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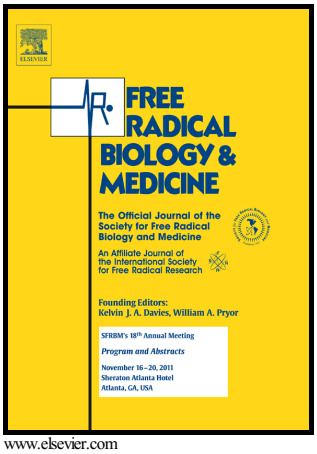

www.elsevier.com

PII: S0891-5849(16)31070-X
DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2016.11.035
Reference: FRB13090

To appear in: *Free Radical Biology and Medicine*

Received date: 18 March 2016
Revised date: 10 November 2016
Accepted date: 21 November 2016

Cite this article as: Jan Niemann, Cindy Johne, Susanne Schröder, Franzisk Koch, Saleh M. Ibrahim, Julia Schultz, Markus Tiedge and Simone Baltrusch An mtDNA mutation accelerates liver aging by interfering with the RO response and mitochondrial life cycle, *Free Radical Biology and Medicine* http://dx.doi.org/10.1016/j.freeradbiomed.2016.11.035

An mtDNA mutation accelerates liver aging by interfering with the ROS response and mitochondrial life cycle

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Abstract

Mitochondrial dysfunction affects liver metabolism, but it remains unclear whether this interferes with normal liver aging. We investigated several mitochondrial pathways in hepatocytes and liver tissue from a conplastic mouse strain compared with the control C57BL/6NTac strain over 18 months of life. The C57BL/6NTac-mtNODLtJ mice differed from C57BL/6NTac mice by a point mutation in mitochondrial-encoded subunit 3 of cytochrome c oxidase. Young C57BL/6NTac-mtNODLtJ mice showed reduced mitochondrial metabolism but similar reactive oxygen species (ROS) production to C57BL/6NTac mice. Whereas ROS increased almost equally up to 9 months in both strains, different mitochondrial adaptation strategies resulted in decreasing ROS in advanced age in C57BL/6NTac mice, but persistent ROS production in C57BL/6NTac-mtNODLtJ mice. Only the conplastic strain developed elongated mitochondrial networks with artificial loop structures, depressed autophagy, high mitochondrial respiration and up-regulated antioxidative response. Our results indicate that mtDNA mutations accelerate liver ballooning degeneration and carry a serious risk of premature organ aging.