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Review

Structure and innervation of the cochlea

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Abstract

The role of the cochlea is to transduce complex sound waves into electrical neural activity in the auditory nerve. Hair cells of the organ of Corti are the sensory cells of hearing. The inner hair cells perform the transduction and initiate the depolarization of the spiral ganglion neurons. The outer hair cells are accessory sensory cells that enhance the sensitivity and selectivity of the cochlea. Neural feedback loops that bring efferent signals to the outer hair cells assist in sharpening and amplifying the signals. The stria vascularis generates the endocochlear potential and maintains the ionic composition of the endolymph, the fluid in which the apical surface of the hair cells is bathed. The mechanical characteristics of the basilar membrane and its related structures further enhance the frequency selectivity of the auditory transduction mechanism. The tectorial membrane is an extracellular matrix, which provides mass loading on top of the organ of Corti, facilitating deflection of the stereocilia. This review deals with the structure of the normal mature mammalian cochlea and includes recent data on the molecular organization of the main cell types within the cochlea.

Keywords: Hair cells; Auditory neurons; Supporting cells; Spiral ganglion; Stria vascularis; Organ of Corti

1. General organization of the cochlea

The cochlear duct is a coiled tube filled with fluid (endolymph). Its walls are lined with cells that constitute the membranous labyrinth (Fig. 1). Among the types of cells in the membranous labyrinth are hair cells which are the sensory cells, and non-sensory cells with auxiliary and supportive functions. The membranous labyrinth is surrounded by an additional fluid space filled with perilymph and lined by cells of mesodermal origin. The entire cochlea is encased in bone, the otic capsule, which is part of the temporal bone. In some mammals, rodents and guinea pigs in particular, the cochlea protrudes into the middle ear cavity. In others, including humans, only a very small portion of the cochlea, the promontorium, can be seen and accessed from the middle ear. Further discussion of the osseous cochlear structures is omitted from this review.

The base of the cochlea is the region where higher frequencies are transduced. The other end of the cochlear duct is called the apical end or apex of the cochlea, where the lower frequencies are transduced. The range of frequencies is tonotopically distributed along the cochlear duct from base to apex. Several morphological gradients have been noted from the base to the apex of the cochlea. Some of the major structures that display conspicuous base-to-apex gradients are summarized in Table 1.

Historically, regions within the cochlea were defined based on their location and appearance. Thus, structures such as the stria vascularis, tectorial membrane (TM), organ of Corti, Reissner's membrane and others have been identified and named and their function characterized. Nevertheless, not all cell types within the cochlea have been characterized in respect to their specific function. Molecular characterization of specific cell types of sub-areas of the cochlea has begun to provide tools to better understand the function of specific cells. Moreover, transgenic mouse technology, which allows expression of specific genes to be manipulated, enhances the understanding of the role of specific molecules and cells in cochlear function.

The ability of the cochlea to transduce such a wide range of sound frequencies and intensities is facilitated by mechanical features of its structure, along with biological features that involve ultra-fast ion channels, feedback mechanisms and an active cochlear amplifier. The cellular and molecular

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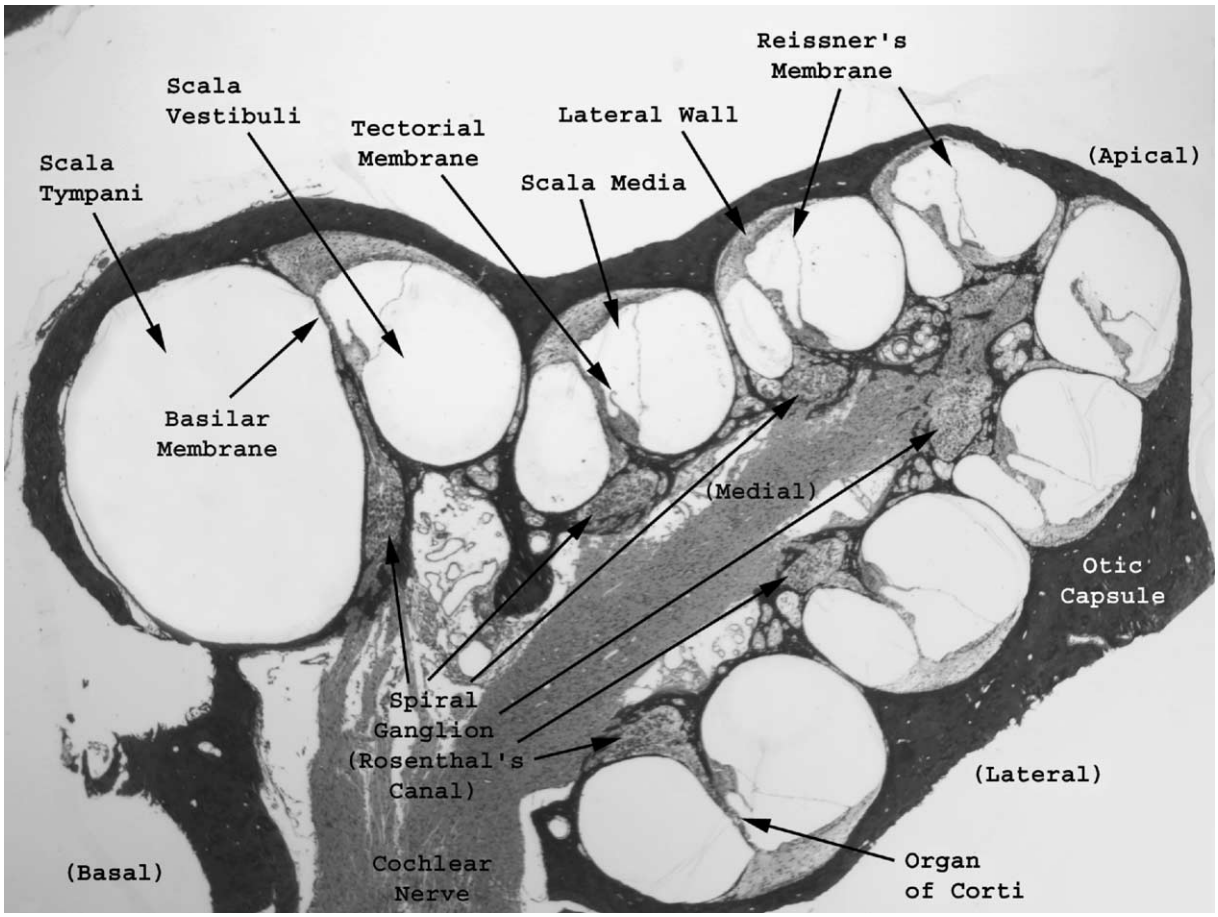

Fig. 1. A low magnification light micrograph of a plastic cross-section of the guinea pig cochlea. The section is cut at a near-mid-modiolar plane. The major tissues and the general organization of the cochlea are depicted. The anatomical directions are noted, with the modiolus being medial and the surrounding otic capsule lateral.

substrates that underlie cochlear function are now being unveiled at a faster pace. The sensory cells of the cochlea are called the hair cells. These cells reside in the organ of Corti, along with several types of supporting cell and extracellular elements. Hair cells are innervated by nerve fibers that send auditory signals into the brainstem (afferent neurons) and to other nerve cells that carry signals from the brain into the ear and influence cochlear function in a feedback loop (efferent neurons).

Table 1
Typical base to apex gradients of several structural parameters in the cochlea

Structure	Gradient change from base to apex
TM	Wider and thicker
BM	Wider and thicker
Outer hair cell	Longer
Outer hair cell stereocilia	Taller, more acute angle, fewer
Outer hair cell SSC	More rows
Inner hair cell stereocilia	Fewer, taller
Deiters and pillar cells	Taller, fewer cytoskeletal elements
Hensen cells	More lipid granules (in guinea pigs)
Fluid spaces	Narrower
Reticular lamina	Less strictly organized
MOC	Fewer terminal
Outer hair cell synapses	More like inner hair cell synapse
Sensitivity to noise and ototoxins	Decreases

The basic anatomy of the cochlea has been described in excellent reviews [269,282]. It is necessary for us to repeat some of the basic facts already available to the reader. In addition, we attempt to update the pool of data on cochlear structure with recently added information. Emphasis in this review is placed on the cells that directly participate in the transduction mechanism, namely, the hair cells and the accessory structures in their immediate vicinity. We concentrate on the mature normal mammalian cochlea and minimize reference to development, non-mammalian species, pathology, physiology and in vitro work.

2. Lateral wall: stria vascularis and spiral ligament

The lateral wall, consisting of the medially located stria vascularis and the laterally located spiral ligament, defines the lateral aspect of the scala media. The stria vascularis is made up of three layers of cells, from medial to lateral:

marginal cells, intermediate cells and basal cells (see Fig. 1 for definitions of orientation in the cochlea).

2.1. Marginal cells

The marginal cells are a homogenous layer of polarized epithelial cells that derive from the membranous labyrinth. These cells are organized as one layer that lines the scala media fluid space. SEM observation of the luminal (endolymphatic) surface of these cells reveals their hexagonal shape and their microvilli-covered surface [13]. The hexagonal shape of their apical surface allows for the packing of a maximal number of cells in a given area. Microvilli are usually indicative of interaction with the luminal fluid: absorption and/or secretion. The cell–cell contacts between marginal cells include classically oriented apical tight junctions, adherens junctions and desmosomes [162]. An unusual feature of this simple epithelium is the absence of a basement membrane. This facilitates close association of these epithelial cells with the vasculature beneath them.

Marginal cells of the stria vascularis have abundance of cytokeratin proteins, which can serve as useful markers for them [15,17,27,170]. Other molecules that have been identified in marginal cells include several molecules associated with ionic pumps and channels. The presence of these specific pumps, and the outcome of deletions of each of the respective genes help reveal the role of marginal cells in strial and cochlear function.

One of the roles of the stria vascularis is to pump Na^+ away from the endolymph. Using immunogold-labeling, the presence of amiloride-sensitive Na^+ channels was demonstrated in the luminal and lateral membranes of marginal cells, suggesting that they could act as an efficient pathway for Na^+ uptake from the endolymph [141]. Using similar methods, a Na–K–Cl cotransporter [59] was localized to the basolateral membrane infolding of marginal cells [207]. In mice deficient for NKCC1, the organ of Corti and several other areas of the cochlea, including cells that do not express this gene, are severely pathological [222]. The process of K^+ recycling in the cochlea has been described [158] and recently reviewed [340].

NaK-ATPase plays an important role in stria vascularis function for generation of the endocochlear potential (EP) and maintenance of the ionic composition of endolymph. Several isoforms of this enzyme have been localized to the stria [54,76]. Marked similarities were found in the developmental and age-related expression patterns of NKCC and NaK-ATPase, suggesting functional cooperation between the two ion transport mediators responsible for generating and maintaining K^+ levels in endolymph and the EP [264].

2.2. Intermediate and basal cells

Lateral to the marginal cells of the stria vascularis are the intermediate cells. These cells interdigitate with the basal aspect of the marginal cells but do not reach the luminal surface. The intermediate cells, which are probably derived from the neural crest, contain melanin, and are often referred to as melanocytes [129]. It is possible that all melanin in the cochlea is produced by melanocytes, yet, melanin granules may be found in all three layers of cells in the stria vascularis, and even in the adjacent spiral ligament. It is likely that cells other than intermediate cells of the stria vascularis acquire melanin by donation from adjacent melanocytes [47]. Animals (and humans) that lack melanin (albinos) can hear normally. However, when melanocytes are missing from the ear (probably due to defects in neural crest cell migration) the stria vascularis is dysfunctional, EP is not generated and hearing is severely impaired [303]. This suggests that melanocytes play an important role in the generation of EP and that this function is independent of melanin. Mice homozygous for mutations in pigmentation genes exhibit inner ear phenotypes [273]. Severe pathology in the stria vascularis, associated with inability to generate EP, appears to be the primary pathology.

Basal cells are located lateral to the intermediate cell layer, adjacent to the spiral ligament. These flat cells form a continuous layer and exhibit a dense network of junctional complexes with neighboring basal cells as well as between basal cells and other cells around them [97]. These cells lack NaK-ATPase, suggesting that their main role may be related to establishing a barrier between the stria vascularis and the spiral ligament. It is not completely clear whether these cells are derived from mesodermal or neural crest origins. Due to the presence of a brain type glucose transporter (GLUT1) in basal cells [139], it is possible to specifically identify them within the stria vascularis. The intermediate filament marker vimentin stains both basal and intermediate cells of the stria vascularis [272], and therefore cannot be used to distinguish between these two cell types.

2.3. The spiral ligament

The spiral ligament is located between the stria vascularis (medially) and the otic capsule (Fig. 1). It is composed mainly of connective tissue elements including extracellular material and cells from mesenchymal origin [209]. The capillary bed for supply and drainage in the ear is prominent in the spiral ligament. In many mammals, five clear sub-areas are distinguished [124]. In addition to containing the capillary bed and providing mechanical support to the stria vascularis, the spiral ligament has other important functions. It anchors the lateral aspect of the basilar membrane (BM). The attachment of the organ of Corti is not a simple passive one. Rather, at least in some mammals, fibroblasts with stress fibers (tension fibroblasts) that contain contractile proteins are present in the tissue that anchors the spiral ligament to the BM, suggesting that the spiral ligament can generate and/or regulate BM tension [126]. Gap junctions are present between fibrocytes in the spiral ligament that underlies the stria vascularis, and between these fibrocytes

and strial basal cells [99]. Hsp27 immunostaining has been demonstrated in tension fibroblasts of the spiral ligament, suggesting a potential role in the regulation and maintenance of the actin cytoskeleton in these cells [177]. Hsp27 may also play a protective role in these cells, which may be required due to their tensile properties and potential for mechanical injury.

Another function of the spiral ligament is related to maintaining the ionic balance in the cochlea. The spiral ligament extends above and below the stria vascularis and reaches the border of the perilymphatic spaces in scala tympani and scala vestibuli. Aided by gap junctions and NaK-ATPase pumps, the spiral ligament is thought to pump K^+ out of the perilymph and transport it for maintaining the high concentration of K^+ in the endolymph [290].

Type II, IV and V fibrocytes function to pump K^+ from the perilymph and produce a K^+ flow to Type I fibrocytes and strial basal cells [290,292]. Pathological changes in fibrocyte subtypes have been linked to noise-induced hearing loss as well as age related hearing loss, where fibrocyte pathology, particularly Type IV, was shown to precede hair cell loss [128].

The autosomal dominant sensorineural deafness DFNA9 is caused by missense mutations in the *COCH* gene, which is expressed in high levels in fibrocytes of the spiral limbus and of the spiral ligament in the cochlea. Antibodies to cochlin, the gene product of *COCH* reveal reduced staining in affected DFNA9 ears as compared with normal ears [250]. While the role of cochlin is not yet understood, DFNA9 demonstrates the importance of specific cell types in the spiral ligament for cochlear function.

Connective tissue markers such as vimentin are useful for identifying spiral ligament cells. Actin stains can be used for identifying stress fibers in stress fibroblasts. Antibodies to cochlin can identify a specific cell sub-type in the spiral ligament. Further characterization of the collagens and other extracellular molecules that are present in different regions of the spiral ligament will provide additional markers for this tissue [51,315].

3. Blood supply

This review does not provide details regarding the vasculature of the cochlea, which is reviewed elsewhere [25,121,255,282]. Normal blood supply is critical for the function of the cochlea. Reduction in its blood supply reduces auditory sensitivity, as evident during certain manipulations and observed in association with chronic noise exposure and aging [163,205,274].

4. Reissner's membrane

Reissner's membrane separates the perilymph of scala vestibuli from the endolymph (Fig. 1). It is made up of two cell layers, forming together an avascular membrane [71,140]. Cells that line the scala media are simple epithelial cells of the membranous labyrinth which rest on a thin basement membrane. The scala vestibuli side of Reissner's membrane consists of mesenchymally derived fibroblasts. This layer is at times discontinuous [140].

The cells of the membrane and the junctional complexes between them form an ionic barrier to the flow of ions. In addition, the membrane can most likely regulate ionic balance (and volume) of the fluids by selectively pumping ions. Three types of ion channels were identified in the apical membrane of the epithelial cells of Reissner's membrane: a stretch-activated nonselective cation, a chloride and a K^+ channel [352]. If the balance of pressure between endolymph and perilymph is disrupted, the membrane bulges.

Due to the presence of two layers of cells, it is usually possible to identify cell types in Reissner's membrane. When specific markers are required, cytokeratin specific antibodies can be used for the epithelial cells and vimentin for the fibroblasts in scala vestibuli.

5. The fluid spaces

The fluid contained in the membranous labyrinth (scala media) is endolymph (Figs. 1 and 2). It has an ionic composition similar to intracellular fluid (high K^+). Endolymph composition is similar among mammals. Endolymph is prevented from leaking into the intercellular space by well-developed tight junctions in the epithelium of the membranous labyrinth. The fluid of scala media can drain into the endolymphatic sac, via the endolymphatic duct. The volume of cochlear fluids has recently been measured in several mammals [316]. The dynamics of fluid movement has been investigated and modeled [265–267].

Perilymph is an extracellular-like fluid (high sodium) that fills the scala vestibuli and scala tympani (Figs. 1 and 4). It is continuous with the CSF via the cochlear aqueduct. The fluid between the cells of the organ of Corti is also continuous with the perilymph. As for endolymph (above), volume measurements were obtained using magnetic resonance imaging [316] and fluid dynamics modeled [265].

6. Organ of Corti

6.1. General considerations: cells and organization

The organ of Corti is the sensorineural end organ for hearing. It includes polarized epithelial cells (hair cells and supporting cells) of placodal origin (membranous labyrinth), a specialized basement membrane with a layer of matrix called BM, nerve endings and the TM [75,120,159,162,288,296,345].

The hair cells and supporting cells are spatially organized in an orderly pattern. The apical surfaces of all cells are

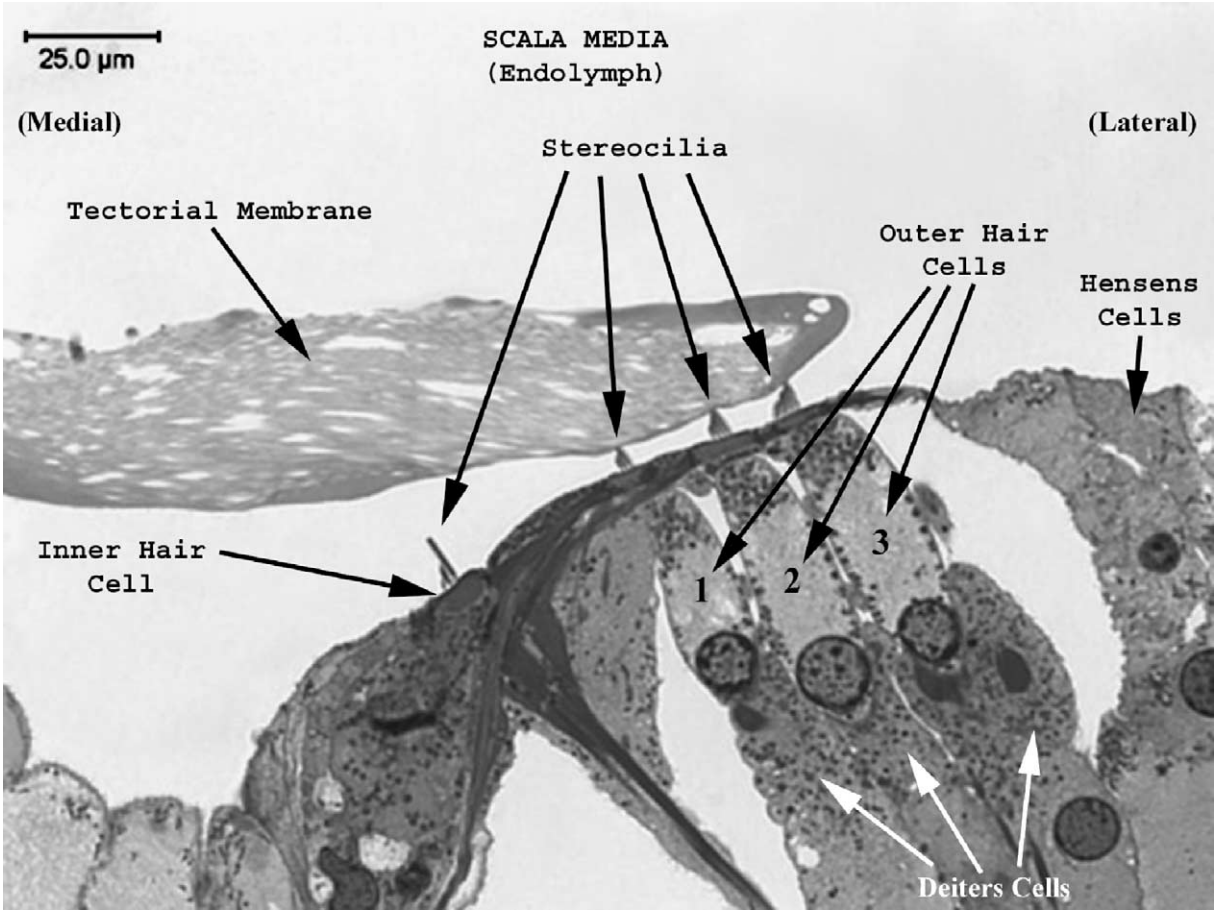

Fig. 2. A plastic cross-section of the mole rat cochlea. The organ of Corti is shown, along with the covering the tectorial membrane. Note that there is no contact between stereocilia of inner hair cell and the tectorial membrane.

joined together by an elaborate set of junctional complexes to form the reticular lamina, which is a barrier between the endolymph of scala media and the perilymph-like fluid in the intercellular spaces bathing the basolateral domains of these cells. The pattern of cell organization in the reticular lamina is known as a "mosaic" epithelium, in which every hair cell is surrounded by four supporting cells. In cross sections, the epithelium appears as pseudo-stratified, with supporting cells spanning the distance between the basement membrane and the reticular lamina. In contrast, the hair cells do not rest upon the BM (Figs. 2 and 4).

There are two types of hair cells, inner and outer, with the inner hair cell (IHC) being the true sensory cell type, sending impulses via the auditory nerve. In contrast, outer hair cells (OHCs) are used to enhance the performance of the cochlea, qualitatively (increased selectivity) and quantitatively (increased sensitivity). The name "hair" cell was chosen because of the tuft of stereocilia that protrude from the apical domain of every cell.

There are no basal (undifferentiated) cells in the organ of Corti. Rather, all cells in the sensory epithelium are differentiated. This is unusual for epithelial tissues, and accounts for the inability of hair cells to be replaced, once lost.

6.2. Inner hair cell

Inner hair cells are pear shaped cells with a round centrally located nucleus (Figs. 2 and 4). One row of inner hair cells runs along the cochlear duct (Figs. 3 and 5). The cells are in contact with the inner pillar cell (on their lateral aspect) and the phalangeal cells (on the other three sides), displaying a complex mixed junction with alternating tight junction and adherens junction specializations. Mature hair cells have neither desmosomes nor gap junctions [111]. The apical portion of the cell (cell surface) along with its stereocilia are bathed in endolymph of scala media, whereas the basolateral domain is bathed in perilymph and surrounded by supporting cells and neuronal terminals. Inner hair cells are positioned on the arcuate zone of the BM (see below), which is enclosed in bony shelves of the osseous spiral lamina. Thus, the BM is immobile in this region, and the inner hair cell body probably does not vibrate in response to sound stimulation.

This review focuses on structures that are directly involved with sound transduction, namely, the stereocilia and the tip links that interconnect them, and the synaptic connection with the afferent neurons. Stereocilia are morphologically

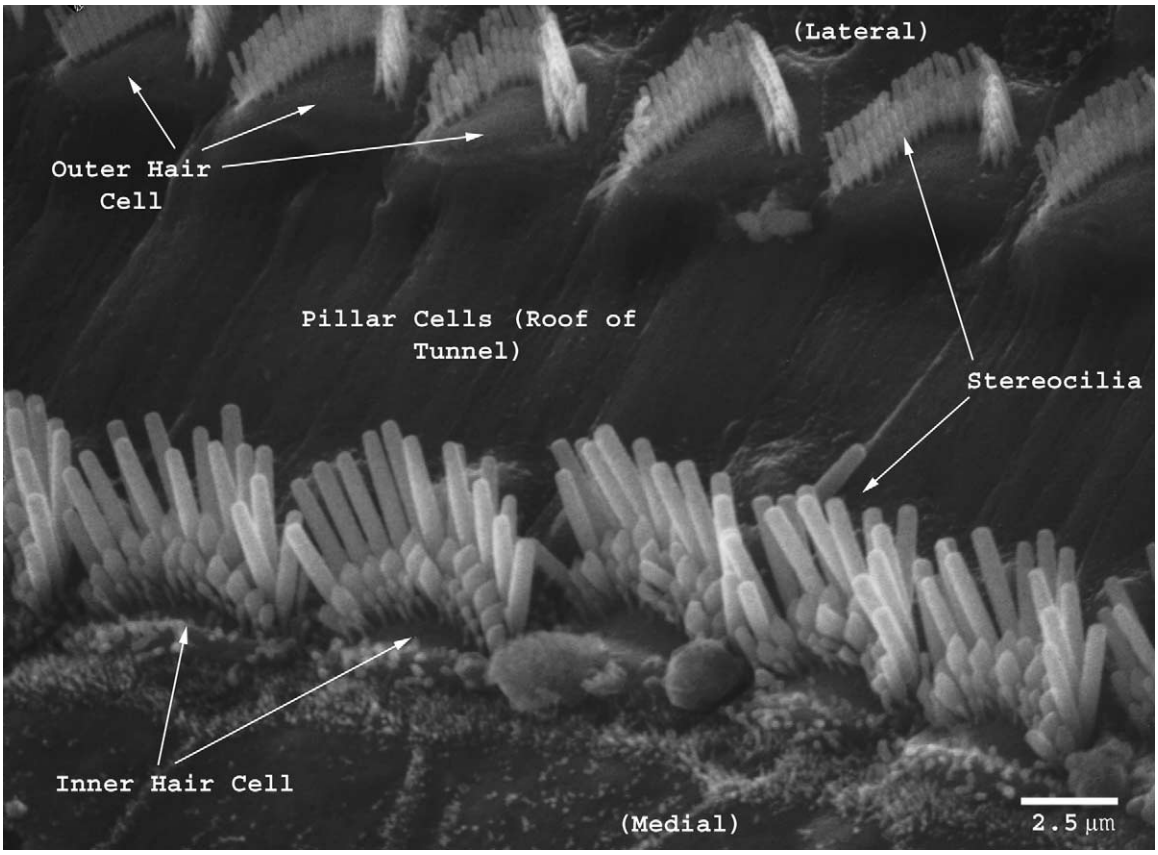

Fig. 3. A scanning electron micrograph of the mouse reticular lamina. One row of inner hair cells and the first row of outer hair cells are seen, along with the supporting cells that are positioned between the sensory cells.

similar to microvilli, except that they are much larger. Each inner hair cell has between 20 and 50 (or more) stereocilia, depending on the species and the location along the cochlear duct, with more stereocilia closer to its basal end. Inner hair cell stereocilia are usually arranged in two main rows, with additional shorter rows seen in some cases in the medial aspect of the tuft (Fig. 3). Stereocilia are cellular projections that are membrane bound. To mechanically extend these

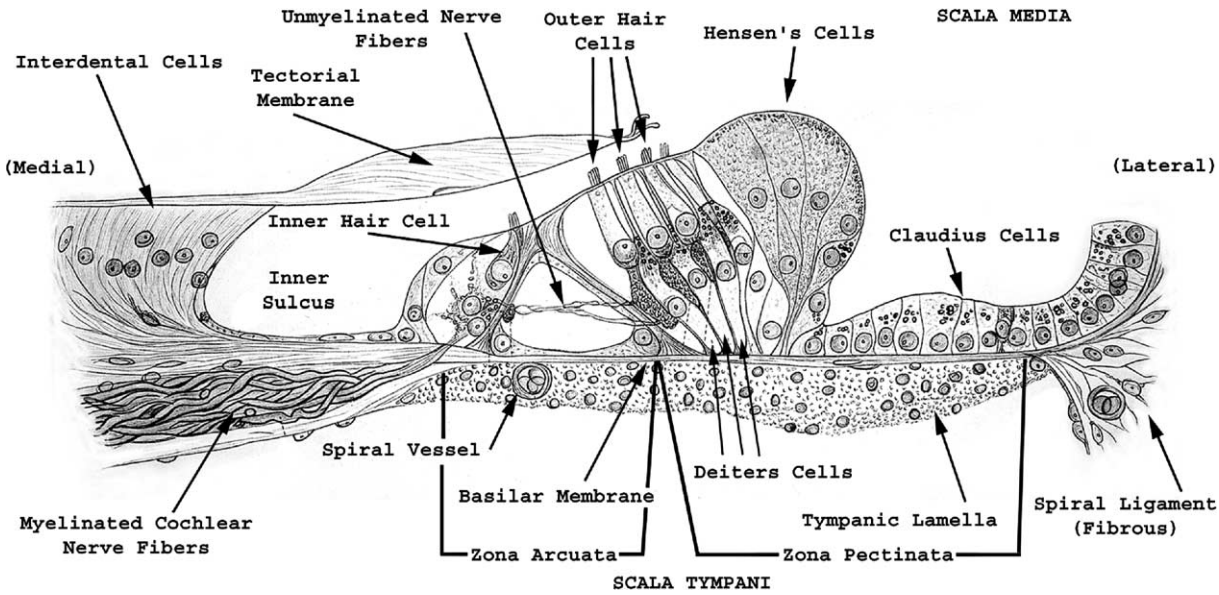

Fig. 4. A schematic representation of the human inner ear. This schematic, modified after Retzius, 1884, shows the different cell types and the extracellular components in the organ of Corti and it immediate vicinity. The orientation is similar to that depicted in Fig. 2.

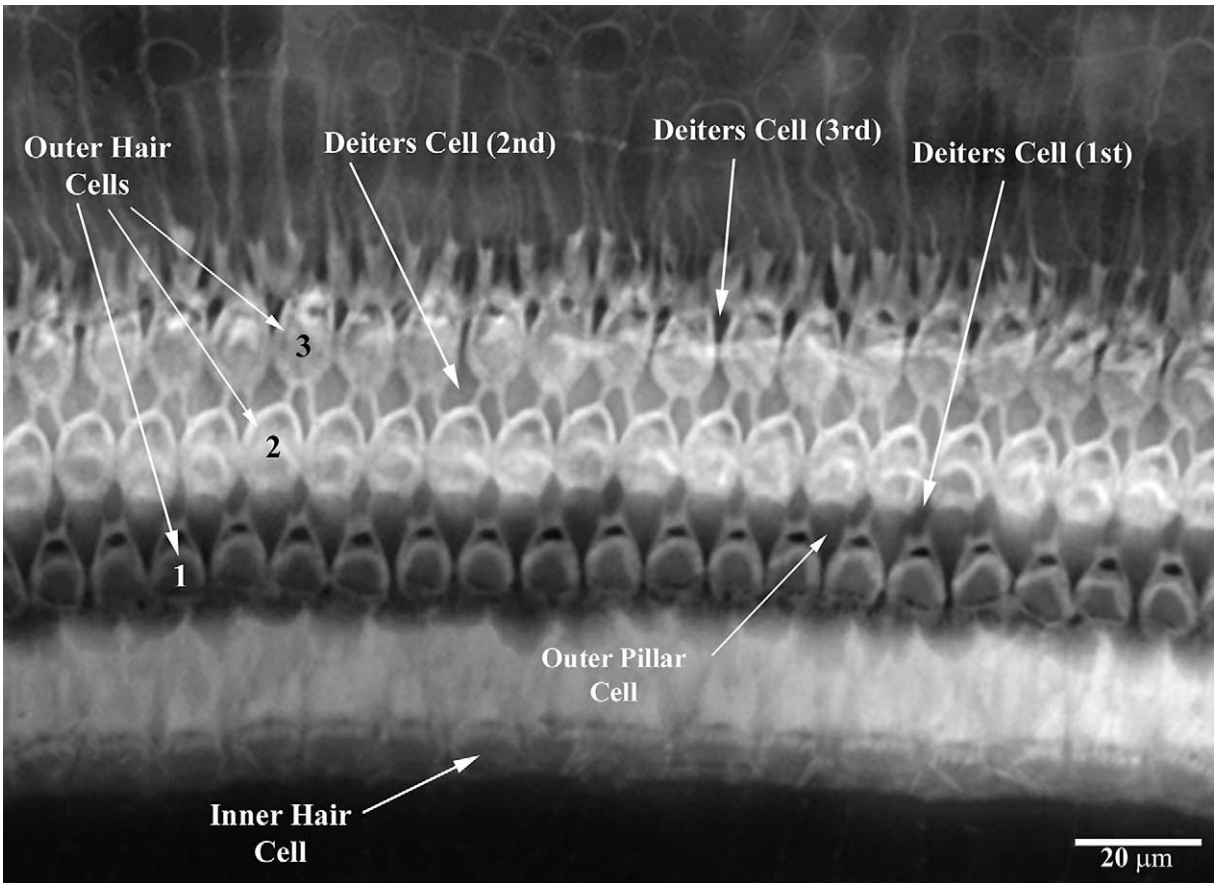

Fig. 5. An epifluorescence micrograph of the guinea pig reticular lamina stained with phalloidin to depict F-actin. The focal plane is at the adherens junctions immediately beneath the luminal surface of the epithelium. The various cell types are marked.

projections and maintain them, the cell uses a dense core of actin filaments along with actin-associated proteins. At the base of each stereocilium is an electron-dense rootlet, which is inserted into the cuticular plate (see below). The apical tips of stereocilia are connected to their neighboring stereocilia (of the adjacent row) with a tip link [225]. Stereocilia are also linked to neighboring stereocilia with side links (see below).

Protrusions or appendages of cells require a cytoskeletal support. True cilia use a microtubule-based mechanical support. Stereocilia of hair cells are cylindrical protrusions of approximately 250 nm in diameter that use an actin-based scaffold. The length of stereocilia varies significantly between species, with ears specialized for high frequency hearing exhibiting the shortest stereocilia (Table 1). Stereocilia are usually tallest in the apical end of the cochlea and decrease in a gradient towards the base. Typical length of inner hair cell stereocilia (the tallest row) is 2–8 μm. Morphometry of stereocilia was performed on cochleae of several mammals [39,251,336,349]. Extreme dimensions have been found in mammals that specialize in high frequency hearing such as the bat, which has very short stereocilia [336] and the mole rat, a low-frequency adapted mammal with very tall stereocilia [242].

The main protein in stereocilia was identified as actin about 25 years ago [93]. Since then, the molecular organization of stereocilia has been investigated in depth. The most detailed analysis of the development and molecular organization of stereocilia was made on material from non-mammalian vertebrates [61,318–322]. Actin filaments in stereocilia are organized in a parallel array and cross linked with fimbrin [289] and other cross linking proteins. Much, but not all of these data hold for mammalian ears, and even among mammals, interspecies variability may occur.

Among the molecules that have been identified in stereocilia, in addition to actin, are unconventional myosins [101]. Mutations of genes encoding myosin VI, myosin VIIa and myosin XV cause hearing loss, associated with severe pathologies in stereocilia. Of these three myosins, only myosin VIIa is a stereocilia specific molecule [117,118]. Defects in myosin VIIA are responsible for deafness in the human and mouse. The C-terminal FERM domain of myosin VIIA binds to a novel transmembrane protein, vezatin, which is a ubiquitous protein of adherens junctions [173]. Vezatin has been localized to the side links of stereocilia.

Novel stereocilia molecules continue to be discovered. For instance, a novel actin-binding protein, 2E4, which is thought to play a unique role in the actin rearrangement

during stereocilia formation, was recently identified [28]. Another protein, stereocilin, which is involved in deafness when its gene is mutated, is expressed in cochlear stereocilia [337]. Integrins serve as fibronectin receptors and mediate attachment of cells to matrix. The α8β1 integrin was localized to stereocilia. In mice homozygous for a targeted mutation of *Itga8* (encoding the α8β1 subunit) a pathological inner ear phenotype is observed [191].

Knowledge of the polarity of actin filaments in stereocilia can help one to understand their development and their interaction with other proteins. Using electron microscopy combined with decoration with subfragment-1 of myosin, it was determined that actin filaments in stereocilia are organized in a parallel paracrystalin array, and that all filaments have identical polarity with the tip of the arrowheads pointing towards the cuticular plate [60,95,281]. One of the proteins which is thought to be involved in organization of actin in brush border microvilli and Sertoli cell-spermatid junctions is espin. Espin has been found in stereocilia of hair cells [359]. In jerker mice, mutants in the espin gene, actin bundling is deficient resulting in a deaf phenotype. Recent work in rat cochlear explants suggest that actin-filament arrays in stereocilia are continuously remodeled by the addition of actin monomers to the stereocilium tips, and that the entire core of a stereocilium is renewed every 48 h [271].

Based on experiments in non-mammalian vertebrates, it is thought that the transduction-channel in auditory hair cells is mechanically-gated and that a spring like mechanism transmits forces for opening the channels and permits their closing. Tip links emerge from the tips of the shorter stereocilia in the hair bundle, and connect with the adjacent taller stereocilium of the next row [220]. Tip links appear to consist of a strand of extracellular material. Further examination has revealed that tip links are right-handed, coiled double filaments that may split into two branches before contacting a taller stereocilium [152]. In another study, the tip link appeared as a helical bundle of three coiled filaments [327]. Further understanding of the molecular composition and organization of the tip links will most likely enhance our understanding of the function of auditory transduction channels. Much of the work on transduction channels has been performed in non-mammalian vertebrates, especially on vestibular hair cells, and therefore is not covered in this review of the organ of Corti. Several excellent reviews of the auditory transduction mechanism have appeared [69,72,106,135,304,324].

The cuticular plate is an organelle located under the apical cell membrane of cochlear hair cells, which serves to anchor and support the actin rootlet of stereocilia. It is essentially a terminal web, similar to that seen in intestinal brush border cells, but thicker, as required for supporting stereocilia, which are much longer than microvilli. Actin filaments in the cuticular plate have a mixed polarity. The lateral edge at the perimeter of the cuticular plate is separated from the actin bundle of the adherens junction [240,317], allowing for vesicle transport from the cell body to the apical (stereocilia) domain [151] (data from frog).

The centrosome of hair cells is located in the fonticulus, an area free of actin in the region of the cuticular plate. The location of the centrosome is the previous site of insertion of the kinocilium, which degenerates in auditory hair cells as they mature. Immuno-stains for tubulin clearly depict the basal body within the centrosome, where actin stain is excluded [238,240,305]. Antibodies specific to the centrosomal proteins pericentrin and γ-tubulin have also been useful for accurately localizing centrosomes in cochlear hair cells and supporting cells [330].

The junctional complexes of inner hair cells include a tight junction near the apical surface, followed by an adherens junction. The adherens junction is associated with a dense ring of circumferential actin. In addition to staining with actin and spectrin, a molecule called CAR has been localized to this circumferential ring [216]. Mature inner hair cells do not have gap junctions or desmosomes. The absence of the latter is consistent with the lack of cytokeratins in these cells, a rather unusual finding for epithelial cells [17,170,243]. Mutations in genes encoding junction proteins have been shown to be involved in deafness [4,348]. The junctional organization of the epithelial mosaic at the level of the reticular lamina is discussed later in this review (see Section 6.5).

The lateral membrane of inner hair cells is not as well characterized as that of the OHCs (below), yet some studies have examined it in detail. Special plaques were identified, which could represent the sites of transmembrane channels. It was estimated that there may be up to 20,000 plaques on each inner hair cell [98]. Markers specific for hair cells are discussed below in the section describing the OHCs.

6.2.1. Inner hair cell neurotransmission

Movement of the hair cell stereocilia in the direction of the taller row opens transduction ion channels, allowing entry of K^+ and calcium ions and generating a transduction current. The transduction current then activates voltage sensitive calcium channels along the IHC lateral wall and base as well as Ca^{2+} activated K channels [138,168,247,356]. There are both slow and fast activating K^+ currents [144]. The end result is release of neurotransmitter at the hair cell base. Movement of stereocilia in the opposite direction closes the stereocilia-related channels and stops the release of neurotransmitter. In the “resting” position of stereocilia (upright) the transduction channels are partially open, leading to a small release of transmitter. This, in turn, generates a spontaneous activity in the auditory nerve and the ascending auditory pathways, even in the absence of sound. The frequency of movement of stereocilia matches the frequency of the sound stimulus. The hair cell—auditory nerve synapse is therefore a highly active one. Moreover, to take advantage of the information encoded by the frequency related release of transmitter requires a synapse where there is rapid post-synaptic effect and equally rapid recovery. With these requirements it is not surprising to find that evidence supports an excitatory amino acid, most likely glutamate, as

the hair cell transmitter, acting on an ionotropic glutamate receptor with subunits configured for rapid recovery.

The inner hair cell synapses with auditory nerve peripheral processes. There are two classes of auditory nerves, with the differentiation termed by their cell bodies. The cell bodies are called spiral ganglion cells (SGCs), since they spiral around the central core (modiolus) in Rosenthal's canal, paralleling the more laterally located sensorineural epithelium until shortly before the apex. Inner hair cells contact the peripheral processes of Type I SGCs, large bipolar neurons that comprise the major population (90–95%) of SGCs. Type II SGCs are smaller, pseudounipolar and their peripheral processes contact with OHCs. Evidence for glutamate as the transmitter at the IHC—Type I SGC synapse includes its presence—from neurochemical [108,344] and immunocytochemical [12,82,333] studies, its release [67,142,143,146], uptake mechanisms [81,104,110,183,221,313], and by the action of glutamate and its agonists providing auditory nerve excitation which is blocked by antagonists [34,50,73,86,147]. In situ hybridization and immunocytochemical studies show both AMPA and NMDA receptor sub-types are expressed in Type I SGCs [171,172,197,215,256,258,259] and while there is evidence for an action on both AMPA and NMDA receptors [73,147,227,229], the most recent pharmacological evidence suggests the major action is at the AMPA receptor [253]. Ultrastructural immunocytochemical studies of the IHC—Type I SGC synapse show that GluR2/3 and GluR4 subunits are placed in the post-synaptic complex, without any GluR1 immunolabeling [197,221]. This pattern of AMPA receptor subunit composition is similar to what is seen in central auditory pathways [137,224] which Raman et al. [237] and Trussell [325] suggest is specialized to allow for the rapid desensitization kinetics necessary for auditory processing. Metabotropic glutamate receptors (mGluR1) may also contribute to the action of glutamate on Type I SGCs [165].

There is also evidence for presynaptic glutamate receptors [197] indicating a potential autocrine loop. Glutamate may not be the only hair cell transmitter. Sewell has demonstrated an auditory nerve activating substance [276]. Moreover the presence of P2X2 receptors in auditory nerve suggests that ATP may also function to modulate auditory nerve activity, although its source remains unknown [48,134].

A highly active glutamatergic synapse has a negative consequence, the potential for excitotoxicity and this appears to be the case at the IHC—Type I SGC synapse. Over-release of transmitter from inner HCs from noise overstimulation or other trauma causes swellings of Type I SGC peripheral processes [150,233,248]. With sufficient over-release, the swollen terminals will burst and the peripheral process will regress toward the habenula perforata, as far as the portion of the process within the canal that becomes myelinated [231]. This is not typical CNS excitotoxicity, where the effect is usually on the soma and the swelling can be immediately fatal to the neuron. Because the connection between the SGC and the IHC is far removed from the soma, at the end of a long extended peripheral process, the excitotoxic effect is restricted to the unmyelinated portion of peripheral process, so it is less destructive. Blocking the glutamate receptor [228] or providing increased amounts of the lateral efferent transmitter dopamine will reduce the swelling or bursting and regression of the peripheral process [55]. When the inner hair cell recovers, the connection can regenerate and the synaptic function will also recover [230,253]. When the inner hair cell dies there is no longer regeneration of processes. Instead, there is eventual secondary loss of the Type I SGCs. It is possible, however, to provide stimulation with a cochlear prosthesis and/or with neurotrophic factors such as GDNF or BDNF [5,77,113,114,122,174,202–204,206,299,300,353] to enhance SGC survival following inner hair cell loss.

The response of auditory nerve fibers is not only a function of the type and subunit composition of the receptors but also of post-synaptic channels. There is a variation in intrinsic properties such as adaptation and inward rectification that varies among auditory nerve fibers and some of this can be correlated with differences in K^+ channels. There are differences in the K^+ channels along a base-apex gradient [3] with SGCs in more apical turns generally having a greater number of the Kv 4.2 subunits and more basally located SGCs having a greater number of Kv 1.1 and 3.1 subunits.

6.2.2. Inner hair cell—auditory nerve synapse

The inner hair cell makes a ribbon synapse with the peripheral process endings of Type I SGCs. Presynaptically, multiple large round vesicles are lined up around a dense body, called a ribbon. Recent studies by Glowatzki and Fuchs [107], reviewed by Trussell [326], point out some special features of the inner hair cell—Type I SGC cell synapse. The ribbons are believed to facilitate a continuous supply of synaptic vesicles containing glutamate allowing a continuous multivesicular release of transmitter. This allows a greater efficacy for each "quantum" release early within a sustained stimulus and sustained release of transmitter over the course of a long stimulus. The synaptic type is an asymmetric one, typical of excitatory amino acid synapses, with large round vesicles presynaptically and a thick post-synaptic density. The inner hair cell makes its synaptic connection with the peripheral process of Type I SGCs, which comprise 90–95% of the SGC population. A Type I SGC has only one peripheral process, which contacts a single inner hair cell, while each inner hair cell receives connections from multiple (10–30) SGCs [185,188,295] with the number varying, depending on the species. The connection between the inner hair cell and the auditory nerve can be further subdivided, based on the spontaneous activity of the auditory nerve. There are auditory nerve fibers with high, low and intermediate spontaneous activity. Each inner hair cell receives connections from all of these categories. Connections with high spontaneous rate fibers are generally more prevalent on the pillar (lateral) side of the inner hair cell, with terminals larger and richer in

mitochondria than the lower spontaneous rate fibers more prevalent on the modiolar (medial) side [185,186,200].

6.2.3. Lateral olivocochlear efferent connections

Lateral olivocochlear (LOC) efferents arise in the lateral superior olive (LSO) of the auditory brain stem and send terminals predominantly or entirely to the ipsilateral cochlea (depending on species) [109,342,346]. These unmyelinated fibers exit the brain stem with the vestibular nerve, join the auditory nerve at the anastomosis of Oort just before entering the cochlea with the auditory nerve. They may spiral through the modiolus in the intraganglionic spiral bundle and enter the organ of Corti through the habenula perforata of Rosenthal's canal where they then spiral in the inner spiral bundle below inner hair cell bases and in the tunnel spiral bundle, in the medial border of the tunnel of Corti. Fibers leave these bundles to terminate on the peripheral processes of Type I SGCs [342,343]. The distribution of LOC terminals is relatively equal along the length of the cochlear spiral, however, recent studies show there are two separate lateral efferent systems, one with discrete tonotopic distribution along the cochlear spiral and another, originating in the shell region around the LSO, with a more diffuse projection [343]. The LOC was shown to contain acetylcholine as a transmitter, based first on cholinesterase stains [341], and then choline-acetyl-transferase (ChAT) immunostaining [8,83,84,338]. The LOC has also been shown to contain a large number of additional neurotransmitters [79] including enkephalin [10,83,90], dynorphin [7,130], dopamine [149,332], CGRP [164,192,277,280,287,312,338] and GABA [82,91,338]. Many of these neurotransmitters have been shown to be co-localized within single LOC neurons and neuronal processes [1,6,9,11,257,260]. Because these unmyelinated fibers are difficult to record from or to stimulate, it has been difficult to determine the function of the LOC. Lesion studies show a compression of auditory nerve spontaneous rates following the loss of the LOC system [187] with an overall decrease in compound action potential [181,182]. Studies suggest that the lateral efferents can change the resting potential or "set-point" within the Type I SGC auditory nerve post-synaptic terminals, depending on which transmitter or transmitters are acting on the auditory nerve. Release of acetylcholine, probably acting on α-7 acetylcholine receptors [66,211], will depolarize the peripheral process and enhance glutamate driven activity [87]. Dynorphin will also depolarize the peripheral process terminal and facilitate driven activity [261]. CGRP has been shown to increase activity of afferent fibers innervating hair cells in the *Xenopus laevis* lateral line [2]. Thus acetylcholine, dynorphin and CGRP are all capable of lowering the set point and potentiating the action of glutamate in achieving depolarization and auditory nerve activity. On the other hand dopamine, enkephalin and GABA are inhibitory and will hyperpolarize, raise the set-point and make the peripheral processes they influence less sensitive to glutamate activation by inner hair cells [20,46,87,217,254]. The function of the LOC may therefore be to produce a range of set-points, generating a continuum of spontaneous activities and sensitivities, which in turn provides a greater dynamic range for the driven activity of the auditory nerve (Fig. 6). An additional function may be a lateral efferent loop or reflex that can change set-points and/or receptor trafficking and allow the dynamic range to be adapted to different levels of activity. This may also provide protection [234]. Recent reviews provide more details on the afferent and efferent pathways of the cochlea and cochlear neurotransmission [85,180,181].

6.3. Outer hair cells

OHCs are mainly innervated by efferent terminals and are known to enhance and modulate the function of the true auditory sensory cell, the inner hair cell. OHCs have evolved an elaborate set of structural and functional features, some of them unique, which allow them to facilitate the exquisite sensitivity and selectivity of the cochlea.

The general shape of OHCs is cylindrical, with a flat apical membrane (Figs. 2 and 4). The nucleus is round and located in the basal portion of the cylinder. The apical domain includes the stereocilia. The basal end rests on a special "seat" provided by a Deiters cell. There are three rows of OHCs, but in some cases a fourth and even fifth row are found, especially in the apical turn or in mammals specializing in low frequency hearing [242]. The lateral membrane of these cells is bathed in the fluid of the space of Nuel, which is biochemically continuous with perilymph. The Deiters cell on which the OHC is seated allows efferent neurons to pass through it, reach the basal domain of the OHC, and form nerve terminals. The apical domain of each OHC is in contact with four different supporting cells, as explained below in the section dealing with the reticular lamina mosaic.

OHCs vary in length among mammals and along the cochlea. OHCs of the basal turn are invariably shorter than those located in the apical turn. OHCs in low frequency adapted mammals are longer than those specializing in high frequency. Typically, OHCs are not shorter than 20 μm and not longer than 70 μm.

The stereocilia of OHCs have a molecular organization similar to that of inner hair cell stereocilia. Tip links and side links also resemble links in inner hair cells. It is possible that ion channels are different between the two types of cochlear hair cells, and data on this are awaited. The basic organization of OHC stereocilia is in three rows (Fig. 3), although additional rows have been seen in some species [242]. The three rows form a W-shaped pattern, with the tip in the lateral aspect of the cell, just above the actin-free area in the cuticular plate, the fonticulus. As in the inner hair cells, the rows of stereocilia are graded, with the tallest being positioned laterally. The angle of the V varies in a gradient along the cochlear duct, with the most acute angle at the apical turn. The width of each stereocilium is slightly larger than those of the inner hair cells [349]. The organization of actin within the stereocilia and the cuticular plate, and the

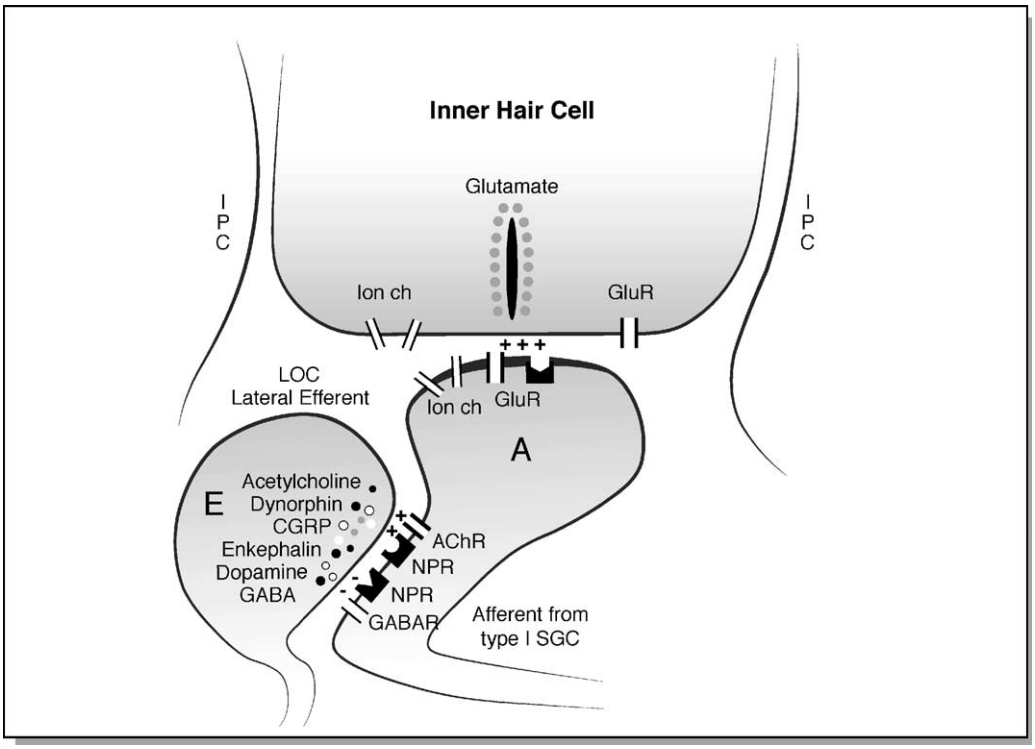

Fig. 6. Schematic of the efferent (E) and afferent (A) connections to the inner hair cell. The "inner hair cell" is surrounded laterally by inner phalangeal cells (IPC). There are ion channels (Ion ch) at the base (shown) and in the lateral wall (not shown) including voltage sensitive calcium channels and Ca^{2+} activated K channels. The inner hair cell transmitter, an excitatory amino acid most likely to be glutamate, is sequestered in large round vesicles around a ribbon and released into the synaptic cleft. A connection is made to an afferent (A) terminal, the peripheral process of a Type I spiral ganglion cell (SGC). Glutamate receptors (GluR) are placed in the active zone of the post-synaptic membrane, with an AMPA type ionotropic membrane spanning receptor (left) and perhaps also a metabotropic, second messenger linked receptor (right) as part of the complex. There may also be pre-synaptic glutamate receptors as part of a feedback system. There are also post-synaptic ion channels including K^+ channels whose subunit composition varies from base to apex along the length of the cochlear spiral. The efferent (E) connection is made by the LOC system and is largely onto the afferents. There are multiple neurotransmitters (listed in diagram) within the lateral efferents, with evidence for co-containment. These can have excitatory (+) or inhibitory (−) actions on post-synaptic receptors. There are ionotropic (membrane spanning) receptors, the acetylcholine receptors (AChr), most likely the nicotinic type using the α-7 subunit with an excitatory action and GABA-A receptors (GABAR) with an inhibitory action. There are also metabotropic (second messenger linked) receptors for the different neuropeptides (neuropeptide receptors—NPRs) with excitatory, inhibitory and other types of actions possible.

anchoring of the rootlet in the cuticular plate is similar to that described for the inner hair cell.

The junctional complexes connecting OHCs to their neighboring supporting cells are similar, but not identical to those found in inner hair cells. The most apical complex, the tight junction, forms a mixed complex with the adherens junction, so that they alternate along an extensive length, sealing the reticular lamina and preventing passage of molecules between the lumen (scala media) and the perilymph in the space of Nuel. This is a unique junctional organization which is thought to be required because of the mechanical exposure and motile function of the cell. The distribution of actin associated with the adherens junction ring is asymmetrical, with more actin in the supporting cell side of the junction. Similar to inner hair cells, there are no desmosomes or gap junctions in OHCs.

The cytoskeleton of OHCs includes actin (and associated proteins) and microtubules (with their associated proteins). As in inner hair cells, intermediate filaments are absent. Actin has been described in the circumferential ring of the adherens junction, the cuticular plate, in association with the lateral wall plasma membrane (see below) and in the sub-nuclear area. Microtubules have been localized to the subcuticular region, the lateral wall and elsewhere in the cytoplasm. Because of space limitations, we can only mention some of the many papers that describe the cytoskeletal components and their organization in OHCs of the organ of Corti [24,92,94,131,169,223,240,281,284,285,314,323].

The presence of a cochlear amplifier has been postulated [58]. Motility (length changes) in OHCs was discovered two years later [23,43,153,355]. Since then, an intense effort has been directed at identifying the mechanism of motility in OHCs. Because the reticular lamina is rather stiff, length changes in the OHC are likely to modulate the distance between the reticular lamina and the BM, and the characteristics of the mechanical vibration presented to the inner hair cell stereocilia. To generate the motility and deliver the length changes to the receiving parts of the organ of Corti, OHCs evolved to be stiff and motile. There is ample evidence that the lateral plasma membrane (sometimes

called “lateral wall”) of these cells, along with associated specialized structures, participate in maintaining the shape and the stiffness of the OHC and generate their motility [22,56,199].

Transmission electron microscopy of the lateral membrane of OHCs reveals a plasma membrane with specialized associated structures [26,96,115,244,323]. One or more layers of vesicles called subsurface cisternae are located along the lateral wall of the OHCs [100,244,262,336]. Micro-pillars are positioned between the plasma membrane and the cisternae, at an angle perpendicular to the membrane [96,244]. Between the cisternae and the plasma membrane, there is a mesh of actin and spectrin, resembling the cortical membrane of erythrocytes [132,133]. On their cytoplasmic side, cisternae, termed “subsurface cisternae” have been shown to be associated with microtubules [242]. In man, mouse and several other mammals, there is only one layer of cisternae along the lateral membrane of OHCs. In other animals, the number varies. In guinea pigs, there are 2–3 layers in the basal turn and the number increases towards the apical turn, reaching as high as 7. With the use of fluorescent membrane probes it was determined that subsurface cisternae are neither Golgi nor ER, but share characteristics of both [226]. Their role is not known [132,335].

OHCs have a dual response to the transduction current generated by the opening of transduction channels in the stereocilia. There can be a release of transmitter at the base, however this is relatively minor compared to the inner hair cells. The major response is a rapid change in the length and stiffness of the OHC, closely coupled to the changing transduction current. The motile response of OHCs then provides a region specific amplification in the movement of the organ of Corti that enhances transduction at the inner hair cells in that specific region of the cochlear spiral (thus increasing both sensitivity and specificity). The length change is generated by conformational changes in motor protein or proteins located in the lateral wall of the OHC [102,153,154]. The putative motor protein was recently identified as prestin, a protein related to pendrin and other sulphate/anion transport proteins [357,358]. It was localized to the plasma membrane of OHCs [357] and its appearance during development coincided with the time of onset of motility [29]. Prestin is a new type of molecular motor, using a direct voltage-to-force conversion. It uses cytoplasmic anions as extrinsic voltage sensors and can operate at microsecond rates, changing OHC length in response to changes in membrane potential [56]. Because of the restricted expression of prestin in OHCs, it has also become a useful and accurate marker for labeling these cells. Mice with a null prestin gene exhibit loss of OHC electromotility in vitro and a 40–60 dB loss of cochlear sensitivity in vivo [246]. These data confirm that prestin is indeed the motor protein responsible for the entire force in the active cochlear amplification and that electromotility and cochlear amplification are directly linked to each other.

The changes in the plasma membrane of the OHC, induced by the changes in prestin, act against the OHC actin/spectrin cortical lattice and the “lateral membrane complex” including the subsurface cisternae. This electromotility of OHCs depends on positive intracellular pressure (turgor). Aquaporins, proteins that regulate water flow through plasma membranes, were localized to the plasma membrane of the OHC [30]. In mice with mutations in an aquaporin gene, *Aqp4*, cochlear dysfunction was identified [201]. The molecular organization of the membrane, especially the lipid components, also influences the stiffness of the cells, through its influence on turgor [214]. Various models for electro-motility have been proposed, based on structural and electrophysiological data related to the membrane and the motor protein [56,184,218,239].

There are several specific molecular markers for the mature OHC. Among these are Myo 6 [275], Myo 7a [119], CAR [216], α-9 acetylcholine receptor [195,360] and prestin [29]. Prestin is an especially useful marker because of its restricted OHC expression.

6.3.1. OHC—auditory nerve synapse

OHCs make a synaptic connection with Type II SGCs [41]. Type II SGCs are smaller, less numerous (5–10%) and less myelinated than the Type I SGCs. One major function of their central connection may be to contribute to an efferent feed-back loop, the medial olivocochlear reflex (described below). As part of this pathway, Type II SGCs make a central connection to the shell region of the cochlear nucleus which in turn projects to the superior olivary complex [31,32,42,210,343,351].

There are few vesicles presynaptically at the synapses between OHCs and Type II SGCs in basal turns of the cochlea and no pre-synaptic ribbons [70,188]. Multiple vesicles and ribbon synapses, as found in inner hair cells, are only seen for OHCs in the more apical turns of the cochlea [232]. Because the OHC—Type II SGC synapse is less active, less is known about its elements than for the IHC synapse. While there is evidence showing glutamate in OHCs [12,80,333] and glutamate receptors are expressed in Type II SGCs [171,172,221], evidence for placement of the receptors into the postsynaptic complex [197] and for an action of glutamate is still lacking (Fig. 7).

6.3.2. Medial olivocochlear efferent connections to OHCs

Medial olivocochlear (MOC) efferents arise from the ventral nucleus of the trapezoid body with other medially located superior olivary complex nuclei, including superior periolivary nucleus (SPN), also contributing in some species (such as cat and guinea pig) but not in others (such as rat) [109,338,342,346]. The MOC processes are both crossed and uncrossed (crossing the auditory brain stem at the floor of the fourth ventricle) innervating both ipsilateral and contralateral cochleae, with the contralateral cochlea receiving the greater input. Many MOC fibers give off collaterals to the cochlear nucleus before they exit the brain stem with the vestibular nerve. They travel with the

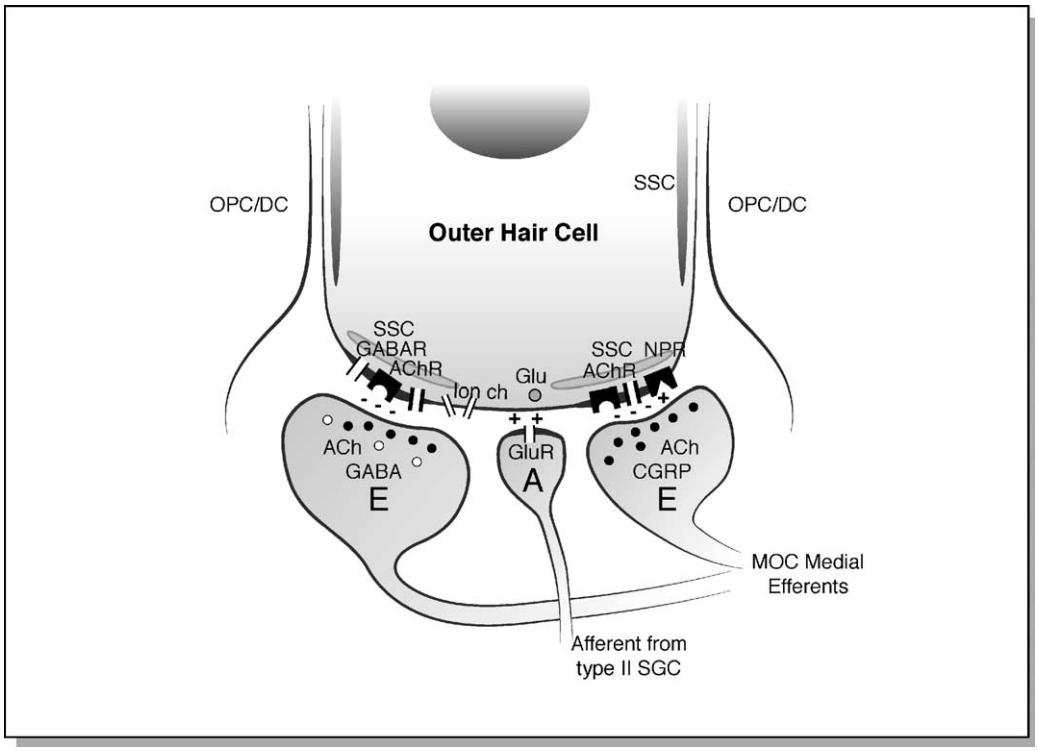

Fig. 7. Schematic of the efferent (E) and afferent (A) connections to the outer hair cell typical for the basal half of the cochlea. An outer phalangeal or Deiters cell (OPC/DC) cups the outer hair cell laterally (shown) and at its base (not shown), with subsurface cisternae (SSC) in the lateral wall of the outer hair cell apposing this. Efferents (E) from the medial olivocochlear (MOC) system make multiple connections to the outer hair cell base and are apposed by sub-synaptic cisternae (SSC). Efferent terminals contain acetylcholine (ACh) and perhaps also GABA and CGRP (their co-containment within terminals is not known). In the active zone in the post-synaptic membrane of the outer hair cell, the efferent terminals are apposed by acetylcholine receptors, including the ionotropic nicotinic type with α-9 and α-10 subunits with an inhibitory action and perhaps also the metabotropic (second messenger linked) type as part of the receptor complex. GABA receptors (GABAR) and a neuropeptide receptor (NPR) for CGRP provide for their action. Specific types of ion channels (Ion ch), including K^+ channels, help to generate the post-synaptic response to efferents. The outer hair cell makes an afferent connection to the peripheral process of type II spiral ganglion cells (SGC). Presynaptic glutamate (Glu) is released from a small vesicular pool at the outer hair cell base and acts at glutamate receptors (GluR) in the postsynaptic afferent.

vestibular nerve until they join the auditory nerve (at the anastomosis of Oort) close to the cochlea and enter the cochlea with the auditory nerve. MOC fibers travel through Rosenthal's canal, and become unmyelinated as they exit the canal through the habenula perforata. They then cross at the mid level of the tunnel of Corti, unlike the Type II SGC peripheral processes that cross on the floor of the tunnel. The MOC fibers then run parallel to the three rows of OHCs forming the outer spiral bundles. MOC fibers leave the bundles and terminate at the bases of multiple OHCs. This synapse is characterized by post-synaptic cisterna, along the length of the synapse. In many, but not all species, this MOC innervation of OHCs has a basal bias, with more terminals on OHCs of the basal turn and the first row, with the number gradually decreasing more apically. Pharmacological [36,37,89,105,166,249] as well as histochemical and immunocytochemical studies [8,83,84,338,341] support acetylcholine as the MOC transmitter. The post-synaptic effect on OHCs is atypical for ACh [88] with an inhibitory action that is blocked by strychnine [179]. Recent molecular studies explain this by showing that OHCs have a unique ACh receptor composition using α-9 and α-10 subunits [74,145,194,195,211,279,360]. The effect of ACh release is a hyperpolarization of the OHC, which changes its set-point (resting potential) [34,36,37,57,78,105,166,311], thus modulating outer hair motility and changing the gain of the cochlear amplifier. ACh also has a direct effect on OHC motility by influencing the OHC axial stiffness [57,311]. The MOC may act in "reflex" fashion by changing the cochlear amplifier as a consequence of the amount of auditory pathway activity and may also act to provide protection from overstimulation by noise [196].

There are additional actions of ACh on the OHC, through other receptor mechanisms, including a "slow effect", that may use a second messenger system and influence intracellular calcium pools [49,78,297,298], and calcium dependent K^+ channels [103,334,354]. Intracellular pathways involving the GTPases RhoA, Rac1 and Cdc42 may regulate OHC motility [155].

GABA has also been shown in medial efferents [12,82,91,197,338] but there is conflicting evidence for the presence of CGRP [164,192,277,280,287,312,338] with its presence now becoming more accepted on the basis of a recent report of the presence of its receptor complex [193]. GABA

receptors have been shown [65] and GABA has been shown to hyperpolarize OHCs and thus may also function to modulate the set-point [219,310], while the action of CGRP remains unknown.

6.4. Supporting cells of the organ of Corti

The supporting cells of the organ of Corti are highly differentiated epithelial cells with distinctive morphological features. Supporting cells surround all the hair cells. Inner hair cells are surrounded by (inner and outer) phalangeal cells (Figs. 2 and 4). OHCs are in contact with Deiters and pillar cells. Hensen cells are positioned further laterally in the organ of Corti. The apical surface of the supporting cells (the top of their head plate) is covered by numerous microvilli that protrude into the endolymph of the scala media. In their basolateral aspect, supporting cells exhibit different sets of cell–cell junctions in their homologous versus heterologous junctions [75,159,162,296,345]. In homologous junctions (supporting cell to supporting cell) there are desmosomes and gap junctions, in addition to the tight and adherens type junctions. In contrast, gap junctions and desmosomes are absent in heterologous junctions (supporting cell to hair cell) [99,159].

Supporting cells have a highly polarized shape. They lack membrane specializations such as those found in OHCs, and therefore their shape is most likely dependent on an elaborate network of cytoskeletal filaments. Indeed, microfilaments, intermediate filaments and microtubules are all present in supporting cells in conspicuous amounts and strict organization. Pillar cells exhibit an extreme organization of junctions and cytoskeletal arrays. The apical junction between the inner and outer pillar cells contains an extremely wide and dense area with desmosomes. The long pillars extend from the basement membrane to the head-plate and contain organized arrays of actin cables and microtubules. Similar cytoskeletal arrays can be found in the phalangeal process of Deiters cells.

Due to the massive array of organized filaments, pillar cells have been used as a model for development of cytoskeletal organization, especially microtubule arrays. The centrosomes appear to play an important role in organizing the microtubule network [330]. In the outer pillar cells, cell surface-associated centrosomes (microtubule organizing centers) appear to have two spatially discrete microtubule-nucleating sites, enabling the specific and complex assembly of microtubules in this elongated cell [331]. A centrosome is present at the apical surface of every supporting cell. Comparing different cells in the organ of Corti for their microtubule isoform (tyrosinated, detyrosinated, acetylated and polyglutamylated isoforms), it was found that microtubules in the pillar and Deiters cells contain predominantly post-translationally modified isoforms (detyrosinated, acetylated and polyglutamylated tubulin), suggesting that microtubules in supporting cells are post-translationally modified to provide stable, long-lived structural support [284]. The organization of microtubules in supporting cells has been described using a variety of methods [14,112,169,190,293,306,314,335]. One of the unique features of microtubules in supporting cells is that each microtubule molecule is composed of 15 protofilaments [263].

Organ of Corti supporting cells contain bundles of cytokeratin intermediate filaments [16,21,27,170,208,243]. The keratin filament arrays appear to anchor microtubule bundles to cell surfaces, especially in areas where supporting cells contact hair cells [208]. Nevertheless, the mystery of the function of intermediate filaments is yet to be resolved, along with the reasons for the absence of these proteins from mature auditory hair cells [27,170,243].

There are several features specific for each type of supporting cells. The apical junctional area between the head plates of inner and outer pillar cells displays one of the most extensive and elaborate complexes of desmosomes and adherens type junctions. The luminal surface of the inner pillar cells covers part of the apical process of the neighboring outer pillar cell. While the number of outer pillars corresponds one to one with the first row OHCs, inner pillars are slightly wider and their number is slightly smaller. The lower portion of inner pillar cells (the stalk) slants medially whereas the stalk of the outer pillar slants in the opposite direction, thereby creating the tunnel of Corti between the two stalks. The basal portion of pillar cells rests on the basement membrane at a site that is more apical along the cochlear duct than the head plates.

Deiters cells have three distinct compartments: cell body, stalk and apical head plate (phalangeal process). The lower compartment is the main cell body, with its base resting on the basement membrane. The upper part is curved as a rounded deep “seat” to accommodate and sustain the basal portion of the OHC. The stalk extends from the main cell body towards the reticular lamina in a slanted angle, and terminates with the head plate that contributes to the reticular lamina (filling the space between OHCs). The head plate is dumbbell shaped (for first and second row Deiters cells). The angle of the stalk is towards the apex of the cochlea and towards the lateral aspect of the organ of Corti [190]. Thus, the head plate does not make contact with the same OHC that occupy the “seat”. Rather, it is positioned laterally and apically. Thus, each Deiters cell is in contact with five different OHCs: one that sits on it and four others that are connected to its apical head plate (see more in Section 6.5). The third row Deiters cell slants in a similar manner, however, its stalk has a different shape. In most mammals, it extends laterally then returns medially to meet the lateral aspect of the third row OHC.

Hensen cells form the lateral border of the organ of Corti. These cells have less complex cytoskeletal organization than the Deiters and pillar cells. Some Hensen cells rest on the basement membrane while others appear to form a second layer, usually on top of Boettcher cells (on the lateral aspect of the Hensen cell area). In the guinea pig cochlea it is easy to identify Hensen cells by their prominent lipid

droplets, which can be observed using light microscope analysis of whole mounts of the organ of Corti, or sections. Lipid droplets are extremely prominent in the apical turns. Tectal cells have also been defined in the Hensen cell area [127].

Supporting cells have functions beyond structural support. There is evidence that these cells participate in regulating the ionic environment within and around the organ of Corti [158]. Most importantly, supporting cells are thought to recycle K^+ by removing it from the organ of Corti to fibrocytes that, in turn, transport it back to the stria vascularis. Mutations in several genes that encode for ion channel proteins cause hearing impairment, and the gene products have been localized to supporting cells. For instance, Kcc4 was localized to supporting cells in the organ of Corti [38]. Mice lacking the K^+/Cl^- co-transporter Kcc4 are deaf. Another supporting cell domain that could participate in cochlear K^+ homeostasis is a dense network of canaliculi called the canalicular reticulum, which is found in the foot body of inner pillar cells. It has been proposed that this reticulum resorbs ions released from inner radial and spiral nerve fibers [294]. An excellent review of K^+ recycling in the inner ear has recently appeared [340].

In addition to their apical intercellular junction (see Section 6.5), gap junctions couple the cytoplasm of supporting cells and allow them to share a micromolecular cytoplasmic environment [99,159]. The role of gap junctions for hearing is crucial, as mutations in genes encoding connexins are common and detrimental for hearing [175]. Four genes, *GJB1*, *GJB2*, *GJB3* and *GJB6*, encode for connexin proteins (Connexin32, Connexin26, Connexin31 and Connexin30, respectively). Mutations in these genes cause hearing impairment [235], emphasizing the importance of supporting cell function in maintaining ionic homeostasis in the cochlea.

There are several specific markers that can be used to distinguish supporting cells from sensory cells, but it is not easy to specifically stain a specific type of supporting cell. Among the supporting cell markers are cytokeratins (see above), KHRI-3 [63,213], and connexins, which are gap junction proteins (not expressed in hair cells) [99,159].

Comparing several morphological parameters of supporting cells at six different places (frequency areas) along the gerbil cochlea revealed differential (site specific) specialization for the two main functions of these cells: contribution to the stiffness of the cochlear partition and to the homeostasis of the ionic environment [291].

There is now evidence showing that supporting cells receive synaptic connections. Recent studies show that Hensen and Deiters cells receive a significant innervation that is predominantly derived from collaterals of Type II SGC afferents [85], with small additional contributions from the efferent system. The function of this innervation remains unknown.

Deiters cells are also capable of a motile response [68], have P2X receptors [48] and ATP can induce their movement [35].

6.5. The reticular lamina

The term reticular lamina describes the cellular mosaic made of the apical domains of hair cells and supporting cells in the organ of Corti. Collectively, the apical membrane of hair cells and supporting cells, and the tight junction complexes between them, make a functional seal between the endolymph of scala media and the perilymph in the organ of Corti. The organization of cells is very precise and regular, allowing a clear identification of cell types when the reticular lamina is viewed from above (Figs. 3 and 5). The apical surface of each hair cell is surrounded by that of supporting cells, making a heterologous junction. Hair cells are not in contact with adjacent hair cells. Supporting cells make heterologous contacts with hair cells and homologous contacts with other supporting cells. Typically, each hair cell is surrounded by four supporting cells at the level of the reticular lamina. The four supporting cells that surround (and contact) a given OHC are cells other than the cell on which this hair cell is seated (at its base). In other words, every OHC is in contact with five different supporting cells, four at the reticular lamina and one at the basal aspect of the cell.

Due to the exquisite organization of the reticular lamina, it is possible to obtain accurate counts of the hair cells from a surface view. It is also possible to detect any deviations from the normal pattern of the reticular lamina. Thus, every missing hair cell can be counted in an experimental preparation.

The intercellular contacts between the cells that make up the reticular lamina are complex and elaborate. Tight junctions contribute to the polarized segregation of membrane proteins in hair cells and to sealing the reticular lamina against leaks, thus preventing mixing of endolymph and perilymph. Beneath the tight junction ring, all cells have a prominent belt of adherens junction complex. The actin belt associated with the adherens junction is more prominent on the supporting cell side of the junction than the hair cell side. Hair cells have no other junctions at the level of the reticular lamina. However, in their homologous junctions, supporting cells display desmosomes and gap junctions. Collectively, the junctional complexes contribute to the mechanical adhesion of the cells and facilitate intercellular communication.

The molecules that mediate cell–cell communication via the junctional complexes belong to different families of cell adhesion molecules. For instance, E-cadherin is localized to the apical intercellular junctions of supporting cells, but is absent from supporting cell–hair cell borders [347]. The complexity of the distribution of junctions and adhesion molecules in the reticular lamina has been demonstrated [178]. Several known mutations in junctional protein encoding genes lead to hearing loss. Mutations in the tight junction gene claudin-14 cause nonsyndromic recessive deafness DFNB29. In situ hybridization and immunofluorescence studies demonstrated mouse claudin-14 expression in the sensory epithelium of the organ of Corti [348]. Mutations in the cadherin-like gene *CDH23*, found in families

with DFNB12 and families with USH1D are associated with hearing loss. *CDH23* has been shown to be expressed in the cochlea [40]. The mouse orhtholog, Cdh23, is mutated in waltzer mice, that exhibit an inner ear phenotype [40,339]. The gene product, otocadherin, was localized to hair cell stereocilia [62]. In another deaf mutant mouse, the Ames waltzer, the mutated gene encodes a protocadherin [4]. Profound deafness and early degeneration of hair cells were found in these mice [241]. Much of the research on adhesion molecules in the cochlea (and elsewhere) is performed in non-mammalian species, especially in the chicken.

7. Extracellular components

7.1. The tectorial membrane

Due to their small mass, cells are relatively insensitive to gravitational forces. Mass-loaded systems have evolved to present gravitational signals to the stereocilia. In auditory hair cells the accessory mass is the TM, an acellular connective tissue overlying the organ of Corti [189,301]. The TM is a long spiral "blanket" that covers the organ of Corti throughout the cochlea, from base to apex. It is medially attached at the spiral limbus to interdental cells which secrete the TM matrix [161,189]. The lower (inferior) aspect of the TM is in contact with the stereocilia of OHCs and with Hensen cells at the lateral edge of the organ of Corti. The dimensions and mass of the TM increase in reverse proportion to the frequency along the cochlear duct. Several distinctive regions have been defined in the TM, including the cover net (superior region), marginal net (lateral aspect, attached to supporting cells in the lateral aspect of the organ of Corti), limbal zone (medial, near the insertion of the TM to the interdental cell area) and a middle zone. The middle zone is above the inner hair cell area. Hensen's stripe is an area in the inferior aspect of the TM, with which inner hair cell stereocilia are thought to interact (directly or indirectly, see below). The area in the inferior surface of the TM where OHC stereocilia are embedded is known as Hardesty's (or Kimura's) membrane.

Ultrastructural examination of the TM reveals at least two types of fibers called fibrils and a non-fibrilar matrix. The two main types of fibrils are called Type A and Type B [167]. The dimensions and organization of the fibrils have been described [19,116].

The TM is composed of collagens and other molecules which appear as fibers and matrix. The molecular composition and organization of the TM is gradually being elucidated. Glycosaminoglycan enriched in chondroitin-4-sulfate is thought to mediate fusion of the different components of the TM [33]. α-Tectorin, a noncollagenous component of the TM was mapped to a chromosomal area that contains deafness mutations [136].

Biochemical assays have been detected in the TM carbohydrates including glucose, *N*-acetylglucosamine, *N*-acetylgalactosamine, galactose, mannose and *N*-acetylneuraminic acid [157]. The matrix around the fibers is highly organized in space [116]. Enzymatic digestion of the TM followed by one dimensional SDS–polyacrylamide gel electrophoresis, combined with amino acid analysis demonstrated that the TM contains at least three different collagens and several non-collagenous, glycosylated polypeptides [245]. Among the collagens are Type V-like collagen, Type II, and Type IX [286]. Using immune-electron microscopy it was shown that Types II and IX collagen are found only in some of the radial fibers [283]. Analysis of the TM composition with lectin binding assays revealed glycoconjugates throughout the membrane, with highest concentration in the cover net area [307]. Keratan sulfate was also described as a component of the TM [308]. X-ray microanalysis studies detected the elemental composition of the TM [18].

It is unclear whether the stereocilia of inner hair cells are attached to the TM. In most mammals studied, data were unable to demonstrate convincingly a direct physical attachment [198] (Fig. 2). In contrast, attachment links between the tips of OHC stereocilia and the TM were documented in several species [161,189,242,329] (Fig. 2). The attachment was to the Type B fibrils of the TM [329].

The importance of the TM for hearing is demonstrated elegantly by mutations in TM encoding genes that are known to cause deafness [160,302]. The gene *otog* encodes otogelin, an *N*-glycosylated protein present in the TM. In mice with targeted disruption of *otog*, hearing is impaired [278]. Another protein, otoancorin, was localized to the attachment zone of the TM with the spiral limbus. Mutation in the corresponding gene, *OTOA*, results in DFNB22 [361]. Mice homozygous for a targeted deletion in α-tectorin have a hearing impairment and their TM is detached from the cochlear epithelium and lacks all noncollagenous matrix [176]. Families with mutations in the human ortholog gene, *TECTA* (DFNA12 and DFNA8), have hearing impairment.

7.2. The basilar membrane

The BM is a complex strand of connective tissue composed of cellular and extracellular components (Figs. 1 and 4). The side of the BM facing the scala media features the basement membrane of the membranous labyrinth epithelium. On the opposite side, facing the perilymph of the scala tympani, several cellular and acellular components of connective tissue can be found. The cellular component is made up of a layer of mesothelial cells that line the scala tympani.

The width of the BM (distance from the modiolar side to the lateral end) and its thickness (the distance from the tympanic border to the basal lamina) were measured in several species [156,212,252,270]. Measurements using methods that do not involve dehydration produce data that are significantly different than traditional microscopy techniques [156]. A clear gradient of size (thickness and width) is

found in most mammals, proportional to the distance from the basal end of the cochlea.

There are several structural domains within the BM. The main distinction is between the medial portion of the BM, called arcuate zone (pars tecta) and the lateral portion called pectinate zone (pars pectinata). The arcuate zone is partly enclosed in osseous spiral lamina, and therefore its ability to vibrate upon sound-induced displacement of the cochlear fluids is restricted. In contrast, the pectinate zone is free to vibrate in response to sound, within the physical constraints of its mass, stiffness and the effects of the active cochlear mechanisms. The border between the arcuate and pectinate zones is usually under the outer pillar cell. The arcuate zone of the BM has small perforations, collectively referred to as the habenula perforata, that accommodate the auditory nerve fibers as they extend from Rosenthal's canal to the organ of Corti.

The BM is composed of matrix and fibers. The fibers exhibit distinctive organization in each of the two parts of the BM. Several matrix molecules have been identified in the BM. Collagen Type II, IV and XI were identified using immunocytochemical and biochemical methods [51,64,315]. Collagen mutations such as Alport syndrome involve hearing impairment [53]. Immunofluorescence has also revealed high levels of fibronectin in the BM [52,268]. The composition and assembly of proteoglycans in the BM have been documented [328]. Tenascin was also identified in the BM [309].

8. Comparative studies of mammalian cochleae

Auditory function varies among mammals in its sensitivity to sound frequencies and intensities. Some animals have evolved to become adapted to extreme hearing environments. Studies of the cochlear morphology of extreme adaptation ears have identified the cochlear structures that are most conspicuously associated with the adaptation. At one extreme of the frequency range are bats, high frequency specialists that use echolocation for navigation and feeding. Several striking features were found in bat cochleae [44,123–125, 148,169,335,336,350]. These include extremely short hair cells and stereocilia throughout the cochlea, conspicuous imprints of inner hair cell stereocilia in the TM, very narrow and thin BM, specially shaped Deiters cells and a specialized pattern of innervation.

In the other extreme, the mole rat is a mammal adapted to low frequency hearing. Its high frequency hearing is limited but the low frequency capability is adapted for communication via seismic signals, used for long distance communication in subterranean tunnels [236]. In the mole rat cochlea, hair cells and stereocilia are long, the number of rows of stereocilia is five (instead of three), supporting cells are tall and their slanting angle is larger than usual, the BM is thicker and wider than usual and the pattern of efferent innervation is unusual [45,242].

9. Summary

The inner hair cell is clearly the center of the cochlear apparatus, as it transduces the mechanical energy brought by sound and initiates the receptor potential and the auditory nerve action potential. It forms the "recepto-neural junction" with the auditory nerve. The inner hair cell body, by itself probably does not vibrate. Movement of its stereocilia relative to each other mediates the mechanically gated ion channels. To perform this function, movement of the fluid and the TM above the inner hair cell stereocilia is crucial. Such movement, in turn, is regulated (sharpened and amplified) by the vibrating region of the organ of Corti, namely, the region of the OHCs. The entire process depends on the passive mechanical features of the cochlear partition (mass and stiffness), the active cochlear amplifier, the electrical environment such as the dc potential gradient between the interior of the inner hair cells and the endolymph, and the biochemical requirements that include energy supplies, ionic concentration (and pumps) and the presence of neurotransmitters and receptors. This review of the structure of the cochlea has presented a general description of inner hair cells with their innervation, and the surrounding structures that are necessary for cochlear function.

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