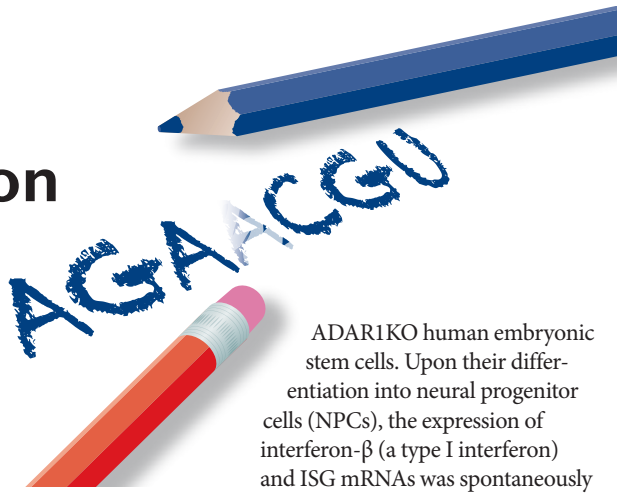
Nature Reviews Molecular Cell Biology | Published online 7 Feb 2018; doi:10.1038/nrm.2018.12

RNA METABOLISM

Interfering with interferon by RNA editing



V. Summersby/Macmillan Publishers Limited

Adenosine deaminase acting on RNA 1 (ADAR1) catalyses adenosine-to-inosine editing, often at non-coding regions of mRNAs. Mutations in ADAR1 cause Aicardi–Goutières syndrome (AGS), which is a neuro-developmental disorder associated with uncontrolled production of interferon, a cytokine normally generated in response to viral infection. Although the expression of the ADAR1 isoform ADAR1p150 is induced by interferon, how ADAR1 deficiency causes AGS remains unknown. Chung *et al.* now show that editing of endogenous mRNAs by ADAR1 prevents deleterious triggering of the interferon response.

Type I interferon is produced in cells with viral double-strand RNA (dsRNA) and leads to the induction of hundreds of antiviral interferon-stimulated genes (ISGs). To understand the potential role of ADAR1 in preventing endogenous dsRNA from inducing the interferon response, the authors generated ADAR1-knockout (KO) and ADAR1p150-only KO human cells. ADAR1 deficiency (either ADAR1 or ADAR1p150) did not affect mRNA abundance of the edited genes, but, following interferon treatment, protein induction of several ISGs was lower in ADAR1-deficient cells compared with wild-type cells.

The polysome profiles of mock- or interferon-treated cells were similar in wild-type cells. By contrast, interferon treatment in ADAR1-deficient cells caused translation shutdown as well as strong inhibition of cell proliferation. Thus, ADAR1 is required for maintaining efficient translation and cell proliferation during the interferon response.

Protein kinase R (PKR) is a dsRNA-activated antiviral ISG. Phosphorylated (activated) PKR (p-PKR) was highly upregulated in ADAR1p150KO cells and especially in ADAR1KO cells following interferon treatment. Both the dsRNA binding and deaminase activities of ADAR1 were necessary to fully suppress PKR activation in these conditions. Furthermore, PKR depletion in interferon-treated ADAR1-deficient cells partially restored ISG protein levels. Interestingly, in interferon-treated ADAR1-deficient cells, p-PKR levels were significantly reduced by inhibition of transcription, but not of translation. Thus, fully functional ADAR1 isomers are necessary to prevent PKR activation and maintain translation during the interferon response; in the absence of ADAR1, PKR activation depends on mRNA production.

To help understand the aetiology of AGS, the authors generated ADAR1KO human embryonic stem cells. Upon their differentiation into neural progenitor cells (NPCs), the expression of interferon-β (a type I interferon) and ISG mRNAs was spontaneously upregulated. This was accompanied by increased PKR activation and by apoptosis. Depletion of MDA5, which is a major cytoplasmic dsRNA sensor and inducer of the interferon response, in ADAR1KO NPCs led to a strong reduction in interferon-β mRNA levels and in ISG protein levels (including PKR). Thus, loss of ADAR1 in NPCs leads to MDA5-mediated interferon-β production, ISG induction, PKR activation and apoptosis.

> “by suppressing PKR activation, ADAR1 prevents interferon-induced translation shutdown and cell death”

In summary, by suppressing PKR activation, ADAR1 prevents interferon-induced translation shutdown and cell death. ADAR1p150, which itself is an ISG, has probably evolved to ensure cell survival during viral infection. Furthermore, ADAR1 editing of endogenous mRNAs could protect neuronal cells from spontaneous and deleterious activation of the interferon response.

Eytan Zlotorynski

ORIGINAL ARTICLE Chung, H. *et al.* Human ADAR1 prevents endogenous RNA from triggering translational shutdown. *Cell* https://doi.org/10.1016/j.cell.2017.12.038 (2018)