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Review

Anti-apoptotic treatment in mouse models of age-related hearing loss

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Abstract

Age-related hearing loss (AHL), or presbycusis, is the most common neurodegenerative disorder and top communication deficit of the aged population. Genetic predisposition is one of the major factors in the development of AHL. Generally, AHL is associated with an age-dependent loss of sensory hair cells, spiral ganglion neurons and stria vascularis cells in the inner ear. Although the mechanisms leading to genetic hearing loss are not completely understood, caspase-family proteases function as important signals in the inner ear pathology. It is now accepted that mouse models are the best tools to study the mechanism of genetic hearing loss or AHL. Here, we provide a brief review of recent studies on hearing improvement in mouse models of AHL by anti-apoptotic treatment.

Keywords: Age-related hearing loss; Mouse model; Apoptosis; Oxidative stress

Contents

1. Introduction

Age-related hearing loss (AHL) is the most common sensory disorder in the elderly population, causing communication problems and adversely impacting the quality of life of affected individuals (Gates and Mills, 2005; Yamasoba et al., 2007; Op de Beeck et al., 2011). Genetic predisposition is one of the major factors in the development of AHL and

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extensive candidate-gene-based association studies on AHL have been conducted recently (Newman et al., 2012; Yamasoba et al., 2013). As mice and humans share similar genetic components, anatomic structures and pathological characteristics, mouse models play a crucial role in understanding the pathogenesis associated with these genes (Angeli et al., 2012; Han et al., 2015). In fact, most inbred mouse strains display at least some degree of AHL, and the age of the onset is known to vary from 3 months in DBA/2J mice to over 20 months in CBA/CaJ mice (Zheng et al., 1999; Noben-Trauth and Johnson, 2009). Part of the early onset of hearing loss in these mice is explained through the presence of a recessive *ahl* allele in the gene of *cadherin 23* (*Cdh23*).

Cdh23, also known as gene of otocadherin, encodes for a calcium-dependent cell adhesion protein (CDH23) that is required for establishing and/or maintaining the proper organization of the stereocilia bundle of hair cells in the cochlea and the vestibule during late embryonic/early postnatal development. CDH23 and protocadherin 15 (PCDH15) interact to form the tip links in the stereocilia. They localize, respectively, to the upper and lower parts of tip links (Kazmierczak et al., 2007). Altered adhesion or reduced stability of CDH23 may confer susceptibility to AHL (Noben-Trauth et al., 2003). It is concluded that the *cadherin 23*^{ahl} (*Cdh23*^{ahl}) allele is associated with a rapid progression of AHL (Johnson et al., 2000; Ohlemiller, 2006; Op de Beeck et al., 2011). Other mapped loci, such as *ahl2* in NOD/LtJ, *ahl4* in A/J and *ahl8* in DBA/2J, et al., contribute to the earlier onset and more rapid progression of hearing loss in these strains (Noben-Trauth and Johnson, 2009).

Histopathologically and pathophysiologically, AHL may variably be accompanied by an age-dependent loss of sensory hair cells, spiral ganglion cells, and degeneration of stria vascularis cells (Op de Beeck et al., 2011; Yamasoba et al., 2013). In fact, apoptosis has been identified as the final common pathway in degradation of the organ of Corti in several types of genetic hearing loss (Bao and Ohlemiller, 2010; Cheng et al., 2011; Op de Beeck et al., 2011; Laine et al., 2007; Niu et al., 2007; Tadros et al., 2008; Schwander et al., 2009). Recent studies on mouse models of AHL, in particular, have revealed that apoptosis contributes to degeneration of cells in the cochlea and anti-apoptotic treatment improves hearing in these mouse models.

2. Current concept on the mechanism of AHL development

Although the pathology of hearing loss is very complicated, extensive genetic and molecular biological studies have provided considerable insight into understanding the mechanisms of cell death. Apoptosis in the cochlea may be triggered by oxidative stress, which produces reactive oxygen species (ROS), according to a current conceptual model (Yamasoba et al., 2007). It is accepted that mitochondria are a major source of ROS and a major site of ROS-induced oxidative damage, which has been proposed to play a causal role in AHL (Ohlemiller et al., 1999; Seidman, 2000; Liu and Yan, 2007; Yamasoba et al., 2007; Someya et al., 2009). The aging theory predicts that in the course of time ROS concentration rises either due to depletion of antioxidant defenders or due to an elevated ROS formation. This causes mitochondrial damage and subsequent release of pro-apoptotic factors that finally induce apoptosis (Op de Beeck et al., 2011). It is hypothesized that the ROS may induce DNA damage, which results in the upregulation of P53, causing chronic activation of the mitochondrial BAK pathway, ultimately resulting in the triggering of apoptotic cell death in the cochleae (Someya and Prolla, 2010). However, other studies pointed that multiple cell death pathways, all potentially linked to oxidative stress, were involved in hair cells of the auditory organ in aging mice (Sha et al., 2009). Despite limitations in the various models of AHL, it appears that ROS formation and apoptosis are key events in the pathology of AHL (Op de Beeck et al., 2011).

3. Anti-apoptotic treatment in mouse models of AHL

3.1. C57BL/6J mice

The C57BL/6J mouse strain is a long-living strain (mean lifespan of approximately 30 months) and the mostly used mouse model for studies of aging and age-associated diseases. It is well known that hearing loss in C57BL/6J mice occurs at about 9–12 months of age. Genome-wide linkage analyses have identified an associated locus (mentioned above as *ahl*) in D10Mit5 – D10Mit31 interval on Chromosome 10 (Chr 10) and further genetic mapping delimited the interval to an 830 kilobases (kb) region on Chr10 (Zheng and Johnson, 2001; Noben-Trauth et al., 2003). Sequencing of genes in this interval identified a functional polymorphism (G753A) in the coding sequence of *Cdh23*. This single nucleotide polymorphism (SNP) occurs at the last position of exon 7 and alters the consensus splice site, leading to in-frame skipping of exon 7. One of the major genetic factors contributing to hearing loss in C57BL/6J mice is the *ahl* locus (Johnson et al., 1997). However, inbred strain variants of the *Cdh23* have been shown to influence the onset and progression of AHL in mice: the CBA/CaJ-derived *Cdh23*$^{Ahl+}$ allele dramatically lessens hearing loss and hair cell death in an otherwise C57BL/6J genetic background, but that the C57BL/6J-derived *Cdh23*^{ahl} allele has little effect on hearing loss in an otherwise CBA/CaJ background (Kane et al., 2012). Study also indicated that loci, in addition to *ahl,* contributed to the differences in hearing loss between C57BL/6J and CAST mice. To be specific, although hearing thresholds in 24-month-old B6. CAST-*Ahl* mice were significantly elevated compared to the normal hearing wild-type CAST/Ei mice, they were still lower than in age-matched C57BL/6J mice (Keithley et al., 2004). Therefore, *Cdh23*^{ahl} homozygosity is necessary but not sufficient on its own to cause accelerated hearing loss in C57BL/6J mice.

Study has shown that AHL in C57BL/6J mice is mediated, at least partly, by Bak-dependent mitochondrial apoptosis. It is speculated that, in response to increased oxidative DNA damage in the aged cochlea, p53 translocates to mitochondria and activates *BCL2-antagonist/killer1* (*Bak*), leading to Bak-