Activation of miR-34a impairs autophagic flux and promotes cochlear cell death via repressing ATG9A: implication for age-related hearing loss

The running title: miR-34a blocks autophagy for cochlear cell death

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Abstract

Age-related hearing loss (AHL) is a major unresolved public health problem. We have previously elucidated that the activation of cochlear miR-34a is correlated with AHL in C57BL/6 mice. A growing body of evidence points that aberrant autophagy promotes cell death during the development of multiple age-related diseases. The aim of this study was to investigate the role of miR-34a-involved disorder of autophagy in the pathogenesis of AHL. Our results showed that miR-34a expression was markedly up-regulated in the aging cochlea companied with blockage of autophagic flux. In the inner ear HEI-OC1 cell line, miR-34a overexpression resulted in an accumulation of autophagosomes and impaired autophagosome-lysosome fusion, and led to cell death subsequently. Notably, ATG9A, an autophagy protein, is significantly decreased after miR-34a overexpression. Knockdown of ATG9A inhibited autophagy flux, which is similar to the effects of miR-34a overexpression. Moreover, ursodeoxycholic acid significantly rescued miR-34a-induced HEI-OC1 cell death by restoring autophagy activity. Collectively, these findings provide a new understanding of the biological effects of miR-34a in the development of AHL and highlight miR-34a as a potential target for AHL treatment.

Key words: miR-34a, autophagy, age-related hearing loss, ATG9A, ursodeoxycholic acid