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Insitutionen för Laboratorie Medicin

MOLECULAR MECHANISMS OF AGING IN MTDNA MUTATOR MICE

AKADEMISK AVHANDLING
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ABSTRACT

Mitochondria are intensely studied in the field of aging. mtDNA mutator mice have a proofreading deficiency in the mitochondrial DNA polymerase POLG, which causes a large amount of point mutations to be accumulated in mitochondrial DNA. These mice have mitochondrial dysfunction and experience a range of premature aging phenotypes.

In this thesis we examine the molecular mechanisms behind the mitochondrial dysfunction and premature aging phenotypes of the mtDNA mutator mice. The main reason for the mitochondrial dysfunction is the inability to assemble respiratory chain complexes. This is due to point mutations in the mitochondrially encoded protein subunits of the electron transport chain. As a consequence of this, these proteins are rapidly broken down and lower levels of respiratory chain complexes I, III and IV are assembled. The vicious cycle hypothesis predicts that an increased load of mtDNA mutations would cause increased reactive oxygen species (ROS) production. In contrast to this, there is no general increase in ROS production in mtDNA mutator mitochondria. Rather, we observed a large decrease in ROS production from reverse electron transfer and a moderate increase in ROS production generated from forward electron transfer. On a combination of complex I and II substrates, mtDNA mutator mitochondria produced significantly less ROS mainly as a consequence of reduced ROS production from reverse electron transfer. Although ROS production was not increased in mtDNA mutator mice, oxidative stress poses a threat. Tissues exposed to ambient oxygen could not defend against oxidation to the same extent as wt tissues. When grown in cell culture at 20% oxygen tension mouse embryonic fibroblasts from mtDNA mutator mice tend to immortalize. This effect is eliminated when cells are grown in only 3% oxygen or on low glucose or galactose. This could possibly be due to altered sensitivity to ROS or a growth enabling effect of a glycolytic metabolism.

As a consequence of the mitochondrial dysfunction mtDNA mutator mice have increased levels of UCP2. One proposed function of UCP2 is to uncouple the electron transport chain from the ATP synthase, by increasing proton conductance through the inner mitochondrial membrane. In contrast to its proposed uncoupling function, UCP2 does not seem to mediate proton conductance in mtDNA mutator mice. However UCP2 appears to mediate a switch to fatty acid metabolism. One major effect of UCP2 depletion in mtDNA mutator mice is early heart pathology. This indicates that UCP2 has a protective role in the mtDNA mutator hearts, perhaps through allowing better utilization of fatty acids. The mtDNA mutator mice provide insight into how mtDNA mutations affect mitochondria and how defective mitochondria affect the aging process.

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