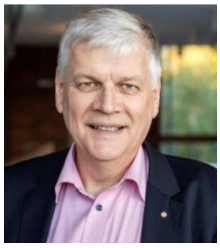
Manipulation of mtDNA expression to treat cancer and obesity



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The mammalian mtDNA is located in the mitochondrial matrix where it is packaged as single molecules coated with mitochondrial transcription factor A (TFAM) and other proteins to form nucleoids. The state of the mitochondrial nucleoid varies between a highly compacted form for genome maintenance and a more relaxed form allowing replication and transcription of mtDNA. The levels of TFAM directly controls mtDNA copy number and influences the oxidative phosphorylation (OXPHOS) capacity in the mouse. The expression mammalian mtDNA is critical for the cellular energy conversion by the oxidative phosphorylation (OXPHOS) system, which consists of the respiratory chain (complex I-IV) and ATP synthase (complex V). The OXPHOS system plays important roles in common forms of human pathology such as cancer and type 2 diabetes. To generate an experimental system where we directly can manipulate mtDNA expression and the OXPHOS capacity, we developed highly specific, small-molecule, allosteric inhibitors of the mitochondrial RNA polymerase. Treatment of mice with human tumor xenografts showed that these inhibitors of mitochondrial transcription (IMTs) cause an energy crisis and decreased tumor growth. Interestingly, IMT-treatment is well tolerated by normal mice and can even have beneficial effects in metabolically challenged obese mice. Our results argue that a detailed molecular understanding of the mammalian mtDNA expression machinery can be used to develop novel treatments for human disease, including cancer and metabolic disease.