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Bioinformatics in Action

sound and silence

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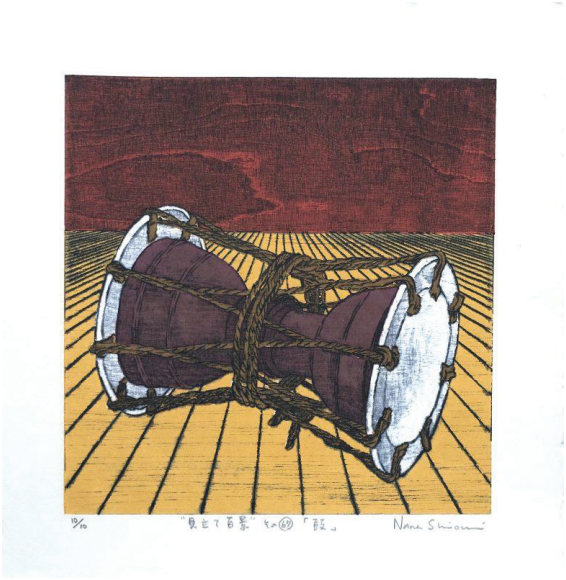
Like smells and tastes, sounds can whizz you back to forgotten places. The shriek of a seagull. The wash of waves. The crack of lightning. A motor's rumble. A Christmas carol. A childhood tune. More often than not, these castaway memories emerge wrapped in a delicate veil of magic. It is a wonderful feeling, of something you would like to know again but cannot, although it is there hidden deep inside you. A feeling we would be unable to remember were it not for our ears. Sound is sensed by way of vibrations that hit parts of our inner ear, an intricate part of mammalian anatomy. Here, vibrations are amplified, causing messages to be relayed to our brain that translates them into noise – which is what the act of hearing is. All sorts of proteins are involved in the perception of sound* but also in its unfortunate contrary: hearing impairment. One particular protein, connexin 26, forms intercellular channels in the cochlea of the inner ear so that molecules can transit from one cell to another. Connexin26 also happens to be involved in many forms of hearing impairment because, when dysfunctional, molecules are no longer able to pass.



One Hundred Views of Mitate No.67 Drum
woodcut print, 2004

by Nana Shiomi

Connexin 26, or Cx26, is one of several proteins that form channels which gather at specific locations – called gap junctions – on cell membranes. Each channel spans the plasma membrane of one cell, crosses a thin extracellular region before plunging into the plasma membrane of a neighbouring cell – thus allowing the passage of molecules from one cell to another. Gap junctions are a means for cells to communicate with one another, while keeping things levelled and regulated, a little like orchestrating a roundtable without letting anything trouble the theme under discussion. As can be expected, gap junctions are expressed in a wide variety of cells, such as neural cells where they support neural differentiation and proliferation, cardiac cells where they dictate contraction, in the lens where mutations can bring about cataracts and in the inner ear to help us hear. In this respect, several mutations in Cx26 are responsible for certain forms of hearing impairment (HI) – an ailment which affects 1 to 3 children out of 1000 at birth or during early childhood.

Gap junctions are dynamic structures, with channels being replaced and recycled on a regular basis. The channels themselves are formed in several steps. To begin with, half-channels are produced within each cell and whipped off to the plasma membrane along microtubular tracks, probably as part of a secretory pathway. In this way, one cell produces one half of a future channel, while the next one over produces the second half. Once in the plasma membrane, each half-channel then travels to a docking region in a gap junction, probably with the help of cytoskeletal actin. Once the two halves have reached their destination, they join in the extracellular region. Thus docked and locked, the two former half-channels now form an entire intercellular channel permeable to specific molecules.

Several proteins form gap junction channels in the mammalian inner ear, which is made up of three main parts: the cochlea, the labyrinth and the vestibule, all three bathed in various fluids. The cochlea is what we use for hearing, while the vestibule and the labyrinth support our sense of balance. Cx26 is widely expressed in the cochlea, where it is involved in the maintenance of ionic and metabolic homeostasis as well as in intercellular signalling. Potassium ions, K^+, are known to be at the heart of sensory transduction. Cx26 could be involved in maintaining cochlear homeostasis by sustaining the dynamics – removal and recycling – of K^+ within the organ. However, there is a great chance that Cx26 is involved in the flux of other molecules too, such as Ca^{2+} ions and inositol phosphates.

The half-channels discussed above are also known as connexons. Each connexon is a hexamer of monomers, or connexins. A fully-fledged gap junction channel is therefore a dodecamer, i.e. the union of two connexons. There are 21 different connexins (one of which is Cx26) in the human proteome, which combine to form homo- or heteromeric connexons. Connexons will then go on to form homo- or heterotypic channels. It is not hard to understand that such combinations create an astounding diversity of gap junction channel composition and function.

Cx26, in particular, has been extensively studied because of its role in sound transduction and hearing impairment. Each connexin has three distinctive structural elements essential for the channel's overall function: four transmembrane alpha helices, an N-terminal helix which protrudes into the lumen of the channel, and two extracellular loops that are essential for connexon docking. Imagine six sets of four alpha helices, i.e. a connexon, that joins to another six sets of four alpha helices to form a full channel. The overall ribbon representation looks like a wonderful firework of party streamers that is reflected on water. More prosaically, channels such as these have been compared to the Japanese hand drum, the tsuzumi, which is narrow in its centre while both ends widen out.

How do molecules travel from one cell to another? Are the channels always open? Or do they close? An elegant 'plug gating' model has been proposed. Each connexin's N-terminal helix (NTH) protrudes into the channel's lumen. When there is no difference between the cells' membrane voltages, the NTHs are held against the inside of the channel thus leaving room for molecules to pass, similar to you pressing against a wall to let something wide pass. When there is a difference in membrane voltage between the two cells, the NTHs are released from the sides and join in the channel's centre to form a plug, through which nothing can pass.

It is a wonderfully refined model. What is more, it seems that Cx26 frequently combines with another connexin (connexin 30), which could explain why waves of Ca^{2+} spread far faster through cells with a combined channel as opposed to one composed only of Cx26. It is easy to understand that if Cx26 is dysfunctional, the transduction of sound will be affected. So far, about 90 mutations have been characterised in the Cx26 gene, several of which directly influence hearing either because connexons are malformed, or because they are mistargeted or fail to dock for example. Today, roughly 6% of the world's population suffers from HI due to genetic and environmental factors. It is an affliction which spreads silently across the world. Understanding the nooks and crannies of our cochlea may help to bring sound back to those who have lost it.

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