How Is The Cytoskeleleton Involved In Mechanical Signal Transduction?

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The underlying mechanisms whereby cells sense and respond to external stimuli are not well understood, but for some time it has been known that the extracellular matrix has an influence on the behavior of cells. For example, changing the flexibility and/or adhesiveness of the matrix can change the shape of cells, and determine whether or not they continue to divide or begin to differentiate. Recently, in a series of elegant experiments, a group of cell biologists in Boston[2,3] have demonstrated the presence of an interconnected molecular network pervading the entire living cell, extending from its outer surroundings into the genes in its nucleus. These investigators used videomicroscopy, highly specific molecular adhesive molecules, and micromanipulation to demonstrate that mechanical connections exist among cell surface receptors (integrins), the cytoskeleton, and nuclear components.[2] Their experiments used tiny beads coated with fibronectin (a protein that binds to integrin receptors on the outer cell surface). Once these beads were bound to integrin receptors they pulled the bound beads laterally at a rate of 10 µm/sec while examining the cell by videomicroscopy. As the bound beads were pulled, not only were the cytoskeletal filaments reoriented, but the nucleus became distorted and nucleoli became redistributed within the nucleus along the axis where tension was being applied. These effects were specific for integrins, since similar experiments using beads coated with another ligand (acetylated low density lipoprotein) for transmembrane metabolic receptors, did not produce a similar effect. The reason for this difference is that when integrin receptors bind a ligand, focal adhesions are formed which mediate the transfer of tensile forces into the cell and its nucleus. (When the other ligand was bound to the cell, focal adhesions did not form.)

These changes in the cell and its nucleus were due to the presence of direct linkages between the cytoskeleton and the nucleus. Cytoplasmic intermediate filaments alone were able to transmit mechanical stress to the nucleus. Actin filaments did the same at low stress levels, although when subjected to high strain they tore. Both populations of filaments function to coordinate changes in the shape of the cell and the nucleus, as well as to anchor the nucleus in place and stiffen it mechanically. Microtubules act to stabilize the nucleus against lateral compression, and also function to hold open the intermediate filament lattice network.

In another series of experiments[3], the group demonstrated how the components of the nucleus are interconnected. When they attempted to remove microsurgically a single nucleolus from an interphase cell, all of the remaining nucleoli came out sequentially, as a result of their being interconnected. Moreover, when they attempted to removed a single chromosome from a mitotic cell, all of the remaining chromosomes came out sequentially, because they also were interconnected by a continuous flexible thread. Testing their preparations with various enzymes revealed that the flexible thread holding the chain of chromosomes together was DNase sensitive, thus leading them to conclude that the thread consisted of DNA. Previous work by others have reported a structural continuity between the nucleus and the cytoplasm, but this study demonstrates that the "entire genome is physically connected and mechanically coupled to the surrounding cytoskeleton, even in mitotic cells"[3].

Evidence for an interconnected molecular network extending throughout the entire living cell and its nuclus offers a different perspective on cell structure and function. It is providing new clues as to the mechanisms whereby a cell responds to external mechanical stimuli. As additional discoveries emerge, they will further challenge cell biologists to rethink how regulatory signals outside the cell may target specific organelles and/or genes inside the cell. ■

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2. Maniotis, A.J., C.S. Chen, and D.E. Ingber, Demonstration of mechanical connections between integrins, cytoskeletal filaments, and nucleoplasm that stabilize nuclear structure, Proc. Natl. Acad. Sci. USA 94:849-854, 1997.

3. Maniotis, A.J., K. Bojanowski, and D.E Ingber, Mechanical continuity and reversible chromosome disassembly within intact genomes removed from living cells, J. Cell Biochem 65:114-130, 1997.