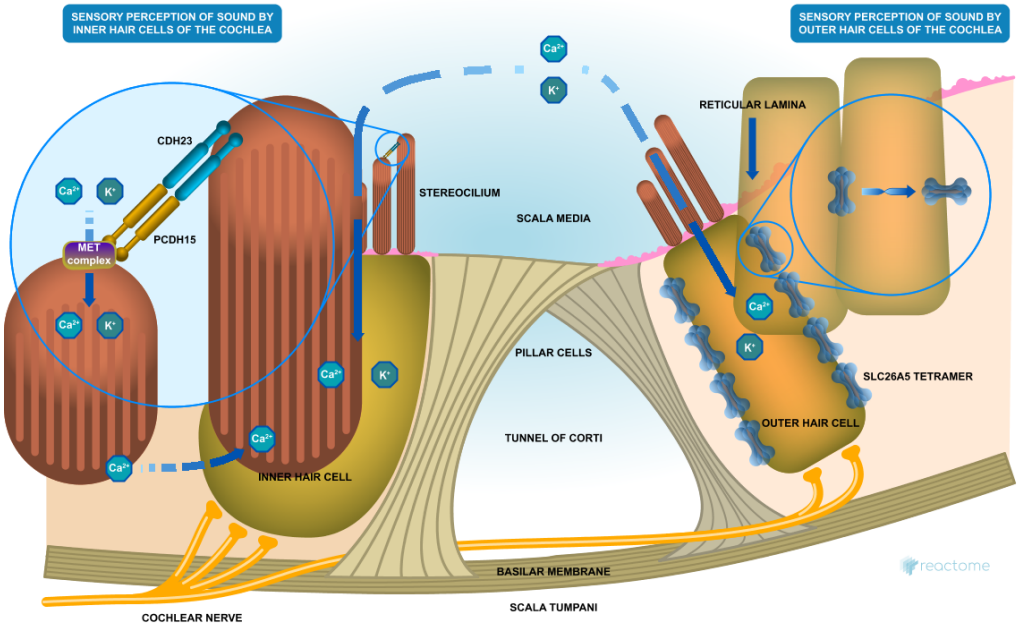
Sensory processing of sound



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Reactome database release: 77

This document contains 3 pathways (see Table of Contents)

Sensory processing of sound ↗

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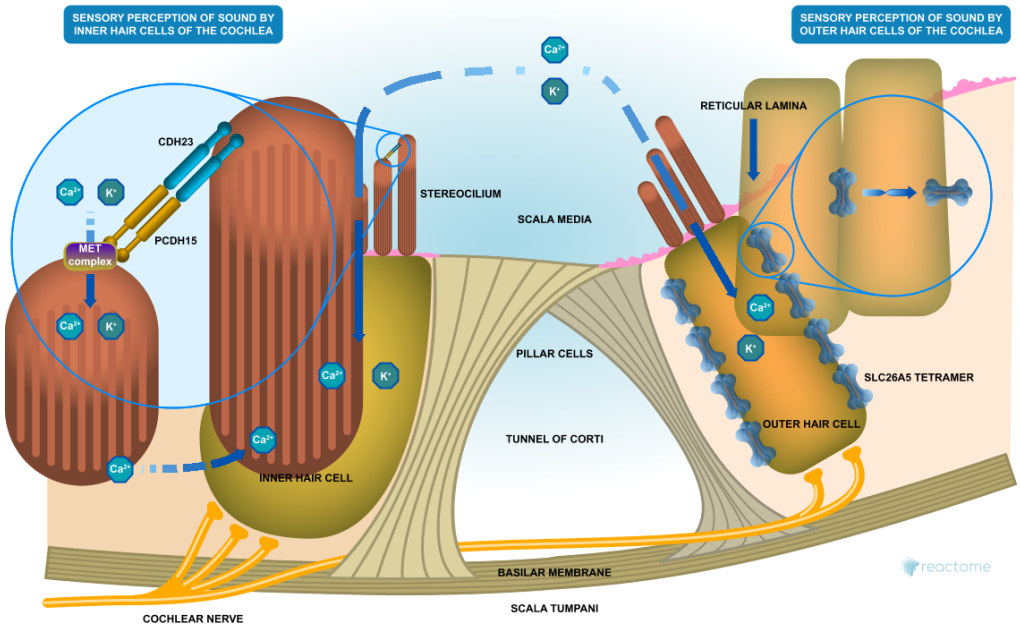

In mammals, sounds are processed in the cochlea, a spiral-shaped organ in the inner ear (reviewed in Basch et al. 2016, Fettiplace 2017, Koppl and Manley 2019). Low frequency sounds are sensed at the distal end (apex) of the cochlea; high frequency sounds are sensed at the proximal end (base) of the cochlea (reviewed in Dallos 1992, Manley 2018). Sound vibrations are transmitted from the eardrum through the three bones of the inner ear (malleus, incus, stapes) and the oval window of the cochlea to the fluids within the cochlea. Within the organ of Corti in the cochlea there are 3 rows of outer hair cells (OHCs) on the external side of the tunnel of Corti and 1 row of inner hair cells (IHCs) on the internal side (Spoendlin 1967). Each IHC synapses with approximately 20 afferent myelinated type I spiral ganglion neurons and functions as a sensory receptor to convert the energy of sound waves to secretion of glutamate neurotransmitter. Multiple OHCs synapse with each unmyelinated type II afferent neuron and OHCs are also synapsed with efferent medial olivocochlear fibers (Spoendlin 1967). The primary function of OHCs, however, is amplification of organ of Corti motions in response to sound (Ryan and Dallos 1975). Amplification is produced by changes in receptor-potential driven cell length caused by changes in the conformation of the unusual membrane protein prestin (SLC26A5, Zheng et al. 2000).

IHCs and OHCs sense the sonic vibrations by deflection of stereocilia on their apical surfaces (reviewed in Fettiplace et al. 2017, McPherson 2018). The stereocilia are arranged in rows of increasing height, with a stereocilium of one row connected to a stereocilium of another row by a tip link composed of a CDH23 dimer on the taller stereocilium joined at its N-termini to the N-termini of a PCDH15 dimer on the shorter stereocilium. CDH23 is connected to the cytoskeleton of the taller stereocilium via MYO7A (MyoVIIa), USH1C (Harmonin), and USH1G (Sans) (reviewed in Peng et al. 2011, Cosgrove and Zallocchi 2014, Barr-Gillespie 2015, Fettiplace 2017, McGrath et al. 2017, Cunningham and Müller 2019, Ó Maoiléidigh and Ricci 2019, Velez-Ortega and Frolenkov 2019) while PCDH15 on the shorter stereocilium interacts with LHFPL5, an auxiliary subunit of the mechanoelectrical transduction channel (MET channel, also known as the mechanotransduction channel), which contains at least TMC1 or TMC2, TMIE, and the auxiliary subunits LHFPL5 and CIB2 (reviewed in Fettiplace 2016, Qiu and Müller 2018, Corey et al. 2019). Deflection of stereocilia in the direction that increases tension on the tip link causes depolarization of the cell by increasing the open probability of the MET channel, which then transports calcium and potassium in-

to the hair cell according to the gradient of those ions between the scala media (containing endolymph at 154 mM K+ and <1 mM Ca2+) at the apex of the cell and the scala tympani (containing perilymph at 7 mM K+) at the base (reviewed in Fettiplace and Kim 2014). Similarly, compression of the tip link by deflection of the stereocilia in the opposite direction decreases the open probability of the MET channel and causes hyperpolarization of the cell.

Depolarization of IHCs causes opening of voltage-gated calcium channels arrayed in stripes on the basolateral membrane close to ribbon synapses formed between the IHC and the afferent fiber of a myelinated type I spiral ganglion neuron. This results in a localized increase in cytosolic calcium ions which interact with Otoferlin (OTOF) on glutamate-containing synaptic vesicles at the ribbon structure to activate exocytosis of glutamate into the synapse formed with the afferent neuron (reviewed in Wichmann 2015, Pangrsic and Vogl 2018). Ribbon synapses are distinguished by electron-dense ribbon structures projecting from the presynaptic membrane into the cytosol and comprising at least BASSOON, RIBEYE (an isoform of CTBP2), and PICCOLINO (an isoform of PICCOLO). The ribbon structures appear to transiently bind synaptic vesicles and facilitate resupply of synaptic vesicles at active zones to refill the pool of readily releasable vesicles (reviewed in Moser et al. 2006, Moser et al. 2020).

In contrast with IHCs, OHCs mainly function in sound amplification by decreasing up to about 4% in length in response to depolarization caused by opening of the MET channel and increasing in length in response to hyperpolarization caused by channel closing, resulting in alternating compression and decompression between the reticular lamina and the basilar membrane. The changes in the length of the OHC are caused by very rapid (microseconds), voltage-sensitive changes in the conformation of the membrane protein prestin (SLC26A5). Stereociliary ATP2B2 (PMCA2) extrudes calcium ions and basally located KCNQ4 extrudes potassium ions to repolarize the OHC.

OHCs are synapsed with efferent cholinergic medial olivocochlear fibers (reviewed in Fritzsch and Elliott 2017, Fuchs and Lauer 2019). Acetylcholine released at the synapse binds an unusual, nicotine-antagonized, nicotinic receptor comprising CHRNA9 and CHRNA10. Upon binding acetylcholine, CHRNA9:CHRNA10 transports calcium ions into the OHC. The calcium activates SK2 potassium channels (KCNN2) and BK potassium channels (KCNMA1:KCNMB1) which extrude potassium ions, hyperpolarize the OHC, and inhibit activation of the OHC.

Loud sounds can cause a temporary threshold shift (temporary loss of hearing) caused by damage to stereocilia and synapses or permanent threshold shift (permanent loss of hearing) caused by damage or death of hair cells and neurons (reviewed in Kurabi et al. 2017).

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Sensory processing of sound by inner hair cells of the cochlea ↗

Location: Sensory processing of sound

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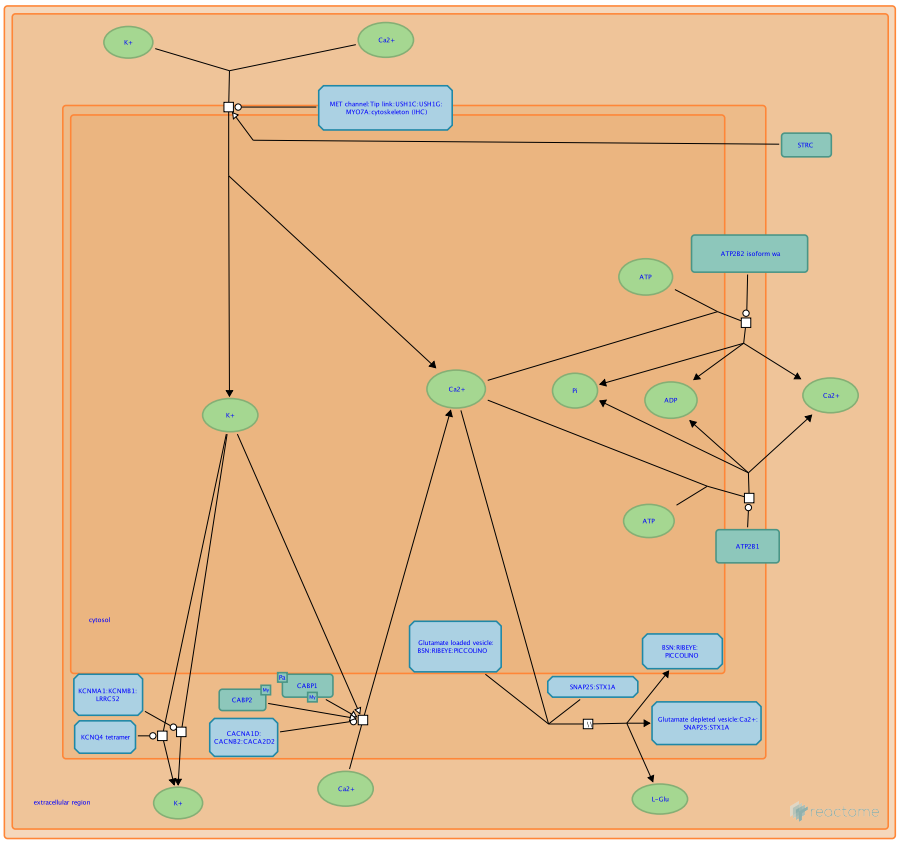

Inner hair cells (IHCs) of the cochlea transduce sound waves into an ionic (mainly potassium) current that leads to exocytosis of glutamate from the IHC and activation of postsynaptic type I afferent fibers of the radial ganglion (reviewed in Meyer and Moser 2010, Moser and Vogl 2016, Fettiplace 2017). IHCs have stereocilia on their apical surface that are arranged in rows of increasing height, a "staircase" arrangement. Stereocilia of different rows are connected by a tip link comprising a CDH23 dimer on the taller stereocilium bound to a PCDH15 dimer on the shorter stereocilium. PCDH15 interacts with LHFPL5, an auxiliary subunit of the mechanoelectrical transduction channel (MET channel, also called the mechanotransduction channel), which contains at least TMC1 (adults) or TMC2 (newborns), TMIE, and the auxiliary subunits LHFPL5 and CIB2 (reviewed in Fettiplace and Kim 2014, Fettiplace 2016).

Deflection of the stereocilia by sound waves creates tension on the tip link that increases the open probability of the MET channel, which then transports calcium and potassium ions from the scala media into the IHC, depolarizing the IHC (reviewed in Fettiplace 2017). The potassium channel KCNQ4 located in the neck region of the cell may also participate in depolarization. The depolarization of the IHC opens voltage-gated Cav1.3 channels (CACNA1D:CACA2D2:CACNB2) located in stripes near ribbon synapses on the basolateral surface of the IHC. The resulting localized influx of calcium ions activates exocytosis of glutamate into the synapse by an interaction between calcium and Otoferlin (OTOF) on glutamate-loaded vesicles in the IHC (reviewed in Wichmann 2015).

Ribbon synapses are characterized by a multiprotein complex, the ribbon, that contains at least BASSOON, RIBEYE (an isoform of CTBP2), and PICCOLINO (a small isoform of PICCOLO) and appears to act to transiently tether vesicles near the synapse and thereby increase the pool of readily releasable vesicles (reviewed in Safieddine et al. 2012, Wichman and Moser 2015, Pangrsic and Vogl 2018, Moser et al. 2020).

ATP2B1 calcium channels, ATP2B2 calcium channels, KCNMA1:KCNMB1:LRRC52 potassium channels, and basolateral KCNQ4 potassium channels transport cations out of the IHC and thereby act to repolarize the cell and limit the duration of the synaptic potentials (reviewed in Patuzzi 2011, Oak and Yi 2014).

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Sensory processing of sound by outer hair cells of the cochlea ↗

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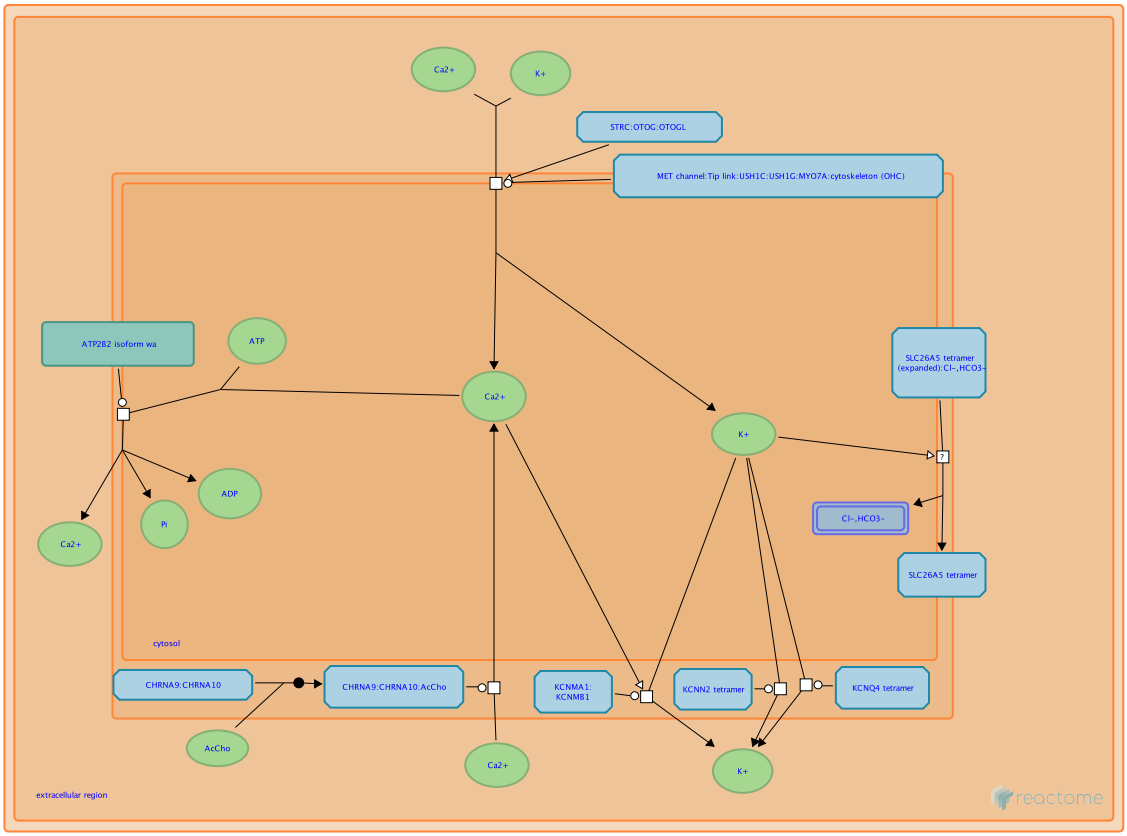

Outer hair cells (OHCs) produce amplification of sound waves in the cochlea by shortening and lengthening in response to sound, a phenomenon called electromotility (reviewed in Kim and Fettiplace 2014, Fettiplace 2016, Fettiplace 2017, Fritzsch et al. 2017, Ashmore 2019). Like inner hair cells, OHCs possess apical stereocilia arranged in rows of ascending height. A taller stereocilium is connected to a shorter stereocilium by a tip link comprising a CDH23 dimer onthe side of the taller stereocilium and a PCDH15 dimer on theapex of the shorter stereocilium. PCDH15 interacts with LHFPL5, a subunit of the mechano-electrical transduction channel complex (MET channel, also called the mechanotransduction channel), which contains TMC1 or TMC2, TMIE, CIB2, and LHFPL5 (reviewed in Fettiplace 2016). Deflection of the stereocilia in one direction produces tension on the tip link that increases the open probability of the MET channel, resulting in depolarization of the OHC. Deflection of the stereocilia in the opposite direction produces compression on the tip link that decreases the the open probability of the MET channel, resulting in hyperpolarization of the OHC.

Sound causes micromechanical motions of the organ of Corti that result in alternating tension and compression in the tip link that produce excitatory-inhibitory cycles of MET channel openings and closings relative to the MET channel's resting open probability. This causes directionally alternating fluxes of K+ and Ca2+, yielding depolarization-hyperpolarization cycles that cause conformational changes in prestin (SLC26A5). These cycles are asymmetrical, with contraction caused by depolarization dominating elongation caused by hyperpolarization due to the asymmetry of the open probability of MET channels. Stereociliary ATP2B2 (PMCA2) extrudes calcium ions and basally located KCNQ4 extrudes potassium ions to repolarize the OHC.

Depolarization of the OHC causes a decrease in length of the OHC due to a very rapid, voltage-sensitive

change in conformation of the membrane protein prestin (SLC26A5), an unusual member of the anion transporter family located in the lateral membrane (Mahendrasingam et al, 2010) that appears to respond to cytosolic chloride by altering its conformation in the plane of the plasma membrane (reviewed in Dallos et al. 2006, Dallos 2008, Hudspeth 2014, Reichenbach and Hudspeth 2014, Ashmore 2019, Santos-Sacchi 2019). Prestin also appears to act as a weak chloride-bicarbonate antiporter (Mistrik et al. 2012). Changes in length of the OHCs cause movement of the reticular lamina toward and away from the basilar membrane.

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Fettiplace, R. (2017). Hair Cell Transduction, Tuning, and Synaptic Transmission in the Mammalian Cochlea. *Compr Physiol, 7*, 1197-1227. ↗

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