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COMMENTARY

Cellular tensegrity: defining new rules of biological design that govern the cytoskeleton

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"...organization exists in the living organism, and this organization is not something fundamentally mystical and unamenable to scientific attack, but rather the basic problem confronting the biologist."

Joseph Needham (Terry Lectures, Yale University, 1936)

INTRODUCTION

Tensegrity architecture, a building system based on tensional integrity rather than compressional continuity, has been proposed to explain how cells and tissues are constructed (Ingber et al., 1981; Ingber and Jamieson, 1982, 1985; Joshi et al., 1985; Fulton and Isaacs, 1986; Ingber and Folkman, 1989a). The purpose of this commentary on tensegrity is to demonstrate how this relatively simple theory can explain much of the complexity of pattern and structure that is observed within the cytoskeleton (CSK) of living cells. A discussion of how tensegrity may be used for information processing, mechanochemical transduction and morphogenetic regulation can be found elsewhere (Ingber and Jamieson, 1985; Ingber and Folkman, 1989a,b; Ryan, 1989; Heidemann and Buxbaum, 1990; Pienta and Coffey, 1991; Hansen and Ingber, 1992; Ingber et al., 1993).

It is now well accepted that the CSK of eukaryotic cells exists as a complex interweaving meshwork of three major classes of filamentous biopolymers: actin-containing microfilaments (MFs), tubulin-containing microtubules (MTs), and intermediate filaments (IFs) containing vimentin, desmin, keratins or neurofilament proteins. Most biologists agree that actomyosin interactions within contractile MFs generate CSK tension and that all three filament systems provide some structural function. However, there is no model of CSK organization that can explain how these filament systems associate and integrate so as to form a continuous "solid" network that can change shape and move. Even less is known about the mechanism by which changes in CSK organization induce alterations in nuclear structure, such as the physical expansion of the nucleus that appears to be required for cell cycle progression (Yen and Pardee, 1979; Nicolini et al., 1986; Ingber et al., 1987).

As cell and molecular biologists, we tend to "think locally" whereas use of time-lapse video microscopy reveals that the CSK "acts globally" in living cells (Trinkaus, 1985). For example, CSK polymerization forces (Tilney and Kallenbach, 1979; Hill, 1981), cytoplasmic hydrostatic pressures (Bereiter-Hahn and Strohmeier, 1987), intragel osmotic pressures (Oster and Perelson, 1987), cortical CSK tension (Albrecht-Buehler, 1987), chemical remodeling events (Stossel, 1989), and both membrane and actin flow (reviewed by Heath and Holifield, 1991) have all been proposed to explain how a cell that exerts *inward-directed* (centripetal) tension on its extracellular matrix (ECM) adhesions (Harris, 1982; Lamoreux et al., 1989) extends processes *outwards*. Even if we accept these models as true, it remains difficult to understand how solid structural elements that are physically interconnected throughout the depth of the cell (Wolosewick and Porter, 1979; Ben Ze'ev et al., 1979; Fey et al., 1984) function as a single harmonious structural entity and undergo dynamic changes in form. Thus, the question of how an integrated CSK is constructed essentially becomes one of architecture rather than one of individual molecules or even simple mechanics.

In this Commentary, I will place these local remodeling phenomena in the context of a globally integrated architectural model and, thereby, provide a mechanical basis for the coordination between part and whole that is so characteristic of the CSK. I will do this using the tensegrity paradigm. Specifically, I will use this model to show how three-dimensional CSK assemblies that include MFs and MTs as well as IFs and the nuclear matrix may be stabilized and structurally integrated. More importantly, I will demonstrate that use of this building system, which is independent of scale, allows us to define basic rules of geometric interconversion in three dimensions that predict many structural motifs that are observed within the CSK of living cells. One of the implications of this model for the cell biologist is that changes in cell shape and motility may result from "tension molding" and chemical remodeling of a continuous, "pre-stressed" molecular lattice (the CSK) rather than solely from local addition and subtraction of individual parts. On the basis of the observation that use of tensegrity by cells is not a special case, I will also briefly

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explore the possiblity that stabilization through tensional integrity may represent a basic principle of biological order.

THE BASIC RULES OF TENSEGRITY

My own introduction to tensegrity (tensional integrity) architecture came in 1975 when I was an undergraduate student at Yale College studying three-dimensional design in a sculpture course of the same name. The instructor (Erwin Hauer) came in one day with an intriguing sculpture that was constructed from six struts (wooden dowels) that did not touch each other; rather, they were pulled up and open into an approximate sphere through interconnection with a continuous series of tension elements (elastic cord). A similar model is shown in Fig. 1. Importantly, when either pushed from above or anchored from below, this structure spontaneously flattened and spread out in a coordinated manner without changing topological relationships between its different structural elements, i.e. without disrupting its structural integrity (Fig. 1B). When the distending force was removed, the structure spontaneously pulled back and, literally, jumped up from the surface to which it had been anchored. I also realized that if this structure were to be anchored at multiple points to a malleable substratum, it would spontaneously retract, pull its attachments together and hence, compress the underlying foundation into folds (Fig. 1C).

This structure intrigued me because it was virtually at the same time that I first became introduced to cell culture. To me, living cells acted in a nearly identical manner; they flattened when attached to highly adhesive plastic dishes (Folkman and Moscona, 1978), detached and rounded when their ECM anchors were enzymatically removed (Revel et al., 1974), physically pulled elastic substrata into "compression wrinkles" (Harris et al., 1980), and spontaneously contracted malleable ECM gels (Emerman and Pitelka, 1977). Thus, I immediately assumed that cells use tensegrity architecture for their organization (Ingber et al., 1981). I soon learned that this was not an accepted belief.

The concept of tensegrity architecture was pioneered by the inventor/architect, Buckminster Fuller, although the first tensegrity model was constructed by his student, the sculptor Kenneth Snelson (Fuller, 1961; Edmondson, 1987). Tensegrity sculptures are held up and open by interconnecting a *continuous* series of tension elements (e.g. elastic string, thin wires) with a *discontinuous* series of compression-resistant struts (e.g. wood sticks, steel beams). These structures are, by definition, independent of gravity whereas compression-resistant structures (e.g. a brick house) would destabilize and break apart in the absence of gravitational force. Tensegrity structures are particularly novel because inward-directed tension can even stabilize highly elongated shapes (Fuller, 1961).

Importantly, the tension elements in tensegrity structures do not have to be elastic strings or thin wires. Rather, these types of building materials are used in models and sculptures to visualize the pattern of the forces that hold the structures together. In fact, the building components in these structures are often *capable* of supporting both tensile and compressive loads (e.g. metal struts in geodesic domes). However, they are tensegrity structures because individual elements only *need* to support one or the other locally. In fact, it was by studying how forces are distributed through geodesic domes that Fuller first discovered the concept of tensegrity (Fuller, 1961; Edmondson, 1987). He found that he could demonstrate that compressional continuity was not required for the stability of geodesic structures by replacing certain rigid elements with thin wires that can only withstand tension. This resulted in construction of structures with nearly identical geodesic patterns; however, the rigid struts did not touch one another; rather, they

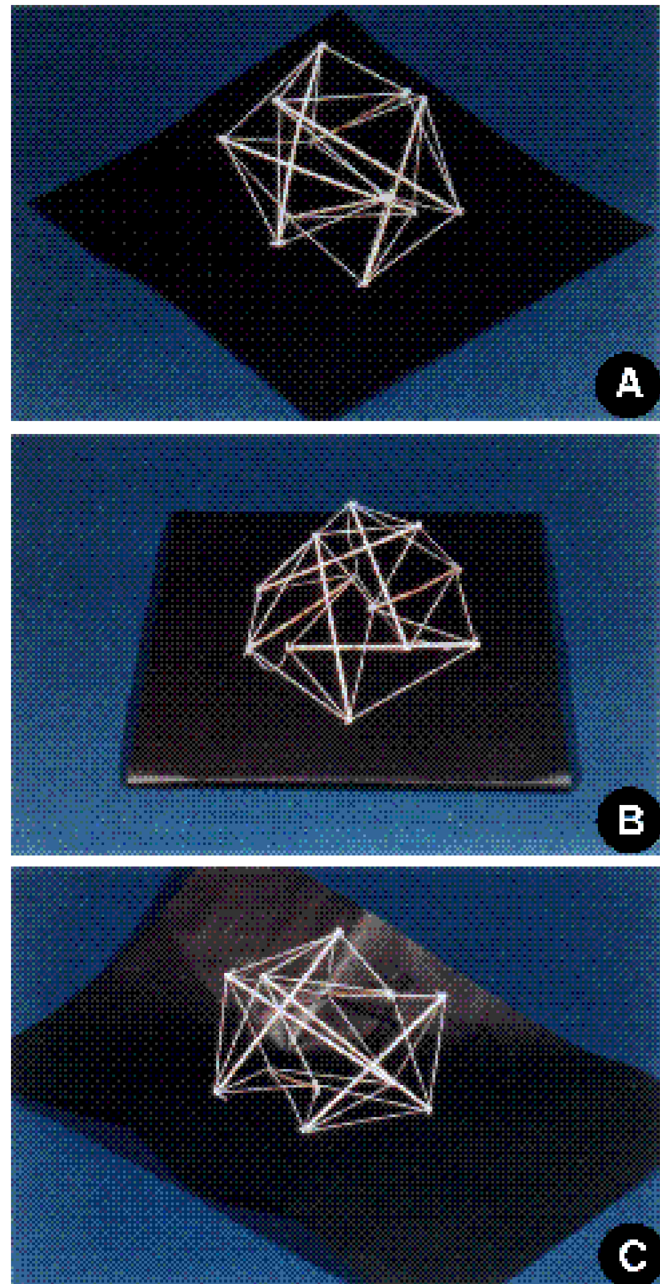

Fig. 1. Tensegrity models constructed from wooden applicator sticks and elastic string. The "cell" model appears round when unattached (A), spreads on a rigid substratum (B), and spontaneously retracts and rounds on a malleable foundation (C).

existed as isolated islands floating in a sea of tension. This is essentially what distinguishes tensegrity architecture from others.

At the molecular level, the effects of gravity are neglible relative to local force interactions (Albrecht-Buehler, 1990). Flight-based experiments confirm that cells (and astronauts) maintain their structural and functional integrity in a microgravity environment. Thus, compression-dependent building systems cannot be used by cells. In contrast, tensegrity arrangements could be easily used to stabilize complex molecular structures, such as the CSK, given that living cells are known to generate internal tension. As I described above, simple tensegrity models (Fig. 1) predict that living cells must adhere to surfaces that can resist compression in order to spread. In addition, when larger nucleated cell models were constructed by establishing tensional integrity between a smaller geodesic tensegrity sphere and the "cell" surface (Ingber and Jamieson, 1985), coordination between cell and nuclear extension was observed (Fig. 2). This behavior closely mimics that seen in living cells cultured on ECM (Ingber et al., 1987; Ingber, 1990). Furthermore, the tensegrity nucleus tended to polarize and move to the cell base, again a characteristic that cells exhibit when they attach to ECM (Ingber et al., 1986). One additional point brought home by these modeling studies is that the cell's focal adhesion sites, along with intervening ECM, must be viewed as integral parts of an "extended CSK". Actin-associated proteins (e.g. talin, vinculin, -actinin) and transmembrane ECM receptors (e.g. integrins) form the molecular bridge that links MFs and ECM (Burridge et al., 1988) and supports force transmission (Lotz et al., 1989; Ingber, 1991; Wang et al., 1992) in living cells.

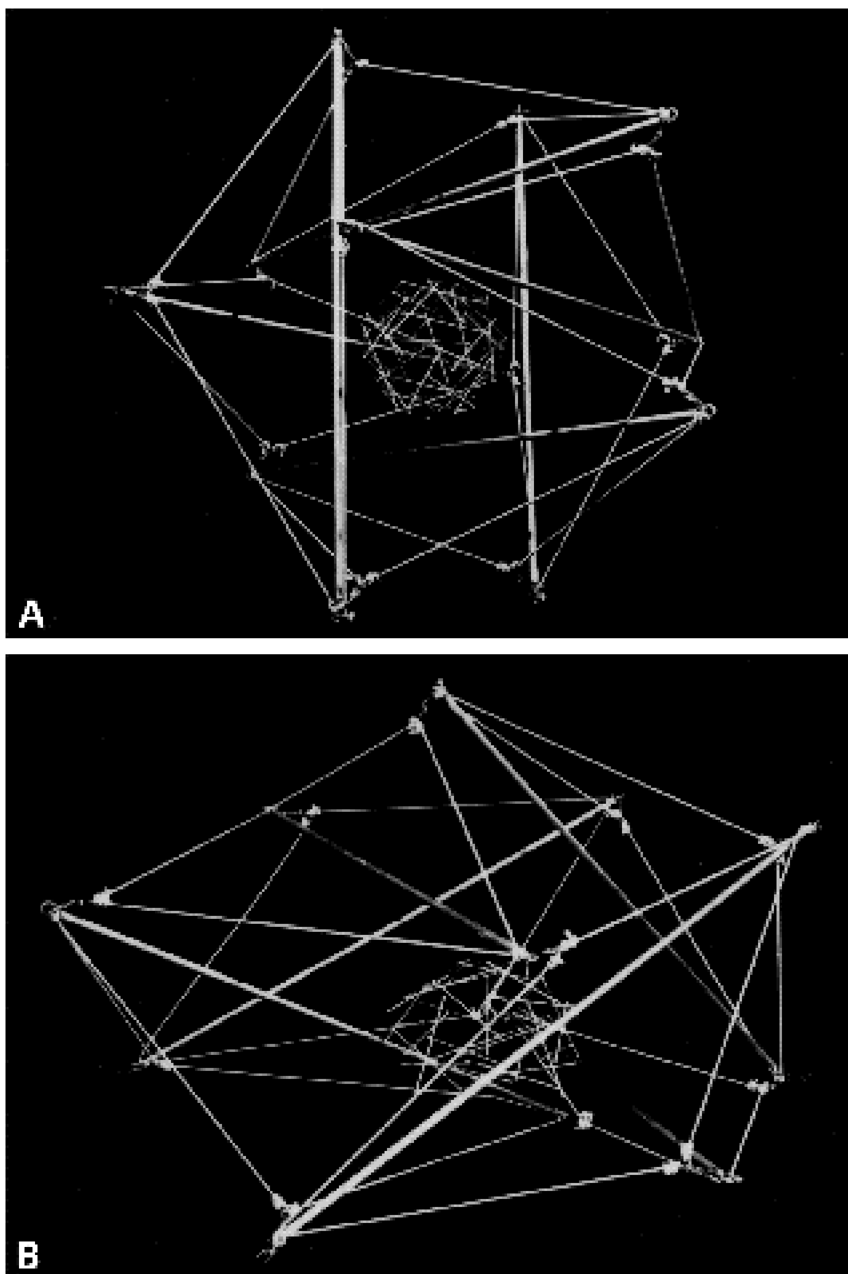

Fig. 2. Nucleated tensegrity models. The "cell" is constructed from aluminum struts and thick elastic cord; the "nucleus" is a geodesic sphere composed of wooden sticks and thin white elastic thread; the cell and nucleus are interconnected by thin black elastic thread, which cannot be seen due to the black background. (A) Cell and nuclear shape are both round in a symmetrical cell that generates internal tension and lacks attachment. (B) The cell and nucleus extend in a coordinated fashion when attached to a non-deformable substratum. The nucleus also polarizes and moves to the base.

CELLULAR TENSEGRITY

I originally presented tensegrity structures as “conceptual” models of cell architecture (Ingber and Jamieson, 1985) because they had only a limited number of structural elements whereas living cells may have thousands, if not more. I also used elastic thread as a way to model tension elements that can undergo extension and shortening via chemical mechanisms. These simplistic models have therefore created a problem for some who want to know, “if cells are tensegrity structures, then where are the huge compression-resistant struts we see in your models?”. Although large compression-resistant struts do in fact exist in certain specialized cells (Wellings and Tucker, 1979; Mogensen and Tucker, 1988; Lloyd and Seagull, 1985; Heidemann and Buxbaum, 1990), I would like to now explain in greater detail how tensegrity architecture may apply to all living cells.

The actin microfilament lattice behaves as if it depends on tensional integrity

It is known that disruption of MTs does not prevent attachment or spreading in many cells (Domnina et al., 1985; Vasiliev, 1987; Middleton et al., 1988) even though it also produces IF retraction (Blose et al., 1984; Hollenbeck et al., 1989). This finding suggests that the actin MF lattice alone is sufficient to support many changes in cell form. So how could tensegrity be involved? The answer is simple. A cell that exerts centripetal tension on *localized* focal adhesions may be defined as a tensegrity structure because otherwise continuous CSK tension is resisted locally by *isolated* regions of the underlying compression-resistant ECM; internal compressional continuity is not observed. For this reason, both animal and plant cells require an attachment substratum that can resist local compression in order to change shape (Folkman and Moscona, 1978; Emerman and Pitelka, 1977; Ingber and Jamieson, 1985; Harris et al., 1990; Hahne and Hoffman, 1984; Ingber and Folkman, 1989b; Opas, 1989; Ingber, 1990).

Importantly, tensegrity may also be utilized at the molecular level, since the only requirement of a tensegrity network is that tension is continuous and compression is local. To explore this possibility, let’s assume for one moment that the actin CSK is a continuous tensegrity network that is composed of MFs that both shorten (generate tension) and vary locally in terms of their relative flexibility (compression-resistance), depending on variations in the density of cross-bridge formation with actin-associated proteins (e.g. -actinin, myosin, tropomyosin). If we can build three-dimensional models that incorporate these characteristics, then we can test whether the tensegrity hypothesis predicts changes in CSK structure that are observed in living cells.

As shown by Fuller, tension-dependent structures gain their stability by “triangulating” their internal support elements and, thus, balancing force vectors in the pattern in which they are naturally distributed in space (Fuller, 1965; Edmondson, 1987). Tensegrity structures that are composed of multiple semi-rigid struts that are under continuous tension and interconnected by relatively flexible joints can be simply constructed using soda straws and elastic thread (Fig. 3). These triangulated structures spontaneously exhibit naturally “isotropic” forms; however, they differ in their size and degree of compaction. Some of these structures are self-supporting (Fig. 3A,C) whereas others must be held open by external forces (Fig. 3B).

The most economical and stable means of tight packing in three dimensions is shown in Fig. 3A; the vertices of this lattice may be thought of as the centers of closely packed spheres (Fuller, 1965). This array was called an “isotropic vector matrix” by Fuller (it is also known as an “octet truss”) because it distributes force equally in all directions and hence, the sum of all force vectors is zero. This construction system is used in many buildings because it resists *external* compression using a minimum of materials (Edmondson, 1987). At the same time, it is often incorporated into designs for “Space platforms” that will function in a microgravity environment because its stability and high load-bearing qualities result from a triangulated distribution of *internal* tensile forces and not from external compression.

One of the most novel qualities of the tensegrity building system is that unstable, loosely packed isotropic lattices (Fig. 3B) are inherently interconvertable with more stable tightly packed structures, specifically tetrahedra (Fig. 3C; Fuller, 1979; Edmondson, 1987). These tetrahedra, in turn, represent the basic building blocks of the highly stable, isotropic vector matrix (Fig. 3A). Importantly, this geometric transformation occurs without altering local spatial relationships between different structural elements and, thus, without losing tensional integrity (Fig. 4). Furthermore, the same loose isotropic lattice (Fig. 3B) can spontaneously remodel into a linear bundle arrangement, if tension is applied along a single axis (Fig. 5).

What about living cells? It is first important to emphasize that cells contain a highly interconnected MF lattice even when round and free of anchorage (Ben Ze’ev et al., 1979; Heuser and Kirschner, 1980). They also can change shape from fully spread to round without altering MF number (Revel et al., 1974) or the total amount of F-actin (Bereiter-Hahn et al., 1990). Thus, any building system that cells use must explain how an intact spherical CSK lattice can rapidly remodel into a highly extended form and *vice versa.*

Electron microscopic analyses of three-dimensional organization of the cytoskeleton are always somewhat limited, since their results are presented as two-dimensional projected images. Nevertheless, these studies consistently depict the MF network of non-spread cells as loosely packed and isotropic (Heuser and Kirschner, 1980; Schliwa and Van Blerkom, 1981). Isotropic does not mean random, rather it indicates a lack of asymmetry. In fact, individual MFs within loose regions of the lattice often appear to intersect at angles of 90° and 120°. These are the same angles that dominate the triangulated tensegrity models. Thus, let’s consider what would happen if the loosely packed tensegrity arrangement shown in Fig. 3B represented a basic repeating unit in the isotropic MF lattice of a round cell.

Once the cell contacts a rigid ECM substratum, local cell surface receptor binding interactions drive membrane flattening until balanced by resisting forces caused by CSK stiffening. Cells apparently have evolved a mechanism to overcome this balance by forming mechanically stable

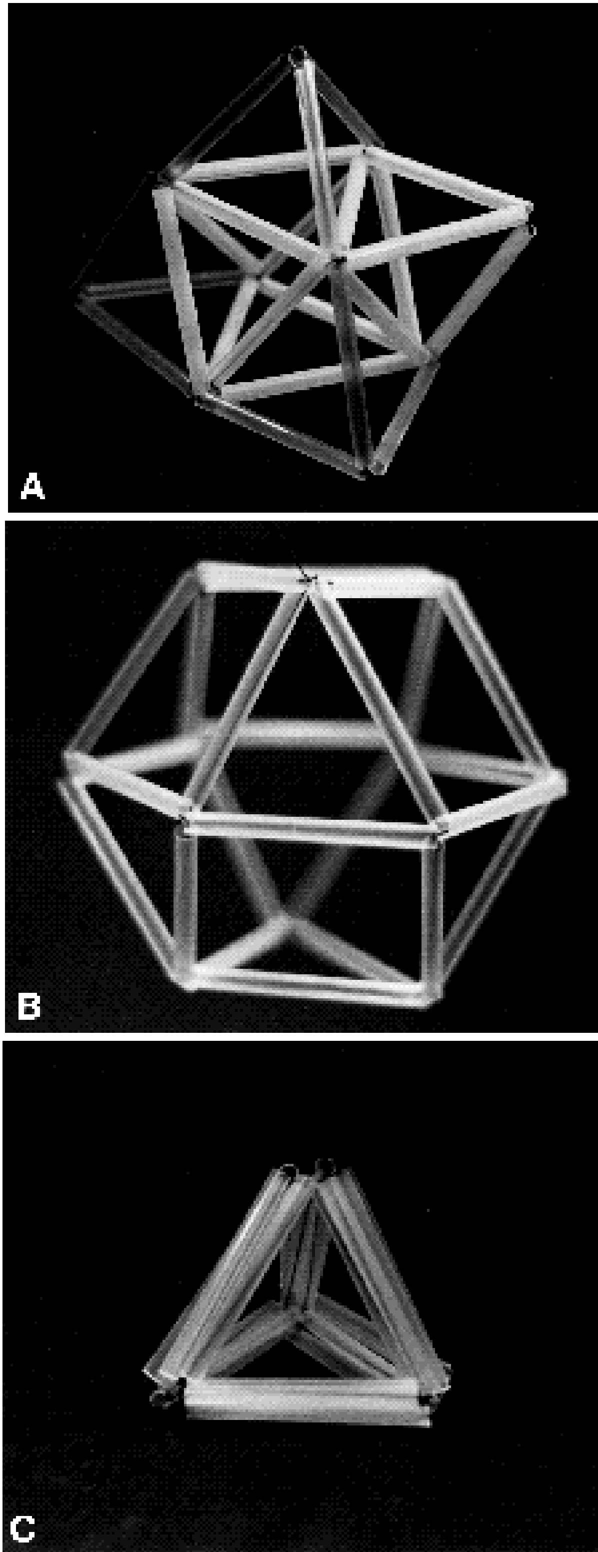

Fig. 3. Tensegrity models of the actin cytoskeleton constructed from plastic soda straws interconnected by a central filament of black elastic thread. (A) The isotropic vector matrix is composed of an array of tetrahedra oriented vertex to vertex, an arrangement which automatically creates octahedral cavities. A single tetrahedron is highlighted in white along the right edge; it has 4 triangular faces, 4 vertices and 6 edges. The central octahedral space is also highlighted. (B) A loose, triangulated isotropic lattice. This highly unstable structure is held open by additional black elastic filaments which are not visible against the black background. (C) The loose isotropic lattice (shown in B) transforms into a highly packed tetrahedron containing multiple struts along each edge (shown here) using the transformation scheme presented in Fig. 4.

transmembrane molecular bridges that transfer CSK tension to the compression-resistant ECM below. Global contraction of the isotropic MF lattice should result in "pull" everywhere; however, the net force vector would orient downward due to resistance by the cell's newly formed basal adhesions. This would produce flattening of the unstable isotropic lattice (Fig. 5A). Increased axial tension between two fixed adhesions (due to actomyosin filament sliding in a living cell; due to horizontal tensile threads in the model) would then induce this flattened lattice to remodel until "bundles" formed which contained parallel "filaments" composed of multiple smaller struts oriented in tandem (Fig. 5A-C). The remaining struts that did not become organized into linear filaments (Fig. 5C) might serve to interconnect the bundle with the less organized lattice above (not shown). Alternatively, because this is a pre-stressed structure (all struts are under tension), a single severing event at one of the vertices would cause the two remaining triangulated struts to unfold spontaneously and realign with the other struts, resulting in an increase in both bundle thickness and length (Fig. 5D). Once remodeling is complete and strut movement ceases, tension will become isometric.

In living cells, shortening of contractile MFs between fixed ECM adhesions similarly generates isometric tension (Isenberg et al., 1976; Kreis and Birchmeier, 1980; Heidemann et al., 1990), induces MF bundling (Isenberg and Wohlfarth-Botterman, 1976; Nagai et al., 1978), and thus results in formation of linear "stress fibers" that align along tension field lines (Greenspan and Folkman, 1977; Opas, 1987; Bereiter-Hahn, 1987). Application of mechanical tension at the cell surface produces similar MF bundling *in vitro* (Franke et al., 1984; Kolega, 1986) and *in vivo* (Wong et al., 1983).

Generation of isometric tension within portions of the MF lattice that are distant from the cell's fixed adhesions could be responsible for other changes in CSK structure. For example, in the apical regions of the isotropic CSK lattice, actomyosin filament sliding should proceed in three dimensions without restriction until the MFs can shorten no further; then only isometric tension will be produced. If the loosely packed, unstable isotropic MF lattice of a round cell (Fig. 3B) were to compact in response to increased internal tension in the manner depicted in Fig. 4, then we would expect to see compact tetrahedra form within the CSK lattice. Each tetrahedron, in turn, would contain multiple MF struts oriented in parallel along its edges (Fig. 3C). Further expansion of this isometric contraction wave through the apical lattice would result in formation of multiple, closely packed tetrahedra, and thus assembly of an isotropic vector matrix (Fig. 3A). This three-dimensional matrix would extend out laterally, resulting in formation of extensive triangulated structures and hexagonal patterns within the MF

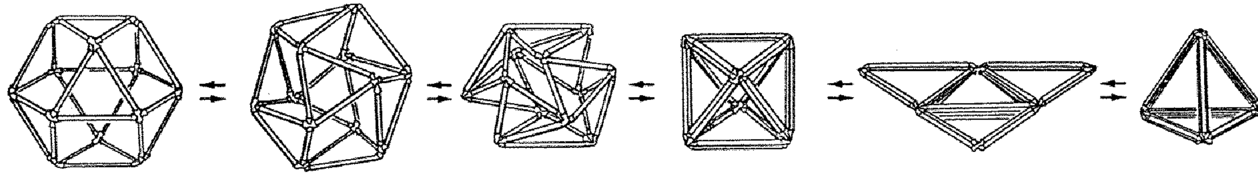

Fig. 4. The loose unstable lattice at the left (see also Fig. 3B) transforms into a highly packed, stable tetrahedron containing multiple struts along each edge (shown at the right) as a result of progressive compacting, equatorial twisting and folding. This geometric interconversion does not require disruption of structural integrity or tensional continuity; Fuller called this interconversion "the jitterbug" (based on figures of Fuller, 1979, and Edmondson, 1987).

lattice (Fig. 6A). Pulling this isotropic vector matrix down over the spherical nucleus, towards the cell's fixed attachment points, would result in dome formation. Specifically, a geodesic dome would form. These structures characteristically exhibit repeating hexagonal units interspersed with occasional pentagonal forms on its surface (more complex polygons might appear during active remodeling within the CSK). Furthermore, each polygon within the "bent" isotropic vector matrix of the forming dome would actually represent a three-dimensional polyhedron, which is itself comprised of multiple tightly packed tetrahedra oriented in a spoke-wheel array (Fig. 7A).

Amazingly, these models predict precisely a wide variety of CSK patterns, including "geodomes" that are observed in cells during their initial phases of spreading *in vitro* (Lazarides, 1976; Osborn et al., 1978; Rathke et al., 1979; Heuser and Kirschner, 1980) and within quiescent tissues *in vivo* (Rafferty and Scholz, 1985). The correspondence between the tensegrity models and hand-drawn depictions of published light and transmission electron micrographs which show the triangulated arrangement of MFs within a CSK geodome are striking (Figs 6 and 7). Moreover, higher-power micrographs (Rathke et al., 1979) also demonstrate that each strut of the geodome contains multiple distinct bundles of MF aligned in parallel (Fig. 7B), as would be expected from a geometric interconversion (Figs 4 and 3C). Large, fully organized triangulated CSK arrangements might not be easily visualized in all cells because of differences in the height of the cell, the shape of the nucleus and the degree of isometric tension generation, and because they are ephemeral. For instance, loss of the vertical force vector in a highly flattened cell might result in formation of arc-shaped bundles, as is observed in certain migrating cells (Heath, 1983), rather than domes.

Interestingly, the struts of geodesic MF domes are thought to be precursors of stress fibers (Lazarides, 1976).

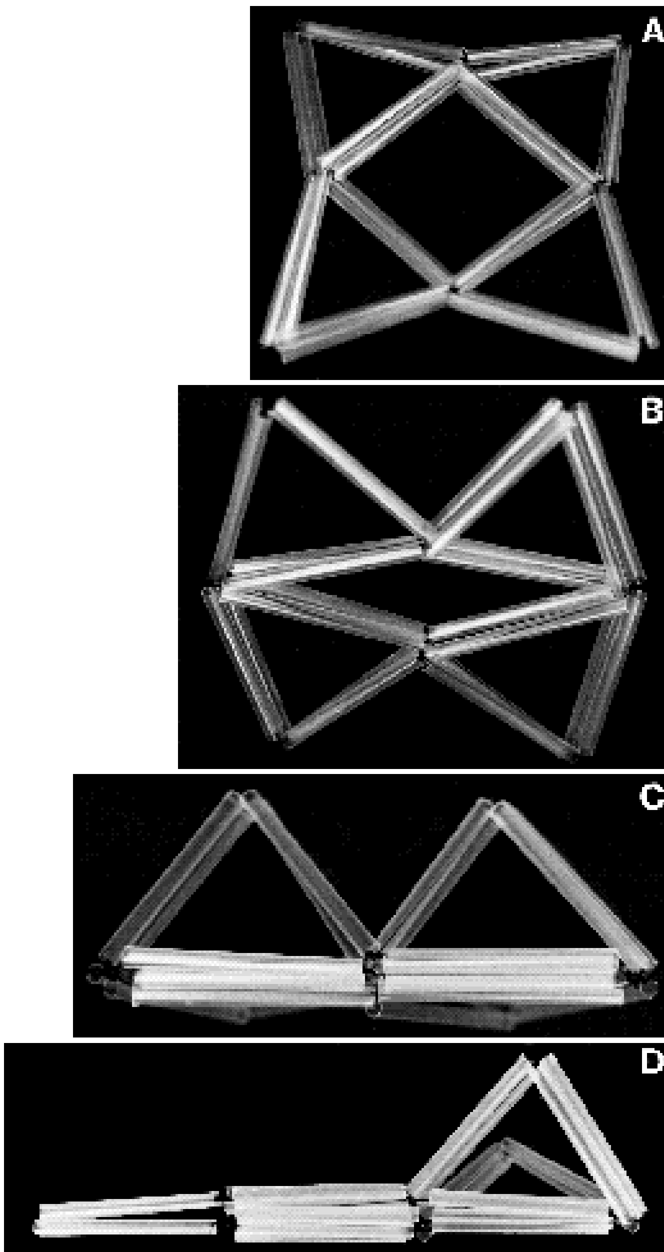

Fig. 5. Tensegrity models of the actin cytoskeleton undergoing "stress fiber" formation. (A) Increased "basal" tension causes the unstable isotropic lattice (see Fig. 3B) to flatten. (B) Application of tension along the horizontal axis (via black tensile threads) results in progressive alignment of struts along the lines of force. (C) Sustained tension application results in formation of bundles of parallel filaments that contain multiple struts oriented in tandem. Triangulated side struts at the top of the bundle serve to interconnect it with the remaining CSK lattice above (not shown). (D) Because the triangulated side struts are pre-stressed, severing a single vertex causes them to straighten spontaneously, thereby promoting bundle elongation and thickening. Similar tension molding of neighboring lattice modules on either side (not shown) would result in further bundle elongation and, hence, formation of "stress fibers" along tension field lines. Note the repetitive "sarcomere-like" banding pattern within the elongated bundle.

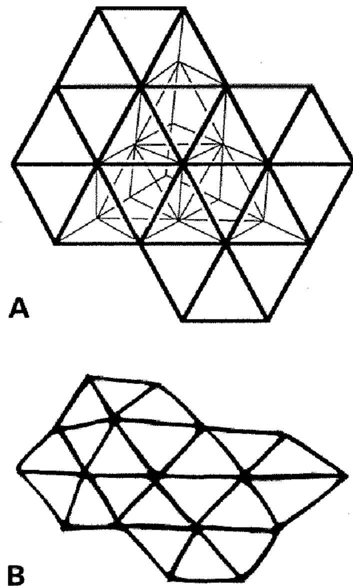

Fig. 6. (A) A view of an extended isotropic vector matrix, which shows that it exhibits a characteristic hexagonal pattern when viewed from above. (B) A hand-drawn depiction of a region from a published immunofluorescence micrograph (Fig. 13 of Lazarides, 1976), which shows the pattern exhibited by an actin geodome in a living cell. Note the correspondence between the hexagonal arrays.

The tensegrity models similarly predict that tightly packed tetrahdra (which comprise the dome) will spontaneously remodel into long bundles if the pattern of tension transmission becomes axial. This potential remodeling is due to the fact that the sequential geometric interconversions depicted in Figs 4 and 5 are completely reversible, if the balance of forces changes. Importantly, the vertices of these triangulated MF networks in living cells are the only regions which do not stain for myosin or tropomyosin, and thus it has been suggested that they should be more flexible than the intervening struts (Lazarides, 1976). Furthermore, the length of these MF struts (approximately 4 μm) corresponds exactly to the spacings that are responsible for the sarcomere-like pattern of stress fibers (Lazarides, 1976; Rathke et al., 1979), again just as the tensegrity models predicted (Fig. 5D).

Taken together, these findings suggest that many of the patterns exhibited by the actin CSK may result from dynamic remodeling of a continuous tensegrity network. Inherent in this type of "pre-stressed" structure is the fact that internal mechanical tension is the driving force that directs CSK pattern formation. However, the MF tensegrity system is unlike any other, in that it uses ATP in conjunction with actomyosin filament sliding to develop internal tension and drive changes in form (Sims et al., 1992). Also, the same type of molecular constituent (i.e. an actin MF) may function as either a force-generator or a compressive load-bearing support, depending on its location inside the lattice (e.g. whether it is in a contractile MF, a highly cross-linked MF bundle, or a fully contracted MF network). In the absence of ATP (*rigor mortis*), the MF lattice would more closely resemble a rigid geodesic structure constructed entirely from non-extensible materials. However, even the stability of this rigid structure would depend on internal tensional continuity rather than compressional integrity.

Finally, I should note that I have not discussed the implications of interconnections between the MF lattice and the surrounding spectrin-ankyrin network that lies beneath the plasma membrane. This cortical net most likely contributes little to *global* cell-shape control, given that it is highly deformable (Petersen et al., 1982) and that cells can spread without altering their total membrane surface area (Erickson and Trinkaus, 1976). Thus, this submembranous network is viewed as an elastic element in this model. Other structural components that were visualized by "elastic" (i.e. distensible) elements in the original tensegrity models (Figs 1 and 2) include changes in CSK filament length and polymerization as well as internal geometric interconversions within the MF lattice (e.g. see Figs 4 and 5).

Tensegrity at a higher level: microtubules as compression-resistant struts

Tensegrity and tension-molding may also pertain to the MT

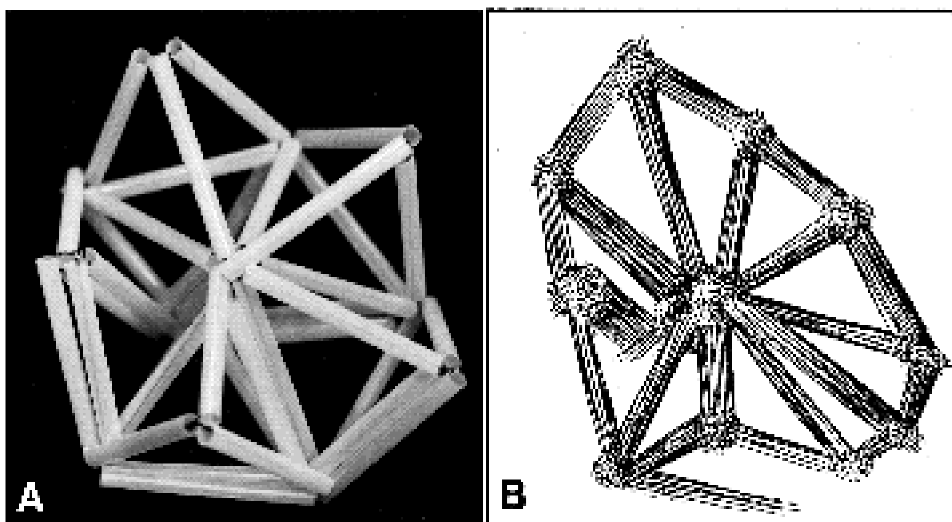

Fig. 7. (A) A tensegrity model constructed from soda straws and elastic thread showing a region from a "bent" isotropic vector matrix, as might be found within a geodesic dome that is forming or remodeling. The vertex on the left is in the process of merging with the central hub and thus, the intervening cross strut is absent. (B) A hand-drawn depiction of a published electron micrograph (Fig. 4a of Rathke et al., 1979) demonstrating a grazing section through a similar triangulated region within the MF geodome of a living cell. The round speckled knobs correspond to the vertices of the hexagons seen by light microscopy (Fig. 6B).

system. For example, tensegrity has been used to explain how changes in MT and MF extension are orchestrated during neurite outgrowth (Heidemann and Buxbaum, 1990). In neurites, drug-induced disassembly of MTs induces cell retraction, but only under conditions in which active tension is generated within the surrounding contractile MF network (Solomon and Magendantz, 1981; Joshi et al., 1985). These data combined with results from a series of other experiments (Dennerll et al., 1988, 1989; Lamoureux et al., 1989) clearly demonstrate that both the stability of axonal form and active neurite extension result from the action of tension which is generated within the continuous MF network and locally resisted by internal compression-resistant MTs. MT struts and ECM tethers also provide complementary and interchangeable load-bearing functions in these cells (Lamoureux et al., 1990), as would be predicted from studies with the tensegrity models (Fig. 1).

Structural stability in many other cells (Tomasek and Hay, 1984; Domnina et al., 1985; Travis and Bowser, 1986; Bereiter-Hahn, 1987; Vasiliev, 1987; Madreperla and Adler, 1989; Bailly et al., 1991) and tissues (Burnside, 1971; Gordon and Brodland, 1987) similarly depends on establishment of a mechanical force balance between competing MT struts and contractile MF networks. This is usually most clear in cells that exhibit an asymmetric or elongated morphology. While disrupting MTs in polygonal cells (e.g. epithelial cells) usually does not inhibit cell flattening (Middleton et al., 1988), it does decrease the rate and efficiency of spreading (Domnina et al., 1985; Vasiliev, 1987). Furthermore, epithelial cells clearly do require intact MTs to spread when they are forced to elongate in an asymmetric fashion due to altered ECM adhesivity or topography (Domnina et al., 1985). Conversely, stabilizing MT against depolymerization slows cell rounding upon trypsinization (Revel et al., 1974). We have found that while intact MTs are not required for endothelial cell flattening, they are absolutely required if MF integrity is *partially* compromised using low concentrations of cytochalasin D. These data indicate that MTs normally act as internal struts that hold the cell outward against the pull of the contractile MF network. However, they may play a secondary or redundant structural supporting role (i.e. relative to MFs) in polygonal cells and in elongated cells during the initial phase of spreading.

Analysis of the mechanical load-bearing characteristics of isolated CSK filaments confirms that MTs have a much greater ability to withstand compression (bending) than MF whereas MFs are better at resisting tension (Mizushima-Sugano et al., 1983). The compressive load-bearing capability of individual MTs also may be greatly enhanced by instituting multiple tensile guy lines along their length (Brodland and Gordon, 1991), as IF appear to do in living cells (Schliwa and Van Blerkom, 1981; Heuser and Kirschner, 1980). MT cross-linking or bundling may produce rigid structures that are even more effective at resisting compression (e.g. mitotic spindles, neurite axons), since close packing results in much greater resistance to lateral filament distortion.

In general, pulling tends to straighten support elements whereas pushing bends. Thus, the observation that MTs commonly exhibit a curved morphology, especially near their distal ends, supports the concept that they resist compression. Furthermore, direct mechanical measurements of living cells demonstrate that disruption of MTs results in a rapid *increase* in the amount of force that is transferred outward across the cell surface and to the ECM (Dennerrll et al., 1988; Danowski, 1989; Kolodney and Wyslomerski, 1992). This is what would be expected of a tensegrity array in which MTs and ECM play complementary compressive load-bearing functions. In contrast, disruption of tension elements should decrease the force that cells exert; this is exactly what was observed when MF integrity was disrupted (Danowski, 1989; Kolodney and Wyslomerski, 1992). Because of their complementary load-bearing functions, MTs are most critical in elongated cell processes that have a relatively low density of stable ECM adhesions (Domnina et al., 1985).

Tensegrity-based force interactions between MTs, MFs and ECM also provide an efficient mechanism for local regulation of CSK filament polymerization. A thermodynamic model which incorporates the tensegrity paradigm has been published (Buxbaum and Heidemann, 1988). In this model, formation of new ECM contacts shifts CSK tension onto the substratum, relieves compression on MT, and hence decreases the critical concentration of tubulin required to support MT assembly (Hill, 1981). Thus, cytoplasmic tubulin subunits previously in equilibrium with the compressed polymer are then added to the polymer until a similar state of compression is regained. However, many less specialized cells tend to maintain a relatively constant mass of MT (Mitchison and Kirschner, 1984; Mooney et al., 1991). If this thermodynamic mechanism is used in all cells, then increasing force transfer to the ECM should similarly lower the critical concentration of tubulin required to maintain equilibrium between MT assembly and disassembly. In other words, the concentration of intracellular tubulin monomer would need to be lowered in order to prevent rampant MT polymerization and a change in the total cellular MT mass. We have recently confirmed that this does in fact occur in cultured cells when they are induced to spread by increasing the number and density of available ECM adhesions (Mooney et al., 1991).

A third layer of structural stability: intermediate filaments as tensile stiffeners

We have not yet considered the role of IFs which interweave with MFs and MTs to form the CSK. This network of relatively stiff coiling filaments stretches from attachment points on the cell surface (e.g. desmosomes, focal adhesions) to the nuclear surface (Lehto et al., 1978; Fey et al., 1984; Green et al., 1986; Bershadsky et al., 1987; Georgatos and Blobel, 1987). They are also, at least in part, held out in an extended array through the action of MTs which counterbalance the inward pull exerted on IFs by surrounding contractile MFs (Hollenbeck et al., 1989). IFs have been suggested to act as "mechanical integrators" (Lazarides, 1980); however, a more-specific functional description remains elusive. While it is clear that IFs can efficiently resist mechanical tension in cells of the epidermis (Kunzenbacher et al., 1982), their function in other cells is not as clear. For example, early microinjection studies with anti-IF antibodies suggested that IFs are not

important for cell shape control (Lin and Feramisco, 1981). However, negative results are difficult to interpret in a system that relies on redundancy for enhanced stability. More recent studies using anti-sense oligodeoxynucleotides clearly demonstrate that loss of IFs reduces mechanical rigidity within living tissues (Torpey et al., 1992).

The tensegrity cell models (Fig. 2) predict that IFs may act to stabilize nuclear form and integrate cell structure whereas the continuous MF lattice would provide the motive force that drives cell and nuclear shape changes. For example, the tendency of tightly packed coils of DNA to unwind and push against the constraining nuclear matrix would result in oscillatory expansion and contraction of the entire nucleus unless an alternative system of stabilization were set in place. In the absence of any additional supports, this motion would tend to be translated into precession or rotation of the nucleus, back and forth, as the coils undergo winding, unwinding and rewinding, during activation of gene transcription or DNA replication (Ausio, 1992; Moser et al., 1983; Nicolini, 1985). This is precisely what happens when IFs are disrupted using acrylamide (Hay and DeBoni, 1991). IFs may normally support and stabilize the nucleus against rotational movements, just as they are thought to resist MT bending (Brodland and Gordon, 1991). IFs also appear to orient mitotic spindles in epidermis (Bereiter-Hahn, 1987) and, along with MTs, position nuclei within syncytia (Wang et al., 1979). Thus, as filamentous coils which harden at high strains (Janmey et al., 1991), IFs are excellent candidates to act as guy lines or tensile stiffeners and, thereby, hold separate parts of the cell (e.g. MTs, MFs, nuclei) in place. IFs may also provide a direct path for mechanical and harmonic information transfer, from nucleus to junctional complex to nucleus, within larger tensegrity tissue arrays (Ingber and Jamieson, 1985; Pienta and Coffey, 1991).

Interestingly, nuclei are similarly suspended from surrounding ECM by CSK ligaments in plant cells; however, the filaments appear to contain MTs and MFs (Flanders et al., 1990). The plant mechanism for nuclear positioning is especially important because the location of these suspensory filaments predicts where future cleavage planes will form. Interestingly, the three-dimensional model that was used to explain the mechanical basis of nuclear positioning was constructed by interconnecting a large rigid ring with a small central nucleus using suspensory springs (Flanders et al., 1990). This "spoked bicycle wheel" structure is yet another example of tensegrity architecture, as previously described by Fuller (1961).

Spatial integration on a smaller scale: nuclear tensegrity

As a separate structural entity, the nucleus may itself be modeled using tensegrity architecture (Fig. 2). The nuclear matrix is the scaffolding that is responsible for higher-order chromosome packing and nuclear organization (reviewed by Pienta et al., 1991). It is composed of a backbone of nuclear-specific proteins (Nakayasu and Berezney, 1991) and hnRNA (Nickerson et al., 1989) as well as multiple hexagonal nuclear pores (reviewed by Hansen and Ingber, 1992). Nuclear actin and myosin have been identified; however, it is unclear whether nuclei actively generate tension. Nevertheless, the nucleus does spontaneously contract when ECM anchors are dislodged and cell rounding is induced (Ingber and Folkman, 1989a; Sims et al., 1992). The nucleus therefore may be viewed as a tensegrity structure in which individual chromatin fibers containing tightly wound coils of DNA represent isolated compression-resistant elements that interconnect with a surrounding nuclear matrix that is under continuous tension.

Expansion of the nucleus would require a change in this force balance. For example, nuclear extension might result from the action of the interconnected contractile MF lattice (Osborn and Weber, 1977; Fey et al., 1984), pulling the nuclear matrix outwards against the cell's fixed ECM adhesions. As described above, IFs might serve to further focus this force and integrate changes in cell and nuclear form. Furthermore, due to the presence of structural interconnections between the nucleus and the cell surface (MF lattice, IFs), mechanical distortion of an entire cell or tissue would also be expected to result in passive nuclear extension. In fact, in vitro studies confirm that mechanical stretching of the plasma membrane results in nuclear form alterations and movement in living cells (Kolega, 1986). They also show that coordinated changes in cell and nuclear shape require both intact MFs (Pienta and Coffey, 1992) and active tension generation within the MF lattice (Sims et al., 1992). In addition, the structural integration observed in the nucleated tensegrity cell models (Fig. 2) provides a mechanical basis for the expansion of nuclear pores and associated increase in nucleocytoplasmic transport rates that are observed when cells progress from round to spread (Feldherr and Akin, 1990; Hansen and Ingber, 1992). Tensionally induced increases in nuclear transport, combined with decreased mechanical resistance to DNA unwinding, may explain why nuclear spreading is required for entry into S phase (Yen and Pardee, 1979; Moser et al., 1981; Nicolini et al., 1986; Ingber et al., 1987).

AN ALTERNATIVE MECHANISM FOR CELL SPREADING AND MOTILITY

The model of CSK organization that is most commonly used to explain cell motility relies on rearward flow of the *entire* MF lattice, coupled with forward polymerization of actin, as a means to generate tractional forces that drive migration (reviewed by Heath and Holifield, 1991). While the rearward "actin flow" model is consistent with data from many studies, there are others which it does not explain (Heath and Holifield, 1991; Gingell and Owens, 1992). Furthermore, to accept this model, one must also accept that MFs can move without restriction inside the cytoplasm. Yet electron microscopic studies reveal a highly anastomotic MF network which is entangled with nets of IFs and MFs a few micrometers behind the leading edge (Heuser and Kirshner, 1980; Bridgman and Daily, 1989). The actin flow hypothesis also does not present a clear mechanical explanation of how the cell integrates leading edge extension with changes in the remaining CSK-nuclear matrix scaffold. Finally, it does not make obvious sense for a living cell which always strives to be most economical to extend

the cell forward by continually fighting the backward flow of its own mass.

Inherent in the tensegrity model is an alternative explanation for cell spreading and motility that may be more realistic, at least in terms of mechanics and energy efficiency. Movement would be produced in the following manner: (1) the MF lattice is tension molded during the initial attachment and spreading phase, as described above, resulting in formation of an interconnected tensile MF network containing basal stress fibers, suprabasal arc-like bundles and apical triangulated domes; (2) formation of ECM contacts results in clustering of transmembrane integrin receptors and associated release of soluble chemical messengers, such as phosphatidylinositol bisphosphate (McNamee et al., 1993); (3) binding of inositol lipids to actin-binding proteins (e.g. gelsolin, profilin) results in a local increase in the concentration of free actin monomer (Janmey et al., 1987; Goldschmidt-Clermont et al., 1990); (4) flexible regions of the MF lattice that are free of tropomyosin and myosin (e.g. vertices on geodomes; Lazarides, 1976; Rathke et al., 1979) provide nucleation sites for new actin polymerization; (5) newly extending MFs, bundle, stiffen and push outwards against the confining plasma membrane, resulting in formation of filopodia (Tilney and Kallenbach, 1979; Hill, 1981; Oster and Perelson, 1987); (6) the opposing MF nets that interconnect the filopodial core with the rear-lying CSK lattice contract; (7) use of the basal focal adhesions as a fulcrum (Harris, 1982; Felder and Elson, 1990; Heidemann et al., 1990) causes the filopodium to waver up and down much as the bones of our arms do when we extend them out against the pull of our muscles; (8) when receptors on the tip of a filopodium attach and form fixed ECM adhesions, tension becomes isometric (Heidemann et al., 1990), resulting in net forward and downward pull on trailing CSK lattice; (9) the surrounding MF meshwork within the lamellopodium is then tensionally stiffened and pulled outward much as a sail is raised up on a mast; (10) continued tension molding results in merging of ventral MF bundles with the MF cores of the filopodia, resulting in linearization and extension of stress fibers (Lazarides, 1976; Rathke et al., 1979); (11) further consolidation of the new extension results when MTs polymerize from their distal ends into the newly remodeled region, due to transfer of compressive loads onto the ECM (Buxbaum and Heidemann, 1988; Heidemann et al., 1990); and (12) the cycle begins once again.

Lamellipodia may rapidly extend forward in this model using poorly developed MF bundles rather than well formed filopodia (Bridgman and Daily, 1989) if the substratum is very adhesive, and thus can bear much of the compressive load. Alternatively, protrusion of lamellipodia could be driven by actomyosin gelation-solation cycles (Trinkaus, 1985; Heidemann et al., 1990) and associated changes in intragel osmotic pressure (Oster and Perelson, 1987). However, these latter mechanisms must be reconciled with electron microscopic images which show that the most rapidly moving portions of the cell contain actin in its most concentrated and most highly cross-linked state (Heuser and Kirschner, 1980).

Portions of the MF lattice that do not become fixed to the non-deformable ECM (i.e. non-adherent filopodia, protruding ruffles) would be expected to move ("flow") centripetally on the dorsal cell surface due to the continuous transmission of tension and conservation of angular momentum, as previously suggested (Heidemann et al., 1990). However, rather than depolymerize, these MF bundles might spontaneously disperse into individual MFs, once they are no longer stabilized by isometric tension (Isenberg and Wolhfarth-Botterman, 1976; Nagai et al., 1978) and then be reincorporated into newly forming networks a few micrometers behind the leading edge. Other rearward flow of actin would be due primarily to actin treadmilling.

Reiteration of this adhesion-tension molding cycle would produce flattening and incremental forward motion of the entire MF lattice, and thus drive cell spreading. Continued binding of ECM receptors and release of actin monomers would sustain actin polymerization and spreading at the leading edge until the forward pull of the cell was balanced by the rearward tug of cell's ECM adhesions and by mechanical resistance associated with CSK stiffening. If the strength of the ECM adhesions were high, continued isometric tension generation would result in increased stress fiber formation as well as outward and downward pull on central nuclear matrix. In fact, cells commonly exhibit increased stress fibers and large nuclei on highly adhesive ECM substrata, which support growth rather than motility (Couchman et al., 1982; Ingber et al., 1987; Ingber, 1990). In contrast, both cell spreading and locomotion would be produced via the same tensional integrity mechanism if the strength of the cell's adhesions or the force transferred to the ECM were slightly decreased so as to destabilize the cellular force balance. Similar changes in cell adhesivity result in isotonic rather than isometric tension generation and, thus, enhanced motility in living cells (reviewed by Opas, 1987). Reiteration of the adhesion-tension molding cycle would continue to pull the entire CSK lattice away from the cell's weakest adhesions until tearing or detachment resulted (Chen, 1981). Resulting retraction of the previously extended, rear-most portions of the CSK lattice would again shift the net force balance forward, and thereby facilitate formation of new ECM adhesions and forward locomotion.

This model is consistent with results of studies that form the basis of the actin flow model. For example, results of experiments in which blocking actin polymerization using cytochalasins induces "actin flow" (Smith, 1988) can be easily explained as resulting from physically dislodging the fixed ends of a lattice that is under continuous tension. Experimental data support this mechanism of cytochalasin action (Schliwa, 1982; Bereiter-Hahn, 1986). Motion of membrane components would result primarily from the action of associated motor proteins (e.g. myosin I) that move along tensionally stabilized cortical MFs, although some rearward motion may be due to membrane that is associated with retracting filopodia and ruffles on the dorsal cell surface (Heidemann et al., 1990). Finally, the observed motion of "arcs" in living cells (Heath, 1983) could be due to peristaltic contraction waves (Dunn, 1980) moving through a three-dimensional MF lattice that spontaneously condenses and expands in response to a passing wave of isometric tension (Fig. 4). Three-dimensional models of

large, interconnected isotropic vector matrices exhibit similar contraction-expansion behavior (Edmondson, 1987).

The tensegrity hypothesis is clearly consistent with the well described role of "cortical" tension in the determination of fibroblast shape and movement (Albrecht-Buehler, 1987). However, it differs in that tension transmission and CSK molding occur throughout the depth of the cell, rather than just beneath the cell surface. This difference is most clear when nuclear shape control is considered. The model can similarly incorporate isolated changes in gel osmotic pressure as additional compression-resistant zones that act locally to resist otherwise continuous CSK tension. Interestingly, use of tensegrity provides an architectural basis for the previously described "global modulation" of the cortical CSK (Yahara and Edelman, 1975) as well. Conversely, disruption of tensional continuity may lead to the loss of structural stability and deregulation of growth and form that is so characteristic of the neoplastic state (Ingber et al., 1981; Ingber and Jamieson, 1982; Ingber and Jamieson, 1985; Ingber et al., 1986; Pienta et al., 1989; Boyd et al., 1991).

IMPLICATIONS FOR BIOLOGICAL DESIGN

Most published theoretical models in biology provide a plausible mechanism to explain a set of experimental findings. However, just because a biological phenomenon *can* be explained by a single theory, this does not mean that it is correct. A simple visual example is that plastic molds, paper cut-outs, and wooden stick figures can all be used to build a structure resembling a dinosaur. However, only a system of rigid bones interconnected by a continuous series of tensile muscles could support a living structure 30 feet high and 100 feet long that can change shape and walk, such as an *Ultrasaurus* (Jensen, 1985). The power of the tensegrity paradigm, in contrast to purely descriptive models (e.g. fractals), is that it provides a tangible and inherently buildable system that predicts how molecules interact to form three-dimensional structures that exhibit specialized form as well as function.

Importantly, analysis of organic and inorganic systems, both large and small, consistently reveals that Nature uses triangulation and tensional integration for structural stability (Fuller, 1965). The carbon-based "Buckminster fullerenes" are the most recent example; however, tensional integrity also applies to construction of viral capsids and clathrin-coated pits as well as nuclei and the CSK, as I described above. Tissue integrity may similarly depend on tensional continuity coupled with local compression-resistant islands (Ingber and Jamieson, 1985; Ryan, 1989) as does the stability of the musculoskeletal frame in insects (Wainwright et al., 1976) as well as man (Otto, 1973).

Thus, given that use of this building system crosses systems boundaries, it is possible that tensegrity may represent one of the most basic principles of biological design. The implications are vast, since the geometric rules of tensegrity are independent of scale and so should apply equally well to both microscopic and macroscopic tensegrity systems. Just as an example: recent analysis of the micromechanics of the lung has revealed that its basic structural element is isotropic, uniformly prestressed, and polyhedral in form (Stamenovic, 1990). If this is so and it is in fact another example of a tensegrity structure (e.g. view the lattice shown in Fig. 3B as a single alveolus), then the interconvertability between the large, unstable isotropic lattice and the compact stable tetrahedron shown in Fig. 4 could easily explain why the lung is unstable in the absence of transpulmonary intrathoracic pressure (Stamenovic, 1990), how it undergoes rapid expansion and contraction during the breathing cycle, and even how it is able to reversibly "collapse" (e.g. following pneumothorax). A similar mechanical approach may help explain conflicting behavior in many other biological systems.

CONCLUSIONS

Why should we care whether or not cells use a specific form of architecture? Most importantly, as suggested by the quotation that opens this Commentary, the question of biological organization is *the* major question in biology. The molecules that make up cells and the cells that comprise tissues continually turn over; it is maintenance of pattern integrity that we call "life". Pattern is a manifestation of structure and structural stability results from establishment of spatial relationships that bring individually destabilized structural elements into balance. Thus, a complete explanation of how cells and tissues function will come from understanding how they are put together, rather than exclusively from analysis of their substance.

In this Commentary I have demonstrated that specific patterns of CSK structure and integration can be modeled in three dimensions using the rules of tensegrity. A corollary to this is that individual support elements will be exquisitely sensitive to tension and, thus, that alterations in the cellular mechanical force balance will drive a structural remodeling cascade at the molecular level. Furthermore, changes in cell shape and motility will be a manifestation of internal oscillatory transformations between locally stable and unstable architectural states. In cells, the critical structural elements include internal compression-resistant struts, suspensory ligaments, and external tethers as well as a system for generating and distributing tension to all interacting parts. In this type of system, the exact molecular composition of individual struts can vary and even the mechanism of tension generation may change (e.g. MT vs MF-based motors; Goldstein and Vale, 1992). Nevertheless, the system will remain a tensegrity structure as long as continuous tension and local compression are required for structural stability.

If cells do use tensegrity, then we will need to change our frame of reference in studies on CSK remodeling and cell shape to include the concept of a pre-stressed CSK. In other words, we need to transform our image of cell architecture from a rigid static view that is largely based on local molecular binding events into one that is mechanically based, globally integrated and dynamic. Inherent in this form of architecture is a mechanism for mechanical information transfer (Ingber and Jamieson, 1985; Pienta and Coffey, 1991; Hansen and Ingber, 1992; Ingber et al., 1993), thermodynamic regulation (Ingber and Jamieson, 1985; Buxbaum and Heidemann, 1988) and hierarchical

integration between all parts, both large and small (e.g. see Fig. 2), that is based entirely on provision of tensional continuity. Thus, a central tenet of tensegrity is that every structural element with the system is poised to sense and immediately respond to physical stimuli from both inside and outside the cell. It is difficult to think of another type of building system that could explain how stretching a tissue, such as skin, results in extension of the ECM, cell, CSK and nucleus in a coordinated manner without producing any structural breakage or disconnection (Ryan, 1989).

From the standpoint of chemical regulation, it is critical to emphasize that the tensegrity model does not make molecular regulators of CSK remodeling any less important; rather it provides a mechanical context that may help us understand their true physiological significance. There are many examples of contradictory results that cannot be easily understood unless the existence of a mechanical force balance between ECM, MTs and MFs is considered (Kreisberg et al., 1985; Rogers et al., 1985; Danowski, 1989; Lamoreux et al., 1990). Demonstration that "chemical" signals, such as phosphorylation cascades, have a large mechanical component (i.e. dramatic changes in protein conformation, size and flexibility; Urry, 1992) suggests that elucidation of the rules by which higher-order molecular architecture is constructed will allow us to understand how cell form and function are controlled in a way in which we never have before.

The answer to whether or not cells use tensegrity architecture rests with the individual. For some, it is an obvious truth. For others, it is a gross simplification of a process that is of such complexity that it is likely beyond all explanation. Others will await direct experimental proof of principle, specifically, demonstration at the molecular level that individual protein subunits are being "pushed" together within certain CSK elements, while others "feel" the pull of continuous tension. Nevertheless, it is only when theory is presented and questions are raised that the critical experiments can be designed and initiated.

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REFERENCES

Albrecht-Buehler, G. (1987). Role of cortical tension in fibroblast shape and movement. *Cell Motil. Cytoskel.* **7**, 54-67.

Albrecht-Buehler, G. (1990). In defense of "nonmolecular" cell biology. *Int. Rev. Cytol.* **120**, 191-241.

Ausio, J. (1992). Structure and dynamics of transcriptionally active chromatin. *J. Cell Sci.* **102**, 1-5.

Bailly, E., Celati, C. and Bornens, M. (1991). The cortical actomyosin system of cytochalasin D-treated lymphoblasts. *Exp. Cell Res.* **196**, 287-293.

Ben Ze'ev, A., Duerr, A., Salomon, F. and Penman, S. (1979). The outer boundary of the cytoskeleton: a lamina derived from plasma membrane proteins. *Cell* **17**, 859-865.

Bereiter-Hahn, J. (1986). Scanning acoustic microscopy visualizes cytomechanical responses to cytochalasin D. *J. Microsc.* **146**, 29-39.

Bereiter-Hahn, J. (1987). Mechanical priniciples of architecture of eukaryotic cells. In *Cytomechanics: The Mechanical Basis of Cell Form and Structure* (ed. Bereiter-Hahn, J., Anderson, O.R. and Reif, W.-E.), pp. 3-30. Springer-Verlag, Berlin.

Bereiter-Hahn, J., Luck, M., Miebach, T., Stelzer, H.K. and Voth, M. (1990). Spreading of trypsinized cells: cytoskeletal dynamics and energy requirements. *J. Cell Sci.* **96**, 171-188.

Bereiter-Hahn, J. and Strohmeier, R. (1987). Hydrostatic pressure in metazoan cells in culture: its involvement in locomotion and shape generation. In *Cytomechanics: The Mechanical Basis of Cell Form and Structure* (ed. Bereiter-Hahn, J., Anderson, O.R. and Reif, W.-E), pp. 261-272. Springer-Verlag, Berlin.

Bershadsky, A.D., Tint, I.S. and Svitkina, T.M. (1987). Association of intermediate filaments with vinculin-containing adhesion plaques of fibroblasts. *Cell Motil. Cytoskel.* **8**, 274-283.

Blose, S.H., Meltzer, D.I. and Feramisco, J.R. (1984). 10-nm filaments are induced to collapse in living cells microinjected with monoclonal and polyclonal antibodies against tubulin. *J. Cell Biol.* **98**, 847-858.

Boyd, J., Pienta, K.J., Getzenberg, R.H., Coffey, D.S. and Barrett, J.C. (1991). Preneoplastic alterations in nuclear morphology that accompany loss of tumor suppressor phenotype. *J. Nat. Cancer Inst.* **83**, 862-866.

Bridgman, P.C. and Dailey, M.E. (1989). The organization of myosin and actin in rapid frozen nerve growth cones. *J. Cell Biol.* **108**, 95-109.

Brodland, G.W. and Gordon, R. (1991). Intermediate filaments may prevent buckling of compressively loaded microtubules. *J. Biomech. Eng.* **112**, 319-321.

Burnside, B. (1971). Microtubules and microfilaments in newt neurulation. *Dev. Biol.* **26**, 416-441.

Burridge, K, Fath, K., Kelly, T., Nucko, G. and Turner, C. (1988). Focal adhesions: transmembrane junctions between the extracellular matrix and cytoskeleton. *Annu. Rev.Cell Biol.* **4**, 487-525.

Buxbaum, R.E. and Heidemann, S.R. (1988). A thermodynamic model for force integration and microtubule assembly during axonal elongation. *J. Theor. Biol.* **134**, 379-390.

Chen, W.-T. (1981). Mechanism of retraction of the trailing edge during fibroblast movement. *J. Cell Biol.* **90**, 187-200.

Couchman, J.R., Rees, D.A., Green, M.R. and Smith, C.G. (1982). Fibronectin has a dual role in locomotion and anchorage of primary chick fibroblasts and can promote entry into the division cycle. *J. Cell Biol.* **93**, 402-410.

Danowski, B.A. (1989). Fibroblast contractility and actin organization are stimulated by microtubule inhibitors. *J. Cell Sci.* **93**, 255-266.

Dennerll, T.J., Joshi, H.C., Steel, V.L., Buxbaum, R.E. and Heidemann, S.R. (1988). Tension and compression in the cytoskeleton II: quantitative measurements. *J. Cell Biol.* **107**, 65-664.

Dennerll, T.J., Lamoureux, P., Buxbaum, R.E. and Heidemann, S.R. (1989). The cytomechanics of axonal elongation and retraction. *J. Cell Biol*. **107**, 073-3083.

Domnina, L.V., Rovensky, J.A., Vasiliev, J.M. and Gelfand, I.M. (1985). Effect of microtubule-destroying drugs on the spreading and shape of cultured epithelial cells. *J. Cell Sci.* **74**, 267-282.

Dunn, G.A. (1980). Mechanisms of fibroblast locomotion. In *Cell Adhesion and Motility, Br. Soc. Cell Biol. Symp.* 3 (ed. Curtis, A.S.G. and Pitts, J.D.), pp. 409-423. Cambridge University Press: Cambridge.

Edmondson, A.C. (1987). *A Fuller Explanation: The Synergetic Geometry of R. Buckminster Fuller.* Birkhauser: Boston.

Emerman, J.T. and Pitelka, D.R. (1977). Maintenance and induction of morphological differentiation in dissociated mammary epithelium on floating collagen membranes. *In Vitro* **13**, 316-328.

Erickson, C.A. and Trinkaus, J.P. (1976). Microvilli and blebs as sources of reserve surface membrane during cell spreading. *Exp. Cell Res.* **99**, 375-384.

Felder, S. and Elson, E.L. (1990). Mechanics of fibroblast locomotion: quantitative analysis of forces and motions at the leading lamellas of fibroblasts. *J. Cell Biol.* **111**, 2513-2526.

Feldherr, C.M. and Akin, D. (1990). The permeability of the nuclear envelope in dividing and nondividing cell cultures. *J. Cell Biol.* **111**, 1-8.

Fey, E.G., Wan, K.M. and Penman, S. (1984). Epithelial cytoskeletal framework and nuclear matrix-intermediate filament scaffold: three-

dimensional organization and protein composition. *J. Cell Biol.* **98**, 1973-1984.

Flanders, D.J., Rawlins, D.J., Shaw, P.J. and Lloyd, C.W. (1990). Nucleus-associated microtubules help determine the division plane of plant epidermal cells: avoidance of four-way junctions and the role of cell geometry. *J. Cell Biol.* **110**, 1111-1122.

Folkman, J. and Moscona, A. (1978). Role of cell shape in growth control. *Nature* **273**, 345-349.

Franke, R.-P., Grafe, M., Schnittler, H., Seiffge, D., Mittermayer, C. and Drenckhahn, D. (1984). Induction of human vascular endothelial stress fibres by fluid shear stress. *Nature* **307**, 648-649.

Fuller, B. (1961). Tensegrity. *Portfolio Artnews Annual* **4**, 112-127.

Fuller, B. (1965). Conceptuality of fundamental structures. In *Structure in Art and in Science* (ed. Kepes, G.), pp. 66-88. Braziller: New York.

Fuller, B. (1979). *Synergetics Portfolio.* R. Buckminster Fuller & Lim Chong Keat, Publishers; Philadelphia & Singapore.

Fulton, A.B. and Isaacs, W.B. (1986). Possible tensegrity models for the cytoskeleton. *J. Cell Biol.* **103**, 409a (abstract).

Georgatos, S.D. and Blobel, G. (1987). Two distinct attachment sites for vimentin along the plasma membrane and the nuclear envelope in avian erythrocytes: a basis for a vectorial assembly of intermediate filaments. *J. Cell Biol.* **105**, 105-115.

Gingell, D. and Owens, N. (1992). How do cells sense and respond to adhesive contacts? Diffusion-trapping of laterally mobile membrane proteins at maturing adhesions may initiate signals leading to local cytoskeletal assembly response and lamella formation. *J. Cell Sci.* **101**, 255-266.

Goldschmidt-Clermont, P.J., Machesky, L.M., Baldassare, J.J. and Pollard, T.D. (1990). The actin-binding protein profilin binds to PIP_2 and inhibits its hydrolysis by phospholipase C. *Science* **247**, 1575-1578.

Goldstein, L.S.B. and Vale, R.D. (1992). New cytoskeletal liasons. *Nature* **359**, 193-194.

Gordon, R. and Brodland, G.W. (1987). The cytoskeletal mechanics of brain morphogenesis: cell state splitters cause primary neural induction. *Cell Biophys*. **11**, 177-238.

Green, K.J., Talian, J.C. and Goldman, R.D. (1986). Relationship between intermediate filaments and microfilaments in cultured fibroblasts: evidence for common foci during cell spreading. *Cell Motil. Cytoskel.* **6**, 406-418.

Greenspan, H. and Folkman, J. (1977). Hypotheses on cell adhesion and actin cables. *J. Theor. Biol.* **65**, 397-398.

Hahne, G. and Hoffmann, F. (1984). The effect of laser microsurgery on cytoplasmic strands and cytoplasmic streaming in isolated plant protoplasts. *Eur. J. Cell Biol.* **33**, 175-179.

Hansen, L.K. and Ingber, D.E. (1992). Regulation of nucleocytoplasmic transport by mechanical forces transmitted through the cytoskeleton. In *Nuclear Trafficking* (ed. Feldherr, C.), pp. 71-86. Academic Press: Orlando, FL.

Harris, A.K. (1982). Traction, and its relations to contraction in tissue cell locomotion. In *Cell Behavior* (ed. Bellairs, R., Curtis, A. and Dunn, G.), pp. 109-134, Cambridge University Press: Cambridge.

Harris, A.K., Wild, P. and Stopak, D. (1980). Silicone rubber substrata: a new wrinkle in the study of cell locomotion. *Science* **208**, 177-180.

Hay, M. and De Boni, U. (1991). Chromatin motion in neuronal interphase nuclei: changes induced by disruption of intermediate filaments. *Cell Motil. Cytoskel.* **18**, 63-75.

Heath, J.P. (1983). Behaviour and structure of the leading lamella in moving fibroblasts. I. Occurence and centipetal movement of arc-shaped microfilament bundles beneath the dorsal cell surface. *J. Cell Sci.* **60**, 331-354.

Heath, J.P. and Holifield, B.F. (1991). Cell locomotion: new research tests old ideas on membrane and cytoskeletal flow. *Cell Motil. Cytoskel.* **18**, 245-257.

Heidemann, S.R. and Buxbaum, R.E. (1990). Tension as a regulator and integrator of axonal growth. *Cell Motil. Cytoskel.* **17**, 6-10.

Heidemann, S.R. Lamoureux, P. and Buxbaum, R.E. (1990). Growth cone behavior and production of traction force. *J. Cell Biol*. **111**, 1949-1957.

Heuser, J.E. and Kirschner, M.W. (1980). Filament organization revealed in platinum replicas of freeze-dried cytoskeletons. *J .Cell Biol*. **86**, 212-234.

Hill, T.L. (1981). Microfilament or microtubule assembly or disassembly against a force. *Proc. Nat. Acad. Sci. USA* **78**, 5613-5617.

Hollenbeck, P.J., Bershadsky, A.D., Pletjushkina, O.Y., Tint, I.S. and Vasiliev, J.M. (1989). Intermediate filament collapse is an ATP-dependent and actin-dependent process. *J. Cell Sci.* **92**, 621-631.

Ingber, D.E. (1990). Fibronectin controls capillary endothelial cell growth by modulating cell shape. *Proc. Nat. Acad. Sci. USA* **87**, 3579-3583.

Ingber, D.E. (1991). Integrins as mechanochemical transducers. *Curr. Opin. Cell Biol.* **3**, 841-848.

Ingber, D.E. and Folkman, J. (1989a). Tension and compression as basic determinants of cell form and function: utilization of a cellular tensegrity mechanism. In *Cell Shape: Determinants, Regulation and Regulatory Role* (ed. Stein, W. and Bronner, F.), pp. 1-32. Academic Press: Orlando, FL.

Ingber, D.E. and Folkman, J. (1989b). Mechanochemical switching between growth and differentiation during fibroblast growth factor-stimulated angiogenesis in vitro: role of extracellular matrix. *J. Cell Biol.* **109**, 317-330.

Ingber, D.E., Madri, J.A. and Jamieson, J.D. (1981). Role of basal lamina in the neoplastic disorganization of tissue architecture. *Proc. Nat. Acad. Sci. 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. *Amer. J. Pathol.* **122**, 129-139.

Ingber, D.E. and Jamieson, J.D. (1982). Tumor formation and malignant invasion: role of basal lamina. In *Tumor Invasion and Metastasis* (ed. Liotta L.A. and Hart, I.R.), pp. 335-357. Martinus Nijhoff: The Hague, Netherlands.

Ingber, D.E. and Jamieson, J.D. (1985). Cells as tensegrity structures: architectural regulation of histodifferentiation by physical forces transduced over basement membrane. In *Gene Expression During Normal and Malignant Differentiation* (ed. Andersson, L.C., Gahmberg, C.G. and Ekblom P.), pp. 13-32, Academic Press: Orlando, FL.

Ingber, D.E. Karp, S., Plopper, G., Hansen, L. and Mooney, D. (1993). Mechanochemical transduction across extracellular matrix and through the cytoskeleton. In *Physical Forces and the Mammalian Cell* (ed. Frangos, J.A. and Ives, C.L.), pp. 61-78. Academic Press: San Diego, CA.

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 Dev. Biol.* **23**, 387-394.

Isenberg, G., Rathke, P.C., Hulsmann, N., Franke, W.W. and Wohlfarth-Botterman, K.E. (1976). Cytoplasmic actomyosin fibrils in tissue culture cells: direct proof of contractility by visualization of ATP-induced contraction in fibrils isolated by laser microbeam dissection. *Cell Tiss. Res.* **166**, 427-443.

Isenberg, G. and Wohlfarth-Botterman, K.E. (1976). Transformation of cytoplasmic actin: importance for the organization of the contractile gel reticulum and the contraction-relaxation cycle of cytoplasmic actomyosin. *Cell Tiss. Res.* **173**, 495-528.

Janmey, P.A., Euteneur, U., Traub, P. and Schliwa, M. (1991). Viscoelastic properties of vimentin compared with other filamentous biopolymer networks. *J. Cell Biol.* **113**, 155-160.

Janmey, P.A., Iida, K., Yin, H.L. and Stossel, T.P. (1987). Polyphosphoinositide micelles and polyphosphoinositide-containing vesicles dissociate endogenous gelsolin-actin complexes and promote actin assembly from the fast-growing end of actin filaments blocked by gelsolin. *J. Biol. Chem.* **262**, 12228-12236.

Jensen, J. (1985). Three new sauropod dinosaurs from the upper jurasic of Colorado. *Great Basin Naturalist* **45**, 697-709.

Joshi, H.C., Chu, D., Buxbaum, R.E. and Heidemann, S.R. (1985). Tension and compression in the cytoskeleton of PC 12 neurites. *J. Cell Biol.* **101**, 697-705.

Kolodney, M.S. and Wysolmerski, R.B. (1992). Isometric contraction by fibroblasts and endothelial cells in tissue culture: a quantitative study. *J. Cell Biol*. **117**, 73-82.

Kolega, J. (1986). Effects of mechanical tension on protrusive activity and microfilament and intermediate filament organization in an epidermal epithelium moving in culture. *J. Cell Biol.* **102**, 1400-1411.

Kreis, T.E. and Birchmeier, W. (1980). Stress fiber sarcomeres of fibroblasts are contractile. *Cell* **22**, 555-561.

Kreisberg, J.I., Venkatachalam, M.A., Radnik, R.A. and Patel, P.Y. (1985). Role of myosin light-chain phosphorylation and microtubules in stress fiber morphology in cultured mesangial cells. *Amer. J. Physiol.* **249**, F227-F235.

Kunzenbacher, I., Bereiter-Hahn, J., Osborn, M. and Weber, K. (1982).

Dynamics of the cytoskeleton of epidermal cells in situ and in culture. *Cell Tiss. Res.* **222**, 445-457.

Lamoureux, P., Buxbaum, R.E. and Heidemann, S.R. (1989). Direct evidence that growth cones pull. *Nature* **340**, 159-162.

Lamoureux, P., Steel, V.L., Regal, C., Adgate, L., Buxbaum, R.E. and Heidemann, S.R. (1990). Extracellular matrix allows PC12 neurite elongation in the absence of microtubules. *J. Cell Biol.* **110**, 71-79.

Lazarides, E. (1976). Actin, -actinin, and tropomyosin interactions in the structural organization of actin filaments in nonmuscle cells. *J. Cell Biol.* **68**, 202-219.

Lazarides, E. (1980). Intermediate filaments as mechanical integrators of cellular space. *Nature* **283**, 249-256.

Lehto, V.-P., Virtanen, I. and Kurki, P. (1978). Intermediate filaments anchor the nuclei in nuclear monolayers of cultured human fibroblasts. *Nature* **272**, 175-177.

Lin, J.-C. and Feramisco, J.R. (1981). Disruption of the in vivo distribution of intermediate filaments in fibroblasts through the microinjection of a specific monoclonal antibody. *Cell* **24**, 185-193.

Lloyd, C.W. and Seagull, R.W. (1985). A new spring for plant cell biology: microtubules as dynamic helices. *Trends Biol. Sci.* December, 476-478.

Lotz, M.M., Burdsal, C.A., Erickson, H.P. and McClay, D.R. (1989). Cell adhesion to fibronectin and tenascin: quantitative measurements of initial binding and subsequent strengthening response. *J. Cell Biol*. **109**, 1795-1805.

McNamee, H., Ingber, D.E. and Schwartz, M.A. (1993). Adhesion to fibronectin stimulates inositol lipid synthesis and enhances PDGF-induced inositol lipid breakdown. *J. Cell Biol.*, in press.

Madreperla, S.A. and Adler, R. (1989). Opposing microtubule- and actin-dependent forces in the development and maintenance of structural polarity in retinal photoreceptors. *Dev. Biol*. **131**, 149-160.

Middleton, C.A., Brown, A.F., Brown, R.M. and Roberts, D.J.H. (1988). The shape of cultured epithelial cells does not depend on the integrity of their microtubules. *J. Cell Sci.* **91**, 337-345.

Mitchison, T. and Kirschner, M. (1984). Dynamic instability of microtubule growth. *Nature* **312**, 237-242.

Mizushima-Sugano, J., Maeda, T. and Miki-Noumura, T. (1983). Flexural rigidity of singlet microtubules estimated from statistical analysis of their contour lengths and end-to-end distances. *Biochim. Biophys. Acta* **755**, 257-262.

Mogensen, M.M. and Tucker, J.B. (1988). Intermicrotubular actin filaments in the transalar cytoskeletal arrays of Drosophila. *J. Cell Sci.* **91**, 431-438.

Mooney, D.J., Langer, R. and Ingber, D.E. (1991). Intracellular tubulin monomer levels are controlled by varying cell-extracellular matrix contacts. *J. Cell Biol.* **115**, 38a.

Moser, G.C., Fallon, R.J. and Meiss, H.K. (1981). Fluorometric measurements and chromatin condensation patterns of nuclei from 3T3 cells throughout G1. *J. Cell. Physiol.* **106**, 293-301.

Nagai, R., Yoshimoto Y. and Kamiya, N. (1978). Cyclic production of tension force in the plasmodial strand of *Physarum polycephalum* and its relation to microfilament morphology. *J. Cell Sci.* **33**, 205-225.

Nakayasu, H. and Berezney, R. (1991). Nuclear matrins: identification of the major nuclear matrix proteins. *Proc. Nat. Acad. Sci. USA* **88**, 10312-10316.

Nickerson, J.A., Krochmalnic, G., Wan, K.M. and Penman, S. (1989). Chromatin architecture and nuclear RNA. *Proc. Nat. Acad. Sci. USA* **86**, 177-181.

Nicolini, C. (1985). Nuclear structure: from the pores to the high-order gene structure. *Cell Biophys.* **7**, 67-87.

Nicolini, C., Belmont A.S. and Martelli, A. (1986). Critical nuclear DNA size and distribution associated with S phase initiation. *Cell Biophys*. **8**, 103-117.

Opas, M. (1987). The transmission of forces between cells and their environment. In *Cytomechanics: The Mechanical Basis of Cell Form and Structure* (ed. Bereiter-Hahn, J., Anderson, O.R. and Reif, W.-E.), pp. 273-286. Springer-Verlag, Berlin.

Opas, M. (1989). Expression of the differentiated phenotype by epithelial cells in vitro is regulated by both biochemistry and mechanics of the substratum. *Dev. Biol.* **131**, 281-293.

Osborn, M. Born, T., Koitsch, H.-J. and Weber, K. (1978). Stereo immunofluorescence Microscopy: I. Three-dimensional arrangment of microfilaments, microtubules, and tonofilaments. *Cell* **14**, 477-488.

Osborn, M. and Weber, K. (1977). The detergent-resistant cytoskeleton of tissue culture cells includes the nucleus and the microfilament bundles. *Exp. Cell Res.* **106**, 339-349.

Oster, G.F. and Perelson, A.S. (1987). The physics of cell motility. *J. Cell Sci. Suppl. 8*, 35-54.

Otto, F. (1973). Pneumatic structures. In *Tensile Structures.* M.I.T. Press: Cambridge, MA.

Petersen, N.O., McConnaughey, W.B. and Elson, E.L. (1982). Dependence of locally measured cellular deformability on position on the cell, temperature, and cytochalasin B. *Proc. Nat. Acad. Sci. USA* **79**, 5327-5331.

Pienta, K.J., Getzenberg, R.H. and Coffey, D.S. (1991). Cell Structure and DNA Organization. *Crit. Rev. Eukaryotic Gene Express.* **1**, 355-385.

Pienta, K.J., Partin A.W. and Coffey, D.S. (1989). Cancer as a disease of DNA organization and dynamic cell structure. *Cancer Res*. **49**, 2525-2532.

Pienta, K.J. and Coffey, D.S. (1991). Cellular harmonic information transfer through a tissue tensegrity-matrix system. *Med. Hypoth.* **34**, 88-95.

Pienta, K.J. and Coffey, D.S. (1992). Nucleo-cytoskeletal interactions: evidence for physical connections between the nucleus and cell periphery and their alteration by transformation. *J. Cell. Biochem.* **49**, 357-365.

Rafferty, N.S. and Scholz, D.L. (1985). Actin in polygonal arrays of microfilaments and sequestered actin bundles (SABs) in lens epithelial cells of rabbits and mice. *Curr. Eye Res.* **4**, 713-718.

Rathke, P.C., Osborn, M. and Weber, K. (1979). Immunological and ultrastructural characterization of microfilament bundles; polygonal nets and stress fibers in an established cell line. *Eur. J. Cell Biol.* **19**, 40-48.

Revel, J.P., Hoch, P. and Ho, D. (1974). Adhesion of culture cells to their substratum. *Exp. Cell Res.* **84**, 207-218.

Rogers, K.A., McKee, N.H. and Kalnins, V.I. (1985). Preferential orientation of centrioles toward the heart in endothelial cells of major blood vessels is reestablished after reversal of a segment. *Proc. Nat. Acad. Sci. USA* **82**, 3272-3276.

Ryan, T.J. (1989). Biochemical consequences of mechanical forces generated by distention and distortion. *J. Amer. Acad. Dermatol.* **21**, 115-130.

Schliwa, M. (1982). Action of cytochalasin D on cytoskeletal networks. *J. Cell Biol.* **92**, 79-91.

Schliwa, M. and Van Blerkom, J. (1981). Structural interaction of cytoskeletal components. *J. Cell Biol.* **90**, 221-235.

Sims, J.R., Karp, S. and Ingber, D.E. (1992). Altering the cellular mechanical force balance results in integrated changes in cell, cytoskeletal, and nuclear shape. *J. Cell Sci.* **103**, 1215-1222.

Smith, S.J. (1988). Neuronal cytomechanics: the actin-based motility of growth cones. *Science* **242**, 708-715.

Solomon, F. and Magendantz, M. (1981). Cytochalasin separates microtubule disassembly from loss of asymmetric morphology. *J. Cell Biol*. **89**, 157-161.

Stamenovic, D. (1990). Micromechanical foundations of pulmonary elasticity. *Physiol. Rev*. **70**, 1117-1140.

Stossel, T.P. (1989). From signal to pseudopod. *J. Biol. Chem.* **264**, 18621-18264.

Tilney, L.G. and Kallenbach, N. (1979). Polymerization of actin. VI. The polarity of the actin filaments in the acrosomal process and how it might be determined. *J. Cell Biol.* **81**, 608-623.

Tomasek, J.J. and Hay, E.D. (1984). Analysis of the role of microfilaments and microtubules in acquisition of bipolarity and elongation of fibroblasts in hydrated collagen gels. *J. Cell Biol.* **99**, 536-549.

Torpey, N., Wylie, C.C. and Heasman, J. (1992). Function of maternal cytokeratin in Xenopus development. *Nature* **357**, 413-415.

Travis, J.L. and Bowser, S.S. (1986). A new model of reticulopodial motility and shape: evidence for a microtubule-based motor and actin skeleton. *Cell Motil. Cytoskel.* **6**, 2-14.

Trinkaus, J. (1985). Protrusive activity of the cell surface and the initiation of cell movement during morphogenesis. *Exp. Biol. Med.* **10**, 130-173.

Urry, D. (992). Free energy transduction in polypeptides and proteins based on inverse temperature transitions. *Prog. Biophys. Mol. Biol.* **57**, 23-57.

Vasiliev, J.M. (1987). Actin cortex and microtubular system in morphogenesis: cooperation and competition. *J. Cell Sci. Suppl*. *8*, 1-18.

Wainwright, S.A., Biggs, W.D., Currey, J.D. and Gosline, J.M. (1976). *Mechanical Design in Organisms.* Edward Arnold: London.

Wang, E., Cross, R.K. and Choppin, P.W. (1979). Involvement of

microtubules and 10-nm filaments in the movement and positioning of nuclei in syncytia. *J. Cell Biol.* **83**, 320-337.
Wang N., Butler J.P. and Ingber D.E. (1992). Integrin 1 transmits mechanical forces across the cell surface and to the cytoskeleton. *Mol. Biol. Cell* **3**, 232a
Wellings, J.V. and Tucker, J.B. (1979). Changes in microtubule packing during the stretching of an extensible microtubule bundle in the ciliate Nassula. *Cell Tiss. Res.* **197**, 313-323.
Wolosewick, J.J. and Porter, K.R. (1979). Microtrabecular lattice of the cytoplasmic ground substance. Artifact or reality. *J. Cell Biol.* **82**, 114-139.
Wong, A.J., Pollard, T.D. and Herman, I.M. (1983). Actin filament stress fibers in vascular endothelium in vivo. *Science* **219**, 867-869.
Yahara, I. and Edelman, G.M. (1975). Modulation of lymphocyte receptor mobility by locally bound concanavalin A. *Proc. Nat. Acad. Sci. USA* **87**, 16-20.
Yen, A. and Pardee, A.B. (1979). Role of nuclear size in cell growth initiation. *Science* **204**, 1315-1317.