

Review

# The potential of miR-183 family expression in inner ear for regeneration, treatment, diagnosis and prognosis of hearing loss

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## Abstract

miRNA-183 family, in normal biology, is expressed in a harmonious and stable manner in the neurosensory organs and cells. Studies have also shown that miRNA-183 family, in different pathways, affects the neurosensory development, maintenance, survival and function. In addition, it has potential neuroprotective effects in response to neurosensory destructive stimulations. miRNA-96 mutation causes hereditary deafness in humans and mice, and therefore affects the inner ear activity and its maintenance. Certain roles have been identified for miR-96 in the maintenance and function of the inner ear. The comparison of the target genes of family-183 in transcriptomes of newborn and adult hair cells shows that hundreds of target genes in this family may affect development and maintenance of the ears. Identifying the genes that are regulated by miRNA-183 family provides researchers with important information about the complex development and environmental regulation of the inner ear, and can offer new approaches to the maintenance and regeneration of hair cells and auditory nerve.

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**Keywords:** miRNA-183 family; Hearing loss; miRNA; Inner ear; Hair cell

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## 1. Introduction

### 1.1. miRNAs

miRNAs are a group of noncoding small RNAs with 21–23 nucleotides in length, which have specific interactions with their special mRNAs. They degrade the mRNA and inhibit the translation. miRNA genes comprise about 1% of the genome of different species, and each of them has hundreds of target genes. Over 2500 miRNAs have been identified in the human genome that regulate 30% of the proteins' coding genes. These small regulatory molecules were first identified in 1993, are found mainly in the chromosomal fragile sites, and in various diseases, are prone to deletion, addition, chromosomal translocation, and epigenetic changes (Bartel, 2004; Bushati and Cohen, 2007).

### 1.2. miRNA biogenesis

miRNA in the nucleus transcribes the gene and produces pri-miRNA and subsequently a precursor named pre-miRNA under the nuclear RNaseIII (endonuclease) enzyme called Drosha. Afterwards, pre-miRNA is transported to the cytoplasm by the protein Exportin 5. The molecule is cleaved by another enzyme called Dicer in the cytoplasm and develops a 21- to 23-nucleotide, double-stranded sequence. One of the strands is decomposed and the other strand is localized in the silencer complex (RNA-RISC) (Fig. 1). This activates the complex targets of the intended mRNA, binds to the mRNA 3'UTR end, and exerts its inhibitory effect. Through inhibiting protein translation or decomposing the target mRNA, miRNA

exerts its effects in regulating gene expression (Bartel, 2004; Bushati and Cohen, 2007; Brennecke et al., 2005).

## 2. miRNA-183 family

The family miRNA-183 consists of three miRs: 183, 96 and 182. These miRNAs are concurrently expressed during development and are required for proper development of the sensory organs (Dambal et al., 2015). miR-96 was the first identified human miRNA of the cluster (Mourelatos et al., 2002), and miR-182 and miR-183 were identified one year later (Lim et al., 2003; Lagos-Quintana et al., 2003; Aravin et al., 2003). The three miRNAs are located adjacent to each other, with about 4 kb-span between miR-96 and miR-182, and transcribed as a long primary transcript. Then, they are processed into three individual precursor miRNAs (Jalvy-Delvaile et al., 2012). The sequence homology of miRs-183, -96 and -182 and the conservation of their genomic organization as a cluster in bilaterian organisms represent an evolutionary benefit. In humans, the cluster is located on chromosome 7, with a 4.2 kb intergenic region between miRs-96 and -182. However, the murine miR-183 cluster is located on chromosome 6 with 3.6 kb between miRs-96 and -182 (Dambal et al., 2015). Mutation in miRNA-96 causes deafness in the locus of DFNA50. However, miRNA-96 is one of the members of miRNA-183 family, and miRNA-183, 182, 96 are all derived from a common primary transcript (Weston et al., 2006; Xu et al., 2007; Saini et al., 2008). In addition, miRNA-183 family members have a highly similar sequence (Mahmoodian sani et al., 2016) (Fig. 2). Interestingly, evolutionary variance from U to A in miRNA-183 causes miRNA-

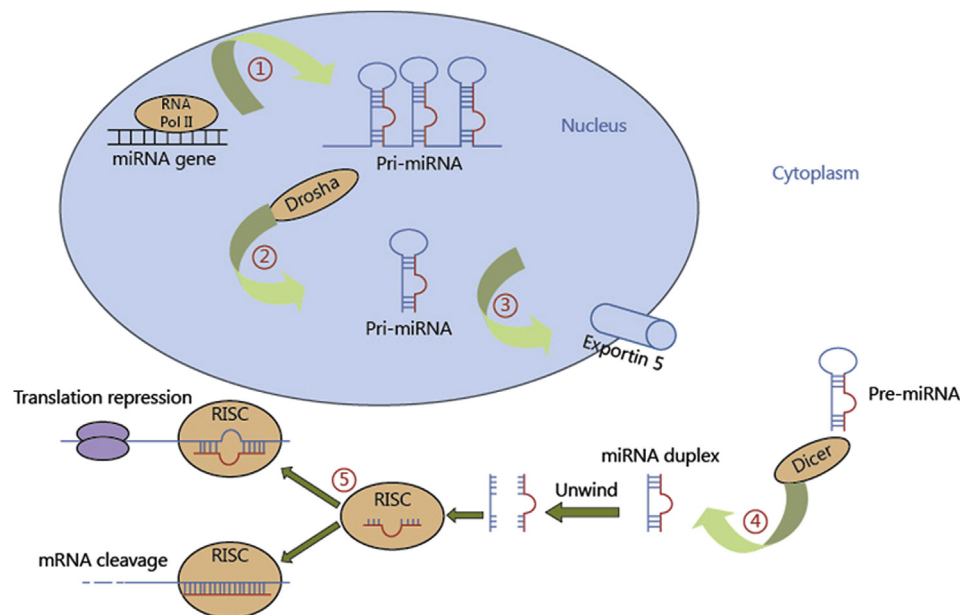


Fig. 1. miRNA biogenesis is a multistep process 1- miRNA genes are transcribed by RNA polymerase II in the nucleus 2- the resulting primary transcript is cleaved by Drosha to produce pre-miRNA 3- exportin-5 mediated transport pre-miRNA to the cytoplasm 4- pre-miRNA undergoes its final processing step, which consists of Dicer-dependent cleavage just below the stem loop to produce a miRNA duplex 5- The mature miRNA strand is subsequently incorporated into the RNA-induced silencing complex (RISC) where it directly binds to a member of the AGO protein family (Bushati and Cohen, 2007; Mahmoodian-sani et al., 2017).

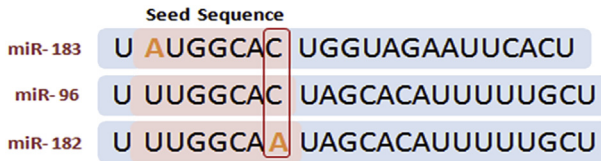


Fig. 2. The mature miR-183, -96 and -182 have approximately identical seed sequences, and a single base difference in the seed sequence of miR-96 and -182 is essential for its mRNA target specificity.

183 to have more widely different target genes, which represents a more unique activity of this miR (Fig. 2) (Saini et al., 2008; Pierce et al., 2008).

### 2.1. Mutations in miR-96 and deafness

Locus DFNA50 in humans on chromosome 7q32 is a new locus of age-dependent non-syndromic dominant autosomal deafness. This site is located on chromosome 6 in mice (Lewis et al., 2009; Modamio-Høybjør et al., 2004). According to reports, three single point mutations in the regions of miR-96 gene were identified in humans and mice (Lewis et al., 2009; Soldà et al., 2011). These studies for the first time showed that miRNA mutation caused a genetic disorder. Study of cell culture showed an 80% reduction in the processing of mutant miR-96 and disorder in identifying target genes, i. e. reducing the target genes and gaining new target genes (Mencía et al., 2009).

However, mutation of miR-96 in *Diminuendo* mice does not affect miRNA processing greatly, but this mutation causes disorder in the target detection. In addition, disorder in the genes, that were not the direct target of mutant miR-96 or miR-96, were detected; however, they are important for the maintenance and function of the inner ear (Lewis et al., 2009). Overall, the data suggest that the mutation in miR-96 results in both loss-of-function (LOF) and gain-of-function (GOF). A mutation was identified in pre-miR-96 in humans that causes progressive hereditary deafness. This mutation causes an 85% reduction in the processing of miR-96, while in the processed

transcript, miR-96 sequence and mRNA target were correct (Soldà et al., 2011); consequently, two families with mutations in miR-96 sequence caused a deeper hearing loss at a young age than the mutations in the pre-miR-96 (Fig. 3) (Soldà et al., 2011; Mencía et al., 2009).

### 2.2. Expression patterns of miRNA-183 family

Homologues of miRNA-183 family members are present in invertebrates of miR-263a, miR-263b and miR-228 which were separated 600 million years ago (Pierce et al., 2008; Sempere et al., 2006). miRNA 183 family members are highly conserved in neurosensory organs and cells in both deuterostomes and protostomes. The members of miRNA-183 family were identified in the inner ear hair cells and sensory neurons in mice (Weston et al., 2006; Lewis et al., 2009; Soukup et al., 2009; Friedman et al., 2009; Weston et al., 2011), and miR-263 family members were detected in Johnston's organs of drosophila and haltere (Pierce et al., 2008), which highlights the role of this family in the development and maintenance of neurosensory system. Similarly, this family was identified in the neurosensory cells of the mice's eyes (Xu et al., 2007; Loscher et al., 2007; Lumayag et al., 2013) and retina of zebrafish (Wienholds et al., 2005). miRNA-183 family expression increases with radiation or is affected by light (Krol et al., 2010), and is associated with circadian rhythm in *Drosophila* (Yang et al., 2008) and mouse (Xu et al., 2007). In addition, this family was identified in the skull and spinal ganglion in mice (Aldrich et al., 2009; Li et al., 2010), chick (Darnell et al., 2006) and zebrafish (Wienholds et al., 2005). In addition, this family was identified in the neuromasts of zebrafish (Wienholds et al., 2005) as well as in the neuromasts and electroreceptors of Salamander skin; eventually, the family was detected in the sensory organ of sea urchin (Pierce et al., 2008). The expression of the family in neurosensory organs and cells in the majority of families (phyla) shows that this family is vital for the formation and operation of the neurosensory organs.

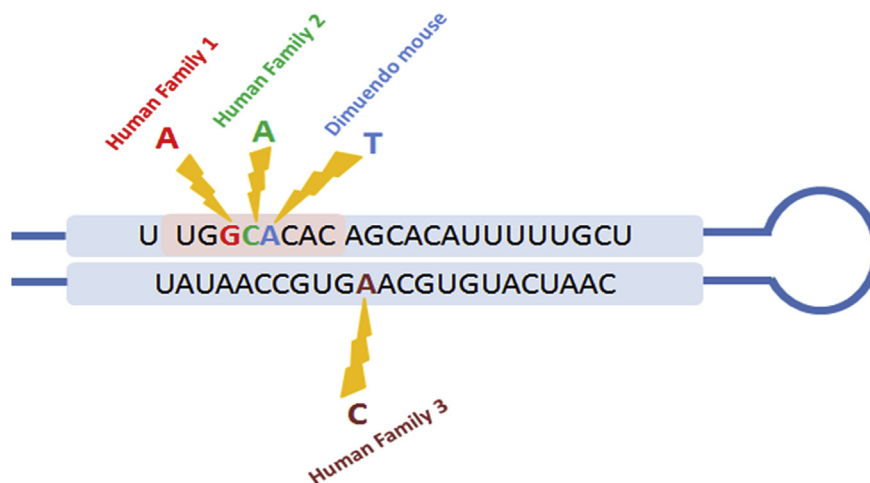


Fig. 3. miR-96 precursor. Mutations in locus DFNA50, miR-96 gene seed sequence or precursor hairpin sequence in humans and mice cause deafness.

### 2.3. Experimental models of miR-183 family activity

Study of experimental models shows different roles of miR-183 family in the development and activities. In the inner ear of Zebrafish, knocking down the family decreases the number of hair cells; therefore, the family is essential for hair cell formation. In addition, increased expression of this family causes production of ectopic hair cells. It has been demonstrated that miR-183 family suffices to induce the formation of hair cells in Zebrafish. In addition, increased expression of miR-182 can compensate the miR-96 knockdown to some extent, which implies overlapping of family activities (Li et al., 2010). In mice, mutations in miR-96 result in circling behaviors, atria activity disorder, defects in synaptogenesis, growth delay, stereocilia disorder in hair cells, and eventually hair cells death and profound deafness (Lewis et al., 2009; Kuhn et al., 2011). Similarly, miR-183 was inactivated in mice with gene-trap technique, and mice showed circling 26 behaviors and imbalance in walking with deep atrial disorder which imply the inner ear's defect. Moreover, knocking down miR-96 in *Xenopus* causes serious eye defect and a defect in the cartilage of the skull (Gessert et al., 2010). In addition, removing miR-96 homologue in invertebrates (miR-263 and miR263-b) in *Drosophila* caused reduction in mechanosensory bristles on the head, chest and inner ommatidia in the eye. Therefore, miR-263 and miR263-b have an important role in the maintenance and pattern of the neurosensory cells. In mice where *Dgcr8* is removed (knocked out) in cone photoreceptors, increased expression of miR-183 and -182 suffices to save and restore normal phenotype, which compensates for the deficiency (Busskamp et al., 2014). However, no retinal phenotype was found in humans or mice with a mutation in the miR-96 (Lewis et al., 2009; Soldà et al., 2011; Mencía et al., 2009). This phenotype was not found in mice where miR-182 was knocked out (Jin et al., 2009). Interestingly, a sponge transgenic mouse where miR-183 family members were removed was placed under the control of an opsin promoter which produced a sequence complementary to miR-183 family members. In this kind of mouse, morphological and functional changes in the eye were not observed after six months. In addition, when they were exposed to 10000lux for 30 min, no change occurred, but the morphological and functional changes were observed in the mouse with the knockout of this family; the mice were found to be vulnerable to light. Similarly, a gene-trap model which inserts a retroviral structure into the upstream splicing acceptor of miR-183 that effectively knocks out this miRNA, leads to synaptic, degeneration, and retinal activity defects. When they are exposed to light, the symptoms are aggravated. The physiological defect in the eye can be detected before the tissue defect (Lumayag et al., 2013). Overall, miR-183 family models in the neurosensory tissues exhibits the importance of the family to protect cells against neural stimuli, with additional roles in development, patterns and synaptogenesis.

The loss of family members results in stereocilia defect in the hair cell, which confirms that each member of the family is required for the hair cell maintenance. In the analysis of

transcriptome of hair cells in adults and newborns, hundreds of target genes were predicted for this family; these genes in hair cells are synchronous with miR-183 co-localized family. This family is highly expressed during hair cell development, and has a reverse slope in mature hair cells with functional activity (Weston et al., 2011). It seems that the dose of this family has a key role in hair cell maintenance and function, and therefore normal hair cell survival patterns were associated with increased expression of family-183, which reflects the potential protective impact that may be helpful for hair cell survival. Since these families are expressed in the neurosensory organs and cells, dysfunction of the family can lead to neurosensory impairment in vision, smell, and touch. These findings along with the controlled studies on the knockdown model of this family with sponge-transgenic technique (Zhu et al., 2011), and knocking out the family with gene-trap technique (Lumayag et al., 2013) showed that the removal of the family could lead to vulnerability to neurosensory stimuli. As a result, defect in synaptogenesis was observed in the knocked-out mice of miR-183 family with gene-trap technique (Lumayag et al., 2013) and the mice with mutant miR-96 (Kuhn et al., 2011). The defects in synaptogenesis may cause hearing loss in knockout models of the family. *Taok1*, a target of miRNA-183, inhibition of miR-183 with morpholino antisense oligos in cochlear organotypic cultures revealed a negative correlation between the expression levels of miR-183 and *Taok1*, suggesting the presence of a miR-183/*Taok1* target pair. The miR-183/*Taok1* target pair is likely to play a role in degenerative process of the cochlea following acoustic overstimulation (Patel et al., 2013).

### 3. Discussion

Aging and exposure to noise are two of the most common causes of hearing loss (Lewis et al., 2009), and if accompanied by genetic defects, they contribute to sensitivity as well (White et al., 2009). Increased life expectancy (Mao et al., 2013) and exposure to environmental noise make a large population at risk of neurosensory hearing damage and dysfunction (Serra et al., 2014). Neurosensory deafness is caused by impairment or loss of mechanosensory hair cells or spiral ganglion neurons (SGNs). In addition, beyond the inner ear, these deficits appear to occur in the central nervous system in the auditory pathway (Tremblay, 2015). For the development of effective therapeutic strategies to treat damaged hair cells, the important step is to identify the regulatory mechanisms involved in hair cell damage (Li et al., 2010). Recent studies suggest that a common mechanism is involved in the development and reprogramming of cells in the inner ear of a large number of vertebrates. Currently, hearing aids can help the majority of the hearing impaired adult population (Woods et al., 2015; Ahmadi et al., 2017). In addition, cochlear implant provides a function by bypassing the hair cell function, which is required for SGNs (Zeng et al., 2008). In addition, the auditory brainstem implants in the cochlear nucleus can bypass the function of the inner ear and SGN and provide modest improvements in speech understanding and



recognition (McCreery et al., 2013). However, none of these hearing aids are able to restore normal and critical hearing range. Although birds and fish can regenerate the hair cells, mammals lack this capacity of regeneration (Burns and Corwin, 2013); however, in a temporary, limited and deficient way, the potential of the hair cells spontaneous generation exists in the cochlea of the neonatal mouse following the hair cells genetic defect (Cox et al., 2014).

### 3.1. miRNA-183 family and molecular therapies have the potential to regenerate hair cell and auditory nerves

Current strategies of the molecular therapies for deafness include gene therapy, hair cell reproduction, and SGNs. For successful regeneration, the production of the complex anatomy of the hair cells, supporting cell (SC) and SGNs are required to achieve operational results. In addition, the SCs are converted to hair cells through transdifferentiation and inhibition of Notch1 in vivo (Maass et al., 2015; Li et al., 2015). Inhibition of Notch pathway in adult cochlea after auditory trauma leads to a relative improvement, which is attributed to transdifferentiation of the SCs to the hair cells (Mizutari et al., 2013). In addition, ectopic expression of Ntf3 in the SC following the auditory trauma repairs synapse (Wan et al., 2014). Exogenous Ntf3 shows that it has the potential to increase the survival of SGN (Landry et al., 2011) and can improve the cochlear implant ability. Overall, access to new treatments and facilitation of hair cells repair or regeneration seem promising. In addition, combined gene therapy has achieved certain successes in cell reprogramming (Kim et al., 2008; Park et al., 2008; Liao et al., 2008), and gene transfer has been replaced with small molecule therapies (Hou et al., 2013; Fukuta et al., 2014). Meanwhile, the regulatory roles of the miRNAs including miRNA-183, and some genes such as ATOH1, POU4F3, and GFII1 have been confirmed in the differentiation of stem cells from hair cells and protecting hair cells during the studies of ear development stages and stem cell research. These genes have potential to help to restore hearing (Chiang et al., 2013). The need for miRNA has been identified in the evolution of ear after blocking miRNAs biosynthesis by genetic engineering strategies during the early stages of ear development and hair cells differentiation. Since hundreds of transcripts are regulated by miRNAs simultaneously, miRNAs can be used as potential therapeutic agents for the repair or regeneration of the hair cells in animal models (Wang et al., 2010). Since a large part of the human transcriptome is regulated by multiple miRNAs, and because of the potential impact of these molecules on gene expression, they can be used for the diagnosis, prognosis and development of drugs. Despite advances in cochlear implants for the treatment of sensorineural hearing loss, hearing improvement is moderate in treated patients. A combination of molecular and stem cells is a viable alternative to cochlear implants which may realize the promise to cure deafness. Transdifferentiation of SC cells into hair cells, which does not happen under natural conditions, may be possible with the help of miRNA, especially miR-183 family in adult mammals.

### 3.2. Therapeutic potential of miR-183 family

Transcriptomic analysis may also help to identify the affected pathways which can serve as new therapeutic mechanisms to protect or restore inner ear neurosensory activity. miRNAs have the potential to be used in the treatment of deafness. As a result, the search for miRNAs as a target to treat deafness can help to offer a promising approach. Molecular therapies are being investigated in clinical trials with anti-miRNA LNA (miravirsin) and mimic miRNA (MRX34), but most of miRNA therapeutics are still in pre-clinical phase (Schmidt, 2014). Identification of miR-183 family target genes and the affected pathways is expected to provide important information about the development and maintenance of the inner ear, and potential pharmaceutical targets to accelerate and develop the protection of the sensory cells.

### 3.3. Potential of miRNA-183 family as a diagnostic and prognostic biomarker

Recently, miRNAs have been seriously considered to serve biomarkers in blood circulation due to their frequency and strength in the serum and plasma. Much more research is needed to prove the concurrency between changes in miRNA profiles and high noise in order to use miRNAs as biomarkers to detect sound-induced hearing loss (Mencía et al., 2009; Sivakumaran et al., 2006). In the recent years, serious efforts have been made to introduce an appropriate molecular marker that can predict the diverse nature of deafness and be used as a diagnostic and prognostic tool alongside other pathological-clinical methods. In addition, the miRNAs have certain disorders in deafness and play a vital role in the development and progression of deafness. Given the fact that most common methods for screening cannot detect deafness at early stages, identification of miRNAs that are released into the bloodstream in the onset and progression of deafness is considered a key approach to early detection of deafness. Therefore, in the near future, by measuring the levels of the miRNAs in the serum samples of deaf people, these molecules can be used as molecular markers for the diagnosis and prognosis of different types of deafness such as deafness due to age-related hearing loss (ARHL) and noise-induced hearing loss (NIHL), Inflammation, cholesteatoma, and Schwannomas.

## 4. Conclusion

miRNAs are a large family of small genes that cause small changes in the expression of the target genes to cause a noticeable impact on the development, specification, maintenance, and survival. The major challenge in the field of miRNAs is to detect the specific biological roles for each miRNA. With regard to the potential of the miRNAs for therapeutic uses, particularly in terms to the possibility of safe and effective targeting of the cells, many questions still remain unanswered in this field, and their roles in abnormal biology and pathology have not yet been completely elucidated. The various effects observed in abnormal biology imply that we

should take into account the therapeutic effects of this family more seriously and the target cells to avoid associated side effects. A more in-depth understanding of the miRNA-183 family in both normal and abnormal biological conditions is required for access to activities of miRNA-183 family for the diagnosis and regeneration potential. Regulation of miRNA by miRNAs concentration, the concentration of the target genes, affinity of binding and the effect on gene expression are complex issues. In addition, it is difficult to determine what combination or subset of genes is responsible for producing the phenotype. In knockout models of miRNA -183 family, miRNA dose appears to be essential for the maintenance and cellular activity; increasing the severity of the disease phenotype reduces the expression and dose of this family. Two key concepts were drawn from the expression of miRNA-183 family in normal and abnormal biology of the neurosensory system: 1- expression and level of expression of miRNA-183 family is essential for the survival and vital activity of neurosensory cells, and 2- misexpression can have profound effects on the development and maintenance of neurosensory organs and cells. Thus, further improvements are essential to evaluate the sensitivity and accuracy of the specific biological roles of miRNA-183 family.

## References

- Ahmadi, H., Daramadi, P.S., Asadi-Samani, M., Sani, M.R.M., 2017. Effectiveness of group training of assertiveness on social anxiety among deaf and hard of hearing adolescents. *Int. Tinnitus J.* 21 (1), 13–19.
- Aldrich, B.T., Frakes, E.P., Kasuya, J., Hammond, D.L., Kitamoto, T., 2009. Changes in expression of sensory organ-specific microRNAs in rat dorsal root ganglia in association with mechanical hypersensitivity induced by spinal nerve ligation. *Neuroscience* 164 (2), 711–723.
- Aravin, A.A., Lagos-Quintana, M., Yalcin, A., Zavolan, M., Marks, D., Snyder, B., et al., 2003. The small RNA profile during *Drosophila melanogaster* development. *Dev. Cell* 5 (2), 337–350.
- Bartel, D.P., 2004. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116 (2), 281–297.
- Brennecke, J., Stark, A., Russell, R.B., Cohen, S.M., 2005. Principles of microRNA–target recognition. *PLoS Biol.* 3 (3), e85.
- Burns, J.C., Corwin, J.T., 2013. A historical to present-day account of efforts to answer the question: “what puts the brakes on mammalian hair cell regeneration?”. *Hear. Res.* 297, 52–67.
- Bushati, N., Cohen, S.M., 2007. microRNA functions. *Annu. Rev. Cell Dev. Biol.* 23, 175–205.
- Busskamp, V., Krol, J., Nelidova, D., Daum, J., Szikra, T., Tsuda, B., et al., 2014. miRNAs 182 and 183 are necessary to maintain adult cone photoreceptor outer segments and visual function. *Neuron* 83 (3), 586–600.
- Chiang, D.Y., Cuthbertson, D.W., Ruiz, F.R., Li, N., Pereira, F.A., 2013. A coregulatory network of NR2F1 and microRNA-140. *PLoS One* 8 (12), e83358.
- Cox, B.C., Chai, R., Lenoir, A., Liu, Z., Zhang, L., Nguyen, D.-H., et al., 2014. Spontaneous hair cell regeneration in the neonatal mouse cochlea in vivo. *Development* 141 (4), 816–829.
- Dambal, S., Shah, M., Mihelich, B., Nonn, L., 2015. The microRNA-183 cluster: the family that plays together stays together. *Nucleic acids Res.* 43 (15), 7173–7188.
- Darnell, D.K., Kaur, S., Stanislaw, S., Konieczka, J.K., Yatskevych, T.A., Antin, P.B., 2006. MicroRNA expression during chick embryo development. *Dev. Dyn.* 235 (11), 3156–3165.
- Friedman, L.M., Dror, A.A., Mor, E., Tenne, T., Toren, G., Satoh, T., et al., 2009. MicroRNAs are essential for development and function of inner ear hair cells in vertebrates. *Proc. Natl. Acad. Sci.* 106 (19), 7915–7920.
- Fukuta, M., Nakai, Y., Kirino, K., Nakagawa, M., Sekiguchi, K., Nagata, S., et al., 2014. Derivation of mesenchymal stromal cells from pluripotent stem cells through a neural crest lineage using small molecule compounds with defined media. *PLoS One* 9 (12), e112291.
- Gessert, S., Bugner, V., Tecza, A., Pinker, M., Kühl, M., 2010. FMR1/FXR1 and the miRNA pathway are required for eye and neural crest development. *Dev. Biol.* 341 (1), 222–235.
- Hou, P., Li, Y., Zhang, X., Liu, C., Guan, J., Li, H., et al., 2013. Pluripotent stem cells induced from mouse somatic cells by small-molecule compounds. *Science* 341 (6146), 651–654.
- Jalvy-Delvaile, S., Maurel, M., Majo, V., Pierre, N., Chabas, S., Combe, C., et al., 2012. Molecular basis of differential target regulation by miR-96 and miR-182: the Glypican-3 as a model. *Nucleic acids Res.* 40 (3), 1356–1365.
- Jin, Z.-B., Hirokawa, G., Gui, L., Takahashi, R., Osakada, F., Hiura, Y., et al., 2009. Targeted deletion of miR-182, an abundant retinal microRNA.
- Kim, J.B., Zaehres, H., Wu, G., Gentile, L., Ko, K., Sebastiano, V., et al., 2008. Pluripotent stem cells induced from adult neural stem cells by reprogramming with two factors. *Nature* 454 (7204), 646–650.
- Krol, J., Busskamp, V., Markiewicz, I., Stadler, M.B., Ribi, S., Richter, J., et al., 2010. Characterizing light-regulated retinal microRNAs reveals rapid turnover as a common property of neuronal microRNAs. *Cell* 141 (4), 618–631.
- Kuhn, S., Johnson, S.L., Furness, D.N., Chen, J., Ingham, N., Hilton, J.M., et al., 2011. miR-96 regulates the progression of differentiation in mammalian cochlear inner and outer hair cells. *Proc. Natl. Acad. Sci.* 108 (6), 2355–2360.
- Lagos-Quintana, M., Rauhut, R., Meyer, J., Borkhardt, A., Tuschl, T., 2003. New microRNAs from mouse and human. *Rna* 9 (2), 175–179.
- Landry, T.G., Wise, A.K., Fallon, J.B., Shepherd, R.K., 2011. Spiral ganglion neuron survival and function in the deafened cochlea following chronic neurotrophic treatment. *Hear. Res.* 282 (1), 303–313.
- Lewis, M.A., Quint, E., Glazier, A.M., Fuchs, H., De Angelis, M.H., Langford, C., et al., 2009. An ENU-induced mutation of miR-96 associated with progressive hearing loss in mice. *Nat. Genet.* 41 (5), 614–618.
- Li, H., Kloosterman, W., Fekete, D.M., 2010. MicroRNA-183 family members regulate sensorineural fates in the inner ear. *J. Neurosci.* 30 (9), 3254–3263.
- Li, W., Wu, J., Yang, J., Sun, S., Chai, R., Chen, Z.-Y., et al., 2015. Notch inhibition induces mitotically generated hair cells in mammalian cochlea via activating the Wnt pathway. *Proc. Natl. Acad. Sci.* 112 (1), 166–171.
- Liao, J., Wu, Z., Wang, Y., Cheng, L., Cui, C., Gao, Y., et al., 2008. Enhanced efficiency of generating induced pluripotent stem (iPS) cells from human somatic cells by a combination of six transcription factors. *Cell Res.* 18 (5), 600.
- Lim, L.P., Lau, N.C., Weinstein, E.G., Abdelhakim, A., Yekta, S., Rhoades, M.W., et al., 2003. The microRNAs of *Caenorhabditis elegans*. *Genes Dev.* 17 (8), 991–1008.
- Loscher, C.J., Hokamp, K., Kenna, P.F., Ivens, A.C., Humphries, P., Palfi, A., et al., 2007. Altered retinal microRNA expression profile in a mouse model of retinitis pigmentosa. *Genome Biol.* 8 (11), 1.
- Lumayag, S., Haldin, C.E., Corbett, N.J., Wahlin, K.J., Cowan, C., Turturro, S., et al., 2013. Inactivation of the microRNA-183/96/182 cluster results in syndromic retinal degeneration. *Proc. Natl. Acad. Sci.* 110 (6), E507–E516.
- Maass, J.C., Gu, R., Basch, M.L., Waldhaus, J., Lopez, E.M., Xia, A., et al., 2015. Changes in the regulation of the Notch signaling pathway are temporally correlated with regenerative failure in the mouse cochlea. *Front. Cell. Neurosci.* 9, 110.
- Mahmoodian sani, M.R., Hashemzadeh-Chaleshtori, M., Mehri-Ghahfarrokhi, A., Ghasemi-Dehkordi, P., Saidijam, M., Jami, M.-S., 2016. MicroRNA-183 family in inner ear: hair cell development and deafness. *J. Audiol. Otol.* 20 (3), 131–138.
- Mahmoodian-sani, M.-R., Mehri-Ghahfarrokhi, A., Ahmadinejad, F., Hashemzadeh-Chaleshtori, M., Saidijam, M., Jami, M.-S., 2017. MicroRNAs: effective elements in ear-related diseases and hearing loss. *Eur. Archives Oto-Rhino-Laryngology* 1–8.
- Mao, Z., Zhao, L., Pu, L., Wang, M., Zhang, Q., He, D.Z., 2013. How well can centenarians hear? *PLoS One* 8 (6), e65565.

- McCreery, D., Han, M., Pikov, V., Yadav, K., Pannu, S., 2013. Encoding of the amplitude modulation of pulsatile electrical stimulation in the feline cochlear nucleus by neurons in the inferior colliculus; effects of stimulus pulse rate. *J. Neural Eng.* 10 (5), 056010.
- Mencía, Á., Modamio-Høybjør, S., Redshaw, N., Morín, M., Mayo-Merino, F., Olavarrieta, L., et al., 2009. Mutations in the seed region of human miR-96 are responsible for nonsyndromic progressive hearing loss. *Nat. Genet.* 41 (5), 609–613.
- Mizutari, K., Fujioka, M., Hosoya, M., Bramhall, N., Okano, H.J., Okano, H., et al., 2013. Notch inhibition induces cochlear hair cell regeneration and recovery of hearing after acoustic trauma. *Neuron* 77 (1), 58–69.
- Modamio-Høybjør, S., Moreno-Pelayo, M., Mencía, A., del Castillo, I., Chardenoux, S., Morais, D., et al., 2004. A novel locus for autosomal dominant nonsyndromic hearing loss, DFNA50, maps to chromosome 7q32 between the DFNB17 and DFNB13 deafness loci. *J. Med. Genet.* 41 (2), e14-e.
- Mourelatos, Z., Dostie, J., Paushkin, S., Sharma, A., Charroux, B., Abel, L., et al., 2002. miRNPs: a novel class of ribonucleoproteins containing numerous microRNAs. *Genes Dev.* 16 (6), 720–728.
- Park, I.-H., Zhao, R., West, J.A., Yabuuchi, A., Huo, H., Ince, T.A., et al., 2008. Reprogramming of human somatic cells to pluripotency with defined factors. *Nature* 451 (7175), 141–146.
- Patel, M., Cai, Q., Ding, D., Salvi, R., Hu, Z., Hu, B.H., 2013. The miR-183/Taok1 target pair is implicated in cochlear responses to acoustic trauma. *PLoS One* 8 (3), e58471.
- Pierce, M.L., Weston, M.D., Fritzsche, B., Gabel, H.W., Ruvkun, G., Soukup, G.A., 2008. MicroRNA-183 family conservation and ciliated neurosensory organ expression. *Evol. Dev.* 10 (1), 106–113.
- Saini, H.K., Enright, A.J., Griffiths-Jones, S., 2008. Annotation of mammalian primary microRNAs. *BMC Genomics* 9 (1), 564.
- Schmidt, M.F., 2014. Drug target miRNAs: chances and challenges. *Trends Biotechnol.* 32 (11), 578–585.
- Sempere, L.F., Cole, C.N., Mcpeck, M.A., Peterson, K.J., 2006. The phylogenetic distribution of metazoan microRNAs: insights into evolutionary complexity and constraint. *J. Exp. Zool. Part B Mol. Dev. Evol.* 306 (6), 575–588.
- Serra, M.R., Biassoni, E.C., Hinalaf, M., Abraham, M., Pavlik, M., Villalobo, J.P., et al., 2014. Hearing and loud music exposure in 14-15 years old adolescents. *Noise Health* 16 (72), 320.
- Sivakumaran, T.A., Resendes, B.L., Robertson, N.G., Giersch, A.B., Morton, C.C., 2006. Characterization of an abundant COL9A1 transcript in the cochlea with a novel 3' UTR: expression studies and detection of miRNA target sequence. *J. Assoc. Res. Otolaryngology* 7 (2), 160–172.
- Soldà, G., Robusto, M., Primignani, P., Castorina, P., Benzon, E., Cesarani, A., et al., 2011. A novel mutation within the MIR96 gene causes nonsyndromic inherited hearing loss in an Italian family by altering pre-miRNA processing. *Hum. Mol. Genet.* ddr493.
- Soukup, G.A., Fritzsche, B., Pierce, M.L., Weston, M.D., Jahan, I., McManus, M.T., et al., 2009. Residual microRNA expression dictates the extent of inner ear development in conditional Dicer knockout mice. *Dev. Biol.* 328 (2), 328–341.
- Tremblay, K.L., 2015. The ear—brain connection: older ears and older brains. *Am. J. Audiology* 24 (2), 117–120.
- Wan, G., Gómez-Casati, M.E., Gigliello, A.R., Liberman, M.C., Corfas, G., 2014. Neurotrophin-3 regulates ribbon synapse density in the cochlea and induces synapse regeneration after acoustic trauma. *Elife* 3, e03564.
- Wang, X.-R., Zhang, X.-M., Zhen, J., Zhang, P.-X., Xu, G., Jiang, H., 2010. MicroRNA expression in the embryonic mouse inner ear. *Neuroreport* 21 (9), 611–617.
- Weston, M.D., Pierce, M.L., Rocha-Sanchez, S., Beisel, K.W., Soukup, G.A., 2006. MicroRNA gene expression in the mouse inner ear. *Brain Res.* 1111 (1), 95–104.
- Weston, M.D., Pierce, M.L., Jensen-Smith, H.C., Fritzsche, B., Rocha-Sanchez, S., Beisel, K.W., et al., 2011. MicroRNA-183 family expression in hair cell development and requirement of microRNAs for hair cell maintenance and survival. *Dev. Dyn.* 240 (4), 808–819.
- White, C.H., Ohmen, J.D., Sheth, S., Zeboudj, A.F., McHugh, R.K., Hoffman, L.F., et al., 2009. Genome-wide screening for genetic loci associated with noise-induced hearing loss. *Mamm. Genome* 20 (4), 207–213.
- Wienholds, E., Kloosterman, W.P., Miska, E., Alvarez-Saavedra, E., Berezikov, E., de Bruijn, E., et al., 2005. MicroRNA expression in zebrafish embryonic development. *Science* 309 (5732), 310–311.
- Woods, D.L., Arbogast, T., Doss, Z., Younus, M., Herron, T.J., Yund, E.W., 2015. Aided and unaided speech perception by older hearing impaired listeners. *PLoS One* 10 (3), e0114922.
- Xu, S., Witmer, P.D., Lumayag, S., Kovacs, B., Valle, D., 2007. MicroRNA (miRNA) transcriptome of mouse retina and identification of a sensory organ-specific miRNA cluster. *J. Biol. Chem.* 282 (34), 25053–25066.
- Yang, M., Lee, J.-E., Padgett, R.W., Edery, I., 2008. Circadian regulation of a limited set of conserved microRNAs in *Drosophila*. *BMC genomics* 9 (1), 1.
- Zeng, F.-G., Rebscher, S., Harrison, W., Sun, X., Feng, H., 2008. Cochlear implants: system design, integration, and evaluation. *IEEE Rev. Biomed. Eng.* 1, 115–142.
- Zhu, Q., Sun, W., Okano, K., Chen, Y., Zhang, N., Maeda, T., et al., 2011. Sponge transgenic mouse model reveals important roles for the microRNA-183 (miR-183)/96/182 cluster in postmitotic photoreceptors of the retina. *J. Biol. Chem.* 286 (36), 31749–31760.