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CURRENT RESEARCH ON A-to-I EDITING IN THE LABORATORY OF RNA BIOCHEMISTRY, FACULTY OF SCIENCE, CHARLES UNIVERSITY

MARTIN POSPÍŠEK

Charles University, Faculty of Science, Department of Genetics and Microbiology, Viničná 5, Praha 2, 120 00, Czech Republic
martin.pospisek@natur.cuni.cz

Current research in the Laboratory of RNA Biochemistry at the Faculty of Science, Charles University is mainly focused on characterization of 5' mRNA end formation, mRNA modifications and translation initiation in eukaryotes and their viruses. Recently, a possible role of the adenosine deaminase acting on RNA 1 (ADAR1) in eukaryotic translation and mutual interactions between viruses and the human host came in the centre of our interest.

ADAR1 is one of two enzymatically active human RNA adenosine deaminases and is responsible for most of the adenosine to inosine (A-to-I) RNA editing events in human cells. ADAR1 is inducible by interferon and constitutes part of the cellular innate immunity and antiviral defence machinery. However, detailed function of ADAR1 in viral infection can differ from virus to virus, can be manifested both as antiviral and/or proviral, and is poorly understood. Dysregulation in ADAR1 protein level or ADAR1-dependent editing were observed in plethora of cancer types. Reduced ADAR1 activity causes Aicardi–Goutières Syndrome that is characterized by childhood severe encephalopathy and high mortality. For a recent review on ADAR1 refer e.g. to Song et al. 2022 (1).

It is assumed that some of the ADAR1 cellular activities are not related to its deaminase enzymatic activity. We prepared an array of human cell lines bearing disrupted genes in the ADAR1 signalling pathway including ADAR1 itself which we use for investigation into the role of ADAR1 A-to-I editing both in translation and during the virus infection. Methods used to achieve our goals comprise, but are not limited to, RNAseq combined with polysome profiling and translatome analysis to map and evaluate A-to-I edited sites in the viral and cellular RNAs and to decipher a role, which A-to-I editing plays in synthesis of celullar and viral RNAs and proteins. Investigation of the ADAR1 regulon has a potential to either establish ADAR1 as an emerging target for new broad-range antivirals or to find novel cellular and viral targets specific for the particular viruses.

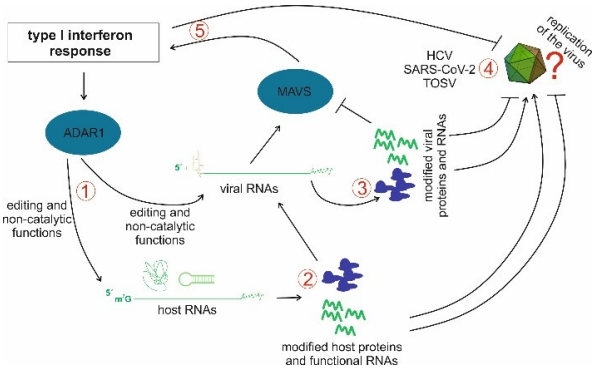

Fig. 1. Overview of the possible research tasks concerning function of ADAR1 regulon during virus infection. Production of ADAR1 is stimulated by IFN. ADAR1 edits both viral and host RNAs, including mRNAs, small RNAs, miRNAs, various ncRNAs etc. It can act both as adenosine deaminase and also by a non-catalytic manner (1). A-to-I edited cellular RNAs can manifest different protein coding, in case of mRNAs) and/or can change their association with other RNAs and proteins. These modified molecules can directly (2) or indirectly (4) influence replication of the virus. The same is valid also for the viral proteins and RNAs (3). The newly-emerged network of modified proteins and RNAs can finally act as either proviral or antiviral environment, depending of the virus and perhaps also the cell origin (4). A-to-I edited RNAs also inhibit MAVS signaling and thus attenuate type I IFN response (5).

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REFERENCE

1. Song B., Shiromoto Y., Minakuchi M., Nishikura K.: Wiley Interdiscip Rev RNA Jan;13(1):e1665 (2022).