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综 述

MicroRNA 调控耳蜗毛细胞发育的分子机制

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摘要：耳聋是严重影响人类生活质量的全球重大健康问题之一。目前，因耳蜗毛细胞损伤而导致的耳聋疾病尚未有成功的治疗方法。MicroRNA (miRNA)作为一类高度保守的内源性非编码小 RNA，在耳蜗以及毛细胞发育过程中发挥着重要作用。本文介绍了 miRNA 在耳蜗毛细胞产生过程中的时空表达，揭示了其不可或缺的重要作用；同时阐述了 miRNA 参与调控耳蜗毛细胞发育中相关转录因子的分子机制，为耳聋的毛细胞移植治疗和毛细胞再生研究提供理论参考。

关键词：miRNA；耳蜗；听力损失；毛细胞

Molecular mechanism of microRNA in regulating cochlear hair cell development

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Abstract: Deafness has become one of the most frequent health problems worldwide, and affects almost every age group. Hair cell damage or absence is the main cause of hearing loss, but there is no successful treatment to heal deafness. MicroRNA (miRNA), as a highly conserved endogenous non-coding small RNA, plays an important role in inner ear cochlea and hair cell development. In this review, we elaborate on the expression and function of miRNAs in cochlear hair cell development, and reveal its indispensable important role. We summarize the molecular mechanism of miRNA in regulating transcription factors involved in cochlear hair cell development, which may provide references and insights for hair cell regeneration *in vivo* and cellular transplantation therapy of deafness.

Keywords: miRNA; cochlea; hearing loss; hair cells

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miRNA 是一类高度保守的内源性非编码小 RNA，通过抑制 mRNA 转录负调控靶基因的表达水平，从而参与调控细胞的生长发育、细胞信号转导、增殖分化、细胞凋亡、脂类代谢、蛋白质降解等过程[1]。1993 年，在秀丽隐杆线虫(*Caenorhabditis elegans*)中最早发现 miRNA 基因 lin-4[2]。它与 lin-14 mRNA 3′-UTR 的碱基序列部分互补，通过降解靶基因 lin-14 参与调控线虫的生长发育[3]。随后越来越多的 miRNA 在植物、无脊椎动物和脊椎动物的组织中被发现[4]。近几年的研究发现 miRNA 在动物耳蜗的各类细胞中表达丰富[5]，已有研究表明 miR-183 家族在内耳毛细胞发育功能的调控中发挥了重要作用[6]。本文归纳总结了耳蜗毛细胞中主要 miRNA 的详细表达分布情况，并以 miR-183 家族的 3 个成员 miR-96、miR-182 和 miR-183 为主，分别阐述 miRNA 在内耳中的时空表达以及在内耳和毛细胞发育过程中参与调控的相关机制，旨在为进一步探索内耳毛细胞的发育分化、体外诱导及原位再生提供理论依据。

1　耳蜗中各类型细胞表达的 miRNA

1.1　内耳的结构与功能

哺乳动物的耳是由外耳、中耳和内耳 3 个部分组成，内耳由负责感受声音的耳蜗和感受位置及运动觉的前庭器官组成[7]。耳蜗螺旋器(Corti 器)坐落在基膜上，由感觉上皮(毛细胞)和支持细胞以及其他一些附属结构组成[8]。Corti 器有 3 排外毛细胞(outer hair cell)和 1 排内毛细胞(inner ear hair cells)[9]。外毛细胞被称为“耳蜗放大器”，增强感觉上皮细胞对不同声音频率的响应能力，形成“机械—电—机械”的正反馈环路[10]。内毛细胞受到声音刺激，纤毛向外侧摆动，触发神经递质谷氨酸的释放，促使听神经传入冲动产生。声音冲动穿过传入神经到达耳蜗螺旋神经节(spiral ganglion)，进一步传到听觉中枢，传达到大脑产生听觉[11]。耳蜗膜性结构包括基膜、前庭膜和盖膜 3 个部分。基膜是上皮组织基底面与深部结缔组织之间的一层薄膜，给耳蜗部分提供韧性和质量，基膜与耳蜗螺旋韧带的蜗管相连形成一定的功能联系[12]。前庭膜起始于蜗轴侧的螺旋缘，与基底膜成 45°，由两层细胞组成的一层薄膜，该膜可调节离子和液体平衡的作用[13]。

1.2　miRNA 在耳蜗中的表达

miRNA 与听觉功能密切相关，在耳蜗各类型的细胞中已经检测出超过 100 种 miRNA[14]，如 miR-183、miR-96、miR-182、miR-124、miR-34a、miR-376 和 miR-135b 等[15]。其中，miR-96、miR-182 和 miR-183 等在小鼠和人的基因组中成簇排列，并且都是朝向同一方向转录生成，所以将这 3 种 miRNA 统称为 miR-183 基因簇或 miR-183 家族[16]。在毛细胞和螺旋神经节中的 miRNA 种类较多，已被证实的有 miR-183 家族、miR-15a、miR-30b、miR-99a、miR-18a、miR-140 和 miR-194 等[17]。在内螺旋沟也检测到 miR-96、miR-182 和 miR-183 共 3 个 miRNA，而在螺旋缘除了检测到 miR-183 家族的 3 个 miRNA 成员，还检测到 miR-205 表达[18]。同时，miR-205 也存在于前庭膜和耳蜗螺旋韧带上[19]。基膜上除了存在 miR-205a，此外还高表达 miR-15a、miR-30b 和 miR-99a 等 miRNA[20]。但是支持细胞只有 miR-15a、miR-30b 和 miR-99a 表达[21]。边缘细胞中存在 miR-376a 和 miR-376b，这些 miRNA 在内耳的其他部位中没有检测出来[22]。

除了上述提及的表达水平较高的 miRNA，在已知成熟 miRNA 中有 102 种在耳蜗中表达，占全身 miRNA 总量的 1/3[23]。组成耳蜗的细胞种类丰富，从 miRNA 的表达情况中可以看出一些组织和细胞存在着相同的 miRNA[24]，比如毛细胞、螺旋神经节、螺旋缘、内螺旋沟等组织都有 miR-96、miR-182 和 miR-183 的存在，前庭膜、螺旋缘、耳蜗螺旋韧带、基膜等组织则都表达了 miR-205a[25]。这些结果为进一步掌握耳蜗的发育过程以及不同细胞组织之间的协同作用提供了研究依据[26]。在耳蜗中不同细胞和组织中主要高度表达的 miRNA 的表达情况如图 1 所示。

2　miRNA 在耳蜗发育过程中的时空表达

2.1　内耳的发育过程

脊椎动物的内耳发育起源于胚胎的外胚层[27]。

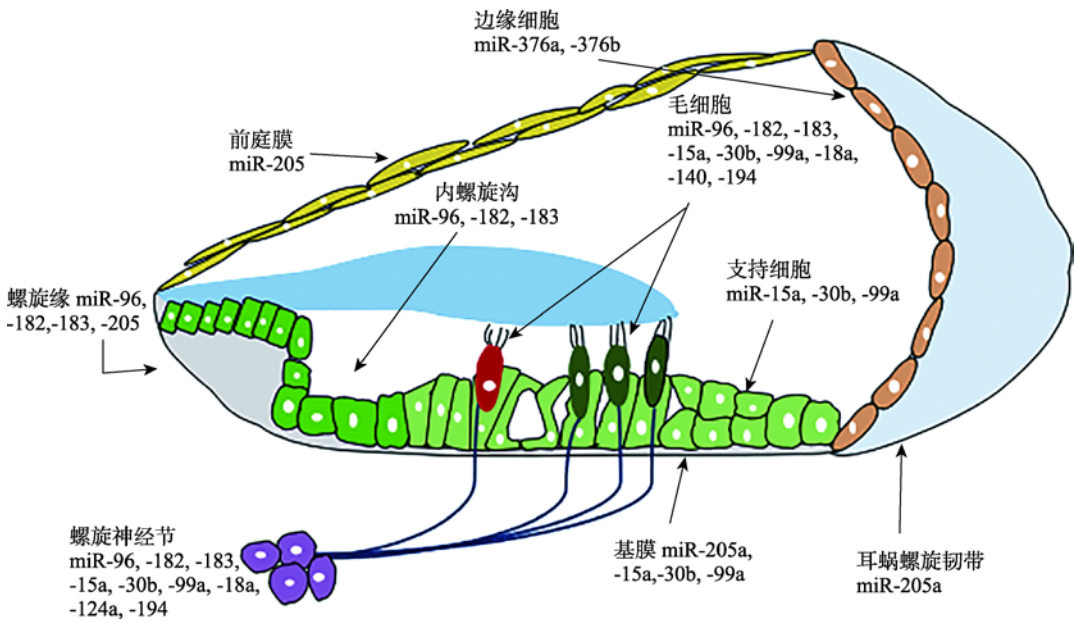

图 1 miRNA 在耳蜗各类细胞中的表达

Fig. 1 Expression of miRNA in the inner ear cochlea cells

听泡(otic vesicle)又称耳囊(otic capsule), 起源于外胚层的听基板，在外胚层表面接近于神经板[28]。内耳的始基听泡发育产生于小鼠胚胎第 8 天(embryonic day 8, E8)至第 11 天, 而人类在胚胎第 4 周末期才发育产生听泡[29]。在此发育阶段，内耳的平衡和听觉神经节也开始发育，该神经节是由内耳原始听泡的前腹内侧细胞从听泡分离并融合形成[30]。小鼠在 E10.5~E14 开始形成前庭和耳蜗，听泡脱离表面外胚层沉降到下方间充质内形成了听囊，听囊背侧发育为前庭部，而听囊腹侧发育为耳蜗部[31]。而感觉细胞的分化期，小鼠约在 E13~E19，耳蜗上皮逐渐分化为感觉上皮，已有可分辨出的支持细胞和毛细胞[32]。出生时, 前庭感觉器官发育已经接近于成熟，耳蜗已成型但体积比成熟期的耳蜗小[33]。出生后，前庭感觉器官、耳蜗逐渐发育成熟[34]，小鼠出生后第 30 天(postnatal day 30, P30)左右内耳器官完全发育成熟[35]。

2.2 miRNA 在动物模型耳蜗中的时空表达

miRNAs 的表达呈现时间、空间及组织细胞的特异性[36]，表明其参与了组织的形态形成和细胞分化的过程[37]。由于人类的耳蜗组织不易获取，关于耳蜗 miRNA 的时空表达研究多局限于模式生物, 再利用外推法来理解其在人类耳蜗中的具体功能[38]。在耳蜗领域最早进行研究的动物模型是小鼠，通过表达谱芯片分析小鼠耳蜗发育过程中不同时间点 miRNA 表达的状况[39]。在小鼠胚胎的整个发育过程中，miR-183 和 miR-182 最早在胚胎期 E9.5 于听泡中表达。随着内耳在胚胎期的进一步发育，miR-183 家族的 3 个成员在 E11.5 时出现表达差异，miR-182 只有 miR-182-5p 表达, 而在 E12 时 miR-96、miR-182 和 miR-183 呈现无差异表达，这可能反映了不同种类 miRNA 在内耳发育中的微小差异[40]。胚胎发育前期在 miR-96、miR-182、miR-183 听囊和螺旋神经节均有表达, E17.5 时开始仅在毛细胞及其神经元中表达[41]。出生时(P0)，耳蜗毛细胞中检测到了 miR-183 家族、miR-15a*、miR-18a*、miR-30a*、miR-99a*、miR-199a*、miR-200*等诸多 miRNAs 的表达[42]。其中 miR-183 家族在小鼠出生后 4-5 天还存在于感觉前体细胞中，随后集中在耳蜗毛细胞呈现高度表达状态[43]。在 P30 时小鼠耳蜗已完全发育，此时在毛细胞中仍然可以检测到 miR-183 家族的表达[44]。从新生小鼠的耳蜗检测出的 miRNA 表达谱开始，经过听觉功能的发育和成熟，miRNA 并没有发生实质性的改变, 这表明 miRNA 的表达在很大程度上是在胚胎发育过程中建立起来的。从耳蜗

发育的整个过程上看，miR-183、miR-96 和 miR-182 的表达呈现出了时空组织的特异性，这种时间和空间上的表达与耳蜗的功能成熟密切相关[45]。miRNA 家族时空表达的特异性见图 2 所示。

3　miR-183 家族与毛细胞发育

3.1　毛细胞概述

人类内耳约有 15 000 个毛细胞，其中作为听觉感受器的耳蜗毛细胞约有 3000 个[46]。耳蜗毛细胞是分化成熟、高度特异性的终末细胞，哺乳动物毛细胞在出生后再生能力非常有限，听觉毛细胞损伤后很难分化形成新的毛细胞[47]。遗传或者获得性因素如年龄增长、耳毒性药物、病毒感染、噪音和外伤等都会使毛细胞受到损伤[48]，从而造成感音神经性耳聋(sensorineural hearing loss, SNHL)[49]。长期以来，感音神经性耳聋患者改善听力的选择仅仅限于助听器、人工耳蜗等设备，但这些方法无法从根本上解决问题[50]。因此，研究毛细胞的发育和再生的机制，可用于指导体外诱导干细胞分化为类毛细胞的研究，并通过细胞移植替换受损毛细胞，为治疗耳聋疾病带来新曙光[51]。

3.2　miR-183 家族

目前在耳蜗毛细胞的 miRNA 研究中，miR-183 家族的研究比较深入[52]。这个家族在进化过程中具有高度保守性，在结构上具有高度同源性(图 3)。miR-183 和 miR-96 之间有约 1 kb 的间隔区，miR-96 和 miR-182 之间有约 2.7~3.5 kb 的间隔区。尽管 3 者之间的序列具有高度的相似性，但是其中微小的序列差异导致它们拥有不同的 mRNA 靶标。miR-183 家族是最先被报道参与了纤毛化的感觉上皮细胞和神经纤毛细胞的器官发生和发育功能的基因簇[53]，它们在某些器官如眼睛、鼻子和内耳中有特殊的表达，对动物感觉器官的发育和功能的形成至关重要[54]。

3.2.1　miR-96

miR-96 首先在人类癌细胞中被检测到，是 miR-183 家族中第一个被发现的 miRNA 成员[55]。miR-96 是一种感觉器官特异性的 miRNA，在哺乳动物耳蜗发

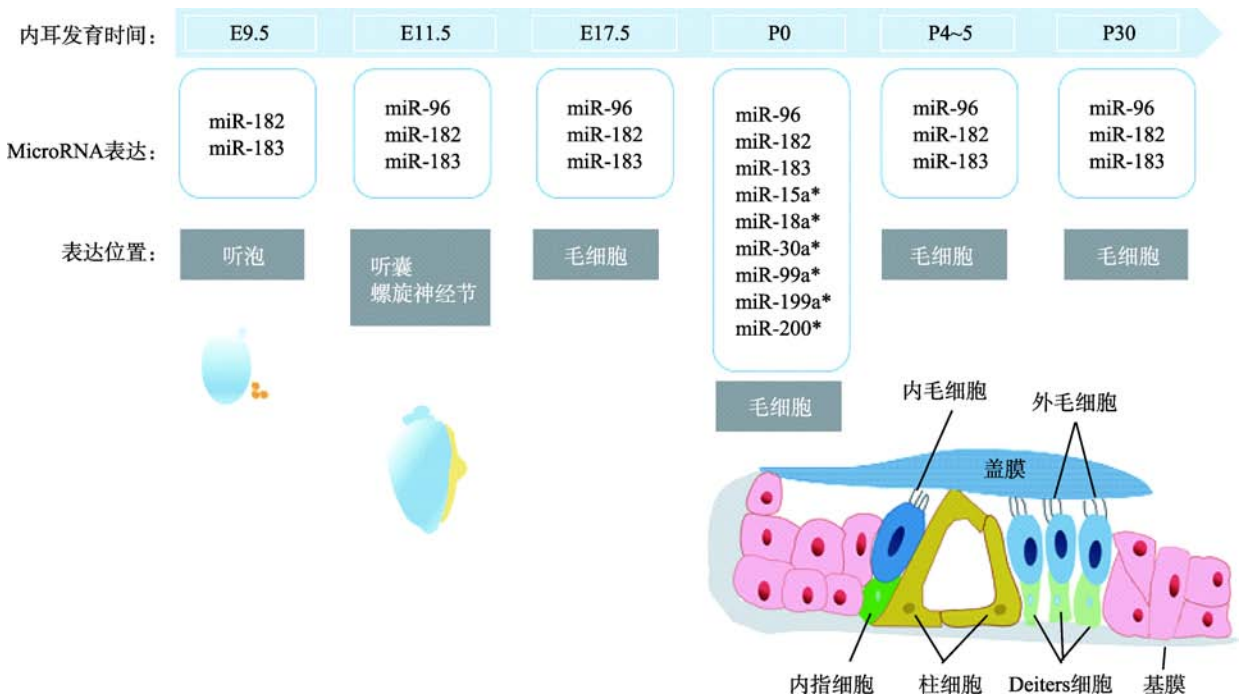

图 2　miR-183 家族在小鼠耳蜗发育过程中表达的时间图

Fig. 2　Time diagram of miR-183 family expression during mouse inner ear cochlear development

E 为胚胎期，P 为出生后。

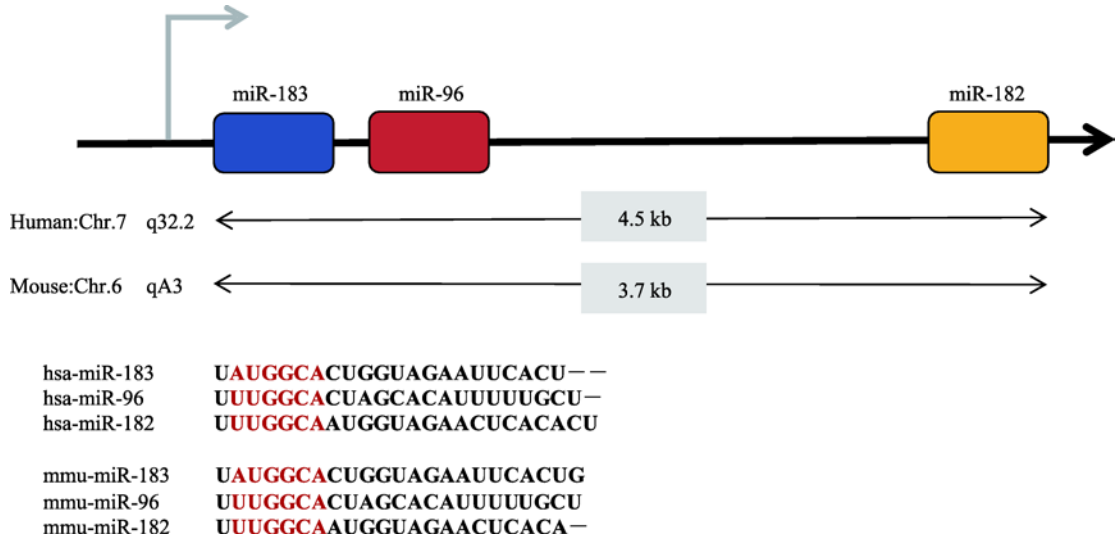

图 3　miR-183 家族基因簇在人和小鼠中的染色体位置及种子序列

Fig. 3　Chromosome positions and seed sequences of miR-183 family gene clusters in human and mouse

红色部分为 microRNA 种子系列。

育期间表达，可导致 *Gfi1*、*Ptprq* 和 *Tmc1* 等重要发育基因表达下调。miR-96 的种子区域的点突变会引起 DNA 序列多态性，导致人和小鼠常染色体显性非综合征性耳聋(non-syndromic hearing loss, NSHL)[56]。miR-96 的种子序列第 4 个碱基 G>A 的突变，是第一个被发现的与遗传性耳聋相关的 miRNA 突变。Mencia 等[57]从遗传性耳聋家系中证实+13G>A 和+14C>A 两个种子区域点突变也会影响成熟的 miR-96 与靶基因的结合效率，从而导致其对耳蜗毛细胞的调节失衡，最终引起了耳聋产生。Lewis 等[58]利用强致癌剂 N-亚硝基-N-乙基脲(N-ethyl-N-nitrosourea, ENU)致小鼠听力损失，进一步对 miR-96 的种子区域点突变进行研究，发现有的突变体小鼠完全听力丧失并且毛细胞纤毛束不规则。Kuhn 等[59]利用 ENU 小鼠突变体来探索 miR-96 在听觉器官发育至成熟过程中的作用机制，发现 miR-96 种子区域的突变影响了 *Slc26a5*、*Ocm*、*Gfi1*、*Ptprq* 和 *Pitpnm1* 等内耳毛细胞相关靶基因的正常表达，毛细胞静纤毛束的成熟和耳蜗内听觉神经连接的重塑都会受到影响，进一步阐明了这一种子区域与听力损失有关[60]，miR-96 可能与内耳毛细胞的静纤毛束的成熟和耳蜗神经的发育密切联系[61]。因此，了解 miR-96 的作用机制有助于进一步解释维持耳蜗正常活动所需基因的有序表达，并有助于深入研究非综合征性聋病发生的机制[62]。

3.2.2　miR-182

miR-182 活性可能与靶基因 *Tbx1* 有关，*Tbx1* 是一种参与毛细胞发育和分化的转录因子[63]。顺铂(cisplatin, CDDP)诱导的毛细胞凋亡前过表达 miR-182，可抑制内源性凋亡途径的 3 个关键基因 *Bax*、*Apaf-1* 和 *caspase*，从而保护耳蜗毛细胞免于细胞凋亡[64]。miR-182 过表达会导致耳蜗毛细胞数量增加，在支持细胞中 miR-182 的低表达可抑制该细胞转分化为毛细胞。因此，在感觉细胞中过表达 miR-182 可以促进毛细胞再生，有望治疗由毛细胞丢失引起的感音神经性耳聋。Hildebrand 等[65]利用隐性常染色体非综合征性耳聋人类家系，在 *RDX*(*DFNB24*)基因的 3′-UTR 中发现了 miR-182 结合位点的 C>A 的纯合子突变。Wang 等[66]将小鼠耳蜗干/祖细胞进行体外培养，发现过表达 miR-182 促进耳蜗干/祖细胞分化成毛细胞，此外，miR-182 还与神经感觉器官、视觉感觉器官等器官的发育调控有关。在针对自闭症的全基因组研究中，Schellenberg 等[67]在接近 miR-182 染色体位点的地方发现了这种疾病的易感基因，miR-182 缺陷会导致自闭症的发生。Xu 等[51]体外研究表明 *MITF* 是 miR-96 和 miR-182 的直接靶点，*MITF* 是建立和维持视网膜发育和维持所必需的转

录因子，miR-182 的异常导致感觉器官发育程序的缺陷。

3.2.3　miR-183

miR-183 能够调控耳蜗内毛细胞的发育分化及成熟的生理过程，miR-183 可通过负调控其下游靶基因，使毛细胞的细胞骨架发生改变[68]。内耳在暴露于噪声 28 d 后 miR-183、miR-96 和 miR-182 的表达水平降低，这与噪声导致外毛细胞的减少有关。在强烈的噪声刺激导致耳蜗毛细胞损伤后，miR-183 可以通过抑制 *Taok1* 的表达来保护强刺激后受到损伤的耳蜗[69]。在体外培养的耳蜗螺旋器中，用吗啡反义寡核苷酸抑制 miR-183 的表达可导致 Taok1 蛋白增加并伴随耳蜗毛细胞的凋亡，说明 miR-183 在调节听觉创伤的耳蜗反应方面具有潜在的作用。Kim 等[70]发现在新霉素诱导耳毒性斑马鱼中抑制 miR-183 表达，会降低毛细胞的再生，反之在斑马鱼胚胎中人工注射 miR-183 可以促进毛细胞正常发育。miR-183 表达的变化先于动物形态学和功能的变化，在小鼠耳蜗发育的过程中，促进细胞增殖和分化的 miR-183 呈上调趋势，而在小鼠衰老时 miR-183 下调，促凋亡通路的调控因子 miR-29 家族和 miR-34 家族成员上调。

4　miRNA 调控耳蜗发育的分子机制

4.1　miRNA 与靶基因

人们对 miRNA 如何控制耳蜗发育的理解始于对 *Dicer1* 突变体动物的研究。在斑马鱼模型中，*Dicer1* 幼体突变体的听觉器官严重畸形[71]。在小鼠中，*Dicer1* 基因在耳部早期发育时缺失，会导致内耳的整体尺寸减小，耳蜗生长受到严重阻碍[72]。*Dicer1* 基因在 pre-miRNA 加工成为成熟 miRNA 过程中至关重要，*Dicer1* 缺失严重影响了内耳的发育，间接地说明了 miRNAs 对耳蜗的重要性。miRNAs 在耳蜗发育过程中参与调控重要基因的表达水平，从而参与了调控耳蜗细胞的增殖、迁移、发育和凋亡等过程。*Sox2* 作为感觉前体细胞区域较早出现的标志之一，在人类耳蜗发育过程中 *Sox2* 的缺失引起了感音神经性耳聋，*Tbx1* 是内耳发育和毛细胞命运有关的转录因子，miR-182 参与了靶基因 *Sox2* 和 *Tbx1* 的表达调控[66]。miR-96 的靶基因是 *Slc26a5*、*Ocm*、*Ptprq* 和 *Pitpnm1*，其中 *Ptprq* 是毛细胞成熟的重要基因[59]。此外，miR-96 的靶基因还包括了渐进性耳聋的 2 个关键基因 *EGFR*(表皮生长因子受体)和 *TRK*(神经营养因子受体)[55]。*C1ic5* 在其 3'-UTR 中包含一个高度保守的 miR-96/-182 结合位点,被认为是 miR-96 和 miR-182 的共同靶基因。Gu 等[73]研究证实 *C1ic5* 基因突变小鼠与 ENU 突变小鼠具有相似的立体纤毛形态，利用脂质体将 miR-96 和 miR-182 转染到耳蜗毛细胞中，可导致 *C1ic5* 在 mRNA 水平和蛋白水平的表达量下降，进一步研究结果表明 *C1ic5* 是由 miR-96 和 miR-182 直接调控的，确认靶序列位于 *C1ic5* 3′-UTR 内的核苷 760~766 bp 之间。miR-183 以 *ltgA3* 为靶基因，通过抑制整合素 α3 的表达来控制耳蜗发育中的细胞增殖[71]。

除了上述的 miR-183 家族参与耳蜗发育的重要靶基因的调控，其他 miRNA 也在耳蜗发育过程中发挥重要作用。*COL9A1* 是负责产生透明软骨组分的基因，miR-9 是 *COL9A1* 的调控因子[72]。miR-124 在耳蜗中的靶基因是 Wnt 信号通路的两个抑制因子 *Sfrp4* 和 *Sfrp5*。miR-124 于耳囊的神经上皮中高水平表达，促进神经细胞分化和轮廓形成[74]。miR-135b 调控耳蜗中的转录激活因子 *PSIP1-P75*[75]。miR-194 在耳蜗神经元和毛细胞中高度表达，通过调控 *Fgf4* 和 *RhoB* 基因影响耳蜗神经细胞的分化[76]。内耳形态发生的关键调节因子是 miR-200，在耳蜗和前庭上皮细胞中选择性表达，通过转录沉默 *Zeb1* 和 *Zeb2* 基因调控上皮–间质转化[77]。磷酸核糖焦磷酸合成酶 1(PRPS1)的突变与一系列非综合征到综合征性听力损失有关，*PRPS1* 表达水平受 miR-376 的调控[78]。总之，这些 miRNA 以及其下游靶基因在耳蜗中组成了复杂的调控网络，共同调控耳蜗的发育过程[79]。有关 miRNA 调控耳蜗发育的靶基因见表 1。

4.2　miRNA 参与的信号通路

耳蜗前体细胞在耳蜗分化的过程中主要产生 3 种谱系的细胞，分别是神经前体细胞、感觉前体细胞和其它细胞[88]。神经细胞产生所必需的细胞因子是 *Sox2* 和 *Ngn1*，*Tbx1* 可以抑制 *Ngn1* 和神经元的

表 1 miRNA 在耳蜗中的靶基因

Table 1 Target gene of miRNA in inner ear cochlea

miRNA	靶基因	参考文献
miR-9	*COL9A1*	[72]
miR-29	*SIRT1*	[80]
miR-34a	*SIRT1*、*bcl-2* 和 *E2F-3*	[81]
miR-96	*TRK* 和 *EGFR*	[52]
	Slc26a5、*Ocm*、*Gfi1*、*Ptprq* 和 *Pitpnm1*	[59]
miR-96/-182	*CLIC5*	[73]
miR-124	*Sfrp4* 和 *Sfrp5*	[74]
miR-135b	*PSIP1-P75*	[82]
miR-140	*NR2F1* 和 *Klf9*	[83]
miR-182	*Sox2* 和 *Tbx1*	[84]
miR-183	*Taok1* 和 *ltgA3*	[70]
miR-194	*Fgf4* 和 *RhoB*	[76]
miR-200	*Zeb1* 和 *Zeb2*	[85]
miR-204	*TMPRSS3*	[86]
miR-224	*Ptx3*	[87]
miR-376	*PRPS1*	[78]

分化，而 miR-182 抑制 *Tbx1* 的表达[89]。感觉细胞的产生时需要 *Jagged1*、*Notch1*、*SOX2*、*BMP-4*、*FGF* 和 *IGF-1* 等基因参与调控，细胞周期蛋白依赖性激酶(Cyclin-dependent kinase)抑制剂 $p27^{kip1}$，$p19^{Ink4d}$ 和 Rb 抑制感觉细胞进入细胞周期，促进感觉前体细胞分化成毛细胞和支持细胞[90]。毛细胞的形成和成熟需要 *MyosinVII*、*Atoh1*、*Espin*、*Brn3c*、*Gfi1* 和 *Barhl1* 等细胞因子的调控[91]。Wnt 信号通路[92]、Notch 信号通路[93]、Shh 信号通路[94]、FGF 信号通路[95]和 TGF 信号通路[96]等信号通路参与了耳蜗的发育过程。其中，经典 Wnt/β-catenin 信号通路作用于耳蜗发育的最初阶段，主要负责调控听囊和听基板的特化；而 Wnt/PCP 信号通路在哺乳动物的毛细胞静纤毛的生长排列和蜗管的延伸过程中发挥着重要作用[97]。miR-183 家族可以通过抑制 *LRP6* 的表达，调控 Wnt/β-catenin 信号通路的传导[98]，而糖原合成酶激酶 GSK3β 通过 Wnt/β-catenin/TCF/LEF-1 信号通路影响 miR-183 家族的表达[99]。在哺乳动物发育过程中，Notch 信号通路参与耳蜗感觉上皮的发育与分化过程，通过侧向抑制作用调控耳蜗感觉前体细胞向毛细胞的分化，从而确保内毛细胞至外毛细胞的正常分化顺序[100]。miR-384-5p 转染细胞后，*Notch1* 的表达水平显著下调[101]，miR-183 通过抑制基因 *NICD3* 和 *NICD4* 从而抑制 Notch 信号通路，参与毛细胞的分化和再生[102]。在耳蜗发育的早期阶段，FGF 信号通路调控早期听基板的形成，在耳蜗发育后期，FGF 信号分子主要参与毛细胞的发育，然而 miRNA 参与 FGF 信号通路调节的报道目前尚未见报道[103]。

miRNA 在耳蜗发育过程中调节细胞凋亡方面还发挥了重要作用[104]。在电离辐射诱导的毛细胞死亡模型中，作为促凋亡因子的 miR-207 通过靶向基因 *Akt3*(*Akt* 是 PI3K/AKT 途径等信号通路的关键基因)发挥了重要作用[105]。miR-182 通过抑制 PI3K AKT 信号通路的直接靶点 *FOXO3a* (促凋亡转录因子)的翻译来抑制细胞凋亡通路，可减轻毛细胞死亡[106]。miR-183 通过抑制 *PDCD4* 的表达,抑制 *TGFβ1* 诱导的细胞凋亡,调控 TGF 通路参与支持细胞和毛细胞的分化[107]。因此，通过下调和上调 miRNA 的表达来精准调控耳蜗干细胞的发育进程并减少毛细胞的凋亡是一种体内原位毛细胞再生的可行策略[108]。miRNA 调控耳蜗发育的分子机制示意图见图 4。

5 miRNA 在治疗聋病方面应用前景

目前已有 6000 余个 miRNA 被找到，这些 miRNA 与生物体中约 1/3 的蛋白编码基因的调控密切相关[109]。miRNA 已被证实是参与诸多内耳相关的病理发生过程的关键因素，如渐进性感音神经性耳聋、老年化耳聋、噪声性耳聋和内耳炎症等[110]。miRNA 还参与了感觉毛细胞束发育、肌动蛋白重组、细胞粘附和内耳形态发生[111]。目前感音神经性耳聋治疗寄希望于毛细胞的移植治疗，细胞移植的关键是获得符合要求的毛细胞[90]。而获得毛细胞的唯一途径是来自于干细胞的体外诱导，所谓利用干细胞治疗感音神经性耳聋的最终目标是将干细胞诱导分化，再移植到毛细胞受损伤的部位作为替代细胞，达到重建损伤耳蜗并修复听力功能[112]。近年来一系列的研究表明胚胎干细胞、间充质干细胞、神经干细胞、内耳干细胞、iPS 细胞等都可以在体外诱导分化为耳蜗类毛细胞[113]。然而，干细胞体外诱导获得的耳蜗

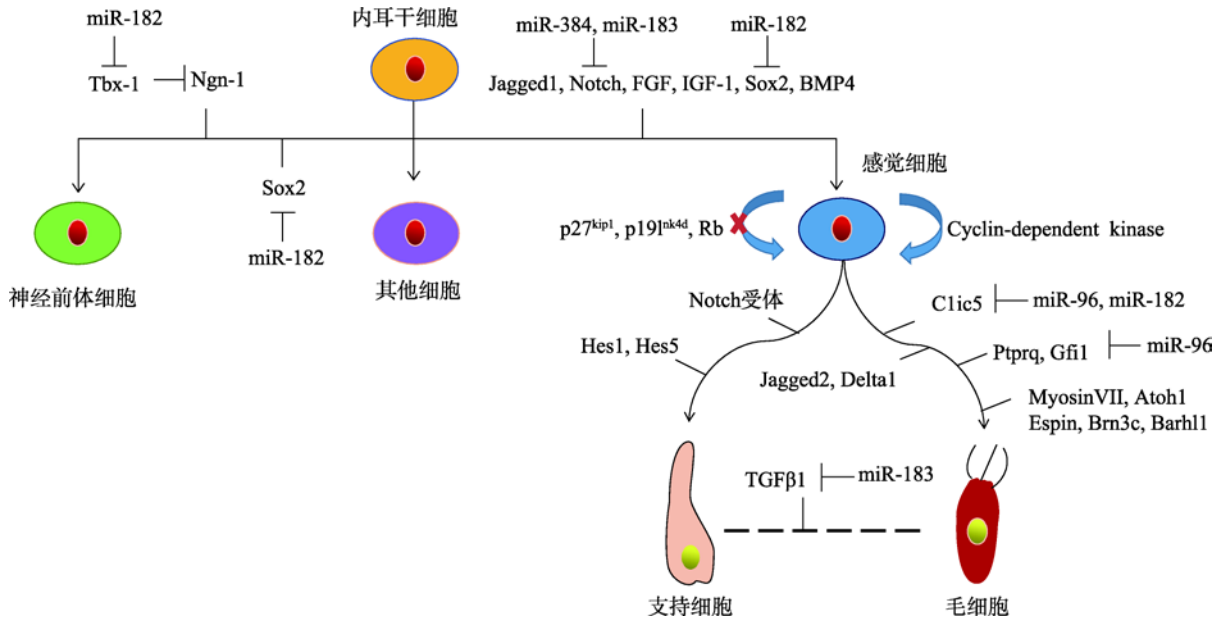

图 4　miRNA 调控耳蜗发育的分子机制示意图

Fig. 4　Molecular mechanism of miRNA in regulating cochlear development

| 表示正调控；⊥表示负调控。

类毛细胞虽然可以表达毛细胞相关的标志性蛋白，如 Brn3c、Aoth1 和 MyosinVII 等，但是扫描电镜观测到的类毛细胞的静纤毛和动纤毛仍与正常毛细胞的纤毛束有差距、神经电生理也有差异[114]。miRNA 已经在毛囊细胞移植[115]、肝脏细胞体外分化[116]、心肌细胞体外分化[117]等方面有成功的案例。为此，本实验室构建过表达 miR-183、miR-182 和 miR-96 的载体导入到胚胎干细胞，利用这种胚胎干细胞研究体外诱导分化为毛细胞的机理，希望获得功能形态更加完整的毛细胞用于细胞移植治疗[37]。

6　结语与展望

耳聋是全球性的疾病问题之一, 世界上有 5 亿人遭受听力丧失的困扰, 其中包括了 3200 万名儿童[118]。根据中国残联的最新数据显示：中国听力残疾的人数已达 2780 万人，听力残疾仅次于肢体残疾，是中国第二大致残疾病[119]。miRNA 与耳蜗及毛细胞发育调控密切相关[120]，耳蜗中 miRNA 数量庞大，且一个 miRNA 可调控多个靶基因，多个 miRNA 也可协同调控一个靶基因，需要进一步明确与耳聋相关联的 miRNA 种类及生物特性。目前，miRNA 在耳蜗中的具体分子机制尚未完全清楚，miRNA 的成熟体究竟是在内耳的单个细胞内参与调控还是以外泌体等方式分泌到细胞外产生作用？内耳中表达了相同 miRNA 的细胞之间具有何种联系？miRNA 参与调控内耳毛细胞纤毛束的具体作用方式是什么？这些问题都值得人们深入探讨。

另外，在耳蜗 miRNA 作用机理研究的基础上，将来可用小分子化合物和关键的 miRNA 共同导入到耳蜗诱导毛细胞的原位再生，也可以用外泌体作为载体负载 miRNA 或者使用 miRNA 拮抗剂，移植耳蜗诱导毛细胞的原位再生。这些以 miRNA 为基础的新技术，将为耳聋的治疗提供新的思路。

参考文献(References)：

[1] Dhungel B, Ramlogan-Steel CA, Steel JC. MicroRNA-regulated gene delivery systems for research and therapeutic purposes. *Molecules*, 2018, 23(7): E1500. [DOI]

[2] Lau NC, Lim LP, Weinstein EG, Bartel DP. An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. *Science*, 2001, 294(5543): 858–862. [DOI]

[3] Tanzer A, Stadler PF. Molecular evolution of a microRNA cluster. *J Mol Biol*, 2004, 339(2): 327–335. [DOI]

[4] Lagos-Quintana M, Rauhut R, Meyer J, Borkhardt A, Tuschl T. New microRNAs from mouse and human. *RNA*, 2003, 9(2): 175–179. [DOI]

[5] Mittal R, Liu G, Polineni SP, Bencie N, Yan D, Liu XZ. Role of microRNAs in inner ear development and hearing loss. *Gene*, 2019, 686: 49–55. [DOI]

[6] Mahmoodian Sani RM, Hashemzadeh-Chaleshtori M, Saidijam M, Jami MS, Ghasemi-Dehkordi P. MicroRNA-183 family in inner ear: hair cell development and deafness. *J Audiol Otol*, 2016, 20(3): 131–138. [DOI]

[7] Fritzsch B, Elliott KL. Gene, cell, and organ multiplication drives inner ear evolution. *Dev Biol*, 2017, 431(1): 3–15. [DOI]

[8] Chan WX, Lee SH, Kim N, Shin CS, Yoon YJ. Mechanical model of an arched basilar membrane in the gerbil cochlea. *Hear Res*, 2017, 345: 1–9. [DOI]

[9] Ulfendahl M, Khanna SM, Decraemer WF. Acoustically induced vibrations of the Reissner's membrane in the guinea-pig inner ear. *Acta Physiol Scand*, 1996, 158(3): 275–285. [DOI]

[10] Mahmoudian-sani MR, Mehri-Ghahfarrokhi A, Ahmadinejad F, Hashemzadeh-Chaleshtori M, Saidijam M, Jami MS. MicroRNAs: effective elements in ear-related diseases and hearing loss. *Eur Arch Oto-Rhino-L*, 2017, 274(6): 2373–2380. [DOI]

[11] Schrauwen I, Hasin-Brumshtein Y, Corneveaux JJ, Ohmen J, White C, Allen AN, Lusis AJ, Van Camp G, Huentelman MJ, Friedman RA. A comprehensive catalogue of the coding and non-coding transcripts of the human inner ear. *Hear Res*, 2016, 333: 266–274. [DOI]

[12] Mahmoodian-Sani MR, Mehri-Ghahfarrokhi A. The potential of miR-183 family expression in inner ear for regeneration, treatment, diagnosis and prognosis of hearing loss. *J Otol*, 2017, 12(2): 55–61. [DOI]

[13] Kwan KY. Single-cell transcriptome analysis of developing and regenerating spiral ganglion neurons. *Curr Pharmacol Rep*, 2016, 2(5): 211–220. [DOI]

[14] Matsunami T, Suzuki T, Hisa Y, Takata K, Takamatsu T, Oyamada M. Gap junctions mediate glucose transport between GLUT1-positive and -negative cells in the spiral limbus of the rat cochlea. *Cell Commun Adhes*, 2006, 13(1–2): 93–102. [DOI]

[15] Lee SH, Ju HM, Choi JS, Ahn Y, Lee S, Seo YJ. Circulating serum miRNA-205 as a diagnostic biomarker for ototoxicity in mice treated with aminoglycoside antibiotics. *Int J Mol Sci*, 2018, 19(9): 2386. [DOI]

[16] He WX, Kemp D, Ren TY. Timing of the reticular lamina and basilar membrane vibration in living gerbil cochleae. *eLife Sciences*, 2018, 7. [DOI]

[17] Monzack EL, Cunningham LL. Lead roles for supporting actors: critical functions of inner ear supporting cells. *Hear Res*, 2013, 303: 20–29. [DOI]

[18] Liu J, Liu W, Yang J. ATP-containing vesicles in stria vascular marginal cell cytoplasms in neonatal rat cochlea are lysosomes. *Sci Rep*, 2016, 6: 20903. [DOI]

[19] Patel M, Hu BH. MicroRNAs in inner ear biology and pathogenesis. *Hear Res*, 2012, 287(1–2): 6–14. [DOI]

[20] Torres L, Juárez U, García L, Miranda-Ríos J, Frias S. External ear microRNA expression profiles during mouse development. *Int J Dev Biol*, 2015, 59(10–12): 497–503. [DOI]

[21] Trujillo-Provencio C, Powers TR, Sultemeier DR, Ramirez-Gordillo D, Serrano EE. RNA extraction from xenopus auditory and vestibular organs for molecular cloning and expression profiling with RNA-seq and microarrays. *Methods Mol Biol*, 2016, 1427: 73–92. [DOI]

[22] Stenfelt S. Inner ear contribution to bone conduction hearing in the human. *Hear Res*, 2015, 329: 41–51. [DOI]

[23] Whitfield TT. Development of the inner ear. *Curr Opin Genet Dev*, 2015, 32: 112–118. [DOI]

[24] Pechriggl EJ, Bitsche M, Glueckert R, Rask-Andersen H, Blumer MJF, Schrott-Fischer A, Fritsch H. Development of the innervation of the human inner ear. *Dev Neurobiol*, 2015, 75(7): 683–702. [DOI]

[25] Chadly DM, Best J, Ran C, Bruska M, Woźniak W, Kempisty B, Schwartz M, LaFleur B, Kerns BJ, Kessler JA, Matsuoka AJ. Developmental profiling of microRNAs in the human embryonic inner ear. *PLoS One*, 2018, 13(1): e0191452. [DOI]

[26] Sai XR, Ladher RK. Early steps in inner ear development: induction and morphogenesis of the otic placode. *Front Pharmacol*, 2015, 6. [DOI]

[27] McLean WJ, McLean DT, Eatock RA, Edge AS. Distinct capacity for differentiation to inner ear cell types by progenitor cells of the cochlea and vestibular organs. *Development*, 2016, 143(23): 4381–4393. [DOI]

[28] Corrales CE, Pan LY, Li HW, Liberman MC, Heller S, Edge AS. Engraftment and differentiation of embryonic stem cell-derived neural progenitor cells in the cochlear nerve trunk: Growth of processes into the organ of corti. *J Neurobiol*, 2006, 66(13): 1489–1500. [DOI]

[29] Varela-Nieto I, Palmero I, Magariños M. Complementary and distinct roles of autophagy, apoptosis and senescence during early inner ear development. *Hear Res*,

2019, 376: 86–96. [DOI]

[30] Robles L, Ruggero MA. Mechanics of the mammalian cochlea. *Physiol Rev*, 2001, 81(3): 1305–1352. [DOI]

[31] Hurd EA, Adams ME, Layman WS, Swiderski DL, Beyer LA, Halsey KE, Benson JM, Gong TW, Dolan DF, Raphael Y, Martin DM. Mature middle and inner ears express Chd7 and exhibit distinctive pathologies in a mouse model of CHARGE syndrome. *Hear Res*, 2011, 282(1–2): 184–195. [DOI]

[32] Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T. Identification of tissue-specific microRNAs from mouse. *Curr Biol*, 2002, 12(9): 735–739. [DOI]

[33] Berghaus A, Nicoló MS. Milestones in the history of ear reconstruction. *Facial Plast Surg*, 2015, 31(6): 563–566. [DOI]

[34] Lee S, Shin JO, Sagong B, Kim UK, Bok J. Spatiotemporal expression patterns of clusterin in the mouse inner ear. *Cell Tissue Res*, 2017, 370(1): 89–97. [DOI]

[35] Roser AE, Gomes LC, Halder R, Jain G, Maass F, Tönges L, Tatenhorst L, Bähr M, Fischer A, Lingor P. miR-182-5p and miR-183-5p Act as GDNF mimics in dopaminergic midbrain neurons. *Mol Ther-Nucl Acids*, 2018, 11: 9–22. [DOI]

[36] Bai YS, Li L, Wei HX, Zhu C, Zhang CQ. The effect of microRNAs on the regulatory network of pluripotency in embryonic stem cells. *Hereditas(Beijing)*, 2013, 35(10): 1153–1166.
白银山, 李莉, 卫恒习, 朱翠, 张守全. MicroRNA 对胚胎干细胞的多能性网络调控. 遗传, 2013, 35(10): 1153–1166. [DOI]

[37] Weston MD, Tarang S, Pierce ML, Pyakurel U, Rocha-Sanchez SM, McGee J, Walsh EJ, Soukup GA. A mouse model of miR-96, miR-182 and miR-183 misexpression implicates miRNAs in cochlear cell fate and homeostasis. *Sci Rep*, 2018, 8(1): 3569. [DOI]

[38] Weston MD, Pierce ML, Rocha-Sanchez S, Beisel KW, Soukup GA. MicroRNA gene expression in the mouse inner ear. *Brain Res*, 2006, 1111(1): 95–104. [DOI]

[39] Li HQ, Kloosterman W, Fekete DM. MicroRNA-183 family members regulate sensorineural fates in the inner ear. *J Neurosci*, 2010, 30(9): 3254–3263. [DOI]

[40] Xiang L, Chen XJ, Wu KC, Zhang CJ, Zhou GH, Lv JN, Sun LF, Cheng FF, Cai XB, Jin ZB. miR-183/96 plays a pivotal regulatory role in mouse photoreceptor maturation and maintenance. *Proc Natl Acad Sci USA*, 2017, 114(24): 6376–6381. [DOI]

[41] Sacheli R, Nguyen L, Borgs L, Vandenbosch R, Bodson M, Lefebvre P, Malgrange B. Expression patterns of miR-96, miR-182 and miR-183 in the development inner ear. *Gene Expr Patterns*, 2009, 9(5): 364–370. [DOI]

[42] Fettiplace R. Hair cell transduction, tuning, and synaptic transmission in the mammalian cochlea. *Compr Physiol*, 2017, 7(4): 1197–1227. [DOI]

[43] Cunningham LL, Tucci DL. Hearing loss in adults. *N Engl J Med*, 2017, 377(25): 2465–2473. [DOI]

[44] Liberman MC, Epstein MJ, Cleveland SS, Wang HB, Maison SF. Toward a differential diagnosis of hidden hearing loss in humans. *PLoS One*, 2016, 11(9): e0162726. [DOI]

[45] Berrettini S, De Vito A, Bruschini L, Fortunato S, Forli F. Idiopathic sensorineural hearing loss in the only hearing ear. *Acta Otorhinolaryngol Ital*, 2016, 36(2): 119–126. [DOI]

[46] Leung MA, Flaherty A, Zhang JA, Hara J, Barber W, Burgess L. Sudden sensorineural hearing loss: primary care update. *Hawaii J Med Public Health*, 2016, 75(6): 172–174. [DOI]

[47] Bermingham-McDonogh O, Reh TA. Regulated reprogramming in the regeneration of sensory receptor cells. *Neuron*, 2011, 71(3): 389–405. [DOI]

[48] Sekine K, Matsumura T, Takizawa T, Kimura Y, Saito S, Shiiba K, Shindo S, Okubo K, Ikezono T. Expression profiling of MicroRNAs in the inner ear of elderly people by real-time PCR quantification. *Audiol Neurol Otol*, 2017, 22(3): 135–145. [DOI]

[49] Pierce ML, Weston MD, Fritzsch B, Gabel HW, Ruvkun G, Soukup GA. MicroRNA-183 family conservation and ciliated neurosensory organ expression. *Evol Dev*, 2008, 10(1): 106–113. [DOI]

[50] Dambal S, Baumann B, McCray T, Williams L, Richards Z, Deaton R, Prins GS, Nonn L. The miR-183 family cluster alters zinc homeostasis in benign prostate cells, organoids and prostate cancer xenografts. *Sci Rep*, 2017, 7(1): 7704. [DOI]

[51] Xu S, Witmer PD, Lumayag S, Kovacs B, Valle D. MicroRNA (miRNA) transcriptome of mouse retina and identification of a sensory organ-specific miRNA cluster. *J Biol Chem*, 2007, 282(34): 25053–25066. [DOI]

[52] Li JY, Ling YH, Huang WH, Sun LM, Li YY, Wang CH, Zhang YH, Wang XD, Dahlgren RA, Wang HL. Regulatory mechanisms of miR-96 and miR-184 abnormal expressions on otic vesicle development of zebrafish following exposure to β-diketone antibiotics. *Chemos-*

phere, 2019, 214: 228–238. [DOI]

[53] Raymond M, Walker E, Dave I, Dedhia K. Genetic testing for congenital non-syndromic sensorineural hearing loss. *Int J Pediatr Otorhinolaryngol*, 2019, 124: 68–75. [DOI]

[54] Li HQ, Fekete DM. MicroRNAs in hair cell development and deafness. *Curr Opin Otolaryngo*, 2010, 18(5): 459–465. [DOI]

[55] Chen J, Johnson SL, Lewis MA, Hilton JM, Huma A, Marcotti W, Steel KP. A reduction in Ptprq associated with specific features of the deafness phenotype of the miR-96 mutant mouse diminuendo. *Eur J Neurosci*, 2014, 39(5): 744–756. [DOI]

[56] Sánchez-Mora C, Ramos-Quiroga JA, Garcia-Martínez I, Fernàndez-Castillo N, Bosch R, Richarte V, Palomar G, Nogueira M, Corrales M, Daigre C, Martínez-Luna N, Grau-Lopez L, Toma C, Cormand B, Roncero C, Casas M, Ribasés M. Evaluation of single nucleotide polymorphisms in the miR-183-96-182 cluster in adulthood attention-deficit and hyperactivity disorder (ADHD) and substance use disorders (SUDs). *Eur Neuropsychopharmacol*, 2013, 23(11): 1463–1473. [DOI]

[57] Mencía A, Modamio-Høybjør S, Redshaw N, Morín M, Mayo-Merino F, Olavarrieta L, Aguirre LA, del Castillo I, Steel KP, Dalmay T, Moreno F, Moreno-Pelayo MA. Mutations in the seed region of human miR-96 are responsible for nonsyndromic progressive hearing loss. *Nat Genet*, 2009, 41(5): 609–613. [DOI]

[58] Lewis MA, Quint E, Glazier AM, Fuchs H, De Angelis MH, Langford C, van Dongen S, Abreu-Goodger C, Piipari M, Redshaw N, Dalmay T, Moreno-Pelayo MA, Enright AJ, Steel KP. An ENU-induced mutation of miR-96 associated with progressive hearing loss in mice. *Nat Genet*, 2009, 41(5): 614–618. [DOI]

[59] Kuhn S, Johnson SL, Furness DN, Chen J, Ingham N, Hilton JM, Steffes G, Lewis MA, Zampini V, Hackney CM, Masetto S, Holley MC, Steel KP, Marcotti W. miR-96 regulates the progression of differentiation in mammalian cochlear inner and outer hair cells. *Proc Natl Acad Sci USA*, 2011, 108(6): 2355–2360. [DOI]

[60] Li YM, Li A, Wu JF, He YZ, Yu HQ, Chai RJ. MiR-182-5p protects inner ear hair cells from cisplatin-induced apoptosis by inhibiting FOXO3a. *Cell Death Dis*, 2016, 7(9): e2362. [DOI]

[61] Patel M, Cai QF, Ding DL, Salvi R, Hu ZH, Hu BH. The miR-183/Taok1 target pair is implicated in cochlear responses to acoustic trauma. *PLoS One*, 2013, 8(3): e58471. [DOI]

[62] MacFarlane LA, Murphy PR. MicroRNA: biogenesis, function and role in cancer. *Curr Genomics*, 2010, 11(7): 537–561. [DOI]

[63] Giraldez AJ, Cinalli RM, Glasner ME, Enright AJ, Thomson JM, Baskerville S, Hammond SM, Bartel DP, Schier AF. MicroRNAs regulate brain morphogenesis in zebrafish. *Science*, 2005, 308(5723): 833–838. [DOI]

[64] Weston MD, Pierce ML, Jensen-Smith HC, Fritzsch B, Rocha-Sanchez S, Beisel KW, Soukup GA. MicroRNA-183 family expression in hair cell development and requirement of MicroRNAs for hair cell maintenance and survival. *Dev Dyn*, 2011, 240(4): 808–819. [DOI]

[65] Hildebrand MS, Witmer PD, Xu S, Newton SS, Kahrizi K, Najmabadi H, Valle D, Smith RJ. miRNA mutations are not a common cause of deafness. *Am J Med Genet A*, 2010, 152A(3): 646–652. [DOI]

[66] Wang XR, Zhang XM, Du JT, Jiang HY. MicroRNA-182 regulates otocyst-derived cell differentiation and targets T-box1 gene. *Hear Res*, 2012, 286(1–2): 55–63. [DOI]

[67] Schellenberg GD, Dawson G, Sung YJ, Estes A, Munson J, Rosenthal E, Rothstein J, Flodman P, Smith M, Coon H, Leong L, Yu CE, Stodgell C, Rodier PM, Spence MA, Minshew N, McMahon WM, Wijsman EM. Evidence for multiple loci from a genome scan of autism kindreds. *Mol Psychiatr*, 2006, 11(11): 1049–1060. [DOI]

[68] Soukup GA, Fritzsch B, Pierce ML, Weston MD, Jahan I, McManus MT, Harfe BD. Residual microRNA expression dictates the extent of inner ear development in conditional dicer knockout mice. *Dev Biol*, 2009, 328(2): 328–341. [DOI]

[69] Bhattacharya A, Cui Y. Knowledge-based analysis of functional impacts of mutations in microRNA seed regions. *J Biosci*, 2015, 40(4): 791–798. [DOI]

[70] Kim CW, Han JH, Wu L, Choi JY. microRNA-183 is essential for hair cell regeneration after neomycin injury in zebrafish. *Yonsei Med J*, 2018, 59(1): 141–147. [DOI]

[71] Van den Ackerveken P, Mounier A, Huyghe A, Sacheli R, Vanlerberghe PB, Volvert ML, Delacroix L, Nguyen L, Malgrange B. The miR-183/ItgA3 axis is a key regulator of prosensory area during early inner ear development. *Cell Death Differ*, 2017, 24(12): 2054–2065. [DOI]

[72] Sivakumaran TA, Resendes BL, Robertson NG, Giersch ABS, Morton CC. Characterization of an abundant COL9A1 transcript in the cochlea with a novel 3UTR: Expression

studies and detection of miRNA target sequence. *Jaro-J Assoc Res Oto*, 2006, 7(2): 160–172. [DOI]

[73] Gu CH, Li XD, Tan Q, Wang Z, Chen LM, Liu YM. MiR-183 family regulates chloride intracellular channel 5 expression in inner ear hair cells. *Toxicol in Vitro*, 2013, 27(1): 486–491. [DOI]

[74] Jiang D, Du JT, Zhang XM, Zhou W, Zong L, Dong C, Chen K, Chen Y, ChenXH, Jiang HY. miR-124 promotes the neuronal differentiation of mouse inner ear neural stem cells. *Int J Mol Med*, 2016, 38(5): 1367–1376. [DOI]

[75] Rudnicki A, Isakov O, Ushakov K, Shivatzki S, Weiss I, Friedman LM, Shomron N, Avraham KB. Next-generation sequencing of small RNAs from inner ear sensory epithelium identifies microRNAs and defines regulatory pathways. *Bmc Genomics*, 2014, 15: 484. [DOI]

[76] Du JT, Zhang XM, Cao H, Jiang D, Wang XR, Zhou W, Chen KT, Zhou J, Jiang HY, Ba L. MiR-194 is involved in morphogenesis of spiral ganglion neurons in inner ear by rearranging actin cytoskeleton via targeting RhoB. *Int J Dev Neurosci*, 2017, 63: 16–26. [DOI]

[77] Park SM, Gaur AB, Lengyel E, Peter ME. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. *Genes Dev*, 2008, 22(7): 894–907. [DOI]

[78] Yan D, Xing YZ, Ouyang XM, Zhu JH, Chen ZY, Lang HN, Liu XZ. Analysis of miR-376 RNA cluster members in the mouse inner ear. *Int J Exp Pathol*, 2012, 93(6): 450–457. [DOI]

[79] Elkan-Miller T, Ulitsky I, Hertzano R, Rudnicki A, Dror AA, Lenz DR, Elkon R, Irmler M, Beckers J, Shamir R, Avraham KB. Integration of transcriptomics, proteomics, and microRNA analyses reveals novel microRNA regulation of targets in the mammalian inner ear. *PLoS One*, 2011, 6(4): e18195. [DOI]

[80] Kurtz CL, Fannin EE, Toth CL, Pearson DS, Vickers KC, Sethupathy P. Inhibition of miR-29 has a significant lipid-lowering benefit through suppression of lipogenic programs in liver. *Sci Rep*, 2015, 5: 12911. [DOI]

[81] Pang JQ, Xiong H, Yang HD, Ou YK, Xu YD, Huang QH, Lai L, Chen SJ, Zhang ZG, Cai YX, Zheng YQ. Circulating miR-34a levels correlate with age-related hearing loss in mice and humans. *Exp Gerontol*, 2016, 76: 58–67. [DOI]

[82] Ling H, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. *Nat Rev Drug Discov*, 2013, 12(11): 847–865. [DOI]

[83] Chiang DY, Cuthbertson DW, Ruiz FR, Li N, Pereira FA. A coregulatory network of NR2F1 and microRNA-140. *PLoS One*, 2013, 8(12): e83358. [DOI]

[84] Lee YJ, Bernstock JD, Klimanis D, Hallenbeck JM. Akt protein kinase, miR-200/miR-182 expression and epithelial-mesenchymal transition proteins in hibernating ground squirrels. *Front Mol Neurosci*, 2018, 11: 22. [DOI]

[85] Burk U, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, Brabletz T. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *Embo Rep*, 2008, 9(6): 582–589. [DOI]

[86] Li YZ, Peng AQ, Ge SL, Wang Q, Liu JJ. miR-204 suppresses cochlear spiral ganglion neuron survival in vitro by targeting TMPRSS3. *Hear Res*, 2014, 314: 60–64. [DOI]

[87] Rudnicki A, Shivatzki S, Beyer LA, Takada Y, Raphael Y, Avraham KB. microRNA-224 regulates Pentraxin 3, a component of the humoral arm of innate immunity, in inner ear inflammation. *Hum Mol Genet*, 2014, 23(12): 3138–3146. [DOI]

[88] Kiernan AE, Xu JX, Gridley T. The Notch ligand JAG1 is required for sensory progenitor development in the mammalian inner ear. *PLoS Genet*, 2006, 2(1): e4. [DOI]

[89] Pan BF, Akyuz N, Liu XP, Asai Y, Nist-Lund C, Kurima K, Derfler BH, Gyorgy B, Limapichat W, Walujkar S, Wimalasena LN, Sotomayor M, Corey DP, Holt JR. TMC1 forms the pore of mechanosensory transduction channels in vertebrate inner ear hair cells. *Neuron*, 2018, 99(4): 736–753.e6. [DOI]

[90] Müller U, Barr-Gillespie PG. New treatment options for hearing loss. *Nat Rev Drug Discov*, 2015, 14(5): 346–385. [DOI]

[91] Bermingham NA, Hassan BA, Price SD, Vollrath MA, Ben-Arie N, Eatock RA, Bellen HJ, Lysakowski A, Zoghbi HY. Math1: an essential gene for the generation of inner ear hair cells. *Science*, 1999, 284(5421): 1837–1841. [DOI]

[92] Fan QQ, Meng FL, Fang R, Li GP, Zhao XL. Functions of Wnt signaling pathway in hair cell differentiation and regeneration. *Hereditas(Beijing)*, 2017, 39(10): 897–907. 范晴晴, 孟飞龙, 房冉, 李高鹏, 赵小立. Wnt 信号通路在毛细胞分化和再生过程中的作用. 遗传, 2017, 39(10): 897–907. [DOI]

[93] Slowik AD, Bermingham-McDonogh O. Hair cell generation by notch inhibition in the adult mammalian cristae. *Jaro-J Assoc Res Oto*, 2013, 14(6): 813–828. [DOI]

[94] Tateya T, Imayoshi I, Tateya I, Hamaguchi K, Torii H,

Ito J, Kageyama R. Hedgehog signaling regulates prosensory cell properties during the basal-to-apical wave of hair cell differentiation in the mammalian cochlea. *Development*, 2013, 140(18): 3848–3857. [DOI]

[95] Mansour SL, Noyes CA, Li CY, Wang XF, Hatch E, Twigg S, WIlkie AOM, Urness L. FGF signaling in inner ear development. *FASEB J*, 2009, 23. [DOI]

[96] Kim HJ, Kang KY, Baek JG, Jo HC, Kim H. Expression of TGFβ family in the developing internal ear of rat embryos. *J Korean Med Sci*, 2006, 21(1): 136–142. [DOI]

[97] Geng RS, Noda T, Mulvaney JF, Lin VYW, Edge ASB, Dabdoub A. Comprehensive expression of wnt signaling pathway genes during development and maturation of the mouse cochlea. *PLoS One*, 2016, 11(2): e0148339. [DOI]

[98] Chen C, Xiang H, Peng YL, Peng J, Jiang SW. Mature miR-183, negatively regulated by transcription factor GATA3, promotes 3T3-L1 adipogenesis through inhibition of the canonical Wnt/β-catenin signaling pathway by targeting LRP6. *Cell Signal*, 2014, 26(6): 1155–1165. [DOI]

[99] Tang XL, Zheng D, Hu P, Zeng ZY, Li M, Tucker L, Monahan R, Resnick MB, Liu M, Ramratnam B. Glycogen synthase kinase 3 beta inhibits microRNA-183-96-182 cluster via the β-Catenin/TCF/LEF-1 pathway in gastric cancer cells. *Nucleic Acids Res*, 2014, 42(5): 2988–2998. [DOI]

[100] Hartman BH, Reh TA, Bermingham-McDonogh O. Notch signaling specifies prosensory domains via lateral induction in the developing mammalian inner ear. *Proc Natl Acad Sci USA*, 2010, 107(36): 15792–15797. [DOI]

[101] Chen ZB Pu MM, Yao J, Cao X, Cheng L. Screening of microRNAs targeting Notch signaling pathway implicated in inner ear development and the role of microRNA-384-5p. *Chin J Otorhinol Head Neck Surg*, 2018, 53(11): 830–837. [DOI]

[102] Zhou W, Du JT, Jiang D, Wang XR, Chen KT, Tang HC, Zhang XM, Cao H, Zong L, Dong C, Jiang HY. microRNA-183 is involved in the differentiation and regeneration of Notch signaling-prohibited hair cells from mouse cochlea. *Mol Med Rep*, 2018, 18(2): 1253–1262. [DOI]

[103] Yang Z, Yao J, Cao X. Roles of the FGF signaling pathway in regulating inner ear development and hair cell regeneration. *Hereditas(Beijing)*, 2018, 40(7): 515–524
杨志, 姚俊, 曹新. FGF 信号通路在内耳发育调控和毛细胞再生中的作用. 遗传, 2018, 40(7): 515–524. [DOI]

[104] Brennecke J, Hipfner DR, Stark A, Russell RB, Cohen SM. Bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in *Drosophila*. *Cell*, 2003, 113(1): 25–36. [DOI]

[105] Tan PX, Du SS, Ren C, Yao QW, Zheng R, Li R, Yuan YW. MicroRNA-207 enhances radiation-induced apoptosis by directly targeting akt3 in cochlea hair cells. *Cell Death Dis*, 2014, 5: e1433. [DOI]

[106] Yamashita H, Takahashi M, Bagger-Sjöbäck D. Expression of epidermal growth factor, epidermal growth factor receptor and transforming growth factor-alpha in the human fetal inner ear. *Eur Arch Oto-Rhino-L*, 1996, 253(8): 494–497. [DOI]

[107] Lu YY, Zheng JY, Liu J, Huang CL, Zhang W, Zeng Y. miR-183 induces cell proliferation, migration, and invasion by regulating PDCD4 expression in the SW1990 pancreatic cancer cell line. *Biomed Pharmacother*, 2015, 70: 151–157. [DOI]

[108] Mendell JT, Olson EN. MicroRNAs in stress signaling and human disease. *Cell*, 2012, 148(6): 1172–1187. [DOI]

[109] Cui J, Zhou B, Ross SA, Zempleni J. Nutrition, microRNAs, and human health. *Adv Nutr*, 2017, 8(1): 105–112. [DOI]

[110] Miguel V, Cui JY, Daimiel L, Espinosa-Díez C, Fernández-Hernando C, Kavanagh TJ, Lamas S. The role of microRNAs in environmental risk factors, noise-induced hearing loss, and mental stress. *Antioxid Redox Sign*, 2018, 28(9): 773–796. [DOI]

[111] Bardin P, Sonneville F, Corvol H, Tabary O. Emerging microRNA therapeutic approaches for cystic fibrosis. *Front Pharmacol*, 2018, 9: 1113. [DOI]

[112] Takeda H, Dondzillo A, Randall JA, Gubbels SP. Challenges in cell-based therapies for the treatment of hearing loss. *Trends Neurosci*, 2018, 41(11): 823–837. [DOI]

[113] Simoni E, Orsini G, Chicca M, Bettini S, Franceschini V, Martini A, Astolfi L. Regenerative medicine in hearing recovery. *Cytotherapy*, 2017, 19(8): 909–915. [DOI]

[114] Shrestha BR, Chia C, Wu L, Kujawa SG, Liberman MC, Goodrich LV. Sensory neuron diversity in the inner ear is shaped by activity. *Cell*, 2018, 174(5): 1229–1246.e17. [DOI]

[115] Sennett R, Rendl M. Mesenchymal-epithelial interactions during hair follicle morphogenesis and cycling. *Semin Cell Dev Biol*, 2012, 23(8): 917–927. [DOI]

[116] Chen H, Sun YM, Dong RQ, Yang SS, Pan CY, Xiang D, Miao MY, Jiao BH. Mir-34a is upregulated during liver regeneration in rats and is associated with the suppression of hepatocyte proliferation. *PLoS One*, 2011, 6(5):

e20238. [DOI]

[117] Liang DD, Li J, Wu YH, Zhen LX, Li CM, Qi M, Wang LJ, Deng FF, Huang J, Lv F, Liu Y, Ma C, Yu ZR, Zhang YZ, Chen YH. miRNA-204 drives cardiomyocyte proliferation via targeting Jarid2. *Int J Cardiol*, 2015, 201: 38–48. [DOI]

[118] Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulkader RS, Abdulle AM, Abebo TA, Abera SF, Aboyans V, Abu-Raddad LJ, Ackerman IN, Adamu AA, Adetokunboh O, Afarideh M, Afshin A, Agarwal SK, Aggarwal R, Agrawal A, Agrawal S, Ahmadieh H, Ahmed MB, Aichour MTE, Aichour AN, Aichour I, Aiyar S, Akinyemi RO, Akseer N, Al Lami FH, Alahdab F, Al-Aly Z, Alam K, Alam N, Alam T, Alasfoor D, Alene KA, Ali R, Alizadeh-Navaei R, Alkerwi A, Alla F, Allebeck P, Allen C, Al-Maskari F, Al-Raddadi R, Alsharif U, Alsowaidi S, Altirkawi KA, Amare AT, Amini E, Ammar W, Amoako YA, Andersen HH, Antonio CAT, Anwari P, Ärnlöv J, Artaman A, Aryal KK, Asayesh H, Asgedom SW, Assadi R, Atey TM, Atnafu NT, Atre SR, Avila-Burgos L, Avokphako EFGA, Awasthi A, Bacha U, Badawi A, Balakrishnan K, Banerjee A, Bannick MS, Barac A, Barber RM, Barker-Collo SL, Bärnighausen T, Barquera S, Barregard L, Barrero LH, Basu S, Battista B, Battle KE, Baune BT, Bazargan-Hejazi S, Beardsley J, Bedi N, Beghi E, Béjot Y, Bekele BB, Bell ML, Bennett DA, Bensenor IM, Benson J, Berhane A, Berhe DF, Bernabé E, Betsu BD, Beuran M, Beyene AS, Bhala N, Bhansali A, Bhatt S, Bhutta ZA, Biadgilign S, Bicer BK, Bienhoff K, Bikbov B, Birungi C, Biryukov S, Bisanzio D, Bizuayehu HM, Boneya DJ, Boufous S, Bourne RRA, Brazinova A, Brugha TS, Buchbinder R, Bulto LNB, Bumgarner BR, Butt ZA, Cahuana-Hurtado L, Cameron E, Car M, Carabin H, Carapetis JR, Cárdenas R, Carpenter DO, Carrero JJ, Carter A, Carvalho F, Casey DC, Caso V, Castañeda-Orjuela CA, Castle CD, Catalá-López F, Chang HY, Chang JC, Charlson FJ, Chen H, Chibalabala M, Chibueze CE, Chisumpa VH, Chitheer AA, Christopher DJ, Ciobanu LG, Cirillo M, Colombara D, Cooper C, Cortesi PA, Criqui MH, Crump JA, Dadi AF, Dalal K, Dandona L, Dandona R, das Neves J, Davitoiu DV, de Courten B, De Leo D, Defo BK, Degenhardt L, Deiparine S, Dellavalle RP, Deribe K, Des Jarlais DC, Dey S, Dharmaratne SD, Dhillon PK, Dicker D, Ding EL, Djalalinia S, Do HP, Dorsey ER, Dos Santos KPB, Douwes-Schultz D, Doyle KE, Driscoll TR, Dubey M, Duncan BB, El-Khatib ZZ, Ellerstrand J, Enayati A, Endries AY, Ermakov SP, Erskine HE, Eshrati B, Eskandarieh S, Esteghamati A, Estep K, Fanuel FBB, Farinha CSES, Faro A, Farzadfar F, Fazeli MS, Feigin VL, Fereshtehnejad SM, Fernandes JC, Ferrari AJ, Feyissa TR, Filip I, Fischer F, Fitzmaurice C, Flaxman AD, Flor LS, Foigt N, Foreman KJ, Franklin RC, Fullman N, Fürst T, Furtado JM, Futran ND, Gakidou E, Ganji M, Garcia-Basteiro AL, Gebre T, Gebrehiwot TT, Geleto A, Gemechu BL, Gesesew HA, Gething PW, Ghajar A, Gibney KB, Gill PS, Gillum RF, Ginawi IAM, Giref AZ, Gishu MD, Giussani G, Godwin WW, Gold AL, Goldberg EM, Gona PN, Goodridge A, Gopalani SV, Goto A, Goulart AC, Griswold M, Gugnani HC, Gupta R, Gupta R, Gupta T, Gupta V, Hafezi-Nejad N, Hailu GB, Hailu AD, Hamadeh RR, Hamidi S, Handal AJ, Hankey GJ, Hanson SW, Hao Y, Harb HL, Hareri HA, Haro JM, Harvey J, Hassanvand MS, Havmoeller R, Hawley C, Hay SI, Hay RJ, Henry NJ, Heredia-Pi IB, Hernandez JM, Heydarpour P, Hoek HW, Hoffman HJ, Horita N, Hosgood HD, Hostiuc S, Hotez PJ, Hoy DG, Htet AS, Hu G, Huang H, Huynh C, Iburg KM, Igumbor EU, Ikeda C, Irvine CMS, Jacobsen KH, Jahanmehr N, Jakovljevic MB, Jassal SK, Javanbakht M, Jayaraman SP, Jeemon P, Jensen PN, Jha V, Jiang G, John D, Johnson SC, Johnson CO, Jonas JB, Jürisson M, Kabir Z, Kadel R, Kahsay A, Kamal R, Kan H, Karam NE, Karch A, Karema CK, Kasaeian A, Kassa GM, Kassaw NA, Kassebaum NJ, Kastor A, Katikireddi SV, Kaul A, Kawakami N, Keiyoro PN, Kengne AP, Keren A, Khader YS, Khalil IA, Khan EA, Khang YH, Khosravi A, Khubchandani J, Kiadaliri AA, Kieling C, Kim YJ, Kim D, Kim P, Kimokoti RW, Kinfu Y, Kisa A, Kissimova-Skarbek KA, Kivimaki M, Knudsen AK, Kokubo Y, Kolte D, Kopec JA, Kosen S, Koul PA, Koyanagi A, Kravchenko M, Krishnaswami S, Krohn KJ, Kumar GA, Kumar P, Kumar S, Kyu HH, Lal DK, Lalloo R, Lambert N, Lan Q, Larsson A, Lavados PM, Leasher JL, Lee PH, Lee JT, Leigh J, Leshargie CT, Leung J, Leung R, Levi M, Li Y, Li Y, Li Kappe D, Liang X, Liben ML, Lim SS, Linn S, Liu PY, Liu A, Liu S, Liu Y, Lodha R, Logroscino G, London SJ, Looker KJ, Lopez AD, Lorkowski S, Lotufo PA, Low N, Lozano R, Lucas TCD, Macarayan ERK, Magdy Abd El Razek H, Magdy Abd El Razek M, Mahdavi M, Majdan M, Majdzadeh R, Majeed A, Malekzadeh R, Malhotra R, Malta DC, Mamun AA, Manguerra H, Manhertz T, Mantilla A, Mantovani LG, Mapoma CC, Marczak LB,

Martinez-Raga J, Martins-Melo FR, Martopullo I, März W, Mathur MR, Mazidi M, McAlinden C, McGaughey M, McGrath JJ, McKee M, McNellan C, Mehata S, Mehndiratta MM, Mekonnen TC, Memiah P, Memish ZA, Mendoza W, Mengistie MA, Mengistu DT, Mensah GA, Meretoja TJ, Meretoja A, Mezgebe HB, Micha R, Millear A, Miller TR, Mills EJ, Mirarefin M, Mirrakhimov EM, Misganaw A, Mishra SR, Mitchell PB, Mohammad KA, Mohammadi A, Mohammed KE, Mohammed S, Mohanty SK, Mokdad AH, Mollenkopf SK, Monasta L, Montico M, Moradi-Lakeh M, Moraga P, Mori R, Morozoff C, Morrison SD, Moses M, Mountjoy-Venning C, Mruts KB, Mueller UO, Muller K, Murdoch ME, Murthy GVS, Musa KI, Nachega JB, Nagel G, Naghavi M, Naheed A, Naidoo KS, Naldi L, Nangia V, Natarajan G, Negasa DE, Negoi RI, Negoi I, Newton CR, Ngunjiri JW, Nguyen TH, Nguyen QL, Nguyen CT, Nguyen G, Nguyen M, Nichols E, Ningrum DNA, Nolte S, Nong VM, Norrving B, Noubiap JJN, O'Donnell MJ, Ogbo FA, Oh IH, Okoro A, Oladimeji O, Olagunju TO, Olagunju AT, Olsen HE, Olusanya BO, Olusanya JO, Ong K, Opio JN, Oren E, Ortiz A, Osgood-Zimmerman A, Osman M, Owolabi MO, Pa M, Pacella RE, Pana A, Panda BK, Papachristou C, Park EK, Parry CD, Parsaeian M, Patten SB, Patton GC, Paulson K, Pearce N, Pereira DM, Perico N, Pesudovs K, Peterson CB, Petzold M, Phillips MR, Pigott DM, Pillay JD, Pinho C, Plass D, Pletcher MA, Popova S, Poulton RG, Pourmalek F, Prabhakaran D, Prasad NM, Prasad N, Purcell C, Qorbani M, Quansah R, Quintanilla BPA, Rabiee RHS, Radfar A, Rafay A, Rahimi K, Rahimi-Movaghar A, Rahimi-Movaghar V, Rahman MHU, Rahman M, Rai RK, Rajsic S, Ram U, Ranabhat CL, Rankin Z, Rao PC, Rao PV, Rawaf S, Ray SE, Reiner RC, Reinig N, Reitsma MB, Remuzzi G, Renzaho AMN, Resnikoff S, Rezaei S, Ribeiro AL, Ronfani L, Roshandel G, Roth GA, Roy A, Rubagotti E, Ruhago GM, Saadat S, Sadat N, Safdarian M, Safi S, Safiri S, Sagar R, Sahathevan R, Salama J, Saleem HOB, Salomon JA, Salvi SS, Samy AM, Sanabria JR, Santomauro D, Santos IS, Santos JV, Santric Milicevic MM, Sartorius B, Satpathy M, Sawhney M, Saxena S, Schmidt MI, Schneider IJC, Schöttker B, Schwebel DC, Schwendicke F, Seedat S, Sepanlou SG, Servan-Mori EE, Setegn T, Shackelford KA, Shaheen A, Shaikh MA, Shamsipour M, Shariful Islam SM, Sharma J, Sharma R, She J, Shi P, Shields C, Shifa GT, Shigematsu M, Shinohara Y, Shiri R, Shirkoohi R, Shirude S, Shishani K, Shrime MG, Sibai AM, Sigfusdottir ID, Silva DAS, Silva JP, Silveira DGA, Singh JA, Singh NP, Sinha DN, Skiadaresi E, Skirbekk V, Slepak EL, Sligar A, Smith DL, Smith M, Sobaih BHA, Sobngwi E, Sorensen RJD, Sousa TCM, Sposato LA, Sreeramareddy CT, Srinivasan V, Stanaway JD, Stathopoulou V, Steel N, Stein MB, Stein DJ, Steiner TJ, Steiner C, Steinke S, Stokes MA, Stovner LJ, Strub B, Subart M, Sufiyan MB, Sunguya BF, Sur PJ, Swaminathan S, Sykes BL, Sylte DO, Tabarés-Seisdedos R, Taffere GR, Takala JS, Tandon N, Tavakkoli M, Taveira N, Taylor HR, Tehrani-Banihashemi A, Tekelab T, Terkawi AS, Tesfaye DJ, Tesssema B, Thamsuwan O, Thomas KE, Thrift AG, Tiruye TY, Tobe-Gai R, Tollanes MC, Tonelli M, Topor-Madry R, Tortajada M, Touvier M, Tran BX, Tripathi S, Troeger C, Truelsen T, Tsoi D, Tuem KB, Tuzcu EM, Tyrovolas S, Ukwaja KN, Undurraga EA, Uneke CJ, Updike R, Uthman OA, Uzochukwu BSC, van Boven JFM, Varughese S, Vasankari T, Venkatesh S, Venketasubramanian N, Vidavalur R, Violante FS, Vladimirov SK, Vlassov VV, Vollset SE, Wadilo F, Wakayo T, Wang YP, Weaver M, Weichenthal S, Weiderpass E, Weintraub RG, Werdecker A, Westerman R, Whiteford HA, Wijeratne T, Wiysonge CS, Wolfe CDA, Woodbrook R, Woolf AD, Workicho A, Xavier D, Xu G, Yadgir S, Yaghoubi M, Yakob B, Yan LL, Yano Y, Ye P, Yimam HH, Yip P, Yonemoto N, Yoon SJ, Yotebieng M, Younis MZ, Zaidi Z, Zaki MES, Zegeye EA, Zenebe ZM, Zhang X, Zhou M, Zipkin B, Zodpey S, Zuhlke LJ, Murray CJL. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, 2017, 390(10100): 1211–1259. [DOI]

[119] He P, Luo YN, Hu XY, Gong R, Wen X, Zheng XY. Association of socioeconomic status with hearing loss in Chinese working-aged adults: A population-based study. *PLoS One*, 2018, 13(3): e0195227. [DOI]

[120] Soukup GA. Little but loud: Small RNAs have a resounding affect on ear development. *Brain Res*, 2009, 1277: 104–114. [DOI]

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