ADAR1 KNOCKOUT LEADS TO GLOBAL DEREGULATION OF TRANSLATION AND TO TRANSLATIONAL SHUTDOWN UPON IFN-A/B TREATMENT IN HUMAN HUH7.5 HEPATOCYTES.

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In recent years, numerous evidence has been accumulated about the extent of A-to-I editing in human RNAs and the key role ADAR1 plays in the cellular editing machinery. It has been shown that A-to-I editing occurrence and frequency are tissue specific and essential for some tissue development, such as liver. Liver and hepatocytes specifically belong to the most affected tissues in ADAR1 KO mice (Hartner JC et al., 2004, J Biol Chem 279: 4894-4902; Wang G et al., 2015, Am J Pathol 185: 3224-3237). To study the effect of ADAR1 function in hepatocytes, we have created Huh7.5 ADAR1 KO cell lines. Upon IFN treatment, the Huh7.5 ADAR1 KO cells show rapid arrest of growth and translation, from which they do not recover. We analyzed translatome changes by employing a method based on sequencing of separate polysome profile RNA fractions. We found significant changes in transcriptome and translatome of the Huh7.5 ADAR1 KO cells. The most prominent changes include global deregulation of translation, negatively affected transcription by RNA polymerase III and changes of snoRNA and Y RNA levels. Furthermore, we observed that ADAR1 KO polysomes are enriched in mRNAs coding for proteins pivotal in a wide range of biological processes such as RNA localization and RNA processing, whereas the unbound fraction is enriched mainly in mRNAs coding for ribosomal proteins and translational factors. All these could also indicate that ADAR1 may play a relevant role in small RNA metabolism and ribosome biogenesis. This work was supported by the project National Institute of Virology and Bacteriology (Programme EXCELES, ID Project No. LX22NPO5103) - Funded by the European Union - Next Generation EU and was recently published in Roucova K. et al., RNA, Published in Advance, June 6, 2024, doi:10.1261/rna.080097.124.