Hearing loss caused by mitochondrial malfunction

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Cellular metabolism is experiencing a *Renaissance*. While mitochondria are classically described as the "cellular energy factory", their roles as signaling platforms start to be unveiled. Furthermore, it is nowadays established that mitochondria are part of a complex organelle network that has fundamental roles in cellular physiology and disease.

Mitochondrial dysfunction presents as pathology associated with perturbations in redox homeostasis, autophagy, metabolic signaling, and apoptosis. However, the underlying molecular mechanisms and the complex tissue-specificity remain largely obscure. The A1555G mtDNA mutation in the 12S rRNA gene causes maternally inherited deafness and increases susceptibility to aminoglycoside-induced hearing loss. This mutation perturbs mitochondrial ribosome function, partly via increased methylation of the 12S rRNA by the mitochondrial methyltransferase mtTFB1, which is a nuclear modifier of the A1555G mutation. We therefore hypothesized that A1555G pathology depends on 12S rRNA hypermethylation. Employing a two-dimensional genomics approach we show 12S rRNA hypermethylation causes superoxide-dependent activation of AMP-dependent protein kinase (AMPK), inducing pro-apoptotic signaling by E2F1. This mitochondrial stress-response pathway is operative *in vivo* as mtTFB1-transgenic mice exhibit ubiquitous 12S rRNA hypermethylation, but tissue-specific activation of E2F1 and apoptosis in the stria vascularis and spiral ganglion neurons of the inner ear. Genetic ablation of E2F1 fully rescues the hearing phenotype. We propose that susceptibility to E2F1-dependent apoptosis in critical cells of the inner ear by this cell-type specific mitochondrial-stress relay explains the irreversible deafness in humans that inherit the common A1555G mutation, and that differences in superoxide→AMPK→E2F1→apoptosis pathway responses provide a framework for the tissue-specific pathology.

Since AMPK is also a major regulator of macroautophagy, we hypothesize that the balance between the pathways AMPK→macroautophagy and AMPK→E2F1→apoptosis determines the tissue-specificity of the apoptosis response and consequent disease phenotype. Our data shows that apoptosis occurs in tissues where the AMPK→autophagy axis is outcompeted by the AMPK→E2F1→apoptosis pathway, while the tissues that effectively induce the autophagic signaling are able to avoid apoptosis. These results lay the path for a new strategy to treat mitochondrial pathology by enhancing the autophagic capacity of tissues.