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The majority of the hearing-impaired suffer from sensorineural hearing loss, which results from damage to the sensory hair cells of the inner ear. The human cochlea contains about 16,000 of these cells, which do not regenerate after damage. In an effort to prevent or reverse deafness, Hudspeth’s group is working to better understand the normal hearing process, the causes of hearing deterioration, and possible means to regenerate hair cells.

Within the cochlea, mechanical signals representing sound are converted into vibrations along the basilar membrane, upon which stand some 16,000 hair cells. Each hair cell is endowed with a few hundred fine “feelers,” or stereocilia, that constitute its hair bundle. Sound-induced vibrations set the hair bundle in motion, evoking electrical responses by opening mechanically sensitive ion channels. As a result of the direct connection between the hair bundle and ion channels, the transduction process of hair cells is remarkably rapid; we can consequently hear sounds at frequencies as great as 20 kHz. The direct nature of auditory transduction also makes the process highly sensitive.

The extraordinary sensitivity of our hearing results from cochlear amplification of its mechanical inputs. Researchers in Hudspeth’s research group are exploring how human hearing benefits from a mechanical amplifier in each hair bundle. They have found that bundles are spontaneously active and that a small force synchronizes this motion with the stimulus. Measurement of the mechanical work performed in this situation confirms that a hair bundle can amplify and tune its mechanical inputs. Members of the research group are now extending these results to the mammalian ear. Identifying the active process in the human cochlea is especially important because hearing loss usually begins with deterioration of this amplifier.

In an effort to learn how hair cells develop, Hudspeth’s group is conducting molecular-biological experiments on the larval zebrafish. In the lateral line of this species, new hair cells continually arise to replace those that die as a result of aging or chemical toxicity. The division of a precursor cell consistently produces a pair of hair cells, each of which responds to water movement toward the anterior, whereas the other is sensitive to posterior flow. To establish which signaling pathways lead to the production of new hair cells, the investigators hope to identify pathways that might be activated in the human ear to foster the replacement of hair cells.

Finally, members of the lab are investigating the regeneration of hair cells in the inner ear of the mouse, a preparation that resembles the human inner ear. They have identified a potent and nontoxic chemical that inhibits a group of enzymes called Lats kinases and fosters the proliferation of supporting cells, an initial step toward hair cell regeneration. Related compounds have proven effective in eliciting the proliferation of neuronal precursors in the eye and even of cardiomyocytes in the heart.

Hudspeth’s research has led to a deepened understanding of the receptor cells of the inner ear and how they contribute to hearing and hearing loss. He hopes that further investigation will indicate both the causes and potential remedies for certain forms of human hearing impairment, an affliction that affects 10 percent of the American population.