brainstem auditory system before the information even reaches the auditory cortex. The STRFs are clearly useful in defining responses to relatively simple stimuli, like noise bands and frequency sweeps. But is this method up to the job of finding the relevant stimuli in complex natural scenes? Can the neural representation of complex real-world auditory stimuli be adequately understood in terms of a temporal sequence of acoustic features? The inability of reverse correlation to detect nonlinear computation may limit its ability to solve this ultimate problem. But in the process, it will define the extent to which nonlinear computations contribute to auditory processing, in proportion to the failure of reverse correlation methods to adequately account for the stimulus selectivity of a neuron (*9*).

References

1. D. H. Hubel and T. N. Wiesel, *Sci. Am.* **241**, 150 (September 1979).
2. D. Marr, *Vision: A Computational Investigation into the Human Representation and Processing of Visual Information* (Freeman, San Francisco, 1982).
3. R. C. deCharms, D. T. Blake, M. M. Merzenich, *Science* **280**, 1439 (1998).
4. N. Suga *et al.*, *Trends Cogn. Sci.* **1**, 13 (1997).
5. N. Kowalski, D. A. Depireux, S. A. Shamma, *J. Neurophysiol.* **76**, 3524 (1996).
6. E. De Boer and P. Kuyper, *IEEE Trans. Biomed. Eng.* **15**, 169 (1968); J. J. Eggermont, A. M. H. J. Aertsen, D. J. Hermes, P. I. M. Johannesma, *Hear. Res.* **5**, 109 (1981).
7. Two recent examples are D. L. Ringach, G. Sapiro, and R. Shapley [*Vision Res.* **37**, 2455 (1997)] and J. J. DiCarlo, K. O. Johnson, and S. S. Hsiao [*J. Neurosci.* **18**, 2626 (1998)].
8. C. Gross *et al.*, *J. Neurophysiol.* **35**, 96 (1972).
9. I. Nelken *et al.*, *ibid.* **78**, 800 (1997).

UPDATE: HUMAN GENETICS

More Deafness Genes

Karen P. Steel and Steve D. M. Brown

New genes underlying genetic deafness have appeared in a rash of reports that continues apace [see previous commentary (*1*)]. In *Nature Genetics*, moderate but dominantly inherited hearing impairment in two large families is shown to be a result of a mutation in the *TECTA* gene, on chromosome 11 (*2*). In addition, on pages 1444 and 1447 of this issue, Probst *et al.* and Wang *et al.* report that the unconventional myosin gene *MYO15* is mutated in the *shaker-2* mutant mouse and in three human families with recessive, nonsyndromic deafness linked to chromosome 17, *DFNB3* (*3*, *4*).

The first new gene implicated in deafness, *TECTA*, encodes the protein α-tectorin, one component of the tectorial membrane, an extracellular matrix that hangs over the hair cells. Each hair cell projects about 100 stereocilia from its upper surface, and the tectorial membrane just touches the tallest of these. During sound stimulation, shearing between the tectorial membrane and the hair cells leads to the deflection of stereocilia bundles. The bending of the stereocilia during sound stimulation pulls on delicate tip links between adjacent stereocilia, which in turn directly opens a transduction channel at the end of the tip link, triggering the response (*5*). This arrangement must be precisely maintained for normal hearing.

The discovery of α-tectorin mutations in people with hearing impairment suggests that the properties of the tectorial membrane are critical for delivering an appropriate stimulus to the hair cells. It also opens up a new class of candidate molecules for the dozens of deafness genes yet to be identified.

The other new gene, *MYO15*, encodes the third myosin molecule implicated in deafness, out of only a handful of deafness-associated genes so far identified. It was found by bacterial artificial chromosome (BAC) rescue, a process in which a nonmutated DNA clone was introduced into the genome of a *shaker-2* mutant homozygote to see whether *shaker-2*'s characteristic deafness and hyperactive behavior could be eliminated. When a BAC clone did succeed in rescuing the phenotype, it was sequenced and the myosin gene identified. Mutations in the gene were found in the *shaker-2* mouse as well as in human families.

The first gene found to affect the sensory hair cells directly also encoded a myosin, myosin VIIA, in the *shaker-1* mouse mutant and Usher syndrome type 1B (*6*, *7*), and this was followed rapidly by the discovery of a second myosin, myosin VI, as responsible for the deafness in the *Snell's waltzer* mouse mutant (*8*). What function of these myosins makes them so critical for hearing? A myosin is believed to be responsible for adjusting the tension on the tip link, but it is myosin 1B that is the favored candidate for this role. Unconventional (non–muscle-like) myosins act as actin-based motors, and are generally thought to use actin filaments as tracks along which to transport their cargos such as intracellular vesicles. Sensory hair cells have an abundance of actin for the unconventional myosins to act on; the stereocilia are filled with actin and are anchored in a dense actin-rich network inside the cell. Thus, the three unconventional myosins that underlie mammalian deafness may help to move vesicles or other cargo around the hair cell, using the abundant actin as a substrate, as in other cell types.

However, these unconventional myosins may have another role. The earliest abnormalities seen in the mouse mutants all involve the actin-rich stereocilia: *shaker-1* mutants show disorganization of the stereocilia bundle (*9*), stereocilia are fused in *Snell's waltzer* mutants, and now *shaker-2* mutants are reported to have abnormally short stereocilia (*3*). These defects all suggest that these unconventional myosins may anchor or otherwise control the actin-based architecture that is vital to hair cell function, in contrast to simply using actin as a substrate for moving cargo. The recent report that diaphanous, a protein that assists in establishing an actin scaffold, is also implicated in progressive hearing loss emphasizes the critical importance of the actin network in hair cell function (*10*). Now the difficult bit begins: establishing exactly what these molecules do in hair cells, and why each one has such a different effect on the ultrastructure of the developing cell.

References

1. K. P. Steel, *Science* **279**, 1870 (1998).
2. K. Verhoeven *et al.*, *Nature Genet.* **19**, 60 (1998).
3. F. J. Probst *et al.*, *Science* **280**, 1444 (1998).
4. A. Wang *et al.*, *ibid.*, p. 1447.
5. A. J. Hudspeth and P. G. Gillespie, *Neuron* **12**, 1 (1994).
6. F. Gibson *et al.*, *Nature* **374**, 62 (1995).
7. D. Weil *et al.*, *ibid.*, p. 60.
8. K. B. Avraham *et al.*, *Nature Genet.* **11**, 369 (1995).
9. T. Self *et al.*, *Development* **125**, 557 (1998).
10. E. D. Lynch *et al.*, *Science* **278**, 1315 (1997).

K. P. Steel is at the Medical Research Council (MRC), Institute of Hearing Research, University Park, Nottingham NG7 2RD, UK. E-mail: karen@ihr.mrc.ac.uk. S. D. M. Brown is in the MRC Mammalian Genetics Unit, Harwell, Oxon OX11 0RD, UK.