The role of inflammation mediated by MKP1 in age-related hearing loss

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1. Background

The stress kinases p38 and JNK are important regulators of cellular physiology that are activated in response to processes that compromise cell integrity. MKP1: Phosphatase 1 (MKP1) has the capacity to regulate the magnitude and duration of MAPK activity through dephosphorylation of Sust16/Thr18 of JNK and Tyr183/185 of p38. The precise role of MKP1 in cochlear health and age-related hearing loss (ARHL) is not yet clear. MKP1 has been found to be upregulated in experiments using cochlear explant tissue. The activation of these kinases contributes to the degeneration of auditory neurons, and the precise role of MKP1 in cochlear health and age-related hearing loss (ARHL) is not yet clear. MKP1 has been found to be upregulated in experiments using cochlear explant tissue.

2. MKP1−/− mice suffered premature and progressive hearing loss from high to low frequencies compared to MKP1+/−

3. Progressive functional decline correlates with morphological alterations

4. MKP1 deficit triggers an exaggerated inflammatory response

5. MKP1 deficiency alters cell cycle, apoptosis and DNA damage response expression profile

6. Conclusions

- MKP1−/− mice showed elevated auditory thresholds compared to wild type mice at every age studied with an early onset at 2 months of age and a progression to profound hearing loss evident at the age of 12 months.
- At the 8- to 12-month-old wild-type mice, the number of surviving cells was reduced to 60% of the young adult population. These findings suggest that MKP1 deficiency promotes an exaggerated inflammatory response.
- DNA sequencing revealed upregulation of apoptosis, DNA damage, cell cycle, signal transduction and inflammatory response genes in MKP1−/− mice at 6 months of age.
- The results indicate that the dual-phosphatase MKP1 in the auditory system, by promoting a decisive role in mechanisms protecting against age-related damage in the cochlea and its propagation.