of many diseases and ailments. Thus, it might be wise to search for a physical cause when chemical or molecular forms of investigation do not suffice."

"These observations also raise the possibility that the molecules that mediate mechanotransduction, including ECM molecules, cell surface adhesion receptors, cytoskeletal components, and related signal transduction molecules may represent future targets for therapeutic intervention in a variety of diseases."

KEY POINTS FROM DAN MURPHY

1) "Mechanical forces are critical regulators of cellular biochemistry and gene expression as well as tissue development."

2) Many "unrelated diseases share the common feature that their etiology or clinical presentation results from abnormal mechano-transduction."

3) There is an "undeniable *physical* basis of disease." **[Key Point]**

4) Abnormal cell and tissue responses to mechanical stress contribute to the etiology and clinical presentation of many important diseases.

5) There is a "strong mechanical basis for many generalized medical disabilities, such as lower back pain and irritable bowel syndrome, which are responsible for a major share of healthcare costs world-wide."

6) Physical interventions can influence cell and tissue function.

7) "Altered cell or tissue mechanics may contribute to disease development." **[Very Important]**

8) "Mechanical forces are critical regulators in biology." **[Key Point]**

9) Because of the recent advances in the molecular basis of disease, there has been a loss of interest in mechanics. **[Not in chiropractic]**

10) "Mechanical forces serve as important regulators at the cell and molecular levels, and they are equally potent as chemical cues."

11) Tissues are composed of groups of living cells held together by an extracellular matrix (ECM).

12) The surface membrane of cells is mechanically attached to all of the cell's organelles, to its nucleus and its chromosomes, and to its synaptic vesicles, by a "filamentous cytoskeleton." **["Filamentous Cytoskeleton"]**

13) Because our bodies are hierarchical structures, mechanical deformation of any tissues results in structural rearrangements in many tissues.

14) Mechanical loads anywhere in the body can affect many tissues and cells because they are physically interconnected.

15) "Forces that are applied to the entire organism (e.g., due to gravity or movement) or to individual tissues would be distributed to individual cells via their adhesions to the ECM support scaffolds that link cells and tissues throughout the body." **[This is consistent with chiropractic perspectives on the subluxation]**

16) If the ECM is less flexible, then stresses will be transmitted to and through the cell. **[Again, this is consistent with chiropractic perspectives on the subluxation]**

17) Living cells contain a cytoskeleton that generate and transfer tensional forces, known as "tensegrity." **[Tensegrenous Matrix]**

18) Changes in the cytoskeletal force balance alter tissue homeostasis.

19) "The physicality of the ECM substrate and degree of cell distortion govern cell behavior regardless of the presence of hormones, cytokines or other soluble regulatory factors." **[Again, this is consistent with chiropractic perspectives on the subluxation]**

20) "Cell-generated tensional forces appear to play a central role in the development of virtually all living tissues and organs, even in neural tissues."

21) "Mechanical forces directly regulate the shape and function of essentially all cell types."

22) Many of the enzymes and substrates that mediate cellular metabolism (e.g., protein synthesis, glycolysis, RNA processing, DNA replication) are physically immobilized on the cytoskeleton and nuclear nucleoskeleton matrix. Consequently, mechanical stresses through the cytoskeletal and nucleoskeletal matrix can alter physiology by physically altering biophysical properties, which in turn alter chemical reaction rates.

23) Mechanical stress stimulates rapid calcium influx in the neuromuscular synapse, again altering function.

24) “All cells also contain ‘stress-sensitive’ (mechanically-gated) ion channels that either increase or decrease ion influx when their membranes are mechanically stressed.”

25) “The global shape of the cell dictates its behavior (e.g., growth versus differentiation or apoptosis), and these effects are mediated through tension-dependent changes in cytoskeletal structure and mechanics.” **[Important]**

26) “These new insights into mechanobiology suggest that many ostensibly unrelated diseases may share a common dependence on abnormal mechanotransduction.”

27) Local mechanical changes in tissue structure may explain why genetic diseases, including cancer, often present focally.

28) Physical therapy, massage, and muscle stimulation have well known therapeutic value because they alter mechanotransduction. **[Chiropractic adjustments and postural corrections should have been included here.]**

29) Most of the clinical problems that bring a patient to the doctor's office result from changes in tissue structure and mechanics.

30) Abnormal cell and tissue responses to mechanical stress may actively contribute to the development of many diseases and ailments. Consequently it may be wise to look for a physical cause for disease.

31) Mechanics must be reintegrated into our understanding of the molecular basis of disease.

CONCEPTS SUPPORTED BY THIS STUDY, FROM DAN MURPHY

THE CHIROPRACTIC CONNECTION

The entire body is mechanically integrated through an extracellular matrix which attaches to cell membranes; cell membranes are attached to cell organelles through a filamentous cytoskeleton, including attachments to the nuclear membrane; the nuclear membrane is attached to the chromosomes through a nucleoskeleton. This is known as tensegrity or the Tensegrenous matrix.

Altered alignment in gravity or altered movement patterns (both are aspects of the subluxaion) adversely affect this tensegrenous matrix, altering the function of cell membranes, cellular organelles, and genetic expression.

THE TRANS FATTY ACID CONNECTION

Trans fatty acids are human-made fat molecules that have an abnormal molecular configuration. Trans fat consumption will incorporate the abnormal molecules into the cell and organelle membranes, altering the membranes biophysical properties. This would also adversely affect the tensegrenous matrix, altering the function of cell membranes, cellular organelles, and genetic expression.

THE OMEGA-3 CONNECTION

Having the innate balance of omega-3 to omega-6 fatty acids ensures optimal membrane fluidity, which would improve the tensegrity of the extracellular matrix / cell membrane interface, as well as the cell membrane cytoskeleton interface.