Scand J Med Sci Sports 2005: 15: 199–201
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DOI: 10.1111/j.1600-0838.2005.00481.x

SCANDINAVIAN JOURNAL OF
MEDICINE & SCIENCE
IN SPORTS

Editorial

Tissue adaptation to mechanical forces in healthy, injured and aging tissues

Molecular biology and genomics have dominated all areas of medicine for the past 30 years. This has led to basic and applied research thrusts that focus almost exclusively on the genetic basis of disease. But the pathological changes in the musculoskeletal system because of injury or aging that are central to the field of Sports Medicine result more directly from alterations in the material properties of living tissues, their mechanical disruption or changes in the way cells sense or respond to normal mechanical cues. The challenge is to understand how living tissues normally adapt to acute and chronic changes in mechanical loading, with the long-term goal of developing new ways to prevent or reverse injury (or degeneration) of muscles, tendons, ligaments, cartilage and bone. Elucidation of the fundamental mechanisms of ''mechanoregulation'' at the cell and tissue level also could lead to novel strategies to improve or enhance normal tissue function and thus, be of great interest to professional athletes and members of the military, as well as ''weekend warriors''.

The 6th Bispebjerg Symposium on Sports Medicine that convened at the Carlsberg Academy of Science on August 19–21, 2004 in Copenhagen, Denmark focused on the question of how living tissues functionally adapt to mechanical loads, as well as how deregulation of this process may lead to tissue damage, disease and degeneration. Some of the most important breakthroughs at the meeting were that experiments analyzing how mechanical forces influence tissue function are now being carried out in living animals, and even in humans. Moreover, results of these studies provide direct support for recent mechanistic insights into the physiological basis of mechanoregulation that have emerged from experiments with cultured cells and tissue explants. As a result of these advances, a new field of mechanical biology is beginning to self-organize that will likely have important implications for Sports Medicine and other forms of clinical care in the future.

To understand mechanotransduction – the process by which mechanical forces are converted into changes in cellular physiology – it is necessary to first envision how cells sense and respond to mechanical loads in living tissues. Virtually all the cells that comprise musculoskeletal tissues experience mechanical stress through physical distortion (strain) of the extracellular matrix (ECM) scaffolds that hold cells together within solid tissues and organs, or through changes in the level of isometric tension (tone or prestress) in the tissue. But these forces are not transmitted equally to the cells at all points across their surface membranes. Instead, mechanical stresses are preferentially transferred across the cell surface and to the intracellular framework of the cell – a molecular lattice called the ''cytoskeleton'' – via transmembrane adhesion receptors such as ''integrins'' that cluster together within specialized ''focal adhesion'' plaques that anchor the cytoskeleton to the ECM at the cell membrane.

Cellular mechanosensation is further complicated by the fact that cells generate their own mechanical (tensional) forces in the contractile microfilaments of their cytoskeleton via acto-myosin interactions, and exert these forces on the cytoplasmic face of these same focal adhesions. Thus, even individual cells exist in a state of isometric tension. All tissues and organs are tensionally prestressed as a result of a balance between these cellular contractile forces and resisting forces exerted by other contractile cells, by stiffened ECMs (e.g., cross-linked collagen bundles, tensed basement membranes), and by macroscale forces acting in the tissue microenvironment (e.g., swelling forces in cartilage, fluid shear stresses in the Haversian canals of bone, hemodynamic forces in the cardiovascular system). The same mechanical stimulus may therefore produce a different response depending on the state of prestress in the cell or tissue, just as plucking a guitar string will produce a different tone depending on the tension in the string.

When a mechanical load is imposed on this preexisting cellular force balance (e.g., by exercising a muscle or through the effects of compression because of gravity on bone), changes in the level of stress applied to integrin receptors of the surface membranes of the cells that make up these tissues will produce physical alterations in the load-bearing

molecular components that form the cytoskeletal backbone of their focal adhesions. All molecules change their shape or alter their motion while carrying out their biochemical functions; physical distortion of these focal adhesion molecules may therefore alter their chemical activities. In fact, application of mechanical stress to surface integrin receptors has been shown to activate numerous intracellular signaling molecules, including the small GTPase Rho that increases cytoskeletal tension and promotes focal adhesion assembly which feed back to strengthen the cell against further injury. Changes in the balance of forces across integrins also results in stress-dependent changes in the transcription of specific genes, including some that encode proteins that are critical for the mechanical strength and dynamic remodeling of their surrounding ECM. Forces applied to the surface membrane at one end of the cell can be focused and channeled through cytoskeletal filaments to produce distortion of structures at the opposite pole and at cell–cell junctions, as well as deep inside the nucleus.

In this manner, stresses applied at the macroscale that mechanically strain ECMs and deform cells and their internal cytoskeleton can trickle down to smaller size scales and be focused on specific molecular components that change their biochemical activities when deformed. Because stresses may be distributed through the cytoskeleton to multiple sites in the cell, mechanical forces may elicit numerous intracellular biochemical responses simultaneously in living cells. The level of prestress within this network tunes the whole system and governs how it will respond to external mechanical loads. This use of structural hierarchies and tensile prestress for mechanical stability and integrated system-wide control is a hallmark of ''tensegrity'' architecture.

In addition, the hierarchical structural networks that mediate force transmission through cells and tissues, and that act to resist external loads, are themselves chemically remodeled in response to stress. For example, exercise conditioning, gravity and aging may modulate the cellular response to mechanical force by altering the prestress within cells and tissues either by changing cytoskeletal structure (e.g., polymerization state) or contractility, or by modulating ECM mechanics (rigidity or compliance) through changes in synthesis, degradation, fibrillogenesis, cross-linking or sulfation state. One way to potentially reverse these changes in prestress may be through exercise training regimens that utilize resistive loading, rather than weight loading.

Numerous studies in virtually all cell types confirm that the effects of mechanical load on both cytoskeletal function and ECM remodeling are mediated by integrins and associated stress-dependent changes of intracellular signaling activities. Thus, integrins or their associated signaling molecules could represent future targets for therapeutic intervention in the Sports Medicine field. Interestingly, each cell type (e.g., muscle, cartilage, tendon or bone) appears to have its own mechanical ''set point'' such that different cells exhibit optimal levels of differentiated function on ECMs that exhibit material properties (e.g., mechanical compliance) most similar to that found in their respective tissue of origin. Thus, any therapy or exercise regimen must be tailored based on tissue type, mechanics and location.

The tight interplay between structure and function and the importance of physical context within highly complex structural hierarchies, make it difficult to fully represent all of the critical features of the mechanoregulatory response in simplified model systems. For example, it is impossible to regenerate the physical and chemical milieu that exists in living tissues *in vitro*. Changes in the ECMs and integrins that physically connect different tissue types (e.g., bone and tendon, tendon and muscle, cartilage and bone) also may be critical for many musculoskeletal disorders, as well as the frailty of aging. Yet, at the same time, many of the mechanistic insights that have emerged from in vitro studies with single isolated cells (e.g., the central role of integrins in mechanotransduction) have been found to be relevant when the same mechanoregulatory processes are analyzed using *in vivo* models. Hence, the challenge for the future is to carry out both types of studies, to develop new methods to read-out changes in physical properties and chemical composition of living tissues *in situ*, and to continually compare and contrast results from these different approaches in order to understand their full biological relevance.

Although mechanical forces are critical for normal tissue development and function, excessive force or repetitive trauma can lead to injury and disease. For instance, while physiological mechanical forces may promote growth of blood capillaries and nerves into appropriate sites during organ morphogenesis, mechanical injury of avascular tissues, such as cartilage or certain tendons, can elicit chemical or inflammatory signals that trigger an angiogenic response. Invasion of capillary blood vessels into these normally avascular tissues, along with associated activation of matrix metalloproteinases, can lead to tissue breakdown, debilitating pain and loss of function. Thus, the recent regulatory approval of multiple angiogenesis inhibitors (e.g., Avastin, Macugen, Thalidomide) for human use in the United States and Europe may provide new tools for clinical care in the field of Sports Medicine, as well as in the Cancer and Ophthalmology areas for which they were initially developed. Similarly, pharmacological inhibitors of ECM degradation, such as tissue inhibitors of metalloproteinases or chemical modifiers of this

process may provide equally useful for treatment of various soft-tissue injuries.

In summary, studies with cultured cells and clinical studies confirm that nature has developed a mechanism for mechanotransduction that involves use of structural hierarchies that span multiple size scales and are composed of a tensed network of muscles, bones, cartilage, tendons, ligaments, along with their internal ECMs, cells and cytoskeletal filaments that focus stresses on specific mechanotransducer molecules. Changes in mechanical loads produces alterations in cellular biochemistry through stress-induced changes in the conformation of a subset of molecules that, in turn, feed back to remodel cell and tissue structures so as to more effectively bear and respond to applied stress. Understanding of the cellular and molecular basis of physiological adaptation to mechanical loads is important and requires additional research because it may lead to development of new therapeutic strategies to accelerate tissue repair or novel design approaches to engineer artificial tissue replacement parts. In addition, it could provide new insight into how athletes might be able to improve their performance. For example, if we could elucidate how fast-twitch muscles are converted to their slow-twitch form that exhibit greater stamina as a result of physical conditioning, it could have a major impact on athletic training regimens, and result in improved forms of physical therapy for injured patients, as well as frail older individuals.

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