Editorial

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Towards the Exploration of the Molecular Mechanism of a Mechanosensitive Channel Gating

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Editorial

Touch, conversion of mechanical stimulus into a specific and essential mode of sensation in humans, is perhaps the most ancient form of signal transduction form common almost in all living creatures [1]. Thus, a significant amount of scientific interest has been focused onto investigating the cellular basis of the mechanotransduction process. Presently, most of the available information stem from the functional experiments where bioelectrical changes to a form of mechanical energy has been recorded in various mechanosensory cells [2]. Recorded membrane currents established that movements of ions across the cell membrane generates the mechanosensitive ion current principally responsible for the transduction of the membrane tension into potential changes. Patch clamp experiments provided the scientific evidences that an ion channel gated by membrane deformation is involved in generation of mechanosensitive membrane current [3]. Though, mechanosensitive currents and associated unitary channel activity has been documented in many cell types, considerably fewer information is presently available about the molecular properties of the MS channels. In comparison to voltage or agonist gated ion channels, the research on the genetic and molecular properties of the MS channel family is in its infancy. Among others, several factors are responsible for the delay. Firstly, in the micro environment of a cell both production and delivery of a calibrated mechanical stimulus is only conditionally possible. Further, sensitivity of the ion channel changes according to the modality of mechanical stimulus. An ion channel may be activated by negative pressure while another responds specifically to positive pressure application or membrane indentation or shear stress. Though, a method for pressure clamping the interior of a patch pipette has been proposed, however a “tension clamp” which would homogenously control the membrane tension, is yet to be invented. Secondly, in comparison to the vast number of toxins and chemicals acting on the voltage or agonist gated channels, number of pharmacological agents acting on the MS channels is so few that whole list is restricted to a single digit only. Further, available chemicals are not specific. The final difficulty in MS channel research is encountered in heterologous expression experiments where the molecular elements connecting tension in the extracellular matrix and/or cytoskeleton to the channel molecule would largely be missing [4].

Though, the way to the goal is rather rough and full of obstacles, however, in the last decade there has been a substantial improvement in the area. Molecular structure of the bacterial mechanosensitive channels has been the firstly explored [5]. The channel molecule has been functionally reconstituted in artificial membranes [6]. It was identified that the bacterial MS channels serves as emergency valves in osmatic shock. However, bacterial MS channels are not present in higher organisms. Alternatively, a set previously known ion channels has been experimented again to explore if they are mechanosensitive. A long list of channels has been shown to be mechanosensitive [7]. The most promising among those candidates was TMC channel. There are several findings indicating that TMC channel is involved in the mechanosensation process in the inner where movement of the hairy cells generates a tension in the kinocilium pulling the MS channel complex to an open state [8]. Apparently, in addition to the MS channel a complex organization of the molecular components tethering the channel to the cytoskeleton and the extracellular matrix is necessary for a proper mechanotransduction function. Thus, it would be rather descriptive to use the term “MS channel complex” to define the molecular mechanism generating an ionic current in response to mechanical stimulus. The molecular machinery taking place in the hair cell is constitutes a typical example of the “tethered model” of mechanotranduction.

Force from lipid membrane, hosting the mechanosensitive channel, might significantly be efficient to gate the MS channel. In this case there would be no need for some additional molecular components than the ion channel molecule. Thus, the “force from lipid” concept defines another group of MS channel which can be activated by the force generated only by the lipid bilayer. Such a channel would be functional in absence of any tethering proteins if it is expressed in artificial membranes [9]. Bacterial MS channels could be assigned into such a category as they are functional

when expressed in artificial lipid membranes. However, they are not present in eukaryotes. Piezo channels, present in metazoans, can functionally be reconstituted in liposomes with a distinct mechanosensitive activity. Thus, piezo proteins, having an intrinsic mechanosensitive property, could be investigated to reveal the molecular basis of mechanical gating in an ion channel. Further, it has been blocked by ruthenium red and grammasutola toxin and activated by yoda1 [10]. The primary protein sequences of the piezo channels family are different from all other ion channel peptides. The initial topology analysis of the rat piezo1 channel indicated that there exist twelve transmembrane segments. Recently, cryo-electron microscopy analysis of the rat piezo 1 channel at a medium resolution revealed the pioneering picture about the homotrimeric channel architecture [11]. Piezo1 forms a trimeric propeller-like structure, with the extracellular domains resembling three distal blades and a central cap. A topological prediction model indicates that residues from 2210 to 2457 (termed the C-terminal extracellular domain, CED) constitute a large extracellular loop followed by the last transmembrane segment at the C terminus. This region forms the cap and is similar to that of C. elegans piezo channel [12]. Recently, by screening 3.25 million compounds a small molecule (yoda1), opening the piezo channel, has been explored [13]. By engineering chimeras between mouse Piezo1 and its Yoda1-insensitive paralog Piezo2, it was identified that part of the 1961–2063 region has an important role in imparting Yoda1 sensitivity to the Piezo1 channel [10].

Mechanosensitive ion channel has long been conceptually addressed due to the lack of solid information about its molecular structure and function due to the experimental limitations [14]. However, by the recent developments, particularly in imaging capacity i.e. cryoelectron microscopy, we have started to explore the gating machinery of the mechanotransducer ion channels.

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