Technology Offer

Mouse model for mitochondrial diseases

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A tRNA^{ALA} heteroplasmy mouse model to study mitochondrial disorders such as encephalomyophathies, that recapitulates symptoms as observed in human patients with disease-causing mutation in the same mitochondrial gene.

Background

Mutations in the mitochondrial DNA (mtDNA) affect mitochondrial function essential for the oxidative phosphorylation system, the aerobic respiration and the efficient production of cellular energy. The resultant devastating mitochondrial disorders are not only involved in encephalomyophathies, especially brain and muscle diseases due to their high-energy requirement but also in a variety of age-associated human diseases. Despite the realization that mitochondrial disease is a relatively common genetic disorder, treatment is still very limited.
The lack of appropriate animal models carrying pathogenic mtDNA mutations, recreating human disease phenotypes, is a big obstacle for *in vivo* testing of novel treatments. Despite enormous efforts, direct manipulation and stable transfection of mtDNA are still not possible. Currently used, indirect methods of mtDNA manipulation do not allow to obtain the hallmark of mtDNA-related diseases, the heteroplasmy, observed as a mosaic pattern of cells mixture of the mutant, dysfunctional and wildtype versions.

Technology

Our researchers developed a transgenic, heteroplasmic mouse with stable pathogenic mutation in the tRNA^{ALA} gene of mtDNA, displaying symptoms as observed in human patients with disease-causing mutation in the same mitochondrial gene. The allele segregation with high levels of mutation behaves similar to common mitochondrial disorder alleles observed in MELAS and MERRF diseases. In addition, the mice have decreasing body mass after 20 weeks and increased expression levels of atrial natriuretic factor, consistent with the development of cardiomyopathy. As in humans, the observed mitochondrial disorder in mice is progressive, showing after 60 weeks widespread mitochondrial dysfunction in the heart, skeletal muscle and the smooth muscle cells of the colon.

Taken together, the developed transgenic mouse model has high clinical relevance to test a variety of novel treatments against mitochondrial dysfunction and this know-how is available for licensing.

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Literature

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