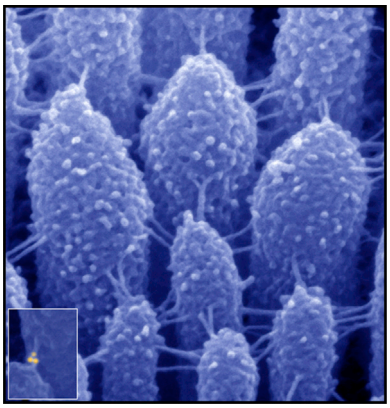
Cell

Making or Breaking the Inner Ear

Hair cells of the mammalian auditory system are able to recover from moderate noise-induced damage but if lost due to repeated or intense damage cannot be replaced. Recent studies provide insights into the restoration of mechanotransduction after moderate damage, reveal likely components of the elusive transduction channel, and unleash the latent capacities of embryonic stem cells to form inner ear sensory epithelia in culture and of supporting cells to give rise to hair cells in vivo.

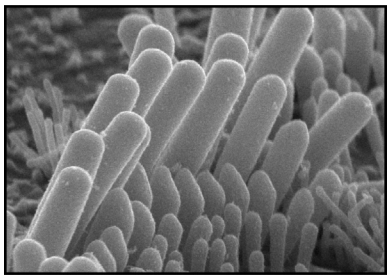


Tip links between stereocilia of an inner ear hair cell and the immunogold particles that label protocadherin 15. Image courtesy of A. Indzhykulian and G. Frolenkov.

Keeping Stereocilia in Tip-Top Shape

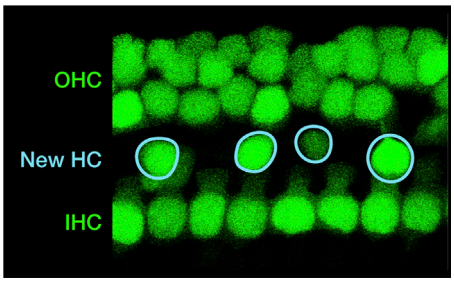
The stereocilia of auditory hair cells are connected by tip links, filamentous structures that are critical to sound detection due to their role in gating hair cell mechanotransduction channels upon deflection of stereocilia by sound. Although tip links can be severed by loud noise, they fortunately have the capacity to regenerate to restore hearing. The process by which this occurs is explored by Indzhykulian et al. (2013), who reveal that tip link composition is more dynamic than was previously thought. The authors use backscatter electron scanning microscopy to visualize tip links and simultaneously localize two of their components, cadherin 23 (CDH23) and protocadherin 15 (PCDH15), following damage. Their findings suggest that the classic picture that has CDH23 concentrated at one end of the tip link and PCDH15 at the other is not found in early regenerating links, which are shorter and have PCDH15 at both ends. The new links assemble at the tops of stereocilia, and their restoration coincides with a return of mechanotransduction, although the transduction currents associated exhibit abnormal Ca(2+)-dependent adaption to sustained deflection of the hair bundle. Only later, when CDH23 is restored to its mature position in the link, is the adaptation returned to normal. Because PCDH15 is not lost from the stereocilia surface after link disruption and is the first to reconstitute functional (albeit altered) links after damage, could this suggest that PCDH15 has a closer association with the elusive mechanotransduction channel than CDH23?
Indzhykulian, A.A., et al. (2013). PLoS Biology 11, e1001583.

Mechanotransduction Channel Exclusive, Stay Tuned!



Mechanotransduction channels are located at the tips of sensory hair bundles (pictured) in the mouse auditory organ. Image courtesy of J. Holt.

A new study by Pan et al. (2013) builds a strong case for TMC1 and TMC2 as components of the long-sought mechanotransduction channel of inner ear hair cells. The two transmembrane channel-like (*Tmc*) genes are well known to auditory researchers, with mutations in TMC1 being a cause of human deafness. The authors record whole-cell and single-channel currents from mouse hair cells lacking expression of *Tmc1*, *Tmc2*, or both, with the single-channel currents achieved by the deflection of single stereocilia. They observe that loss of either *Tmc* decreases mechanotransduction, and loss of both eliminates it. This is not to say, however, that properties of the channels are identical. TMC1 and TMC2 exhibit markedly different adaptation properties, calcium selectivity, and single-channel conductance. It will be interesting, as explored by Indzhykulian et al. (discussed above), to assess the restoration of mechanotransduction currents following loss of tip links to see whether there is differential use of *Tmcs* during the process of regeneration. Pan et al. further reveal that wild-type hair cells display a range of single-channel properties, whereas hair cells lacking either *Tmc1* or *Tmc2* have a less variable range of electrophysiological properties, which the authors suggest could reflect differential channel composition. The authors posit that gradients of differential channel composition could contribute to the mammalian cochlea's tonotopic axis—that is, its graded sensitivity to different frequencies of sound along its length. A striking result that is perhaps the clearest indication that TMC1 constitutes part of the channel itself and is not merely associated comes from the expression of the fittingly named *Beethoven* (*Bth*) point mutation in *Tmc1*, used as a model of progressive hearing loss, which reduces single-channel currents and calcium permeability. A challenge remaining for the future is the in vitro reconstitution of the channel and a mechanistic understanding of how it is gated.
Pan, B., et al. (2013). Neuron 79, 504–515.



New hair cells generated by β-catenin overexpression. OHC, outer hair cells; IHC, inner hair cells. Image courtesy of A. Edge.

Supporting Actor Thrust into Lead Role

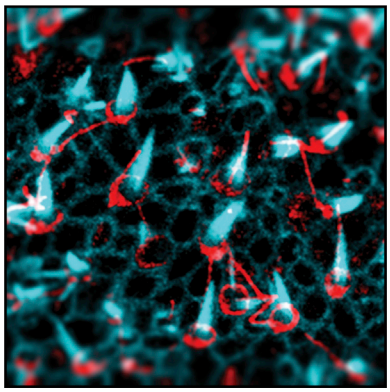
Once lost, mammalian inner ear hair cells are gone forever. New work by Shi et al. (2013) suggests that this bleak situation, a major reason for noise-induced hearing loss, is not because resident supporting cells intrinsically lack all capacity for hair cell regeneration. During development and in other vertebrates during regeneration, supporting cells serve as progenitors for hair cells, but mammalian-supporting cell proliferation or differentiation into hair cells have never been observed in vivo in response to damage. Shi et al. now show that forced overexpression of β-catenin in the subpopulation of supporting cells that express Lgr5 (a G-protein-coupled receptor that is a stem cell marker in other epithelia) can trigger proliferation and the generation of new hair cells. These new hair cells occupy ectopic positions in the sensory epithelia, and functionally integrating them presents a further challenge. A next step may be to inducibly express β-catenin in supporting cells after damage has occurred to see whether the induced hair cells might occupy the position of those that are lost.

From Spheres to Inner Ears

The latest complex tissue to be generated in vitro from mouse embryonic stem cells is the inner ear sensory epithelia. This impressive feat, accomplished by Koehler et al. (2013), will be a boon to the study of inner ear development and of balance and hearing disorders. By using the technique known as SFEBq (serum-free floating culture of embryoid-body-like aggregates with quick reaggregation) combined with the well-timed administration of morphogenetic cues, the authors guide mouse embryonic stem cells to make vesicles with features of inner ear sensory epithelia, complete with functional hair cells innervated by sensory neurons via a specialized synapses unique to the inner ear. The signals needed to accomplish this are surprisingly few, though their timing delivery is critical, with the SFEBq culture first treated with bone-morphogenetic protein 4, which initiates nonneural ectoderm, and the transforming growth factor β inhibitor SB431542 to quell induction of mesoderm or endoderm. This is followed by fibroblast growth factor 2 and a BMP inhibitor to trigger the cells to adopt a preplacodal fate (the inner ear arises from the otic placode). Further analysis of the resulting tissue shows that it bears most similarity to vestibular organs, and it will be interesting to see what further tweaks to the culture's system might yield epithelia more similar to auditory regions and to begin to model diseases of the inner ear.

Koehler, K.R., et al. (2013). Nature 500, 217–221.

Robert P. Kruger



Stereocilia (cyan) and kinocilia (red) protruding from a stem-cell-derived sensory epithelium. Image courtesy of K.R. Koehler.