Mechanosensitive Ion Channels

Mechanosensitivity in Cells and Tissues

Volume 1

Series Editors

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Foreword

Mechanosensitivity in Cells and Tissues as an Overall Regulatory System

Kamkin and Kiseleva's assembly of leaders in the mechanosensitivity field provides an excellent broad based and up-to-date book, with chapters in the first part discussing mechanically gated channels (mechanogated), mechanosensitive channels (MGC, MSC) systems (as the editors air the nomenclature in their editorial), the second describing their signaling, and the third presenting aspects of cell mechanobiology. Conceptually starting with tension at the surface membrane, the book's theme moves on to some molecular mechanisms, and then on to MSC as initiating complex cell signal cascades, sometimes invoking signalsomes. Mechanosensitivity is also described in organs.

Mechanosensitivity does not only relate to very soft deformable tissue, but chapters also focuses on cells and tissues concerned essentially with skeletal growth and development. The state of the art covered in the book heralds, to me, a slant to mechanosensitivity in general.

Galileo remarked in 1638 that longer bones were thicker for a given structural strength (Galilei, 1638) (translation in (Crewew & da Silavio, 1939)), and this was followed in 1859 by Darwin's noting that flying ducks have underdeveloped legs as compared with terrestrial bound ones (Darwin, 1859).

These early observations were already suggesting a compensatory homeostatic feedback system applying to the whole organism. Based on the wide-ranging and authoritative chapters, I propose that mechanogated, mechanosensitive systems in biology as a whole preserves physiological, integrative homeostasis as closed feedback control systems, and Fig. 1 is indication of how this could fit into system biology. Feedback interaction is between the mechanosensor to spatiotemporal integration of systems and organs. Mechanoelectric Feedback in heart has already been similarly viewed and invokes mechanosensitivity as the detector/transducer in feedback control of electrophysiology. (Lab, 1999) Although I have applied the homeostatic feedback notion to heart, this book suggests that I can broaden this mechanical homeostatic process to biology in general, for mechanosensitivity exists throughout the phyla - bacteria to mammalian tissue.

In pursuing this notion, I used a type of meta-analyses — an accepted method to address a defined clinical topic, sometimes as a hypothesis (treatment X works). The current approach is roughly analogous, examining this book as well as the literature with the proposal in mind. My analysis roughly encompasses literature over 20 years or so, using "Entrez Pubmed," with search terms such as "Mechanotransduction,"

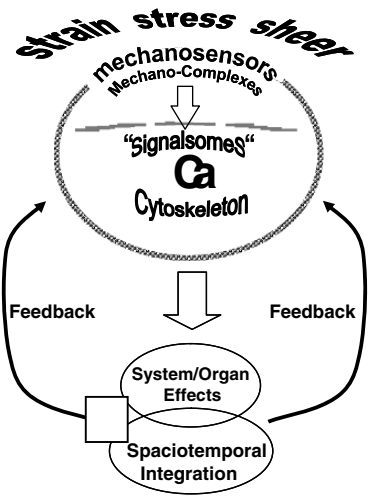

Fig. 1 Stress,strain, and sheer forces (very top) affect the membrane Mechanosensors / Mechano-complexes and then into the cell, feeding down (top block arrow - "feed-forward") down signal-somes and signal cascades often involving calcium. Importantly, influences via the cytoskeleton modulate (bottom block arrow) organ and spatiotemporal integration. These feed back ("return" - outside curved black arrows) via the same or alternate paths to modulate the consequences of the initiating mechanical changes

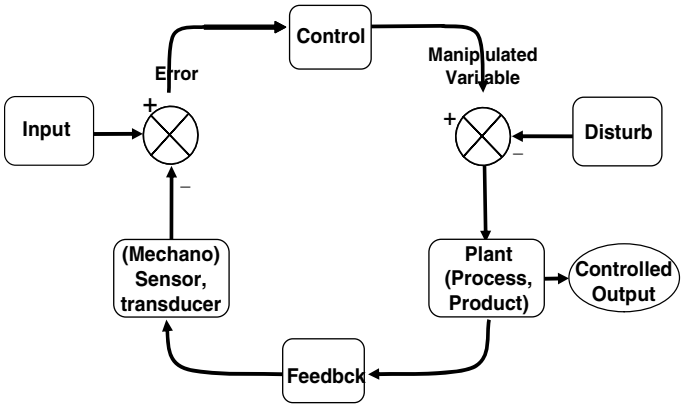

Fig. 2 Simplified block diagram of mechanosensitivity as a homeostatic feedback control system. The mechanosensors or transducers (bottom left element in loop) have mechanical inputs (top left) to a summing point (left crossed circle in loop). These via the control mechanisms and transfer functions going clockwise reach another summing point, interacting with the factors disturbing the system (top right – "disturb"). The product of these interactions (bottom left element – "plant", in loop) would produce a controlled output (elipse – bottom right). The plant/process element feeds back to influence the mechanosensor or transducer.element

"Mechanosensitivity," "Mechanogated channels," and "Stretch activated channels", and "Mechano Feedback." The findings were then organised into appropriate components of feedback control loops, see Fig. 2.

The "feedback" label in heart (Lab, 1999) was negative and when the Feedback Loop is altered (gain changes) it heralds pathology, with arrhythmia, hypertrophy.

It can also apply in the vasculature with its regulatory flow dynamics (Lehoux *et al*., 2006). In this case an altered loop can produce atherosclerosis. Growth & proliferation, repair and regeneration can also be treated in analogous fashion, and altered loop gains here produce cancer.

Although several elegant reviews covering aspects of mechanobiology (for example (Ingber, 2003; Ingber, 2006)) offer an open system view with feed forward descriptions, my current proposal in this article is for mechanosensitivity to involve closed negative feedback systems. As a homeostatic regulatory system, it has several putative characteristics found in other regulatory systems with biophysical, biochemical and physiological regulatory functions, operating from the molecule to the organ/system.

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Foreword

The book "Mechanosensitivity in Cells and Tissues: Mechanosensitive Ion Channels" edited by Andre Kamkin and Irina Kiseleva impressively demonstrates the diversity of cellular effects depending on mechanical stimuli. Coming from basic biophysical mechanisms of mechanosensitivity of the lipid bilayer, ionic channels including K^+, Cl^-, and nonselective channels in bacteria as well as in eukaryotic multicellular organisms are reviewed. Examples demonstrating the physiological role of mechanosensitive channels in cellular and organ physiology include odontoblasts and chondrocytes. Moreover information is given on mechanosensitive signaling cascades in articular chondrocytes, osteoblastic and mesenchymal stem cells as well as on in neuronal and cardiac cells where mechanosensitive cation channels are described.

When I was asked to write the foreword to this compelling book I doubted about what I as a stem cell researcher could say about mechanosensitivity of cells? But looking at the more recent studies in this field, and in particular on detailed insights in the earliest events of cellular development in the embryo – eureka - mechanical effects including migration and mechanosensitivity turn out to be ones of the most primal and archaic mechanisms of self organisation. Cellular mechanosensitivity is probably the most basic biological principle that is presumably expressed in every cellular phenotype and plays a pivotal role in manifold physiological mechanisms and especially in early embryonic development. There is compelling evidence that physical forces, including gravity, tension, compression, pressure and shear forces influence growth and remodelling in nearly all living tissues on a cellular level. Proliferation, growth, differentiation, secretion, movement, signalling as well as gene expression have been shown to be altered by applying mechanical stress directly to the respective cells. In parallel with the identification of more and more cellular targets of mechanosensitivity there is an increasing interest of basic and applied scientists in this field. Just looking at the number of publications in Pubmed[1] as a measure of the scientific impact which well reflects the interest of the scientific community in this specified research area, one can identify a dramatic rise of interest within the last year. While the field of mechanosensitivity attracted around 100 papers per annum from 2000 to 2005 the number immensely jumped to more than 450 in the year 2006.

[1] Pubmed-listed publications with the term "mechanosensitivity" in the title/abstract

This might also be due to the fact that great technological advances in areas such as nanotechnology, micromanipulation, biological imaging and computer modelling have enabled us to analyze mechanotransduction: how forces affect the biochemical activities of individual molecules, both in isolation and within living cells. Also, the detailed analysis of mechanosensitive ionic channels using 2D crystallography, electronparamagnetic resonance spectroscopy, fluorescence resonance energy transfer spectroscopy as well as computational modelling based on molecular dynamics and Brownian dynamics gave a new impact in this field. Mechano-regulation is once again becoming a central focus in fields ranging from molecular biophysics and cell biology to human physiology and clinical medicine.

The present book demonstrates the various aspects of mechanosensitivity. It thus considerably contributes to a better understanding of the primary processes in cellular mechanosensitivity and highlights the electrophysiological responses. Together with other well known signalling cascades directly coupled to the cytoskeleton and thus to cellular mechanical responses our picture on these important signalling processes becomes more and more detailed and hopefully will integrate into the complex cellular processes such as embryonic development and differentiation of cells as well into the complex physiological organic functions.

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Editorial

Mechanically Gated Channels and Mechanosensitive Channels

Andre Kamkin and Irina Kiseleva

Cell reaction to mechanical stress is one of the oldest cellular functions from the point of view of evolution. Response to mechanical stress in different forms is present in all organisms, from bacteria to mammals. Mechanical stimulus triggers different electrophysiological and biochemical responses in cells. It can influence physiological processes at the molecular, cellular, and systemic level. During last 20 years there was major progress in both phenomenological description of cell membrane responses to mechanical stress and in investigation of signaling pathways and mechanism underlying cellular responses to mechanical stress. Ion channels, reacting to membrane deformation, were shown to play the key role in one of the mechanisms, through which the cell responds to mechanical stimulus. This channels were originally called mechanosensitive channels (MSC). Creation of the patch clamp method allowed Guharay and Sachs (1984) to record first whole cell MSC currents.

Present book is devoted to discussion of the latest findings in the field of MSC research. The Volume was compiled by a group of scientists from all over the world, who are considered to lead the development of the field. The book comprises three parts, first discussing mechanosensitive channels, second–mechanosensitive signaling and the third–cell mechanobiology. At the same time such set up of reviews is rather conventional and is designed for the readers convenience since all presented topics intersect.

The first part presents topics dealing with mechanosensitive channels. MSC is a channel whose conductivity is a response to membrane deformation. At the same time back in 1998 Sachs and Morris noted that among MSCs under investigation there are channels, that recognize mechanical deformation as a proper physiological signal, and those, that react to mechanical stimulation with slight changes in kinetics. For the latter channels the authors introduced the term—channels with weak mechanosensitivity (Sachs and Morris, 1998). Recent findings call for new definitions and new specific terminology.

Ability of mechanosensitive ion channels to change their spatial organization from closed to open state during the transition period presently is considered to be their major distinctive characteristic, while permeability modulation of voltage-gated channels and ligand-gated channels during mechanical stress can no longer be used for defining a channel as one properly responding to mechanical stress (Sachs

and Morris, 1998), although all channels that recognize mechanical deformation as a proper 2 physiological signal have been called—mechanically gated channels (MGC)—by a number of authors (Hamill and Martinac, 2001; White, 2006; Zhang and Hamill, 2000).

Many authors divide mechanically gated channels (MGC) into stretch activated channels (SACs) that underlie mechanically gated whole-cell current during cell stretching and are registered under pipette (although their identity as SACs has not been proven), and volume activated channels (VAC) for the second corresponding category of channels (Baumgarten et al, 2005).

Recent works by Honoré et al, (2006) and Sunchya & Sachs (2007) show that SICs, isolated earlier into a separate group, are most probably typical SAC channels in pre-stretch state. As for PACs, their existence remains questionable considering implications of Laplaces law. Those issues are addressed by Kamkin et al. in the first Chapter of present Volume (Kamkin et al, 2007).

Mechanosensitive channels (MSC) as a term recently is usually used to describe channels that only modulate their permeability in response to mechanical stress (Morris et al, 2006). Definition of this term in such way allows further division of MSCs into two groups—mechanosensitive voltage-gated channels (MSCVG) and mechanosensitive ligand-gated channels (MSCLG).

At the same time during preparation of Chapters of this Volume we did not insist on strict use of this novice definition. Therefore in many Chapters, including our own, traditional abbreviations are used for readers convenience and according to the context MSC can mean either MGC or MSC.

The first part of the Volume begins with a Chapter, devoted to experimental methods of studying MSC and possible mistakes in data interpretation (Kamkin et al, 2007). Authors discuss the most widely used experimental methods, which are used in the field of MSC research, and their limitations. The following Chapter deals with the role of lipid bilayer mechanics in functioning of mechanosensitive channels, that respond to membrane tension. The authors discuss the role of bilayer deformation in the context of the well known mechanosensitive channel MscL (Ursell et al, 2007). It is followed by discussion of mechanosensitive channels, which are gated by membrane tension. It goes without saying that transformation of mechanical stimulus into biological response is one of the most exiting problems in physiology, pathology and practical medicine. The authors discuss two different theoretical models of it which are used now. The first one is based on the assumption that channels are 'tethered' to cytoskeleton and/or to extracellular components, which thus exert forces on the channel, which in turn leads to gating. The second model postulates that the channel protein directly senses biophysical changes that occur within the membrane, when it is under tension (Blount et al, 2007). The discussion is continued in the following Chapter, which is describing studies of the bacterial mechanosensitive channels. It elucidates the nature of the imaged structures of the protein, the interactions between the protein and the lipid, the conformational changes, which are involved in channel gating, and the specific roles played by various protein 3 domains (Martinac and Corry, 2007). The reader, interested in bacterial MSC research, can acquire useful insight into mechanosensory transduction in simple animal models, such as the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*

(Kourtis and Tavernarakis, 2007). Further discussion concentrates on mechanosensitive ion channels in odontoblasts, which are post-mitotic cells, involved in the dentine formation throughout the life of the tooth and which are suspected to play a role in tooth pain transmission. Two kinds of mechanosensitive K^+-channels are discussed: TREK-1 channels, belonging to the two-pore-domain potassium channel family, and high-conductance Ca^{2+}-activated potassium channels (K_{Ca}), activated by stretching of the membrane as well as osmotic shock. (Magloire et al, 2007). The discussion of the topic is further broadened by the Chapter discussing K^+-channels in articular chondrocytes, their putative roles in mechanotransduction, metabolic regulation and cell proliferation (Mobasheri et al, 2007). Recent studies have indicated that SAC, integrins, growth factor receptors, cytoskelton, extracellular matrix and other various molecules contribute to the osmotransduction. However, little is known about how these molecules sense the osmotic and mechanical stresses and how they function in order to transduce the stress downstream their signaling cascade. Separate Chapter deals with osmotransduction through volume-sensitive Cl^- channels (Niisato and Marunaka, 2007). The final Chapter in the first part of the Volume is devoted to mechanosensitive channel TRPV4. It is known that the TRPV4, a member of the TRP family, that has 6-transmembrane domains, was initially identified as a hypoosmolality-activated Ca^{2+} permeable channel. Recent findings suggest that TRPV4 along with other molecules together constitute a physiological response, such as cell volume regulation, epithelial permeability, and vascular dilatation (Suzuki, 2007).

The second part of the Volume deals with discussion of mechanotransduction, which is defined as the biochemical response of cells to mechanical stimulation (Pingguan-Murphy and Knight, 2007; Liedert et al, 2007, Calaghan, 2007). This part of the Volume describes signaling cascades, which participate in modulation of mechanosensitive channels function (Pellegrino, 2007), and discusses regulation of intracellular signaling transduction pathways by mechanosensitive ion channels (Boriek and Kumar, 2007).

Up to date several stretch-activated signaling pathways have been identified. In 2004 Lammerding et al. and in 2005 Lab described cardiac specific schemes of signal transduction pathways, which are involved in the cellular response to mechanical stimulation. Their generalizations united multiple experimental observations into a comprehensive theoretical model of mechanosensitivity, which may become very useful for generation and testing of novel hypothesis further promoting development of the field. At the same time Cingolani et al., 2005 reported their scheme of hypothetical intracellular hypertrophic pathway, triggered by myocardial stretch, and Liedert et al., (2005) presented their model of signal transduction pathways in 4 mechanotransduction in bone cells. First three Chapters of the second part of our Volume deal with those topics.

Current research in our field goes beyond investigation of the stretch-activated signaling cascades into advocating the possibility that mechanoelectro-chemical transduction forms a part of a network of mechanically linked crosstalk (Mechanically Mediated Crosstalk: MMC) (Lammerding et al, 2004; Lab, 2005). Mechanical components can hypothetically provide the bond between interactions at molecular, cellular, and macro levels to enable such crosstalk. Although our Volume focuses

on stretch activated channels, stresses and strains can affect functioning of other membrane channels or receptors, which are located downstream signaling cascades, which include SACs. A cellular mechanical transformation can thus trigger several different short and/or long term ionic or other downstream responses. Several cell signaling cascades have been implied and, mostly via intracellular Ca^{2+}, can affect membrane electrophysiology. MMC can shape downstream signals leading to alterations of intracellular Ca^{2+} signaling. MMC can also span other regulatory systems and processes, such as the autonomic nervous system, and in addition, can operate through the whole heart as an integrative system (Lab, 2005).

The first Chapter of this part is devoted to mechanosensitive purinergic calcium signaling in articular chondrocytes (Pingguan-Murphy and Knight, 2007). In some respect it intersects with Chapter 7 by Mobasheri et al (2007), while focusing on the influence of physiological mechanical stimuli on intracellular Ca^{2+} signalling in articular chondrocytes and its potential role in cartilage mechanotransduction. This review examines the downstream cellular response to mechanically-activated purinergic Ca^{2+} signaling and its importance in maintenance of tissue homeostasis (Pingguan-Murphy and Knight, 2007). Next Chapter discuses involvement of mechanotransduction in various signal transduction pathways, including the activation of ion channels and other mechanoreceptors in the membrane of the bone cell, resulting in gene regulation in the nucleus (Liedert et al, 2007). Next Chapter of this part of the Volumedescribes the role of caveolae in stretch-activated signaling. The review sums up the latest data relating to the role of caveolae in Ca^{2+} regulation, role of caveolae in G protein-coupled receptor signal cascades and the role of caveolae in mechanotransduction. In this Chapter authors also discuss the relationship between mechanotransduction, caveolae and disease (Calaghan, 2007).

The role of signaling cascades in modulation of MSC in the central nervous system is discussed in terms of leech neurons model in the next Chapter. It covers multimodal activation by membrane potential, intracellular calcium and pH, as well as powerful modulation by adenosine nucleotides (Pellegrino et al, 2007).

Boriek and Kumar (2007) in their Chapter discuss the role of MSC in the regulation of different mechanosensitive signaling proteins and signaling pathways. They describe how mechanical stretch causes Ca^{2+} and other ions influxes through the MSC and how this leads to the 5 activation of signaling cascades, leading to activation of several kinases and phosphatases. They conclude that activation of these intermediate signaling molecules leads to the activation of transcription factors leading to the increased expression of mechanosensitive genes. Chapter reveals how an increased Ca^{2+} influx in response to mechanical stretch could also lead to the activation of these transcription factors via Ca^{2+}-responsive proteins, such as protein kinase C (Boriek and Kumar, 2007).

The third part of the Volume is devoted to cell mechanobiology. First Chapter of this part of the Volume describes the effects of mechanical stimulation in vertebrate hearts. It contains discussion of differences in vertebrate hearts and myocyte structures, and the effect of stretch on cardiac force and electrical activity (Shiels and White, 2007). Final Chapter of the Volume provides a throughout discription of mechanobiology of fibroblasts. The authors focus on mechanobiological responses

of fibroblasts and on fibroblast specific cellular mechanotransduction (Thampatty and Wang, 2007).

The volume dwells on the major issues of mechanical stress influencing the ion channels and intracellular signaling pathways. In our opinion the book presents the latest achievements in the field and provides a broader vision of the field to experts, working on related topics of fundamental and clinical research. It can also provide a useful insight for practicing physicians, which can improve their understanding of cellular mechanisms, underlying different pathologies. We also hope that this Volume will attract more attention to the field both from researchers and practitioners and will assist to efficiently introduce it into the practical medicine.

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