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Review Article

Molecular biology of hearing

Abstract

The inner ear is our most sensitive sensory organ and can be subdivided into three functional units: organ of Corti, stria vascularis and spiral ganglion. The appropriate stimulus for the organ of hearing is sound, which travels through the external auditory canal to the middle ear where it is transmitted to the inner ear. The inner ear houses the hair cells, the sensory cells of hearing. The inner hair cells are capable of mechanotransduction, the transformation of mechanical force into an electrical signal, which is the basic principle of hearing. The stria vascularis generates the endocochlear potential and maintains the ionic homeostasis of the endolymph. The dendrites of the spiral ganglion form synaptic contacts with the hair cells. The spiral ganglion is composed of neurons that transmit the electrical signals from the cochlea to the central nervous system. In recent years there has been significant progress in research on the molecular basis of hearing. An increasing number of genes and proteins related to hearing are being identified and characterized. The growing knowledge of these genes contributes not only to greater appreciation of the mechanism of hearing but also to a deeper understanding of the molecular basis of hereditary hearing loss. This basic research is a prerequisite for the development of molecular diagnostics and novel therapies for hearing loss.

Keywords: inner ear, cochlea, hair cell, organ of Corti, spiral ganglion, deafness

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1. Introduction

The sensory perception of sound (auditory perception) in the inner ear is made possible by a multitude of physiological, biophysical and biochemical processes. In the recent past, significant advances have been made in research into the molecular foundations of processes such as mechanoelectrical transduction by hair cells, adaptation, electromotility and cochlear homeostasis. There has been considerable progress in identifying and characterizing genes and gene defects responsible for producing genetic hearing loss and deafness. These genes code for proteins with a very wide range of functions, including transcription factors, structural proteins and ion channels. Detailed knowledge about these genes and the function of the gene products forms the basis for understanding the mechanism of hearing and the pathogenesis of hearing impairment. The literature contains a number of excellent reviews of the physiology and molecular biology of the hearing process, to which reference will be made in this paper.

The following sections of this review will focus especially on the molecular biological foundations of the process of hearing, with reference to the anatomy of the inner ear and the underlying physiological basis. At the appropriate points, the molecular pathogenesis of particular genetic hearing impairments will also be explained in more detail. These parts of the paper are intended to bridge basic research and clinical practice and, in order to distinguish them from the main body of the text, are printed in *italics*.

2. Molecular biology of hearing

2.1 The organ of Corti

2.1.1 Introduction and overview

The organ of Corti is the sensorineural end-organ involved in our sense of hearing. This organ houses two different subtypes of secondary sensory cells (receptors), namely the inner and the outer hair cells, as well as the supporting cells [1], [2], [3]. The cochlea contains some 15,000 hair cells arranged along the cochlear duct to form one row of inner hair cells and three rows of outer hair cells (Figure 1). The inner hair cells are the true sensory cells that transmit impulses via the auditory nerve [4]. The function served by the outer hair cells is that of qualitative amplification (by increasing selectivity) and quantitative amplification (by increasing sensitivity).

It is on the hair cells that the structure crucial for stimulus reception is located: the hair bundle (Figure 1). Hair bundles, which are the mechanosensitive organelles of the hair cells, consist of a kinocilium and several stereocilia. The individual stereocilia are joined at their ends by what are known as tip links [5]. Hair cells and supporting cells are arranged in a mosaic epithelium in which each

hair cell is surrounded by four supporting cells. All the cells of the organ of Corti are differentiated and, unlike in other epithelial tissues, there is no basal cell layer consisting of undifferentiated cells. This is the reason why the organ of Corti lacks regenerative capacity [6].

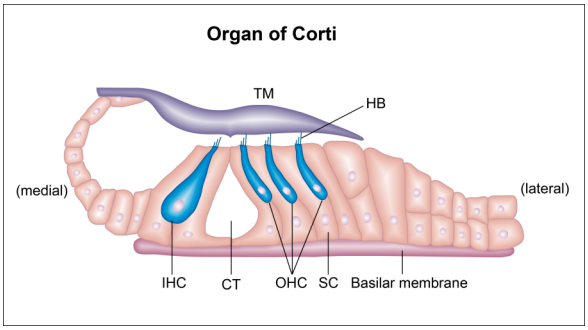

Figure 1: Schematic representation of the organ of Corti. The figure shows the different cell types and extracellular structures in the organ of Corti. Abbreviations: TM (tectorial membrane), OHC (outer hair cells), IHC (inner hair cells), HB (hair bundle), SC (supporting cells), CT (Corti's tunnel).

2.1.2 Tonotopy

Airborne sound that has passed the external auditory canal leads to vibration of the eardrum. These vibrations are then transmitted via the auditory ossicles to the stapes footplate and hence to the perilymph of the scala vestibuli. According to the theory of v. Bekesy und Ranke [7], the movement of the stapes results in volume displacement of the perilymph and, in turn, displacement of the basilar membrane and the cochlear duct. The resulting travelling wave proceeds from the stapes towards the helicotrema and has a local maximum (which depends on the frequency of the initial stimulus) at the basilar membrane [6]. This is the principle underlying the tonotopic organization of the cochlea. The displacement of the basilar membrane, the tectorial membrane and the endolymph gives rise to shear forces that tangentially displace the hair bundle protruding from the hair cells and constitute sufficient stimulus for the mechanosensitive sensory cells.

2.1.3 Mechanotransduction

The organ of Corti harbors the inner hair cells which are secondary sensory cells or mechanoreceptors. This unique cell type has the distinct ability to transform mechanical force into a bioelectrical signal and the neuronal activity of the spiral ganglion cells. The underlying mechanism is known as mechanoelectrical transduction [8], [9], [10], [11]. The crucial components of the transduction apparatus of the sensory hair cells responsible for sound transformation are the tip link, a filamentous protein structure that interlinks the stereocilia, and ion channels [12], [13], [14]. During the process of hearing, the hair bundle is mechanically displaced which gives rise to shear forces between the individual stereocilia that form the hair bundle [14]. Hair bundles respond with extreme sensitivity to mechanical displacement. Within the range of the normal auditory threshold, the hair bundles are displaced by less than 1 nm [15] and the angle of displacement does not exceed ~1° [16]. Hair cells respond to displacement of the hair bundles by opening and closing ion channels. In the absence of a stimulus, the channels switch between open and closed phases and have a probability of opening (P o) of ~0.1 [17]. Displacement of the hair bundle towards the highest stereocilia (i.e. positive displacement) increases the probability of opening, whereas displacement towards the shortest stereocilia (i.e. negative displacement) closes the ion channels [17].

2.1.3.1 Hair bundle and transduction apparatus

Although the mechanoelectrical transduction of the hair cells has been intensively researched, it remains unclear which protein is responsible for the biophysical process of mechanotransduction. With the previous emphasis having been on biophysical studies, only in recent years has greater attention been paid to the molecular basis of mechanotransduction and it is likely that, fairly soon, the transduction channel will have been identified and the process of mechanotransduction fully explained. The key molecules of the hair bundle include cadherins, myosins and scaffolding proteins [18]. Protocadherin 15 (PCDH15) and cadherin 23 (CDH23) form the kinociliary links between the kinocilium and the longest stereocilium, as well as the tip links that connect the stereocilia [19], [20], [21], [22]. (Figure 2). Myosin VI (MYO6) is detectable in large quantities in the region of the cuticular plate on the apical side of the hair cells, and is also found in the stereocilia. Myosin VIIa (MYO7A) is expressed in the stereocilia. Notably, high expression levels of this protein have been found in the region of the ankle links. Usherin and the G-protein-associated receptor 1 (VLGR1) can be detected at the base of the stereocilia, where they form what are known as ankle links. These links are found in vestibular hair cells. Interestingly, in auditory hair cells ankle links have only been observed at the developmental stage [17] (Figure 2). Based on currently available data, cadherin 23, protocadherin 15 and myosin 1c are regarded as the most likely candidates to form the central element of the transduction apparatus of the hair cells [23], [24], [25] (Figure 3).

Usher syndrome. *Mutations in the genes coding for myosin VIIa, cadherin 23 und protocadherin 15 lead to different types of Usher syndrome* [26], [27]. *Mutations of the human MYO7A gene have been identified as the genetic cause of Usher syndrome type 1B* [28], [29] *and type 2A* [30] (Table 1).
Usher syndrome is the most frequent autosomal recessive form of syndromic hearing loss associated with a visual impairment as well as a hearing impairment. In most cases, those affected have been deaf or have had moderate to severe hearing loss from birth. Vision, however, shows progressive deterioration only from the age of 10

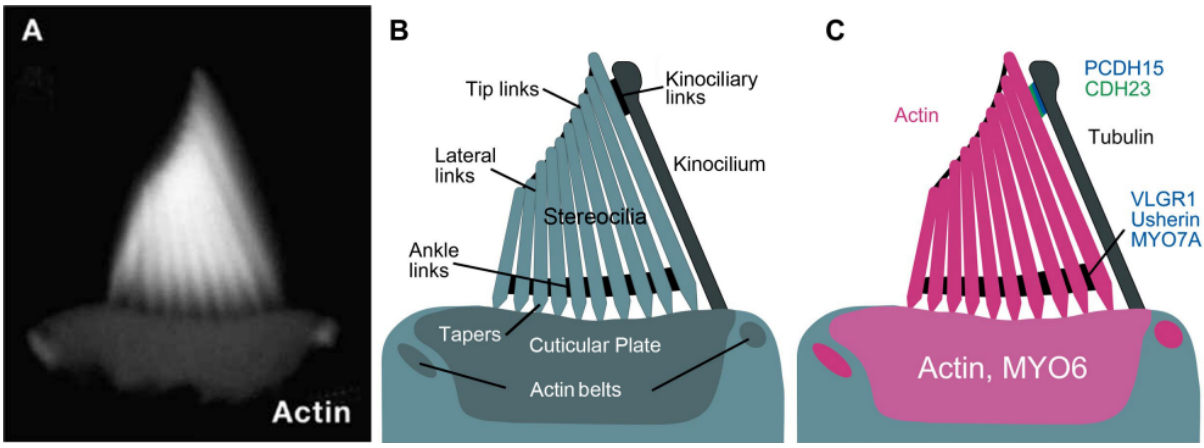

Figure 2: Anatomy and key molecules of the hair bundle. (a) Hair bundle of an isolated bullfrog hair cell stained with phalloidin in order to detect F-actin. (b) Anatomical structures of the hair bundle corresponding to the microscopic image in (a). Hair bundles consist of many stereocilia and one kinocilium. The kinocilium is not required for mechanotransduction and, like the kinociliary links, is no longer detectable in mature hair cells. (c) Key molecules of the hair bundle. Protocadherin 15 (PCDH15) and cadherin 23 (CDH23) form the kinociliary links between the kinocilia and the longest stereocilia as well as the tip links between the stereocilia. VLGR1 and usherin form the ankle links at the base of the stereocilia. Ankle links are found in vestibular hair cells and can be observed in auditory hair cells only during the developmental stage. Myosin VI (MYO6) is found largely on the apical side of the hair cells in the region of the cuticular plate. Myosin VIIa (MYO7A) is detectable in the stereocilia and the ankle links. (Fig. (a) reprinted from Gillespie & Müller [17] with permission from Elsevier, figures (b) and (c) modified after Gillespie & Müller [17]).

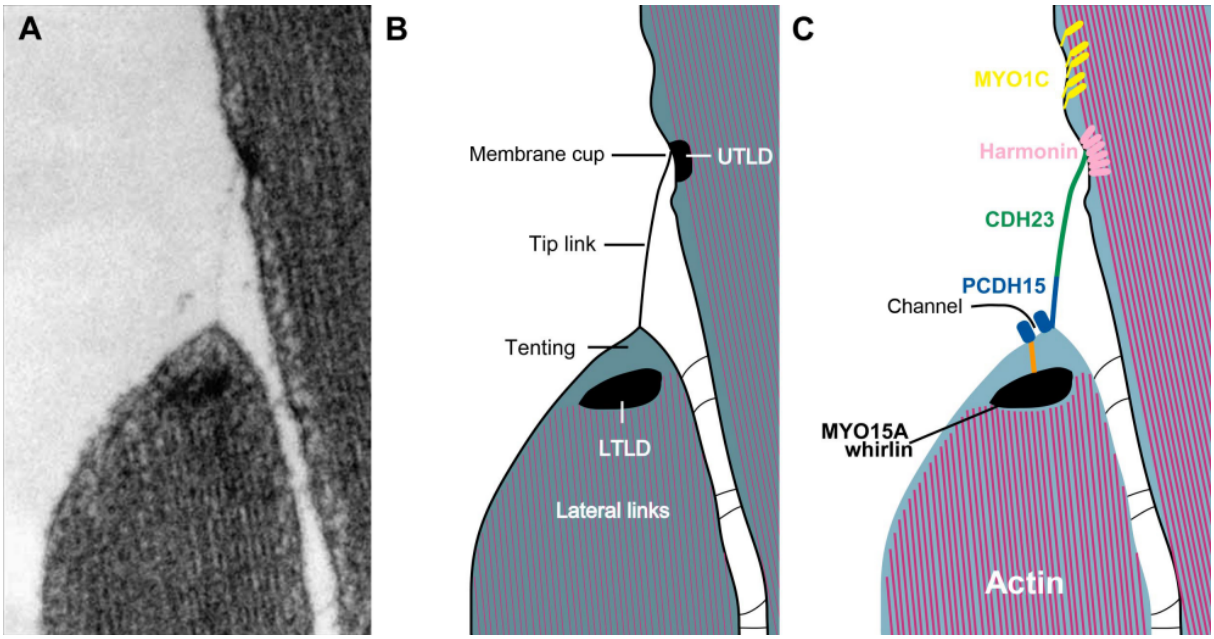

Figure 3: Anatomy and key molecules of the transduction apparatus. (a) Electron microscopy image of two adjacent stereocilia in a hair bundle. The two stereocilia are joined by a tip link. (b) Relevant structures in the region of the tip link. Abbreviations: Lower tip-link density (LTLD), upper tip-link density (UTLD) (c) Key molecules in the region of the tip link. Abbreviations: Myo1C (myosin 1c), CDH23 (cadherin 23), PCDH15 (protocadherin 15), MYO15A (myosin 15a) (Fig. (a) image courtesy of R.A. Jacobs and A.J. Hudspeth, reprinted from Gillespie & Müller [17] with permission from Elsevier, figures (b) and (c) modified after Gillespie & Müller [17].

onwards. Retinopathia pigmentosa is also present and, in typical cases, this initially leads to night blindness with an increasingly restricted field of vision and, at a later stage (depending on the Usher subtype), to blindness. Additionally, some patients suffer from balance impairments resulting from defects of the vestibular organ, and from a cataract [31], [32].

2.1.3.2 Adaptation

A distinctive feature of the hair cells is their ability to adapt. This unique mechanism ensures that the hair cell can respond without its sensitivity being compromised, even when the stereocilia are continuously displaced on a scale of many nanometres. The molecular mechanism of adaptation is already fairly well understood [33]. After

Table 1: Genes associated with hearing loss [18]. Listed below is a selection of genes, the proteins for which they code, the available mouse mutants and the form of hearing loss associated with each gene mutation. All genes listed are expressed in hair bundles and are essential for the development and/or function of the hair bundles.

Gene	Protein	Mouse mutants	Usher syndrome subtype	Other forms of deafness in humans
MYO7A	Myosin VIIa	Shaker 1; headbanger	USH1B	DFNB2, DFNA11
USH1C	Harmonin	Deaf circler; targeted mutation	USH1C	DFNB18
CDH23	Cadherin 23	Waltzer; Salsa	USH1D	DFNB12
PCDH15	Protocadherin 15	Ames Waltzer	USH1F	DFNB23
USH1G	SANS	Jackson shaker	USH1G	–
USH2A	Usherin	Targeted mutation	USH2A	–
GPR98	VLGR1	Gpr98del7TM; targeted mutation	USH2C	–
DFNB31	Whirlin	Whirler	USH2D	DFNB31
ACTB	β cyto-actin	Not available	–	Syndromic hearing loss
ACTG1	γ cyto-actin	Targeted mutation	–	DFNA20/ 26
ESPN	Espin	Jerker	–	DFNB36
PTPRQ	PTPRQ	Ptprq − / −	–	–
MYO6	Myosin VI	Snell's waltzer; tailchaser		DFNA22, DFNB37
RDX	Radixin	Targeted mutation	–	DFNB24
MYO3A	Myosin IIIa	Not available	–	DFNB30
MYO15A	Myosin XV	Shaker 2		DFNB3
SLC26A5	Prestin	Targeted mutation		Non-syndromic hearing loss

Abbreviations: DFNA, autosomal dominant inheritance; DFNB, autosomal recessive inheritance. A comprehensive list of genes involved in hearing loss can be found at http://hereditaryhearingloss.org and http://hearingimpairment.jax.org/index.html.

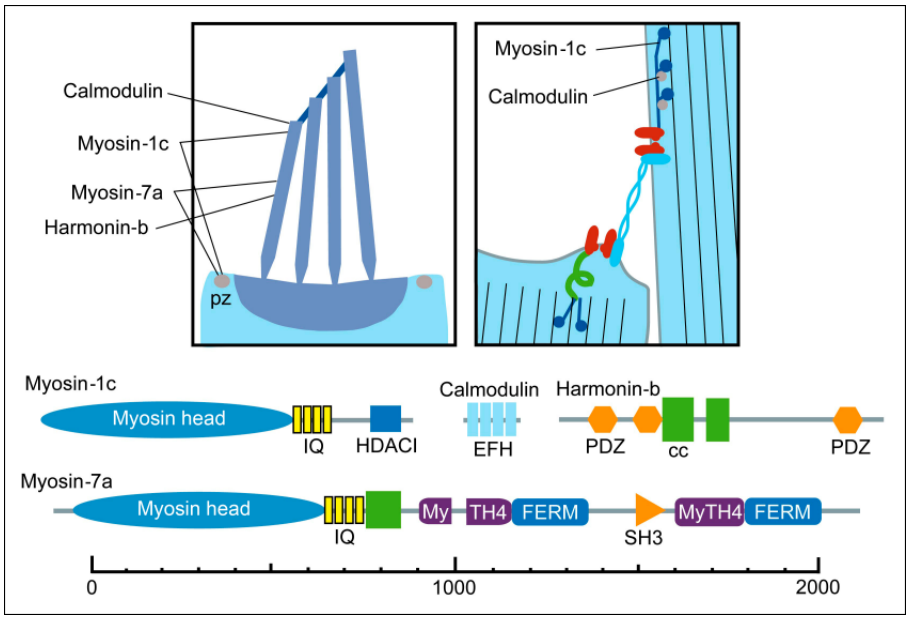

Figure 4: Proteins associated with adaptation. Myosin 1c is detectable in the hair bundle and reaches its highest concentration at the two ends of the tip links. Myosin VIIa is found in the whole hair bundle. Both proteins are also detectable in the region of the pericuticular zone (pz). Abbbreviations: IQ (regulatory light-chain-binding domain), HDACI (histone deacetylase interacting domain), EFH (EF hand domain), cc (coiled-coil domain), MyTH4 (myosin tail homology domain 4), FERM (4.1/ezrin/radixin/moesin-like domain), SH3 (Src homology 3 domain), PDZ (PSD-95/ Dlg/ ZO-1-like domain) (Figure modified after Vollrath et al. [9]).

the stereocilia have been displaced, the tip link is first stretched and the transduction channel opened. K^+ and Ca^{2+} ions now pass simultaneously from the endolymph into the hair cells via the opened mechanoelectrical transduction channels. The result is depolarization of the hair cell. The influx of Ca^{2+} causes myosin molecules to separate from the actin filaments. This process is probably mediated by the Ca^{2+}-binding protein called calmodulin (Figure 4). Within 100 ms of the channel's opening, the upper attachment site of the tip link is displaced downwards. This relaxes the tip link, the channel can close once more, the influx of K^+ subsides, and the hair cell can again react with maximum sensitivity to displacement from the new position. The locational shift of this upper attachment site is made possible by what is known as the adaptation motor. If the stereocilia return to their upright rest position, the adaptation motor is deflected back up to the starting position and the tip link's optimal tension at rest is restored: the hair cell is adapted.

The two specific mechanisms that appear to be responsible for this adaptation process are termed 'fast adaptation' and 'slow adaptation' [4], [17]. 'Fast adaptation' occurs in both cochlear and vestibular hair cells. This mechanism is based on an influx of Ca^{2+} ions into the transduction channel and, in mammals, is associated with movements of the hair bundle towards the stimulus. 'Slow adaptation' is mediated by the adaptation motor. This involves the upper attachment site of the tip link on the stereocilium being displaced downwards. The tip link relaxes and the hair cell is once again ready to respond to displacements.

Myosin 1c, located at the end of the tip link, has been postulated as a likely central component of the adaptation motor, although numerous other myosins also appear to be involved in this process [34] (Figure 4).

The key molecules of the tip links are myosin XVa (MYO15A) and whirlin. These are found at the end of the actin filaments of the stereocilia (Figure 3c). A mutation in the gene that codes for whirlin results in Usher syndrome type 2D [18] (Table 1).

2.1.4 Cochlear amplification

Cochlear amplification [33], [35], [36], [37] aids dynamic-range control, by means of which it enables sounds of low sound pressure level (SPL) to be perceived. It is regarded as being a non-linear, up to 1,000-fold amplification of the travelling wave on the basilar membrane at its maximum point (up to around 50 dB). Cochlear amplification is necessary for the perception of sound of low SPL. Sounds with a high SPL are, therefore, amplified far less than those of low SPL.

The mechanisms underlying cochlear amplification include the prestin-mediated somatic motility of the outer hair cells [33], [36], [38] as well as active movements of the hair bundles (stereociliary motility) [39]. Outer hair cells have the ability to change their size and thus to exert mechanical force on the basilar membrane. This is the mechanism behind the somatic motility of the outer hair cells. Upward movement of the basilar membrane is followed by displacement of the stereocilia and depolarization of the outer hair cells. The contraction of the outer hair cells triggered in this way causes greater movement of the basilar membrane in response to a sound stimulus [40].

2.1.4.1 Somatic motility

It is assumed that prestin, a very rapidly motile motor protein, is responsible for somatic motility in the outer hair cells [41], [42]. For example, it has been shown that cells transfected with prestin exhibit electromotility of up to 0.2 µm. The expression of prestin can be immunohistologically detected in the region of the lateral membrane of the outer hair cells, where somatic electromotility takes place. Inner hair cells that show no motility do not exhibit expression of prestin. Other indications of the central importance of prestin in connection with cochlear amplification are provided by findings from studies with prestin-deficient mouse mutants, which prove that prestin forms the basis for the electromotile ability of the outer hair cells [4].

Prestin. *The importance of prestin for the function of the outer hair cells is impressively demonstrated in the prestin knockout mouse, in which both a partial loss of DPOAE and hearing loss can be observed* [43]. *In humans, inherited defects of this motor protein lead to sensorineural hearing loss* [44], [45].

Prestin (derived from 'presto', which means 'fast' in Italian) is a glycoprotein that consists of 744 amino acids and has a molecular weight of 81.4 kDa. It is an anion transporter that is responsible for electroneutral exchange of chloride and carbonate in the outer hair cells. This motor protein has the special ability to change its size by adopting different conformation states. The protein is in its 'short' state when the cell membrane is depolarized, the chloride anions being bound to prestin on the cytoplasmic side of the membrane. If the cell membrane is hyperpolarized, bound chloride anions are translocated to the extracellular membrane side and prestin is in its 'long' state. The conformational alteration undergone by prestin is directly associated with a corresponding change in the size of the outer hair cells [4], [41], [42], [43].

2.1.4.2 Stereociliary motility

Stereociliary motility is another mechanism that aids cochlear amplification. What is involved are active movements of the hair bundle which are influenced by the two processes of mechanotransduction and adaptation [4], [39], [46]. The precise role of somatic and stereociliary motility in humans remains the subject of controversy. It is, however, regarded as proven that these amplification mechanisms give rise to active otoacoustic emissions (OAE). Detection of OAE is of clinical relevance

as it provides information about the function of the outer hair cells and their amplification mechanisms.

2.1.5 The tectorial membrane

The tectorial membrane consists of acellular connective tissue and covers the hair cells of the organ of Corti from the base of the cochlea to its apex (Figure 1). Medially, the tectorial membrane is in contact with the interdental cells of the spiral limbus. In ultrastructural investigations, two specific structures – the fibrils and the non-fibrillar matrix – have been identified as major components of the tectorial membrane [6].

Tectorial membrane proteins. *The importance of the tectorial membrane for hearing has been demonstrated in studies on mice that describe severe hearing loss resulting from mutations of the alpha-tectorin gene* [47]. *In these animals, the tectorial membrane is detached from the auditory sensory epithelium and exhibits loss of the non-collagen matrix. Alpha-tectorin is an extracellular matrix protein and, as such, is a vital component of the tectorial membrane. Families with a mutation of the human orthologous gene TECTA (DFNA12 and DFNA8) show hearing loss* [48]. *The Otog gene codes for otogelin, an N-glycosylated protein of the tectorial membrane* [49]. *Targeted disruption of this gene leads to hearing loss* [50]. *Otancorin, another protein which is located in the connecting region between the tectorial membrane and the spiral limbus, is coded by the OTOA gene. Mutation of this gene leads to DFNB22* [51].

Various functions have been proposed for the tectorial membrane. There is, for example, speculation about the importance of the tectorial membrane for the tonotopic organization of the cochlea, since – like many other cochlear structures – this membrane changes its size as it runs from the base to the apex of the cochlea [4], [6].

2.2 The stria vascularis

2.2.1 Introduction and overview

The stria vascularis is a linear organ on the outer wall of the cochlear duct of the cochlea. Permeated by a network of capillaries, it consists of three different types of cell: marginal cells, intermediary cells and basal cells (Figure 5). All of these cell types are of importance for the function of the stria vascularis [6].
The stria vascularis is composed of two epithelial cell layers. One layer is formed by marginal cells, with the second layer composed of intermediary and basal cells. The extracellular space between these two layers is very narrow (with a width of only 15 nm), and is known as the intrastrial space. This space is electrically separated from the perilymph, the endolymph and the adjacent extracellular fluids. Gap junctions (channel-forming protein complexes) connect together the individual cell types of the spiral ligament and allow intercellular exchange of organic and anorganic ions, amino acids, etc., by means of diffusion (Figure 5) [4], [52], [53], [54], [55].
The stria vascularis is of central importance for cochlear homeostasis. It is responsible for forming the endocochlear potential and for maintaining the ionic composition of the endolymph (Figure 5).
An impairment of the endocochlear potential, the volume-regulating mechanisms or the ion composition can cause severe disturbances in the homeostasis of the cochlear fluid followed by hearing loss [52], [53], [56].

2.2.2 Ion homeostasis

The endolymph in the scala media has, in contrast to the other extracellular spaces of the body, a very high concentration of extracellular potassium (approx. 140 mmol/l) and a strong positive charge known as the endocochlear potential (approx. +85 mV). Both the endocochlear potential and the high potassium concentration are generated by the stria vascularis. The K^+ gradient, together with the endocochlear potential, forms the basis for the mechanoelectrical transduction of the hair cells. Figure 5 schematically depicts the process of cochlear potassium circulation and the mechanisms behind the formation of the endocochlear potential. In these processes, the potassium channels are of particular importance [52], [53] (Figure 5). This is impressively demonstrated where dysfunction of these potassium channels occurs. The result is disturbance of potassium homeostasis in the cochlea, leading to hearing loss [4]. Table 2 shows a list of genes that influence cochlear potassium homeostasis in the event of mutation and induce hearing loss.

KCNQ1. *KCNQ1 codes for the alpha subunit of the cardiac voltage-dependent KVLQT1 potassium channels and the potassium channels of the stria vascularis* (Table 2). *In the inner ear, this channel enables potassium to be secreted into the scala media by marginal cells. An autosomal dominant point mutation of the KCNQ1 gene, which is located on the short arm of chromosome 11 (gene locus 11p15.5), leads to the Jervell-Lange-Nielsen syndrome. This syndrome describes a complex of symptoms involving cardiac long QT syndrome type 1 (LQT1) and hereditary cochlear hearing loss. Pathophysiologically, the outcome is a repolarization disorder of the cardiomyocytes with pathological afterdepolarization resulting from an extended refractory period and insufficient potassium secretion by the marginal cells of the stria vascularis. The reduced concentration of endolymphatic potassium causes transduction by the hair cells to be impaired* [57].

KCNQ4. *The KCNQ4 gene codes for a member of the KCNQ4 family of voltage-controlled potassium channels and is located at the DFNA2 gene locus* (Table 2) [58], [59]. *KCNQ4 is involved in basolateral potassium secretion by the hair cells* [60]. *Mutation of the KCNQ4 gene leads to progressive, non-syndromic hearing loss* [61]. *This involves gradual loss of hearing, typically beginning*

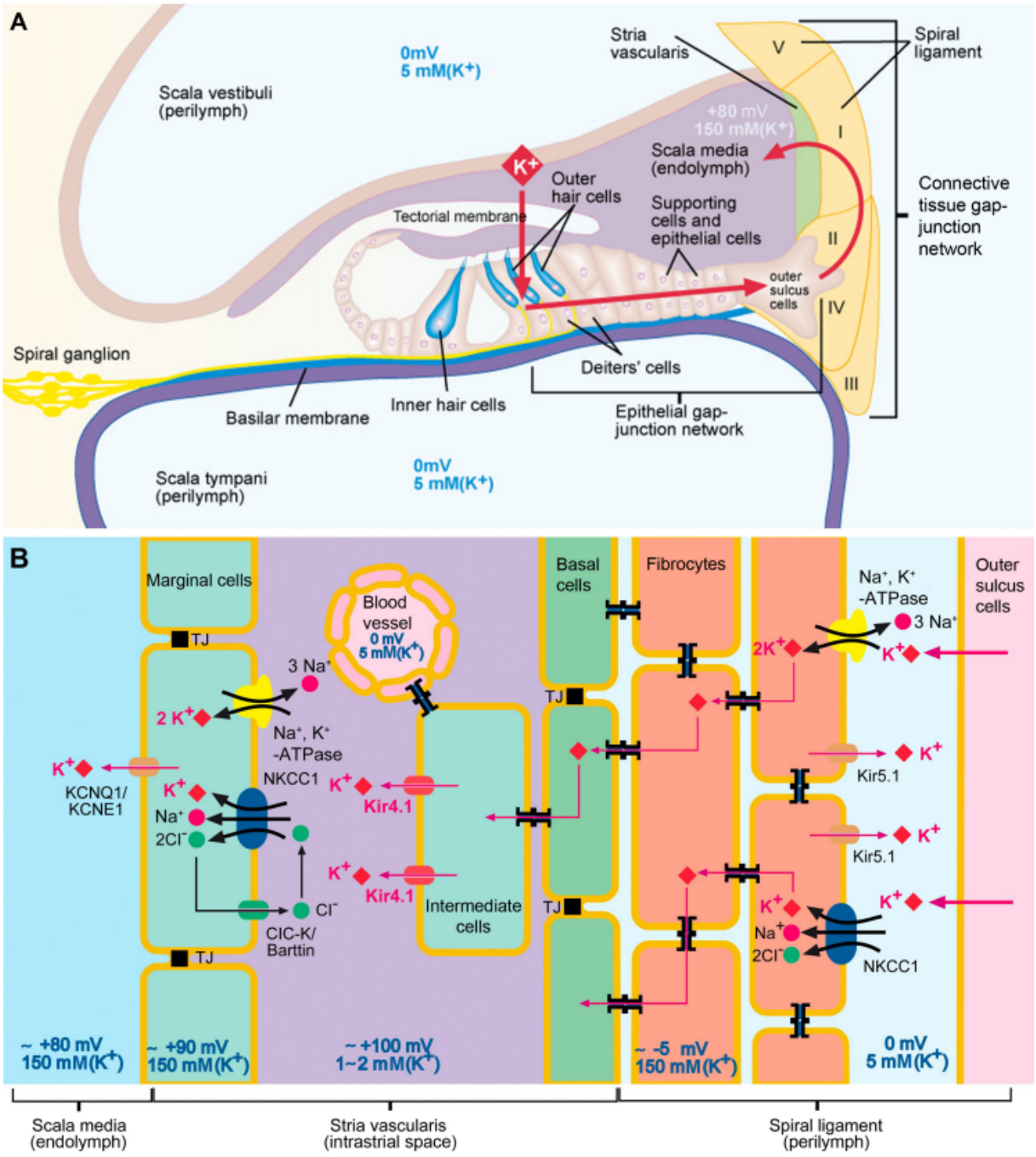

Figure 5: Schematic model of cochlear potassium circulation and the formation of the endocochlear potential. (a) K^+ ions that escape from the hair cells are taken up by Deiters cells. K^+ is subsequently transported via the epithelial gap junction network to the type II and type IV fibrocytes of the spiral ligament. The epithelial gap junction network consists of supporting cells, epithelial cells and the outer sulcus cells. K^+ is then taken up by the type II and type IV fibrocytes and transported to the stria vascularis via the connective tissue gap junction network. The connective tissue gap junction network consists of fibrocytes, basal cells and intermediate cells. K^+ is eventually released via the stria vascularis into the endolymph of the scala media. The diagram also shows the K^+ concentration ($[K^+]$) and the potential of the various cochlear fluids. (b) The figure shows the ion transport system of the stria vascularis and the spiral ligament, which are the crucial components for cochlear potassium circulation and the formation of the endocochlear potential. As in (a), the K^+ concentration ($[K^+]$) and the potential of the various cochlear fluids is shown. Abbreviations: NKCC1 (Na^+ K^+ $2Cl^-$ cotransporter), TJ (tight junctions) (Figure modified after Hibino & Kurachi [53]).

Table 2: Currently known genes that, in the case of mutation, alter K^+ homeostasis [4]. The gene, the coded protein, its location and function are listed, as well as the associated type of hearing loss.

Gene	Coded protein	Protein location	Protein function	Type of hearing loss
KCNE1	KCNE1	Marginal cells	K^+ channel	Jervell-Lange-Nielsen syndrome
KCNQ1	KCNQ1	Marginal cells	K^+ channel	Jervell-Lange-Nielsen syndrome
KCNQ4	KCNQ4	Outer and inner hair cells	K^+ channel	DFNA2
GJB2	Cx26	Fibrocytes in SL and SLi, epithelium on BM, intermediate and basal cells	Gap junction protein	DFNB1 / DFNA3 hereditary palmoplantar keratoderma with hearing loss
GJB6	Cx30	Fibrocytes in SL and SLi, supporting cells of the organ of Corti	Gap junction protein	DFNA3
GJB3	Cx31	Fibrocytes in SL and SLi, epithelium on BM	Gap junction protein	DFNA2, AR-non-syndromic hearing loss
GJB1	Cx32	Fibrocytes in SL and SLi, epithelium on BM	Gap junction protein	X-linked Charcot-Marie Tooth disease and hearing loss
GJA1	Cx43	Fibrocytes in SL and SLi, epithelium on BM, intermediate and basal cells	Gap junction protein	AR non-syndromic hearing loss
BSND	Barttin	Marginal cells	Cl^- channel	Bartter syndrome type 4

Abbreviations: SL (spiral ligament); Sli (spiral limbus); BM (basilar membrane); AR (autosomal recessive), Cx (connexin), DFNA (deafness, autosomal dominant), DFNB (deafness, autosomal recessive).

early adulthood (i.e. the second decade of life) with relatively well-preserved language ability [58], [62], *which deteriorates to severe hearing impairment within around 10 years*.

In recent years, the crucial role of the connexins in cochlear potassium homeostasis has become increasingly evident (Table 2). Connexins are a family of transmembrane proteins that form the gap junctions in cells. They allow the direct exchange of molecules up to around 1 kDa in size. Connexins are important functional elements of the potassium cycle in supporting cells of the organ of Corti, the spiral ligament and the stria vascularis [63].

Connexin 26 and 30. *Mutations in the genes that code for connexin 26 and 30 are the cause of numerous types of non-syndromic hereditary hearing loss* [63]. *In more than 85 % of cases, they lead to prelingual hearing impairment or deafness from birth. Other organic conditions or malformations of the inner ear are not detectable. Connexin 26 is expressed in the numerous gap junctions of the supporting cells of the sensory hair cells of the cochlea, the spiral ligament and the spiral limbus* [64], [65]. *The GJB2 gene, which codes for connexin 26, is located on the gene locus DFNB1* (Table 2) [66]. Over half of recessive non-syndromic hearing *impairments are triggered by GJB2 mutations* [66], [67], [68]. *One specific mutation (35delG) is responsible for over 70% of all GJB2 mutations* [69], [70], [71]. *Connexin 30 is the protein product of the GJB6 gene which, like GJB2, is located at the gene locus DFNB1* (Table 2). *A 324 kb deletion of the GJB6 gene is directly associated with recessive non-syndromic hearing loss* [72], [73].

2.2.3 Fluid homeostasis

Cochlear fluid homeostasis is of crucial importance in bringing about the endocochlear potential and mechanotransduction. A very good review of the complex details involved is found in [4]. The inner ear contains three different extracellular fluids highly unusual in their composition: the endolymph, the perilymph and the intrastrial fluid. The scala media of the cochlea contains endolymph, whereas the scala vestibuli and the scala tympani are filled with perilymph. The endolymph is potassium-rich and sodium-poor. The perilymph and the intrastrial fluid, however, contain high levels of sodium and little potassium. The composition of these fluids in the inner ear is regulated by a large number of ion channels and ion transporters [74]. As already indicated above, the different electrolyte concentrations in these cochlear fluids are crucial for the formation and maintenance of the endocochlear potential. In the stria vascularis, an Na-K-Cl cotransporter and an Na^+/K^+-ATPase provide ion transport, resulting in a high concentration of sodium and a low

concentration of potassium in the intrastrial fluid. ClC-K/Barttin channels ensure that Cl^- is transported back into the intrastrial space. The location and function of the various components of this system are schematically illustrated in [53] (Figure 5).
The significance of the Na-K-Cl cotransporter and the Na^+/K^+-ATPase is particularly evident when experimentally inhibited by loop diuretics, which can bring about suppression of the endocochlear potential [4].

Bartter syndrome. *A mutation of the barttin gene, which codes for the essential β-subunit of the barttin ClC-K channel, leads to bartter syndrome type 4, which is characterized by deafness and renal salt loss* [75]. *The co-incidence of a mutation of the Cl^- channel CLCNKA (CLCK-1) and CLCNKB (CLCK-2) has also been identified as a partial cause of the syndrome* [76], [77], [78]. *The result of these mutations is disruption to the formation of the endocochlear potential, which is the cause of the resulting deafness* [79], [80], [81].

The regulation of Ca^{2+} concentration within the endolymph is also of vital importance to the physiological function of the organ of Corti. The concentration of Ca^{2+} is crucial not only for generating the transduction potential, but also for adaptation and cochlear amplification [82], [83], [84]. The regulation of the cochlear fluid is also highly important to cochlear function [54], [55]. Under pathological conditions, a longitudinal flow pattern of the endolymph appears to be involved in fluid homeostasis. Enlargement of the endolymphatic space thus leads to endolymph flow towards the base of the cochlea and, in this way, reduces the volume of the endolymph. This reduction in the size of the endolymphatic space results in endolymph flow towards the apex of the cochlea and increases the volume of the endolymphatic space. Under physiological conditions, however, no appreciable changes in volume of the endolymph appear to occur [54].
Various pore-like, water-permeable channels, the aquaporins, would seem to be responsible for the transmembrane transport of water in the inner ear, including the epithelium of the endolymphatic space. There are currently initial indications that aquaporin 4, in particular, is of especial importance in the inner ear, as hearing loss is observed in the transgenic knockout mouse [4], [85], [86].

Ménière's disease. *A characteristic feature of Ménière's disease is an endolymphatic hydrops which can be caused by elevated levels of vasopressin. Vasopressin antagonists are, however, able to induce the collapse of the endolymphatic compartment* [87]. *The mechanism underlying this observation is unclear. It is, however, supposed that vasopressin up-regulates the expression of aquaporin 2 and, by this means, brings about increased water reabsorption* [88], [89]. *The ability of glucocorticoids to relieve the symptoms of Ménière's disease is also attributed to a reduction in vasopressin production and its influence on the expression of aquaporins* [90].

Cochlear fluid homeostasis, ion homeostasis and the endocochlear potential are of crucial significance for normal function of the inner ear. Vasopressin, aldosterone and glucocorticoids can serve as examples of how the fluid homeostasis of the inner ear is also influenced by hormones [90], [91]. Various effects of vasopression have been reported and include the regulation of aquaporin expression in cell membranes as well as the activity of $Na^+/K^+/2\ Cl^-$ cotransporters and Na^+ channels in strial marginal cells and type II fibrocytes of the spiral ligament (Figure 5). Aldosterone is also a hormone that appears to modulate the fluid homeostasis of the inner ear by raising the activity of epithelial Na^+ channels and Na^+/K^+-ATPase [92]. The possible consequence of these effects is a high endolymphatic K^+ concentration which results in a hydrops due to osmotic displacement of fluid. Glucocorticoids, on the other hand, can elicit effects that are contrary to those of vasopressin. This provides an explanation for the positive effects of glucocorticoids in the treatment of Ménière's disease which are most likely to be attributable to a reduction in vasopressin production and control of aquaporin expression [4].

2.3 The spiral ganglion

2.3.1 Introduction and overview

The spiral ganglion is a mass of nerve cells that are responsible for the afferent innervation of the organ of Corti (Figure 6). The spiral ganglion cells are located in Rosenthal's canal, which coils around the modiolus of the cochlea. It contains the cell bodies of the afferent neurons, the dendrites which lead to the hair cells, and axons which run into the cochlear nucleus of the brainstem. The afferent fibres of the type I spiral ganglion neurons are myelinated and lead to the inner hair cells. The afferent fibres of the type II spiral ganglion neurons, which are not myelinated, lead to the outer hair cells. More than 90% of the afferent fibres originate at the inner hair cells; each fibre generally has synaptic contact with only one inner hair cell, with each inner hair cell being innervated by around 10–30 fibres. The outer hair cells are innervated by only around 10% of the afferent nerve fibres, with many outer hair cells converging on a single fibre (Figure 6). This differential innervation pattern reflects differences in the functional significance of the inner and outer hair cells. The auditory information is finally transmitted to the brainstem via the afferent system [4].

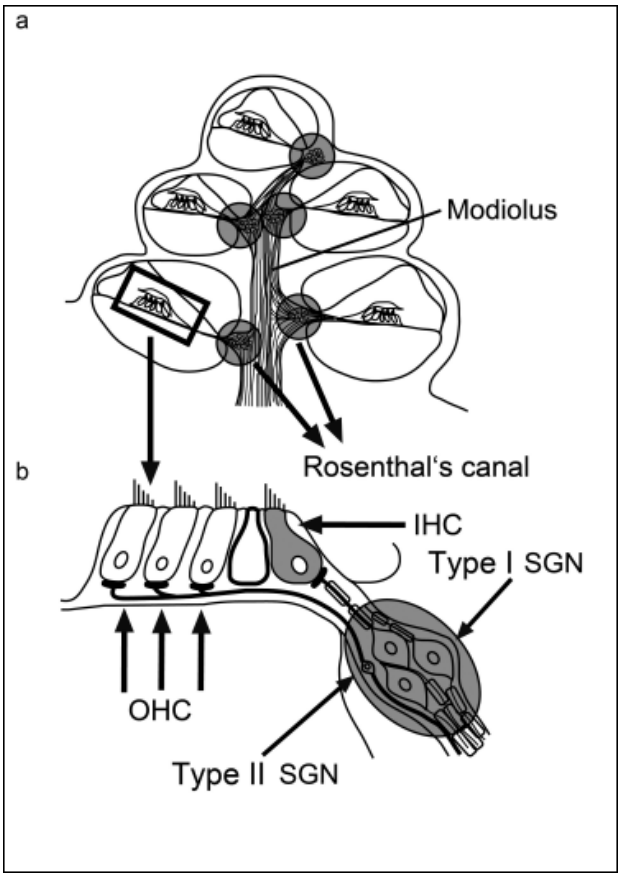

Figure 6: Schematic representation of the cochlea and the afferent innervation of the hair cells. (a) The axis of the cochlea (modiolus) harbors the spiral ganglion cells. The cell bodies are located in Rosenthal's canal. (b) The afferent innervation of the hair cells takes place via the nerve fibres of the spiral ganglion cell neurons (SGN). Type I spiral ganglion neurons are myelinated and lead to the inner hair cells (IHC).Type II spiral ganglion neurons are not myelinated and lead to the outer hair cells (OHC). Each type II cell forms synaptic contacts with numerous outer hair cells. Type I cells, however, typically show contact with only one inner hair cell (Figure modified after Rusznák & Szücs [119], by kind permission of Springer Science + Business Media).

2.3.2 Hair cell synapses

Hair cells form synapses with the axons of the spiral ganglion neurons (Figure 7). These afferent synapses are highly specialized in both form and function. The ribbon synapse consists of a presynaptic active zone and a synaptic ribbon. The synaptic ribbon is less than 1 µm in size and is surrounded by around 100 synaptic vesicles. Ionotropic AMPA-type glutamate receptors are located in the region of the postsynaptic nerve endings (Figure 7) [93]. The complex structure of the ribbon synapse allows a high transmission rate with a short refractory period. At the ribbon synapse, type $Ca_v1.3$ calcium channels are activated by a receptor potential of the hair cell. Subsequently, glutamate receptors are activated at the postsynaptic nerve fibre endings. In this way, excitatory postsynaptic potentials are generated that are transmitted to the central nervous system in the form of action potentials. The structure and function of the afferent hair cell synapse are described in detail in a number of excellent review papers [94], [95], [96], [97].

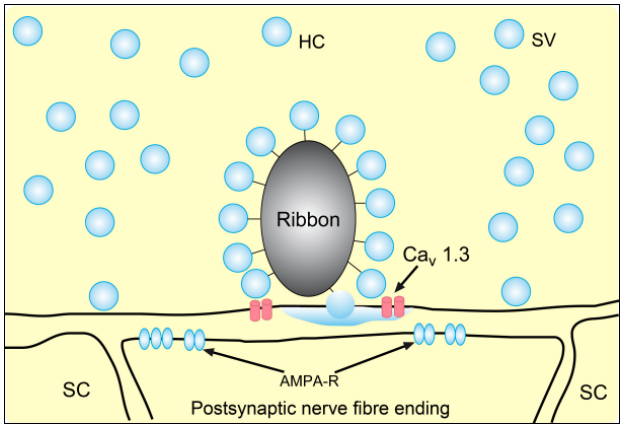

Figure 7: The ribbon synapse of the inner hair cell. The afferent synapse of the inner hair cells (HC) consists of a presynaptic active zone with the synaptic ribbon (diameter 0.2 µm), a protein nanomachine to which the synaptic vesicles (diameter 35-40 nm) are bound. The postsynaptic nerve fibre ending contains numerous ionotropic AMPA-type glutamate receptors (AMPA-R). Each active zone contains some 50 $Ca_v1.3$ calcium channels and 30 glutamate-containing synaptic vesicles (SV). Abbreviations: SC (supporting cells), (Figure modified after Fuchs et al. [120]).

$Ca_v1.3$ calcium channels, otoferlin. *Work using mouse models has demonstrated how a disorder of the inner hair cells and their synapses leads to hearing loss and deafness. When the $Ca_v1.3$ calcium channel is genetically suppressed, calcium flow in the inner hair cells is reduced by 90% and no acoustically evoked brainstem potentials can be demonstrated* [98], [99], [100]. *A mutation in the OTOF gene, which codes for the protein otoferlin, leads to a synaptic defect in type DFNB9 prelingual hearing loss in humans* [101], [102]. *Auditory brainstem potentials can be evoked in the DFNB9 mouse model, so that cochlear implantation is indicated in DFNB9* [103], [104]. *Both in the $Ca_v1.3$ knockout and in the otoferlin knockout, the result is almost complete blockage of synaptic transmission with severe hearing impairment, and a pattern of auditory neuropathy or synaptopathy* [105]. *There are also acquired auditory synaptopathies, such as in hyperbilirubin anaemia and hypoxia in premature infants* [105], [106]. *Selective damage to the inner hair cells can be triggered by platinum-containing chemotherapeutic agents* [107] *and by noise trauma* [108]. *It is assumed that excitatory damage is caused to the postsynaptic spiral ganglion neurons by excessive glutamate release* [105].

2.3.3 Sound coding in the auditory nerve

The tonotopic organization of the cochlea continues in the afferent system. Each site on the basilar membrane is, in the main, mechanically stimulated by one specific frequency. Depending on its innervation site in the cochlea, an afferent neuron is most intensely stimulated when the sound signal includes a frequency component that

stimulates the hair cells most strongly at this site. Each afferent neuron has the characteristic of a frequency filter in the form of its frequency tuning curve. At higher sound intensities, the auditory nerve fibres are increasingly also stimulated by other (both lower and higher) frequencies. Here, tonotopy is complemented by a second coding principle, namely phase locking. This is related to the timing of the action potentials, which have a fixed relationship with the phase of the receptor potential. Phase locking is also of importance for determining the direction of sound sources, as the interaural time difference is analysed for this purpose [4].

2.3.4 Efferent innervation of the cochlea

It has been shown that two distinct types of nerve fibres are responsible for the efferent innervation of the cochlea (Figure 8) [109]. Myelinated medial olivocochlear fibres (MOC) run from the medial superior olive to the ipsilateral and contralateral cochlea, where they are connected to outer hair cells via cholinergic synapses. Non-myelinated lateral olivocochlear fibres (LOC) originate from the lateral superior olive and run mainly to the ipsilateral cochlea, where they form synaptic contacts with afferent type I neurons of the spiral ganglion [4] (Figure 8). The functions of the efferent system include that of improving the signal-noise ratio [110], [111], [112], expanding the dynamic range in intensity coding [113], controlling cochlear amplification [114], [115], and protecting the cochlea from loud sounds [116], [117], [118].

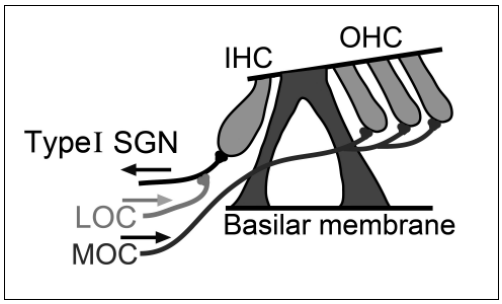

Figure 8: Schematic representation of the efferent innervation of the organ of Corti. Myelinated mediale olivocochlear fibres (MOC) form synaptic contacts with outer hair cells (OHC). Non-myelinated lateral olivocochlear fibres (LOC) form synaptic contacts with afferent type I spiral ganglion neurons (type I SGN), which lead to the inner hair cells (IHC). Key to arrows: right-facing = efferent, left-facing = afferent, (Figure modified after Guinan [109]).

3. Outlook

As in many other disciplines of modern medicine, scientific advances in the fields of genetics and molecular biology have transformed our understanding of the hearing process and of genetic hearing impairments.
It is proving possible to identify and characterize an increasing number of genes and proteins involved in the development and the function of hearing. This scientific progress in basic research is of high clinical relevance, as it is the prerequisite for genetic counselling and for early detection and therapy of genetic hearing impairment. The speed with which hearing research is advancing – in the field of inner ear regeneration, for example – provides good grounds for hope that biological causal approaches to therapy for hearing loss will become clinical reality in the foreseeable future.

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Conflict of interest

The authors declare that they have no conflict of interest in connection with this study.

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