Hearing lessons from flies

Studying the auditory system of the fruit fly can reveal how hearing works in mammals.

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Related research article

Li T, Giagtzoglou N, Eberl D, Nagarkar-Jaiswal S, Cai T, Godt D, Groves AK, Bellen HJ. 2016. The E3 ligase Ubr3 regulates Usher syndrome and MYH9 disorder proteins in the auditory organs of Drosophila and mammals. eLife 5:e15258. doi: 10.7554/eLife.15258

Image

A montage of scolopidia – the structures that fruit flies require for hearing.

The myosin motor proteins play a variety of roles inside cells, such as transporting cargo around the cell and maintaining the structure of the cell’s internal skeleton. Myosins also make important contributions to our sense of hearing, which can be revealed by studying conditions such as Usher syndrome (a severe sensory disorder that causes congenital deafness and late-onset blindness). In humans and other mammals, two myosin proteins called myosin VIIa and myosin Ila have been linked to deafness, but we do not understand how these proteins interact.

Now, in eLife, Andrew Groves, Hugo Bellen and co-workers – including Tongchao Li of Baylor College of Medicine as first author – report evidence of a conserved molecular machinery in the auditory organs of mammals and the fruit fly Drosophila (Li et al., 2016). Furthermore, the screen identified an enzyme called Ubr3 that regulates the interaction of the two myosins in Drosophila.

Auditory organs convert the mechanical energy in sound waves into electrical signals that can be interpreted by the brain. In mammals, this conversion happens in “hair cells” in the inner ear. These cells have thin protrusions called stereocilia on their surface, and the tips of these stereocilia contain ion channels called MET channels (which is short for mechano-electrical transduction channels).

Five proteins associated with the most serious form of Usher syndrome – known as USH1 – are key components of the molecular apparatus that enables the MET channels to open and close in response to mechanical force. The USH1 proteins are restricted to the tips of the stereocilia, where they form a complex (Figure 1; Prosser et al., 2008; Weil et al., 1995). Two of the USH1 proteins work together to join the tip of each stereocilium to its next-highest neighbor, forming bundles of stereocilia (Kazmierczak et al., 2007). Deflecting these bundles stretches the stereociliary bundles, which opens the MET channels and triggers the hair cell to produce an electrical signal (Pan and Zhang, 2012). Thus, the USH1 protein complex is essential for maintaining the structural integrity of stereocilia.

Flies do not have ears as such, but they are still able to detect sounds through their antennae. Despite the auditory organs of flies and mammals having different structures, they work in a similar way. In Drosophila, structures called scolopidia, which are found suspended in the second segment of the antenna, sense sound vibrations relayed from the third segment (Figure 1). Cells called cap cells and scolopale cells anchor the tip of the scolopidia to the joint between the second and third segments. The scolopale cells also secrete a protein to form the dendritic cap that connects a sensory neuron with the joint. This structure allows the...
mechanical forces produced by the sound waves to be transmitted to the neuron, activating the MET channels and causing the sensory neuron to produce an electrical signal.

Inactivating the gene that produces myosin VIIa causes the scolopidia to detach from the joint and causes the protein that forms the dendritic cap to be distributed abnormally (Todi et al., 2005; Todi et al., 2008). Now, Li et al. – who are based at Baylor, the Texas Children’s Hospital, the University of Iowa and the University of Toronto – show that inactivating the gene that encodes the enzyme Ubr3 has the same effect.

Ubr3 is a type of E3 ubiquitin ligase. These enzymes regulate a number of cell processes by helping to join small proteins called ubiquitins onto other proteins. Using a forward genetic screen, Li et al. found that Ubr3 is enriched in the tips of scolopidia, particularly at the ends of the sensory neurons and in the scolopale cells closest to the joint between the second and third segments.

Li et al. show that Ubr3 and another E3 ubiquitin ligase called Cul1 negatively regulates the addition of a single ubiquitin to myosin II. This means that the loss of Ubr3 increases the rate of the “mono-ubiquitination” of myosin II, which leads to stronger interactions between myosin II and myosin VIIa. Importantly, the mono-ubiquitination of myosin II and the interaction between myosin II and myosin VIIa helps to ensure that they (and also the fly equivalents of Usher proteins) localize correctly to the scolopidial tip. Thus, Ubr3 is crucial for maintaining the structure and function of scolopidia.

Overall, the results presented by Li et al. argue that a conserved model underlies hearing
In both Drosophila and mammals. In this model, the negative regulation of mono-ubiquitination of myosin IIa (or myosin II in the case of Drosophila) by Ubr3 promotes the formation of the myosin IIa-myosin VIIa complex (or the myosin II-myosin VIIa complex in Drosophila). The myosin complex then transports the USH1 protein complex to the tips of the stereocilia (or scolopidia) to establish the sound-sensing structure that enables the MET channels to work.

Using the power of fly genetics, Li et al. have identified new components involved in the development and function of auditory organs, and linked them to genes known to play a role in human deafness. Undoubtedly, future studies of these deafness-related genes in the Drosophila auditory organ will bring more insights into the interplay among the molecules, including the USH1 proteins, that are important for hearing.

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