Mechanical Signaling

DONALD INGBER

Departments of Pathology and Surgery, Harvard Medical School/Children's Hospital, Boston, Massachusetts 02115, USA

KEYWORDS: mechanical signaling; integrins; tissue engineering

In order to determine design criteria for tissue engineering, it is necessary to understand how complex physiological pathways function within the physical context of real tissues. It is recognized that tissue patterning and architecture are influenced by sequential activation of gene expression and metabolic pathways; however they are also significantly affected by mechanical factors. Mechanical stresses applied to cell surface adhesion receptors (e.g., integrins) can activate intracellular signaling pathways and induce gene transcription. Mechanical stresses that produce cell distortion also can switch cells between growth, differentiation, motility, and apoptosis programs.

Tissue growth and development are controlled through interplay between soluble cytokines, insoluble adhesion molecules, and mechanical forces. Importantly, all three types of signals converge on cell surface adhesion receptors that couple extracellular anchoring scaffolds (extracellular matrix, other cells) to the intracellular cytoskeleton. Recent work from many laboratories shows, for example, that integrins mediate transmembrane transfer of mechanical signals and that some forms of mechanochemical transduction occur within the specialized cytoskeletal complex known as the focal adhesion that forms at the site of integrin binding. However, while individual signaling cascades may integrate within the focal adhesion, the whole cell appears to function as the "mechanosensor" when it comes to behavioral control at the cell level. For example, application of mechanical stresses to integrins can activate specific signaling pathways and turn on gene expression equally well in round and spread (mechanically distorted) cells. Yet, round cells integrate those signals with other cues and turn on a cellular suicide program (apoptosis), whereas spread cells take in the same inputs and translate them into a growth response.

Taken together, these results suggest that when it comes to the engineering of artificial tissues, cell shape and extracellular matrix mechanics must be regarded as equally important contributors to developmental regulation as chemical signals. In fact, surgeons already make use of mechanical forces to achieve desired *in vivo*

Address for correspondence: Donald Ingber, Children's Hospital/Harvard Medical School, Enders 1007, 300 Longwood Avenue, Boston, MA 02115. Voice: 617-355-8031; fax: 617-232-7914.
donald.ingber@tch.Harvard.edu

Ann. N.Y. Acad. Sci. 961: 162–163 (2002).

responses (as in distraction osteogenesis and skin expansion). Thus, it is critical that future approaches to tissue engineering incorporate relevant aspects of cellular mechanoregulation. Factors that may be important for tissue engineering design include level and direction of mechanical strain as well as use of dynamic versus static force regimens. Selection of the appropriate oscillation frequency, amplitude, and work cycle form (e.g., sinusoidal versus step function) for force application also may be critical for the tissue remodeling response. But equally important will be the material properties and form of the microengineered tissue scaffolds (artificial extracellular matrices) on the micron scale because this is the physical microenvironment the cell experiences and hence, the design feature that has a most direct impact on cell behavior.

SELECTED READING

1. HUANG, S. & D.E. INGBER. 1999. The structural and mechanical complexity of cell growth control. Nat. Cell Biol. **1:** E131–E138.
2. MEYER, C.J., F.J. ALENGHAT, P. RIM, *et al.* 2000. Mechanical control of cAMP signaling and gene transcription through activated integrins. Nat.Cell Biol. **2:** 666–668.
3. CHEN, C.S. & D.E. INGBER. 1999. Tensegrity and mechanoregulation: from skeleton to cytoskeleton. Osteoarthritis Cartilage **7/1:** 81–94.
4. CHICUREL, M., C.S. CHEN & D.E. INGBER. 1998. Cellular control lies in the balance of forces. Curr. Opin. Cell Biol. **10:** 232–239.
5. CHICUREL, M.E., R.H. SINGER, C. MEYER & D.E. INGBER. 1998. Integrin binding and mechanical tension induce movement of mRNA and ribosomes to focal adhesions. Nature **392:** 730–733.
6. CHEN, C.S., M. MRKSICH, S. HUANG, *et al.* 1997. Geometric control of cell life and death. Science **276:** 1425–1428.
7. SINGHVI, R., A. KUMAR, G. LOPEZ, *et al.* 1994. 1994. Engineering cell shape and function. Science **264:** 696–698.
8. INGBER, D.E. 1993. The riddle of morphogenesis: a question of solution chemistry or molecular cell engineering? Cell **75:** 1249–1252.
9. INGBER, D.E. 1991. Integrins as mechanochemical transducers. Curr. Opin. Cell Biol. **3:** 841–848.