

# Integrins, Tensegrity, and Mechanotransduction

Donald E. Ingber

*Departments of Pathology & Surgery, Children's Hospital & Harvard Medical School,  
Boston, MA 02115*

## ABSTRACT

Physical forces, such as those due to gravity, play an important role in tissue development and remodeling. Yet, little is known about how individual cells sense mechanical signals or how they transduce them into a chemical response. Rather than listing the numerous signal pathways that have been found to be sensitive to mechanical stimulation, we need to place potential molecular signaling mechanisms within the context of the entire cell. The model presented is based on the concept that cells use tensegrity architecture to organize their cytoskeleton and stabilize their form. Studies with stick and string tensegrity cell models predict that living cells are hard-wired to respond immediately to external mechanical stresses. This hard-wiring exists in the form of discrete cytoskeletal filament networks that mechanically couple specific cell surface receptors, such as integrins, to nuclear matrix scaffolds and to potential transducing molecules that physically associate with the cytoskeleton. If these signaling molecules do function in a "solid-state", then mechanical stresses may be transduced into biochemical responses through force-dependent changes in cytoskeletal geometry or through local alterations in thermodynamic or kinetic parameters. Changes in cytoskeletal tension (prestress) also may play a role in signal amplification and adaptation. Recent experimental results are described which provide direct support for the tensegrity theory.

---

## INTRODUCTION

This article is a brief synopsis of a lecture presented in the Halstead Symposium on Advances in Space Biology - Animal Research that convened in Charlotte, North Carolina on October 26, 1996 as part of the Annual meeting of the American Society for Gravitational and Space Biology. The lecture reviewed work on the molecular and cellular basis of mechanotransduction that was made possible in part by funding to my laboratory from the Space Biology Program at NASA. I can honestly say that this funding would have not been possible if it were not for the vision and continued support of Thora Halstead. She gave me a chance when no others would do so by funding my first grant proposal. Thus, it is my honor to present this lecture in her honor.

The original grant proposal I submitted to NASA in 1986 was designed to develop an apparatus that would permit us to pull directly on specific cell surface receptors using magnetic particles and thus, to test our hypothesis that transmembrane extracellular matrix (ECM) receptors, or what are now known as "integrins", mediate mechanical signal transfer across the cell membrane. Although it

required many years, this work eventually was successfully completed (Wang et al., 1993; Wang and Ingber, 1994; Wang and Ingber, 1996). Our original hypothesis that integrins may function as mechanochemical transducers emerged from the concept that cells use a particular form of architecture, known as tensegrity, to organize their cytoskeleton (CSK) and thus, to stabilize their shape (Ingber et al., 1981; Ingber and Jamieson, 1985; Ingber, 1993; Ingber et al., 1994). The tensegrity theory not only predicted that cell surface adhesion receptors might function as mechanoreceptors, it also provided a potential explanation for how living cells physically and biochemically respond to external mechanical stress (Ingber and Jamieson, 1985; Ingber, 1997). In this lecture, I review our working hypotheses and the tensegrity model as well as the progress we have made in terms of testing these hypotheses over the past 15 years. A more in depth description of this work can be found in many recent publications from our laboratory (see full Reference list below).

## SIGNAL TRANSDUCTION VERSUS SIGNAL INTEGRATION

I know that many of you, as members of ASGSB, are interested in understanding how gravity and other mechanical signals are transduced into biochemical changes inside the cell. I have been to many meetings over the past year that focus on signal transduction. Some focus on signaling by growth factors, others by ECM, and others like this one concentrate on mechanotransduction. Essentially, one tends to hear the same type of lecture presented in all of these meetings. The lecturer maps out his or her favorite signaling pathway (e.g., MAP kinase, inositol lipid hydrolysis, protein tyrosine phosphorylation, etc.) with a series of arrows and then goes about identifying the cascade of upstream and downstream signaling components.

I have a very different purpose here today. My basic message is that we will never fully understand cell regulation if we focus on any single signaling mechanism or think about growth factor signaling, integrin signaling, and mechanical signaling as isolated transduction processes. For example, cells in a healing wound most likely sense multiple simultaneous inputs: the same time the cell binds a growth factor, it may form a new ECM adhesion and it also may feel the mechanical tug of the surrounding tissue. Yet, the cell produces only one concerted response: it either grows or differentiates or moves or dies

locally. Thus, the key is not which pathway is turned on, rather it is how all of these different signaling pathways are integrated inside the cell.

## MECHANOCHEMICAL SWITCHING

Let me begin with the take home message: living cells are literally hard-wired so that they can filter the same set of inputs to produce different functional outputs and this mechanism. Furthermore, this switching mechanism is largely controlled mechanically through physical deformation of the cell and CSK.

We were first able to make this point some years ago by plating cells on bacteriological petri dishes coated with different densities of immobilized ECM molecules, such as fibronectin (Ingber et al., 1987; Ingber, 1990; Ingber and Folkman, 1989; Ingber et al., 1990). Endothelial cells can not adhere to these dishes in the absence of serum or adsorbed ECM components. Thus, when we plated cells on these dishes in chemically-defined, serum-free medium, we found that cell, CSK, and nuclear spreading increased in parallel as the ECM coating density was raised. Even though the medium contained a saturating amount of soluble growth factor (FGF), DNA synthesis and cell doubling rates also increased in an exponential manner as the ECM density was raised and cell spreading was promoted. Furthermore, as the ECM density was lowered and growth was shut off, differentiation was turned on. Using capillary endothelial cells we found that capillary tube formation was induced in a period of hours when cells were plated on these dishes. When primary rat hepatocytes were used, we could demonstrate that this shape-dependent switching between growth and differentiation occurs at the level of gene expression (Mooney et al., 1992; Hansen et al., 1994) and depends on the presence of an intact CSK (Mooney et al., 1995).

More recently, we developed a technique whereby we could vary cell shape and CSK form independently of the ECM density (Singhvi et al., 1994). We did this by fabricating ECM-coated adhesive islands of defined geometry on the micron scale using a novel micropatterning technology that was initially developed for the microchip industry by George Whitesides' group at Harvard (Prime and Whitesides, 1991). When we fabricated circular islands 20  $\mu\text{m}$  in diameter, coated them with fibronectin, and then plated cells on them, we obtained round cells of the same size. When we fabricated square adhesive islands, we obtained living cells with 90° corners. This result demonstrates that the old view that surface membrane tension controls cell shape is incorrect and confirms instead that the CSK is the critical determinant of cell morphology.

We used this micropatterning technique to ask whether cell shape can alter cell function independently of growth factors or integrin binding. We found that when hepatocytes were cultured in EGF-containing medium on different sized adhesive islands, DNA synthesis increased

in parallel as the size of the island was raised (Singhvi et al., 1994). Furthermore, as growth was turned on, a concomitant switching off of differentiation (secretion of the liver-specific protein albumin) was observed. More recently, we confirmed similar shape-dependent control of growth and apoptosis in capillary endothelial cells (Chen et al., 1997).

It is important to emphasize that related studies from our laboratory and others has revealed that this shape-dependent control of cell cycle progression occurs many hours after activation of all of the early signaling events that tend to gain the greatest attention of the biological community (e.g., after activation of FAK kinase, MAP kinase, JNK kinase, PI-3 kinase, fos, myc, jun, etc.) (Hansen et al., 1994; Ingber et al., 1995; Bohmer et al., 1996). This is a beautiful example of the signal filtering I referred to in the beginning. With the same growth factor and integrin signaling pathways turned on, one obtains different functional outputs depending on whether the cell is spread or round.

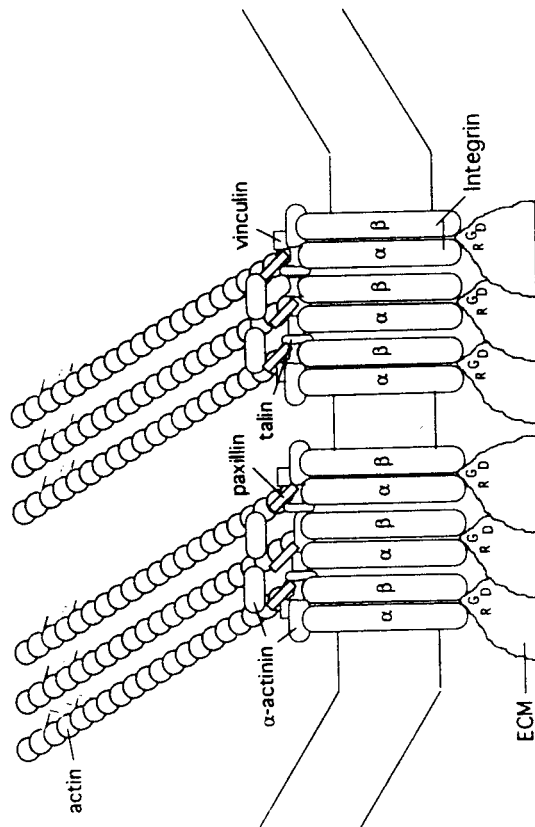
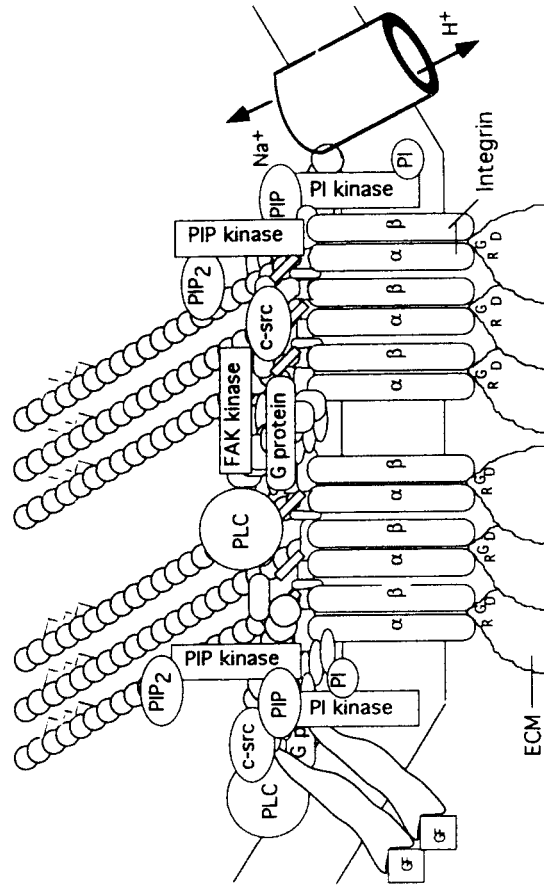
## SIGNAL INTEGRATION WITHIN THE FOCAL ADHESION

Well how can this work? How can adhesion and spreading shift cells between different gene programs? Part of the explanation is based on how cells restructure their CSK when they adhere to ECM. Cell attachment to ECM is mediated by binding of specific transmembrane receptors, such as integrins (Hynes, 1992). These receptors cluster in specialized anchoring complexes, or spot welds, that are known as focal adhesion complexes (FACs) where they physically interconnect with actin-associated molecules, such as talin and vinculin (Burrige and Chrzanowska-Wodnicka, 1996).

Essentially, we have found that part of the mechanism of signal integration is based on the spatial organization of signaling molecules within the cell. Specifically, our laboratory (Plopper et al., 1995; McNamee et al., 1996), Ken Yamada's group (Miyamoto et al., 1995a), and a number of others (reviewed in Burrige and Chrzanowska-Wodnicka, 1996) have found that many of these signaling molecules that are turned on by both integrins and growth factor receptors are immobilized on the CSK and specifically concentrated within the FAC at the site of integrin binding. These signaling molecules include tyrosine kinases, such as FAK kinase and src kinase, inositol lipid kinases, ion channels (Na<sup>+</sup>/H<sup>+</sup> antiporter), small molecular weight G proteins (e.g., rho), and even a subset of growth factor receptors (e.g., the high affinity FGF receptor, Fig. 1).

There are two important points here. The first is that proximity between different transducing molecules provides a way to integrate integrin and growth factor signaling pathways at the cell surface. For example, Helen McNamee, a graduate student in my laboratory found that integrin clustering activates phosphatidylinositol

# SIGNAL INTEGRATION IN THE FOCAL ADHESION COMPLEX



kinases within the focal adhesion complex and thereby, controls the synthesis of phosphatidylinositol-4,5-bisphosphate at the site of integrin binding (McNamee et al., 1996). Working in collaboration with Martin Schwartz at Scripps Institute we found that by controlling the availability of this natural lipid substrate for phospholipase C, ECM and integrin binding can regulate downstream inositol lipid signaling events (e.g., PKC activation, calcium release; McNamee et al., 1993) as well as actin polymerization and stress fiber formation in response to growth factor stimulation (reviewed in Burridge and Chrzanowska-Wodnicka, 1996). Thus, this is a beautiful example of how growth factors and ECM work hand-in-hand to control signal transduction and cell function.

The second point is this finding that these signaling molecules essentially function when in a "solid state", that is, when immobilized on insoluble CSK scaffolds (Plopper et al., 1995; McNamee et al., 1996). This observation is recurring again and again in biological systems: RNA processing, translation, glycolysis, and DNA synthesis all appear to take place on insoluble protein networks within the cytoplasm and nucleus (reviewed in Ingber, 1993b). This type of solid-state biochemistry provides a possible mechanism to explain the incredible efficiency of biochemical reactions that are observed in living cells that we can not mimic in a test tube. It also has important implications for how mechanical deformation of the cell and CSK could alter biochemical reactions, as I will describe below. However, the question remains: How could modifying ECM geometry change CSK structure and thereby, alter cell function?

## CELLULAR TENSEGRITY

Over the past fifteen years, we have begun to uncover basic architectural rules that govern cell and tissue organization and define their mechanical behavior. Specifically, we have found that living cells and tissues use a form of architecture, called tensegrity, to organize and mechanically stabilize their CSK (Ingber et al., 1981; Ingber and Jamieson, 1985; Ingber et al., 1986; Sims et al., 1992; Ingber, 1993a; Wang et al., 1993; Wang and Ingber, 1994; Ingber et al., 1994; Maniotis et al., 1997; Tagawa et al., 1997; Stamenovic et al., 1996; Ingber, 1997). This type of building system gains its mechanical stability through transmission of continuous tension via geodesic paths and through the presence of an internal prestress. In the case of living cells, this prestress is created by the presence of internal compression elements that resist the inward pull of surrounding tensile actomyosin filament networks. Microtubules provide this function in hypertrophic cardiomyocytes (Tagawa et al., 1967), neurites (Buxbaum and Heideman, 1988), hepatocytes (Mooney et al., 1995), endothelial cells (Maniotis et al., 1997) and likely many other cell types (reviewed in Ingber, 1993a). Cross-linked actin bundles also act as compression struts in filopodia (Sheetz et al., 1992).

Local intragel osmotic pressures may also act in a similar manner to resist the pull of surrounding CSK networks.

Using simple string and string tensegrity models, we have shown that this architectural system can explain how living cells retract flexible ECM substrates; how cell and nuclear shape change in a coordinated manner when cells spread or retract on a rigid dish (Ingber and Jamieson, 1985; Sims et al., 1992; Ingber, 1993a); how cell polarize when they adhere to ECM (Ingber et al., 1986); and how microtubules can interfere with the contractile function of a cell (Tagawa et al., 1997). We also have shown that simple tensegrity models can explain how actin networks transform between highly triangulated polygonal nets and linear stress fibers in response to increased tension (Ingber, 1993a). Another property of tensegrity structures is that all of the interconnected elements undergo global rearrangements when stress is applied locally (Wang et al., 1993). This results in a linear stiffening response in that these structures increase their mechanical stiffness as the level of applied stress is raised. Amazingly, when we finally developed a method to measure cytoskeletal stiffness in living cells using magnetic particles, we found that cells exhibit similar stiffening behavior (Wang et al., 1993; Wang and Ingber, 1994; Wang et al., 1996) as do many living tissues (McMahon, 1984). Working with Dmitrije Stamenovic (Boston University), we recently developed a mathematical basis to explain this fundamental mechanical behavior (Stamenovic et al., 1996). This mathematical approach has revealed that there are two key terms that determine how a living cell responds mechanically when stressed: architecture and prestress.

Even with these abilities to depict and predict the complex behaviors of living cells, still many molecular biologists and mechanical engineers tend to view the cell mechanically as an elastic membrane filled with a viscous fluid-like cytoplasm or, in other words, as a "balloon filled with molasses". We reasoned that if living cells are hard-wired as predicted by the tensegrity models, then by pulling rapidly on adhesion receptors on the cell surface, we should be able to produce deformation within the depth of the cytoplasm and nucleus. Using a magnetic bead twisting technique, we were able to demonstrate that integrins (Wang et al., 1993; Wang et al., 1996; Ezzell et al., 1997) and other adhesion receptors that interact with the internal CSK (e.g., selectins; Yoshida et al., 1996) transfer mechanical stresses across the cell surface over a specific molecular pathway. More recently, Andrew Maniotis and Christopher Chen working in my laboratory were able to demonstrate that when integrins on the surface membrane of living endothelial cells were pulled by micromanipulating bound microbeads or micropipettes, cytoskeletal filaments reoriented, nuclei distorted, and nucleoli redistributed along the axis of the applied tension field (Maniotis et al., 1997a). These effects were specific for integrins, independent of cortical membrane distortion, and mediated by direct linkages between the cytoskeleton

and nucleus. We discovered that actin microfilaments only could mediate force transfer to the nucleus at low strain. In contrast, intermediate filaments effectively mediated force transfer to the nucleus at both low and high levels of deformation. These filament systems also acted as molecular guy wires to mechanically stiffen the nucleus and stabilize its position in the cell. In contrast, microtubules acted to hold open the intermediate filament lattice and to stabilize the nucleus against lateral compression. Furthermore, filamentous connections between different chromosomes could also be demonstrated in mitotic as well as interphase cells (Maniotis et al., 1997b). Taken together, these results support the tensegrity hypothesis by demonstrating that molecular connections between integrins, cytoskeletal filaments, and nuclear scaffolds may provide a direct path for mechanical signal transfer throughout living cells.

## SUMMARY

Our results suggest that cell surface adhesion receptors (e.g., integrins, cell-cell adhesion molecules), interconnected CSK networks, and associated nuclear scaffolds function as a structurally unified system. This system gains its mechanical stability and long range flexibility from tensional continuity, discrete load-bearing members and the presence of internal prestress. These are the fundamental requirements of tensegrity architecture. Use of tensegrity also could serve to concentrate stresses and hence, focus mechanical energy on mechanochemical and mechano-electrical transducing molecules that physically associate with the insoluble CSK. In addition, it may provide a mechanism to orchestrate and tune the entire cellular response to stress. A more indepth description of the molecular and cellular basis of mechanotransduction as well as the role of tensegrity in this process has been recently published (Ingber, 1997).

Our work also suggests that the specialized focal adhesion complexes that mediate mechanical coupling between CSK, integrins, and ECM, may represent potentially important sites for signal integration since molecules that transduce signals from ECM, growth factors, and mechanical stresses all appear to concentrate at this site. Similar signal integration also may occur within junctional complexes at the lateral cell borders. Mechanochemical transduction may, in turn, result from changes in the CSK geometry or mechanics that alter local thermodynamic or kinetic parameters. The effects of changing force balances between ECM tethers, actin microfilaments and microtubules on microtubule polymerization provides one direct example of this type of tensegrity-based thermodynamic regulation (Buxbaum and Heidemann, 1988; Mooney et al., 1994).

Direct mechanical coupling across the cell surface and through the CSK could serve to modulate slower diffusion-based chemical signaling pathways and coordinate functional changes throughout the depth of the

cytoplasm and nucleus. Thus, in simplest terms, the CSK may be viewed as mechanical filter: the same chemical or mechanical input will produce a different output (e.g., growth versus differentiation) depending on the geometry and mechanics of this structural framework. Use of tensegrity by cells also may help to explain how gravity may alter CSK structure and thereby, control cellular biochemistry and gene expression. For example, gravitational acceleration may alter prestress and thus change the tone in the entire interconnected network, thereby modulating both its mechanical and chemical behavior. Perhaps, it is for this reason that scale is so critical in studies on gravity sensation.

## Acknowledgements

This work was supported by grants from NASA, NIH, and ACS. During the course of these studies, Dr. Ingber was a recipient of a Faculty Research Award from the American Cancer Society.

## REFERENCES

- Bohmer, R.M., Scharf, E., and Assoian, R.K. 1996. Cytoskeletal Integrity is required throughout the mitogen stimulation phase of the cell cycle and mediates the anchorage-dependent expression of Cyclin D. *Molecular Biology of the Cell* 7:101-111.
- Burridge K., and Chrzanowska-Wodnicka M. 1996. Focal adhesions, contractility, and signaling. *Annual Review of Cell and Developmental Biology* 12:463-519.
- Buxbaum R.E., and Heideman S.R. 1988. A thermodynamic model for force integration and microtubule assembly during axonal elongation. *Journal of Theoretical Biology* 134:379-90.
- Chen C.S., Mrksich M., Huang S., Whitesides G., and Ingber DE. 1997. Geometric control of cell life and death. *Science*, in press
- Dike L., and Ingber DE. 1996. Integrin-dependent induction of early growth response genes in capillary endothelial cells. *Journal of Cell Science* 109:2855-2863.
- Ezzell R.M., Goldmann W.H., Wang N., Parasharama N., and Ingber DE. 1997. Vinculin promotes cell spreading by mechanically coupling integrins to the cytoskeleton. *Experimental Cell Research* 231:14-26.
- Hansen L., Mooney D., Vacanti J.P., and Ingber, D.E. 1994. Integrin binding and cell spreading on extracellular matrix act at different points in the cell cycle to promote hepatocyte growth. *Molecular Biology of the Cell* 5:967-975.

- Hynes, R.O. 1992. Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 69:11-225.
- Ingber, D.E. 1990. Fibronectin controls capillary endothelial cell growth by modulating cell shape. *Proceedings of the National Academy of Science U.S.A.* 87:3579-3583.
- Ingber, D.E. 1991. Integrins as mechanochemical transducers. *Current Opinions in Cell Biology* 3:841-848.
- Ingber, D.E. 1993a. Cellular Tensegrity: defining new rules of biological design that govern the cytoskeleton. *Journal of Cell Science* 104:613-627.
- Ingber, D.E. 1993b. The riddle of morphogenesis: a question of solution chemistry or molecular cell engineering? *Cell* 75:1249-1252.
- Ingber, D.E. 1997. Tensegrity: the architectural basis of cellular mechanotransduction. *Annual Review of Physiology* 59:575-599.
- Ingber D.E., Dike L., Hansen L., Karp S., Liley H., Maniotis A., McNamee H., Mooney D., Plopper G., Sims J., and Wang N. 1994. Cellular tensegrity: exploring how mechanical changes in the cytoskeleton regulate cell growth, migration, and tissue pattern during morphogenesis. *International Review of Cytology* 150:173-224.
- Ingber, D.E., and Folkman J. 1989a. Mechanochemical switching between growth and differentiation during fibroblast growth factor-stimulated angiogenesis in vitro: role of extracellular matrix. *Journal of Cell Biology* 109:317-330.
- Ingber, D.E., and Folkman J. 1989b. How does extracellular matrix control capillary morphogenesis? *Cell* 58:803-805.
- Ingber, D.E., and Jamieson J.D. 1985. Cells as tensegrity structures: architectural regulation of histodifferentiation by physical forces transduced over basement membrane. In: Andersson L.C., Gahmberg C.G., Ekblom P., eds. *Gene Expression During Normal and Malignant Differentiation*. Academic Press: Orlando, pp. 13-32.
- Ingber, D.E., Madri J.A., and Folkman J. 1987. Extracellular matrix regulates endothelial growth factor action through modulation of cell and nuclear expansion. *In Vitro Cell and Developmental Biology* 23:387-394.
- Ingber, D.E., Madri J.A., and Jamieson J.D. 1981. Role of basal lamina in the neoplastic disorganization of tissue architecture. *Proceedings of the National Academy of Science USA* 78:3901-3905.
- Ingber, D.E., Madri J.A., and Jamieson J.D. 1986. Basement membrane as a spatial organizer of polarized epithelia: exogenous basement membrane reorients pancreatic epithelial tumor cells in vitro. *American Journal of Pathology* 122:129-139.
- Ingber, D.E., Prusty, D., Frangione J., Cragoe E.J. Jr, Lechene C., and Schwartz M. 1990. Control of intracellular pH and growth by fibronectin in capillary endothelial cells. *Journal of Cell Biology* 110:1803-1812.
- Ingber, D.E., Prusty D., Sun Z., Betensky H., and Wang N. 1995. Cell shape, cytoskeletal mechanics and cell cycle control in angiogenesis. *Journal of BioMechanics* 28:1471-1484.
- Maniotis A., Chen C., and Ingber, D.E. 1997a. Demonstration of mechanical connections between integrins, cytoskeletal filaments and nucleoplasm that stabilize nuclear structure. *Proceedings of the National Academy of Science U.S.A.* 94:849-854.
- Maniotis A., Bojanowski K., and Ingber, D.E. 1997b. Mechanical continuity and reversible chromosome disassembly within intact genomes microsurgically removed from living cells. *Journal of Cellular Biochemistry* 65:114-130.
- Miyamoto, S., Akiyama, S.K. and Yamada K.M. 1995. Synergistic roles for receptor occupancy and aggregation with integrin transmembrane functions. *Science* 267:883-885.
- McMahon, T.A. 1984. *Muscles, Reflexes, and Locomotion*. Princeton University Press, NJ.
- McNamee H., Ingber D., and Schwartz M. 1993. Adhesion to fibronectin stimulates inositol lipid synthesis and enhances PDGF-induced inositol lipid breakdown. *Journal of Cell Biology* 121:673-678.
- McNamee H.P., Liley H.G., and Ingber, D.E. 1996. Integrin-dependent control of inositol lipid synthesis in the focal adhesion complex. *Experimental Cell Research* 224:116-122.
- Mooney, D., Hansen, L., Farmer, S., Vacanti, J., Langer, R., and Ingber, D. 1992. Switching from differentiation to growth in hepatocytes: control by extracellular matrix. *Journal of Cell Physiology* 151:497-505.
- Mooney D., Hansen L, Langer R., Vacanti J.P., and Ingber, D.E. 1994. Extracellular matrix controls tubulin monomer levels in hepatocytes by regulating protein turnover. *Molecular Biology of the Cell* 5:1281-1288.

- Mooney D., Langer R., and Ingber, D.E. 1995. Cytoskeletal filament assembly and the control of cell shape and function by extracellular matrix. *Journal of Cell Science* 108:2311-2320.
- Plopper G., McNamee H., Dike L., Bojanowski K., and Ingber, D.E. 1995. Convergence of integrin and growth factor receptor signaling pathways within the focal adhesion complex. *Molecular Biology of the Cell* 6:1349-1365.
- Prime, K.L., and Whitesides, G.M. 1991. Self-assembled organic monolayers: model systems for studying adsorption of proteins at surfaces. *Science* 252:1164-1167.
- Schwartz, M.A., Lechene, C., and Ingber, D.E. 1991. Insoluble fibronectin activates the Na<sup>+</sup>/H<sup>+</sup> antiporter by clustering and immobilizing integrin  $\alpha 5\beta 1$ , independent of cell shape. *Proceedings of the National Academy of Science U.S.A.* 88:7849-7853.
- Sheetz M.P., Wayne D.B., and Pearlman A.L. 1992. Extension of filopodia by motor-dependent actin assembly. *Cell Motility and Cytoskeleton* 22:160-69.
- Sims J., Karp S., and Ingber, D.E. 1992. Altering the cellular mechanical force balance results in integrated changes in cell, cytoskeletal, and nuclear shape. *Journal of Cell Science* 103:1215-1222.
- Singhvi R., Kumar A., Lopez G., Stephanopoulos G.N., Wang D.I.C., Whitesides G.M., and Ingber, D.E. 1994. Engineering cell shape and function. *Science* 264:696-698.
- Stamenovic D., Fredberg J., Wang N., Butler J., and Ingber D. 1996. A microstructural approach to cytoskeletal mechanics based on tensegrity. *Journal of Theoretical Biology* 181:125-136.
- Tagawa H., Wang N., Narishige T., Ingber, D.E., Zile M.R., and Cooper I.V.G. 1997. Cytoskeletal mechanics in pressure overload cardiac hypertrophy. *Circulatory Research* 80:281-289.
- Wang N., Butler J.P., and Ingber, D.E. 1993. Mechano-transduction across the cell surface and through the cytoskeleton. *Science* 260:1124-1127.
- Wang N., and Ingber, D.E. 1994. Control of cytoskeletal mechanics by extracellular matrix, cell shape, and mechanical tension. *Biophysical Journal* 66:2181-2189.
- Wang N., and Ingber, D.E. 1996. Probing transmembrane mechanical coupling and cytomechanics using magnetic twisting cytometry. *Biochemistry and Cell Biology* 73:1-9.
- Yoshida M., Westlin W.F., Wang N., Ingber, D.E., Rosenweig A., Resnick N., and Gimbrone M. 1996. Leukocyte adhesion to vascular endothelium induces e-selectin association with the actin cytoskeleton. *Journal of Cell Biology* 133:445-455.