

## Abstract

# The Role of DNA Repair Complex DNA-PK in HIV-1 Transcription<sup>†</sup>

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<sup>†</sup> Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 16 July 2020

**Abstract:** The human DNA-dependent protein kinase (DNA-PK), composed of the heterodimeric protein Ku and catalytic subunit DNA-PKcs, is a sensor of double-strand DNA breaks in the non-homologous end-joining DNA repair pathway. The key role of DNA-PK in the post-integrational repair of HIV-1 has been shown. It has also been suggested that DNA-PK can participate in the regulation of HIV transcription, although the mechanism is unclear. To clarify the impact of each DNA-PK subunit on the transcription of HIV-1, HEK 293T cells, in which each of the DNA-PK components was depleted, were transfected with reporter vectors containing firefly luciferase under the control of HIV LTR promoter. We detected a positive influence of both Ku subunits, but not of DNA-PKcs, on the transcription from the HIV promoter. Ku is known to interact with HIV-1 TAR RNA, playing an essential role in viral transcription; nonetheless, the deletion of the TAR-coding region from LTR did not alter the Ku effect. Human small noncoding 7SK RNA participates in HIV-1 transcription. The direct binding of recombinant Ku and in vitro transcribed 7SK RNA was demonstrated using EMSA. In addition, we identified the interactions of endogenous Ku with proteins HEXIM1 and Cdk9 from the 7SK RNP complex. These results suggest that Ku exerts its effects on HIV-1 transcription via interaction with the 7SK RNP complex. However, we cannot rule out an indirect effect of Ku on transcription via the regulation of the levels of some transcription factors participating in HIV-1 transcription. We performed a transcriptome analysis of wild type HEK 293T cells and those with depleted DNA-PK subunits. The genes regulated by each subunit were defined and the genes that were mainly dependent on Ku subunits were selected. Among them, we identified transcription factors enhancing HIV-1 transcription, whose levels were downregulated in Ku-depleted cells. The study was supported by RFBR grant №18-04-00542 and RSF grant №17-14-01107.

**Keywords:** HIV transcription; DNA-PK complex; 7SK snRNA



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