Mitochondrial protein TMEM70: key role in the biogenesis of ATP synthase verified in a mouse knockout model

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TMEM70 is a transmembrane protein localized in the inner mitochondrial membrane and involved in the biogenesis of the eukaryotic ATP synthase, which is the main producer of ATP in cells. The molecular role of TMEM70 in this process is not yet known. *TMEM70* mutations cause isolated deficiency of ATP synthase often resulting in a fatal neonatal mitochondrial encephalocardiomyopathy in patients.

To clarify the exact function of this factor, we generated *Tmem70* knockout mice by embryonic stem cell technology. While the heterozygous mice were viable and developmentally normal, the homozygous embryos were distinctly growth retarded and died during the embryonic development about 9.5 days *post coitum*. Confocal microscopy revealed delayed development of the cardiovascular system and electron microscopy indicated disturbed mitochondrial morphology in the homozygous when compared to the wild type embryos. Blue native electrophoresis demonstrated isolated defect of ATP synthase in the homozygous embryos with the content of fully assembled F_1Fo ATP synthase decreased to less than 20% of wild types and marked accumulation of F_1 assembly subcomplex. Consequently, decrease in ADP-stimulated State 3 respiration, respiratory control index and ATP/ADP ratios indicated compromised mitochondrial ATP production.

In contrast, comparison of the viable heterozygous and wild type mice aged 5 and 14 weeks did not show any significant differences in the heart and liver content of respiratory chain complexes, oxygen consumption, ATP synthase assembly and ATPase hydrolytic activity. On the other hand, we observed decreased fractional shortening, the parameter of the heart function, in heterozygous compared to wild type mice.

In conclusion, this first direct demonstration of the biological role of TMEM70 in experimental animals shows that *Tmem70* deficiency in the mouse has lethal consequences that are analogous to *TMEM70* dysfunction in humans.

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