lacking detectable *p53* alterations supported ONYX-015 replication and cytolysis[2]. Understanding how p53 suppresses ONYX-015 replication is clearly important, and may provide additional insights into p53 function.

If ONYX-015 proves effective, it will be a boon for cancer therapy. After all, *p53* mutation is the most frequent genetic alteration in human tumors, so strategies to attack *p53* mutant cells have widespread utility. What's more, there is a desperate need for better approaches to treat these tumors: *p53* mutant tumors are inherently more aggressive, and may be less responsive to standard therapies, than their *p53* normal counterparts. Even if ONYX-015 encounters setbacks in the clinic, its development represents a milestone in cancer therapy. In particular, it provides welcome evidence that cancer cells can be outsmarted, and reinforces the belief that basic cancer research will produce additional strategies to eliminate cancer cells by finesse rather than dynamite.

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Motors, channels and the sounds of silence

Mutations in myosin VIIA and connexin 26 lead to hereditary non-syndromic hearing loss

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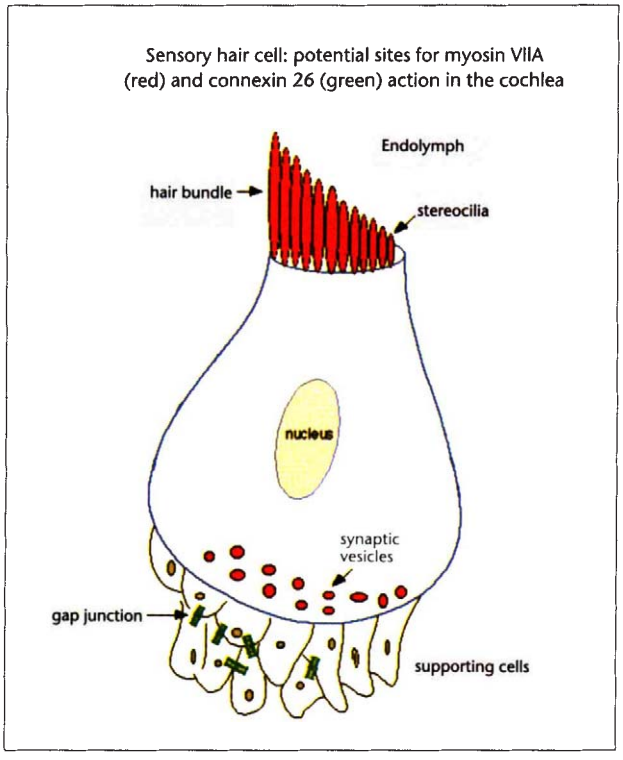
THE COCHLEA IS one of the most intricate organs in our body, responsible for our sense of hearing through the use of a mere 16,000 hair cells, the sensory cells of the inner ear. Many functions are crucial for the proper workings of the inner ear, including cell membrane depolarization and mechanoelectrical transduction, transmitter release, and ion transport. Consequently, mutations in a gene involved in just one of these cellular functions can upset the whole balance, and ultimately lead to the loss of hearing. So it should be no surprise that more than one hundred genes may be involved in the orchestration and regulation of this mechanical sense. As reported in a recent issue of *Nature*[1] and this month's *Nature Genetics*[2, 3], three groups have independently identified mutations that upset this delicate balance resulting in non-syndromic deafness. Approximately 30 genes for syndromic deafness, where hearing loss is associated with other abnormalities, have been cloned so far. However, these are the first reports of genes involved in non-syndromic deafness, the most common form of genetic deafness that is characterized by hearing impairment that is not associated with other abnormalities[1–3].



Sensory hair cell: potential sites for myosin VIIA (red) and connexin 26 (green) action in the cochlea

Salome G. Waelsch, a pioneer in mouse embryology and genetics, could not have made a more accurate prediction regarding the cloning of genes involved in hearing when in 1991 she said it would "not be long before...small molecular changes in a gene product would be identified...in genetic studies of hearing defects"[4]. Estimates suggest that there are between thirty and 100 genes responsible for recessive hearing loss alone, so that the "gene hunters" in the hearing field have a very promising future[5]. This potential is now beginning to be realized with the identification of genes involved in non-syndromic deafness.

Defining the molecular basis of non-syndromic deafness got off to a slow start mostly because of difficulties in mapping genes for this disease. The boost needed to accelerate the field came in 1995, with the mouse providing the key entry into the beginnings of the molecular unraveling of non-syn-

dromic deafness. Mutations were found in two unconventional myosins in mouse mutants exhibiting autosomal recessive deafness, myosin VIIA in shaker-1 mice[6] and myosin VI in Snell's waltzer mice[7]. In humans, myosin VIIA mutations were found to cause Usher's syndrome type IB, a syndromic deafness with progressive blindness[8]. Unconventional myosins are molecular motors that bind to actin, hydrolyze ATP, and translocate along actin filaments. They have been implicated in cell locomotion, phagocytosis, secretion, organelle transport, and mechanoregulation of membrane protein function. Now, mutations in myosin VIIA have been found to be responsible for non-syndromic deafness in humans. Weil and co-workers[3] found linkage to chromosome 11q13 in a large consanguineous Tunisian family whose members were affected with profound deafness. As the gene encoding myosin VIIA was known to map to this region, the authors performed mutation analysis and discovered a splicing defect in one of the exons in the 5′ region of this molecular motor. Mutations in myosin VIIA were also found by Liu *et al.*[2] using a different approach. They analysed mutations in small families with non-syndromic deafness, where linkage could not be performed. The ability to perform such an analysis is invaluable, since most deaf individuals are part of small families, precluding linkage analysis.

Kelsell and colleagues[1] have discovered mutations in an unrelated membrane protein, connexin 26, in individuals with hereditary sensorineural deafness. The connexin family of transmembrane proteins form cylindrical channels in gap junctions, which are distributed along the lateral surfaces of adjacent cells and are sites used to transfer small molecules, such as intracellular signaling molecules and ions, between cells. Perhaps of most interest, the investigators observed that different mutations in the same connexin gene caused both recessive (DFNB1) and dominant (DFNA3) hearing loss.

How do these newly identified gene products function in hearing? During the process of hearing, the mechanical force of sound is converted into electrical signals (mechanoelectrical transduction). In the cochlear hair cells, hair bundles, composed of stereocilia, lie on the apical surface of the cells and oscillate in response to sound (see figure). The sliding of adjacent stereocilia opens transduction channels, allowing an influx of endolymphatic K^+ into the hair cells, which leads to cell membrane depolarization. Depolarization activates voltage-sensitive Ca^{2+} channels in the basolateral surface, and subsequent Ca^{2+} inflow triggers neurotransmitter release onto the postsynaptic terminals of the VIIIth cranial nerve. Thus, in the cochlea, mutations in a protein composing the transduction apparatus, affecting the structure of the stereocilia, involved in synaptic vesicle release or participating in K^+ transport, may very well result in hearing impairment.

Myosin VIIA is expressed along the stereocilia of the hair cell, and its cellular localization suggests that it is the intracellular anchor of the basal links that connect each stereocilium to its neighbor[9]. Myosin VIIA is also present within the hair cell and may play a role in membrane trafficking such as that associated with synaptic vesicle release. In the cochlea, gap junctions are known to exist between the supporting cells that surround hair cells[10]. Connexin 26 may form the cell-to-cell pathway for recycling K^+ ions back to the endolymph following auditory transduction.

Two very intriguing questions (among others) remain. Why do proteins that would appear to have general functional properties in the cells of many tissues, such as transport of ions and synaptic vesicle trafficking, have specific specialized functions in the hair cell of the cochlea? We might expect that mutations in myosins and connexins would be lethal, or at best, cause multi-organ defects. One possibility is that other unconventional myosins and connexins, both part of large protein families, play a redundant role only in non-cochlear tissue, compensating for specific inactivating mutations. As we discover the specific role of each of these proteins in the cell, and in the cochlea in particular, this question will be resolved. And how do mutations in the same gene influence a recessive or dominant mode of inheritance? Modifier genes may play a key role in determining how a mutation will be inherited. Once again, the mouse is leading the way. Noben-Trauth and colleagues at The Jackson Laboratory have recently identified a modifier affecting hearing in the mouse, indicating that the same allele may show a semidominant and recessive mode of inheritance depending upon its genetic background (K. Noben-Trauth, personal communication).

What does all this mean from a biomedical point of view? The identification of genes whose mutations are responsible for deafness in the human community will certainly facilitate the development of gene therapy approaches, which is already underway. If we begin discussing cures or treatments for non-syndromic deafness, then we must begin to address a controversial issue in the deaf community: Is deafness, or hearing loss, a genetic defect we should correct, or another culture with an alternative (sign) language[11]? The answer may depend on whether a person is prelingually deaf, and therefore has an established place in the deaf community from the start, or loses his/her hearing later in life, having to deal with the adjustments of hearing loss in a "hearing" community. The recent identification of genes involved in non-syndromic deafness will undoubtedly fuel this debate.

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