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Review

The ion channels to cytoskeleton connection as potential mechanism of mechanosensitivity ☆

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ABSTRACT

As biological force-sensing systems mechanosensitive (MS) ion channels present the best example of coupling molecular dynamics of membrane proteins to the mechanics of the surrounding cell membrane. In animal cells MS channels have over the past two decades been very much in focus of mechanotransduction research. In recent years this helped to raise awareness of basic and medical researchers about the role that abnormal MS channels may play in the pathophysiology of diseases, such as cardiac hypertrophy, atrial fibrillation, muscular dystrophy or polycystic kidney disease. To date a large number of MS channels from organisms of diverse phylogenetic origins have been identified at the molecular level; however, the structure of only few of them has been determined. Although their function has extensively been studied in a great variety of cells and tissues by different experimental approaches it is, with exception of bacterial MS channels, very little known about how these channels sense mechanical force and which cellular components may contribute to their function. By focusing on MS channels found in animal cells this article discusses the ways in which the connections between cytoskeleton and ion channels may contribute to mechanosensory transduction in these cells. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters. This article is part of a Special Issue entitled: Reciprocal influences between cell cytoskeleton and membrane channels, receptors and transporters. Guest Editor: Jean Claude Hervé.

Contents

1. Introduction

Mechanical force acts upon physical contact. It can compress, bend, break, stretch and twist a material. All living cells have the ability to transduce mechanical forces. Applied to the sensory physiology of animals and humans this force manifests itself in general senses of touch, pain, pressure, vibration or proprioception, as well as in hearing as a special sense. Mechanical force sensing possibly arose some 3.8 billion years ago with the appearance of the first unicellular organisms [1], which were frequently exposed to sudden changes in osmolarity of their living environments. Coping with osmotic forces acting on cell membranes of primordial microbes, was very likely the first form of mechanosensory transduction in living cells with mechanosensitive membrane proteins as the prototype of mechanical force sensors. Similar to mechanosensitive channels found in bacteria these proto-mechanosensors were designed to protect the proto-microorganisms from sudden changes in external osmolarity [2,3]. However, it should be mentioned that osmolarity regulation also accompanied the first metabolism and who came first is not clear.

Mechanosensitive (MS) channels are currently considered to be the major mechanosensors transducing mechanical stimuli exerted on membranes of living cells into electrical or chemical intracellular signals

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and are together with cytoskeleton and, most notably muscle, firmly established biological mechanosensors [4–6]. This is certainly the case in bacterial cells, which harbor two types of MS channels belonging to the MscL and MscS families of membrane proteins [7]. Opening of MscL and MscS by mechanical force protects bacterial cells from bursting when challenged by hypo-osmotic shock [8]. The force transmission occurs through the lipid bilayer alone and no other cellular component in the form of an associated protein is required for the activation of the bacterial MS channels. This type of gating MS channel by mechanical force is referred to as the "bilayer mechanism" [2]. Unlike bacterial cells, animal cells lack the rigid cell wall. They possess instead, an excess membrane area in the form of ruffles, folds, and microvilli, which protect the membrane bilayer from excessive strain. The excess membrane area is supported by extracellular matrix (ECM), which serves as external scaffolding, and cortical cytoskeleton (CSK), whose contraction and expansion locally regulate the mechanosensitivity of MS channels in animal and human cells [9]. In this context it should be mentioned that AFM analysis of cell volume regulation suggested that during osmotic swelling cells did not become stiff but became softer [10] contrary to the expectation that the cell membrane should act as the constraining element upon a hypoosmotic challenge. This result seems consistent with the notion that cytoskeleton could act as a cross-linked gel, which finds support in the fact that cells can be exposed to 7 atm of osmotic pressure [10] that would produce much more strain than it can be absorbed by membrane ruffles [11–19].

Although several different types of animal ion channels including NMDA receptors [20], TREK-1 potassium channel [21] and TRPC1 ion channels [22] can be activated by tension developed in the lipid bilayer, other types of MS channels including MEC-4/MEC-10, TRP or Piezo channels may in addition to the lipid bilayer, require cytoskeletal-matrix linkages for their proper function (Table 1). One of the key studies that provided the first clue that animal cell MS channels were not strictly gated by a tethered mechanism was reported by Zhang et al. [23]. This study was significant in that it provided the motivation for subsequent successful attempts to demonstrate that animal cell MS channels can be reconstituted and activated by membrane tension in pure lipid bilayers. Furthermore, it indicated that the CSK may serve the role of modulating the dynamic gating of bilayer gated MS channels. Actually, mechanotransduction in cells of animals and humans may involve a variety of mechanosensory mechanisms based on cytoskeleton and extracellular matrix as force-transducing cellular components [24]. Since both ECM and CSK structures may be involved to tethering to MS transduction channels this model of MS channel gating by mechanical forces has been referred to as the "dual-tether model" and was first proposed for vertebrate hair cell transduction [6].

The aim of this article is to provide a brief overview of the present knowledge and ideas about potential mechanism of mechanosensitivity involving connections between cytoskeleton and MS channels in animal cells.

2. Animal hair cell model of MS channel activation

The ability of the auditory system to detect the dynamic range of sound encompassing over six orders of magnitude with sensitivity at atomic dimensions presents an evolutionary masterpiece in development of sensory physiology in higher eukaryotes [24]. At the centre of the sound detecting system are the hair cells of the inner ear. These acoustic sensory receptors are finely tuned structural components located in the hair bundle organelle (Fig. 1A). Stereocilia slide with respect to each other upon deflection of the hair bundle (Fig. 1B), which causes stretching of the tip link. The resulting tension in the hair cell membrane activates mechanoelectric transduction channel (Fig. 1C), whose gate is believed to be coupled to a cytoskeletal elastic element of unknown identity [25]. The connection between the hair cell cytoskeleton and the mechanosensitive transduction channel enables the channel to open and close very rapidly without moving the hair bundle.

The "gating spring model" [26] of the animal hair cell is typical for the "tethered model" of mechanotransduction as opposed to the "bilayer model", which was briefly mentioned with regard to the gating of bacterial MS channels [2]. In the tethered model mechanical force is assumed to originate from a cytoskeletal component, which acts as a gating linker connected to the mechanotransduction channel (Fig. 1C). (Given that the elasticity or springiness of tip links is unknown and elasticity of the channel could provide compliance sufficient for mechanotransduction "gating spring" is here and further in the text referred as "gating linker"). Whereas the model shown in the figure places the transduction channel close to the upper end of the tip link current models of the hair cell place the channel only at the lower end of the tether [27]. This was conclusively shown in recent Ca^{2+} imaging experiments of the stereocilia using hair bundles of rat inner hair cells [28]. In contrast to bullfrog hair cells inner hair cells of the rat have three rows of large-diameter stereocilia, which provided sufficient spatial and temporal resolution for unambiguous localization of the transduction channel at the lower end of the tip link.

Despite many years of research, the identities of the channel and gating linker remain elusive. Several types of MS channels characterized in other mechanotransduction systems have been suggested as candidates for the hair cell MS transduction channel. Members of the DEG/ENaC family, the P2X family, as well as the TRP family are among the candidates [25]. TRPA1 has caused much excitement in this respect because of its localization in hair cells, functional properties and 17 ankyrin intracellular domains characteristic of TRPA1, which were suspected to play a role of the gating linker [29]. However, the knockout mice lacking TRPA1 did not show any hearing deficits [30]. Instead, these mice exhibited reduced sensitivity to noxious cold, mustard oil and bradykinin, the known activators of TRPA1 [31]. Furthermore, given the functional properties of the hair cell MS transduction channel, which include a conductance of 300 pS suggesting a large channel pore, high permeability for Ca^{2+} and large organic molecules such as aminoglycosides or a fluorescent styryl dye, none of these candidate channels fulfils these requirements [32]. The transmembrane proteins TMC1 and TMC2 are necessary for hair cell mechanotransduction and hence have also been considered as potential candidates for the transduction channel [33,34], although no evidence has been provided for their function as ion channels.

With regard to the gating linker, significant progress has recently been made by identification of components of the mechanotransduction machinery of hair cells (Fig. 1D). Besides the tip links formed by cadherin-23 (CDH23) homodimers other proteins including the tip-link component PCDH15, the motor protein myosin 7A (Myo7A) and the adaptor proteins harmonin and sans, a Myo7A-binding protein, are the essential components of the mechanotransduction machinery. This is because tip links of stereocilia are thought to confer high directional and vibrational sensitivity on the mechanotransduction process in the hair cells. Given that the stiffness of myosin was determined to be in the range 0.7–2.0 pN/nm [35] similar to the stiffness of the gating linker [36], this level of compliance makes myosin a good candidate for the gating linker of the MS transduction channel. The tetraspan TMHS of stereocila has recently been added as another important component of the mechanotransduction machinery [37]. It binds to PCDH15 and regulates tip-link assembly. Disrupting this process causes deafness as demonstrated by Tmhs mutations in hurry-scurry (hscy) mice [38].

Despite the progress made in studies of hair cell mechanotransduction the molecular identity of the hair cell mechanotransduction channel remains unknown and there are no experimental data showing direct connections between the MS transduction channel and an accessory protein [29], which are required for its function. Consequently, as an alternative hypothesis the possibility of lipid gating of animal channels has been considered by many researchers [4,6,20,22,39–42]. Very recently this hypothesis has been made more general by connecting it to membrane lipid rafts [43]. In this model the lipid bilayer may also serve not only as the gating linker in hair cells, but a cholesterol- and

Table 1
Diversity of ion channels involved in mechanosensory transduction. ECM (extracellular matrix) CSK (cytoskeleton) *Amphipaths (GsMTx4, PUFA's, membrane phospholipids), APB (2-aminoethoxydiphenyl borate). g = conductance, pS = 10^{-12} A. Modified from [78]; with permission.

MS ion channel	Gating mechanism	Voltage sensitivity	g (pS)	Ionic selectivity	Oligomer	Block	Refs
ENaC	Membrane tension, CSK/ECM, cholesterol-rich domains	Voltage independent	10	P_{Na}/P_K = 5–100 P_{Ca}/P_K ~ 0.4	Tetramer	Amiloride, pyrazinoyl quaternary amines	[78,81,6,130–133]
TRPC1	Lipid bilayer Amphipaths*	Voltage independent	20	Ca^{2+} permeable Non-selective	Tetramer	La^{3+}, $Gd3^{+}$,	[78,103,112,99,134–136]
TRPC6	Amphipaths (lipid bilayer?)	Inward/outward rectification	31	Non-selective P_{Ca}/P_{Na} = 5	Tetramer	GsMTx-4, Gd^{3+}	[78,103,94,137,99,134,135]
TRPV1	ECM	Voltage independent	1.3–2.2	Non-selective P_{Ca}/P_{Na} = 3.8 (heat), 9.6 (vanilloids)	Tetramer	Neomycin, A-425619, ruth. red	[103,78,138,135]
TRPV2	ECM?	Inward rectification	~60	Non-selective P_{Ca}/P_{Na} = 3	Tetramer	Ruth. red, La^{3+}	[78,103,139,135]
TRPV4	ECM Amphipaths (lipid bilayer?)	Voltage independent	~90	Cation-selective P_{Ca}/P_{Na} = 6	Tetramer	Ruth. red	[78,105,140,141,134,135]
TRPM3	Membrane tension, Sphingolipids	Voltage independent	65–133	Non-selective P_{Ca}/P_{Na} = 1.6, Mn^{2+}	Tetramer	La^{3+}, Gd^{3+}, 2-APB	[78,109,107,135,142]
TRPM4	Membrane tension	Voltage dependent	25	Monovalent cations	Tetramer	ATP	[78,143,144,142]
TRPM7	Membrane tension	Outward rectification	105	Cation-selective P_{Ca}/P_{Na} = 3	Tetramer	Gd^{3+}, ruth. red, sphingosine FTY720	[78,108,135,145,146]
TRPP1 TRPP2	CSK	Voltage independent	~2–3 × 10^3 (−100 mV) 3–4 × 10^3 (+100 mV)	Cation-selective Na^+, K^+, Ca^{2+}	Tetramer, di-trimer	Gd^{3+}, GsMTx-4	[78,147–149,135]
TRPA1	CSK, lipid bilayer	Depolarization re-opening	~100	P_{Ca}/P_{Na} = 0.8	Tetramer	Gd^{3+}, ruth. red	[78,135,142]
TREK1 2P-type K^+ channel	Membrane tension Amphipaths (lipid bilayer?)	Outward rectification	84–116	K^+ selective	Dimer	Gd^{3+}, Mg^{2+}, amlodipine, amiloride	[78,114,150,151]
TREK2 2P-type K^+ channel	Membrane tension Amphipaths (lipid bilayer?)	Inward rectification	65–179	K^+ selective	Dimer	Mg^{2+}, Ba^{2+}	[78,152,153]
TRAAK 2P-type K^+ channel	Membrane tension Amphipaths (lipid bilayer?)	Inward rectification	66–110	K^+ selective	Dimer	Gd^{3+}, amiloride	[78,114,154,155,151]
NMDA receptor	Lipid bilayer Amphipaths ECM	Voltage dependent Mg^{2+} block	45–60	Cation selective Ca^{2+} permeable Divalent cation block	Tetramer	Mg^{2+}	[78,156,20,157]
Piezo 1	Lipid bilayer (?)	Voltage independent		Cation selective Na^+, K^+, Ca^{2+} and Mg^{2+}	Tetramer	GsMTx-4, Gd^{3+}, ruth. red	[124,121,120,122,158]
Piezo 2	Lipid bilayer (?)	Voltage independent		Cation selective Na^+, K^+, Ca^{2+} and Mg^{2+}	Tetramer	Gd^{3+}, ruth. red	[120,121,158]

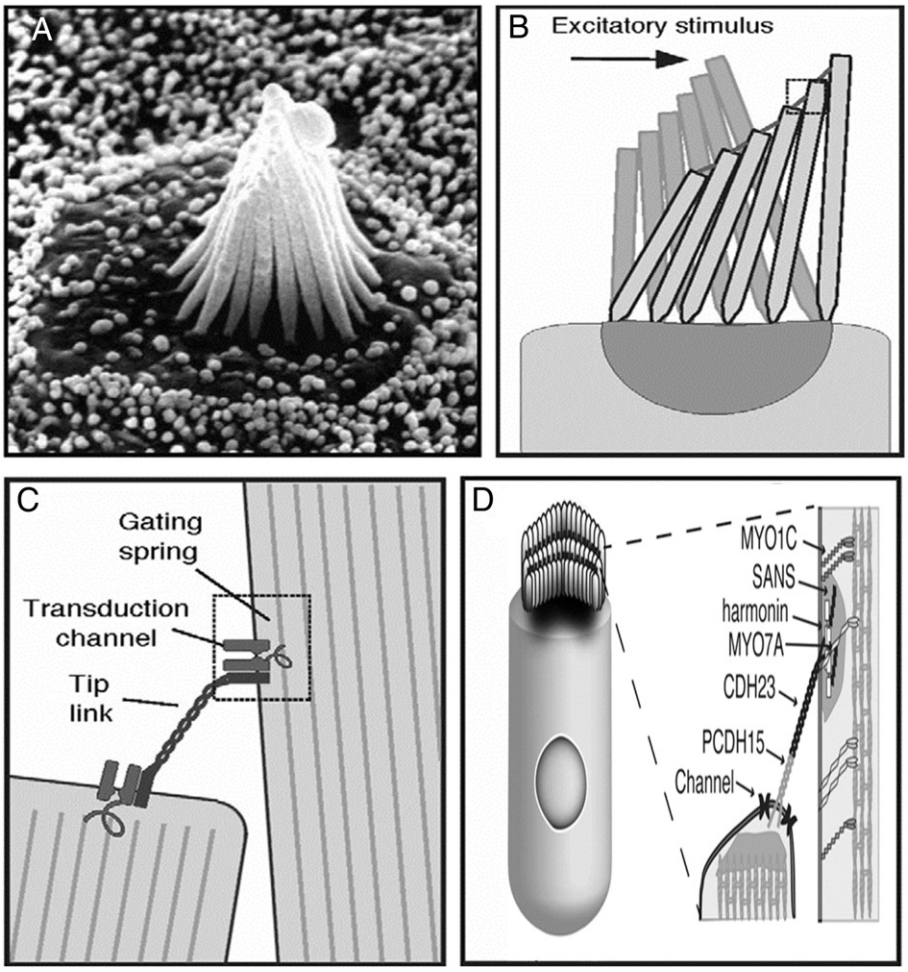

Fig. 1. Model of hair cell mechanotransduction. (A) Scanning electron micrograph of the bullfrog's sacculus hair bundle. (B) Deflection of the hair bundle (arrow) causes sliding of stereocilia slide with respect to each other. (C) The membrane tension is transmitted to the mechanosensitive transduction channel by stretching the tip link. (D) Components of the hair cell cytoskeleton that form tip links are located in proximity to tip links of hair cells. The gate of the transduction channel is coupled to an elastic tip link element of unknown identity, which allows the mechanosensitive transduction channel to open and close rapidly.
Adapted with permission from [25] and [37].

sphingolipid-enriched lipid environment, such as in lipid rafts, may also take a role of the "spring" transmitting the mechanical force to MS channels in general. The idea that domains such as lipid rafts can contain channels, whose function is affected by channel clustering within such domains, is not new [44,45]. Moreover, recent work on bacterial [46–48] as well as Piezo 1 MS channels [49] indicates that channel interactions in domains are defined by the channel clusters themselves for which the lipid bilayer acts as the "spring" transmitting mechanical stimuli.

The newly proposed mechanism of lipid-rafts playing a role of the spring presents a hybrid between the lipid bilayer mechanism proposed for gating bacterial MS channels over 20 years ago [2,50] and the tethered mechanisms frequently used to explain gating by mechanical forces of MS channels in animal cells [9,51,52]. This model seems to be supported by the fact that salicylate, an anionic amphipath, reduces hearing and suppresses some forms of otoacoustic emissions, whereas chlorpromazine, a cationic amphipath, shifts the operating range of outer hair cell nonlinear capacitance and electromotility up to 30 mV in the depolarizing direction [53]. Consequently, similar to bacterial and some eukaryotic MS channels shown to be activated by the bilayer tension and amphipaths [20,50,54] the transduction channel in hair cells may also be affected by the changes in the transbilayer pressure profile caused by insertion of amphipathic compounds into one of the leaflets of the lipid bilayer [55]. In addition, cholesterol- and sphingolipid-enriched lipid rafts [56] were previously proposed to control the mechanosensitivity of ion channels based on experiments showing that mechanosensitivity of gramicidin A could be switched from stretch activation to stretch inactivation by subnanometer changes in thickness of the lipid bilayer, which may occur if an ion channel is moving between the thinner lipid bilayer and a thicker lipid raft [57]. Further indication for ion channel regulation by membrane cholesterol and lipid rafts comes from a recent study showing that inhibition of stretch-activated channels in human leukemia cells after cholesterol depletion was mediated via actin remodelling initiated by disruption of lipid rafts [58]. That the channels in leukemia cells were affected by cholesterol depletion is not the proof for a causal relation between disruption of lipid rafts and inhibition of MS channel activity, although the correlation between the two suggests a possibility of the two phenomena being causally related.

3. Cellular force foci

Animal cells are constantly subjected to compression, shearing, and stretch due to contraction of the CSK, change in volume or shape to compensate for the effects of external forces. In either instance, cells are adapting at the microscale. More than a decade ago, a hypothesis was put forward that conformational changes in MS ion channels mediating conversion of mechanical stimuli into electrical or chemical signaling are involved in surveying and regulating cellular dynamics and the

elaborate biochemistry that controls the distortion of the cell membrane [59]. Similar to MS transduction channels in hair cells a direct connection of MS channels to the CSK and/or ECM may also be essential to confer directional sensitivity to the mechanotransduction processes in neuronal cells such as mechanosensory neurons in *Caenorhabditis elegans* [6] or skeletal muscle cells [60].

External mechanical stimuli acting on cell membranes are focused and distributed throughout the tissue by ECM via the physical coupling between ECM molecules (e.g. fibronectin) and the CSK through integrins. By forming focal adhesions on the surface of animal cell membranes integrins allow mechanical forces to be focused on CSK components, which may mediate directly or indirectly transmission of forces to membrane proteins [61]. To fulfill this role the CSK integrin networks are organized as 'tensegrity' structures prestressing the cells into a state of isometric tension, which is thought to keep the cell shape stabilized by the network of opposing tension and compression elements [62,63]. By balancing steady-state forces the ECM may allow the transmission of fast mechanical oscillations possibly through direct physical connections with MS ion channels. ECM may thus be a device to transmit the force but not one to directly open the channel. To explore whether forces applied to integrins are translated into MS channel activity, magnetic manipulation techniques were used to apply mechanical stimuli directly to integrins via magnetic biobeads [64]. These experiments confirmed that application of a magnetic field led to a rapid increase in intracellular Ca^{2+} in e.g. capillary endothelial cells, which could be suppressed by the MS channel blocker Gd^{3+}, whereas application of magnetic field to magnetic beads attached to non-integrin transmembrane proteins, which do not promote focal adhesions, did not lead to an increase in intracellular Ca^{2+}. ECM–integrin–CSK focal adhesion linkages therefore, seem to be important for gating of some MS channels, because deformation of the cell membrane by itself was not sufficient to activate MS channels and thus cause an increase in intracellular Ca^{2+} concentration.

Another technique based on phalloidin-conjugated plastic fluorescent micro-beads attached to the actin stress fibers was used to explore the involvement of the CSK in MS channel activation from human umbilical vein endothelial cells (HUVECs) [65]. Force was applied by optical tweezers to the actin fibers (Fig. 2) [66]. Simultaneously with the application of traction force by optical tweezers MS channel currents were recorded from HUVECs using the whole-cell patch clamp technique (Fig. 2B). These experiments clearly show that tugging on actin fiber activates MS channels. Since the molecular nature of the channels is unknown, the experiments do not provide evidence for a direct actin-channel interaction. They however, provide compelling evidence for both a tethered mechanism and that internally generated forces may activate MS channels. The recent studies on cell migration that indicate the activation of the GsMTx-4 sensitive MscCa occurs during the migration cycle which is recognized as being strongly actin-dependent in terms of force generation seem to confirm this notion [40]. The force required to elicit MS channel currents was about 5.5 pN (10–12 N) (43). Since the CSK network is highly expandable (area expansion modulus $K_A \sim 10^{-2}$ mN/m) [5] this force strength was sufficient to distort the filament structure of actin stress fibers to the extent sufficient to prevent cofilin from severing the fibers [66]. Note that this force is also sufficient to expand an MS channel protein by 5.5 nm^2 under membrane tension of ~1.5 mN/m (1.5 dyn/cm) [67], which is in the range of membrane tensions reported to gate MS channels [5]. Furthermore, the MS currents activated by traction force were abolished after disassembly of actin stress fibers by cytochalasin-D suggesting that mechanical stimuli were transmitted through actin fibers connected to MS channels [65]. However, this does not exclude involvement of the lipid bilayer in stress distribution.

4. MS ion channels activated by the tethered mechanism

Integrins may either directly bind to certain types of MS channels or associate with macromolecular complexes on the surface of cell membranes and thus indirectly interact with MS channels as documented for DEG/ENaC and TRP ion channels, which led to a proposition that integrins interact with MS channels in focal adhesions [64]. Consequently, in animal cells MS channels may be activated by channeling mechanical forces via integrins across the cell membrane rather than via distortion of the lipid bilayer [68]. It is important to mention here that mechanical stresses in the cell are not uniformly distributed as demonstrated by measurements of local stresses in specific cell proteins by genetically encoded FRET-based force sensors [69–74].

DEG/ENaC ion channels have been shown to mediate responses to gentle touch in *C. elegans* [75,76]. The touch-sensitive channel presumably formed by association of MEC-4 and MEC-10 proteins, is attached to a number of intracellular and extracellular MEC/DEG proteins forming a touch-sensitive complex (Fig. 3A) [6,77]. Mechanical forces such as stretch and shear stress were also reported to activate a structural homolog of the DEG/MEC family of ion channels, the epithelial sodium ENaC channel, which has been associated with touch detection, blood pressure regulation, and hypertension [78]. ENaC is expressed on the apical surfaces of a variety of epithelial cells, where it contributes to salt and water homeostasis by absorption of sodium ions [79]. Although ENaC channels were not mechanosensitive at either the whole-cell or the single-channel level when expressed and investigated for activation by membrane tension in *Xenopus* oocytes [80] ENaCs have nevertheless been linked to the mechanosensory transduction processes because

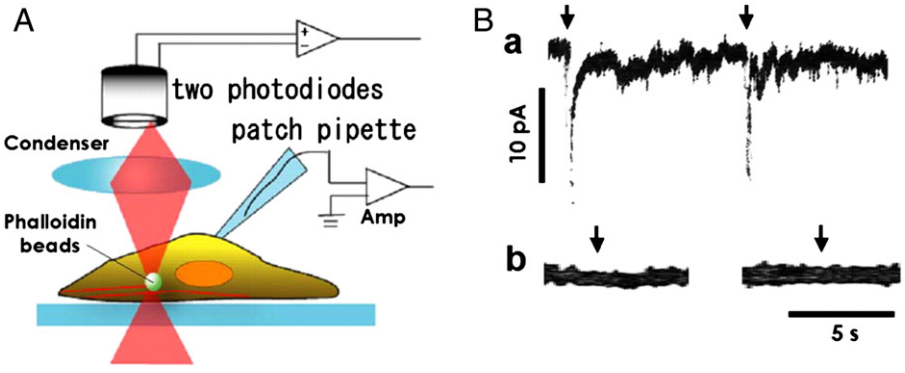

Fig. 2. Activation of MS channels by applying mechanical force to beads attached to actin stress fibers. (A) Phalloidin-conjugated 40 nm fluorescent beads were microinjected into HUVECs. These beads bound to the actin stress fibers and were trapped by laser optical tweezers. The movement of the trapping point was monitored with two photodiodes. Whole-cell patch-clamp recordings were made from the same cell. (B) A transient inward current was induced when the optical tweezers transiently passed an aggregate of phalloidin coated beads (shown by the two arrows in (a)). No current was induced when the same experiment was made with control beads (b).
Adapted with permission from [66].

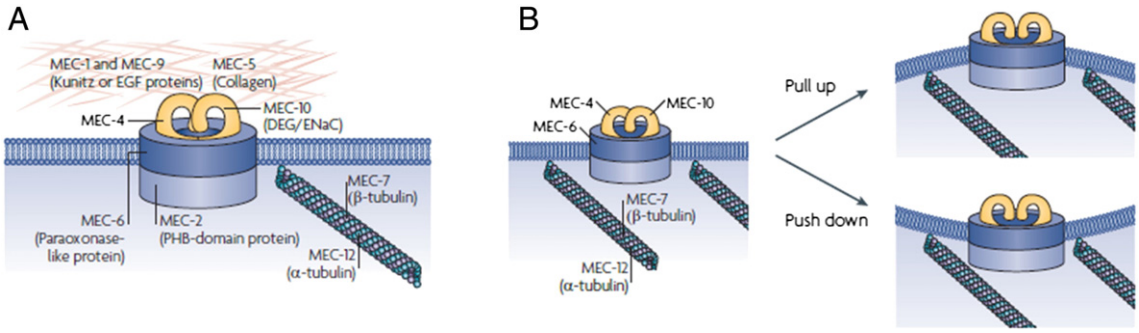

Fig. 3. Multi tether and single tether model of gentle touch in *Caenorhabditis elegans*. (A) Proteins that are needed in the touch receptor neurons. The extracellular proteins MEC-1 and MEC-9 as well as MEC-5 (collagen in mammals) might associate with the DEG/ENaC complex, which consists of MEC-2, MEC-4, MEC-6 and MEC-10. The specialized microtubules with MEC-7 and MEC-12 tubulins are needed for touch sensitivity, but probably do not associate with the channel complex. (B) A single-tether model for the mechanosensory MEC-4 channel, which is needed for gentle touch in *C. elegans*. Movement of the channel through its connection to extracellular matrix proteins changes the interaction with the membrane, thereby leading to the opening of the channel. Such a model explains how the channel can be opened by both the application and the removal of touch.
Reproduced with permission from [6].

endogenously expressed channels in cortical duct cells or B lymphocytes could be activated upon mechanical stimulation [81,82]. In addition, the gating of ENaC channels by mechanical forces could be modified by introduction of residue mutations in the pore region [83] as well as by lipid order, which was manipulated physically (temperature) and pharmacologically by agents, chlorpromazine and Gd^{3+}, known to decrease and increase bilayer order, respectively [84]. Furthermore, there is evidence that ENaC proteins are essential in mediating myogenic vasoconstriction in animal brain and renal arteries [85] suggesting further that these proteins may indeed be required for mechanosensation. With regard to the mechanism of activation of DEG/ENaC channels by mechanical forces dual-tether mechanism has generally been accepted to explain the mechanosensory transduction in touch receptor neurons of *C. elegans* [86]. However, recent results showing that the regulation of the lipid environment, particularly the presence of cholesterol, is important for the function of mechanosensory transduction complex in *C. elegans* indicate that the dual-tether model is unfavorable. As an alternative model the "single-tether" model has been proposed (Fig. 3B) [6], which combines previously contemplated possibility of transmission of mechanical forces to MS channels via both membrane bilayer as well as ECM/CSK tethers [87,88]. This model is based on the assumption that the position of a channel protein relative to the membrane bilayer determines the conformation of the channel, such that a single tether pulling on the channel alters the interaction between the channel and the membrane bilayer and consequently the forces within it ("force-from-lipids" hypothesis [6,50,87,89]), which opens the channel. The observation that in both key models (hair cell and *C. elegans* receptor) removing the tether reduces but does not eliminate completely the response to force led to the revision of the dual-tether model to the single-tether model compatible with the force-from-lipids notion. In mice carrying mutations in protocadherin-15 or cadherin-23, some are completely without tip links. Nonetheless the transduction currents remain, though reduced, and sometimes out of phase with the stimuli [90]. In addition, the tip link cadherin is too stiff to be compatible with the compliance of a gating linker [91]. This led to the view that the gating linker must either be a part of the channel or the membrane itself. While it was popular to think that the ankyrin repeats of some putative TRP channels are the spring [29], there is no evidence that any TRP is the transduction channel. Thus, the hearing-research community has apparently contemplated the possibility of force from lipids for several years already [27,28,39]. In the worm, mec-7 (beta-tubulin) knockout removes the microtubules completely, but only reduces and does not remove the transduction current [41]. Furthermore, the channels (mec-4) do not map to the ends of the microtubules [92]. Together, all these recent observations and findings appear to point towards the fusion of the previously opposite views (i.e. bilayer mechanism vs. tether mechanism) via the single-tether model compatible with the force-from-lipid concept of the MS channel gating by mechanical stimuli.

A number of TRP channels, which play an important role in cellular calcium signaling and homeostasis, can be activated by mechanical forces resulting from membrane stretch or osmotic forces [78]. There are about 33 animal genes encoding TRP channels, which have been categorized into six subfamilies including TRPC (canonical), TRPV (vanilloid), TRPA (ankyrin), TRPM (melastatin), TRPP (polycystin), and TRPML (mucolipin). Within the TRPC subfamily TRPC1 and TRPC6 channels are involved in mechanosensation. The TRPC1 channels, which are expressed in the brain, heart, testis, ovaries, smooth muscles, endothelium, salivary gland, and liver [93], were reported to be activated directly by membrane stretch. In addition, heterologous expression of human TRPC1 in *Xenopus* oocytes substantially increased the density of MS channels and cation currents in patch clamp experiments after applying different step pressures to the membrane [22].

Importantly, using channel density determined from a number of channels found in a membrane patch in patch clamp experiments as a measure of in situ channel density may not be reliable because of the parallel elastic contribution of the CSK, which becomes disrupted by patch excision resulting in much larger currents compared to whole-cell currents. However, TRPC1 currents were abolished by co-treatment with TRPC1-specific antisense RNA indicating that cation currents in *Xenopus* oocytes corresponded to human TRPC1 currents. TRPC6, the second member from this subfamily, can be activated by diacylglycerol acting directly on a lipid membrane and altering the channel's lipid environment [94]. TRPC6 mechanosensitivity was further demonstrated in experiments in which these channels were activated by mechanically or osmotically induced membrane stretch. Importantly, osmotic stress was shown not to be a comparable stimulus to direct mechanical stimulation [10] because osmotic stress and corresponding volume change acts as a mechanical stimulus only in red blood cells [49] and bacterial protoplasts [95]. Decreased expression of TRPC6 channels reduced arterial smooth muscle depolarization and constriction of blood vessels in response to pressure [96]. Furthermore, the most potent blocker of MS ion channels currently known, GsMTx-4, a 34 amino acid peptide isolated from the tarantula spider *Grammostola spatulata* [97] has been linked to specificity for some MS channels, in particular TRPC1 and TRPC6, in heterologous expression systems [22,98] as well as 'in situ'. However, the heterologous expression of TRPC1 and TRPC6 in COS and CHO cells [99] showed that the MS currents were not significantly altered by overexpression of these proteins, although both TRPC1 and TRPC6 could be highly expressed in these cells, which indicates that further studies are needed to understand the functioning of the TRPC channels as possible mechanosensors in different cell types. Given that both TRPC1 and TRPC6 have three and four ankyrin repeats near the N

terminus, respectively, the ankyrin repeats may function as tether conveying mechanosensitivity to both channels according to the single tether model [6], although a molecular dynamic study examining elastic properties of ankyrin and cadherin repeats suggested that only the extension and stiffness of large ankyrin repeats (>12) would match those predicted by the gating-spring model [91]. From the TRPV family of vanilloid receptor channels, which have three to five ankyrin repeats in their N termini, TRPV1, TRPV2, and TRPV4 receptors can function as mechanosensors. The mechanosensitivity of TRPV1 was documented in mice lacking the receptor that showed altered secretion of adenosine triphosphate (ATP) in response to mechanical stretch [100], although the release of ATP is known to activate P2X/Y channels that have similar conductance and selectivity to TRP channels [101]. TRPV1 has also been shown to respond to changes in osmolarity, both to hypertonic and hypotonic media, although it is important to remember that osmotic stress is not a comparable stimulus to direct mechanical stimulation [10]. A stretch of amino acids from the TRPV1 N-terminus is required for osmosensitivity. Neurons from a mouse N-terminal splice variant could not respond to hypertonic medium, whereas neurons for the wild-type mouse could [100]. The TRPV2 expressed in murine aortic myocytes functions as an osmotically sensitive cation channel that can be activated by cell swelling in response to hypotonic solutions [102]. Their expression in vascular smooth muscle cells further suggests that they may act as a stretch sensor involved in blood flow regulation. The TRPV4 channel is expressed in neurosensory cells that are responsive to systemic osmotic pressure, inner ear hair cells, sensory neurons, Merkel cells, as well as kidney, liver, and heart cells [103]. TRPV4 is polymodally regulated by warm temperature, metabolites of arachidonic acid, as well as hypotonicity [104]. Importantly, deletion of ankyrin repeats reduced channel sensitivity to lowered extracellular osmolarity [105] suggesting that the single-tether mechanism of the channel activation by mechanical forces may underlie the gating of TRPV4 by mechanical forces. However, the 310 pS unitary conductance was shown not to be that of TRPV4 by subsequent experiments indicating that no definite statements can be made about mechanosensitivity of TRPV4. TRPM3, TRPM4, and TRPM7 have also been reported to be involved in mechanotransduction [78]. The TRPM3 proteins are expressed in kidney, brain, and pancreatic cells [78] and TRPM4 channels are expressed at higher levels in cerebral arteries where their activation by membrane stretch was reported to contribute to vasoconstriction [106]. The activity of the heterologously expressed TRPM3 and TRPM7 splice variants could be enhanced by sphingolipids [107] and shear stress and direct stretch [108], respectively. Both TRPM3 and TRPM7 can be activated by osmotic swelling [108,109]. The MS polycystin complex composed of TRPP1 and TRPP2 proteins is involved in autosomal dominant polycystic kidney disease [110]. The complex is expressed at high levels in the cilia of renal epithelial cells, where it detects shear stress from flow of fluid and functions as a MS calcium ion channel [111]. The TRPA1 channel is expressed in nociceptive neurons, where it contributes to cold, mechanical, and chemical nociception [30]. TRPA1 has already been mentioned as a candidate channel functioning in the mechanosensory epithelia of the inner ear [29]. It is characterized by 17 ankyrin repeats, which were proposed to play a role of the gating linker connected to the mechanosensory transduction channel [91]. However, TRPA1 is unlikely to be the still elusive mechanosensory transduction channels since no hearing deficits have been observed in TRPA1 knockdown mice [30]. With regard to mechanosensitivity of TRP channels discussed above, it is worthwhile mentioning recent important observations made in the *Drosophila* compound eye, which demonstrated that TRP channels (TRP and TRPL) are ultimately mechanosensitive channels that sense force from lipids, even though they are well-known to be in a complex with several other known proteins in a known scaffold attached to cytoskeleton [112].

TREK-1, a mechanosensitive 2P-type K^+ channel, presents another good example of the MS channel–bilayer–cytoskeleton interaction. It is worth mentioning here that TRAAK, a close relative of TREK-1, is to date the only eukaryotic MS channel, whose crystal structure has been solved [113]. The TREK1 channel is regulated by a variety of physical and chemical stimuli, including membrane stretch, intracellular acidosis, temperature, arachidonic acid, and intracellular phospholipids (Table 1). Membrane stretch reversibly activated the TREK1 channel with the positive pressure being less effective than negative pressure (in the inside-out patch configuration), indicating preferential channel opening by a specific membrane curvature [114]. Patch excision or chemical disruption of the actin cytoskeleton increased the number of active channels, suggesting that the membrane tension is likely to be directly transmitted to the channel via the lipid bilayer and the cytoskeleton seems to act only as a tonic suppressor that limits channel activity induced by membrane stretch [114–117]. Channel activity is increased by inner leaflet phospholipids such as phosphatidylinositol, phosphatidylserine, and phosphatidylethanolamine [118] in agreement with the finding that amphipathic molecules, similar to bacterial MS channels [2], modulate the activity of TREK-1 directly via a bilayer-coupling effect whereby a differential insertion of the compound into the respective leaflets of the lipid bilayer changes the curvature imitating stretch. In addition, cytoplasmic pH plays a critical role in gating of the TREK1 channel by mechanical stimuli. The C-terminal glutamate E306, suggested to act as a proton sensor, becomes protonated at low intracellular pH, which affects electrostatic coupling of the charged cluster of residues within the C-terminal region with anionic phospholipids of the inner leaflet of the bilayer. This in turn affects channel gating properties [118,119]. Interestingly, the expression of TREK1 was shown to alter the cytoskeletal network leading to the formation of membrane protrusions rich in actin, which suggests dynamic channel–cytoskeleton interaction that could influence neuronal transmission and synaptogenesis [117]. Activation of TREK1 by membrane stretch shows also pronounced, cytoskeleton-independent desensitization within 100 ms of application of the stimulus [116]. Deletion of the C-terminal domain of the channel reduced the channel sensitivity to mechanical stimulation and rendered channels with faster inactivation times [114,116].

Piezo proteins have recently been identified as non-selective cation channels conducting Na^+, K^+, Ca^{2+} and Mg^{2+} ions [120,121]. Piezo1 currents are inhibited by GsMTx-4 [122], a 34 amino acid peptide, which is the only drug known to specifically affect cationic mechanosensitive channels [123]. The Piezo1 channels remain mechanosensitive upon heterologous expression [124,125]. Also, Piezo1 remains constitutively active upon reconstitution into asymmetric bilayers [120]. However, the reconstituted channels exhibit altered properties by showing no inactivation and no mechanosensitivity making them highly altered from the wild type channels recorded in cells, which makes it difficult to conclude that the reconstituted channels are the same specific Piezo1 channels. Human hPiezo1 is known to be responsible for a variety of human diseases involving cell volume [49], whereas Piezo2 channels function in mechanosensory transduction in senses of touch and pain. They may be components of animal skin mechanoreceptors [126] and thus, they could require connections to cytoskeletal proteins to function as MS channels. Since hPiezo1 has been demonstrated to have a dimension change equal to MscL it may be sensing bilayer tension comparable to bacterial MS channels [49]. Similar experiments have not been done with Piezo2 channels. In the context of heterologous expression experiments with TRP channels, particularly with widely available cell lines, it is important to mention that Piezo channels (Piezo1) are present in the background of these cells (e.g. HEK cells) [49]. The research on Piezo channels is quite young and more detailed measurements are needed to establish the mechanism by which the Piezo channels are activated by mechanical forces.

5. Epilogue

Towards the end of this review it is worthwhile to speculate about experiments that could resolve the issue of the coupling mechanisms

that underlie gating of the MS channels discussed in this article. There are a couple of approaches one may employ to address this question.

To demonstrate convincingly mechanosensitivity of an MS channel as its intrinsic property the best way to do it is to use liposomal reconstitution of purified MS channel proteins, which is currently the gold standard for assessing intrinsic mechanosensitivity [127]. Provided that a purified MS channel protein of interest is available for reconstitution this approach gives the advantage of not only examining the channel mechanosensitivity unobscured by cellular components but also checking possible effects of various lipids on the channel activity, as it has already been done with several MS channel proteins [20,47,128]. If a purified protein of an MS channel of interest is, however, not available the next best approach would be to co-express one of the bacterial MS channels (e.g. MscL) with the MS channel under study and compare the mechanosensitivity of the channel with the mechanosensitivity of MscL, which to date serves as a model of a prototypical MS channel [2]. This has been done with hPiezo1 channels [49]. Given that MS channels occupy different membrane areas by adopting the two basic conformational states the difference in the area $\Delta A = A_o - A_c$ occupied by an open (A_o) compared to a closed (A_c) channel accounts for the free energy difference ΔG between these two conformations, which is dependent on membrane tension T (i.e. $\Delta G = T\Delta A$). hPiezo1 has been demonstrated to have an area change $\Delta A \sim 20\ nm^2$ equal to MscL [49] and thus, hPiezo1 may be gated by bilayer tension similar to MscL [2]. If the area change happens to be much smaller than ΔA of MscL or hPiezo1 one may suspect the involvement of CSK and/or ECM as accessory elements in transduction of mechanical stimuli to the channel either directly or indirectly via membrane cholesterol-rich domains. In that case one would have to employ other methods and techniques in addition to the patch clamp, such as fluorescence microscopy techniques (e.g. FRET, FLIM, Ca^{2+} imaging), depletion of membrane cholesterol by cyclodextrin, CSK mutagenesis or magnetic pulling cytometry [129] to examine the connections between the MS channel and other membrane components.

6. Conclusions

Mechanosensory transduction in animal cells is based on complex interactions between the lipid bilayer and a large variety of membrane proteins. MS channels play a prominent role in these interactions and are subject of intensive research aiming to determine the mechanism of activation and modulation of ion channels by mechanical forces acting on the membrane bilayer and components of ECM and CSK tethered to ion channels such as TRP, DEG/ENaC and Piezo proteins enabling animal and human cells to respond to mechanical stimuli by translating them into biologically meaningful signals. Given that one of the remaining challenges still presents molecular identification of the mechanoelectric transduction channel in hair cells we may expect that future research will progress by resolving how the MS channel tethering to ECM and/or CSK directly or indirectly via membrane cholesterol-rich domains contributes to the channel mechanosensitivity not only in specialized mechanoreceptors but also in non-specialized cells associated with mechanosensation.

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