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G6PD Overexpression Protects from Oxidative Stress and Retard Age-related Hearing Loss Progression

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Ageing of the auditory system is associated with the incremental production of reactive oxygen species (ROS) and the accumulation of oxidative-derived damage in macromolecules, which contribute to cellular malfunction, compromise cell viability and, finally, causes functional decline. The cellular detoxification power partially relies in NADPH production, which is a cofactor for major cellular antioxidant enzymes. NADPH is mainly produced by glucose-6-phosphate dehydrogenase (G6PD), an enzyme that catalyzes the rate-limiting step in the pentose phosphate pathway.

We show here that the transgenic mouse *G6PD*-Tg, which shows enhanced NADPH production along life, maintains lower auditory thresholds than wild type mice during ageing. *G6PD* overexpression preserved inner (IHC) and outer hair cells (OHC), OHC innervation and number of synapses per IHC. Transcripts for antioxidant enzymes were increased whereas levels of pro-apoptotic proteins were reduced in 3-month-old *G6PD*-Tg. Consequently, nitration of proteins, mitochondrial damage and $TUNEL^+$ apoptotic cells were reduced in 9-month-old *G6PD*-Tg compared to wild type mice. Unexpectedly, *G6PD* overexpression triggered low grade inflammation that was effectively resolved in young mice, as shown by the absence of cochlear cellular damage and macrophages infiltration.

In conclusion, we propose here that NADPH overproduction from an early stage is an efficient mechanism to maintain the balance between the generation of ROS and the cell detoxification power along ageing and, therefore to prevent hearing loss progression.

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PD 79

Autophagy regulates the degeneration of the auditory cortex through the AMPK-mTOR-ULK1 signaling pathway

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Presbycusis is the most common sensory impairment associated with aging; however, the underlying molecular mechanism remains unclear. Autophagy has been demonstrated to serve a key role in diverse diseases; however, no studies have examined its function in central presbycusis. The aim of the present study was to investigate the changes of autophagy in the physiological processes of the auditory cortex and its role in the degeneration of the auditory cortex, as well as the related mechanisms using naturally aging rats and a D-galactose (D-gal)-induced mimetic rat model of aging. The present study demonstrated that autophagy increased from 3 months to 15 months in the normal saline (NS) control group, while it decreased in the D-gal group. Compared with the age-matched NS group, the D-gal group demonstrated significantly increased levels of the autophagy-related proteins, LC3 and Beclin 1 (BECN1) and the anti-apoptotic proteins B-cell lymphoma (BCL)2 and BCL-extra large (BCL-xL) at 3 months, with no obvious changes in cell apoptosis level and neuron ultrastructural morphology. However, LC3, BECN1, BCL2 and BCL-xL were decreased at 15 months in the D-gal group, with cell apoptosis significantly increased and substantial neuron degeneration. Additionally, 5' AMP-activated protein kinase (AMPK) activity was enhanced, and mechanistic target of rapamycin (mTOR) and ULK1 phosphorylation (Ser 757) activities were inhibited at 3 months compared with those of the NS group, while the opposite was observed at 9 and 15 months. The present results suggested that autophagy increases from young to adult and decreases at old age in the physiological processes of the auditory cortex, and has anti-apoptotic as well as anti-aging functions in the degeneration of the auditory cortex. Additionally, autophagy was regulated through AMPK activation and mTOR suppression, and impairment of autophagy may serve a key role in the degeneration of the auditory cortex, even in the pathogenesis of central presbycusis.