Nature Reviews Molecular Cell Biology | Published online 10 May 2017; doi:10.1038/nrm.2017.51

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RNA DECAY

The anti-apoptotic function of ADAR1

> ADAR1p110 protects specific mRNAs… from Staufen 1-mediated decay

Adenosine deaminase acting on RNA 1 (ADAR1; also known as DRADA) catalyses adenosine to inosine editing in double-stranded RNA (dsRNA), often in inverted Alu repeats located at non-coding regions of mRNAs. The smaller of two ADAR1 isoforms, ADAR1p110, is ubiquitously expressed and is localized in the nucleus, but its function is largely unknown. Sakurai *et al.* now show that in response to cellular stress, ADAR1p110 is exported to the cytoplasm, where it binds to dsRNA of anti-apoptotic mRNAs and, independently of its RNA-editing activity, prevents their decay.

The authors found that following the induction of stress by ultraviolet (UV) irradiation or heat shock in glioblastoma cells, the localization of ADAR1p110 temporarily and reversibly shifted to the cytoplasm. This was dependent on the phosphorylation of ADAR1p110 at one or more of five Thr and Ser residues by the MAP kinase kinase 6 (MKK6)–p38 signalling pathway. Analysis of the nuclear targets of p38 revealed that simultaneous depletion of MSK1 (also known as S6Kα5) and MSK2 (also known as S6Kα4) abolished the UV-induced cytoplasmic localization of ADAR1p110.

Cytoplasmic localization of ADARp110 — both of the wild-type protein following UV-irradiation and of a phoshomimetic ADARp110 mutant in normal conditions — was blocked by the depletion of exportin 5 (EXP5). Furthermore, the binding of phosphomimetic ADARp110 to the EXP5 complex *in vitro* was significantly higher than that of a phosphorylation-deficient mutant. Thus, phosphorylation of ADAR1p110 in the nucleus by MSK1 and MSK2 promotes its nuclear export by the EXP5 complex.

Depletion of ADAR1 induced apoptosis in UV-irradiated cancer cell lines. This was not observed when the larger ADAR1 isoform, ADAR1p150, was specifically depleted, suggesting that ADAR1p110 has an anti-apoptotic function. Interestingly, a deamination-defective ADAR1p110 mutant rescued ADAR1-depleted, irradiated cells from apoptosis, indicating that the suppression of stress-induced apoptosis is independent of the RNA-editing function of ADAR1p110, and is most probably mediated by its dsRNA-binding function.

The level of expression of hundreds of mRNAs, many of which have anti-apoptotic function, was significantly decreased in ADAR1-depleted cells following UV irradiation. Most of these transcripts contained dsRNA arising primarily from inverted Alu repeats in their 3′ untranslated region (3′ UTR), which were previously reported to associate with the RNA decay protein Staufen 1. Depletion of Staufen 1 in ADAR1-depleted cells prevented UV-irradiation-induced apoptosis and restored the expression of most of the mRNAs. Moreover, Staufen 1 bound to dsRNA in the 3′ UTRs of several tested transcripts, and its binding was significantly increased by ADAR1 depletion, indicating that ADAR1p110 competitively inhibits binding of Staufen1 to dsRNA.

Together, these results show that ADAR1p110 is a stress-response protein with an anti-apoptotic function. Cellular stress causes ADAR1p110 phosphorylation by the MKK6–p38–MSK1/MSK2 signalling pathway, which leads to ADAR1p110 nuclear export by the EXP5 complex. In the cytoplasm, ADAR1p110 protects specific mRNAs that contain dsRNA structures in their 3′ UTRs from Staufen 1-mediated decay, by inhibiting their interaction with Staufen 1.

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ORIGINAL ARTICLE Sakurai, M. *et al.* ADAR1 controls apoptosis of stressed cells by inhibiting Staufen1-mediated mRNA decay. *Nat. Struct. Mol. Biol.* http://dx.doi.org/10.1038/nsmb.3403 (2017)
FURTHER READING Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. *Nat. Rev. Mol. Cell Biol.* **17**, 83–96 (2016)