Journal of
Otorhinolaryngology & Facial Plastic Surgery
Vol: 2017; e3.

Review Article

Signaling Pathways Involved in Auditory Hair Cells Development

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Article Info

Received: Jun 2017
Accepted: July 2017
Publish: 20 Aug 2017

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Keywords:
Signaling pathways, Auditory Hair Cells, Regeneration.

Abstract

Auditory hair cells (HCs) cannot be spontaneously regenerated or replaced in mammalian damaged cochlea which leads to permanent deafness. On the other hand, regenerative ability of HCs in lower vertebrates such as birds and amphibians causes that researchers investigate underlying mechanisms and pathways which can possibly induce mammalian cochlear HCs regeneration and hearing recovery. Signaling cascades of HCs regeneration in lower vertebrate can be considered as the potential therapeutic option for the hearing loss in human. This paper reviews current knowledge about the main signaling pathways involved in HCs development in the mammalian cochlea.

Cite this article that: Khoshsirat Sh, Ahmady Roozbahany N, Niknazar S. Signaling Pathways Involved in Auditory Hair Cells Development. Journal of Otorhinolaryngology & Facial Plastic Surgery. 2017; 2017; e3.

Introduction

Spiral organ of the cochlea, the organ of Corti is composed of sensory HCs and accessory supporting cells (SCs) (1). Auditory HCs are highly specialized cells that transduce sound vibrations into neural signals (2). Unlike non-mammalian vertebrates, mammalian HCs have not regenerative capacity which leads to irreversible hearing loss (3, 4). Studies of birds' auditory system show that damage to HCs can be regenerated and hearing function restored (4). During regeneration, SCs can be differentiated or transdifferentiated into HCs through a combination of mitotic and non-mitotic mechanisms. Proliferation and transdifferentiation process of SCs is started by the signals of dying HCs (5). In mammals, this mechanism only occurs during inner ear development in fetal period (6). Although it is recently reported that auditory HCs regeneration is happened in the mice cochlea during a short time of postnatal period (7), but definite mechanism of HCs regeneration is not clear yet. Studies have shown that various cascades including Atoh1, Wnt, Shh, Fgf and Notch signaling pathways are critical during HCs development and regeneration (8-12). In this review we provide an overview of the main mechanisms and signaling cascades that lead to auditory HCs regeneration.

Atoh1

Atoh1 (atonal basic helix-loop-helix transcription factor 1) or Math1 is the first gene that was discovered during inner ear development and involved in HCs differentiation (13). Atoh1 expression was observed in the basal region of the cochlea at embryonic day 14.5 (E14.5) which responsible for HCs differentiation (one row of inner HCs and three rows of outer HCs) at E15.5. Previous studies provide evidence indicating that Atoh1 positive cells can generate SCs in addition to HCs. In neonatal cochlea, SCs can convert to HCs in response to Atoh1 overexpression (14-16). However, Atoh1 ability in HCs generation from surrounding SCs is extremely decreased in adult or uninjured cochlea (17, 18). It has been reported that adenoviral-mediated overexpression of Atoh1 in kanamycin-induced damaged cochlea leads to HCs regeneration and improve deafness in guinea pigs (19). Although Atoh1 gene expression plays a critical role in development of cochlear HCs, it is insufficient to produce functional auditory HCs. Other signaling mechanisms (e.g. Wnt, Shh, Fgf and Notch) also contribute in regulation of HCs development and regeneration.

Wnt

Wnt signaling pathway has a many key roles in animal development and includes

intracellular signaling pathways (canonical Wnt pathway, the non-canonical planar cell polarity (PCP) and Wnt/calcium pathways) that transmit signals into a cell via cell surface receptors. This pathway is an evolutionarily conserved and highly complex signaling cascade that involves in regulation of important events such as cell proliferation and migration, neural patterning and cell polarity during development (20). Wnt/β-catenin and PCP pathways have been observed in the development of the mammalian cochlea. Wnt/β-catenin signaling is required for regulation of cell proliferation, cell fate and differentiation of HCs during early cochlear development (21, 22). It has been demonstrated that inhibition of canonical Wnt/β-catenin signaling blocks prosensory cell evolution at early stages of cochlea development (21). Furthermore, Wnt/β-catenin up regulation can induce Leucine-rich repeat G-protein-coupled receptor 5 (Lgr5) which acts as HCs progenitors in neonatal mammalian cochlea (23, 24). Planar polarity of HCs is established by the non-canonical Wnt/PCP pathway during cochlear development (25).

Shh

The Hedgehog (HH) signaling pathway is essential for vertebrate embryonic development. Sonic hedgehog (SHH) is the best known ligand of the hedgehog signaling cascade. SHH is critical for patterning of the central nervous system (CNS) like induction of neural tube, tooth and lung development (26-28). SHH modulates cochlear HCs regeneration through regulating the retinoblastoma (Rb) proteins activity in rat. Rb proteins repress cell growth by preventing cell from entering the cell cycle. Inhibition of Rb proteins activity causes cells to divide. Previous study has shown that SHH treatment can lead to inhibition of Rb protein in neonatal cochlea explant culture, which induces HCs regeneration following neomycin damage (29). However, SHH role in the auditory HCs regeneration is largely stays unknown.

Fgf

Fibroblast growth factor (FGF) signaling pathway is initiated through the binding of FGF ligands to FGF receptors (FGFR1, FGFR2, FGFR3 and FGFR4) (30). FGF signaling pathway has important roles during CNS development (31). During the development of the inner ear, it is responsible for otic placode induction and initial otocyst formation (32). FGF also regulates cochlear HCs formation at later stages (33, 34). Interruption of FGF signaling by FGF receptor inhibitor significantly decreases HCs and SCs development (11). In addition, FGF signaling cascade is linked to Atoh1 expression during inner ear evolution (35).

Notch

The Notch signaling pathway is important in cell differentiation, proliferation and cell death. This pathway is critically required during the development of the inner ear (36), and acts through two mechanisms including lateral induction and lateral inhibition. Interaction between the Notch ligand and Notch receptor influences on neighboring cells and promote prosensory cell formation through Notch signal-mediated lateral induction in early stage of cell development (37, 38). Lateral inhibition of Notch signaling is critical for establishing the size and prosensory regions in later stage of the inner ear evolution. HCs and surrounding SCs are precisely arranged in mosaic pattern in the mammalian organ of Corti by Notch lateral inhibition effect (39). It was reported that the blockade of Notch signaling by γ-secretase inhibitors can lead to excessive regeneration of HCs in the zebrafish lateral line (40). In mammals, inhibition of Notch signaling by γ-secretase inhibitor causes adjacent SCs can be converted into HCs in the postnatal period (41).

Conclusion

Understanding the mechanisms and signaling cascades involved in auditory HCs development and regeneration can lead to designing effective therapeutic strategies for hearing loss recovery in human.

Funding/ Support

None to declare.

Conflict of Interest

The authors declare no conflict of interest.

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