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Table of Contents

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P-09-009
The role of components of the DNA-repair complex DNA-PK in transcription regulation

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The trimeric complex DNA-PK, composed of DNA-binding heterodimer Ku and the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs), is a participant of DNA double-strand breaks repair pathway through the non-homologous end joining (NHEJ). The Ku heterodimer formed by Ku70 and Ku80 subunits acts as the main sensor of DSBs which triggers a cascade of phosphorylation events required for the subsequent DSB repair. In addition to NHEJ, Ku is involved in various cellular processes such as V(D)J recombination, AP-site repair, telomere maintenance, apoptosis, transcription, and translation. Also, Ku is suggested to participate in human immunodeficiency virus-1 (HIV-1) replication at the stages of integration and transcription although the exact mechanism of Ku-dependent transcriptional regulation is unclear. To clarify the way of Ku-mediated regulation of HIV transcription a set of HEK 293T derived sublines with a stable depletion of either Ku70, Ku80 or DNA-PKcs subunits was established using CRISPR/Cas9 technology. Then using a luciferase reporter system with firefly luciferase under the control of promoters (viral promoters CMV, SV40, TK and HIV promoter LTR and also cellular promoter PGK), we observed a strong reduction in luciferase expression from all tested promoters under depletion of Ku70 and especially Ku80 subunit. Surprisingly, the influence of DNA-PKcs knockout on the transcription efficiency from all promoters and particular HIV promoter was not detected. To elucidate the influence of the DNA-PK subunits on the cellular transcription, we performed a transcriptome analysis of wild type HEK 293T cells and those with depletion of either Ku70, Ku80 or DNA-PKcs. The genes regulated by each subunit were defined, and the genes dependent on the all DNA-PK complex were separated. The work was supported by the RSF grant 17-14-01107.

P-09-010
Transcription of damaged DNA by bacterial RNA polymerase

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DNA lesions can significantly affect DNA replication and transcription and must be repaired to avoid mutations. During transcription-coupled repair, RNA polymerase acts as a sensor of lesions in the template DNA strand. According to the prevalent model, mostly based on studies in *Escherichia coli*, the Mfd translocase then dislodges the stalled transcriptional complex and recruits the nucleotide excision repair enzymes to the site of the lesion. However, many molecular details of translesion transcription by bacterial RNA polymerase remain unclear. In this work, we studied RNA synthesis on damaged DNA templates by RNA polymerases from *E. coli* and *Deinococcus radiodurans*. We found that despite the great difference in stress tolerance of these two organisms their RNA polymerases behave similarly on DNA lesions. DNA modifications greatly affecting its structure (thymine dimers, 1,N6-ethenoadenine, AP-sites) significantly inhibit transcription while 8-oxoguanine and O-6-methylguanine decrease the RNA polymerase fidelity. We further showed that the Mfd protein from *D. radiodurans* can dissociate transcription elongation complexes paused at the sites of lesions. Moreover, Gfh transcription factors increase this pause and stimulate transcription complex disassembly by Mfd. Interestingly, the transcription elongation factor GreA, which normally reactivates backtracked transcription complexes, has an inhibitory effect on translesion synthesis by *D. radiodurans* RNA polymerase. This suggests that elongation complexes blocked at the lesions do not undergo backtracking and GreA binding may stabilize an enzyme conformation unfavorable for nucleotide addition. Thus, we conclude that diverse types of lesions in the template DNA strand differently affect transcription and may lead to transcriptional mutagenesis or blockage of RNA synthesis, which can be modulated by regulatory factors. This work was supported by the Russian Science Foundation (grant 17-14-01393).

DNA editing and modification

P-10-001
Transcription factor Ets-2 regulates the expression of key lymphotropic factors

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Ets-2 is a transcription factor (TF) that functions either as an activator or as a repressor of transcription and is involved in diverse biological functions, such as cell mitosis, development, differentiation, apoptosis and the regulation of immunity. Recent work in our laboratory has shown that in naive T helper cells IL-2 expression is blocked by Ets-2. In this work we studied the role of Ets-2 in the regulation of expression of key lymphotropic factors that play a pivotal role in the expression of genes involved in activation and differentiation of T and B cells; in particular, we examined the TFs NFAT2, NF-κB p65, c-Jun and the kinase CDK10. To this end, Jurkat, H938 (T lymphocytic cell lines) and HEK cells (embryonic kidney cell line), were transfected with increasing amounts of an Ets-2 overexpressing vector (pCDNA-ets2), in the presence (P/I) or absence (CM) of mitogens. Assessment of Ets-2 overexpression at the transcriptional level was performed by real time PCR. Ets-2 overexpression and lymphotropic factor expression at protein level were assessed by Western blot. Overexpression of Ets-2 in Jurkat and H938 cells induced the levels of NFAT2, NF-κB p65 and c-Jun under both CM and P/I conditions. In contrast, in stimulated HEK cells, the overexpression of Ets-2 resulted in a reduction in c-Jun and in CDK10 levels, whereas in non-stimulated HEK cells it resulted in an increase in c-Jun and CDK10 levels. Overexpression of Ets-2 in unstimulated H938 cells resulted in reduced CDK10 protein levels, whereas in stimulated cells Ets-2 over-induced CDK10 levels. In conclusion, Ets-2 is involved in the regulation of expression and synthesis of key lymphotropic factors. Our results set the stage for further studies to elucidate the role of Ets-2 in the regulation of signaling pathways involved in the activation and differentiation of T and B lymphocytes.

P-10-002
Application of plant ROS1 5-methylcytosine-DNA glycosylase from *Nicotiana tabacum* as tool for human epigenome editing

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DNA methylation is a reversible epigenetic mark for transcriptional gene silencing in diverse organisms including plants and animals. In higher eukaryotes, two general modified DNA bases 5-methylcytosine (mCyt) and its oxidized derivative 5-hydroxymethylcytosine (hmCyt) play epigenetic roles. In mammals, active

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