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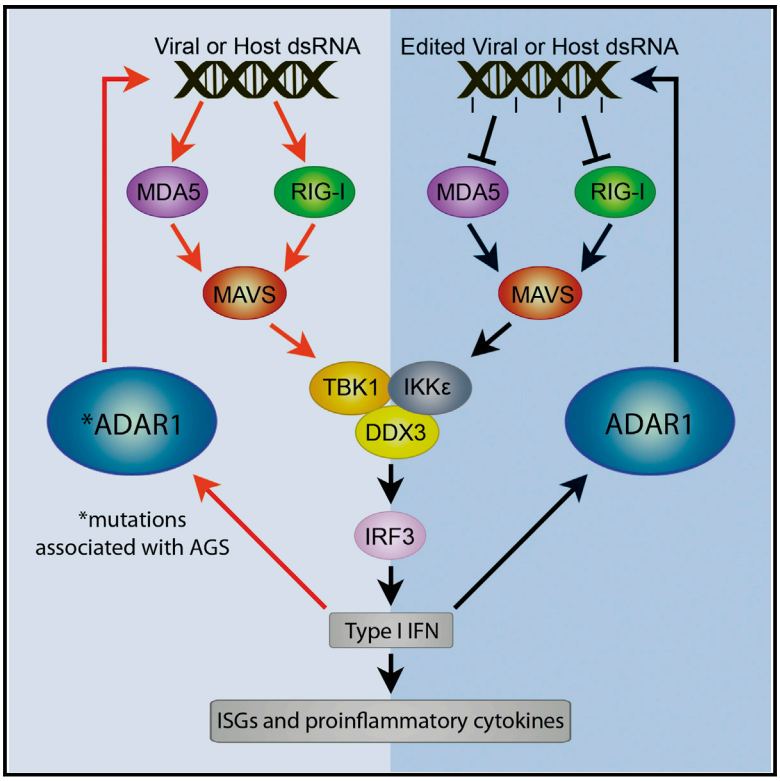
Cell Reports

The RNA-Editing Enzyme ADAR1 Controls Innate Immune Responses to RNA

Graphical Abstract



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In Brief

Mice lacking *Adar1* have a heightened immune response and stress-related apoptosis. Mannion et al. demonstrate that this mutation can be rescued to birth by generating a double mutant with *Mavs*, an innate immune gene, indicating the central role ADAR1 plays in innate immunity.

Highlights

Adar1 mutant mouse embryonic lethality is rescued in *Adar1*; *Mavs* double mutants

Aberrant antiviral responses in the *Adar1* mutant are due to loss of RNA editing

Human *ADAR1* mutations causing AGS affect primarily the interferon-inducible isoform

We propose that inosine helps innate immunity to distinguish cellular from viral RNA

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The RNA-Editing Enzyme ADAR1 Controls Innate Immune Responses to RNA

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SUMMARY

The ADAR RNA-editing enzymes deaminate adenosine bases to inosines in cellular RNAs. Aberrant interferon expression occurs in patients in whom *ADAR1* mutations cause Aicardi-Goutières syndrome (AGS) or dystonia arising from striatal neurodegeneration. *Adar1* mutant mouse embryos show aberrant interferon induction and die by embryonic day E12.5. We demonstrate that *Adar1* embryonic lethality is rescued to live birth in *Adar1*;*Mavs* double mutants in which the antiviral interferon induction response to cytoplasmic double-stranded RNA (dsRNA) is prevented. Aberrant immune responses in *Adar1* mutant mouse embryo fibroblasts are dramatically reduced by restoring the expression of editing-active cytoplasmic ADARs. We propose that inosine in cellular RNA inhibits antiviral inflammatory and interferon responses by altering RLR interactions. Transfecting dsRNA oligonucleotides containing inosine-uracil base pairs into *Adar1* mutant mouse embryo fibroblasts reduces the aberrant innate immune response. *ADAR1* mutations causing AGS affect the activity of the interferon-inducible cytoplasmic isoform more severely than the nuclear isoform.

INTRODUCTION

In vertebrates, viral double-stranded RNAs (dsRNAs) in the cytoplasm bind and activate RIG-I (retinoic acid-inducible gene I)-like cytoplasmic viral sensor proteins (RLRs) (for review, see Takeuchi and Akira, 2010). The known features that these sensors use to discriminate virus and pathogen RNAs from host cytoplasmic RNAs include the presence of dsRNA ends and 5′ triphosphates. RLRs translocate on dsRNA, and some RLRs may scan dsRNA to help distinguish between host and virus molecules. Cytoplasmic viral RNAs usually lack modifications, because most viruses do not encode modifying enzymes. It has been proposed that nucleic acid modifications of cellular RNAs help innate immune sensors to avoid aberrant activation by host nucleic acids (Gehrig et al., 2012; Karikó et al., 2005; Vitali and Scadden, 2010). Consistent with this idea, transfection of in-vitro-transcribed RNA into cultured cells generates an innate immune response. However, if the RNA is synthesized to contain naturally occurring modified bases, then the modified RNA does not cause innate immune induction (Karikó et al., 2005; Warren et al., 2010).

Suppression of responses of innate immune RNA sensors by modifications normally present in host RNAs could act as thresholding mechanisms to help prevent aberrant responses. Response thresholding mechanisms may be required because some cellular RNAs do contain RNA duplexes or have 5′ triphosphates. RNA duplexes in host RNAs are particularly hazardous; some Alu hairpins are still present in 3′ UTRs of mature mRNAs in the cytoplasm (Capshew et al., 2012). Transcription also occurs over most of the human genome, which inevitably generates further dsRNA that may reach the cytoplasm (Kapranov et al., 2007). The RIG-I and MDA5 (melanoma differentiation associated gene 5, IFIH1; interferon induced with helicase C domain 1) sensors are activated by binding RNA duplexes and signal through the MAVS (mitochondrial antiviral signaling) adaptor protein to activate NFκB, IRF3/7, and AP1. This activates transcription of genes encoding type I interferon (IFN) and proinflammatory cytokines. Secreted type I IFN binds to cell-surface type I IFN receptors to amplify and spread the antiviral response, inducing transcription of a large set of antiviral, IFN-stimulated genes (ISGs). Aberrant or chronic activation of IFN-stimulated defense processes is very damaging to the host.

Experiments in cultured cells do not test the overall importance of RNA modification for restraining innate immune responses in whole-model organisms or in human diseases.