

In conclusion, we suggest that cochlin could cross-link type II collagen fibers in the semicircular canal and is responsible for the structural integrity of the vestibule in order to withstand the stress associated with fluid movement. Further studies are needed to determine the nature of interaction between cochlin and type II collagen.

### Acknowledgements

This work was supported by the Acute Profound Deafness Research Committee of the Ministry of Health, Labor and Welfare, Tokyo, Japan. We thank Dr. Kuni H. Iwasa for their helpful criticisms of the manuscript.

### References

- [1] S.K. Bhattacharya, S.P. Annangudi, R.G. Salomon, R.W. Kuchtey, N.S. Peachey, J.W. Crabb, Cochlin deposits in the trabecular meshwork of the glaucomatous DBA/2J mouse, *Exp. Eye Res.* 80 (2005) 741–744.
- [2] S.K. Bhattacharya, E.J. Rockwood, S.D. Smith, V.L. Bonilha, J.S. Crabb, R.W. Kuchtey, N.G. Robertson, N.S. Peachey, C.C. Morton, J.W. Crabb, Proteomics reveal Cochlin deposits associated with glaucomatous trabecular meshwork, *J. Biol. Chem.* 280 (2005) 6080–6084.
- [3] S.J. Bom, M.H. Kemperman, Y.J. de Kok, P.L. Huygen, W.I. Verhagen, F.P. Cremers, C.W. Cremers, Progressive cochleovestibular impairment caused by a point mutation in the *COCH* gene at DFNA9, *Laryngoscope* 109 (1999) 1525–1530.
- [4] A. Colombatti, P. Bonaldo, The superfamily of proteins with von Willebrand factor type A-like domains: one theme common to components of extracellular matrix, homeostasis, cellular adhesion, and defense mechanisms, *Blood* 77 (1991) 2305–2315.
- [5] A. Colombatti, P. Bonaldo, R. Doliana, Type A modules: interacting domains found in several non-fibrillar collagens and in other extracellular matrix proteins, *Matrix* 13 (1993) 297–306.
- [6] Y.J. de Kok, S.J. Bom, T.M. Brunt, M.H. Kemperman, E. van Beusekom, S.D. van der Velde-Visser, N.G. Robertson, C.C. Morton, P.L. Huygen, W.I. Verhagen, H.G. Brunner, C.W. Cremers, F.P. Cremers, A Pro51Ser mutation in the *COCH* gene is associated with late onset autosomal dominant progressive sensorineural hearing loss with vestibular defects, *Hum. Mol. Genet.* 8 (1999) 361–366.
- [7] E. Fransen, M. Verstreken, W.I. Verhagen, F.L. Wuyts, P.L. Huygen, P. D'Haese, N.G. Robertson, C.C. Morton, W.T. McGuirt, R.J. Smith, F. Declau, P.H. Van de Heyning, G. Van Camp, High prevalence of symptoms of Meniere's disease in three families with a mutation in the *COCH* gene, *Hum. Mol. Genet.* 8 (1999) 1425–1429.
- [8] R. Grabski, T. Szul, T. Sasak, R. Timpl, R. Mayne, B. Hicks, E. Sztul, Mutations in *COCH* that result in non-syndromic autosomal dominant deafness (DFNA9) affect matrix deposition of cochlin, *Hum. Genet.* 113 (2003) 406–416.
- [9] T.E. Hardingham, A.J. Fosang, Proteoglycans: many forms and many functions, *FASEB J.* 6 (1992) 861–870.
- [10] T. Ikezono, S. Shindo, M. Ishizaki, L. Li, S. Tomiyama, M. Takumida, R. Pawankar, A. Watanabe, A. Saito, T. Yagi, Expression of cochlin in the vestibular organ of rats, *ORL J. Otorhinolaryngol. Relat. Spec.* 67 (2005) 252–258.
- [11] T. Ikezono, S. Shindo, L. Li, A. Omori, S. Ichinose, A. Watanabe, T. Kobayashi, R. Pawankar, T. Yagi, Identification of novel Cochlin isoform in the perilymph: insights to Cochlin function and the pathogenesis of DFNA9, *Biochem. Biophys. Res. Commun.* 314 (2004) 440–446.
- [12] H. Kaname, T. Yoshihara, T. Ishii, H. Tatsuoka, T. Chiba, Ultrastructural and immunocytochemical study of the subepithelial fiber component of the guinea pig inner ear, *J. Electron. Microsc.* 43 (1994) 394–397.
- [13] U. Khetarpal, Autosomal dominant sensorineural hearing loss: further temporal bone findings, *Arch. Otolaryngol. Head Neck Surg.* 119 (1993) 106–108.
- [14] U. Khetarpal, DFNA9 is a progressive audiovestibular dysfunction with a microfibrillar deposit in the inner ear, *Laryngoscope* 110 (2000) 1379–1384.
- [15] U. Khetarpal, H.F. Schuknecht, R.R. Gacek, L.B. Holmes, Autosomal dominant sensorineural hearing loss: pedigree, audiologic findings and temporal bone findings in tow kindreds, *Arch. Otolaryngol. Head Neck Surg.* 117 (1991) 1032–1042.
- [16] E.N. Manolis, N. Yandavi, J.B. Nadol Jr., R.D. Eavey, M. McKenna, S. Rosenbaum, U. Khetarpal, C. Halpin, S.N. Merchant, G.M. Duyk, C. MacRae, C.E. Seidman, J.G. Seidman, A gene for non-syndromic autosomal dominant progressive postlingual sensorineural hearing loss maps to chromosome 14q12–13, *Hum. Mol. Genet.* 5 (1996) 1047–1050.
- [17] N.G. Robertson, C.W. Cremers, P.L. Huygen, T. Ikezono, B. Krastins, H. Kremer, S.F. Kuo, M.C. Liberman, S.N. Merchant, C.E. Miller, J.B. Nadol Jr., D.A. Sarracino, W.I. Verhagen, C.C. Morton, Cochlin immunostaining of inner ear pathologic deposits and proteomic analysis in DFNA9 deafness and vestibular dysfunction, *Hum. Mol. Genet.* 15 (2006) 1071–1085.
- [18] N.G. Robertson, S.A. Hamaker, V. Patriub, J.C. Aster, C.C. Morton, Subcellular localization, secretion, and post-translational processing of normal cochlin, and of mutants causing the sensorineural deafness and vestibular disorder, DFNA9, *J. Med. Genet.* 40 (2003) 479–486.
- [19] N.G. Robertson, L. Lu, S. Heller, S.N. Merchant, R.D. Eavey, M. McKenna, J.B. Nadol Jr., R.T. Miyamoto, F.H. Linthicum Jr., J.F. Lubianca Neto, A.J. Hudspeth, C.E. Seidman, C.C. Morton, J.G. Seidman, Mutations in a novel cochlear gene cause DFNA9, a human nonsyndromic deafness with vestibular dysfunction, *Nat. Genet.* 20 (1998) 299–303.
- [20] N.G. Robertson, B.L. Resendes, J.S. Lin, C. Lee, J.C. Aster, J.C. Adams, C.C. Morton, Inner ear localization of mRNA and protein products of *COCH*, mutated in the sensorineural deafness and vestibular disorder, DFNA9, *Hum. Mol. Genet.* 10 (2001) 2493–2500.
- [21] N.B. Slepecky, J.E. Savage, T.J. Yoo, Type II, IX and V collagen in the inner ear, *Acta Otolaryngol.* 112 (1992) 611–617.
- [22] G. Van Camp, R.J.H. Smith, Hereditary hearing loss homepage, URL: <http://webh01.ua.ac.be/hhh/>.
- [23] W.I. Verhagen, P.L. Huygen, W. Bles, A new autosomal dominant syndrome of idiopathic progressive vestibule-cochlear dysfunction with middle-age onset, *Acta Otolaryngol.* 112 (1992) 899–906.
- [24] W.I. Verhagen, P.L. Huygen, E.J. Theunissen, E.M. Joosten, Hereditary vestibule-cochlear dysfunction and vascular disorders, *J. Neurol. Sci.* 92 (1989) 55–63.
- [25] J.F. Willott, L.S. Bross, S. McFadden, Ameliorative effects of exposing DBA/2J mice to an augmented acoustic environment on histological changes in the cochlea and anteroventral cochlear nucleus, *J. Assoc. Res. Otolaryngol.* 6 (2005) 234–243.

