AIMS Biophysics

AIMS Biophysics, 3(1): 63-74.
DOI: 10.3934/biophy.2016.1.63
Received: 21 August 2015
Accepted: 11 January 2016
Published: 20 January 2016

http://www.aimspress.com/journal/biophysics

Review

Mechanosensitive ion channels

Ken Takahashi, Yusuke Matsuda, and Keiji Naruse *

Cardiovascular Physiology, Graduate School of Medicine, Okayama University, Okayama, Japan

* **Correspondence:** Email: knaruse@md.okayama-u.ac.jp.

Abstract: Cell surface receptors are involved in numerous important biological processes including embryogenesis, tissue differentiation, and cellular homeostasis. Among them, mechanosensitive ion channels play an essential role in cellular functions of every cell including neurons, cardiomyocytes, and osteocytes. Here, we discuss types, roles, structures, and biophysical factors that affect the functions of mechanosensitive ion channels.

Keywords: ion channels, mechanosensing; mechanotransduction

1. Introduction

Cellular membranes consist of lipid bilayers that separate the inside and outside of a cell. Surface receptors, among a multitude of membrane proteins incorporated in the bilayer, play a role in receiving signals from the environment outside. G-protein-coupled receptors are typical examples of the surface receptors, which receive chemical substances and commence signal transduction in the cell [1,2]. Yet another class of the surface receptors are ion channels, more than 400 of which are thought to be coded in the human genome [3]. The signals are typically chemical substances including hormones [4] and neurotransmitters [5]. For example, verapamil, a substance which belongs to phenylalkylamine class, inhibits the activity of L-type calcium channels in cardiomyocytes and thereby attenuates hypertension [6].

Yet another form of the signal, which affects the surface receptors, is the mechanical stimulus. Mechanosensitive ion channels (MS channels) change their conformation and function in response to mechanical stimuli, including pressure, shear stress, and osmolarity [7,8,9]. Function or malfunction of MS channels confer a vast range of biological processes, including tactile sensation [10], cell volume regulation [11], synapse formation [12], heart rate regulation [13], arrhythmia [14],

pulmonary arterial hypertension [15], muscular dystrophy [16], polycystic kidney disease [17], and tumor progression [18]. Astonishingly enough, even the process of photoreception is suggested to be derived from MS channels in fly vision via membrane contraction evoked by light exposure [19]. Here, we discuss the role of MS channels in life activity at first, then the molecular structure, and the biophysical principle for their action (Figure 1).

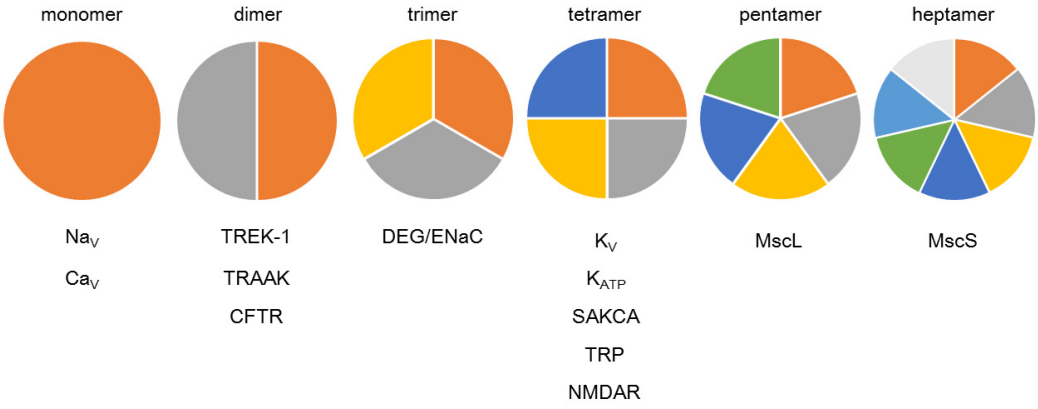

Figure 1. Number of pore forming subunits in mechanosensitive ion channels.

1.1. Expression of mechanosensitive ion channels in organs and their function

MS channels are expressed in a vast range of cells and involved in various biological functions [16,20–26]. Designations of MS channels and their location of expression are summarized in Table 1.

The transient receptor potential (TRP) channels were first found in Drosophila and now 28 TRP subtypes are identified. TRPA1 (transient receptor potential cation channel, subfamily A, member 1) channel is widely expressed in tissues, including sensory neurons [27], inner ear hair cells [20], periodontal ligament cells [28], and pancreatic beta cells [29]. This channel was originally found as a cold sensor [30], but now it is also known as mechanosensor, for example, in the viscera [31].

TRPC1 (Transient receptor potential cation channel, subfamily C, member 1) channel is expressed in cardiomyocytes [32], sensory nerve ending of the atrial volume receptors [33], and spinal neurons [34]. TRPC1 regulates migration of renal epithelial cells by creating a calcium gradient, which determines the axis of cellular movement [35]. Considering embryonic development, migration can be described as a continuous process as cellular migration is a fundamental process in multicellular organisms, including humans. In the spinal axon, TRPC1 senses hardness of the surrounding environment and guides development of the axon [34]. TRPC3, together with TRPC6, is expressed in dorsal root ganglion neurons and is involved in touch sensation [36]. As later mentioned, TRPC1, 3, and 6 are expressed in the heart and involved in the development of cardiac hypertrophy. Besides, TRPC6 is also expressed in podocytes and is mechanically gated by membrane stretch [37]. Gain of function mutation of this protein causes nephrotic syndromes [38].

Blood vessels are sensing blood pressure and regulating their diameter to control blood flow appropriately. The epithelial sodium channel (ENaC) is expressed in epithelial cells, distal nephrons, gastrointestinal tract, skin, and cerebral arteries [39,40]. ENaC, together with transient receptor

potential channels later mentioned, plays important roles in the pressure-induced myogenic response in cerebral arteries.

Table 1. Ion channels regarded as mechanosensitive.

Channels	Location	Ref.
Sodium channels		
$Na_V1.5$	muscle, heart, gut	[43]
$Na_V1.6$	Neuron	[44]
DEG/ENaC	epithelial cells, distal nephrons, gastrointestinal tract, skin, mechanoreceptor neurons	[39,86]
Potassium channels		
K_V1		[87]
TREK-1	Cardiomyocyte	[88,89]
TRAAK	neuron, retina	[74,78,90]
K_{ATP}	atrial myocyte	[91,92]
SAKCA	ventricular myocyte	[93]
KCNQ (K_V7)	cochlear hair cells, peripheral nerve mechanoreceptor	[42]
Calcium channels		
$Ca_V1.2$	Cardiomyocyte, intestinal smooth muscle cell, knee joint neuron	[47,94]
Chloride channel		
CFTR	epithelial cell, cardiomyocyte atrial myocyte, SA node	[95,96]
Non-specific cation channels		
TRPA1	sensory neuron, inner ear hair cell, periodontal ligament cells, pancreatic beta cells	[20,27–29,31,97]
TRPC1	cardiomyocyte, atrial volume receptor, spinal neuron	[32–34,98]
TRPC3	sensory neuron, cochlear hair cell	[36]
TRPC6	vascular smooth muscle cell, cardiomyocyte, sensory neuron, cochlear hair cell, podocyte	[36,37,99,100]
TRPM3	nociceptive neuron, kidney, brain, retina, periodontal ligament cell	[101–104]
TRPM4	Purkinje fiber, SA node, cerebral artery, fibroblast, endothelial cell, astrocyte	[105]
TRPM7	atrial fibroblast, odontoblast, mesenchymal stem cell	[65,106]
TRPP1	renal epithelial cells	
TRPP2	renal epithelial cells, endocardial cell	[107]
TRPV1		
TRPV2	cardiac muscle	
TRPV4	atrial myocyte, atrial volume receptor, endocardial cell, cardiac fibroblast, osteoblast	[33,64,107,108]
NMDAR	Neuron	[109]

Hearing is one of the typical mechanosensitive processes. While TRPA1 is a well-known MS channel in the inner ear hair cells, response to auditory stimulus persists even after the knockdown of that protein [41]. On the other hand, KCNQ4, voltage-gated KQT-like subfamily Q member 4, is also expressed in the mechanosensitive hair cells of the inner ear and auditory neurons [42]. Mutation of this channel causes deafness (non-syndromic sensorineural deafness type 2). Intriguingly, KCNQ4 is also expressed in peripheral mechanoreceptors including hair follicle and Meissner corpuscle and is involved in tactile sensation. Other candidates for MS channels responsible for hearing are TRPC3/6. Co-expression of TRPC3 and TRPC6 is also observed in the cochlear hair cells, and double knockout of these genes shows impairment of hearing [36].

Several classes of voltage-gated cation channels are also regarded as mechanosensitive. For example, a voltage-gated sodium channel, $Na_V1.5$, is expressed in electromechanical tissues, including the muscle, heart, and gut [43]. $Na_V1.6$ channel is expressed in neurons [44]. A voltage-gated calcium channel, $Ca_V1.2$, is expressed in cardiomyocytes [45], intestinal smooth muscle cells [46], and knee joint afferents [47]. It is suggested that nociceptive mechanical stimuli to the knee joint evoke excitation of afferent nerve via $Ca_V1.2$ [47].

1.2. Role of mechanosensitive channels in the heart

Mechanical stimuli affect the frequency of heartbeat. Stretch-activated ion channels are thought to play this role, and several MS channels are candidates for them. For example, TRPM4 channel is expressed in the heart and has a role in cardiac conduction [48]. Deletion of TRPM4 causes abnormality in cardiac electric conduction [49], and overexpression of the gene is the cause of progressive familial heart block type I [50]. Another candidate is TRPM7, which influences diastolic membrane depolarization and cardiac automaticity in the sinoatrial node [51]. This channel is expressed in atrial fibroblasts and plays a role in atrial fibrillation [52].

Cardiac hypertrophy is a consequence of long time exposure to pressure/volume overload. TRPC1/3/6 are candidates for the responsible channels for this mechanosensitive pathological process [53]. TRPC1 knockout mice lack maladaptive hypertrophic alteration in response to pressure overload [32]. In the patch clamp experiment using the TRPC1 knockout cardiomyocytes, TRPC-like current in response to mechanical stimulus was not observed [32]. On the other hand, blockade of TRPC3 and TRPC6 channels at the same time inhibit cardiac hypertrophy [54]. These channels are thought to form heterotetramers.

Of course the cellular mechanosensitivity does not serve only for pathological processes in the heart. TRPV4 (Transient receptor potential cation channel, subfamily V, member 4) and TRPP2 (Transient Receptor Potential Polycystic 2) channels are expressed in the endocardium and control development of cardiac valves via expression of Klf2a. In drosophila, TRPA channel is responsible for cardiac mechanosensitive response [55]. Thus, MS channels play indispensable roles for cardiac physiology and pathology.

1.3. Role of mechanosensitive channels in the bone

Considering that bone is an organ, which bears loads due to gravity all the time, it is quite natural that this organ has specific contrivance for mechanosensitive response. Remodeling of bone is controlled both systemically and locally. Mechanical stress is a critical factor for bone mass

regulation [56]. Unloading of mechanical stress causes severe decrease of bone mass. For example, when a tooth is lost, load to the root of the facing tooth will be lost and thereby the mass at nearby jawbone decreases. Other examples are bedridden patients and astronauts under microgravity [57].

The bone tissue is maintaining its physiological function due to the functions of osteoclasts, osteoblasts, lining cells (osteoblasts in a rest condition), and osteocytes (developed osteoblasts). These cells are maintaining homeostasis by sensing and transmitting mechanical stimuli. MS channels play a role in the bone mechanotransduction [58]. TRP [59] and BK_{Ca} [60] channels are thought to be mechanosensors in the bone.

Increase in DNA synthesis and decrease in ALP activity are observed in response to stretch stimulus in the osteoblast-like cells [61]. Among the factors, which induce bone formation, the calcium signaling pathway is thought to play an important role. There is a close relationship between MS channels and bone function. For example, mutation of TRPV4 gene causes skeletal dysplasias, including metatropic dysplasia and parastremmatic dysplasia [62]. Although unloading will usually cause bone loss, this mechanosensitive alteration is cancelled in TRPV4 deficient mice [63]. Besides, TRPV4 is involved in the flow-induced calcium signaling in osteoblasts [64]. Another TRP channel responsible for bone mechanosensitivity is TRPM7, which is expressed in human bone marrow mesenchymal stem cells and plays a pivotal role in osteogenesis [65].

1.4. Structure of mechanosensitive ion channels

Historically, many researches regarding MS channels have been done using bacterial mechanosensitive channel, especially MscL (mechanosensitive channel of large conductance), whose high-resolution three dimensional crystal structure was solved [66–70]. Using this structure, biophysical principles, which govern the dynamics of mechanosensitive conformational changes have been revealed by many groups steadily. Recently, high resolution three dimensional structures of eukaryote MS channels have been revealed eventually [71–75]. These structures will help us to reach a higher level of understanding cellular mechanosensitivity.

Whereas dedicated researches are still in progress, it seems that specific features responsible for the mechanosensitivity of ion channels are lacking at present. This is very different from the case of six transmembrane voltage-gated channels, which have well conserved amino acid sequence from bacteria to human, namely “voltage sensor”, at S4 transmembrane helix [76]. The structure of MS channels is very diverse. For example, the number of pore forming subunits ranges from two to seven (Fig. 1). Na_V and Ca_V channels have only one pore forming subunit which consists of four homologous domains. TREK-1 [77], TRAAK [78], and CFTR [73] channels have two pore forming subunits. Voltage gated (K_V) and ATP-sensitive (K_{ATP}) potassium channels, SAKCA (stretch activated K_{Ca}) channels, TRP channels, and NMDAR (N-methyl-D-aspartate receptor) channels have four pore forming subunits. Some TRP channels form heterotetramers such as TRPC3/TRPC6. Bacterial mechanosensitive channels of large conductance (MscL) channel have five identical subunits, and mechanosensitive channels of small conductance (MscS) channel have seven identical subunits. So far any common or conserved “mechanosensor” domains have not been identified. Ion selectivity is also diverse; there are sodium, potassium, calcium, and chloride channels of various ion selectivity. Besides, most of the TRP channels are nonspecific cation channels. These facts imply that each MS channel has individual manner of conformational change in response to mechanical stimulus.

Interaction with other proteins is a critical factor, which determines the mechanosensitivity of the channel. For example, SAKCA channel has a pore-forming α-subunit and a regulatory β-subunit [79]. The α-subunit consists of four subunits and is regulated by the β-subunits in 1:1 stoichiometry (reviewed in [79]). The β-subunits significantly affect the kinetics of α-subunit. Recently, an intriguing fact regarding an MS channel and adhesome proteins was discovered. That is, TRPM4 channel is associated with cytoskeleton-related proteins such as filamin and vinculin, involved in disassembly of focal adhesions, thereby regulating cellular migration and contractility [80]. This finding will connect two areas hitherto individually treated MS channels and adhesomes together and deepen our understanding of cellular mechanosensitive response.

1.5. Biophysical principles, which govern the behavior of mechanosensitive ion channels

Every surface receptor, including MS channels, that resides in the cellular membrane that is composed of lipid bilayers. If an MS channel is to change its conformation in response to surrounding mechanical stimulus, it receives the stimulus from either or both of the following molecules: lipid and/or protein. The former case is called "bilayer mechanism", in which the MS channel may receive energy for conformational change totally from the surrounding lipid bilayer and doesn't require any associating proteins. Bacterial MscL and MscS are the typical examples of this mechanism. In eukaryotes, ENaC, TREK-1, TRAAK, TRPA1, TRPC1/6, TRPM3/4/7, NMDA receptor, and Piezo 1/2 channels are thought to work with the bilayer mechanism [81].

Phospholipids composed of lipid bilayers can be classified by several categories, including the length of acyl chain, the number of double bonds in acyl chain, the electric charge of lipid head groups, and the morphology of the lipid molecule in the membrane. These factors describe the lipid-channel interaction and determine the kinetics of the MS channel. For example, MscL channels are easy to open in lipids with shorter acyl chains [82]. Another factor, which is important for the MS channel activity, is curvature of the lipid bilayer. Some phospholipids (such as lysophosphatidylcholine, which have only one acyl chain) and amphipathic substance (such as chlorpromazine), bend the lipid bilayer locally and change the pressure profile in the bilayers [83]. With regard to the pressure profile, spider toxin GsMTx-4 is often used to block the activity of the "bilayer mechanism" channels because it interacts with membrane lipids and alters the profile.

Recently, more specific lipid-channel interactions were reported. In the case of TRAAK channel, an acyl chain extrudes into a small cavity of the TRAAK protein by blocking the hole in the resting state. Interestingly, however, this blockade is released along with the rotation of transmembrane helices in the conducting state [74].

While we discussed the "bilayer mechanism" so far, eukaryotic cells usually have solid cytoskeletal networks underneath the surface lipid bilayers, which prevent direct force transmission from the lipid bilayers to the MS channel. Some MS channels require binding to associating protein(s), such as cytoskeletal proteins and/or extracellular matrix proteins, for their activation in response to mechanical stimulus. This case is called "tethered mechanism". ENaC [84] and TRP [85] channels are thought to work in this way. This mechanism is characterized in the touch receptor of *Caenorhabditis elegans*. For the touch receptor ENaC to open, MEC-7 (beta-tubulin) and MEC-12 (alpha-tubulin) are necessary. Mechanotransduction at the cochlear hair cells is thought to be a typical example of this "tethered mechanism".

2. Conclusion

Mechanotransduction is fundamental to life activity. Cellular surface receptors reside at the border between inside and outside of the cell, and ion channels serve as the earliest messenger in the cellular signaling pathway. MS channels play indispensable roles in tissue development, cardiovascular regulation, and sensory signal transduction. Knowledge obtained from researches regarding MS channels will contribute to understand the physiology and pathology of life, and ultimately, to better our life.

Acknowledgements

This work was supported by a grant from JSPS KAKENHI (26220203).

Conflict of Interest

The authors declare that there is no conflict of interests.

References

1. Yu FX, Zhao B, Panupinthu N, et al. (2012) Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. *Cell* 150: 780–791.
2. Yu FX, Guan KL (2013) The Hippo pathway: regulators and regulations. *Genes Dev* 27: 355–371.
3. Lee A, Fakler B, Kaczmarek LK, et al. (2014) More than a pore: ion channel signaling complexes. *J Neurosci* 34: 15159–15169.
4. Asuthkar S, Elustondo PA, Demirkhanyan L, et al. (2015) The TRPM8 protein is a testosterone receptor: I. Biochemical evidence for direct TRPM8-testosterone interactions. *J Biol Chem* 290: 2659–2669.
5. Changeux JP (2012) The nicotinic acetylcholine receptor: the founding father of the pentameric ligand-gated ion channel superfamily. *J Biol Chem* 287: 40207–40215.
6. Elliott WJ, Ram CV (2011) Calcium channel blockers. *J Clin Hypertens (Greenwich)* 13: 687–689.
7. Grigg P (1986) Biophysical studies of mechanoreceptors. *J Appl Physiol (1985)* 60: 1107–1115.
8. Kung C (2005) A possible unifying principle for mechanosensation. *Nature* 436: 647–654.
9. O'Neil RG, Heller S (2005) The mechanosensitive nature of TRPV channels. *Pflugers Arch* 451: 193–203.
10. Woo SH, Ranade S, Weyer AD, et al. (2014) Piezo2 is required for Merkel-cell mechanotransduction. *Nature* 509: 622–626.
11. Baumgarten CM, Clemo HF (2003) Swelling-activated chloride channels in cardiac physiology and pathophysiology. *Prog Biophys Mol Biol* 82: 25–42.
12. Tyler WJ (2012) The mechanobiology of brain function. *Nat Rev Neurosci* 13: 867–878.
13. Takahashi K, Kakimoto Y, Toda K, et al. (2013) Mechanobiology in cardiac physiology and diseases. *J Cell Mol Med* 17: 225–232.

14. Bett GC, Sachs F (2000) Whole-cell mechanosensitive currents in rat ventricular myocytes activated by direct stimulation. *J Membr Biol* 173: 255–263.
15. Song S, Yamamura A, Yamamura H, et al. (2014) Flow shear stress enhances intracellular Ca2+ signaling in pulmonary artery smooth muscle cells from patients with pulmonary arterial hypertension. *Am J Physiol Cell Physiol* 307: C373–383.
16. Lansman JB, Franco-Obregon A (2006) Mechanosensitive ion channels in skeletal muscle: a link in the membrane pathology of muscular dystrophy. *Clin Exp Pharmacol Physiol* 33: 649–656.
17. Nauli SM, Alenghat FJ, Luo Y, et al. (2003) Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 33: 129–137.
18. Chen YF, Chen YT, Chiu WT, et al. (2013) Remodeling of calcium signaling in tumor progression. *J Biomed Sci* 20: 23.
19. Hardie RC, Franze K (2012) Photomechanical responses in Drosophila photoreceptors. *Science* 338: 260–263.
20. Corey DP, Garcia-Anoveros J, Holt JR, et al. (2004) TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells. *Nature* 432: 723–730.
21. Ito H, Aizawa N, Sugiyama R, et al. (2015) Functional role of the TRPM8 ion channel in the urinary bladder assessed by conscious cystometry and ex vivo measurements of single-unit mechanosensitive bladder afferent activities in the rat. *BJU Int*.
22. Jin Y, Li J, Wang Y, et al. (2015) Functional role of mechanosensitive ion channel Piezo1 in human periodontal ligament cells. *Angle Orthod* 85: 87–94.
23. Inoue R, Jian Z, Kawarabayashi Y (2009) Mechanosensitive TRP channels in cardiovascular pathophysiology. *Pharmacol Ther* 123: 371–385.
24. Davidson RM, Tatakis DW, Auerbach AL (1990) Multiple forms of mechanosensitive ion channels in osteoblast-like cells. *Pflugers Arch* 416: 646–651.
25. Mienville J, Barker JL, Lange GD (1996) Mechanosensitive properties of BK channels from embryonic rat neuroepithelium. *J Membr Biol* 153: 211–216.
26. Farrugia G, Holm AN, Rich A, et al. (1999) A mechanosensitive calcium channel in human intestinal smooth muscle cells. *Gastroenterology* 117: 900–905.
27. Vilceanu D, Stucky CL (2010) TRPA1 Mediates Mechanical Currents in the Plasma Membrane of Mouse Sensory Neurons. *Plos One* 5: e12177.
28. Tsutsumi T, Kajiya H, Fukawa T, et al. (2013) The potential role of transient receptor potential type A1 as a mechanoreceptor in human periodontal ligament cells. *Eur J Oral Sci* 121: 538–544.
29. Cao DS, Zhong L, Hsieh TH, et al. (2012) Expression of Transient Receptor Potential Ankyrin 1 (TRPA1) and Its Role in Insulin Release from Rat Pancreatic Beta Cells. *Plos One* 7: e38005.
30. Story GM, Peier AM, Reeve AJ, et al. (2003) ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell* 112: 819–829.
31. Brierley SM, Hughes PA, Page AJ, et al. (2009) The ion channel TRPA1 is required for normal mechanosensation and is modulated by algesic stimuli. *Gastroenterology* 137: 2084–2095 e2083.
32. Seth M, Zhang ZS, Mao L, et al. (2009) TRPC1 channels are critical for hypertrophic signaling in the heart. *Circ Res* 105: 1023–1030.

33. Shenton FC, Pyner S (2014) Expression of transient receptor potential channels TRPC1 and TRPV4 in venoatrial endocardium of the rat heart. *Neuroscience* 267: 195–204.
34. Kerstein PC, Jacques-Fricke BT, Rengifo J, et al. (2013) Mechanosensitive TRPC1 channels promote calpain proteolysis of talin to regulate spinal axon outgrowth. *J Neurosci* 33: 273–285.
35. Fabian A, Fortmann T, Dieterich P, et al. (2008) TRPC1 channels regulate directionality of migrating cells. *Pflugers Arch* 457: 475–484.
36. Quick K, Zhao J, Eijkelkamp N, et al. (2012) TRPC3 and TRPC6 are essential for normal mechanotransduction in subsets of sensory neurons and cochlear hair cells. *Open Biol* 2: 120068.
37. Anderson M, Kim EY, Hagmann H, et al. (2013) Opposing effects of podocin on the gating of podocyte TRPC6 channels evoked by membrane stretch or diacylglycerol. *Am J Physiol Cell Physiol* 305: C276–289.
38. Mene P, Punzo G, Pirozzi N (2013) TRP channels as therapeutic targets in kidney disease and hypertension. *Curr Top Med Chem* 13: 386–397.
39. Kellenberger S, Schild L (2002) Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure. *Physiol Rev* 82: 735–767.
40. Kim EC, Choi SK, Lim M, et al. (2013) Role of endogenous ENaC and TRP channels in the myogenic response of rat posterior cerebral arteries. *PLoS One* 8: e84194.
41. Cuajungco MP, Grimm C, Heller S (2007) TRP channels as candidates for hearing and balance abnormalities in vertebrates. *Biochim Biophys Acta* 1772: 1022–1027.
42. Heidenreich M, Lechner SG, Vardanyan V, et al. (2012) KCNQ4 K(+) channels tune mechanoreceptors for normal touch sensation in mouse and man. *Nat Neurosci* 15: 138–145.
43. Beyder A, Rae JL, Bernard CE, et al. (2010) Mechanosensitivity of Nav1.5, a voltage-sensitive sodium channel. *J Physiol*.
44. Wang JA, Lin W, Morris T, et al. (2009) Membrane trauma and Na+ leak from Nav1.6 channels. *Am J Physiol Cell Physiol* 297: C823–834.
45. Bodi I, Mikala G, Koch SE, et al. (2005) The L-type calcium channel in the heart: the beat goes on. *J Clin Invest* 115: 3306–3317.
46. Lyford GL, Strege PR, Shepard A, et al. (2002) alpha(1C) (Ca(v)1.2) L-type calcium channel mediates mechanosensitive calcium regulation. *Am J Physiol Cell Physiol* 283: C1001–C1008.
47. Just S, Heppelmann B (2003) Voltage-gated calcium channels may be involved in the regulation of the mechanosensitivity of slowly conducting knee joint afferents in rat. *Exp Brain Res* 150: 379–384.
48. Guinamard R, Chatelier A, Demion M, et al. (2004) Functional characterization of a Ca(2+)-activated non-selective cation channel in human atrial cardiomyocytes. *J Physiol* 558: 75–83.
49. Demion M, Thireau J, Gueffier M, et al. (2014) Trpm4 gene invalidation leads to cardiac hypertrophy and electrophysiological alterations. *PLoS One* 9: e115256.
50. Kruse M, Schulze-Bahr E, Corfield V, et al. (2009) Impaired endocytosis of the ion channel TRPM4 is associated with human progressive familial heart block type I. *J Clin Invest* 119: 2737–2744.
51. Sah R, Mesirca P, Van den Boogert M, et al. (2013) Ion channel-kinase TRPM7 is required for maintaining cardiac automaticity. *Proc Natl Acad Sci U S A* 110: E3037–3046.
52. Du J, Xie J, Zhang Z, et al. (2010) TRPM7-mediated Ca2+ signals confer fibrogenesis in human atrial fibrillation. *Circ Res* 106: 992–1003.

53. Domes K, Patrucco E, Loga F, et al. (2015) Murine cardiac growth, TRPC channels, and cGMP kinase I. *Pflugers Arch* 467: 2229–2234.
54. Seo K, Rainer PP, Shalkey Hahn V, et al. (2014) Combined TRPC3 and TRPC6 blockade by selective small-molecule or genetic deletion inhibits pathological cardiac hypertrophy. *Proc Natl Acad Sci U S A* 111: 1551–1556.
55. Senatore S, Rami RV, Semeriva M, et al. (2010) Response to Mechanical Stress Is Mediated by the TRPA Channel Painless in the Drosophila Heart. *PLoS Genet* 6: e1001088.
56. Skerry TM, Suva LJ (2003) Investigation of the regulation of bone mass by mechanical loading: from quantitative cytochemistry to gene array. *Cell Biochem Funct* 21: 223–229.
57. Carmeliet G, Vico L, Bouillon R (2001) Space flight: a challenge for normal bone homeostasis. *Crit Rev Eukaryot Gene Expr* 11: 131–144.
58. Robling AG (2012) The interaction of biological factors with mechanical signals in bone adaptation: recent developments. *Curr Osteoporos Rep* 10: 126–131.
59. Everaerts W, Nilius B, Owsianik G (2010) The vanilloid transient receptor potential channel TRPV4: from structure to disease. *Prog Biophys Mol Biol* 103: 2–17.
60. Rezzonico R, Cayatte C, Bourget-Ponzio I, et al. (2003) Focal adhesion kinase pp125FAK interacts with the large conductance calcium-activated hSlo potassium channel in human osteoblasts: potential role in mechanotransduction. *J Bone Miner Res* 18: 1863–1871.
61. Winter LC, Walboomers XF, Bumgardner JD, et al. (2003) Intermittent versus continuous stretching effects on osteoblast-like cells in vitro. *J Biomed Mater Res A* 67: 1269–1275.
62. Nishimura G, Lausch E, Savarirayan R, et al. (2012) TRPV4-associated skeletal dysplasias. *Am J Med Genet C Semin Med Genet* 160C: 190–204.
63. Mizoguchi F, Mizuno A, Hayata T, et al. (2008) Transient receptor potential vanilloid 4 deficiency suppresses unloading-induced bone loss. *J Cell Physiol* 216: 47–53.
64. Suzuki T, Notomi T, Miyajima D, et al. (2013) Osteoblastic differentiation enhances expression of TRPV4 that is required for calcium oscillation induced by mechanical force. *Bone* 54: 172–178.
65. Xiao E, Yang HQ, Gan YH, et al. (2015) Brief reports: TRPM7 Senses mechanical stimulation inducing osteogenesis in human bone marrow mesenchymal stem cells. *Stem Cells* 33: 615–621.
66. Perozo E, Cortes DM, Sompornpisut P, et al. (2002) Open channel structure of MscL and the gating mechanism of mechanosensitive channels. *Nature* 418: 942–948.
67. Gullingsrud J, Kosztin D, Schulten K (2001) Structural determinants of MscL gating studied by molecular dynamics simulations. *Biophys J* 80: 2074–2081.
68. Sukharev SI, Sigurdson WJ, Kung C, et al. (1999) Energetic and spatial parameters for gating of the bacterial large conductance mechanosensitive channel, MscL. *J Gen Physiol* 113: 525–539.
69. Sawada Y, Murase M, Sokabe M (2012) The gating mechanism of the bacterial mechanosensitive channel MscL revealed by molecular dynamics simulations: from tension sensing to channel opening. *Channels (Austin)* 6: 317–331.
70. Deplazes E, Louhivuori M, Jayatilaka D, et al. (2012) Structural investigation of MscL gating using experimental data and coarse grained MD simulations. *PLoS Comput Biol* 8: e1002683.
71. Moiseenkova-Bell VY, Stanciu LA, Serysheva, II, et al. (2008) Structure of TRPV1 channel revealed by electron cryomicroscopy. *Proc Natl Acad Sci U S A* 105: 7451–7455.
72. Long SB, Tao X, Campbell EB, et al. (2007) Atomic structure of a voltage-dependent K+ channel in a lipid membrane-like environment. *Nature* 450: 376–382.

73. Rahman KS, Cui G, Harvey SC, et al. (2013) Modeling the Conformational Changes Underlying Channel Opening in CFTR. *Plos One* 8: e74574.
74. Brohawn SG, Campbell EB, MacKinnon R (2014) Physical mechanism for gating and mechanosensitivity of the human TRAAK K+ channel. *Nature* 516: 126–130.
75. Lee CH, Lu W, Michel JC, et al. (2014) NMDA receptor structures reveal subunit arrangement and pore architecture. *Nature* 511: 191–197.
76. Okamura Y (2007) Biodiversity of voltage sensor domain proteins. *Pflugers Arch* 454: 361–371.
77. Milac A, Anishkin A, Fatakia SN, et al. (2011) Structural models of TREK channels and their gating mechanism. *Channels (Austin)* 5: 23–33.
78. Brohawn SG, del Marmol J, MacKinnon R (2012) Crystal structure of the human K2P TRAAK, a lipid- and mechano-sensitive K+ ion channel. *Science* 335: 436–441.
79. Takahashi K, Naruse K (2012) Stretch-activated BK channel and heart function. *Prog Biophys Mol Biol* 110: 239–244.
80. Caceres M, Ortiz L, Recabarren T, et al. (2015) TRPM4 Is a Novel Component of the Adhesome Required for Focal Adhesion Disassembly, Migration and Contractility. *PLoS One* 10: e0130540.
81. Martinac B (2014) The ion channels to cytoskeleton connection as potential mechanism of mechanosensitivity. *Biochim Biophys Acta* 1838: 682–691.
82. Andersen OS, Koeppe RE, 2nd (2007) Bilayer thickness and membrane protein function: an energetic perspective. *Annu Rev Biophys Biomol Struct* 36: 107–130.
83. Yoo J, Cui Q (2009) Curvature generation and pressure profile modulation in membrane by lysolipids: insights from coarse-grained simulations. *Biophys J* 97: 2267–2276.
84. Cueva JG, Mulholland A, Goodman MB (2007) Nanoscale organization of the MEC-4 DEG/ENaC sensory mechanotransduction channel in Caenorhabditis elegans touch receptor neurons. *J Neurosci* 27: 14089–14098.
85. Zhang W, Cheng LE, Kittelmann M, et al. (2015) Ankyrin Repeats Convey Force to Gate the NOMPC Mechanotransduction Channel. *Cell* 162: 1391–1403.
86. Eastwood AL, Goodman MB (2012) Insight into DEG/ENaC channel gating from genetics and structure. *Physiology (Bethesda)* 27: 282–290.
87. Tabarean IV, Morris CE (2002) Membrane stretch accelerates activation and slow inactivation in Shaker channels with S3-S4 linker deletions. *Biophys J* 82: 2982–2994.
88. Maingret F, Patel AJ, Lesage F, et al. (1999) Mechano- or acid stimulation, two interactive modes of activation of the TREK-1 potassium channel. *J Biol Chem* 274: 26691–26696.
89. Xian Tao L, Dyachenko V, Zuzarte M, et al. (2006) The stretch-activated potassium channel TREK-1 in rat cardiac ventricular muscle. *Cardiovasc Res* 69: 86–97.
90. Lolicato M, Riegelhaupt PM, Arrigoni C, et al. (2014) Transmembrane helix straightening and buckling underlies activation of mechanosensitive and thermosensitive K(2P) channels. *Neuron* 84: 1198–1212.
91. Van Wagoner DR (1993) Mechanosensitive gating of atrial ATP-sensitive potassium channels. *Circ Res* 72: 973–983.
92. Gu Y, Preston MR, El Haj AJ, et al. (2001) Three types of K(+) currents in murine osteocyte-like cells (MLO-Y4). *Bone* 28: 29–37.
93. Kawakubo T, Naruse K, Matsubara T, et al. (1999) Characterization of a newly found stretch-activated KCa,ATP channel in cultured chick ventricular myocytes. *Am J Physiol* 276: H1827–

1838.
94. Peng SQ, Hajela RK, Atchison WD (2005) Fluid flow-induced increase in inward Ba2+ current expressed in HEK293 cells transiently transfected with human neuronal L-type Ca2+ channels. *Brain Res* 1045: 116–123.
95. Zhang WK, Wang D, Duan Y, et al. (2010) Mechanosensitive gating of CFTR. *Nat Cell Biol* 12: 812.
96. Gadsby DC, Nagel G, Hwang TC (1995) The CFTR chloride channel of mammalian heart. *Annu Rev Physiol* 57: 387–416.
97. Brierley SM, Castro J, Harrington AM, et al. (2011) TRPA1 contributes to specific mechanically activated currents and sensory neuron mechanical hypersensitivity. *J Physiol* 589: 3575–3593.
98. Maroto R, Raso A, Wood TG, et al. (2005) TRPC1 forms the stretch-activated cation channel in vertebrate cells. *Nat Cell Biol* 7: 179–185.
99. Spassova MA, Hewavitharana T, Xu W, et al. (2006) A common mechanism underlies stretch activation and receptor activation of TRPC6 channels. *Proc Natl Acad Sci U S A* 103: 16586–16591.
100. Kuwahara K, Wang Y, McAnally J, et al. (2006) TRPC6 fulfills a calcineurin signaling circuit during pathologic cardiac remodeling. *J Clin Invest* 116: 3114–3126.
101. Grimm C, Kraft R, Sauerbruch S, et al. (2003) Molecular and functional characterization of the melastatin-related cation channel TRPM3. *J Biol Chem* 278: 21493–21501.
102. Brown RL, Xiong WH, Peters JH, et al. (2015) TRPM3 expression in mouse retina. *PLoS One* 10: e0117615.
103. Son GY, Yang YM, Park WS, et al. (2015) Hypotonic stress induces RANKL via transient receptor potential melastatin 3 (TRPM3) and vaniloid 4 (TRPV4) in human PDL cells. *J Dent Res* 94: 473–481.
104. Vriens J, Held K, Janssens A, et al. (2014) Opening of an alternative ion permeation pathway in a nociceptor TRP channel. *Nat Chem Biol* 10: 188–195.
105. Fruhwald J, Camacho LJ, Dembla S, et al. (2012) Alternative splicing of a protein domain indispensable for function of transient receptor potential melastatin 3 (TRPM3) ion channels. *J Biol Chem* 287: 36663–36672.
106. Kwon M, Baek SH, Park CK, et al. (2014) Single-cell RT-PCR and immunocytochemical detection of mechanosensitive transient receptor potential channels in acutely isolated rat odontoblasts. *Arch Oral Biol* 59: 1266–1271.
107. Heckel E, Boselli F, Roth S, et al. (2015) Oscillatory Flow Modulates Mechanosensitive klf2a Expression through trpv4 and trpp2 during Heart Valve Development. *Curr Biol* 25: 1354–1361.
108. Adapala RK, Thoppil R, Luther DJ, et al. (2012) TRPV4 channels mediate cardiac fibroblast differentiation by integrating mechanical and soluble signals. *J Mol Cell Cardiol*.
109. Kloda A, Lua L, Hall R, et al. (2007) Liposome reconstitution and modulation of recombinant N-methyl-D-aspartate receptor channels by membrane stretch. *Proc Natl Acad Sci U S A* 104: 1540–1545.

AIMS Press