

# MODELING RNA POLYMERASE INTERACTION IN PLASTIDS OF PLANTS, ALGAE AND MITOCHONDRIA OF CHORDATES: HUMAN BEARING THE MELAS MUTATION AND RAT WITH HYPOSECRETION OF THYROID HORMONE

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*Motivation and Methods:* We introduced a concept, a mathematic model and its computer realization that describe the interaction between bacterial and phage type RNA polymerases, protein factors and secondary structures during transcription, including transcription initiation and termination. The model accurately reproduces virtually all relevant experimental data available on plastids of plants and algae, and mitochondria of chordates (frog, rat and human). The model was shown to accurately reproduce changes of gene transcription level observed in polymerase sigma-subunit knockout and heat shock experiments on plastids of plants and algae; and most evidence on bulk RNA contents and RNA half-life times in mitochondria of frog, healthy human, human bearing the MELAS mutation, healthy rat, and rat with hyposalivation of thyroid hormone. Predicted transcription characteristics are: percentage of polymerases terminated in both directions at a protein-dependent terminator; binding intensities of the regulatory protein factor (mTERF) with the termination site; transcription initiation intensities of all promoters in three chordate species (frog, healthy human, human with MELAS syndrome, healthy rat, and hypothyroid rat with aberrated mtDNA methylation). Absolute levels of gene transcription are obtained, while only relative RNA contents are known for selected genes from the experiment.

*Results:* A model was introduced to describe the interaction between moving ribosomes on RNA (a polysome) and ribonucleases. We identified putative factors mediating the MELAS syndrome development in human: the decrease of Phe-tRNA, Val-tRNA and rRNA contents in the cell. In human with MELAS syndrome the model predicts the noticeable 1.21-fold decrease of the mTERF-DNA binding intensity and the 7.75-fold decrease of the HSP1 promoter efficiency. Transcription levels of tRNA-Phe and rRNA drop 3.84- and 1.2-fold, respectively, that suggests possible implications for the MELAS phenotype. Intensities of the mTERF binding and LSP transcription initiation are equal between eu- and hypothyroid rats. The total intensity of transcription initiation from promoters HSP1 and HSP2 is 2.15-fold lower in the hypothyroid, which conforms well to the experimentally known methylation patterns of relevant DNA loci in eu- and hypothyroids. We describe the correlation between changes in methylation patterns of the mTERF binding site and three promoters in hypothyroid rat, and between changes in intensities of the mTERF binding and transcription initiations.

*Availability:* The corresponding computer program and a user guide are available at <http://lab6.iitp.ru/en/rivals>.