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REVIEW ARTICLE **OPEN ACCESS**

Succinct look to the ERM protein family in Earshot Impairment

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ABSTRACT
Noise Induced Hearing Loss (NIHL) is a one of the occupational diseases caused by an exposure of impulsive sound or continuous loud sound at various levels over an extensive period of time at different workplaces. Diverse functional proteins are responsible for hearing acuity which is present in Techtorial Membrane, Inner hair cells, Outer hair cells and stereocilia in the cochlea. The ERM protein family (ezrin, radixin and moesin) are chief structural designers of the cell cortex and they link plasma membrane phospholipids and proteins to the underlying cortical actin cytoskeleton. Cell cortex is a versatile and heterogeneous structure that leads to cell uniqueness and behaviour. ERM protein family is also a key member in the junction for the physical and functional organization of the cell cortex. Recent studies in several model systems have reported staggering on their regulation that leads to activation and deactivation with their various interacting partners. This review attained a brief look towards the ERM protein family in the ear deafness itinerary.
Keywords: Actin cytoskeleton, Ezrin, Moesin, NIHL, Plasma membrane, Radixin, Stereocilia.

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INTRODUCTION

Every day we encounter sound in our environment, the devices used for entertainment, automobiles, traffic, mines and industries. When an individual is exposed to harmful sounds that are too loud or get connected with these loud sounds over a long time and because of the sensitive structures of the inner ear can be damaged, causing Noise-Induced Hearing Loss (NIHL) [1]. NIHL can be caused by a one-time exposure to impulsive sound as well as by repeated exposure to continuous loud sound at various levels over an extensive period of time.

The incidence rate is astonishing that 360 million people in the world suffer from impaired hearing loss. This constitutes a substantial 5.3% of the world's population. In India, 63 million people (6.3%) endure from critical auditory loss in that, four in every 1000 children suffer from severe to profound hearing loss. Approximately occurrence of adult-onset deafness in India was found to be 7.6% and childhood onset deafness found to be 2%. More than 30 million Americans are exposed to hazardous sound levels on a regular basis and 10 million populations have noticed irreversible NIHL. Individuals of all ages, including children, adolescents, young adults, and older people, can develop NIHL with reference to noise level in habitat and at workplace [2].

Ear is one of the sensory organ which is responsible for hearing and balancing.

Hearing is a series of quickly occurring events in which the ear converts sound waves into electrical signals and causes nerve impulses to be sent to the brain, where they are interpreted as sound. The ear has three main parts: the outer, middle, and inner ear. Sound waves enter through the outer ear, called as pinna and reach the eardrum to vibrate. The vibrations are transmitted through three tiny bones in the middle ear called the ossicles. These three bones are named the hammer, anvil, and stirrup which is nothing but the malleus, incus, and stapes respectively. The stapes transmits the intensified vibrations through the oval window and into the fluid that fills the inner ear. The vibrations move through fluid in the snail-shaped auditory part of the inner ear called as cochlea. It also initiates the changes that lead to

the production of the nerve impulses. These nerve impulses are transfer to the brain, where they are elucidated as sound. Cochlea contains hair cells and it act as mechano-sensors for sound perception, acceleration, and fluid motion [3]. Exposure to harmful sound caused damage to the sensitive hair cells of the inner ear and to the nerve endings. The damage that occurs slowly over years of continuous exposure to loud noise is associated with various changes in the structure of the hair cells. Various type of sounds like harmonious to inharmonious, the population of hair cells deflects in dissimilar ways, which allowing the brain to distinguish among various sounds in vowel and consonant while recognizing the language [1,4].

In cochlea there are the most sensitive Inner hair cells (IHCs) and Outer hair cells (OHCs) which are responsible for signal transduction. IHCs lying in a single row along the internal side of the tunnel of the corti, they are connected to type I spiral ganglion neurons. IHCs are pear shaped and nucleus is centrally located. IHCs are non-motile and contain 20-25 cilia per cell arranged in "U" shape. It should be noted that 95% afferent nerve ends at IHC's. OHCs are cylindrical in shape. Nucleus in the OHCs is located towards the bottom side of inner ear. OHCs are surrounded by lipid membrane and 160 cilia per cell are arranged in "W" shape [5].

Diverse functional proteins are responsible for hearing acuity which is present in Tectorial Membrane (TM), IHCs, OHCs and stereocilia in the cochlea.

During process of hearing, stereocilial OHCs are microvillar like projections, supported by bundles of actin, contacted with the TM plays a vital role in hearing. Myosin, a trans-membrane inner ear protein, otoferin, cadherin 23 (CDH 23), stereocilin, harmonin, protocadherin-15, whirlin, ezrin-radixin-moesin (ERM Family), prestin, worfferin, wolframin, connexin 26 and 30, claudin 14, tricellulin, cochlin, , alpha-tectorine are the proteins present in the cochlea which plays a important role in the hearing itinerary. Proteins present in the inner ear are dysfunctional by multiple mechanisms such as loss of protein–protein interactions, targeted degradation, mechanical damage, cytotoxicity, ischemia, metabolic exhaustion, ionic imbalance, etc [6].

ERM PROTEIN FAMILY

Cellular structures are the major building blocks of organ connected by biomolecules like proteins and nucleic acids. The cell cortex is a dynamic and heterogeneous structure that controls cell integrity and activities. Hearing perception is mainly the output of the stereocilial movements in the inner ear cochlea links to the underlying cortical actin cytoskeleton. The stiffness and flexibility of these cells are dependent on the ERM proteins (ezrin, radixin and moesin), which are majorly responsible for links between plasma membrane phospholipids and actin cytoskeleton proteins [7]. Mechanical exhaustion and derangement of stereocilia in loud sound is detrimental to health of the ear, in this stereocilial structures losses connectivity between cytoskeleton actin bundles with one another which eventually losses the integrity of the ERM family proteins. So this is alarming situation in hearing loss patients to focus on these integrity maintenance proteins.

Ezrin was identified in 1983, isolated from chicken intestinal epithelial brush borders. It named after Ezra Cornell, a founder of Cornell University. Its predicted molecular weight is 69 kDa to 80 kDa. The other member of ERM family, Radixin a 80 kDa molecule was isolated from rat hepatocyte cell junctions and it found to be localized in the cytoplasmic surface of adherent junctions in many cell types. It was named for the Latin word *radix*, which means root or foundation. Last member of ERM family i.e., Moesin a 77 kDa molecule was originally isolated from the bovine uterus as a potential heparin surface-binding protein which is known as membrane-organizing extension spike protein. The ERM family proteins are adjacently linked membrane conjoined proteins directly to actin filaments with the cell cortex. These proteins are ostensibly inert structures even though they are not static connectors. The point of fact is the ERM proteins are also crucial modulators of structural design during extremely dynamic cell behaviours, serving as mitosis, migration and junction remodelling [8]. In stereocilia, filamentous actins (F-actin) are the linear polymers of globular actin (G-actin) monomers. They appear as microfilaments in cytoskeleton and they are the part of contractile machinery in muscles and non-muscles cells [9]. Scaffolding is crucial in signal transduction between the intracellular and extracellular compartments of the stereocilial cell as well as interacting with other membrane proteins to the actin cytoskeleton. Thus, ERMs are involved in regulating several cellular processes including reorganization of actin cytoskeleton, cell survival, membrane dynamics, cell migration, adhesion and regulation of membrane protrusion [10]. The mutational studies of ERM Family proteins on various families (Iranian and Pakistani) reported are shown in table below

Table: Importance of ERM protein family in hearing studied in different models

Author & Year of Publication	Title	Model	Study Design	Conclusion
Shahid Y. Khan *,et al,* [11]	Mutations of the RDX Gene Cause Nonsyndromic Hearing Loss at the DFNB24 Locus	Human	In this study, two mutant alleles of RDX from Pakistani families are predicted to affect the actin-binding motif of radixin responsible for neurosensory hearing loss. Pure tone audiometry using air and bone conduction were performed at different frequencies. Sequence analysis of RDX in the DNA samples from the DFNB24 family revealed protein in the FERM domain. Candidate genes were identified using the Genome Bioinformatics web browser. Antibodies and Immunocytochemistry was used to immunolocalize radixin in mouse inner ear hair cells.	Radixin is expressed along the length of stereocilia of hair cells from both the organ of Corti and the vestibular system.
Men, Y.,*et al,* [12]	LKB1 Is Required for the Development and Maintenance of Stereocilia in Inner Ear Hair Cells in Mice	Mice	LKB1 knockout mice (Atoh1-LKB1-/- mice) were evaluated LKB1 function in the inner ear. Auditory brainstem responses (ABR) and distortion product to acoustic emissions (DPOAEs) tests significantly decreased in the hearing sensitivities of the Atoh1- LKB1-/- mice. Immunostaining analysis, Western blot, Scanning electron microscopy and Histology was used to reveal actin-binding proteins (ezrin/radixin/moesin) involved in the regulation of the actin cytoskeleton of hair cell in Stereocilia and phosphorylation of ERM proteins (pERM) was significantly decreased in mutant mice.	Decreased pERM may be responsible for the impaired stereocillia function which indicated that LKB1 is essential for the development and maintenance of stereocilia in the inner ear.
Shearer A. E., *et al,* [13]	A Novel Splice Site Mutation in the RDX Gene Causes DFNB24 Hearing Loss in an Iranian Family	Human	Genomic DNA was genotyped for SNPs using Affymetrix 50K XBA GeneChips. All genotypes were determined using the BRLMM genotyping algorithm and data examined with PEDSTATS for Mendelian inheritance errors. All linkage analyses were performed with MERLIN. The Lander–Green multipoint linkage mapping algorithm assumes linkage equilibrium.	Identified the splice site mutation in the RDX gene and cause DFNB24 hearing loss in the Iranian population understand the function of radixin protein in the inner ear.
Zhao, H. *et al,* [14]	Large Membrane Domains in Hair Bundles Specify Spatially Constricted Radixin Activation	Chick	The membrane composition of bundles was determined by lipid mass spectrometry with purified chick vestibular bundles. Confocal imaging of isolated bullfrog vestibular hair cells which determines bundle membrane segregates spatially into at least three large structural and functional domains. Protein mass spectrometry was used to determine bundles from chick vestibular hair cells contain a complete set of proteins that transport, synthesize, and degrade PI(4,5)P2.	Membrane domains in stereocilia within hair bundles that allow compartmentalization of Ca^{2+} extrusion and assembly of protein complexes at discrete locations.
Kitajiri S, *et al,* [15]	Radixin deficiency causes deafness associated with progressive degeneration of cochlear stereocilia	Mice	The organ of Corti isolated from the cochlea with mAbs specific for ezrin, radixin, or moesin using immunofluorescence micrographs in adult wild-type mice at the age of 3, 5 wk and 40 d of age. Deafness of $Rdx^{-/-}$ mice was examined by loss of Preyer's reflex in $Rdx^{-/-}$ mice. The vestibule and the balance function of 5-wk-old $Rdx^{-/-}$ mice was determined by scanning EM of the $Rdx^{-/-}$ and $Rdx^{-/-}$ crista ampullaris of the vestibule.	Radixin is indispensable for the hearing ability in mice through the maintenance of cochlear Stereocilia.
Pataky F, *et al,* [16]	Radixin is a constituent of stereocilia in hair cells	Chicken	In this study prepared antipeptide antisera directed against chicken radixin and ezrin. Immunocytochemical studies isolated hair cells; anti-radixin produced an intense band of labeling at the bases of hair bundles from the chicken, frog, mouse etc. Electron microscopic immunocytochemistry disclosed radixin labeling commenced in the stereociliary taper, peaked in the lower stereociliary shaft, and	Radixin is a prominent constituent of Stereocilia and participate in anchoring the "pointed" ends of actin filaments to the membrane.

			declined progressively toward the hair bundle's top.	
Lee K, . *et al,* [17]	Autosomal Recessive Nonsyndromic Hearing Impairment due to a Novel Deletion in the RDX Gene	Human	The RDX gene cytoskeletal actin of stereocilia is responsible for ARNSHI due to DFNB24 in consanguineous Pakistani family using genome scan of 405 short tandem repeat markers with average spacing of 9 cM. Genotype data was analysed by PedCheck in order to identify Mendelian inconsistencies and MERLIN. Two-point linkage analysis was performed with MLINK of the FASTLINK package. Multipoint linkage analysis was carried out using Allegro1.2c. Multipoint linkage analysis, genetic map positions were used on the Rutgers combined linkage-physical map of the human genome Build 36 version.	RDX isoforms which encode the coiled-coil region of the α-helical domain are considered necessary for proper function of hair cell stereocilia.

MECHANISM OF ERM PROTEIN

The ERM are metamorphic hoard of three co-related proteins (ezrin, radixin and moesin) that possess band of Four point one (4.1) as a common origin. Band 4.1 is a part of protein superfamily. The 4.1 proteins are described by their domain structure; apart from the actin-binding domain they have FERM (F- 4.1 protein, Ezrin, Radixin and Moesin) and FERM-adjacent domains along with a unique C-terminal domain [18]. The FERM domain is a widespread protein module associated in involving proteins attachment to the plasma membrane at the N terminal [19]. The activity of the FERM domain is to dispense numerous modes of regulation through binding of regulatory ligands, phosphorylation of the FERM associated domain.

Regulation of ERM protein with their interactive diverse binding protein:

Architecturally, N-terminal ERM association domain N-ERMAD (N-ezrin-radixin-moesin association domains) also known as amino terminus of the ERM Proteins is an approximately 1-296 amino acid FERM Domain that fold and joined together to form a cloverleaf structure. The FERM region is meticulously flanked via central (around 200 amino acid) α-helical domain that form coiled coils [20] and arbitrate interaction with Protein Kinase A (PKA) [21]. The carboxylic terminal tail consists of 107 residues contains the F-actin binding site by which ERMs intercede with the actin cytoskeleton [22]. In whole ERM family members have distinct domains in which the N-terminal head and C-terminal tail called as N- and C-ezrin-radixin-moesin association domains (N-ERMAD and C-ERMAD) respectively. These arbitrated to homotypic and heterotypic head-to-tail intercommunication with ERM proteins depicted in figure A [19, 20, 21]. The N-ERMAD is different from the C-ERMAD association domain in which it is an easily altered domain in inactive phase when treated with SDS (sodium dodecyl sulphate) reagent reported by Godwin A. [9] ERMs occurs in a dormant, inactive closed conformation within the cytosol. The C-ERMAD region binds to F1,F2 and F3 in the FERM domain, by joining of both the F-actin and the regulatory subdomain protein kinase A (PKA) in association with directly and indirectly binding protein partners [22,23] as depicted in figure B. The binding of C-ERMAD domain and the FERM domain is strengthened by the α-helical domain [19]. Activation of ERMs needs accessibility of the binding sites in the FERM domain and those of the F-actin biding sites in the C-terminal domain. This activation is accomplish by phosphatidylinositol 4,5-bisphosphate (PIP2) mediated uncoupling of the C-terminal domain from the FERM domain as depicted in figure B [24].

Interaction of ERM protein function is in harmony by a two-step process of open and closed conformation i.e., active and inactive activity respectively. They are mainly synchronized through conformational changes generated by phospholipids and kinases mediated phosphorylation, and thereby results in activation of the ERM proteins. Recent studies revealed that phosphorylation and dephosphorylation is playing a vital role in ERM activity. The ERM interactions are regulated by phosphorylation by binding protein PIP_2. Activities of phosphatase and PIP2 hydrolysis is also responsible for dephosphorylation and inactivation of the proteins in the regulation of ERM proteins. The enrolment of the ERMs to a region of the plasma membrane consist of extreme amount of phosphoinositides such as PIP_2 depicted in figure C. PIP_2 bring to unveil a preserve regulatory threonine phosphorylation residue (T567, T564 and T558 in ezrin, radixin and moesin respectively) situated in the C-ERMAD domain [26]. This activates a subsequent activation machinery through which PIP_2 firstly binds to a sub-domain in N-terminal FERM domain followed by plasma membrane translocation and phosphorylation of the threonine residues [27]. Inhibition of PIP_2 –ERM interaction is confirmed by mutational studies along with translocation to the plasma membrane shows importance of PIP2 interaction in activation of FERM domain.

The activation of ezrin occurs in synergism of the two factors: Primarily binding of the N-terminal domain to phosphatidylinositol (4,5)bis-phosphate(PIP_2) and secondly by phosphorylation of threonine T567 in the C-terminal domain. Binding to actin filaments (via C-terminal) and to membrane proteins (via N-terminal) stabilizes the protein's conformation in its active mode. The membrane proteins like (CD44) and Intracellular Adhesion Molecule -2 (ICAM-2) are indirect binding partners of ezrin, while EBP50 (ERM binding protein 50) can associate with ezrin directly.
Initially, ezrin express but then regress and are replaced during development of stereocilia with radixin. Ezrin localizes unusually to the stereocilia during development but cannot fully compensate for the loss of radixin [28].

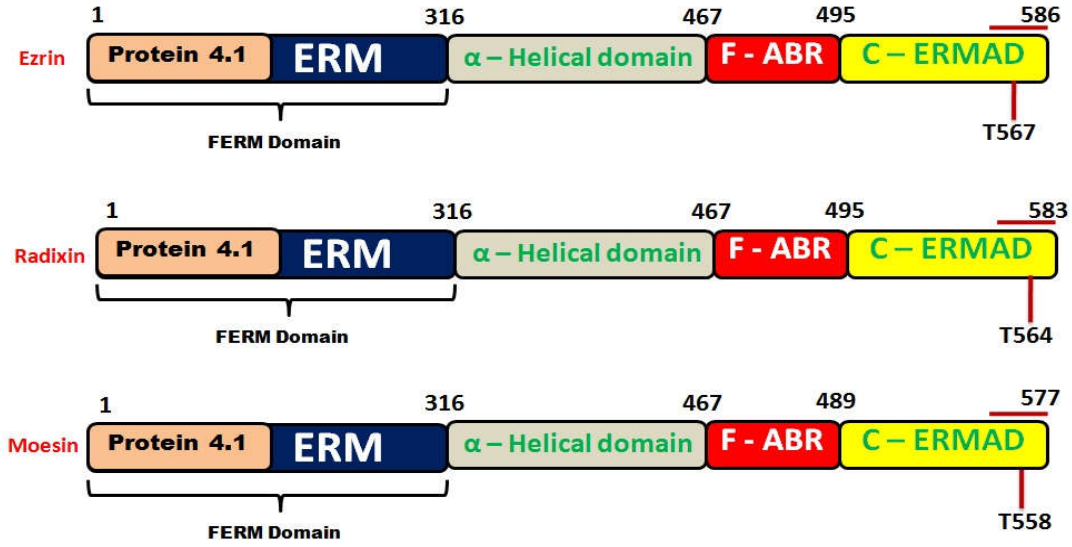

Figure A: Structural representation of ERM Proteins. ERM proteins have three distinct domains: The N-terminal FERM Domain (Band 4.1 + ERM), α-helical region which is followed by linker region and C-terminal Ezrin:Radixin:Moesin Association Domain(C-ERMAD), F-actin binding region in the C-ERMAD. In Ezrin:Radixin:Moesin, C-ERMAD showed threonine phosphorylation site at C-terminal.

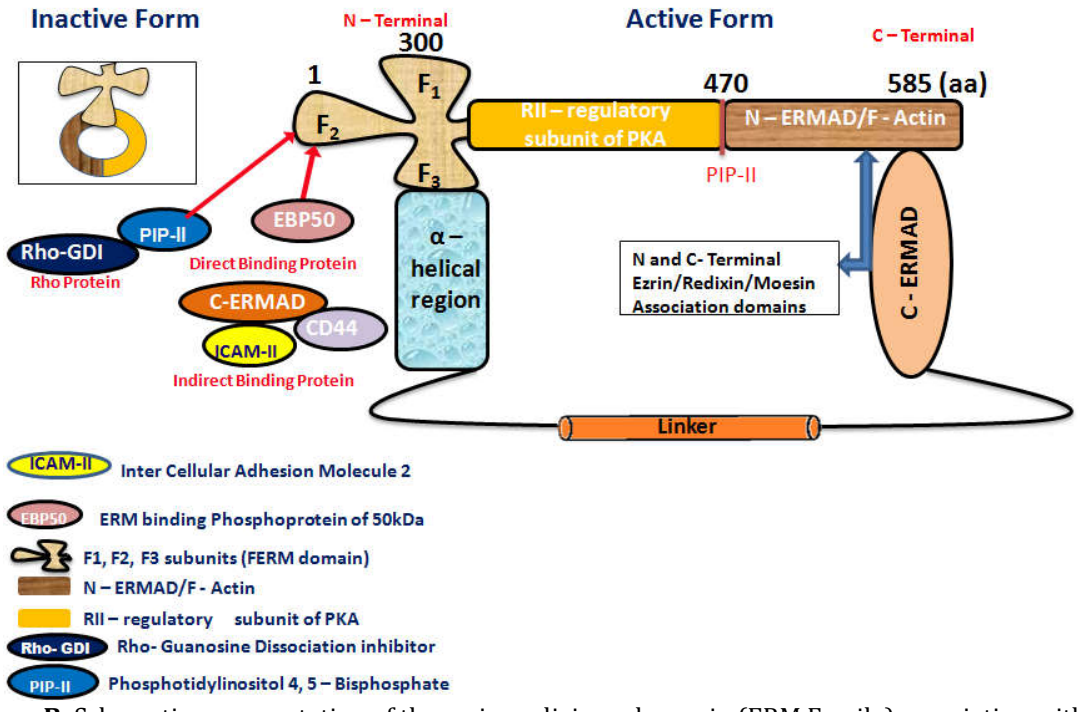

Figure B: Schematic representation of the ezrin, radixin and moesin (ERM Family) association with N-terminal clover-shaped FERM Domain and C-terminal C-ERMAD.

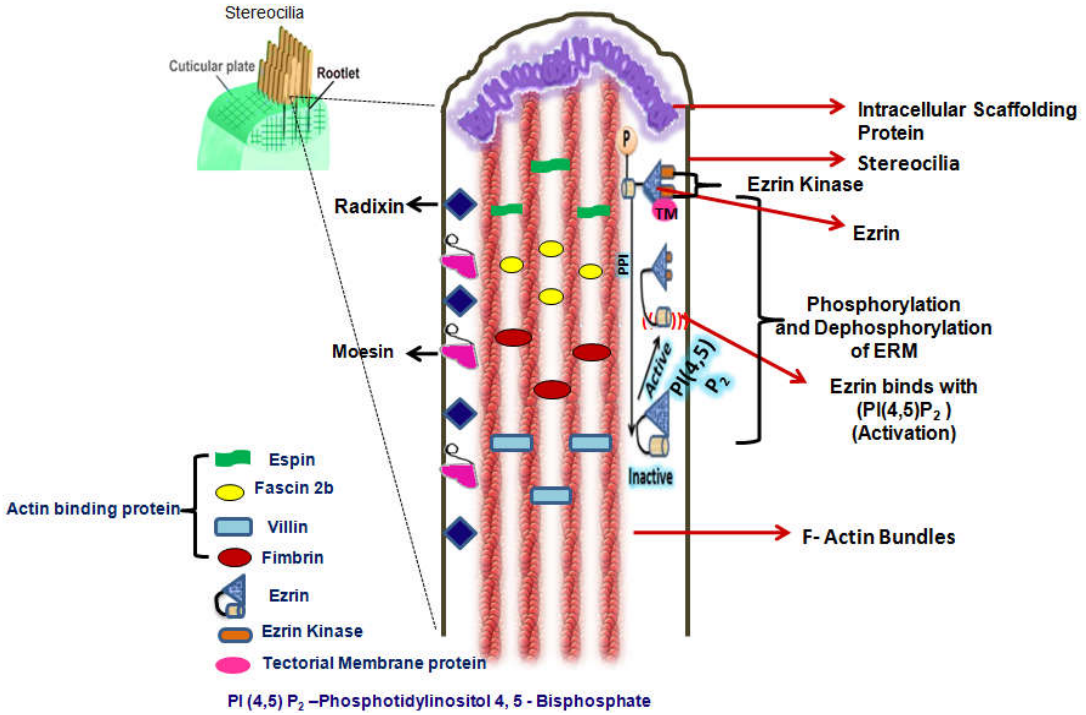

Figure C: Representation of co-ordination of Ezrin with Tectorian Membrane Protein (TM Protein) with the help of Ezrin Tyrosine Kinase (Substrate). Phosphorylation via PI(4,5)P_2 and Dephosphorylation via PPI of ERM Family Proteins shows association of actin binding filaments with plasma membrane.

Radixin and Moesin:

In many cases, binding of ERM proteins to the cytoskeleton is bolster by phosphorylation of the protein. Activation of the small Rho GTPase, Rho-A and not Rac or Cdc42 was able to lead phosphorylation of both radixin and moesin. In radixin, phosphorylation of a conserved threonine 564 residue is satisfactory to avoid the communication of the FERM domain at the N-terminus with the F-actin binding domain at the C-ERMAD terminus and this results in constitutive opening of the membrane and F-actin binding domains [29].

CONCLUSION

ERMs are dynamic and versatile protein family of the physical and functional veracity. They also play a pivotal role in maintaining cellular integrity and also interceding signal transduction from diverse extracellular inputs by their interactive protein partners. The perception of hearing is depends on the interaction and coordination of stereocilia with each other. The stereocilial integrity is depends on the cytoskeleton actin binding filaments association along with plasma membrane which are coordinated by phosphorylation of FERM domain ERM family which has important link in the hierarchy of the functional pathways to hearing essential elements.

The furthermore studies on the three distinct ERM Proteins which determine whether they carry out diverse function and regulation of the ERM family and their interaction protein partner is important hearing perspective or not. This review provides a new framework of ERMs protein family with respect to hearing loss. Rather than focusing on ezrin, scientist can concentrate on radixin as it replaced after maturation in the functional cascade of events which unable to give clear picture of mechanism for diagnosis where radixin is a prominent constituent of Stereocilia and participate in anchoring the ‘‘pointed’’ ends of actin filaments to the membrane which is easy to determine by specific tools like ELISA for early diagnosis in hearing loss patients.

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REFERENCES

1. Noise-Induced Hearing Loss: NIDCD Fact Sheet: website; Available on: https://www.nih.gov/nidcd.
2. Varshney S. (2016). Deafness in India: Indian J Otol;22:73-6.
3. Jain RK., Pingle SK., Tumane RG., Thakkar LR., Jawade AA., Barapatre A., Trivedi M.(2018). Cochlear Proteins Associated with Noise-induced Hearing Loss: An Update. Indian J Occup Environ Med. May-Aug;22(2):60-73. doi: 10.4103/ijoem.IJOEM_43_18. Review. PubMed PMID: 30319226; PubMed Central PMCID: PMC6176698.
4. Xue L., Ouang X., Xia J., Jing Z., Arti P., Fang Li., Li D et.al (2003). Prestin, a cochlea motor protein is defective in non syndromin hearing loss. Human Molecular Genetics;1115-1162.
5. Website: Available on: https://en.m.wikipedia.org/stereocilia
6. McClatchey AI. (2014). ERM Proteins at a glance:127:3199-3204.
7. McClatchey AI. ERM proteins: Quick Guide: Current Biology**:** Vol 22:No.18:R784.
8. Website: Available on: https://www.mechanobio.info/cytoskeleton-dynamics/what-is-the-cytoskeleton/what-are-actin-filaments
9. Ponuwel GA. (2016). A glimpse of the ERM proteins: Ponuwei Journal of Biomedical Science:23:35.
10. Baines AJ., Lu HC., Bennett PM. (2014). The Protein 4.1 family: hub proteins in animals for organizing membrane proteins. Biochim Biophys Acta. Feb;1838(2):605-19. doi: 10.1016/j.bbamem.2013.05.030. Epub 2013 Jun 4. Review. PubMed PMID:23747363.
11. Khan SY., Ahmed ZM., Shabbir MI., Kitajiri S., Kalsoom S., Tasneem S., Shayiq S., Ramesh A., Srisailpathy S., Khan SN., Smith RJ., Riazuddin S., Friedman TB., Riazuddin S. (2007). Mutations of the RDX gene cause nonsyndromic hearing loss at the DFNB24 locus. Hum Mutat. 28(5):417-23. PubMed PMID: 17226784.
12. Men Y., Zhang A., Li H., Zhang T., Jin Y., Li H., Zhang J., Gao J. (2015). LKB1 Is Required for the Development and Maintenance of Stereocilia in Inner Ear Hair Cells in Mice. PLoS One. 14;10(8):e0135841. doi: 10.1371/journal.pone.0135841. eCollection. PubMed PMID: 26274331; PubMed Central PMCID: PMC4537123.
13. Shearer AE., Hildebrand MS., Bromhead CJ., Kahrizi K., Webster JA., Azadeh B., Kimberling WJ., Anousheh A., Nazeri A., Stephan D., Najmabadi H., Smith RJ., Bahlo M. (2009). Anovel splice site mutation in the RDX gene causes DFNB24 hearing loss in anIranian family. Am J Med Genet A. 149A(3):555-8. doi:10.1002/ajmg.a.32670. PubMed PMID: 19215054; PubMed Central PMCID: PMC2650742.
14. Zhao H., Williams DE., Shin JB., Brügger B., Gillespie PG. (2012). Large membrane domains in hair bundles specify spatially constricted radixin activation. J Neurosci. 28;32(13):4600-9. doi:10.1523/JNEUROSCI.6184-11.2012. PubMed PMID: 22457506; PubMed Central PMCID: PMC3324267.
15. Kitajiri S., Fukumoto K., Hata M., Sasaki H., Katsuno T., Nakagawa T., Ito J., Tsukita S., Tsukita S. (2004). Radixin deficiency causes deafness associated with progressive degeneration of cochlear stereocilia. J Cell Biol. 16;166(4):559-70. PubMed PMID: 15314067; PubMed Central PMCID: PMC2172208.
16. Pataky F., Pironkova R., Hudspeth AJ. (2004). Radixin is a constituent of stereocilia in hair cells. Proc Natl Acad Sci U S A. 24;101(8):2601-6. PubMed PMID: 14983055; PubMed Central PMCID: PMC356996.
17. Lee K., Amin Ud Din M., Ansar M., Santos-Cortez RL., Ahmad W., Leal SM. (2011). Autosomal Recessive Nonsyndromic Hearing Impairment due to a Novel Deletion in the RDX Gene. Genet Res Int. 2011;2011:294675. doi:10.4061/2011/294675. Epub PubMed PMID: 22567349; PubMed Central PMCID: PMC3335613.
18. Chishti AH., Kim AC., Marfatia SM., Lutchman M., Hanspal M., Jindal H., Liu SC., Low PS., Rouleau GA., Mohandas N., Chasis JA., Conboy JG., Gascard P., Takakuwa Y., Huang SC., Benz EJ Jr., Bretscher A., Fehon RG., Gusella JF, Ramesh V., Solomon F., Marchesi VT., Tsukita S., Tsukita S., Hoover KB., et al. (1998). The FERM domain: a unique module involved in the linkage of cytoplasmic proteins to the membrane. Trends Biochem Sci. Aug. 23(8):281-2. Review PubMed PMID:9757824.
19. Pore D., Gupta N. (2015). The ezrin-radixin-moesin family of proteins in the regulation of B-cell immune response. Crit Rev Immunol. 35(1):15–31.
20. Algrain M., Turunen O., Vaheri A., Louvard D., Arpin M. Ezrin contains cytoskeleton and membrane binding domains accounting for its proposed role as a membrane-cytoskeletal linker. (1993). J Cell Biol. 120(1):129–39.
21. Pore D., Bodo J., Danda A., Yan D., Phillips JG., Lindner D., Hill BT., Smith MR., Hsi ED., Gupta N. (2015). Identification of Ezrin-Radixin-Moesin proteins as novel regulators of pathogenic B-cell receptor signaling and tumor growth in diffuse large B-cell lymphoma. Leukemia. 29(9):1857–67.
22. Pearson MA., Reczek D., Bretscher A., Karplus PA. (2000). Structure of the ERM protein moesin reveals the FERM domain fold masked by an extended actin binding tail domain. Cell. 101(3):259–70.
23. Gary R., Bretscher A. (1995). Ezrin self-association involves binding of an N-terminal domain to a normally masked C-terminal domain that includes the F-actin binding site. Mol Bio. Cell. 6(8):1061–75.
24. Fehon RG., McClatchey AI., Bretscher A. (2010). Organizing the cell cortex: the role of ERM proteins. Nat Rev Mol Cell Biol.:11(4):276–87.
25. Canals D., Jenkins RW., Roddy P., Hernandez-Corbacho MJ., Obeid LM., Hannun YA. (2010). Differential effects of ceramide and sphingosine 1-phosphate on ERM phosphorylation: probing sphingolipid signaling at the outer plasma membrane. J Biol Chem. 285(42):32476–85.

26. Nakamura N., Oshiro N., Fukata Y., Amano M., Fukata M., Kuroda S., Matsuura Y., Leung T., Lim L., Kaibuchi K. (2000). Phosphorylation of ERM proteins at filopodia induced by Cdc42. Genes Cells. 5(7):571–81.
27. Fievet BT., Gautreau A., Roy C., Del Maestro L., Mangeat P., Louvard D., Arpin M. (2004). Phosphoinositide binding and phosphorylation act sequentially in the activation mechanism of ezrin. J Cell Biol. 164(5):653–9.
28. Sauvanet C., Jessica Wayt J., Pelaseyed T., Bretscher A. (2015). Structure, Regulation, and Functional Diversity of Microvilli on the Apical Domain of Epithelial Cells. Article *in* Annual Review of Cell and Developmental Biology: DOI: 10.1146/annurev-cellbio:100814-125234.
29. Bretscher A. (1999). Regulation of cortical structure by the ezrin-radixin-moesin protein family. Curr Opin Cell Biol. 11(1):109–16.

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