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The tectorial membrane: One slice of a complex cochlear sandwich

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Abstract

Purpose of review—The review is both timely and relevant as recent findings have shown the tectorial membrane plays a more dynamic role in hearing than hitherto suspected, and that many forms of deafness can result from mutations in tectorial membrane proteins.

Recent findings—Main themes covered are (i) the molecular composition, structural organisation and properties of the tectorial membrane, (ii) the role of the tectorial membrane as a second resonator and a structure within which there is significant longitudinal coupling, and (iii) how mutations in tectorial membrane proteins cause deafness in mice and men.

Implications—Findings from experimental models imply that the tectorial membrane plays multiple, critical roles in hearing. These include coupling elements along the length of the cochlea, supporting a travelling wave and ensuring the gain and timing of cochlear feedback are optimal. The clinical findings suggest stable, moderate-to-severe forms hereditary hearing loss may be diagnostic of a mutation in *TECTA*, the gene encoding one of the major, non-collagenous proteins of the tectorial membrane.

Keywords

Tectorial membrane; *TECTA*; cochlea; deafness genes; hearing loss

Introduction

The tectorial membrane (TM) of the inner ear is a ribbon-like strip of extracellular matrix that spirals along the entire length of the cochlea. It attaches along its medial side to the surface of the spiral limbus, stretches across the spiral sulcus, and lies over the surface of the organ of Corti where it affixes to the tips of the sensory hair bundles of the outer hair cells (Fig. 1a). The TM was once thought to act merely as stiff beam pivoting around its attachment point to the spiral limbus, with the shearing motion generated between the surface of the organ of Corti and the TM in response to sound-induced vibrations of the basilar membrane driving the hair bundles. Recent experimental findings suggest more complex modes of TM behaviour, including an ability to propagate travelling waves at audio frequencies along its length [1•]. In this brief review we will summarise what is known to date about the composition, structure and properties of the TM, its role in hearing, and how mutations in TM proteins cause deafness.

Composition

The TM is composed of several genetically distinct types of collagen, collagen Types II, V, IX and XI and three non-collagenous glycoproteins, α -tectorin (Tecta), β -tectorin (Tectb) and otogelin [2-8]. Tecta, Tectb and otogelin are proteins that are only expressed at high levels in the inner ear and they account for ~50% of the protein present in the TM. The cDNA sequences for otogelin and Tecta predict large, modular glycoproteins (313 and 239 kDa respectively), whilst the sequence for Tectb encodes a much smaller protein (36 kDa) (Fig. 1b).

The Tecta cDNA sequence predicts a protein with an N-terminal entactin G1-like domain, a large central zonadhesin-like (ZA) domain with 2 partial and 3 full and von Willebrand Factor (vWF) Type D repeats, and a C-terminal zona pellucida (ZP) domain. The protein is post-translationally cleaved at two sites to yield three fragments that roughly encompass the different domains and remain disulphide cross-linked to each other. The Tectb sequence predicts a protein with a single ZP domain. The ZP domain is a protein polymerisation module that has been identified in more than 100 proteins and it may enable Tecta and Tectb to form homo and heteropolymers [9]. The otogelin protein sequence comprises multiple vWF type D repeats like those in Tecta, a threonine/serine/proline rich domain, five vWF type B repeats, and a C-terminal cysteine knot. All three TM proteins contain multiple predicted sites for N-glycosylation and there is evidence Tecta is a light, keratan sulphate proteoglycan [10]. The uronic acid content of the TM is not high [11], and the GAG content is low [12] so the large proteoglycans that are typical of cartilage are unlikely to be major components of this matrix.

Structure

The central core of the TM is composed of bundles of 20 nm diameter collagen filaments that are imbedded in an unusual striated-sheet matrix [13] (Fig 1c). The striated sheet matrix is formed by two types of fine-diameter (7-9 nm) filaments, a light and a dark staining type that lie in parallel within the plane of each sheet and are extensively linked along their length by staggered cross bridges [13]. The available evidence indicates the striated-sheet matrix is tectorin based. Features located around the surface of the TM (Fig. 1c) include the covernet - an anastomosing network of large calibre fibrils that run predominantly longitudinally over the upper surface of the TM, the marginal band - a dense thickening of the lateral edge of the TM, Kimura's membrane - a thickening of the lower surface into which the hair bundles of the outer hair cells are imbedded, and Hensen's stripe - a ridge that runs longitudinally along the lower surface of the TM immediately adjacent to the hair bundles of the inner hair cells.

The dimensions of the TM vary along the length of the cochlea; its radial width and cross-sectional area increase from the basal to the apical end of the cochlea. There is a radial gradient in collagen fibril packing density across the TEM with a greater density in the limbal than the middle zone, but there are no gradients in collagen fibril density along the length of the TM [14]. The collagen filament bundles (collagen fibrils) are oriented radially across the TM with an offset of ~15 degrees towards the apical end of the cochlea. Recent second harmonic imaging experiments of isolated TMs have suggested the orientation of collagen fibrils relative to the surface of the organ of Corti differs as function of position along the length of the cochlea [15].

Anisotropy and stiffness gradients

There is evidence for anisotropy in the TM [16,17] with the radial stiffness of the TM being greater than the longitudinal stiffness, as one might expect from the observed distribution of

collagen fibrils. A recent study [18•] has also reported that the stiffness of the TM normal to its lower surface is significantly larger than its lateral stiffness in the region of the hair cells, a property that may facilitate deflection of the outer hair cell stereocilia when the TM slides over the organ of Corti. Whilst some studies have found no evidence for a longitudinal variation in stiffness as a function of position along the length of the cochlea [16,19], three recent papers [20,21, 22••] have shown otherwise. Measurements of equilibrium stress-strain relationships revealed segments of the isolated tectorial membrane from the basal end of the cochlea had a larger transverse stiffness than those from the mid-apical region [20]. Using an atomic force microscope indenter probe with a tip radius of 1 μm , Gueta and colleagues [21] found that Young's modulus decreased ~10 fold between the apical and basal ends of the isolated mouse TM. This longitudinal difference in stiffness was found only in the region of the TM overlying the hair cells and was attributed to the change in the packing density of the covernet fibrils. Finally, measuring at five different points along the gerbil hemicochlea preparation using a calibrated needle with a 25 μm diameter tip vibrating at 10 Hz, Richter and colleagues [22••] found base-to-apex decreases in both the radial and transverse stiffness of the TM of -4.9 dB/mm and -4.0 dB/mm respectively, a change in stiffness as a function of length similar to that previously reported for the basilar membrane.

Secondary cochlear frequency map

It has been suggested [23,24] that, at each place along the cochlea, the TM resonates at frequencies below the best frequency of the basilar membrane and thus provides an efficient mass load to the stereocilia of the outer hair cells at their best frequency (Fig. 2). The ability of the TM to oscillate at acoustic frequencies has been shown experimentally [25-28]. A second peak of sensitivity in basilar membrane tuning curves [29,30••] and a local minimum of the neural suppression tuning curves [30••] are also observed at ~0.5 octaves below the best frequency in the high-frequency region of the mouse cochlea and are thought to be due to the TM resonance. A secondary cochlear frequency map, which characterises changes in the TM resonance frequency along the cochlea, has been derived from the *in vivo* responses of the cochlea [31-33•]. The base-to-apex increase in the cross-sectional area of the TM [34], and the base-to-apex decrease in TM stiffness [20,21, 22••] provide the theoretical basis for this secondary frequency mapping.

Multimodal vibrations of the TM

Due to its anisotropy [16,17] and the frequency dependency [17,35] of its mechanical properties, the TM is unlikely to move as a rigid rod or behave as a lump inertia. Vibrations of the TM at a given location along the cochlea will be dominated by the transverse or radial components depending on frequency. This complex vibration trajectory is indicative of a second vibration mode, and is evident for frequencies < 0.5 octave below the best frequency in the apical turn of the guinea-pig cochlea [27]. The TM also supports multiple internal vibration modes. For frequencies < 3 kHz the lower surface of the TM and the reticular lamina oscillate with similar amplitude but counterphase, leading to changes in shape and volume of the subreticular space that create direct fluid coupling between outer and inner hair cells.

TM travelling waves

In most current models of cochlear mechanics the TM is simplified to a structure that has infinite stiffness in the radial direction but no elastic coupling along the length of the cochlea. This simplification is unacceptable in view of the growing body of data indicating the TM has a finite radial stiffness comparable to that of the outer hair cell stereocilia [17,22••, 35] and significant longitudinal coupling along its length [1••, 17]. It has been recently shown that the TM is, *in vitro*, capable of supporting a radial travelling wave along

its length [1•] and theoretical considerations indicate there may be a complex frequency and level dependence in the relative motion of the TM and the reticular lamina [36]. The TM resonance described previously could be considered as a point approximation of a TM travelling wave. Although TM travelling waves have yet to be demonstrated in situ, they impose additional requirements on the degree of synchronisation necessary between the movements of cochlear structures required to provide effective amplification. If the outer hair cells, the cells that amplify cochlear motion, are excited through interactions between travelling waves in the basilar membrane and the TM (Fig. 3), then the effective excitation could be limited to a restricted cochlear segment where the wavelengths of these two waves are similar [1•, 37].

Analysis of the TM function using mouse mutants

Experimental data obtained in vivo from mice with mutations in *Tecta* and *Tectb* have furthered our understanding of how the tectorial membrane operates, confirming the many of roles suggested from in vitro studies and revealing additional functions.

In *Tecta*^{ΔENT/ΔENT} mice that are homozygous for an in-frame deletion of the entactin G1-like of Tecta, mice, the TM lacks most all non-collagenous matrix and is completely detached from both the surface of the organ of Corti and the spiral limbus [29]. A second peak of sensitivity that is normally observed at ~0.5 octaves below the best frequency in basilar membrane tuning curves is not detectable these in mice, confirming that it is dependent on the presence of a TM. Furthermore, measurements of cochlear microphonic potentials (extracellular potentials resulting from transducer currents in outer hair cells) reveal that the outer hair cells in *Tecta*^{ΔENT/ΔENT} mice can be driven at high sound pressure levels in the absence of a TM and that they are fluid coupled, responding to velocity rather than to displacement. Accordingly, the neural threshold audiograms reveal a frequency-dependent hearing loss in these mice. There is an ~60-80 dB hearing loss in the 20 kHz region, but this loss reduces as the stimulus frequency increases, presumably as the thickness of the fluid boundary layer over the organ of Corti decreases and allows the hair bundles to be stimulated by fluid flow. Cochlear microphonic measurements also reveal that the mechano-electrical transducer of the free-standing hair bundles of the outer hair cells in the *Tecta*^{ΔENT/ΔENT} mice are not biased towards the most sensitive region of their operating range, as they are in wild-type mice. As a consequence, the ability of the outer hair cells to operate as efficient amplifiers of basilar membrane motion is compromised [see also 38]. The cochlear responses of the *Tecta*^{ΔENT/ΔENT} mouse therefore demonstrate that the TM is, in addition to acting as a second resonator, also crucial for the sensitive operation of the outer hair cells.

Mice heterozygous for the Tecta Y1870C mutation, a missense mutation that is found in TECTA and causes a stable, moderate-to-severe (60-80dB) hearing loss in an Austrian family, have a TM with a severely reduced limbal attachment zone, an unusual hump-backed shape, an enlarged sub-tectorial space, a loss of striated-sheet matrix in the sulcal region, and a detachment of Kimura's membrane [39]. Despite the rather abnormal morphology of the TM, most attributes of outer hair cell function and basilar membrane motion appear normal in the *Tecta*^{Y1870C/+} mice. The basilar membrane is sharply tuned with negligible loss in sensitivity, the second resonance is present in the basilar membrane response, and the phase and symmetry of the cochlear microphonic potentials are normal. Neural threshold audiograms, however, reveal a 60 dB loss in sensitivity in the auditory nerve indicating that the TM plays a critical role in ensuring the motion of the outer hair cell hair bundles drives the hair bundles of the inner hair cells. The enlarged sub-tectorial space seen in the *Tecta*^{Y1870C/+} mice may compromise the fluid coupling between inner and outer

hair cell bundles that has been proposed to result from the counterphase motion of the TM and the reticular lamina [28].

Mice homozygous for a functional null deletion in the *Tectb* gene have a TM that remains attached to the spiral limbus and the surface of the organ of Corti [30••]. The TMs of the *Tectb*^{-/-} mice lack any sign of the organised striated-sheet matrix that is characteristic of the TMs of wild type mice. Instead the collagen fibrils are imbedded in a matrix formed by apparently randomly dispersed, rather irregular looking filaments that are probably formed by Tecta. There is a marked loss in cochlear sensitivity for frequencies below 20 kHz in the *Tectb*^{-/-} mouse, presumably due to the distinct enlargement and swelling of the TM that is seen in the apical end of the cochlea in these mutants. There is no significant change in the dimensions of the TM in the basal, high-frequency end of the cochlea of *Tectb*^{-/-} mice and, according to measurements of basilar membrane displacements, the threshold is only about 10 dB higher. Remarkably, however, the high-frequency basilar membrane frequency tuning curves are actually sharper than those of wild type littermates. Furthermore, the neural masking tuning curves in this cochlear region are also much sharper with the Q₁₀ dB being almost three times greater than that in wild types. The finding that both neural and basilar membrane frequency tuning are enhanced by the loss Tectb has led to the suggestion that tuning in the active cochlea depends on the degree of longitudinal elastic coupling within the TM, and that such coupling is reduced in the absence of the organised striated-sheet matrix within which the collagen fibrils are normally imbedded. Two mechanisms could be responsible for sharpening of the tuning. Reduced elastic coupling may lead to a decrease in the TM space constant, and hence a decrease in the number of outer hair cells acting in synchrony along the cochlea to boost mechanical responses locally. Sharpening of the tuning should also be observed if reduced TM elasticity leads to a decrease in the wavelength of the TM travelling wave that has been described in vitro [1••]. A shorter wavelength would mean that effective interaction between the basilar and tectorial membranes occurs over a shorter stretch of the cochlea. The responses of *Tectb*^{-/-} mutants reveal the counter demands of cochlear tuning and sensitivity, and the need to compromise between these requirements in the mammalian cochlea.

Hearing defects have also been described in mice with mutations in *Col 11a2* and *Col 9a1*, chains of two of the collagens in the TM. Thus far, only ABR threshold data are available from these mice [5,40,41]. Although defects have been reported in structure of the TM and the organisation its collagen fibrils in these mutants, the widespread expression of these collagen chains throughout many structures in the ear makes it hard to evaluate whether these mutations are specifically affecting the function of the TM. An otogelin null mutant mouse has also been produced [42]. The TM is attached to the cochlear epithelium in the *Otog*^{-/-} mouse and its ultrastructure is normal apart from the presence of atypical rod-like structures in the limbal zone [42]. These mice have severe balance defects and exhibit varying degrees of deafness, but it is not clear how the mutation affects hearing. More direct measures of TM properties and cochlear function in these mice would be valuable.

TECTA is a deafness gene

Mutations in *TECTA* have been identified as the cause of hereditary hearing loss in 15 different families distributed throughout the world to date [see 43• for recent summary]. Analysis of the clinical phenotypes resulting from these mutations indicates a number of interesting correlations with genotype [44]. The inactivating, presumably loss-of-function mutations in *TECTA* are all recessive and cause a prelingual hearing deficit that is stable and, in most cases, moderate to severe across all frequencies, although with a tendency to be more pronounced in the mid-frequency range. This clinical phenotype is distinguishable from that caused by recessive, deafness-causing mutations in most other genes and has been

suggested to be diagnostic of a potential *TECTA* mutation [43•]. Although not proven formally these mutations may cause a phenotype similar to those observed in the *Tecta*^{ΔENT/ΔENT} mice described above in which there is a near total lack of all non-collagenous TM proteins and structures, and the TM is completely detached from the sensory epithelium. In contrast, all the missense described in *TECTA* are dominant, with mutations in the vWF type D repeat domain causing a high-frequency hearing loss and those in the ZP domain causing a hearing loss in the mid-frequency range [45]. Finally, the dominant missense mutations in *Tecta* that involve cysteine residues all cause progressive hearing loss, suggesting they may disrupt disulphide bonds and thereby destabilise matrix structure. In contrast, the missense mutations involving amino acids other than cysteine all result in stable forms of hearing impairment.

Conclusion

Recent observations have changed our understanding of TM function. Transgenic mice have shown the TM is a structure that can influence the sensitivity and tuning properties of the cochlea in several ways. It ensures the gain and timing of cochlear feedback are optimal, that the hair bundles of the inner hair cells are driven efficiently by the outer hair cells, and it may influence the extent to which different elements are coupled along the length of the cochlea. In vitro studies have revealed anisotropy and longitudinal stiffness gradients, and an ability of the TM to support a longitudinally propagating travelling wave. The extent to which such travelling waves occur in vivo, and how their propagation is influenced by mutations in various TM proteins are clearly essential and exciting areas for future research.

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a

b

C

Figure 1.

- a) Diagram showing how the hair cells of the organ of Corti lie sandwiched between two extracellular matrices, the basilar (BM) and tectorial (TM) membranes. Three zones can be distinguished in the TM, the limbal zone (LZ) by which the TM is attached to the spiral limbus, the medial zone (MZ) that stretches over both the internal sulcus (IS) and organ of Corti (OC), and the lateral marginal band (MB). HS = Hensen's stripe, CN = covernet. The longitudinal, radial and transverse axes of the cochlear partition are indicated to the right.
- b) Domain structures of the three non-collagenous glycoproteins of the TM. Red = vWF type D repeat, purple = vWF type B repeat, green = ZP domain, C = cysteine knot, TSP = threonine/serine/proline rich region, ENT = nidogen/entactin G1 domain, black = hydrophobic N-terminal signal peptide (right) or hydrophobic C-termini (left), yellow = region lacking any significant homology to other proteins.
- c) A Toluidin blue stained section from the mouse cochlear duct (centre) and transmission electron micrographs (surrounding) showing the ultrastructure of the different regions and peripheral features of the TM.

Figure 2.

Basic mechanical model of a cochlear segment incorporating the TM resonance. Masses of the tectorial and basilar membrane in each segment are M_{TM} and M_{BM} , respectively. K_{BM} denotes stiffness of the basilar membrane. K_{TM} is stiffness of the TM's limbal attachment. Movements of the masses are damped by corresponding dash-pots R_{TM} and R_{BM} . Vibrations of the basilar membrane, driven by pressure difference, P , between the scalae, are transmitted to the TM via stiffness K_{OHC} of the outer-hair-cell hair bundles.

Figure 3.

Diagram illustrating hypothetical interactions between the pressure driven basilar membrane travelling wave (blue) and the TM travelling wave (red) propagating along the TM due to elastic coupling. f_{BM} and f_{TM} indicate places of the basilar and tectorial membrane resonances for a give frequency of stimulation. The radial TM travelling wave may determine the extent (shaded area of equal wavelength) to which feedback from the outer hair cells can amplify motion of the basilar membrane (BM).