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Mini Review

Research Progress on Hair Cell Injury and Related Regenerative Mechanisms

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Abstract

Inner ear hair cells are a central component of the auditory system. However, it is susceptible to genetic defects, noise exposure, ototoxic drugs, and aging, because mammals have limited ability to regenerate spontaneously, hair cell loss or damage may lead to permanent hearing loss. Although cochlear implantation, gene therapy and antioxidant drugs employment are effective methods to treat hearing loss, the related effects are not ideal. By searching Pubmed, CNKI, Wanfang and other large databases, this review summarizes the damage mechanisms of cochlear hair cells mainly involve the breakage of tip links, mechanical damage of the core of the ciliary fiber actin, synaptic damage, as well as Oxidative stress by ROS intervention system. At the same time, the mechanism of hair cell regeneration may be related to gene regulation and epigenetic mechanism. In the future, with the continuous focus of research hotspots, the mechanism of inner ear hair cell regeneration and the therapeutic drugs derived from it will gradually be explained clearly.

Keywords: Hair cells, Hearing loss, Regeneration, Mechanisms, Treatment

Abbreviations: ABR: Auditory Brainstem Response; HC: Hair Cell; IHC: Inner Hair Cell; PTS: Permanent Threshold Shift; ROS: Reactive Oxygen Species; SGN: Spiral Ganglion Neuron; TTS: Temporary Threshold Shift

Introduction

The inner ear is a highly sophisticated and intricate organ of the human body that enables auditory perception by connecting with the external environment. However, hearing impairment remains one of the most prevalent disabilities worldwide now days. According to the 2021 data published by WHO, approximately 5% of the global population, or 430 million individuals, are affected by hearing loss; it is projected that this number will increase to around 700 million by the year 2050 [1]. Hearing loss not only adds to physical and financial obligations, but also causes psychological discomfort and mental problems like cognitive decline and depression [2]. Aging, excessive noise exposure, environmental chemical toxins, aminoglycoside drugs and genetic factors can all cause cellular damage further leading to hearing loss [3]. Although the etiologies of hearing loss are diverse, hair cell (HC) damage and/or loss as well as spiral ganglion neuron (SGN) degeneration represent the most common causes. HCs and SGNs serve as crucial sensors for auditory function, with the former responsible for converting external sound signals into electrical impulses that are transmitted to the brainstem via SGNs [4]. Recent studies indicate that the mammalian cochlea would only regenerate during embryonic development and early neonatal period, while adult hair cells lack this ability [5,6]. The complex spiral organ structure of these cells makes them more susceptible to getting damaged, which can result in permanent hearing loss [7]. Therefore, HC loss or injury as well as SGN degeneration might result in irreversible hearing loss.

At present, the FDA and China state drug administration have yet to approve any drugs or methods for prevention and treatment of hearing loss caused by chemotherapy drugs. Investigating the mechanisms underlying hearing loss and regeneration caused by cochlear hair cells is therefore crucial from a clinical standpoint. In order to serve as a guide for the future development of pertinent therapeutic interventions, this review provides a systematic over-

view of recent research progress on the mechanisms disclosing cochlear hair cell injury as well as a detailed account of the molecular pathways regulating mammalian hair cell regeneration.

Mechanisms of Cochlear Hair Cell Injury

Multiple ototoxic factors, including noise, aging, genetic defects, and ototoxic drugs, may further disrupt the normal morphology of hair cells. These damages may show up as the mechanical transduction complex of hair cells not functioning properly, the loss of certain ribbon synapses, or even the direct death of hair cells.

Breakage of the Tip Links

Disruption of the tip links is a common category of hair cell injury. Protocadherin 15 and cadherin 23 hetero tetramers [8] together form this structure, which is required for the coupling of mechanical stimuli and open MET channels. CDH23, which connects the actin stereo-ciliary core, is placed in the upper half of this class of structures, and interacts with PCDH15, which is in the lower half, in a certain manner. Myosin located at the insertion of the tip links (myosin Ic [9] or myosin VIIa [10]) provides resting tension by movement, making hair cells very sensitive to small shifts in the hair bundle. Intense stimulation of hair bundles can aggravate tip link load and cause midline breakage. In addition, overstimulation of fluid jets or stiff probes, as well as the disruption of calcium chelator binding to cadherin, can also disrupt tip links *in vitro*.

Mechanical Damage to the Fibrous Actin Core of the Stereocilia

Studies have shown that excessive stimulation sometimes accounts for the damage to the core of the stereociliary fibrous actin and reversibly reduces the stiffness of hair bundles [11]. After exposure to a series of harmful factors, transmission electron microscopy and scanning electron microscopy were used to observe multiple abnormal changes in the core of the static cilia fibrous actin, including actin depolymerization, loss of the fibrous actin cross-links, fine root breakage and static cilia fusion [12,13].

Synaptic Damage

Type I auditory SGNs feature connections with inner hair cells (IHCs) that have ribbon presynaptic characteristics. Rapid neurotransmitter release and the ability to modulate responses to stimuli may be achieved by the accumulation of vesicles containing the neurotransmitters around scaffold proteins linked to presynaptic membranes [14,15]. However, both the presynaptic bands and the postsynaptic terminals may be damaged by vigorous stimulation of hair cells [16]. Incomplete repair of SGNS and ribbon synapses after injury is also linked to the phenomena of concealed hearing loss [17,18].

Oxidative Stress by ROS Intervention Systems

Excessive oxidative stress may increase hair cell apoptosis or necrosis [19]. Hair cells can be killed or damaged by a variety of reasons, and this can lead to oxidative stress. The primary contributor is the generation of reactive oxygen species (ROS). Increased calcium levels in hair cells and increased ROS generation by mitochondria have both been linked to noise stress [20]. It has also been demonstrated that intense stimulation increases the metabolic requirement of hair cells, which in turn increases reactive oxygen species (ROS) levels and causes intracellular damage, including the activation of cell death pathways [21]. As a result, some researchers have proposed using antioxidants as therapeutic medications for the treatment and prevention of hearing loss [22].

Mechanisms of Cochlear Hair Cell Regeneration

Fish and amphibians, for example, may replace lost sensory hair cells. However, sensorineural hearing loss caused by the death of auditory hair cells is often permanent in animals. Regenerative hair cells have been found to include both mitogenic and non-mitogenic mechanisms [23]. Regulation of these genes in neonatal animal's results in the development of new hair cells and supporting cells; these genes include *P27kp1*, *RB*, and *Myc*. In the adult mammalian cochlea, relatively little has been accomplished by manipulating specific genes involved in cochlear hair cell formation, such as *Atoh1*, *Notch*, and *Wnt*. Epigenetic processes may regulate hair cell regeneration alongside genetic manipulations, since the regeneration response of mouse utricle support cells seems to be strongly linked to chromatin structure.

Synergistic Gene Regulation Associated with *Atoh1*

Overexpression of *Atoh1* induces upregulation of hundreds of genes in utricle explants cultures, of which appeared to be key genes for hair cell expression in nascent hair cells [24]. This overexpression is responsible for the trans differentiation of neonatal mammalian ear supporting cells into hair cells. This reprogramming of auditory hair cells happens naturally only during the perinatal or preauditory phases, and there are developmental-related limitations in hair cell regeneration ability [25], according to research conducted on adult mammalian cochleas.

The expression of *Atoh1* or related genes may be useful for overcoming roadblocks encountered during hair cell growth. By analyzing *Atoh1* mediated Sertoli cell-to-hair cell trans differentiation, the researchers were able to identify the transcription factors needed to enhance *Atoh1* activity. In normal development, Isl1 is expressed alongside *Atoh1* and the two work together to promote Sertoli-to-hair-cell differentiation through *Atoh1* [26].

Cooperative Gene Regulation Associated with Notch Signaling

The Notch signaling pathway is crucial for typical hair cell maturation. During the process of spontaneous cochlear hair cell regeneration in newborn animals, the expression of *Notch* target genes *Hey1*, *Jag1*, *HeyL*, *Hes1*, and *Hes5* is reduced [27]. Overexpressing the intracellular domain of *Notch1* during the window period of spontaneous hair cell regeneration led to a reduction in the number of spontaneously regenerated hair cells by 92% [27], indicating that spontaneous hair cell regeneration is regulated by

Notch signaling and confirming that the above down regulation is beneficial to the transformation of Sertoli cells into hair cells. Subsequent research demonstrated that *Atoh1* may bind to the *Hes5* promoter, producing cross-effects, and that *Hes1*, a *Notch* downstream transcription factor, suppresses *Atoh1* overexpression, indicating an overlap between *Atoh1* and *Notch* signaling [28]. Loss of *Hes1* causes more inner hair cells, whereas loss of *Hes5* causes more outer hair cells. Although *Hes5* and *Hes1* have a common ancestor in the transcription factor gene family, *Hes5* alone is unable to evoke hair cell renewal in the absence of *Notch*- related genes [29].

Beyond the confines of the Notch pathway, we may investigate the potential for cooperative gene regulation. An important regulator of *Myc/Notch* coactivation is the mTOR pathway, which controls cell growth, survival, and proliferation. The effects of Myc/NICD-mediated reprogramming are regulated by mTOR, as shown by the treatment of adult mouse cochleas with mTOR inhibitors [30]. Therefore, the reprogramming and trans differentiation of Sertoli cells may benefit from the finely controlled route provided by the co-activation of mTOR and Myc-Notch.

Epigenetic Mechanisms of Hair Cell Regeneration

The field of epigenetics is showing promise as researchers uncover more cellular pathways and genes critical for hair cell formation and growth. *Atoh1*, a critical gene in hair cell development, has a strong positive correlation with histone acetylation levels, indicating that epigenetic processes may govern *AtoH1*-mediated hair cell differentiation and maturation. Numerous epigenetic modifications exist, and these may either deactivate or activate genes. Gene expression is typically suppressed when the DNA methylation enzymes of the DNA methyltransferases (DNMT) family modify DNA. Inhibition of DNMT3A expression leads to lower expression of otic placode markers and smaller otic vesicles [31], demonstrating the need of DNMT3A for otic placode formation during early ear development. Treatment of cochlear cells with the acetyltransferase inhibitor curcumin dramatically decreased *Atoh1* mRNA and H3K9ac levels, suggesting that H3K9 histone acetylation is another epigenetic change necessary for *Atoh1* production during hair cell development.

Conclusion

Hearing loss research, and specifically ototoxicity research, has been gaining traction in recent years as scientists seek ways to better protect hair cells from harm and restore auditory function after injury. Investigation of a variety of ear protectors, including antioxidants, anti-inflammatory drugs, neurotrophic factors, and intrinsic cell death pathways in hair cells, may pave the way for the development of comprehensive therapeutic approaches for ototoxic hearing loss.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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