

 TRANSCRIPTION

# A mitochondrial switch between transcription and replication

In addition to nuclear DNA, eukaryotic cells contain circular mitochondrial DNA (mtDNA). Transcription of mtDNA is directed by two promoters — the light-strand promoter (LSP) and heavy-strand promoter (HSP) — which are located on opposite DNA strands. Interestingly, transcription terminates prematurely downstream of the LSP at a G-rich region (which is termed conserved sequence block II (CSBII) and is located near an origin of replication) owing to the formation of a G-quadruplex between the RNA and the non-template DNA strand. This generates a replication primer that initiates mtDNA replication. However, it was not known whether transcription and replication of mtDNA occur simultaneously without interfering with each other, and whether the transcription machinery can regulate mtDNA copy number. In this study, Agaronyan *et al.* show that the

mitochondrial transcription elongation factor TEFM serves as a molecular switch between replication and transcription.

The authors set out to investigate the effect of TEFM on promoter-driven transcription of mtDNA and found that in the presence of TEFM, mitochondrial RNA polymerase transcribes through the CSBII, which suggests that TEFM prevents the synthesis of the replication primer for mitochondrial DNA polymerase and thus prevents replication. Further investigating this transcription anti-termination effect, they showed that TEFM interacts with the nascent transcript, possibly interfering with G-quadruplex formation, and with the downstream DNA, enhancing the mitochondrial RNA polymerase–DNA association.

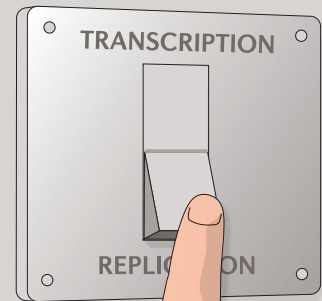
Next, the authors demonstrated that TEFM increased the stability and efficiency of the mitochondrial RNA

polymerase during synthesis of long RNAs, suggesting that TEFM also functions as a processivity factor.

Thus, on the basis of their findings, the authors propose that transcription and replication are mutually exclusive processes, with TEFM serving as a molecular switch that prevents the formation of a replication primer and increases processivity of the elongation complex to promote transcription and inhibit replication. The proposed mechanism may be essential for the regulation of mtDNA copy number during various developmental processes and may have implications for various mitochondrial functions and pathologies.

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