Regulation of Human Mitochondrial DNA Replication and Transcription

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin, Göteborgs Universitet, kommer att offentligen försvaras i Hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 5 februari 2021, klockan 09.00.

av **Majda Mehmedović**

Fakultetsopponent:
Professor Maria Solá,
Molecular Biology Institute of Barcelona (IBMB-CSIC), Spanien

Avhandlingen baseras på följande delarbeten:

I. Farge G, **Mehmedovic M**, Baclayon M, van den Wildenberg SMJL, Roos WH, Gustafsson CM, Wuijte GJL, Falkenberg M.
In vitro-reconstituted nucleoids can block mitochondrial DNA replication and transcription. *Cell Reports*. 2014 July 10; 8(1):66-74

II. **Mehmedović M**, Martucci M, Spåhr H, Ishak L, Peter B, Mishra A, van den Wildenberg SM, Falkenberg M, Farge G.
Disease causing mutation (P178L) in mitochondrial transcription factor A results in impaired mitochondrial transcription initiation. *Manuscript 2021*

III. Jemt E, Persson Ö, Shi Y, **Mehmedovic M**, Uhler JP, Dávila López M, Freyer C, Gustafsson CM, Samuelsson T, Falkenberg M.
Regulation of DNA replication at the end of the mitochondrial D-loop involves the helicase TWINKLE and a conserved sequence element. *Nucleic Acids Research*. 2015 October 30; 43(19):9262-75

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Regulation of Human Mitochondrial DNA Replication and Transcription

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ABSTRACT

Mitochondria are organelles in eukaryotic cells, which through oxidative phosphorylation (OXPHOS) produces most of the ATP used to drive cellular processes. The organelle contains its own genetic material, mitochondrial DNA (mtDNA), which encodes 13 key components of the OXPHOS machinery. For its maintenance and expression, mtDNA is dependent on a large number of nuclear factors. Our understanding of these processes has progressed significantly during the last years, but much is still unknown.

The mitochondrial genome is completely coated by TFAM, which acts to compact mtDNA molecules into nucleoid structures. In this thesis we have examined how nucleoid formation contributes to regulation of mitochondrial replication and transcription. Our studies demonstrate that TFAM packaging regulates mtDNA availability, thereby directing levels of replication and transcription *in vitro*. These findings therefore reveal that TFAM has the potential to function as an epigenetic regulator of mtDNA transactions.

Second, we investigate the characteristics of a newly discovered mutation in TFAM that causes severe mtDNA depletion and early onset-liver failure in infants. Using a combined effort with biochemical, biophysical and cell biology techniques, we demonstrate that the mutant form of TFAM impairs transcription initiation from mitochondrial promoters. The mutant protein also impairs compaction of mtDNA.

Finally, we investigate a replication pre-termination event that leads to the formation of a displacement loop (D-loop) structure in mtDNA. We demonstrate that replication initiated at the origin of heavy-strand replication and transcription coming from the opposite direction (initiated at the heavy strand promoter) are both terminated at an evolutionary conserved sequence, which we term coreTAS. We also provide data, which suggest that coreTAS plays an important role in the regulated switch between D-loop formation and full-length replication.

Keywords: mitochondria, mtDNA, TFAM, transcription, replication, nucleoid, D-loop

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