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Adenosine deaminase acting on RNA (ADAR1), a suppressor of double-stranded RNA–triggered innate immune responses

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Edited by Luke O'Neill

Herbert "Herb" Tabor, who celebrated his 100th birthday this past year, served the *Journal of Biological Chemistry* as a member of the Editorial Board beginning in 1961, as an Associate Editor, and as Editor-in-Chief for 40 years, from 1971 until 2010. Among the many discoveries in biological chemistry during this period was the identification of RNA modification by C6 deamination of adenosine (A) to produce inosine (I) in double-stranded (ds) RNA. This posttranscriptional RNA modification by adenosine deamination, known as A-to-I RNA editing, diversifies the transcriptome and modulates the innate immune interferon response. A-to-I editing is catalyzed by a family of enzymes, adenosine deaminases acting on dsRNA (ADARs). The roles of A-to-I editing are varied and include effects on mRNA translation, pre-mRNA splicing, and micro-RNA silencing. Suppression of dsRNA-triggered induction and action of interferon, the cornerstone of innate immunity, has emerged as a key function of ADAR1 editing of self (cellular) and nonself (viral) dsRNAs. A-to-I modification of RNA is essential for the normal regulation of cellular processes. Dysregulation of A-to-I editing by ADAR1 can have profound consequences, ranging from effects on cell growth and development to autoimmune disorders.

Herbert "Herb" Tabor, M.D., served *The Journal of Biological Chemistry* as a member of the Editorial Board, as an Associate Editor, and then as Editor-in-Chief for 40 years until 2010 when he became Co-Editor (1). Among the many paradigm-shifting discoveries in biological chemistry during this period was the identification of RNA modification by C6 deamination of adenosine (A) to produce inosine (I) in double-stranded RNA (dsRNA)[2] (2, 3). This process is known now as A-to-I editing (4–8). The focus of this JBC Review is on one of the mammalian enzymes that catalyzes A-to-I editing, the adenosine deaminase acting on RNA1 (ADAR1) (9). ADAR1 plays a major role in immunity, most notably as a suppressor of the innate immune interferon (IFN) responses triggered by cellular sensors of dsRNA. This article is dedicated to Herb Tabor on the occasion of his 100th birthday. Herb is a truly remarkable individual. He is synonymous with JBC. For me, beginning as a JBC author first when a graduate student and then continuing years later as a member of the JBC Editorial Board and subsequently as an Associate Editor, it has been a special privilege to work together with Herb and learn so much from him. Herb Tabor is a scholar, a leader, and a gentleman. Happy Birthday, Herb!

Deamination of adenosine in dsRNA structures by ADARs

The C6 deamination of adenosine to produce inosine in dsRNA (Fig. 1, *upper*) was discovered in *Xenopus* during antisense RNA studies. It was found that stable dsRNA hybrid structures were not formed and protected against digestion with ssRNA-specific RNases, and the structures displayed altered mobility under native gel electrophoresis conditions (10, 11). It was then shown that these changes in dsRNA behavior resulted from covalent deamination of adenosine to inosine that occurred in both *Xenopus* (2) and mammalian cells (3). Deamination of adenosine in dsRNA can destabilize the RNA structure as a resultant I-U mismatch pair is less stable than an A:U base pair (2, 3, 12). ADAR enzymatic activity was purified and characterized from bovine nuclear extracts (13) and from cultured HeLa cells (14). The findings, described in JBC, revealed that the nuclear dsRNA adenosine deaminase purified from cells not treated with interferon was a mixture of size forms, ranging from ~80 to ~100 kDa. Molecular cDNA and genomic cloning then established that there are three gene members of the mammalian ADAR family, designated *ADAR1* (*ADAR*), *ADAR2* (*ADARB1*), and *ADAR3* (*ADARB2*) (4–8).

ADAR1 proteins and their expression

The sequence for the human ADAR1 cDNA predicts an ORF of 1226 amino acids (15–17). There are two size isoforms of ADAR1, referred to as p110 and p150 (16). Antibodies prepared against recombinant ADAR1 recognize two proteins present in extracts from human cell lines: one ~110 kDa (p110) that is constitutively expressed, and the other ~150 kDa (p150) that is inducible by IFN (16). p110 is nuclear, whereas p150 is both cytoplasmic and nuclear (16–19). The gene for ADAR1 maps to

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[2] The abbreviations used are: dsRNA, double-stranded RNA; ADAR, adenosine deaminase acting on RNA; IFN, interferon; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation associated gene 5 protein (IFIH1); OAS, oligoadenylate synthetase; PKR, RNA-dependent protein kinase; RIG-I, retinoic acid-inducible gene-1; RLR, RIG-I–like receptor; 2-5A, 2′-5′-oligoadenylate; LCMV, lymphocytic choriomeningitis virus; miR, microRNA; pri, primary; MEF, mouse embryo fibroblast; ssRNA, single-stranded RNA.

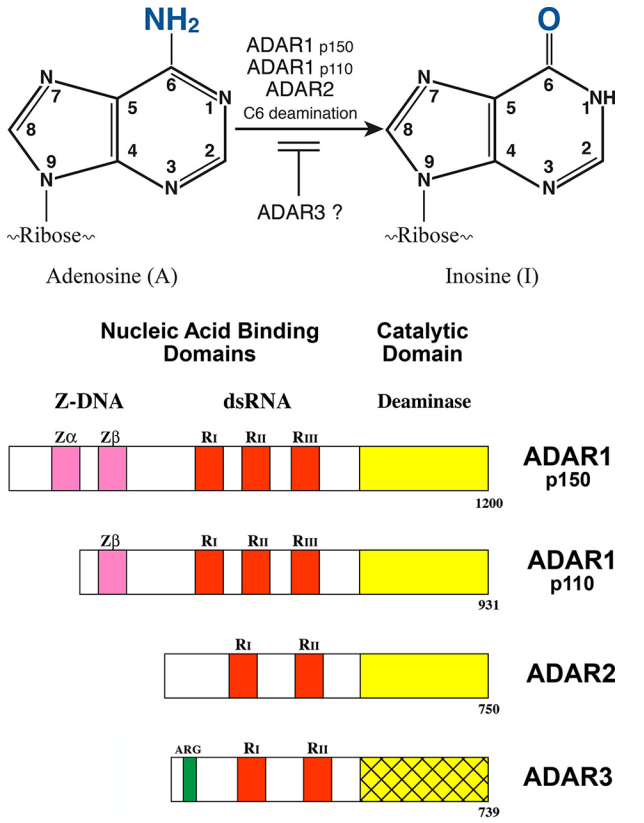

Figure 1. RNA editing by ADARs. *Upper panel,* C6 deamination of adenosine (A) in duplex RNA to produce inosine (I) catalyzed by ADARs. ADAR1, both the IFN-inducible p150 and the constitutively expressed p110, and ADAR2 possess deaminase activity. ADAR3 lacks deaminase activity and is implicated as a negative regulator of editing by ADAR1 and ADAR2. *Lower panel,* domain organization of ADAR proteins. The nucleic acid–binding domains include repeated dsRNA-binding domains (*red,* R_I, R_{II}, and R_{III}), either two (ADAR2 and ADAR3) or three (ADAR1 p110 and p150) copies. The N-terminal region of ADAR1 p150 possesses two copies of a Z-DNA–binding domain (*pink,* $Z\alpha$ and $Z\beta$), and ADAR3 has an arginine-rich ssRNA-binding domain (*green,* ARG). The deaminase catalytic domain (*yellow*) is C terminus; ADAR3 (*cross-hatched yellow*) is not yet demonstrated to possess enzymatic activity. (Adapted from Ref. 5.)

a single locus, chromosome 1 q21 for human *ADAR1* (20, 21) and chromosome 3 F2 for mouse *Adar1* (22). Genomic and cDNA sequence analyses are consistent with a single *ADAR1* gene, which in the human is about ~40 kbp and includes 17 exons (23). Expression of the human (24–26) and mouse (27) *ADAR1* genes is driven by multiple promoters, one of which is IFN-inducible and the others are constitutively active. The IFN-inducible p150 protein initiates from AUG1 present in exon 1A of the IFN-inducible human transcript, and the constitutive p110 protein initiates from the in-frame AUG296 present in exon 2 as the constitutive alternative exon 1B lacks an AUG (23). Alternative forms of exons 6 and 7 also occur (27–29). Expression of the mouse *Adar1* gene and its exon organization involves strategies of alternative promoter usage and alternative splicing conceptually similar to that of the human *ADAR1* gene (23, 27–31). Exon 7a is found in constitutively-expressed transcripts that specify p110, predicted to be 931 amino acids (human) or 903 amino acids (mouse). The smaller exon 7b is present in IFN-inducible human ADAR1 transcripts that specify p150, predicted to be 1200 amino acids (human) or 1152 amino acids (mouse) (23).

ADAR1 is both ubiquitously expressed (27, 32, 33) and inducible by IFN (16, 24, 27, 32–35). Canonical JAK–STAT signaling responsible for transcriptional activation of gene expression by IFNα/β involves binding of IFN to its cognate cell-surface receptor that is found on most types of cells. Activation of JAK1 and TYK2 kinases then mediates the phosphorylation of STAT1 and STAT2 transcription factors that associate with the IRF9 factor, translocate to the nucleus, and bind at the interferon-stimulated response DNA element to drive the inducible gene expression (36, 37). The IFN-inducible *ADAR1* promoter possesses a consensus ISRE element (23), both the human (24) and mouse (29) genes. Induction of the p150-encoding transcripts by IFN depends upon both STAT2 and IRF9, but the requirement for STAT1 varies between cell lines; detectable induction occurs in the absence of STAT1 in mouse but not human cells (29, 35).

The domain structures of the mammalian ADARs are summarized in the Fig. 1 (*lower panel*) schematic. Both p110 and p150 ADAR1 are active dsRNA adenosine deaminases (16, 28, 38). The C-terminal region of ADAR1 specifies the catalytic domain; three copies of the dsRNA-binding domain are present in the central region of p150 and p110 (15–17, 39). p150 is N-terminally extended compared with p110; the additional p150 sequence includes the $Z\alpha$ Z-DNA–binding domain (5, 8). Substitution mutations of the His (H) and Glu (E) amino acid residues in the conserved CHAE sequence of the ADAR1 catalytic core abolishes A-to-I deaminase activity (39–41). Active ADAR1 is a dimer (42–44). The RNA-binding domains present in ADAR1 p110 and p150 (15–17, 39) are homologous to the repeated dsRNA-binding domain discovered earlier in the dsRNA-dependent protein kinase PKR (45–48). Substitution mutations of a conserved lysine residue within the core of each of the RNA-binding domains (39) as well as deletion mutations (40) revealed that the RIII copy linearly adjacent to the deaminase catalytic domain is the most important for enzymatic activity, and the central RII copy is the least important (39). The repeated Z-DNA–binding domain present in p150, $Z\alpha$ and $Z\beta$, was identified as a domain homologous to the N-terminal region of the poxvirus E3L interferon antagonist protein (16, 49) and was shown to bind Z-DNA (50). $Z\alpha$ can also bind Z-structured dsRNA (51). The physiological significance of the Z-domains, and the nucleic acid bound by them within cells, is not fully understood. Functionally distinct dsRNA-binding domains are associated with splice variants of ADAR1 (28). The dsRNA-binding domains contribute to the A-to-I editing selectivity of the catalytic domains of ADAR1 and ADAR2 (38, 52–55). This is illustrated by the recombinant chimeric PKR–ADAR1 protein, where the dsRNA-binding domains from PKR replace those of ADAR1; significant deaminase editing activity is retained with a synthetic dsRNA substrate but not with natural (GluRB or 5HT-2cR) substrates (52). Human ADAR1 and ADAR2 have a 5′ nearest neighbor preference of U > A > C > G and a 3′ nearest neighbor preference of G > C ~ A > U and G > C >U ~ A, respectively (54). For ADAR2, the preferences appear to derive from differential base flipping of the targeted adenosine out of the double helix substrate rather than from direct recognition of neighboring bases (56).

ADAR2 and ADAR3 proteins

In addition to ADAR1, there are two more mammalian ADARs, ADAR2 and ADAR3 (4–8). The single mammalian gene for ADAR2 encodes multiple size isoforms of ADAR2 protein by alternative promoter usage and alternative splicing, with major isoforms predicted to be 701 and 750 amino acids for the human protein (23). ADAR2 is an active A-to-I deaminase, localizes to the nucleus, possesses two copies of the dsRNA-binding domain, and a C-terminal catalytic domain. As discussed in the following section, although ADAR1 is responsible for most of the A-to-I editing observed in mammalian cells, ADAR2 is generally responsible for the highly selective editing observed in the comparatively small number of identified exonic coding sites (8, 33). ADAR3 differs from ADAR1 and ADAR2 in an important manner: ADAR3 has not yet been demonstrated to possess enzymic activity (5–8). Expression of ADAR3 is limited to regions of the brain (57), unlike the ubiquitous expression seen for ADAR1 (4–8).

Substrate RNAs and roles of A-to-I editing

Transcripts encoding the glutamate and serotonin 2C receptors were among the first substrates identified, and the highly specific A-to-I editing of them is exquisitely well characterized (38, 58–63). The editing of GluRB and 5HT-2cR transcripts occurs within exonic sequences at the pre-mRNA level prior to splicing, thereby leading to amino acid substitutions in the expressed receptor proteins that alter their function. Editing specificity is dictated by unique cis-acting inverted repeat sequences predicted to form imperfect duplex structures in the substrate RNAs. Based on results of complementation studies, the glutamine (Q) to arginine (R) site of GluRB is the main target of ADAR2 as the knockin of GluRB encoding arginine at the Q/R site largely rescues the mouse *Adar2* knockout phenotype (62). ADAR3 binding to the GluRB pre-RNA inhibits ADAR2 editing at the Q/R site, with elevated inhibition of Q/R editing in glioblastoma cells (63). In addition to specific editing events that recode mRNA genetic information, thereby leading to amino acid substitutions during translation (GluRB, 5HT-2cR), the editing of an amber UAG termination codon to generate a tryptophan UIG codon occurs in hepatitis D virus, thereby permitting synthesis of large delta antigen (5, 64).

RNA-seq strategies with high coverage and high accuracy have identified many A-to-I editing sites in RNA isolated from cultured cells and animal tissues (8, 33). Although a few additional nonrepetitive exon–coding sites were found, the vast majority of the ~2 million-plus human A-to-I editing events occur in repetitive noncoding sequences (mostly *Alu* sequences in the human) (8, 33, 65–71). The extent of editing seen at a given site is typically partial, with editing at most sites less than 20% (7, 68, 73). However, the values vary widely, from near 100% (for the GluRB Q/R site) to less than 1% (7, 68). ADAR1 appears predominantly responsible for A-to-I editing of noncoding sites and ADAR2 for editing of coding sites (33). Furthermore, the knockin of the catalytically inactive E861A mutant of *Adar1* gives normal mice when rescued by the concurrent knockout of *Mda5*, indicating that protein recoding by ADAR1 catalyzed A-to-I editing is not essential for normal mouse development and homeostasis (72). When 557 loci containing 11,103 editing sites were analyzed in untreated and IFN-treated WT and mutant mouse MEF cells, it was found that the vast majority of A-to-I editing events were dependent upon ADAR1 and not ADAR2; furthermore, this editing was enhanced by IFN treatment in a manner dependent upon the p150 isoform of ADAR1 (73).

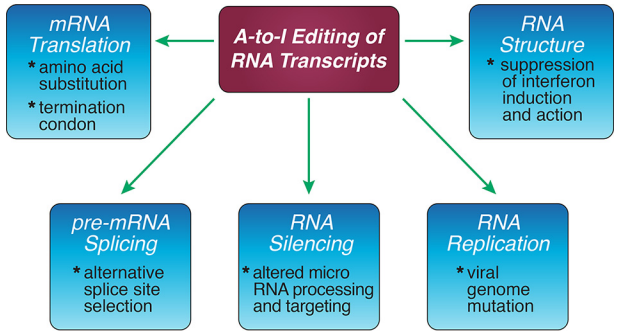

Figure 2. Biochemical mechanisms by which A-to-I editing of RNA transcripts possessing double-stranded structure may affect gene expression and product function. Because I base-pairs as G instead of A, A-to-I RNA editing has the capacity to alter processes, including mRNA translation by altering codons and hence coding potential, pre-mRNA splicing by changing splice site recognition sequences, and RNA silencing by altering microRNA production or targeting. A-to-I editing may also lead to RNA mutations of viral genomes and transcripts by changing template and hence product sequences during RNA-dependent RNA replication. Finally, A-to-I editing may lead to I-U mismatches in place of A:U bp, thereby destabilizing dsRNA structures and hence affecting the activity of dsRNA sensing proteins of the interferon response, including the MDA5 RIG-I–like receptor, protein kinase PKR, and 2′-5′-oligoadenylate synthetase OAS–RNase L. (Adapted from Ref. 146.)

Biochemical mechanisms

A-to-I editing of RNA transcripts affects multiple processes of mammalian cells and their viruses (Fig. 2). Among the mechanisms by which ADARs act, in addition to effects exerted on mRNA translation, are those on pre-mRNA splicing and microRNA processing and targeting. For RNA viruses, editing of viral RNA sequences also can potentially lead to genome mutation. For ADAR1, A-to-I editing events observed in mouse and human RNA transcripts largely occur in noncoding repetitive sequences that form duplex structures, and the major role of this editing is the suppression of innate immune interferon responses.

mRNA translation

Because inosine generated by deamination of adenosine base-pairs as if the I were a G instead of an A, A-to-I RNA editing has the capacity to alter decoding during mRNA translation, thereby leading to amino acid substitution in the protein product. As discussed above, among the earliest and best-characterized examples of editing that affects translation and gives rise to protein products with altered function are the editing of the cellular *GluRB* and *5HT2cR* transcripts encoding neurotransmitter receptors and hepatitis D virus RNA encoding delta antigen. In these cases, the editing is highly selective, changing a codon and thereby recoding genetic information within the pre-mRNA, leading to amino acid substitutions or elimination of a termination codon. Only a very few exon

recoding sites have been identified among the many A-to-I sites in the human transcriptome (8, 33, 70, 71).

Pre-mRNA splicing

Most introns are of the U2-type and are flanked by GT-AG splice site dinucleotides. Because I is recognized as G by the spliceosome machinery, alternative 5′-AT or AA-3′ sites can be converted into canonical sites by editing. A-to-I editing leading to alternative splicing during the processing of pre-mRNA was first demonstrated for ADAR2 transcripts. This ADAR2 autoediting of its own pre-mRNA creates a 3′ AG splice site (AA changed to AI (AG)) for alternative splicing (74). Human nuclear prelamin A recognition factor transcript includes an *Alu*-exon that depends upon A-to-I editing for exonization in a tissue-dependent manner, again by creation of a functional 3′ AG splice site (75). Tumor-associated intronic editing of the HNRPLL splicing factor transcript by ADAR1 p110 and ADAR2 generates a novel variant containing an additional exon 12A (76). A comprehensive survey of noncanonical splice sights using deep transcriptome profiling identified seven U2/U12-like noncanonical sites that are converted to canonical sites by A-to-I editing (77). Three of the noncanonical sites are AT-AG, and four are GT-AA, and all are involved in alternative splicing (77).

MicroRNA silencing

The discovery that A-to-I editing may affect RNA silencing by microRNAs (miRs) provides an additional manner by which ADARs impact gene expression. Editing effects are observed at the level of processing of miR precursor RNA to produce a functional miR (illustrated by miR-142 and miR-151) or by altering the targeting of the miR (illustrated by miR-376 and miR-378). Pri-miRNA precursors are processed by Drosha and Dicer endonucleases together with dsRNA-binding proteins to produce mature miRs. Estimates are that ~20% of the pri-miRs are subject to editing by the ADARs (78). Editing of the pri-miR-142 impairs processing by the Drosha DGCR8 complex, reducing the amount of mature miR-142 produced (79). Editing of the pri-miR-151 impairs cleavage by Dicer-TAR RNA-binding protein complex (80). Editing within the seed sequence of miR-376 by ADAR2 alters targeting and subsequent silencing (81), whereas ADAR1 creates an miR-378 recognition site in the 3′-UTR of the human aryl hydrocarbon receptor transcript (82). Furthermore, comprehensive analyses of miRNA-seq datasets of human cancer tissues identified multiple editing sites in miRs and their 3′-UTR targets (83, 84). ADARs are potent dsRNA-binding proteins and in some instances impair knockdown efficiency of siRNAs independent of their catalytic activity (85, 86).

Viral RNA mutation

Viruses that possess RNA genomes typically encode a viral RNA-dependent RNA polymerase that transcribes and replicates the genome. If complementary sequences are generated, dsRNA structures may arise that would provide targets for editing. This, then, might generate viral RNA mutations. Editing within a template RNA strand by ADAR to substitute an "I" for an "A" would lead to a complementary change in the product RNA strand following replication by the viral polymerase. ADAR A-to-I editing then would generate either A-to-G or U-to-C transitions dependent upon the strand sequenced. Studies of a number of viruses reveal that ADARs are both antiviral and proviral, dependent upon the virus–host combination, a subject that has been reviewed (5). Viral A-to-I substitution editing has a long history, beginning with measles virus. Viral RNAs from brain autopsies of subacute sclerosing pan-encephalitis patients were found to possess extensive A-to-G (U-to-C) transitions characteristic of ADAR editing (87). For measles virus deficient in C protein expression, defective interfering dsRNAs are generated frequently and early, activate PKR, and impair virus growth (88, 89). These dsRNA structures are destabilized by ADAR-mediated hypermutations, and ADAR1 suppresses measles virus-induced apoptosis and PKR activation (90, 91). Increased A-to-G and U-to-C mutations characteristic of ADAR editing are described for lymphocytic choriomeningitis virus (LCMV), with bias to the glycoprotein region of the S segment RNA under conditions of increased p150 expression during infection (92). Possibly editing of a virion surface component, such as the LCMV glycoprotein, might create changes in a neutralization epitope thereby facilitating escape from immune surveillance.

Suppression of innate immune interferon responses

dsRNA has a long history in the interferon field (93). dsRNA is an inducer of IFN production, and dsRNA is an activator of some IFN-induced proteins responsible for IFN's actions. Interferon was the first cytokine discovered, identified by Isaacs and Lindenmann (94) during studies on virus interference. They observed that viral infection (with influenza A virus) induced the production of a secreted cellular factor that possessed the ability to interfere with virus growth, both of the homologous inducing virus and also of heterologous (Sendai and Newcastle disease) viruses. The interferon system now is recognized as the cornerstone of innate antiviral immunity. Considerable detail has been learned about the signal transduction pathways by which viral infection through the production of dsRNA leads to the induction of IFN (95–98). Likewise, two cellular responses that play central roles in the antiviral and proapoptotic actions of IFN are triggered by dsRNA: the activation of protein kinase PKR, and the activation of 2′-5′-oligoadenylate synthetases OAS. PKR (47, 99, 100) and OAS (101, 102) sense dsRNA that leads to their enzymatic activation or, in some instances, antagonism of activation.

MDA5–MAVS

Among the sensors that detect the presence of viral (nonself) dsRNA and trigger the production of IFN are the family of cytosolic receptor proteins known as RIG-I–like helicase receptors. These include MDA5 and RIG-I (Fig. 3). Different characteristic features of viral dsRNAs are sensed by MDA5 and RIG-I (95, 97, 98). However, it is now apparent that in the absence of ADAR1, endogenous cellular (self) dsRNA also triggers MDA5 signaling via the MAVS adaptor to activate innate immune proinflammatory responses (32, 41, 103–105). The crystal structure of MDA5 bound to dsRNA provides insight into the structural basis of dsRNA recognition, filament formation, and

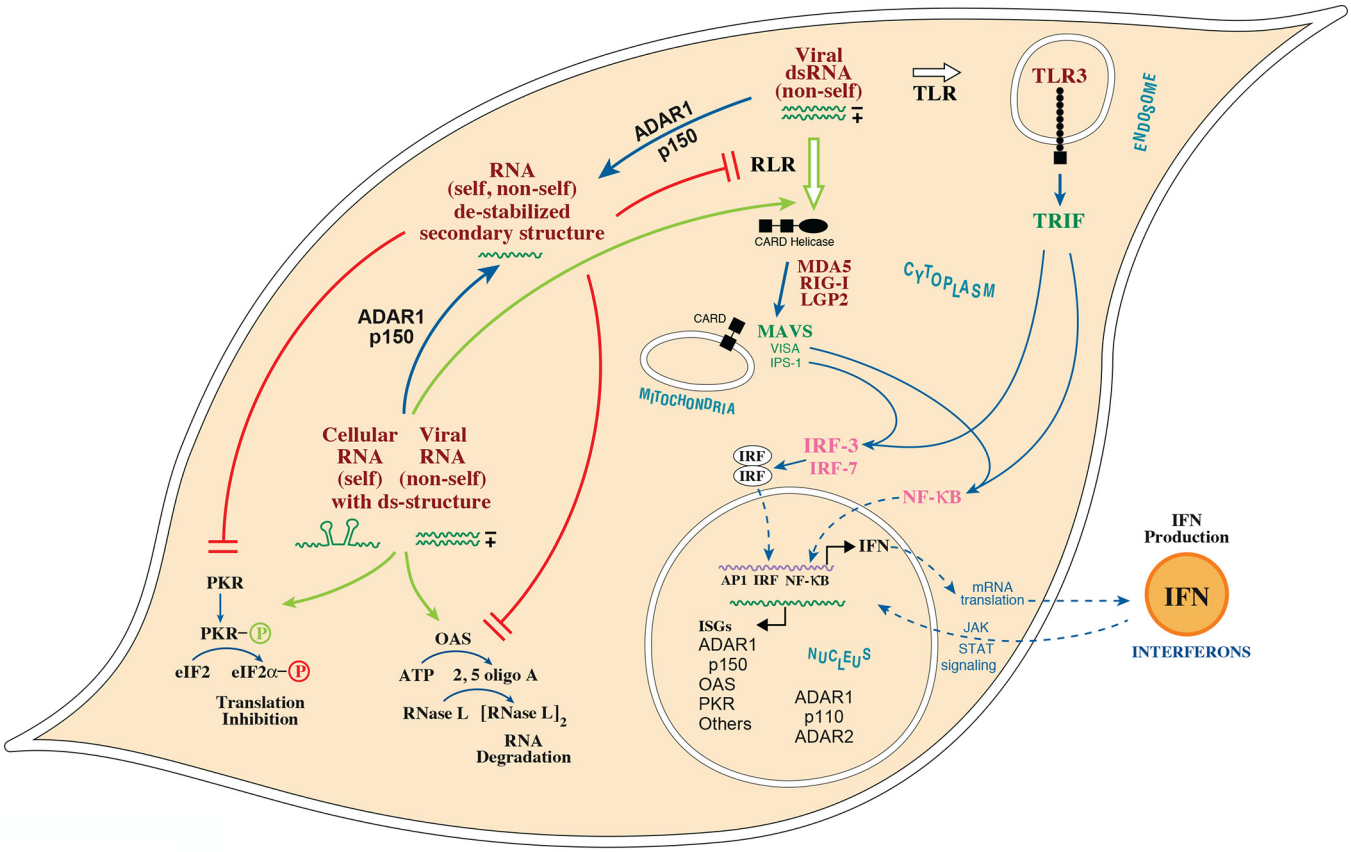

Figure 3. Model summarizing the role of ADAR1 as a suppressor of dsRNA-triggered innate immune responses. Cytoplasmic RLR and endosomal membrane-associated TLR3 sense dsRNA to mediate the production of type I IFN through activation of interferon-regulatory (*IRF*) and NF-κB transcription factors. The RLR family of proteins includes the MDA5 sensor that detects cytoplasmic dsRNAs, both viral (nonself) and cellular (self), and signals via the mitochondrial adaptor MAVS (IPS-1 and VISA) to produce IFN. Among the IFN-induced proteins are the PKR protein kinase and OAS synthetases, also cytoplasmic dsRNA-binding proteins. PKR, when activated by dsRNA-dependent autophosphorylation, phosphorylates translation initiation factor eIF2α thereby leading to an inhibition of translation. OAS, when activated by dsRNA, produces 2′-5′-oligoadenylates, which then activate the 2–5A–dependent RNase L thereby leading to RNA degradation. The p150 isoform of ADAR1 is IFN-inducible and both cytoplasmic and nuclear, whereas ADAR1 p110 and ADAR2 are both nuclear proteins and constitutively expressed. Under conditions of ADAR1 p150 deficiency, cellular RNAs (self) with double-stranded structure accumulate to sufficiently high concentration, above the threshold, and trigger activation of cytoplasmic dsRNA sensors, including MDA5, PKR, and OAS. In the presence of ADAR1 p150, A-to-I editing leads to inactivation of cellular (self) dsRNAs and impairment of dsRNA-triggered innate immune responses, as the dsRNA concentration is below the threshold. Infection leads to increased levels of viral dsRNA (nonself) present in infected cells compared with the cellular dsRNA (self) present in uninfected cells, thereby triggering activation of dsRNA sensors MDA5, PKR, and OAS. (Adapted from Ref. 73.)

signal activation via the MAVS adaptor. MDA5 recognizes the internal duplex structure, whereas RIG-I recognizes the terminus of dsRNA (106). *Alu:Alu* dsRNAs formed by inverted repeat *Alu*-containing transcripts are ligands of MDA5. A-to-I editing suppresses filament formation of WT MDA5, whereas unmodified *Alu:Alu* dsRNAs activate WT MDA5 under conditions of ADAR1 deficiency (107). Gain-of-function mutation of MDA5 allows mis-recognition of self, cytosolic inverted repeat *Alu* dsRNAs (107).

ADAR1 down-regulates the sensing of both cellular (self) and viral (nonself) dsRNAs. Measles virus is an example of an RNA virus that activates RIG-I–like receptor signaling via MAVS to induce IFNβ gene transcription (108). Although C mutant virus is a robust inducer of IFNβ in human cell lines expressing ADAR1, wildtype (WT) measles virus by contrast is a poor inducer (108). However, WT virus becomes an excellent IFN inducer, comparable with that of the C mutant, under conditions of ADAR1 deficiency (109). Optimal suppression of IFNβ induction in WT virus-infected cells by ADAR1 p150 requires deaminase catalytic activity but not Z-DNA– binding activity (110). PKR kinase enhances both measles virus induction of IFNβ and apoptosis, mediated by cytosolic sensor signaling through MAVS, with the amplification of IFNβ induction occurring through eIF2α-mediated translational control (111, 112).

Mouse models of ADAR1 deficiency provided novel insight into the functional significance of ADAR1-mediated suppression of dsRNA detection and hence suppression of triggering of type I interferon and autoinflammatory responses. Genetic disruption of *Adar1* in mice achieved by deleting both p150 and p110 (30, 31), by knocking out only p150 expression (104) or by knocking in the expression of the catalytic-deficient *Adar1* E861A mutant (41), results in embryonic lethality characterized by disintegration of the fetal liver. The conditional knockout of *Adar1* (32) and the knockin of the E861A mutant lacking editing activity (41) both result in an interferon signature of gene expression and high levels of cell death. ADAR1 is essential for normal murine erythropoiesis (113). However, the embryonic lethality and interferon signature phenotypes of *Adar1* mutant mice can be rescued by concurrent deletion of either the MDA5

RIG-I–like receptor (41) or the MAVS mitochondrial adaptor (103, 105) but not the RIG-I receptor (105). An *Ifnar* interferon receptor mutation only partially rescues the *Adar1* mutant embryonic lethality, and while the *Mavs* mutation rescues embryo survival to live birth, the mutant mice die shortly after birth (103, 105). By contrast, the concurrent *Mda5* mutation rescues the *Adar1* E861A mutation to live birth and well beyond. *Adar1*(E861A)-*Mda5* double mutant mice appear normal, including their life span (7, 72). This suggests that the absence of ADAR1-editing activity is tolerated in the absence of MDA5. One possibility, given the differences between the MDA5 and MAVS rescues, is that under conditions of ADAR1 enzyme deficiency, the MDA5 dsRNA sensor may possibly function by an additional mechanism that is independent of the well established signaling via mitochondrial MAVS. Another possibility is that the knockin of the E861A catalytic mutant protein, while lacking editing activity, still possesses dsRNA-binding activity, and it is this dsRNA-binding activity that in the absence of functional MDA5–MAVS signaling contributes to the rescue phenotype beyond birth. However, the fact that the concurrent deletion of either *Mda5* or *Mavs* does rescue the *Adar1* embryonic lethality phenotype strongly suggests that the accumulation of self dsRNA structures recognized by MDA5 and signaling through MAVS is responsible in large part for the *Adar1* mutant phenotypes.

Independent roles of the ADAR1 p110 and p150 proteins have been identified, with regulation of the MDA5 sensor activity by p150, whereas both p150 and p110 affect multiorgan development in the mouse (41, 104, 105, 113). Evidence also has been provided that ADAR1 regulates dsRNA sensing in the setting of ischemic stress in the liver, where ADAR deficiency leads to increased RIG-I– dependent IFN production, inflammation, and organ damage following ischemic stress (114). By contrast to the embryonic lethality phenotype of *Adar1* ablation (30–32, 41, 104), the *Adar2* and *Adar3* mouse knockouts do not display embryonic lethality. Furthermore, postnatal death of the *Adar2* mutant mouse remarkably is rescued by knockin of the edited form of the GluR-B Q/R site (62), although ADAR2 is required for normal physiology more broadly (115). An extended phenotypic analysis of 320 parameters showed the mice were hypermetabolic, had a hearing deficit, and displayed increased serum IgE levels (115). RNA editing by ADAR2 is metabolically regulated, for example in pancreatic islets and beta cells (116). *Adar3* knockout mice are born following predicted Mendelian ratios and do not display any atypical developmental characteristics (117). Mice with the *Adar3* gene disrupted by deletion of exon 3 (which includes the two copies of the dsRNA-binding domain, Fig. 1, *lower panel*) do, however, show deficits in learning and memory (117).

A-to-I editing by ADAR1 may lead to I-U mismatches in place of A:U bp, thereby destabilizing dsRNA structures and hence suppressing the activity of dsRNA-sensing proteins of the interferon response, including not only the MDA5 RIG-I–like receptor considered above, but also the protein kinase PKR and the 2′-5′-oligoadenylate synthetase OAS–RNase L (41, 109, 110, 118, 119). In addition to destabilizing effects of deamination mediated by ADAR catalytic activity, ADARs are also potent dsRNA-binding proteins (16, 23). The potential effect of sequestration of dsRNA or perturbation of intermolecular interactions involving dsRNA in the absence of editing may also occur (120, 121).

PKR

The PKR protein is a dsRNA sensor (Fig. 3). Binding of dsRNA by PKR leads to dimerization and activation by autophosphorylation. Activated PKR then catalyzes the phosphorylation of serine 51 of the α-subunit of protein synthesis initiation factor eIF2, which leads to an inhibition of translation (47, 93, 100, 122–125). PKR is both antiviral and pro-apoptotic. ADAR1 deficiency leads to increased activation of PKR and reduced virus growth (90, 119). The formation of stress granules, cytoplasmic aggregates of stalled translation initiation complexes, is a hallmark of viral infection. Stress granule formation is PKR-dependent for several viruses, including measles virus and hepatitis C virus (110, 126). ADAR1 suppresses both the activation of PKR and the formation of stress granules in cells infected with either WT or V mutant measles virus but not the C mutant (90, 109, 110). C mutant measles virus produces large amounts of viral dsRNA and grows poorly compared with either WT or V mutant virus. The C mutant is an efficient activator of PKR even in the presence of ADAR1, leading to an inhibition of viral protein synthesis and reduced C mutant virus growth (88, 89). In the absence of infection, activation of PKR by cellular (self) RNAs is suppressed by ADAR1 (73). In uninfected mouse *Adar1* null MEFs (lacking p110 and p150) and *Adar1* p150 null MEFs, but not *Adar2* null or WT MEFs, PKR becomes activated following IFN treatment as measured by increased phosphorylation of eIF2α and formation of stress granules (73). Deep sequencing of mouse exonic loci containing A-to-I editing sites using RNA from mutant and WT cells reveals that the majority of editing in MEFs is by ADAR1, with hyper-edited sites found in predicted duplex structures of cellular (self) RNAs (33, 73). Likewise, conceptually similar conclusions are reached with human 293 cell lines generated using CRISPR-Cas technology lacking both p110 and p150, or only lacking p150: ADAR1 blocks translational shutdown by preventing hyperactivation of the PKR kinase triggered by endogenous (self) RNA (127). Both dsRNA binding and catalytic activity of ADAR1 p150, but not Z-DNA– binding activity, appear necessary to maximally prevent activation of PKR (110, 127).

OAS–RNase L

In humans there are three IFN-inducible and catalytically active OAS enzymes, OAS1, -2, and -3. OAS is a dsRNA sensor (Fig. 3). Upon binding dsRNA, OAS is activated and synthesizes 2–5A from ATP. The 2–5A oligomers then are bound by RNase L, which mediates dimerization and activation of RNase L (93, 102). Activation of RNase L is mainly dependent upon OAS3 during infection with a range of human viruses (128). Activated RNase L is an endonuclease and cleaves both viral and cellular RNAs. Like PKR, RNase L is both antiviral and proapoptotic (102). The cell lethal phenotype of ADAR1 deletion in the human A549 cell line is rescued by knockout of either RNase L or MAVS or by expression of a viral 2′-5′-phosphodiesterase antagonist that degrades 2–5A and prevents activation of RNase L (118). RNase L, at least in A549 cells, is a major deter-

minant of the cell death phenotype triggered by ADAR1 deficiency following accumulation of endogenous (self) dsRNA and activation of OAS (118). RNase L and PKR share homology in their pseudokinase (RNase L) and kinase (PKR) domains, and both are inhibited by sunitinib, an ATP competitive inhibitor used to suppress angiogenesis and tumor growth (129). Activation of RNase L by 2–5A also leads to the production of small cleavage products from endogenous self-RNA that amplify IFNβ production by the RIG-I–like receptor–MAVS pathway (130). The effect of sunitinib on inflammation triggered by ADAR1 deficiency is unknown.

Human disease and ADAR

Altered A-to-I editing is linked to a variety of human diseases and is an area of increased investigation (8, 33, 131–137). Among the disorders associated with changes in ADAR-editing activity is Aicardi-Goutieres syndrome, a childhood autoimmune disorder characterized by an elevated type I interferon signature and caused in part by mutations in *ADAR1* that reduce activity (138, 139), similar to the elevated interferon signature seen in mice lacking functional *Adar1* (32, 41). Dysregulation of A-to-I editing also is observed in cancers, often with A-to-I RNA editing levels elevated in tumor tissue compared with normal tissue (131–137). For example, depending upon the cell type, cancer progression has been linked to an up-regulation of ADAR1 in liver, lung, and esophageal cancers and myeloma (137, 140) or down-regulation of ADAR2 in glioblastoma (63, 137), although exceptions occur where ADAR1 is down-regulated, for example in metastatic melanoma (137, 142). Most studies to date have used sequencing strategies to identify changes attributed to A-to-I editing at the transcriptome level. Recent findings extend RNA-seq studies and demonstrate that editing contributes to proteomic diversity in a breast cancer model through coding sequence changes, including of the COPA transcript where increased editing correlates with poorer survival time (141).

Summary

A model by which ADAR1 p150 may suppress innate immune interferon responses triggered by cellular (self) RNA, but yet permits activation of the responses by viral (nonself) pathogen RNA, is summarized in Fig. 3. The findings described herein are consistent with the notion that A-to-I editing activity by ADAR1 in uninfected IFN-treated cells is capable of reducing the effective steady-state concentration of endogenous cellular (self) dsRNA structures to levels below the threshold concentration ordinarily required to trigger activation of the cellular dsRNA sensors (MDA5, PKR, and OAS). By contrast, in the absence of ADAR1 p150, the functional concentration of endogenous cytoplasmic self dsRNA increases to a level above the threshold necessary to trigger activation of MDA5, PKR, and OAS. Likewise, pathogen infection produces substantially elevated levels of dsRNA, well above the threshold both in the presence and absence of ADAR1. This then triggers activation of the MDA5, PKR, and OAS sensors, with the efficiency dependent upon the robustness of pathogen dsRNA production, as illustrated by the differences observed between WT (low dsRNA production) and C mutant (high dsRNA production) measles virus. Thus, ADAR1 regulates sensing of cellular (self) dsRNA structures, minimizing autotriggering of innate immune responses under conditions of low concentrations of dsRNA, yet permitting sensor activation by high concentrations of viral (nonself) dsRNAs produced in infected cells (73, 90, 127).

Challenges and opportunities in the A-to-I editing field

Although considerable progress has been made toward understanding the regulation of mammalian *ADAR* genes, the activities of their encoded ADAR proteins, and the functional roles that the A-to-I editing events play in biologic processes, much remains to be learned.

The major and possibly sole essential role of ADAR1 is the suppression of dsRNA-triggered innate immune IFN responses through editing of cellular dsRNA structures, with a few million editing sites identified in human transcripts mostly occurring in noncoding repetitive sequences (7, 8, 33, 143). For MDA5, PKR, and OAS, whether combinations of cellular transcripts are unique or overlapping and to what extent the editing must occur to cross the threshold necessary to suppress dsRNA sensing by MDA5, PKR, and OAS is largely unknown. Likewise, it is unclear whether the suppression of individual dsRNA sensors by ADAR1 results solely from a destabilization of duplex regions of RNA structure by generating base pair mismatches. The converse relates to which cellular (self) dsRNA transcripts in the unedited form have sufficient duplex character and abundance to activate a given dsRNA sensor. This is not yet delineated under conditions of ADAR1 deficiency for MDA5, PKR, or OAS. In the case of ADAR1, another need is to more fully define the functional roles of the p110 constitutively expressed nuclear isoform compared with the IFN-inducible p150 isoform that is the only known cytoplasmic ADAR. The molecular basis of the RNA substrate selectivity of the catalytically active ADAR1 and ADAR2 proteins and the roles played by the repeated RNA-binding domain copies compared with the catalytic domain in conferring substrate selectivity are not fully resolved. The role of the Z-DNA binding domains, Zα and Zβ, is not clear in p150. Comparatively little is known regarding the functional role of the ADAR3 protein, an ADAR not yet shown to possess catalytic activity that seems to act as a negative regulator of the enzymatically active ADARs. ADAR1 deficiency is linked to human diseases, exemplified by Aicardi-Goutieres syndrome. Changes in ADAR activity, typically an increased ADAR1 activity, are seen in some cancers. Assessing the effect of therapeutic modulation of ADAR activity as an approach to regulate innate immunity and inflammatory responses is largely unexplored. Finally, opportunity exists to utilize ADAR as a tool. Engineered nucleotide substitution of an "I" (= G) for an "A" by targeted adenosine deamination catalyzed by an ADAR catalytic domain using a site-directed guide strategy has potential for creating RNA mutations (144, 145).

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