Space Life Sciences Research Highlights

Research Offers Intriguing Evidence that Mechanical Forces Regulate Cell Function

How do cells sense and respond to mechanical forces such as gravity? Donald Ingber has spent the past 20 years trying to answer this question. His work provides important evidence that mechanical tension— generated through molecular interactions within the cell's skeleton—regulates many biological functions.

Mechanical forces, including gravity, clearly play a fundamental role in the development of cells into tissues and organs, but exactly how living cells sense mechanical signals and convert them to a biochemical response is poorly understood.

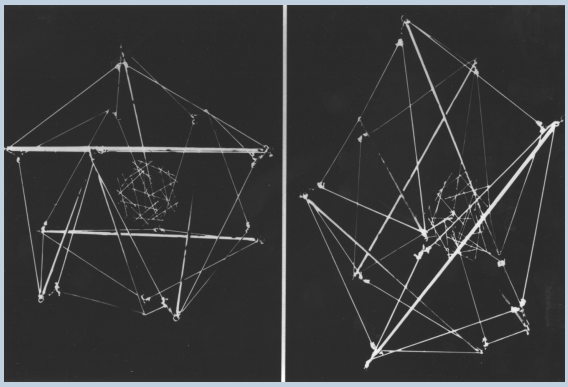
As Donald Ingber pondered this problem, he found himself questioning the conventional scientific image of the cell as a viscous gel surrounded by a membrane. He thought that this model failed to explain many observed properties of cells. For example, when single cells are placed on different surfaces, they take on different shapes. When you squeeze a cell and then let go, the cell springs back to its original shape.

Ingber was also struck by the fact that cells in living tissue respond in an integrated fashion to multiple simultaneous external signals. Most research in cell biology, however, focuses on delineating the pathway by which a specific protein or enzyme transmits its signal to the cell. Ingber doubted that a complete understanding of cell regulation could be achieved by focusing on any signaling mechanism in isolation.

"The key is not which pathways are turned on, but how all these signals are integrated inside the cell and how this integration occurs within the structural complexity of a living cell," he says.

As a student, Ingber—now Harvard Medical School professor of pathology at Children's Hospital in Boston—became interested in the work of R. Buckminster Fuller, who designed the geodesic dome. Ingber began to evolve a still-controversial alternative model of the cell as a system, wired together in a similar manner to a geodesic dome, that senses and transmits mechanical forces.

A geodesic dome is a framework of rigid struts that is stable because of the way it balances mechanical stresses. Tensional forces which are transmitted throughout the entire structure are balanced by certain struts that resist being compressed locally.

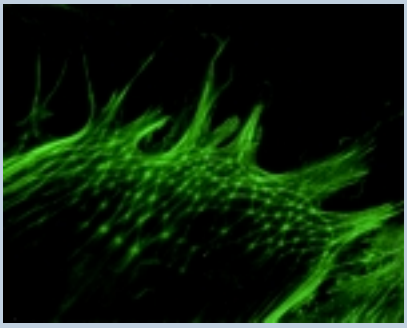


Cell tensegrity models constructed with sticks and string. The model on the right shows the distortion that occurs when an external stress is applied.

By contrast, a conventional building gets its structural stability from continuous compression due to the force of gravity. Fuller coined the term "tensegrity" (short for tensional integrity) to describe the structural balancing act that gives a geodesic dome its stability.

"Nature tends to use tensegrity structures because they are efficient and flexible while maintaining strength," says Ingber. Proteins, enzymes, viruses, and—at the other end of the scale—the human body are tensegrity structures, he says. Bones are the compression struts; muscles, tendons, and ligaments the tension-bearing components. "Tensegrity explains why the tissues, cells, and connective tissue in my arm move in an integrated, coordinated way without breaking. It's stable but it has flexibility."

According to Ingber's hypothesis, the cell is also a tensegrity structure. The cell, he says, resembles a tent, which is attached to the ground on the outside by pegs and supported on the inside by poles. In the tissues of humans and animals, the "ground" that cells are attached to is a mesh-like protein matrix. Proteins called integrins that span the cell membrane are the "tent pegs" that anchor the cell to this extracellular matrix.



Cytoskeleton of an endothelial cell illustrating the geodesic dome nature of the cytoskeleton. The cytoskeleton appears bright green due to immuno-fluorescence staining.

Inside, a mesh of protein filaments makes up the cell's internal skeleton, or cytoskeleton. The smallest ones, threadlike microfilaments, provide tension, pulling the cell's contents toward the nucleus. Thicker, hollow filaments, or microtubules, serve as compression struts—the "poles" that hold the tent up. Intermediate-sized filaments connect the small and large filaments and also hold the nucleus in place in the center of the cell.

"Our work shows that the cytoskeleton is the system that senses and transmits mechanical forces," says Ingber. These filaments also act as a scaffolding through which biochemical messengers such as enzymes and receptors transmit their signals to the cell. Thus, mechanical forces are as important to understanding cell regulation as biochemical signals.

Ingber initially found little support for this unorthodox view of cell structure. His ideas did, however, attract the attention of NASA, which is interested in identifying the fundamental mechanisms by which cells perceive gravity. "NASA had the flexibility and vision to support this research long before any other funding agencies were open to it," Ingber says.

To test the hypothesis that cells sense mechanical forces transmitted via specific cell surface molecules, Ingber and his colleagues developed a method of pulling on membrane receptors using magnetic particles. When they pulled on integrins—the "tent pegs"—they found that the cytoskeleton got stiffer and stiffer. When they pulled harder, the chromosomes in the cell's nucleus moved in response to this stress. Pulling on other cell membrane proteins produced no such effect.

"These studies confirmed that mechanical forces are transmitted over specific molecular pathways in living cells," says Ingber. "Integrins preferentially transfer mechanical forces across the cell surface."

In another experiment, the researchers used a microscopic needle to spear a single chromosome. As they pulled out their "catch," all 46 chromosomes emerged, connected by a fine thread that also linked to the cytoskeleton. These findings confirmed that molecular elements extending from the cell surface through the cytoplasm and into the depth of the nucleus are mechanically connected or "hard-wired" in living cells.

A further intriguing finding is that a cell's shape seems to determine its function. The investigators forced cells to take on different shapes—flat, round, square, and so on—by placing them on tiny "islands" of extracellular matrix created with microfabrication techniques developed for the microchip industry. Flat cells divided, but round cells died. "Mechanical restructuring of the cell and cytoskeleton apparently tells the cell what to do," says Ingber. "Cell shape is a visual manifestation of an underlying balance of mechanical forces that convey critical regulatory information to the cell."

Recently, Ingber and his team showed that when a protein called vinculin (a member of the integrin family) is removed from cells by genetic engineering, the effect is like removing a tent peg: the mechanical "coupling" from integrin to the cytoskeleton disappears. In addition, the cell loses the ability to move and change its shape. "When you put vinculin back in, you restore the cell's control over its shape and ability to move," says Ingber.

He and his colleagues have also shown that, by exerting stress on integrins with magnetic particles, they could induce formation of microcompartments for protein synthesis (the process of making new proteins) to form at integrin clustering sites on the cell membrane.

These insights into how mechanical forces regulate cell function will not only enhance our fundamental understanding of how gravity—and its absence in space—affects living things, they may also ultimately lead to the development of bioengineered tissues to treat disease, as well as to other new materials designed to mimic the properties of cells, says Ingber. "By understanding how cells respond to chemical and mechanical information, we may be able to develop synthetic materials and devices with mechanical and chemical processing efficiencies approaching that of cells, which is far beyond anything we have right now."

References

1. Ingber D. How cells (might) sense microgravity. *FASEB J.* 13 Suppl:S3-15, 1999.
2. Chen CS; Ingber DE. Tensegrity and mechanoregulation: from skeleton to cytoskeleton. *Osteoarthritis Cartilage* 7(1):81-94, 1999.
3. Goldmann WH; Galneder R; Ludwig M; Xu W; Adamson ED; Wang N; Ezzell RM. Differences in elasticity of vinculin-deficient F9 cells measured by magnetometry and atomic force microscopy. *Exp Cell Res.* 239(2):235-42,1998.
4. Ingber DE. The architecture of life. *Sci Am.* 278(1):48-57, 1998.