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Epigenetic and Signaling Pathway Regulation in Hair Cell Regeneration

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Abstract

Loss of sensory hair cells in the inner ear results in two global health impairments: hearing loss and balance disorders. In humans and other mammals, auditory hair cells damage is permanent and causes irreversible hearing loss. By contrast, hair cells in non-mammalian vertebrates are able to regenerate, prompting studies into the epigenetic mechanisms and signaling pathways that regulate hair cell regeneration. This review paper describes the current knowledge of the roles of epigenetic modifications and various signaling pathways in hair cell regeneration, and tries to understand how modulating their activity to promote the regenerative potential of supporting cells/progenitor cells. Understanding the mechanisms in regulating hair cell regeneration of vertebrates might shed light on the potential therapeutic targets in humans.

Keywords: Hair cells; Regeneration; Epigenetic; Signaling pathways

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Sensory hair cell loss in the inner ear is the major cause of hearing and vestibular impairment, and the sensory hair cells are sensitive to a wide variety of noxious insults, including aging, illness, acoustic trauma, noise exposure, genetic disorders, and ototoxic drugs. Normally hair cells do not regenerate in adult mammals [1] but a very limited degree of hair cell regeneration can occur in vestibular sensory epithelium and in early postnatal mammalian cochlea [2-7], thus hair cell loss in humans and other mammals lead to permanent deafness and / or balance disorders. In contrast, spontaneous regeneration of hair cells occurs in many non-mammalian vertebrates such as amphibians, birds, and fish [8-11]. The precise mechanisms responsible for initiating and maintaining – or preventing – hair cell regeneration are still not completely understood. It has been shown that many candidate molecules and pathways are involved in the regeneration of hair cells, including HDACs, LSD1, Atoh1, Wnt, Shh, Fgf and Notch signaling pathways. Thus, a better understanding how epigenetic and genetic factors impact hair cell regeneration might point to rational targets for reversing hearing problems in humans.

Redundant roles of HDACs in hair cell regeneration

Coordinated and strictly regulated gene expression is essential for diverse biological processes such as cellular survival, differentiation, development and regeneration of tissues in vertebrates, and epigenetic chromatin remodeling is an important regulation process that regulates gene transcription Kouzarides

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[12]. In most cases, chromatin architecture regulation are achieved by histone posttranslational modifications, including methylation, acetylation, phosphorylation, and ubiquitination, which alter histones interaction with DNA and nuclear proteins [13,14]. Histone modifications have been implicated in the regulation of cell fate decisions, as well as normal tissue development and maintenance. Aberrant histone modifications have been associated with pathologies and diverse human diseases such as cancer. Histone acetylation is one of the most common histone modifications and is essential for many developmental processes. Two types of enzymes responsible for regulating histone acetylation states are histone acetyltransferases (HATs) and histone deacetylases (HDACs). Generally, HATs add acetyl groups to lysine residues and enhance gene transcription, while HDACs remove those acetyl groups from histone tails repressing gene transcription. HDACs are subdivided into four major classes based on homology to their yeast counterparts [15-17]. Class I HDACs, including HDAC1, -2, -3, and -8, are expressed widely across cell types and play an important role in regulating cell survival and proliferation [18,19]. Class II HDACs, including HDAC4, -5, -6, -7, -9, and -10, are defined by their similarity to the yeast HDA1 and function as a shuttle between nucleus and cytoplasm [20,21]. Class III are referred to as the sirtuins, and requires NAD⁺ for its enzymatic activity. Class IV, HDAC11, shares similarity with both class I and II enzymes [18]. HDACs have specific functions in normal embryonic development [22]. For instance, Class I HDACs have been shown to be involved in the regulation of multiple aspects of developmental processes, including neuronal differentiation and liver morphogenesis [23-25]. Class I HDACs are also required for proper formation of the eye, craniofacial cartilage, pectoral fin, heart, and exocrine pancreas [26-30]. The vast majority of studies of the functions of HDACs have focused on the potential of HDAC inhibitors (HDACis) and knockdown or overexpression of HDACs. Aberrant expression of HDACs has been reported in various cancer types [31-35] and HDACis are currently attracting enormous attention as anticancer drugs because of their ability to inhibit cancer cell proliferation, induce cell-cycle arrest, and cause cell death [36-38]. Although HDAC activity has been demonstrated to play a vital role in cellular differentiation, apoptosis, migration, proliferation, survival, as well as cell cycle regulation via the formation of complexes with various transcription factors [22,39], very little is known about histone regulation in the inner ear. Previous studies have shown that aminoglycoside antibiotics treatment decreased histone acetylation in the nuclei of mammalian hair cells [40,41]. HDAC inhibitors were shown to increase acetylation of core histones and rescue hair cells from damage by aminoglycoside antibiotics [41,42]. More recent work suggested that HDACs are expressed within the organ of Corti during the first postnatal week of development, and may help to develop new therapeutics in the treatment of hearing loss and hearing regeneration [43]. In the auditory field of non-mammalian vertebrates, two recent studies describe that HDACs are required for zebrafish posterior lateral line (PLL) formation and pharmacological inhibition of HDAC activity disrupts PLL primordium migration, suppresses primordial cell proliferation, and reduces hair cell numbers within neuromast [44,45]. HDAC inhibition causes a significant reduction in cell proliferation by altering the expression of cell cycle

regulatory proteins [45]. He et al. showed the HDAC1 expression in the developing otic vesicles of zebrafish and investigated the function of HDAC1 during inner ear morphogenesis [46]. HDAC1 knockdown results in smaller otic vesicles, abnormal otoliths, malformed semicircular canals, and fewer sensory hair cells, and HDAC1 dysregulation causes attenuated expression of a subset of key genes required for otic vesicle formation during zebrafish organogenesis. In mouse auditory system, HDAC3 can be detected in the otic vesicles at embryonic day 10, and this has provided the basis for further studies of the biological functions of HDAC3 in the development of the auditory organs [47]. Recently reported the presence of HDAC3 in the zebrafish PLL primordium and newly deposited neuromasts, and indicated that HDAC3 has essential roles in zebrafish PLL formation by activating Fgf signaling [48]. Building upon the crucial roles of HDACs during development, numerous studies have focused on HDACs in the modulation of many tissues regeneration. Recent work in *Xenopus* tail regeneration suggested that HDAC1 is expressed during the early stage of regeneration and that pharmacological blockage of HDACs could inhibit regeneration and induce aberrant expression of genes that are known to be critical for tail regeneration [49]. It has been reported that HDAC activity is required for the regeneration of sensory epithelia in the avian utricle [50]. Histone deacetylation is a positive regulator of regenerative proliferation, and inhibition of HDACs is sufficient to prevent supporting cells from entering into the cell cycle. A subsequent study on damaged zebrafish lateral line system demonstrated that inhibition of HDAC function by TSA, a potent class I and II HDAC inhibitor, can affect hair cell regeneration in neuromasts by altering the histone acetylation state. Studies conducted using bromodeoxyuridine (BrdU) labeling show that hair cells in lateral line and inner ear can undergo continuous proliferation [51-53]. However, pharmacological inhibition of HDACs results in decreased proliferation of the progenitor cell population in regenerated neuromasts. The reduction in supporting cell proliferation causes a reduction in the number of regenerated hair cells but does not affect cell death. These data indicate that HDACs are required for hair cell regeneration in the zebrafish lateral line neuromasts after neomycin-induced cell death and that HDACs might be potential therapeutic targets for the induction of hair cell regeneration and supporting cell proliferation. Thus far, the precise mechanisms by which individual HDACs affect hair cell regeneration are still not clear. Further analysis is needed to identify the specific HDACs that regulate hair cell regeneration, which should aid in the elucidation of regeneration mechanisms in the human inner ear. Identification of the specific target genes that are being regulated by HDACs should also help to elucidate the role these genes play in the regenerating zebrafish neuromast. Recent advances in microarray or RNA-seq has provided important clues for understanding epigenetic regulation of hair cell regeneration [54].

Functions of histone methylation in hair cell regeneration

Histone methylation is a major covalent of histone modification that have been linked to the regulation of gene transcription. Histone methylation is catalyzed by the histone methyltransferases, while

the removal of methyl groups from histone lysine residues is catalyzed by the histone demethylases [55]. Recent studies have demonstrated the specific function of histone methyltransferases /demethylases in many cellular processes such as cell cycle regulation, differentiation, survival, death, and proliferation [56,57]. Lysine-specific demethylase 1 (LSD1; KDM1; AOF2) was the first discovered histone demethylase and belongs to the superfamily of the flavin-dependent monoamine oxidases [58]. The enzyme is able to modulate gene expression through demethylation of lysines 4 and 9 of histone H3 by interacting with a variety of molecular partners [58-64]. Some studies have demonstrated that LSD1 plays important roles in many important cellular processes, including proliferation and differentiation [65-67]. It has been reported that LSD1 is implicated in neural stem cell proliferation. Either chemical inhibition of LSD1 activity or small interfering RNA (siRNA) knockdown of LSD1 expression led to dramatically reduced neural stem cell proliferation [68]. Numerous studies have shown that down regulation of LSD1 might promote the initiation and invasion of various tumors, such as colorectal, neuroblastoma, lung, gallbladder and prostate cancer [69-75]. In addition, recent work found that maintenance of high levels of histone 3 lys4 dimethylation (H3K4me2) through the pharmacological inhibition of LSD1 attenuates neomycin-induced hair cell apoptosis [76]. During hair cell development, it has been reported that inhibition LSD1 activity suppresses cell proliferation and decreases hair cell numbers in the zebrafish lateral line [77]. Given the integral roles of LSD1 in hair cell differentiation, extensive work has been undertaken to characterize its involvement in hearing regeneration. He and colleagues demonstrated that mitotic hair cell regeneration after neomycin damage decreases when 2-PCPA is used to inhibit LSD1 activity in the zebrafish lateral line system. LSD1 play a crucial role in cellular proliferation by regulating the expression of genes such as *p21*, *p27*, *CDK2*, *CDK4*, *CDK6*, *cyclinD1*, and *cyclinE1* [78]. This work also suggested that the underlying mechanism behind 2-PCPA's effects on hair cell regeneration might be through inactivation of both the Wnt/ β -catenin and Fgf signaling pathways. This study provides new insights into the mechanisms of hair cell regeneration in zebrafish and suggests that epigenetic regulators might be a novel therapeutic target for the treatment of hearing loss.

The role of Atoh1 transcription factor in hair cell regeneration

Atoh1 is recognized as a single master switch necessary and sufficient to control the hair cells development [79-81]. In the inner ear, Atoh1 is expressed in hair cells as well as in a subpopulation of precursors. Disruption of Atoh1 gene in precursor cells result in a failure of hair cell formation in the cochlea [82,83]. Although, the transient expression of Atoh1 during development is essential for the survival and formation of functional hair cells, the expression becomes more crucial during hair cells maturation and during the development of stereociliary bundles [84,85]. In contrast, overexpression of Atoh1 triggers the formation of functional mechanosensory hair cells in embryonic and neonatal mouse cochlea and most of the new hair cells acquired hair cell fate from two supporting cell types, including

pillar cells and deiter cells [82,86-88]. Based on their critical role in hair cell development, various studies have focused on defining the role of Atoh1 in hair cell regeneration after damage in mature cochlea. The viral mediated delivery of Atoh1 gene in nonsensory cells stimulate the hair cells regeneration and partially restore the hearing in ototoxic damage model of mature guinea pig [89]. However, it is necessary to have the presence of supporting cells in organ of Corti to further transdifferentiate into hair cells [90]. Recently, another study showed that the effectiveness of viral mediated Atoh1 delivery is inconsistent and dependent on timing of expression after ototoxic damage in mature cochlea [91]. Collectively, these findings suggest that the Atoh1 critically promote the regeneration and survival of hair cells; however, it's not sufficient alone to fully convert the nonsensory cells into mature hair cells after severe ototoxic damage.

The role of Wnt signaling pathway in hair cell regeneration

Wnt signaling pathway is indispensable for various modes of operation during development and adult life including proliferation, determining the cell fate, maintaining progenitors and participation in cellular polarization. Wnt pathway triggers upon binding of wnt ligands to their respective Frizzled transmembrane receptor and generally categorized into distinct intracellular canonical and non-canonical signaling pathways [92-94]. Our primary focus is to discuss the role of canonical Wnt pathway in hair cells regeneration. Non-mammals such as fish and birds retain the ability to regenerate hair cells and restore hearing spontaneously after damage [8,95]. However, adult mammals lack the competence to regenerate hair cells after ototoxic insult [96]. The β -catenin dependent canonical pathway regulates the cell fate and proliferation in sensory epithelium [97]; the nuclear translocation and the binding of β -catenin to TCF/LEF transcription factor complex activates the downstream expression of wnt target genes, including *Lgr5*, *Axin2*. Multiple studies, in recent years have reported that the canonical Wnt pathway is involved in hair cell regeneration. The expression of Wnt target gene *Lgr5*, *Lgr6* and *Axin2* in cochlear supporting cells indicate the existence of active Wnt signaling pathway in neonatal cochlea [98,99]. *Lgr5+* cells have been demonstrated as an enriched population of hair cell progenitors both *in vitro* and *in vivo* [7,100,101]. The addition of Wnt agonist enhanced the proliferation and hair cell regeneration efficiency of *Lgr5+* progenitor cells in the inner ear [100-102]. Moreover, the forced expression of β -catenin triggers the Atoh1 expression in colonies derived from isolated supporting cells and promotes the hair cells formation *in vivo* and *in vitro* [101,103,104]. Similarly, the conditional overexpression of β -catenin in *Lgr5+* progenitors expands the proliferation and regeneration capability of supporting cells to generate hair cells [100,101,105]. Another Wnt downstream target gene, *axin2* has also been reported to label another inner ear stem cell population, which named tympanic border cells; and the isolated the *Axin2+* cell also retain the capacity to regenerate hair cells in the inner ear [100]. In sum, these studies in regenerating sensory hair cells in neonatal mice cochlea revealed that the canonical Wnt signaling have the potential to stimulate hair cells regeneration by capitalizing the supporting cell pool, which is known to be enriched with hair cells

precursors. However it remains to be examined whether this pool of supporting cell which harboring the hair cells progenitors can regenerate the new hair cells in response to Wnt activation in damaged adult mammalian cochlea.

The role of notch signaling pathway in hair cell regeneration

Notch signaling pathway determines the sensory region in the inner ear and regulates the differentiation of mechanosensory hair cells [105-107]. Notch signaling arbitrates the process of lateral induction by activating *Jagged 1*, which is necessary to specify prosensory cells [107]. It seems that Notch signaling is mandatory to establish the size and maintenance of prosensory region. The Loss of Notch signaling during early development results in complete absence or partially smaller sensory region having decrease hair cells and supporting cells [107,108]. In contrast, the transient overexpression of NICD in mouse inner ear formed an ectopic hair cells and supporting cells in sensory region [108,109]. The process of lateral inhibition in inner ear established the mosaic pattern of hair cells and supporting cells. During development, hair cells expressed Delta1 and Jagged ligands that interact with Notch receptor on supporting cells, which releases the NICD in supporting cells that up-regulate the expression of *Hes1* and *Hes5*. Accumulation of *Hes1* and *Hes5* inhibit the expression of *Atoh1* in supporting cells thus preventing it from hair cell formation [107,110]. Apart from their involvement in development, Notch signaling has been considered to define their role in hair cell regeneration. Damage mediated via aminoglycoside drug triggers the increase of proteins involved in Notch activation including *Jagged 1*, *Hes1*, and *Hes5* [111]. Another study highlighted that the inhibition of Notch signaling through γ -secretase inhibitor results in trans-differentiation of supporting cells into hair cells [112]. The expression of *Atoh1* transcription factor seems to be increased upon Notch inhibition and stimulate the regenerative potential of supporting cells in drug damage model [113]. In Utricle, the down-regulation of *Hes5* and up-regulation of *Atoh1* promote the hair cells regeneration upon treatment with neomycin and γ -secretase inhibitor [114,115]. In addition, Few studies have also shown that the conditional deletion of *Rbpsuh* gene or use of γ -secretase inhibitor in undamaged cochlear model encourage the supporting cells to acquire hair cell fate [116,117]. Taken together, these findings suggest that the localized Notch activity significantly participated in inhibiting direct transdifferentiation of supporting cells into hair cells. However, promising strategies need to be defined in order to inhibit Notch signaling to further disrupt the lateral inhibition and allowing the supporting cells to regenerate hair cells in mammalian cochlea.

The role of Shh signaling pathway in hair cell regeneration

Sonic Hedgehog pathway is essential for determining the sensory hair cell fate and patterning during inner ear development [118]. Shh was first reported to be expressed in spiral ganglion neuron cells with gradually decreased levels from basal to apical neurons [119]. Sonic hedgehog signaling begins when specific stimuli trigger the cells to secrete Shh ligand, which binds to the membrane

receptor patched 1, resulted in activation of another membrane protein smoothed. This combination of membrane protein stimulates the downstream pathway where Gli transcription factors translocate to the nucleus and regulate the expression or repression of Shh target genes. Knowledge about the role of Shh signaling in hair cell regeneration is largely remains unknown. One study demonstrated that the exogenous Shh treatment of neonatal cochlea, in explant culture, induces the regeneration of hair cells by inhibiting the expression of retinoblastoma protein after neomycin damage [120]. Several studies have been reported to characterize the role of Shh signaling in guiding prosensory cells formation during development. Cochlea isolated from *Gli3* mutant mice treated with Shh signaling inhibitor, in explant culture, showed a large sensory epithelium, while the treatment with Shh halts their expansion [121]. Another study showed that the conditional deletion of *smo* gene in the cochlea displayed an accelerated differentiation of hair cells in apex. Nevertheless, the expression of constitutively active allele of *smo* in the cochlea exhibited no rows of outer hair cells, which suggests that it restricts the differentiation of outer hair cells [122]. Collectively, these studies highlighted the role of Shh signaling during the development of cochlea. However, there are a lot of unaddressed questions need to be answered regarding their involvement in hair cells regeneration in postnatal cochlea.

The role of FGF signaling pathway in hair cell regeneration

Fibroblast growth factor (FGF) signaling pathway is critical for the development of the inner ear, especially when the otic placode thickened from ectoderm and invaginate to form otic vesicle. It further participates in the morphogenesis of inner ear [123-125]. The FGF pathway becomes activated when the FGF protein signal through the four known FGF receptors, including FGFR1, FGFR2, FGFR3 and FGFR4 Pickles [126]. Multiple studies have illustrated that the targeted deletion of *Fgfr1* gene disrupts the prosensory cell formation, which later generates fewer hair cells and supporting cells in the organ of Corti; because in the absence of FGFR1 receptor, the cochlear duct is unable to maintain the pool of sensory precursor cells [127,128]. Similarly, the deliberate interruption of FGF signaling during embryonic development using FGF receptor inhibitor severely reduce the hair cells and supporting cells formation. Interruption of FGF signaling also reduces the *Atoh1* expression [129], suggesting the involvement of FGF signaling in hair cells differentiation. The role of FGF signaling during hair cell regeneration has not been thoroughly defined in mammalian cochlea. It has been reported that *fgfr3* is up-regulated in the cochlea after acoustic damage [130]. However it still remains unclear how it affects the hair cell regeneration in cochlea. On the contrary, some studies have reported the decreased expression of *Fgfr3* in chicken and zebra fish lateral line after damage [131,132]. Likewise, reduced expression of *Fgfr3* and *Fgf20* was reported when analyzed the transcriptome expression profiles, during the regeneration of chicken utricle *in vitro* [54]. In sum, these studies highlighted the major involvement of FGF signaling during inner ear development, in order to govern the prosensory cell formation and hair cell differentiation. However, the detailed role of FGF signaling in regulating the hair cell regeneration still need to be further investigated in the future.

Reciprocal interaction between Wnt and notch pathway in hair cell regeneration

Cellular signaling pathways are interconnected with each other and recent studies have been focused on the simultaneous modulation of these signaling pathways in order to induce the hair cell regeneration. The reciprocal interaction between the Wnt and Notch pathway during cell fate determination have been thoroughly studied in various tissues [117,133-135]. Previous finding shows that there are some similarities and coordination in their actions. Wnt signaling acts upstream of Notch and it regulates the Notch genes in a positive manner such as β -catenin regulates the expression of Jag1 in otic placode and during prosensory cell formation [133,136]. The canonical Wnt signaling pathway induces proliferation of supporting cell to generate hair cells in neonatal cochlea [100,106]. Similarly, the down-regulation of Notch signaling also stimulates the supporting cells to proliferate and generate hair cells [113]. Though, Wnt signaling have no effects on adult mice, while suppression of Notch signaling turn the supporting cells into hair cells via transdifferentiation [113]. A current study pinpointed that Notch inhibition up-regulates the β -catenin expression, which further stimulates the proliferation of Wnt responsive Lgr5+ supporting cells to mitotically regenerate hair cells in postnatal cochlea [118]. Another study shows that Notch inhibition activates regenerative potential of supporting cells to form hair cell, which also moderately, depends on wnt signaling [135]. A recent study in zebrafish also reveals that the hair cell regeneration requires the localized interaction between the Wnt and Notch signaling [137]. These finding suggests the interplay of Wnt and Notch pathway may evoke the regenerative potential of neonatal supporting cells. However, the precise molecular mechanism behind this interaction still need to be further investigated in the future.

Reciprocal interaction between Atoh1 and Wnt pathway in hair cell regeneration

The interaction between Atoh1 and Wnt signaling is getting more and more attention in recent years. The involvement of Atoh1

in cell fate determination during development is thoroughly studied [79,82]. However, there is little understanding about their interaction with other pathways and their participation in hair cells regeneration. A study performed during embryonic development reported that the Atoh1 is a Wnt target and the activation of Canonical Wnt signaling via up-regulation of β -catenin positively regulates the expression of Atoh1 [103]. It also generates supernumerary hair cells in cochlea [104] suggesting Wnt signaling works upstream of Atoh1 in order to regulate their expression and ultimately stimulate the proliferation and hair cell differentiation. In postnatal cochlea, one recent study demonstrated that the constitutive expression of Atoh1 together with β -catenin, proliferate and trans-differentiate 10 fold more hair cells from Lgr5+ progenitor cells as compared to previous reports *in vivo* [138]. Collectively, these findings highlighted the most probable strategy for hair cell regeneration, which is to first activate the Wnt signaling to stimulate the proliferative potential of cochlear supporting cells and further initiate the expression of Atoh1 and inhibit the Notch signaling in order to promote their differentiation potential into hair cells in the mammalian inner ear.

Conclusion

In recent years, tremendous progress has been made in revealing the mechanisms involved in hair cell damage and regeneration. Given that the important roles of epigenetic mechanisms and signaling pathways during differentiation, cellular reprogramming, as well as stem cell maintenance, it seems likely that investigating and manipulating the epigenetic changes together with the signaling pathway during hair cell regeneration may lead to new therapeutic avenue to treat or prevent hearing loss in humans. This review has helped to define the epigenetic regulations and various signaling mechanisms in hair cell regeneration. In addition, understanding how various signaling mechanisms function to modulate sensory hair cell regeneration and how epigenetic regulation affect the complex signaling events have become a major focus for future research toward ultimately functional hair cell regeneration and hearing recovery.

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