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Review:

Atoh1 regulation in the cochlea: more than just transcription

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Abstract: More than 80% of all cases of deafness are related to the death or degeneration of cochlear hair cells and the associated spiral ganglion neurons, and a lack of regeneration of these cells leads to permanent hearing loss. Therefore, the regeneration of lost hair cells is an important goal for the treatment of deafness. Atoh1 is a basic helix-loop-helix (bHLH) transcription factor that is critical in both the development and regeneration of cochlear hair cells. *Atoh1* is transcriptionally regulated by several signaling pathways, including Notch and Wnt signalings. At the post-translational level, it is regulated through the ubiquitin-proteasome pathway. In vitro and in vivo studies have revealed that manipulation of these signaling pathways not only controls development, but also leads to the regeneration of cochlear hair cells after damage. Recent progress toward understanding the signaling networks involved in hair cell development and regeneration has led to the development of new strategies to replace lost hair cells. This review focuses on our current understanding of the signaling pathways that regulate Atoh1 in the cochlea.

Key words: Atoh1; Huwe1; Cochlea; Hair cells; Regeneration; Post-translational regulation
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1 Introduction

Hair cell formation is dependent on the basic helix-loop-helix (bHLH) transcription factor Atoh1, which is both necessary and sufficient for hair cell differentiation during development (Bermingham *et al*., 1999). Atoh1 overexpression in the inner ear via genetic or pharmacological manipulation has been shown to result in new hair cell formation in the cochlea and to restore hearing in experimental animal models (Zheng and Gao, 2000; Izumikawa *et al*., 2005; Gubbels *et al*., 2008). The transcriptional and post-translational regulations of Atoh1 have been shown to involve several overlapping signaling pathways. Transcriptional regulation of Atoh1 by Wnt or Notch signaling or post-translational regulation by the Huwe1-ubiquitin-proteasome pathway has been shown to sucessfully convert inner ear progenitor cells into hair cells (Shi *et al*., 2010; 2013; 2014; Mizutari *et al*., 2013; Bramhall *et al*., 2014; Cheng *et al*., 2016). These studies have led to novel approaches for the regeneration of hair cells in the inner ear. This review focuses on recent advances in our understanding of the signaling pathways that regulate Atoh1 in the cochlea.

2 Hearing impairment

Hearing impairment is one of the most prevalent disabilities in industrialized countries, and it is estimated that 360 million people have moderate to profound

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hearing deficiency globally (WHO, 2017). Most cases of hearing impairment involve sensorineural hearing loss caused by the degeneration or loss of two specific inner ear cell types: cochlear hair cells, which act as the primary mechanoreceptors for sound transduction, and the connected auditory nerve neurons, which transmit electrical signals from the synapsed inner hair cells to the brain (Davis, 1983).

Loss of cochlear hair cells caused by genetic mutations, ototoxic medications, noise overexposure, autoimmune disease, or aging is irreversible in mammals because they have very limited ability to spontaneously regenerate hair cells after loss, and there are currently very few methods to regenerate hearing function after hair cell damage, especially in adult animals (Izumikawa *et al*., 2005; Mizutari *et al*., 2013). Vestibular hair cells have a limited regenerative capacity (Forge *et al*., 1993; Warchol *et al*., 1993; Wang *et al*., 2015), but spontaneous hair cell regeneration after damage or hair cell loss has been reported only in the newborn murine cochlea (Bramhall *et al*., 2014; Cox *et al*., 2014). For deafness caused by loss of cochlear hair cells, cochlear implants are surgically implanted into the inner ear to stimulate the spiral ganglion. However, cochlear implants depend on the remaining functional spiral ganglion neurons, the loss of which can severely compromise their efficacy (Incesulu and Nadol, 1998). The regeneration or replacement of damaged cochlear hair cells is thus the ultimate goal for the treatment of hearing loss.

Several different approaches for hair cell regeneration have been attempted, including cell therapy, gene therapy, and pharmacological therapy. A few attempts at cell transplantation into the damaged cochlea have been reported, but most have shown extremely limited survival of transplanted cells and the inability of these cells to differentiate into mature hair cell types (Hu *et al*., 2005; Hu and Ulfendahl, 2006). Gene therapy involving the overexpression of Atoh1 has been shown to be a successful strategy for converting supporting cells into hair cells, thereby restoring hearing loss after damage (Izumikawa *et al*., 2005; Richardson and Atkinson, 2015). Gene augmentation (Akil *et al*., 2012; Askew *et al*., 2015; Pan *et al*., 2017), as well as emerging CRISPR-Cas9 genome editing methods (Zou *et al*., 2015; Zuris *et al*., 2015; Mianné *et al*., 2016), also provides promising experimental paradigms for treating genetic deafness. However, the complexity of the inner ear anatomy, as well as a lack of ideal vector systems and appropriate delivery methods, has made the delivery of foreign genetic material into the inner ear challenging (Husseman and Raphael, 2009; Shu *et al*., 2016). Pharmacotherapy using local delivery of small molecule compounds to convert inner ear progenitors into hair cells seems to be a more physiologically relevant approach to regenerating lost hair cells after damage (Mizutari *et al*., 2013). However, a successful therapy will require a better understanding of the underlying mechanisms controlling hair cell formation and regeneration.

3 Atoh1, a bHLH transcription factor, is required for hair cell differentiation and regeneration after damage

bHLH transcription factors orchestrate cell fate commitment and specification during development (Lo *et al*., 1991; Ross *et al*., 2003), and a homologous group of "proneural" bHLH transcription factors plays a central role in neurogenesis. Several proneural bHLH transcription factors, including Atoh1, Neurog1, Neurod1, and Ascl1, contribute to the development of inner ear neurons and hair cells (Bertrand *et al*., 2002; Fritzsch, 2003; Tiveron *et al*., 2003; Jahan *et al*., 2013).

Atoh1, the mammalian homolog of the Drosophila gene *atonal* (also known as *Math1* for "mouse *atoh1*" and *HATH1* for "human *atoh1*") (Ben-Arie *et al*., 1996), is a bHLH transcription factor that is both necessary and sufficient for the formation and differentiation of inner ear hair cells. Animal studies have shown that *Atoh1*-knockout mice fail to form cochlear and vestibular hair cells (Bermingham *et al*., 1999) as a result of progenitor cell apoptosis (Chen *et al*., 2002). In gain-of-function studies, overexpression of *Atoh1* in mice by viral delivery led to ectopic hair cell formation in organ of Corti explants (Zheng and Gao, 2000). In vivo and in utero experiments in mice confirmed that forced upregulation of *Atoh1* leads to the formation of extra hair cells (Woods *et al*., 2004; Izumikawa *et al*., 2005; Staecker *et al*., 2007; Gubbels *et al*., 2008; Liu *et al*., 2012; 2014; Atkinson *et al*., 2014), but very little is known about how cells regulate the level of *Atoh1*, especially in the cochlea.

4 Atoh1 level is critical for hair cell development and regeneration in mice

Proper spatiotemporal expression of *Atoh1* is key for the differentiation and viability of hair cells. *Atoh1* is expressed in mice in the inner ear progenitors before they have committed to the hair cell fate. It is first detected in the prosensory cells of the basal cochlear turn of the embryonic cochlea at embryonic day (E) 13.5. The expression of *Atoh1* surges at the base of the cochlea by E14.5 and starts to appear in the apical turn by E17.5. *Atoh1* expression begins to decline immediately after birth in the basal turn and by postnatal day 4 in hair cells in the apical turn (Yang *et al*., 2010; Pan *et al*., 2012).

Atoh1 affects not only hair cell differentiation, but also hair cell viability. Embryonic reduction of *Atoh1* led to significant cochlear hair cell loss and abnormal hair cell bundle formation in a transgenic mouse model (Pan *et al*., 2012). Temporally, *Atoh1* is critical for the survival of hair cell progenitors at the base of the cochlea in a 72-h window from E13.5 to E16.5, and deletion of *Atoh1* outside this developmental window does not affect survival (Cai *et al*., 2013). Although *Atoh1* overexpression in the supporting cells leads to ectopic hair cell formation, transgenic mouse models have shown that persistent *Atoh1* overexpression in the cochlear hair cells leads to hair cell death and eventual hearing loss (Liu *et al*., 2012). A similar phenotype was also seen when Atoh1 protein degradation mechanisms were disrupted (Cheng *et al*., 2016).

5 Atoh1 is widely expressed

In addition to hair cell formation, Atoh1 plays important roles in the differentiation and formation of several other cell types. *Atoh1* knockout induces cell loss in several tissues, including cerebellar granule cells (Ben-Arie *et al*., 1997; Flora *et al*., 2007; Forget *et al*., 2014), retrotrapezoid nucleus (RTN) neurons in the medulla (Wang *et al*., 2005; Huang *et al*., 2012; Ruffault *et al*., 2015), dorsal commissural interneurons in the spine (Miesegaes *et al*., 2009), intestinal goblet cells (Yang *et al*., 2001; VanDussen and Samuelson, 2010), and Merkel cells in the skin (Ben-Arie *et al*., 2000; Fröhlich *et al*., 2009; Morrison *et al*., 2009; Maksimovic *et al*., 2014; Wright *et al*., 2015). The distribution of Atoh1 in cells other than inner ear hair cells and the associated phenotypes in loss-of-function assays are listed in Table 1.

Atoh1 expression has also been reported to be associated with tumorigenesis. *Atoh1* acts as a tumor suppressor gene in the colon and skin, as it antagonizes tumor formation and growth, and many colorectal cancer and Merkel cell carcinoma patients show genetic mutations of *Atoh1* (Bossuyt *et al*., 2009). However, *Atoh1* acts as an oncogene in medulloblastoma (Zhao H. *et al*., 2008; Flora *et al*., 2009; Ayrault *et al*., 2010), indicating its multiple roles in differentiation and proliferation in different cell types.

6 Signaling pathways that regulate Atoh1

6.1 Notch signaling pathway

Notch signaling plays a key role in *Atoh1* regulation and inner ear development (Jarriault *et al*., 1995; Lanford *et al*., 1999; Brooker *et al*., 2006). The major role of Notch signaling is to regulate cell fate decisions through lateral inhibition during development. It acts as a mediator between prosensory cells during development, leading these cells to differentiate into hair cells and supporting cells. Thus, Notch signaling is utilized to establish the structural pattern of hair cells and supporting cells in the cochlea (Kelley, 2003).

The inner ear is derived from the otic placode, which is recognized initially as a thickening near the hindbrain at E8 in mice. The otic placode invaginates by E10.5 to form an otocyst that contains prosensory cells and ganglion neuroblasts. The determination of hair cell or supporting cell fate is influenced by Notch signaling, and developing hair cells express *Atoh1* along with the Notch ligands *Jag2* and *Delta1*. These ligands bind to Notch1 in adjacent cells and induce the release of Notch intracellular domain (NICD) from their membranes. Upregulation of inhibitory bHLH transcription factors such as *Hes1* and *Hes5* follows after the increase of NICD, and expression of *Atoh1* is blocked, leading to inhibition of hair cell fate and development of supporting cells (Kelley, 2003; 2006).

Pharmacological inhibition of Notch signaling by γ-secretase inhibitors increases the number of cochlear hair cells in neonatal cochlear explants

Table 1 Atoh1 expression and its function in cell types other than hair cells

Cell type	Function of Atoh1	Phenotype in loss-of-function assays	Reference
Cerebellar granule cells	Maturation and proliferation	Missing external germinal layer (EGL) of the developing cerebellum	Ben-Arie *et al*., 1997; Wang *et al*., 2005; Flora *et al*., 2007; Forget *et al*., 2014
Retrotrapezoid nucleus (RTN) neurons of the medulla	Migration of neurons and establishment of essential connections with the pre-Bötzinger complex	RTN neurons fail to develop and establish connections with the respiratory rhythm-generating center in mammals	Rose *et al*., 2009; Huang *et al*., 2012; Ruffault *et al*., 2015
D1 commissural interneurons of the spinal cord	Ventral migration and fate determination of D1 interneurons	Progenitors adopting roof plate or D2 interneuron fates	Miesegaes *et al*., 2009
Intestinal goblet cells	Secretory lineage fate determination	Failure to form intestinal secretory cells	Yang *et al*., 2001; Shroyer *et al*., 2007; VanDussen and Samuelson, 2010
Merkel cells	Specification of Merkel cells	Absence of Merkel cells	Ben-Arie *et al*., 2000; Morrison *et al*., 2009; van Keymeulen *et al*., 2009; Maksimovic *et al*., 2014

(Yamamoto *et al*., 2006; Takebayashi *et al*., 2007; Bramhall *et al*., 2014; Li *et al*., 2015; Maass *et al*., 2015) and increases the differentiation of inner ear stem cells into hair cells (Jeon *et al*., 2011). In an in vitro lineage-tracing study involving genetically marking supporting cells with a fluorescent reporter, treatment with γ-secretase inhibitors after aminoglycoside-induced hair cell damage has been shown to promote hair cell regeneration through the direct transdifferentiation of supporting cells in the cochlea (Bramhall *et al*., 2014). An in vivo study also showed that direct round-window application of γ-secretase inhibitors resulted in recovery of cochlear function after noise-induced hair cell damage. This was evidenced by increased *Atoh1* expression and direct conversion of supporting cells into hair cells, as measured by a similar genetic tagging model (Mizutari *et al*., 2013).

The responsiveness of the cochlea to γ-secretase inhibitors has been shown to be position-dependent and age-dependent. The apical region of the cochlea exhibits a stronger response in terms of transdifferentiation of supporting cells into hair cells compared to the basal region, and the response declines rapidly with age (Mizutari *et al*., 2013; Bramhall *et al*., 2014; Maass *et al*., 2015).

6.2 Wnt/β-catenin signaling pathway

The Wnt pathway plays a critical role in patterning and cell fate specification in the early development of the inner ear (Stevens *et al*., 2003; Gregorieff and Clevers, 2005; Riccomagno *et al*., 2005; Ohyama *et al*., 2006). In canonical Wnt signaling, Wnt binds to receptors on the cell membrane surface to disrupt the destruction complex consisting of axin, adenomatosis polyposis coli (APC), glycogen synthase kinase 3β (GSK-3β), and Disheveled (Dvl). This prevents β-catenin from being degraded in the cytoplasm. β-Catenin then translocates into the nucleus and subsequently forms nuclear β-catenin/Tcf complexes that drive the expression of Wnt target genes. In non-canonical Wnt signaling, Wnt proteins can work in a β-catenin-independent manner via the planar cell polarity (PCP) and Wnt/calcium pathways (Jansson *et al*., 2015).

Wnt/β-catenin signaling induces patches of hair cells and supporting cells in the auditory sensory epithelium and is involved in establishing or maintaining the distinction between sensory domains that contain hair cells and non-sensory domains in the inner ear (Stevens *et al*., 2003). Overexpression of β-catenin increases *Atoh1* expression in neuroblastoma cells and neural progenitor cells. This upregulation is due to the interaction of β-catenin with the 3'-enhancer of the *Atoh1* gene (Shi *et al*., 2010). Conditional knockout of β-catenin inhibits hair cell formation from sensory progenitors, while constitutive upregulation of β-catenin expands sensory progenitors and results in the formation of extra hair cells (Shi *et al*., 2012; 2014; McLean *et al*., 2017).

The Notch and Wnt/β-catenin signaling pathways interact with each other. As mentioned earlier, β-catenin increases *Atoh1* expression through interaction

with the 3' enhancer of *Atoh1*, and this accounts for the effect of Notch inhibition on *Atoh1*. Shi *et al*. (2010) found that inhibition of Notch signaling increases β-catenin expression, while simultaneous inhibition of β-catenin abolishes the increase in *Atoh1* expression caused by Notch inhibition. Thus, β-catenin expression is required not only for increased expression of *Atoh1*, but also for the mitotic generation of hair cells in the cochlea after Notch inhibition (Li *et al*., 2015). Interestingly, a combination of Notch inhibition and Wnt signaling activation seems to have synergistic effects on the proliferation and transdifferentiation of progenitors or supporting cells in the neonatal cochlea, especially in the basal turn that usually shows only limited ability to form new hair cells after birth (Ni *et al*., 2016; McLean *et al*., 2017).

6.3 Post-translational regulation of Atoh1: the CK1-Huwe1-ubiquitin-proteasome pathway

Increasing evidence has shown that *Atoh1* gene expression is tightly regulated by overlapping pathways, some of which have been described above. Post-translational regulation of Atoh1, however, is only now beginning to be understood. The ubiquitin-proteasome pathway (UPP) is the major post-translational regulatory system in eukaryotes, and it plays an important role in the development and physiology of eukaryotic cells (Tai and Schuman, 2008). The UPP has been implicated in the regulation of stem cell differentiation and lineage commitment via proteolytic degradation of key regulatory proteins. Specific protein substrates are conjugated by polyubiquitylation in an adenosine triphosphate (ATP)-dependent process and then targeted by the proteasome, the machinery by which proteins are degraded. The system is highly selective and tightly regulated. It not only degrades misfolded or damaged proteins, but is also essential for regulating cell-signaling pathways (Naujokat and Šarić, 2007).

The UPP consists of three key enzymes: a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), and a ubiquitin ligase (E3). E3 catalyzes polyubiquitin (and sometimes monoubiquitin) chain formation by transferring ubiquitin that has been activated by E1 and E2 onto the lysine residues of specific substrates. Huwe1 (HECT, UBA, and WWE domain containing 1) is a large 4371-amino acid HECT-domain E3 ubiquitin ligase that is involved in proteasomal degradation of several protein substrates, including Atoh1 in the cerebellum and in the cochlea (Forget *et al*., 2014; Cheng *et al*., 2016). Huwe1 binds to Atoh1 and forms a lysine 48-cojugated polyubiquitin chain on Atoh1 as a signal for proteasomal degradation (Cheng *et al*., 2016). As a result, overexpression of Huwe1 decreases Atoh1 levels, while inhibiting Huwe1 increases the half-life of the Atoh1 protein.

A “degron” is a sequence element or modification that is sufficient to be recognized or targeted by an E3 ligase to promote ubiquitylation (Varshavsky, 1991). Atoh1 is found to be enriched in serine residues in the C-terminus, and many of the serines are conserved among different species. Casein kinase 1 (CK1), a serine/threonine selective protein kinase, phosphorylates Atoh1 at its serine-enriched C-terminal region, specifically serine 334, to form a phosphodegron that enhances the Atoh1-Huwe1 interaction and the subsequent ubiquitylation of Atoh1 (Cheng *et al*., 2016). The overexpression of CK1 increases the degradation of Atoh1, while inhibition of CK1 stabilizes Atoh1.

Interestingly, other sites, including other conserved serines at the C-terminus, have been reported to contribute to Atoh1 stability. Forget *et al*. (2014) found that sonic hedgehog (SHH) controls the phosphorylation of serine 328 and serine 339 of Math1 through protein phosphatase 2A (PP2A) activity to protect Atoh1 from degradation. Tsuchiya *et al*. (2007) reported that Atoh1 protein is expressed in normal colon tissue, but it is degraded by GSK3β in cancer tissue through phosphorylation of serine 54 and serine 58 of Hath1 (the equivalent of serine 52 and serine 56 of Math1).

The biological roles of Huwe1 in development and neurogenesis have recently been described (Zhao X. *et al*., 2008; 2009; D'Arca *et al*., 2010; Dominguez-Brauer *et al*., 2016; Urbán *et al*., 2016). Atoh1 degradation by Huwe1 is required for proper neuronal migration and differentiation in the cerebellum (Forget *et al*., 2014) because uncontrolled Atoh1 expression in the cerebellum leads to early postnatal lethality and interferes with cerebellar development (Helms *et al*., 2001). Spatiotemporal control of the Atoh1 protein level by Huwe1 is essential for cochlear hair cell fate determination and survival (Cheng *et al*., 2016), and conditional knockout of Huwe1 in

the cochlear supporting cells at the embryonic or early postnatal stage leads to extra hair cells in the cochlea. However, hair cell death is observed when Huwe1 is conditionally knocked out in the cochlear hair cells, and this phenotype appears to be correlated with an increase in Atoh1 protein expression. This is in line with a previous study showing that *Atoh1* overexpression in the hair cell causes hair cell death (Liu *et al*., 2012). Thus, the termination of Atoh1 activity after hair cell differentiation and maturation seems to be critical for normal cell patterning in the cochlea. Although several substrates of Huwe1 have been found to be associated with cell apoptosis, including Mcl-1, protein phosphatase 5 (PP5), p53, Myc, and cdc6 (Chen *et al*., 2005; Hall *et al*., 2007; D'Arca *et al*., 2010; Kurokawa *et al*., 2013), further studies are required to unravel the mechanisms of hair cell death underlying Huwe1 deletion and Atoh1 overexpression.

7 Concluding remarks

Atoh1 is a key transcription factor in the development and regeneration processes of the inner ear. Several signaling pathways have been shown to be involved in the regulation of its expression in the cochlea, including the Notch, Wnt, and ubiquitin-proteasome pathways. The studies reviewed in this article have shown that proper spatiotemporal control of Atoh1 expression is essential for inner ear development, not only at the transcriptional level, but also at the post-translational level (concluded in Fig. 1). Forcing Atoh1 overexpression or manipulating Atoh1-enhancing signaling pathways is one of most efficient strategies known for regenerating damaged hair cells. Incorporating knowledge of how Atoh1 is regulated will lead to a better understanding of cochlear development and to more insights into therapeutic strategies for hair cell regeneration.

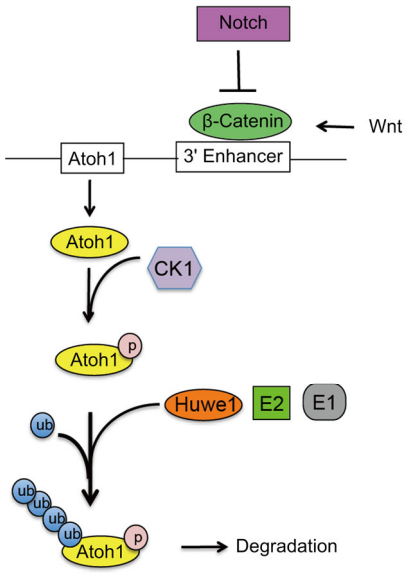

Fig. 1 Summary of Atoh1 regulation

Wnt signaling activates *Atoh1* expression through interactions between β-catenin and the 3' enhancer of *Atoh1*. Overexpression of Notch signaling decreases β-catenin and decreases *Atoh1* expression, while inhibition of Notch leads to upregulation of β-catenin and increased *Atoh1* expression. At the post-translational level, CK1 binds to and phosphorylates Atoh1 to facilitate interaction with the E3 ubiquitin ligase Huwe1, which orchestrates ubiquitin transfer events from E1 (ubiquitin-activating enzyme) and E2 (ubiquitin-conjugating enzyme). This in turn leads to the polyubiquitylation and proteasomal degradation of Atoh1. Figure adapted and modified from Shi *et al*. (2010) and Cheng *et al*. (2016)

Compliance with ethics guidelines

Yen-Fu CHENG declares that he has no conflict of interest.

This article does not contain any studies with human or animal subjects performed by the author.

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中文概要

题　目：Atoh1 转录因子在耳蜗内的转译后调节

概　要：Atoh1 属于 bHLH 转录因子家族成员，其对耳蜗毛细胞的胚胎发育及损伤后再生具有重要作用。许多讯号通道在转录水平上对 Atoh1 有调节作用，包括 Notch 和 Wnt 通道。在蛋白转译后水平，Atoh1 是经由泛素-蛋白酶通道所调节。体外细胞实验及体内动物实验都显示：经由上述讯号通道的调节手段不仅影响耳蜗发育，也导致毛细胞的损伤后再生。本综述回顾了耳蜗内各个对 Atoh1 调节讯号通道研究的进展，并聚焦于泛素-蛋白酶通道对 Atoh1 进行转译后调节及其对毛细胞发育的影响。

关键词：Atoh1；Huwe1；耳蜗；毛细胞；再生；转译后调节

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Dr. Yen-Fu CHENG, the author of this article, is a new editorial board member of *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*. His main research interests include: (1) developmental biology of the auditory system, (2) regenerative medicine of the inner ear, and (3) precision medicine of otolaryngology-head and neck surgery. After receiving his medical degree from Taipei Medical University and finished his residency in Otolaryngology-Head & Neck Surgery from Taipei Veterans General Hospital, he obtained a PhD degree from the Harvard/MIT Division of Health Sciences and Technology in 2014. He resumed his position of research fellow physician at Harvard Medical School/Massachusetts Eye and Ear Infirmary in 2016, and currently he is a physician scientist at Taipei Veterans General Hospital and assistant professor at Taipei University of Nursing and Health Sciences, China.