Hearing Research 349 (2017) 182–196

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Cochlear hair cell regeneration after noise-induced hearing loss: Does regeneration follow development?

Fei Zheng, Jian Zuo*

Department of Developmental Neurobiology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 322, Memphis, TN 38105, United States

ARTICLE INFO

Article history:
Received 20 June 2016
Received in revised form
22 November 2016
Accepted 20 December 2016
Available online 26 December 2016

Keywords:
Hearing loss
Hair cell regeneration
Development
Epigenetics
Direct conversion
Drug discovery

ABSTRACT

Noise-induced hearing loss (NIHL) affects a large number of military personnel and civilians. Regenerating inner-ear cochlear hair cells (HCs) is a promising strategy to restore hearing after NIHL. In this review, we first summarize recent transcriptome profile analysis of zebrafish lateral lines and chick utricles where spontaneous HC regeneration occurs after HC damage. We then discuss recent studies in other mammalian regenerative systems such as pancreas, heart and central nervous system. Both spontaneous and forced HC regeneration occurs in mammalian cochleae *in vivo* involving proliferation and direct lineage conversion. However, both processes are inefficient and incomplete, and decline with age. For direct lineage conversion *in vivo* in cochleae and in other systems, further improvement requires multiple factors, including transcription, epigenetic and trophic factors, with appropriate stoichiometry in appropriate architectural niche. Increasing evidence from other systems indicates that the molecular paths of direct lineage conversion may be different from those of normal developmental lineages. We therefore hypothesize that HC regeneration does not have to follow HC development and that epigenetic memory of supporting cells influences the HC regeneration, which may be a key to successful cochlear HC regeneration. Finally, we discuss recent efforts in viral gene therapy and drug discovery for HC regeneration. We hope that combination therapy targeting multiple factors and epigenetic signaling pathways will provide promising avenues for HC regeneration in humans with NIHL and other types of hearing loss.

Contents

Abbreviations: NIHL, noise induced hearing loss; HC, hair cell; SC, supporting cell; OHC, outer hair cell; IHC, inner hair cell; CNS, central nervous system; TM, tympanic membrane; RNA-seq, RNA sequencing; TF, transcription factor; iPSC, induced pluripotent stem cell; ESC, embryonic stem cell; HPF, human postnatal fibroblast; mEB, mouse embryoid body

* Corresponding author.
E-mail addresses: fei.zheng@stjude.org (F. Zheng), jian.zuo@stjude.org (J. Zuo).

http://dx.doi.org/10.1016/j.heares.2016.12.011

1. Noise-induced hearing loss and its military relevance

Hearing impairments, including hearing loss and tinnitus, are the most common military service-connected disabilities. There are many sources of potentially damaging noise in military settings, including weapons systems, engines, and explosions. The prevalence of hearing problems in the US military operation in Afghanistan and Iraqi ranged from 7.3% to 26.6% among more than 90,000 veterans who received the Veterans Health Administration health care (Frayne et al., 2011). Hearing loss significantly affects performance, and is one of the top reasons why soldiers cannot be redeployed (Casali, 2010; Hawkins and Wightman, 1980). Given the importance of auditory acuity in perceiving commands and sensing enemy activity, it is clear that even mild hearing loss increases the risk to military personnel. Service-related injuries that result in hearing loss have decreased with the advent of hearing protection, but many military personnel still develop NIHL by the end of their tour. Hearing loss that restricts or prevents continued military service can result in the loss of personnel, including some of the most effective and experienced officers and non-commissioned officers. Furthermore, NIHL is irreversible, resulting in a permanent disability. As a result, 4.1 million US veterans currently receive disability compensation and treatment for service-connected hearing disability at a total cost of more than $2 billion annually (US Department of Veterans Affairs, 2017; Page 53). Among those veterans who suffer from NIHL, a resulting breakdown in communication with caregivers and family members can impede their reintegration into society and exacerbate their depression and anxiety. In view of these consequences, the US Department of the Navy has recently declared “The Naval Global War on Noise” (Naval Safety Center, 2007).

One common but extreme cause of NIHL and tinnitus is explosions. The blast injuries occur frequently in situations where blast exposure cannot be predicted, where the intensity of the blast exceeds the protective capability of the available mechanical protective devices, or where protective devices are simply not available (Arnold et al., 2003, 2004; Patterson and Hamernik, 1997). In wars or terrorist attacks, such blasts are particularly damaging to both military personnel and civilians. In addition to damaging the central nervous system (CNS), blast injuries most commonly cause disruption or damage to the auditory sensory system. The damage to the peripheral auditory sensory system due to the extreme physical force of a blast is often diverse and may include rupture of the tympanic membrane (TM, ear drum), fracture of the middle ear bones, dislocation of sensory hair cells from the basilar membrane, and loss of spiral ganglia that innervate hair cells (Hamernik et al., 1987; Patterson and Hamernik, 1997; Roberto et al., 1989). In studies of humans with blast injury, approximately 17%–35% were afflicted with severe TM rupture (Garth, 1994; Gondusky and Reiter, 2005; Xydakis et al., 2007), and 33%–78% exhibited moderate to severe sensorineural hearing loss [hair cell (HC) and ganglion loss] as a result of exposure to terrorist or military explosions (Cave et al., 2007; Fausti et al., 2009; Gondusky and Reiter, 2005; Hoffer et al., 2010; Nageris et al., 2008).

Regenerative therapies may provide a means of hearing restoration to allow individuals with NIHL (and other types of hearing loss) to continue in military service, thereby reducing the attrition of the armed forces. This is particularly important when blast injury or post-traumatic stress disorder is associated with the hearing loss.

In this review, we will first discuss the lessons from recent regeneration studies in non-mammalian vertebrates (zebrafish and chicken) and other mammalian regenerative tissues (pancreas, heart and CNS), and then focus on the recent progresses on cochlear HC regeneration *in vivo*, specifically highlighting the differences between SC-to-HC direct lineage conversion and HC development, and essential roles of epigenetics in HC regeneration. Finally, we will summarize recent development in gene therapy and drug delivery for regenerative purposes.

2. Regeneration in non-mammalian vertebrates and other mammalian tissues

NIHL is primarily caused by damage to mechanosensory HCs in the cochlea (Hamernik et al., 1989; Johnsson and Hawkins, 1976; Liberman and Dodds, 1984; Wang et al., 2002). The cochlea is a coiled structure in the inner ear that contains the auditory epithelium known as the organ of Corti. The organ of Corti contains HCs, which detect incoming sound, and supporting cells (SCs) (Fig. 1). HCs are subdivided into inner hair cells (IHCs), which are responsible for transmitting detected sound waves to auditory regions of the brain, and outer hair cells (OHCs), which are responsible for amplifying the sound (Dallos, 2008; Dallos et al., 2008). Only mammals have OHCs, which are unique because they primarily receive efferent signaling from the brain (Dallos, 2008) and express the motor protein prestin, allowing them to be electromotile and resulting in their ability to modulate sound (Dallos, 2008). NIHL results in the preferential loss of OHCs; IHCs are lost only in severe cases of NIHL (Hamernik et al., 1989).

Unfortunately, humans and other mature mammals cannot replace lost HCs in the organ of Corti, so the loss of HCs can lead to permanent deafness. However, birds, fish, and other non-mammals can recover lost hearing either by proliferating SCs and then converting them into functional HCs or by directly transdifferentiating SCs to HCs (Adler and Raphael, 1996; Baird et al., 1996; Corwin and Cotanche, 1988; Jones and Corwin, 1996; Ryals and Rubel, 1988; Warchol and Corwin, 1996). Interestingly, mature mammalian vestibular end organs, such as utricle, exhibit limited HC regeneration after damage, which occurs almost exclusively by transdifferentiation (Golub et al., 2012; Jung et al., 2013; Slowik and Bermingham-McDonogh, 2013). Notably, the regeneration of vestibular HCs declines with age (especially in the early developmental stage) and is not sufficient to compensate HC loss (Burns et al., 2012; Gopen et al., 2003; Kirkegaard and Nyengaard, 2005;