An ion transporter involved in congenital deafness
Focus on “Human pendrin expressed in Xenopus laevis oocytes mediates chloride/formate exchange”

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Congenital hearing impairment is inherited in about one-half of all cases. Of the 1 in 2,000 annual births so affected (11), a large proportion (>1 in 10,000) (2, 4, 12) have defects in the anion transport protein, pendrin. Clinical findings include progressive hearing loss, displasia of the cochlea, a widened vestibular aqueduct (2), and sometimes thyroid problems (19), including goiter (Pendred syndrome) (14).

The disease is caused by several different mutations in pendrin (2, 5, 12, 15). Pendrin is an 86-kDa protein (4) that maps to human chromosome 7 (1, 4, 19). Pendrin mRNA has been localized to several cell types of the inner ear (5), which may be involved in resorption of endolymphatic fluid (20). Endolymphatic fluid is rich in K+ and has a highly positive potential relative to the plasma (20). Pendrin mRNA levels are highest in the thyroid (4) and may be localized to the follicular cells (5). Lower levels of pendrin mRNA are also found in the fetal kidney and fetal brain (4).

Pendrin has structural similarity to a variety of transport proteins (4), including sulfate transporters and the more closely related DRA (downregulated in adenoma) (16) and DTD (diastrophic dysplasia) proteins (7).

Direct measurement of transport properties of the recombinant protein in Xenopus oocytes showed that pendrin transported halides, including iodide, but not sulfate (18). Iodide transport by pendrin is consistent with thyroid disease in Pendred syndrome.

In the current article in focus, Scott and Karniski (Ref. 17, see page C207 in this issue) further explore the anion transport properties of pendrin. They now show that pendrin mediates the transport of formate (chloride/formate exchange). The Km for chloride and inhibitor sensitivity (18) are similar to the properties of the renal chloride/formate exchanger (9), but it is not known whether renal chloride/formate exchange activity is due to pendrin. Kidney disease has not been found to be associated with mutations in pendrin, but loss of chloride/formate exchange (or other anion transport activity of pendrin) in the inner ear could be a direct or indirect cause of the structural changes such as dilation of the vestibular aqueduct and other cochlear defects (2).

The findings of this article are an important part of a large and successful effort to understand the genetic and functional basis of congenital hearing impairment (see “Online Mendelian Inheritance in Man” http://www3.ncbi.nlm.nih.gov/Omim). An important goal of these studies is to understand how these proteins participate in normal physiological processes and how mutations lead to disease. This article helps to demonstrate that functional studies are absolutely essential to confirm and extend predictions made from computational analysis (“bioinformatics”). Substrate specificity, turnover numbers, regulatory properties, stoichiometry, electrogenesis, to name a few functional properties, are defined by appropriate functional measurements. Comparing and contrasting the wild-type and mutant proteins to determine how the mutations affect the above properties and other properties such as cellular trafficking, degradation, and ion gradients is now possible and required for further progress.

Deafness and loss of inner ear structure is also a common finding in mouse models where a variety of other transport genes, including the Na+-K+-2Cl- co-transporter (3, 6), the Ca2+-ATPase (10), a K+ channel (13), and the H+-ATPase (8), have been ablated or mutated. These models demonstrate that ion transport processes play important yet poorly understood roles in developmental processes that are involved in creation and maintenance of anatomic structures in the ear and elsewhere.

Elucidation of the role of anion transport by pendrin in the gross anatomic changes in the inner ear and thyroid will be an important next step in understanding congenital hearing impairment and perhaps providing therapies.

Lessons learned from these studies may also lead to the further understanding of other diseases such as cystic fibrosis, where mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) result in...
in complex changes in epithelial cell function and, ultimately, morbidity and death, which are not easily related to the chloride channel functions of CFTR alone.

REFERENCES


