Lmna develop a post-natal cardiac and skeletal muscular dystrophy[13] reminiscent of Emery-Dreifuss muscular dystrophy. In addition to muscular dystrophy, the mice lack discernable white adipose tissue, a feature not observed in the human muscular dystrophies associated with mutation of *LMNA*.

Whither mechanism?

Unfortunately, these genetic discoveries have generated not a whiff of insight into the mechanisms by which specific mutations in the lamin A/C gene might cause either regional loss of adipose tissue or the two distinct cardiac syndromes with which some mutations are associated. So what can be said of the lamins?

Lamins A and C form a dimer through their central rod domains and interact with chromatin and integral proteins of the inner nuclear membrane through binding sites in the rod domain and C-terminal globular tail. The lamins have been implicated in mediating DNA replication, chromatin organization, spatial arrangement of nuclear pore complexes, nuclear growth and anchorage of nuclear-envelope proteins[11].

The fact that FPLD is caused by a limited number of missense mutations that affect two closely-spaced residues of the C-terminal tail implies that this region of the protein is involved in one or more activities required by adipocytes in specific tissue beds. It is critical that the molecular interactions between lamin A/C and adipocyte nuclear and cytoplasmic proteins are characterized, assuming such interactions take place. The mechanism by which the implicated missense mutations alter adipocyte function may thereby become clear. At this point, however, we do not know which adipocyte functions to evaluate; the defect in FPLD could involve proliferation of preadipocytes, adipocyte differentiation, regulation of programmed cell death or any one of a large number of metabolic changes that would alter adipocyte mass.

The link between regional adipocyte loss and insulin resistance must also be clarified. Once again, the current finding provides little help in this regard. Perhaps adipocyte loss affects insulin sensitivity through reduced levels of adipocyte-derived circulating factors, such as leptin[14]. Alternatively, mutant lamin A/C may effect the disorder through its mediation of metabolic events in other tissues, such as muscle or liver. What is the basis for puberty-induced adipose tissue loss in this disorder? Do sex steroids influence lamin expression, or affect a pathway influenced by lamin mutation?

As incomplete as our understanding is (from a functional perspective), the new genetic findings raise provocative questions about a larger and unanticipated role of the nuclear membrane and its protein constituents in adipocyte function and metabolic disease. For example, type 2 diabetes is a common metabolic disorder that typically involves altered size of specific adipocyte depots and insulin resistance. Investigation of the lamins and the pathways in which they act may shed light on the aetiology of this common, complex disorder. The genes that, when mutated, cause other types of lipodystrophy will doubtless provide additional surprises—opening up hitherto unsuspected pathways that regulate adipose mass and insulin sensitivity. □

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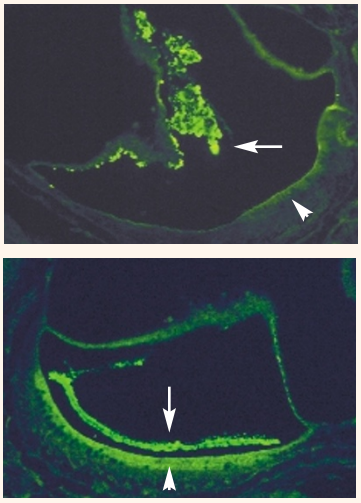
A take on the tectorial membrane

Deafness is a common sensory impairment, and many different genes can be involved. Early research in deafness naturally focused upon the sensory hair cells in the inner ear. Hair cells have an array of finger-like extensions called stereocilia protruding from their apical surface. The tallest stereocilia touch an extracellular gel; in the cochlea, this gel is the tectorial membrane. When vibration enters the cochlea, the tectorial membrane and the hair cells are moved about different pivot points, causing a shearing motion that bends the stereocilia, opening the transduction channels and leading to hair-cell depolarization and synaptic activity.

The tectorial membrane has been a rather neglected partner in the process, despite the finding—nearly two years ago—that mutations in *TECTA*, which encodes a component of its matrix, cause deafness in humans[1]. Until recently, there were no histological studies of how defects in the tectorial membrane effect genetic deafness. Two studies remedy this deficit. In December's issue of *Nature Genetics*, Richard Smith and colleagues reported that mice with a targeted disruption of *Col11a2*, encoding a component of collagen, have aberrant tectorial membranes. Their constituent fibrils are disorganized and more widely-spaced[2] than normal—features associated with moderate hearing impairment. *COL11A2* mutations are also found in forms of syndromic and non-syndromic deafness (DFNA13). Now, on page 139, Marie-Christine Simmler and colleagues[3] describe ultrastructural defects of the tectorial membrane in mice with a disrupted otogelin (*Otog*) gene, again associated with hearing impairment. In these mutants, the extracellular membranes of the 'balance' organs of the inner ear (the otolithic membranes and the cupulae) are even more severely disorganized and detach from the hair cells (see figure), leading to balance defects. The tectorial membrane is notoriously susceptible to histological artefact, making it difficult to study, but these reports, together with the earlier report of *TECTA* mutations in human deafness[1], highlight its importance in auditory function and its potential involvement in human genetic deafness.



Lost without otogelin. The otolithic membrane (arrow) has lost contact with its sensory hair cells (arrowhead) in the inner ear of a mouse deficient of otogelin (upper panel).

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