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Upper tip-link density Intermicrovillar protein: a linkage of stereocilia in hearing

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ABSTRACT

Noise in any form is a preventable cause of hearing loss in societies causing an inner ear structural damage, which involve in detection of sound through deflection of mechanosesnsory stereocilia. Stereocilia consists of large set of proteins involved in transduction of signals to sensory hair cells. The stereociliary scaffolding protein, harmonin, SANS and myosin7a, a tripartite complex play a key role in transduction of sound signals with protein-protein interactions that activate the large complexes responsible for hearing. From this tripartite complex, a Harmonin bridges cadherin 23 to cytoskeletal actin core of the stereocilium which is essential for the developmental differentiation of stereocilia. Harmonin is also associated with the tip link proteins for intermolecular association of stereociliary actin filaments for transduction of sound. Defects in this protein cause prelingual and moderate-to-severe degree of hearing loss. Our cram is mainly focusing on the mechanisum of the harmonin in hearing to gear up identification of disease in early stages. **Keywords:** Cytoskeletal actin, Harmonin, Myosin7a, Prelingual deafness, SANS, Stereocilia, Tripartite complex, USH1C

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INTRODUCTION

Unwanted sound (Noise) is created during daily routine and environmental activity; it causes detrimental health hazards to human being. High levels of noise remain a problem in all regions of the world. Noise greater than 85dB were experience during gunfire, explosive, machinery, power tools, jet engine, musical instruments, aviation, heavy traffic which may cause Noise Induced Hearing Loss (NIHL) [1]. Continuous and intense noise exposure may change inner ear structure that leads to NIHL. It becomes more complex while dealing with work environment due to its intensity, exposure time, and other risk factors.

According to World Health Organization (WHO), 278 million people have reported for disability of hearing impairment (2005). United States of America stated that, about 30 million workers were exposed to hazardous noise (NIOSH, 1998). In Germany, 4-5 million people (12–15% of the workforce) were exposed to high noise levels (WHO, 2001). Deafness in Southeast Asia ranges from 4.6% to 8.8% and in India, 63 million people (6.3%) suffer from significant auditory loss) [2]. Accordingly, Occupational safety health Administration (OSHA), National Institute of Occupational safety and health (NIOSH) have given permissible exposure limit (PEL) for an 8 hour/day is 85dB and 90 dB respectively for all workers. The conditions are improved in developed countries with the introduction of protective measures) [3]..The average noise level data suggested that developing countries are scarce due to industrialization which is not always accompanied by protection) [4]. Regular exposures to noisy sounds for prolonged period possess a serious risk of irreversible hearing loss) [5]..

Sound induced vibration travel to outer, middle and inner ear and bombarded at tympanic membrane. It connects with chain of three tiny bones namely malleus, incus, and stapes that amplify and transmit a sound wave to inner ear. Cochlea is the part of the inner ear. It consists of scala media, suspended from osseous spiral lamina within the bony labyrinth scala media. The bony labyrinth divided into two fluid filled compartment, the apical scala vestibule and basal scala tympani. The scala media contain organ of corti which is responsible for transmitting sound impulses to the fibers of cochlear nerves. Scala media is an endolymph filled cavity inside the cochlea, located in between the tympanic duct and the vestibular

duct, separated by the basilar membrane and Reissner's membrane (the vestibular membrane) respectively. The basilar membrane supports the sensory structure of the organ of corti. It encloses sensory cell, support cell and gelatinous tectorial membrane. The apical surface of hair cell and their support cell form a regular tightly joined planar mosaic and form reticular lamina. The boundary between endolymph and perilymph are formed by reticular lamina in which stiff junctions prevent mixing of the two fluids. The stereocilia are in endolymph, however the hair cell bodies are in perilymph. During transduction Potassium ions flowing through the hair cells are recycled back to the scala media via the supporting cells and the stria vascularis) [6].. The inner hair cells are closer to modulus line up into single continuous row are able for mechanotransduction, the transformation of mechanical force into an electrical signal, which is the basic principle of hearing) [7].. Three to five rows of the outer hair cells of stereocilia are located at the apex region of basilar membrane. Outer hair cells of stereocilia are arranged in V or W pattern, with the wide part of the "W" facing the tunnel of Corti. The sensory hair cell of the auditory organ alters sound energy i.e. mechanical energy into electrical impulses through Mechanoelectrical-transduction (MET) channels) [8]. The mechanosensitive ion channels involved in this process are located at the tip of the stereocilia are linked by tip-link, connect the top of a lower Stereocilia, where the MET channel is localized, to the side of an adjacent upper one; and are thought to contribute to resting tension and regulate adaptation) [9]. This review is focused on the molecular mechanism of cytoskeletal binding of upper and lower tip link density proteins with an intermicrovillar connection necessary for hearing acuity.

Tiplinks

Tip link are four-stranded link that couple with the tip of one stereocilium to the adjacent taller stereocilium of cell to cell adhesion complex. The recent studies were shown that in mature hair cell, tips links initially interact with CDH23 and PCDH15) [10]. which is composed of Protocadherin 15 (PCDH15) dimers matures into a heterodimer of PCDH15 and Cadherin 23 (CDH23) homodimers localized to the lower and upper tip link density to adjacent stereocilia respectively) [11]. Where each tip link is a symmetric protein complex containing CDH23 to connect the upper part of stereocilia and PCDH15 connect to lower part of stereocilia referred as the upper tip-link density (UTLD) and the lower tip-link density (LTLD) proteins. Tip links play important role in hearing transduction, since they are coupled with mechanoelectrical-transduction (MET) channels [12-14]. Sound induced deflection of stereocilia which can cause tension to tip links can open the mechanoelectric channels) [8] as depicted in the figure 1.



Figure 1:In this diagram it shows the connectivity between the two stereocilia in which tiplinks (cadherin 23 and protocatherin 15) are coupled together with tripartite complex i.e. Harmonin, SANS and Myosin7a in stereocilia connected with actin bundles for communication of signal transduction from upper tip link density (UTLD) to lower tiplink density (LTLD). The actin bundles which are essential component of stereociliary length required necessary proteins like Espin, Fasin, Vilin and fimbrin for proper functioning of hearing acuity.

Pickles *et al* studied the lower and upper density termination points by TEM showing variety of proteins present at lower end of the tip link having whirlin, a submembranous molecular complex protein, controls and coordinates polymerization of actin in stereocilia of hair cells) [15]. Whirlin deficient mouse studied by Mburu *et al* and Holme *et al* showed whirling behavior with deafness gene DFNB31) [16]. The actin binding, inhibitory proteins of actin polymerization are Myosin XVa, myosin VIIa, twinfilin and an actin regulating protein, EPS8 are also present at lower patch of tip link [17,18]. The upper density patch is enriched with scaffold protein with ankyrin repeats (ANKS4B), are SANS, along with myosin 1c, myosin 7a, [19,20]. and harmonin-b, which found during early development of the hair cell. These UTLD and LTLD are also rich with calmodulin, a multifunctional intermediate calcium-binding and unbinding messenger protein [20]. Stereocilia is anchored to actin through interaction of their cytoplasmic domains with tripartite complexes of harmonin, SANS and Myosin7a [19].

Among these tripartite molecules, primarily harmonin plays important role in maintaining harmony of the hair cells which is key molecule in establishing a relation of two adjacent stereocilia by linkages of tip link. Harmonin is concentrated at UTLDs where CDH23 molecules inserted into the stereociliary membrane. Harmonin is encoded by USH1C gene in human. It also plays a critical role in the development and maintenance of cochlear hair cells. It has three isoforms i.e. harmonin-a, b & c. Harmonin c is shorter than a and b [21]. The position of the harnmonin c is not clear till date in literature. Harmonin a is present at the lower stereocilia as depicted in figure 2a. [22].



Figure:2 The given diagram shows the Harmonin isoforms structure in detail (Harmonin a, Harmonin b, Harmonin c,) longest isoform is grouped in harmonin-b which contains three PDZ domains along with one additional coiled coil regions (CC1,CC2) compared to harmonin a and c. Structurally harmonin-b encloses three PDZ domain i.e. (postsynaptic density protein, Drosophila dice large tumor suppressor, Zonnula occlundend-1protein) two coiled-coil (CC1,CC2) and one PST domains (a domain rich in proline, serine and threonine). USH 7a is showing two FERM domain with SAH and SH₃(2a, 2b)

A **coiled coil** proteins_is a motif_having alpha-helices are coiled together like strands involved in important biological functions of regulation of gene expression. One of the coiled coil protein is a Tropomyosin, that binds to seven consecutive actin subunits along with the pitch helix of actin filaments. Once tropomyosin bound with actin core, they start polymerization at end-to-end and constantly stabilizes F-actin and regulates various acting-binding proteins including myosin which is the member of cargo transporting class-7-15 which are frequently found at sensory hair cells of stereocilia. [23,24]. SANS is another supportive putative scaffolding protein which encodes a gene USH1G. SANS, which binds to harmonin and myosin-7a in vitro , and possibly to the intracellular domains of cadherin-23 and protocadherin-15, is located at the lower tip-link insertion point in the developing hair bundle and at the

upper tip-link insertion point in the mature hair bundle. It contains a series of four ankyrin repeats and a sterile α -motif (SAM) domain, with an intervening 95-aa central region (CENT) and a C-terminal PDZ domain-binding consensus motif [25]. depicted in figure 2a. Boëda B, *et al.* and Bahloul A, *et al* suggested that USH1 protein cooperates in hair bundle development and predicted that harmonin-b anchors to the stereocilial actin filament by transient fibrous lateral links in which myosin 7a creates tension on these links, but the role of SANS is still unknown. SANS is directly interacts in vitro with both the myosin 7a tail and harmonin, hence SANS is not been detected within the hair bundle.

The third motor protein molecule of the tripartate assembly is Myosin7a, maintains the necessary mechanical tension across the cadherin links for the cytoskeletal attachment of the tip links along with regulation of stereociliary growth. Mutations in the genes of MYO7A responsible for intracellular movement, elongation of stereocilia, along with defects in hair bundle morphology. Prosser *et al* have confirmed the importance of myosin in regulation of the F-actin rearward flow which increases the actin treadmilling, from this it is being opined that MYO7A may be help in regulation of proteins for restriction of actin formation.^{Error! Bookmark not defined.} According to Batiste Boeda *et al*, harmonin-b interacts directly with myosin 7a, which is absent from the disorganized hair bundles of myosin7a mutant mice, suggesting that myosin 7a conveys messages to harmonin-b along with the actin core of the developing stereocilia also it was proposed that the shaping of the hair bundle relies on a functional unit composed of myosin 7a, harmonin-b, and cadherin 23 that is essential to ensure the cohesion of the stereocilia depicted in figure 3.



Figure 3: The above diagram shows detail mechanism of the Harmonin to the actin fiament and plasma membrane. The adherence in between the tripartite complex Harmonin, SANS and Myosin7a the stereocilia and the plasma membrane associated tip links (cadherin 23 and protocatherin 15). The tip link cadherin 23 holds the N-terminal PDZ domain and on the other hand the motar protein Myosin7a hold by the actin filaments, the proper holding or arrangement of the proteins in this junction is very crucial for transduction of sound signals with protein-protein interactions which activates the large complex of proteins.

Harmonin is very importantly playing its central role in maintaining the transduction of signals with specific protein-protein interactions that activate the assembly of large protein complexes. Not astonishingly, disrupting of these interactions may play a role in human diseases. Mutations in USH1C gene of harmonin, protein in PDZ domain, are responsible for Usher syndrome type 1C, an autosomal recessive disorder distinguished by congenital sensorineural deafness, vestibular dysfunction and delayed onset retinitis pigmentosa (RP) eventually leading to blindness Study of the gene liable for Usher syndrome has been especially informative for our understanding of hair bundle development. There are five USH1 genes that codify known products: myosin VIIA (MYO7A), the two cell-cell adhesion cadherin proteins cadherin-23 (CDH23) and protocadherin-15 (PCDH15), and the scaffold proteins harmonin (USH1C) and SANS (USH1G). [26].

Usher syndrome (USH) is divided into three types. Usher type I (USH1) is the most severe form and is characterized by severe to profound congenital deafness, vestibular areflexia, and prepubertal onset of progressive RP. Type II (USH2) displays moderate to severe hearing loss, absence of vestibular dysfunction, and later onset of retinal degeneration. Type III (USH3) shows progressive postlingual hearing loss, variable onset of RP, and variable vestibular response. From this review it is firm that networking of harmonin with PDZ-domain, SANS, and motor protein myosin has vital role in interactions

of inter stereocilia, which maintains the structural integrity of supramolecular signaling uptake for disease free human kind.

	First	Title of Paper	Tested	Study design	Conclusion
	author		model		
1	B.Boëda	Myosin VIIa,	mouse and	Mouse and rat model	The shaping of the hair bundle
	et al.[27]	harmonin and	rat	were used to study	relies on a functional unit composed
		cadherin 23, three		harmonin which	of myosin VIIa, harmonin b and
		Usher I gene		directly interacts with	cadherin 23 that is essential to
		products that		cadherin 23. Further,	ensure the cohesion of the
		cooperate to shape		two polyclonal	stereocília.
		the sensory hair		antibodies directed	
		cell bundle		against the harmonin	
				PSI domain were	
				interaction Mouse	
				vostibulo harmonin h	
				was investigated from	
				F13 and restricted to	
				the emerging stereocilia	
				of the hair cells.	
				Harmonin b induces a	
				resistance of actin	
				filament to latrunculin	
				A and cytochalasin D	
				were studied in vitro	
				model. Later, Harmonin	
				b was co-localizes with	
				hEcad±cad23 in co-	
				transfected HeLa cells.	
2	Jan	Scaffold protein	Mice or	In vitro and in vivo	Molecular linkage were identified
	Reiners	harmonin (USH1C)	Wistar rats	models were used to	between the pathophysiology in
	et al, [28]	provides molecular		test possible	USH1 and USH2 in a mutual
		links between		interactions between	interactome related to the
		tume 1 and tume 2		NPC2 and harmonin	common prenotype in USH.
		type I and type 2		Further glutathione S-	
				transferase (GST)	
				USH2 proteins and	
				NBC3 were	
				investigated to bind	
				with harmonin	
				isoform a1. His-tagged	
				harmonin was pulled	
				down from three GST-	
				fused cytoplasmic tail	
				fragments of USH2A,	
				VLGR1b and NBC3 to	
				confirm these	
				interactions in vivo	
				h VI CP1h and NPC2	
				o, v Luivin alla IVDUS	
				immunonrecinitated	
				with harmonin a1	
				were determined by	
				immunoprecipitation(I	
				P) assays. Finally	
				results were further	
				verified in yeast two-	
				hybrid interaction	
				assays.	

Table 1: Detailed information about the harmonin and related proteins with different studymodel

3	Grillet N et al [29]	Harmonin Mutations Cause Mechanotransducti on Defects in Cochlear Hair Cells	Mice	To determine the subcellular distribution of harmonin in hair cells, antibody (H3) raise against the PDZ3 domain of Harmonin and Hair Cells which is present in harmonin-a and -b splice variants. Harmonin- PDZ2AAA/AAA Mice Are Deaf and Show Defects in Hair Bundle Morphology were studied. Further, dfcr Mice Are Deaf but Show No Defects in Hair Bundle Morphology was also investigated. Hair Bundles in the Cochlea of dfcr Mice Lack UTLDs but Contain Tip Links, analysis of Mechanotransduction currents in OHCs from dfcr Mice and adaptation in OHCs from dfcr Mice were also analyzed.	Harmonin is a UTLD component and contributes to establishing the sensitivity of Mechanotransduction channels to displacement.
4	Yu IM, Planelles -Herrero <i>et al</i> [30]	Myosin 7 and its adaptors link cadherins to actin	human Myo7a and Myo7b genes	The harmonin-a PDZ3c/Myo7b MF2 interaction was determined by crystal structures of Myo7b MF2 and of PDZ3c/Myo7b MF2 complex at 2.44 and 1.88 Å resolution analysis.	Myo7/harmonin-a/SANS:ANKS4B tripartite complexes that link cadherins to the actin-rich core in stereocilia and microvilli.
5	Crawley SW et al [31]	ANKS4B is essential for intermicrovillar adhesion complex formation	CACO-2BBE, COS7, and HEK293FT cells	ANKS4B targets to the BB using the ANKR domain. Localization of endogenous ANKS4B in intestinal and kidney tissue sections from USH1C knockout (KO) mice were studied. ANKS4B, USH1C and MYO7B could form a stable tripartite complex were investigated in vitro model. ANKS4B interacts with multiple IMAC components was also determined.	It was revealed ankyrin repeat and sterile α motif domain containing 4B (ANKS4B) localizes to the tips of adherent brush border microvilli and is essential for intermicrovillar adhe sion.
6	Yan J <i>et al</i> [32]	The structure of the harmonin/sans complex reveals an unexpected interaction mode	coding sequence of harmonin NPDZ1	In this study, harmonin N-terminal domain and PDZ1 form a structural and functional supramodule that	The synergistic PDZ1/SAM and PDZ1/carboxyl PDZ binding-motif interactions, between harmonin and Sans, lock the two scaffold proteins into a highly stable complex. Mutations in

8 Vorpy syndrome proteins Data was used syndrome proteins Data was used billing the complex formation of harmonin and Sats was used billing the complex formation of the harmonin and Sats un USH1 patients are shown to determining the impact of USH1C and USH1 patients was disrupt the formation of the harmonin fractact max shelpful in The functional domain structures of harp and harmonin, their interaction under native conditions and their co-tocalization suggest they constitute a scaffolding complex to expressed in harmonin and staff was very shelpful used to the they protein the interacts with harmonin in epithelial tissues The functional domain structures of harp and harmonin, their interaction under native conditions and their co-tocalization suggest they constitute a scaffolding complex to calitate signal transduction in epithelia. 8 Vorpy ELelbovi 10 Met of Martin Martin epithelial tissues Adefect in harmonin and co- localization of native harmonin were used to chromosome 16, and ths mouse homologue to chromosome 7. GST fusion protein purification, facterial expression constructs encoding CST. FDP22 and GST-PD23 of harmonin were used to transform complex te Lobi harmonin were used to transform complex te Lobi harmonin were used to transform complex te Lobi harmonin the term sten harmonin were used to transform complex te Lobi harmonin the met used to transform complex te Lobi harmonin the read to transform complex te Lobi harmonin the term sten harmonin the read to transform complex te Lobi harmonin the read to transform complex te Lobi harmonin the term the the mous inner cars multiple tissue harmonin protein genetic (SHT CD), encoding a PD2- conset te Lobi to transform the mous inner cars multiple tissue harmonin the mous inner to the read the time term the the mous inner cars multiple tissue harmonin the mous inner to the mous inn			of the true II-le		hinda to Conth	harmonin and Cana
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		Usher syndrome		cDNA library derived	
		type 1C		from inner ear sensory	
		oppo re		areas. In patients we	
				found a splice-site	
				mutation, a frameshift	
				mutation	
				and the expansion of	
				an intronic variable	
				number of tandem	
				repeat (VNTR) were	
				identified in	
				population of Acadian	
				descendants from	
				Louisiana and in a	
				Lebanese family. It	
				was also determined	
				in the mouse inner ear,	
				only the sensory hair	
				cells express	
				harmonin.	
				Immunohistofluoresce	
				nce analysis was	
				performed using the	
				purified MBP-D6	
				polycional antibody14	
				raised against the	
				Derformed nucleotide	
				using the Constice	
				Computer Group	
				Package	
9	Anarisi	Novel mutations in	Human	To identify mutations	A non-sense mutation (n.C224X)
-	MI et al	the USH1C gene in		of USH1C gene in the	and a frame-shift mutation
	[35]	Usher syndrome		Spanish population	(p.D124TfsX7) mutations in USH1C
	[]	patients		were screened by	are responsible for 1.5% of USH1
		1		direct sequence	disease in patients of Spanish.
				NM_153676.2 for	
				exons 1–14 and 16–28,	
				and with the	
				consensus sequence	
				NM_005709.2 for exon	
				15, using the BLAST	
				program Further,	
				computational analysis	
				of splicing variants and	
				missense variants	
				were investigated	
				computational analysis	
				with the programs	
				SIFT, PolyPhen, and	
				Pmut to infer the	
				pathologic effect of	
				these variants	

CONCLUSION

High level of noise remains a problem in all regions of the world. As large set of proteins are responsible for hearing loss as suggested by scientists and estimating that, assembly of tripartite complex i.e harmonin, sans and myosin7a is important for maintaining the transduction signal of sensory hair cells with the protein-protein interactions and very crucial for hearing. The PDZ domain scaffolding protein harmonin which holds Sans and myosin7a if this anchoring is not properly done the complex is unable to performed the proper transduction mechanism, which is very important part of hearing acuity.

The other hypothetical insight of the review is on early diagnosis of mutational changes in the first trimester of the pregnancy along with early therapeutic gear up in developmental stages of the infant, which will be helpful for the early diagnosis of disease.

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