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Mechanosensitive ion channels

An evolutionary and scientific tour de force in mechanobiology

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Mechanosensitive (MS) ion channels are to date the best characterized biological force-sensing systems. They present the best example of coupling protein conformations to the mechanics of the surrounding cell membrane. Studies of MS channels conducted over the last 28 years have from their serendipitous discovery[1,2] and confusion about their artifactual nature[3] to their molecular identification[4-6] and structural determination[7-10] greatly contributed to our understanding of molecular mechanisms underlying the physiology of mechanosensory transduction.

Mechanotransduction is ancient, dating back some 3.8 billion years when the first life forms appeared of which microbes form the largest group.[11] Diversity, number and adaptability of microbial cells enabled them to populate all kinds of environments supporting life. Mechanical forces primordial cells must have sensed and responded to first resulted predominantly from osmotic pressure intrinsically linked to the essential role that water plays for the existence of life. MscL and MscS channels, whose discovery in bacteria[12,13] coincided inherently with the advent of the patch-clamp technique,[14] serve today as a paradigm for mechanosensory transduction. They are currently the best biophysical models used to study molecular principles of mechanosensory transduction.[15-17] Their primary function is that of emergency valves releasing excess osmolytes upon hypo-osmotic stress to which bacterial cells become exposed in their living environments.[5,17]

In cells and tissues of eukaryotes, MS ion channels were first documented in patch clamp experiments by exposing membrane patches of red blood cells to hypotonic shock[18] or by applying negative pressure to membrane patches of frog muscle[1] and chick skeletal muscle cells.[2] Despite much electrophysiological information, molecular characterization of the MS channel role in mechanotransduction in eukaryotes has been slow compared with the progress made in the research on bacterial MS channels. This is because of the experimental advantages bacteria offer for molecular biological, biochemical and structural work, which greatly facilitated the cloning and crystallization of bacterial MS channels.[19,20] The crystal structure of the human MS ion channel TRAAK, a member of the two pore domain K+ channel family controlling the resting membrane potential in neuronal cells, has only very recently been solved and reported.[9]

In animals and humans, MS ion channels function as molecular transducers of mechanical stimuli in senses of hearing and touch, blood pressure and cell volume regulation, as well as stretch-induced stimulation of muscle and bone development, for example.[21-23] With regards to pathology of various diseases scientific and medical communities have in recent years become increasingly aware of the role that MS channels apparently play in heart hypertrophy and arrhythmias, muscular dystrophy, polycystic kidney disease, neuronal degeneration and tumor metastasis.[24-28] Most recently, a new exciting development presents a discovery of a family of eukaryotic MS ion channels that has been identified in insect, animal and human cells called Piezo, whose name is derived from the Greek piezein meaning "to squeeze or press".[29,30] Although the research on Piezo1 and Piezo2 channels[31,32] is still very young and the mechanism by which the Piezo channels sense stress will require detailed measurements to identify functional components involved in their gating by mechanical force they seem to function mainly in mechanosensory transduction underlying senses of touch and pain. When the cell experiences stress, they are signaling the organism that an appropriate physiological response is required. Furthermore, a recent study indicated that Piezo1 could play a vital role in maintaining homeostatic cell numbers in epithelia.[33] In addition, two mutations in Piezo1 have been shown to cause a condition called Xerocytosis, a hereditary disease characterized by the inability to regulate cell volume of red blood cells.[34] Hence, the Piezo channels are the first type of MS channels documented to underlie a human disease linked to mechanical pathologies. Finally, another very recent study suggested that loss of Piezo1 expression could cause increased cell migration and metastasis in lung tumors.[35]

This special issue of *Channels* assembles 11 papers from a number of leading scientists working in the MS channel field. Out of eight research papers, two papers describe the role TRP-type MS channels play in the physiology of skeletal muscles[36]and pathology of prostate cancer (see also the cover of this special issue).[37] Four papers focus on bacterial MS channels. The first one describes novel insights into the functioning of the large conductance MscL channel,[38] whereas the second study is using computational analysis of the MscL gating mechanism to determine the amino acid residues which by sensing membrane tension promote the channel opening.[39] This is followed by a report on the behavior of the small conductance MscS and MscK channels under extreme conditions of high hydrostatic pressure[40] and the first description of YnaI, YbiO and YjeP (MscM), the three novel types of MS channels identified in

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E. coli,[41] in the third and the fourth paper, respectively. One of the two remaining research papers compares the gating properties of the Piezo1 channels in the whole-cell and cell-attached patch recording modes,[42] whereas the second one describes modulation of the voltage-gated $Na_v1,5$ channels by local anesthetics.[43] That voltage-dependent Na^+ channels[44,45] as well as K^+ and Ca^{2+} channels,[46] could also play a role in mechanosensation has previously been suggested. This notion is further substantiated by a very recent report showing that small physiologically relevant changes in membrane tension can cause a shift in the voltage range over which voltage-gated K^+ channels normally operate.[47] In addition to these research papers three reviews are part of this special issue. The first one summarizes up-to-date knowledge of the Piezo family of MS channels.[48] It discusses their role as key players in responses of eukaryotic cells to mechanical stimuli and comments on their involvement in a disease resulting from mutations in Piezo1. The second review focuses on the regulation of MS channel function by membrane lipid mechanics. It further discusses similarities between responses of pore-forming antimicrobial peptides and bacterial MS channels to membrane tension and elaborates on the usefulness of these peptides as models for studies of general principles underlying activity and evolution of MS channels.[49] Finally, the third one provides a succinct overview of mammalian touch receptors, summarizes their complex role in mechanosensory transduction pathways of the touch reception and links their function to the recent studies on mechanosensitive ion channels suspected to serve as the primary transducers of various types of innocuous and noxious mechanical stimuli.[50] Although the limited selection of papers in this issue cannot do justice to all the great achievements of many scientists working in the field, it presents a cross-section of recent significant contributions that have advanced our understanding of the structure and function of these fascinating membrane proteins.

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