Peroxisomes Get Loud: A Redox Antidote to Hearing Loss

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Pejvakin (PJVK), a protein originally identified in Persian families with sensorineural hearing loss, regulates peroxisomal dynamics and the antioxidant defense triggered by noise exposure in hair cells and auditory neurons of the inner ear. These findings bring peroxisomes to the forefront of noise-induced hearing loss research.

The ability to respond to auditory cues is a highly prized evolutionary innovation in vertebrates, providing significant advantages for communication and the perception of environmental stimuli. The mammalian inner ear is a particularly intricate structure, engineered through natural selection for the detection of a wide range of sound frequencies and energies. Transduction of air pressure waves into meaningful sounds relies on a neural interface provided by highly specialized hair cells in the cochlea that transmit mechanical information to primary auditory neurons with remarkable precision for subsequent decoding in the auditory cortex (Figure 1A). As with all nervous tissue, the ability of hair cells to withstand damage and self-repair is severely limited. In particular, their exposure to high-energy sounds (>100–120 dB) results in mechanical trauma leading to irreparable structural damage and permanent hearing loss. Prolonged exposure to lower thresholds of high-energy sound (>85 dB) is a major cause of oxidative stress in hair cells, which may also lead to cell death and hearing loss (Wong and Ryan, 2015). Indeed, noise-induced hearing loss (NIHL) is a main cause of auditory disability and one of the most prevalent occupational hazards (Nelson et al., 2005). In this issue of *Cell*, Delmaghani et al. (2015) show that Pejvakin (PJVK or DFNB59), a protein originally linked to a congenital form of hearing loss in Persian families (Delmaghani et al., 2006), localizes to the peroxisomes in hair cells and auditory neurons and mediates a dynamic adaptive reaction involving peroxisomal proliferation/fission to buffer harmful oxidative stress (Delmaghani et al., 2015). Furthermore, the authors conduct a successful proof-of-principle gene therapy approach to correct hearing loss in *Pjvk*-deficient mice.

Over the last decade, a handful of studies linked mutations in *DFNB59* to different forms of autosomal recessive sensorineural hearing loss with variable phenotypic manifestations; however, the function of the protein remained elusive owing to its lack of well-defined functional domains, sorting signals, and limited sequence identity with other proteins. Earlier studies localized *Pjvk* protein and mRNA in afferent auditory neurons and hair cells, but it is also ubiquitously expressed across major mouse organs (Delmaghani et al., 2006; Schwander et al., 2007).

In a systematic phenotypic assessment of *Pjvk*-deficient mice, Delmaghani et al. discovered that young $Pjvk^{-/-}$ mice develop a progressive form of sensorineural hearing loss caused by their littermate vocalizations, an otherwise innocuous stimulus for wild-type pups. This exacerbated susceptibility to NIHL under normal acoustic conditions was not due to gross anatomical or histological abnormalities but rather to a progressive postnatal loss of hair cell function and number, suggesting that the auditory phenotype was a result of a specific defect in the cellular adaptation to normal noise levels. This phenotype correlated with abnormally high levels of oxidative stress markers in the cochlea and gene expression changes consistent with a redox imbalance. Pjvk was shown to localize in peroxisomes, not only in sensory cells of the inner ear, but also in other unrelated cell types, where it mediates peroxisomal proliferation either autonomously or associated with experimentally induced oxidative stress.

Oxidative stress in the inner ear has been long associated with noise-induced damage, including findings of polymorphisms in peroxisomal enzymes and other redox systems linked to NIHL susceptibility (Konings et al., 2007; Wong and Ryan, 2015). In fact, antioxidant therapy has been tested with some success in models of NIHL and age-related hearing loss (Fetoni et al., 2013; Heman-Ackah et al., 2010). The study by Delmaghani et al. is the first one to directly point at peroxisomal dynamics as a first line of antioxidant defense against normal noise exposure, without apparent mitochondrial involvement, and opens many unresolved questions with important implications for the biology of peroxisomes and its relationship with other cellular functions.

One of the major observations of the study is that sound exposure upregulates *Pjvk* expression in hair cells, inducing the proliferation or fission of pre-existing peroxisomes. PJVK is thus proposed to enable an adaptive homeostatic program in response to the accumulation of reactive oxygen species (ROS) induced

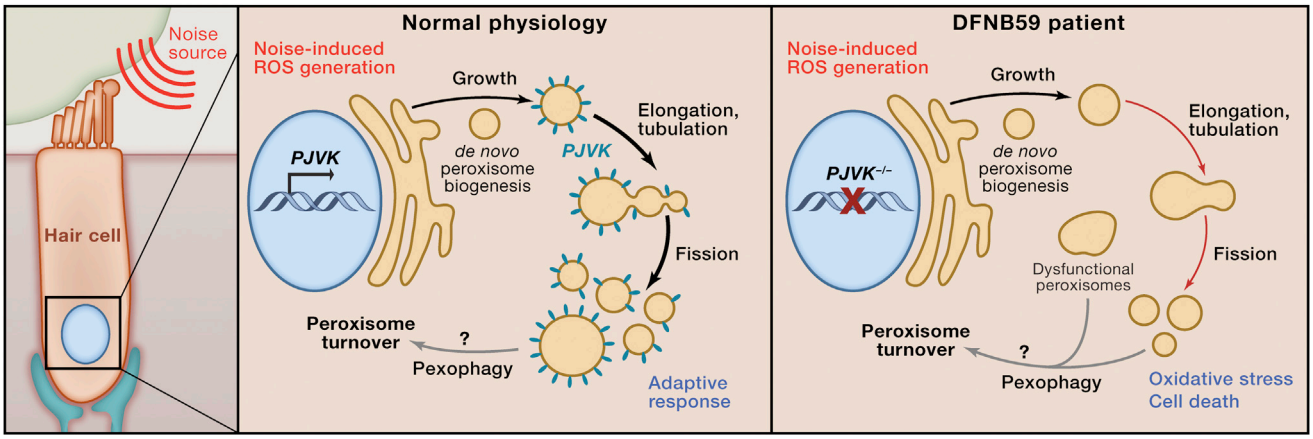

Figure 1. The Biology of PJVK and Peroxisome Dynamics

Sensory cells in the organ of Corti (outer and inner hair cells) carry out mechanotransduction of air pressure waves into electrical signals that are transmitted to primary auditory neurons in the spiral ganglion, which relay these signals for the cortical representation of sound. Hair cells and auditory neurons are particularly sensitive to reactive oxygen species (ROS) generated by exposure to noise. Upregulation of *PJVK* engages an adaptive program modulating peroxisome dynamics, in particular the proliferation/fragmentation of peroxisomes. PJVK locates at the surface of peroxisomes, where it may interact with peroxins and other proteins that mediate crucial steps during the elongation and fission of peroxisomes (PEX11), as well as proteins that regulate pexophagy (PEX3, ATM, PEX5). Thus, PJVK expression contributes to maintain cell viability by increasing the buffering capacity against oxidative stress in part through modulating peroxisome function.

by noise (Figure 1B). Peroxisomes are extraordinarily dynamic ER-derived organelles that interact with other subcellular compartments in the regulation of major cellular functions related to the metabolic and redox status of the cell (Smith and Aitchison, 2013). Peroxisome biogenesis is crucial for normal physiology and its deficiency leads to serious conditions of the Zellweger spectrum, where hearing loss is a common symptom in the context of general neurodegeneration.

Although de novo peroxisome biogenesis is not regulated by PJVK, subtler biogenesis defects secondary to protein trafficking or membrane lipid alterations cannot be excluded. It is also not entirely clear whether the defects observed in peroxisome biology in *Pjvk*$^{-/-}$ hair cells are due to a disruption in the peroxisomal fission machinery or in the turnover of this organelle by pexophagy (Figure 1B). Peroxisomes can operate as a source and a sink of ROS, therefore cellular redox balance depends on a delicate equilibrium between their biogenesis, proliferation, and turnover. A recent report linked the overproduction of ROS to increased pexophagy in a process regulated by the ataxia telangiectasia mutated (ATM) kinase and the peroxisome importer receptor PEX5 (Zhang et al., 2015). This pathway might also be compromised in *Pjvk*$^{-/-}$ hair cells, leading to the appearance of dysfunctional peroxisomes. The presence of cell-type-specific protein partners may also shed light on the essential function of PJVK in the inner ear.

In addition to NIHL, the most common form of auditory impairment is age-related hearing loss (Wong and Ryan, 2015). Aging is a process characterized by a generalized decline in antioxidant defenses and PJVK might represent a possible therapeutic target on this front, provided that its activity turns out to be sufficient for protecting the sensory epithelium from age-related oxidative damage. Gene therapy approaches using adeno-associated viruses to restore or enhance PJVK function in the cochlea represent an attractive strategy to treat highly prevalent forms of hearing loss in the near future.

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