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REVIEW

ADAR RNA editing in human disease; more to it than meets the I

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Abstract We review the structures and functions of ADARs and their involvements in human diseases. ADAR1 is widely expressed, particularly in the myeloid component of the blood system, and plays a prominent role in promiscuous editing of long dsRNA. Missense mutations that change ADAR1 residues and reduce RNA editing activity cause Aicardi–Goutières Syndrome, a childhood encephalitis and interferonopathy that mimics viral infection and resembles an extreme form of Systemic Lupus Erythmatosus (SLE). In *Adar1* mouse mutant models aberrant interferon expression is prevented by eliminating interferon activation signaling from cytoplasmic dsRNA sensors, indicating that unedited cytoplasmic dsRNA drives the immune induction. On the other hand, upregulation of ADAR1 with widespread promiscuous RNA editing is a prominent feature of many cancers and particular site-specific RNA editing events are also affected. ADAR2 is most highly expressed in brain and is primarily required for site-specific editing of CNS transcripts; recent findings indicate that ADAR2 editing is regulated by neuronal excitation for synaptic scaling of glutamate receptors. ADAR2 is also linked to the circadian clock and to sleep. Mutations in *ADAR2* could contribute to excitability syndromes such as epilepsy, to seizures, to diseases involving neuronal plasticity defects, such as autism and Fragile-X Syndrome, to neurodegenerations such as ALS, or to astrocytomas or glioblastomas in which reduced ADAR2 activity is required for oncogenic cell behavior. The range of human disease associated with *ADAR1* mutations may extend further to include other inflammatory conditions while *ADAR2* mutations may affect psychiatric conditions.

Introduction

Thirty years ago, the first two biochemical studies describing ADAR (*A*denosine *dea*minase acting on *R*NA), enzymatic activity were published (Bass and Weintraub 1987; Rebagliati and Melton 1987). It was initially expected that this double-stranded (ds) RNA unwinding activity was due to an RNA helicase. However, within a year, it was shown that 'unwinding' activity was due to weakened dsRNA base-pairing because adenosines were hydrolytically deaminated at position C6 to inosines (Bass and Weintraub 1988; Polson and Bass 1994). ADARs are very widespread and found in all metazoan species so far examined. Mammalian genomes have five genes encoding ADAR proteins; ADAR1 and ADAR2 are active deaminase enzymes, ADAR3 has no known editing activity and two further, closely related, testis-specific ADAD1 and ADAD2 proteins lack key catalytic residues.

As in the case of RNA splicing and other types of RNA processing, human mutations affecting ADAR RNA editing can be trans-acting when they affect the ADAR enzymatic machinery or cis-acting when they affect the editing of a particular edited transcript. This review will focus on effects of trans-acting *ADAR* mutations or changes in ADAR proteins in human disease. A recent publication provides the first example of a human disease variant affecting a specific RNA editing substrate. Three potassium channel *Kv1.1* mutations associated with the human disorder Episodic Ataxia Type-1 are located within the RNA duplex structure required for

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RNA editing and decrease RNA editing both in vitro and using an in vivo assay; editing also changes amino acids in this case (Ferrick-Kiddie et al. 2017). Other sequence variants that affect individual RNA editing events in cis have been detected in genome-wide investigations of RNA editing in normal tissues (Park et al. 2017).

ADAR1

ADAR1 protein-RNA interactions

The *ADAR1* gene encodes a constitutively expressed ADAR1 p110 isoform, and a larger IFN inducible ADAR1 p150 isoform (Kim et al. 1994; O'Connell et al. 1995; Patterson and Samuel 1995). The ADAR1 isoforms share the C-terminal catalytic deaminase domain, three dsRNA-binding domains (dsRBD), and one N-terminal Z DNA-binding domain (Zβ); the P150 isoform has an additional N-terminal Z DNA-binding domain (Zα) (Fig. 1).

Most of our understanding of how ADAR1 interacts with RNA comes from the extensive studies on binding by the deaminase domain and the dsRBDs of ADAR2 (see "ADAR2" below). The additional type of domain in ADAR1 is the Z DNA-binding domain first identified in this protein. One of the suggested functions of this domain is to guide ADAR1 to actively transcribed genes as this is where Z DNA is thought to occur (Herbert and Rich 1999). The role of the Z DNA-binding domains in ADAR1 function is not yet clear.

The crystal structure of the Zβ DNA-binding domain revealed that it consists of a three α helix bundle, flanked on both sites by antiparallel β sheets, the topology being α β α α β β, representing a helix-turn-helix β-sheet fold (Athanasiadis et al. 2005; Schade et al. 1999; Schwartz et al. 1999). It was found that the Zβ domain does not interact with Z DNA, even though this domain is conserved in higher vertebrate

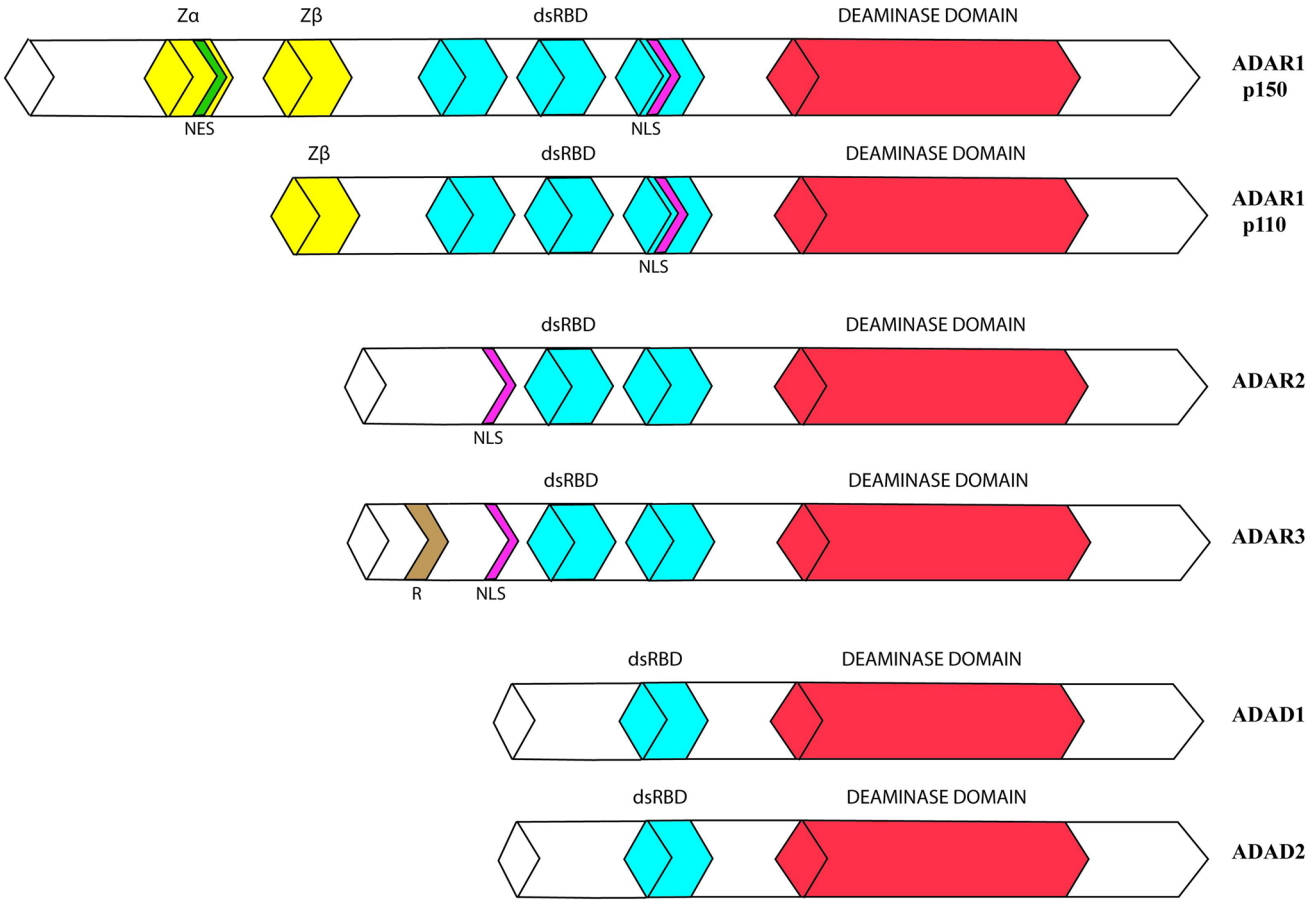

Fig. 1 Domain structures of human ADARs. All ADARs have similar domain organizations with a C-terminal deaminase domain (*red*) and different numbers of dsRNA-binding domains (dsRBDs) (*blue*). In addition, ADAR3 has an RG rich region at the N-terminus (*brown*). Two major isoforms of hADAR1 protein exist, the constitutively expressed nuclear ADAR1 p110 isoform, and the interferon inducible ADAR1 p150 cytoplasmic isoform. Both isoforms have the Zβ domain (ZBD) (*yellow*) and a nuclear localization sequence (NLS) (*pink*). The Zα DNA-binding domain and the nuclear export sequence (NES) (*green*) are present at the N-terminus of the longer ADAR1p150 isoform

ADAR1 proteins (Schwartz et al. 1999), and present also in the p110 isoform. The ADAR1 Zα domain binds Z DNA and also has the ability to bind Z dsRNA (Brown et al. 2000), where, depending on sequence, a transition from right-handed A to left-handed Z form is also possible; dsRNA may be a key natural target of Z DNA-binding domains. The Z DNA-binding domain is complementary in shape and electrostatic properties to the sugar-phosphate backbone of the Z DNA strand. The Z DNA-binding domain is structurally related to the winged helix-turn-helix DNA-binding domains that recognize specific sequences in the major groove of B DNA; however, the recognition helix is not used in the same way for Z DNA-binding.

Human ADAR1 localizes to the cytoplasm, nucleus and nucleolus, with high concentrations also in nuclear speckles (Desterro et al. 2003). The nuclear localization sequence (NLS) is located in the third dsRBD (Strehblow et al. 2002) whereas the nuclear export signal (NES) is at the N-terminus (Poulsen et al. 2001). Thus, the ADAR1p150 isoform shuttles and is predominantly cytoplasmic whereas the constitutive p110 isoform is mainly nuclear. The Zα domain in ADAR1p150 causes it to localize to cytoplasmic stress granule (Ng et al. 2013). Localization of ADAR1 p150 to stress granules does not require enzymatic activity as active and inactive mutants both localize. The Zα domain has homology with Zα domains from E3L and ZBP1, which also localize to stress granules.

The up-regulation of *ADAR1* transcripts during inflammation causes the production of different isoforms with different localizations within the cell (Yang et al. 2003b). These include another isoform, p80, starting from M519 and lacking Zβ and dsRBD 1, generated by alternative splicing of exon 2. Antibodies against the C-terminus detected p150, p110 and p80 in mouse splenocytes and HeLa cells. Two additional variants of p80 and p110 that result from alternative splicing at the end of dsRBD 3 increased during treatment with ConA or IL-2 (Yang et al. 2003b). These variants localized differently from p80 and p110 in cytoplasm and nucleus in transfected HeLa and NIH3T3 cells expressing EGFP-tagged proteins, suggesting that these different isoforms are targeted to different locations during inflammation.

Aicardi–Goutières Syndrome and mouse *Adar1* mutant models

A to I RNA editing is the most abundant RNA modification in the human transcriptome (Athanasiadis et al. 2004; Qiu et al. 2016); it is tissue specific (Picardi et al. 2015) and changes dynamically during early embryogenesis (Qiu et al. 2016). ADAR1 site-specifically edits some of the same sites as ADAR2 in CNS transcripts; ADAR1 appears to be mainly subsidiary to ADAR2 for site-specific editing within the CNS where both ADARs are present though not in other tissues outside the CNS, where ADAR1 predominates. However, across the human transcriptome A to I editing is observed at far more sites in non-coding sequences than in coding sequences (Athanasiadis et al. 2004; Bahn et al. 2015; Peng et al. 2012; Qiu et al. 2016; Wang et al. 2013). It appears to be mainly ADAR1 that is involved in this promiscuous RNA editing; A to I editing in transcripts encoding repetitive *Alu* elements is the most abundant. Editing in hairpin-forming inverted *Alu* repeats in 3′ UTRs and intronic sequences in pre-mRNAs as well as in noncoding RNAs contributes over 99% of ADAR editing sites (Bahn et al. 2015; Bazak et al. 2014).

Homozygous or compound heterozygous mutations in *ADAR1* cause Aicardi–Goutières Syndrome (AGS) (Livingston et al. 2014; Rice et al. 2012). AGS is a rare and often fatal childhood encephalopathy with increased levels of interferon (IFN), and symptoms that mimic congenital virus infections (Crow and Manel 2015). *ADAR1* mutations, including some of the AGS-associated variants, alternatively cause childhood dystonia due to striatal neurodegeneration (Livingston et al. 2014), or spastic paraplegia with corticospinal motor system degeneration (Livingston et al. 2014), in other patients. AGS is like an extreme form of Systemic Lupus Erythematosus (SLE), a much more common disease that involves periodic increases in interferon expression (Crow and Manel 2015). Mutations in innate immune nucleic acid sensors contribute to SLE and to other inflammatory diseases and further investigation may show ADAR1 involvement in other inflammatory diseases.

The AGS mutations are missense mutations mainly on the surface of the deaminase domain with one other in the N-terminal Zα domain of ADAR1 p150. The AGS mutations reduce editing activity to different extents (Mannion et al. 2014); with the exception of *ADAR G1007R* none of the individual mutations that occur in patients entirely eliminates ADAR1 editing activity. Many patients are from consanguineous families and are homozygous or transheterozygous for mutant combinations that together also do not eliminate all editing activity; *ADAR1 G1007R* is the only heterozygous mutant that causes AGS, probably because it binds dsRNA well (Heale et al. 2009; Rice et al. 2012) and may interfere with the normal protein to cause disease dominantly. Some remaining editing activity is presumably required for live birth. Based on the structure of the ADAR2 deaminase domain-*Brf2* RNA complex it is clear that several of the ADAR1 deaminase domain AGS mutations change residues that make RNA contacts [for structure images see Fisher and Beal (2017)]. Mutations on other parts of the deaminase domain may affect RNA-binding by indirect interactions across the deaminase domain surface (Fisher and Beal 2017) or they may impair interactions with RLR proteins, or with other constitutive RNA helicases that may

also act as dsRNA sensors before RIG-I and MDA5, which are induced by IFN (Zhang et al. 2011).

In mice the *Adar1* gene (this gene is named *Adar* in the Mouse Genome Informatics (MGI) database, http://www.informatics.jax.org/) consist of 15 exons, Northern blot analysis revealed transcripts of 7 and 5 kb (Mittaz et al. 1997; Slavov et al. 2000), and nuclear ADAR1p110 and cytoplasmic ADAR1p150 proteins are produced. There are high expression levels in adult mice in the brain, spleen, follicular B cells and macrophages and lower levels in the pancreas, eyes and testis. After treatment with lipopolysaccharide (LPS), to induce interferon (IFN) expression, induction of both ADAR1 isoforms was observed after 4 h (Yang et al. 2003a). Mouse *Adar1* null mutants are embryonic lethal by day E12.5, with aberrant IFN expression and loss of hematopoietic cells (Hartner et al. 2004, 2009; Wang et al. 2004). Apoptosis in different embryonic organs including vertebra and heart was observed in *Adar1* mutant mouse embryos (Wang et al. 2004). We rescued *Adar1* null mutant embryonic lethality in $Adar1^{\Delta 2-13}$;*Mavs* mice in which signaling from three interacting, cytoplasmic, antiviral RIG-I-like dsRNA receptors (RLRs) (Mannion et al. 2014) is prevented by loss of their shared mitochondrial antiviral signaling (MAVS) adapter protein. $Adar1^{\Delta 2-13}$;*Mavs* mice still die at P0.5 and the cause of death is unknown.

In another study using an $Adar1^{7-9}$ mutant allele (Pestal et al. 2015) some $Adar1^{7-9}$;*Mavs* double mutant pups survive beyond the day of birth but still die within several weeks. The $Adar1^{7-9}$ mutant allele may be able to produce a truncated ADAR1 protein with only dsRBDs and this may partly ameliorate the mutant phenotype (Walkley et al. 2012). Further evidence that ADAR1 protein or truncated ADAR1 proteins also make editing-independent contributions to suppression of aberrant innate immune responses, probably because they still bind particular RNAs, come from a recent study on an $Adar1^{E861A}$ catalytically inactive mutant (Liddicoat et al. 2015). The catalytically inactive mutant is also embryonic lethal but dies about 2 days later than the *Adar1* deletion mutants. Also, deletion of the *IfiH1* gene encoding Mda5, the RIG I-like receptor (RLR) activated by long dsRNA, fully rescued the $Adar1^{E861A}$ catalytically inactive mutant (Liddicoat et al. 2015). This *IfiH1* mutant did not rescue the $Adar1^{\Delta 2-13}$ null mutant in our study (L.K, unpublished), nor in the other study using the $Adar1^{7-9}$ mutant allele (Pestal et al. 2015). $Adar1^{E861A}$;$Ddx58^{-/-}$ double mutants lacking RIG I, which is activated by short dsRNA, did not show rescue of $Adar1^{E861A}$ mutant embryonic lethality (Liddicoat et al. 2015). Therefore, activation of MDA5 is the main reason for high expression of ISGs and embryonic lethality in $Adar1^{E861A}$. Transfection into $Adar1^{\Delta 2-13}$;*Trp53* MEFs also indicate that the suppressor of this pathway is the ADAR1 p150 isoform; p110 may have other roles in development—some substrates are edited primarily by the nuclear p110 isoform, e.g., 5-*HTR2C* mRNA (Pestal et al. 2015).

The information from the mouse studies gives the understanding of *ADAR1*-mutant AGS illustrated in Fig. 2. Constitutively expressed nuclear ADAR1p110 converts A to I in dsRNA produced during cellular transcription. Edited dsRNAs are unable to activate the main cytoplasmic RIG I-like receptors (RLRs), MDA5 and RIG-I. Viral dsRNA, or cellular dsRNA that is unedited due to absence or inactivation of ADAR1, is detected in the cytoplasm by MDA-5 or RIG-I. Upon activation, these receptors interact with the MAVS adaptor protein located on the mitochondrial membrane and activate IRF3, IRF7 and NFκB. IRF3 and IRF7 phosphorylation lead to their translocation into the nucleus and induction of type I IFN. Activation of NFκB leads to transcription of proinflammatory cytokines. The interferon response includes a resolution phase (Schoggins et al. 2011); one of the proteins induced later by increased type I IFN is ADAR1 p150. This protein, mainly localized in the cytoplasm, edits all dsRNA regardless of its origin. Such edited dsRNA does not activate MDA-5 and RIG-I, and this leads to a termination of further IFN signaling. A more recent publication extends this model by showing that very early in the response to virus infection ADAR1p110 is rapidly degraded in a ubiquitin-dependent process (Li et al. 2016), presumably to amplify dsRNA detection by the antiviral sensors; both ADARp110 and ADARp150 are increased again later in the interferon-coordinated process.

Heterozygous loss of function mutations in *ADAR1* also cause Dyschromatosus Symmetrica Hereditaria (DSH1), an otherwise apparently harmless skin condition with pigmented macules due to aberrant melanocyte distributions; some DSH1 patients have been shown to also have a low aberrant expression of interferon (Rice et al. 2012). Increased basal interferon expression leading to improved resistance to infectious disease might account for DSH1 being a not-uncommon condition in certain regions of China. The innate immune system needs to respond to different infections rapidly but proportionately and the inflammation process normally resolves quickly thereafter. At the level of human population evolution this need for balance may lead to evolutionary trade-off selection (Medzhitov 2010; Okin and Medzhitov 2012; Ramos et al. 2015). For instance, SLE is particularly prevalent in African-American women; proinflammatory human genetic variants that protect against long-established major lethal pathogens such as malaria, especially in children, may be maintained in some populations even though these variants may incur inflammatory costs, especially later in life. Genetic variants affecting innate immune sensing of nucleic acids affect detection not only of viruses but also of other pathogens such as malaria and TB. Variants of *ADAR1* may set different inflammatory

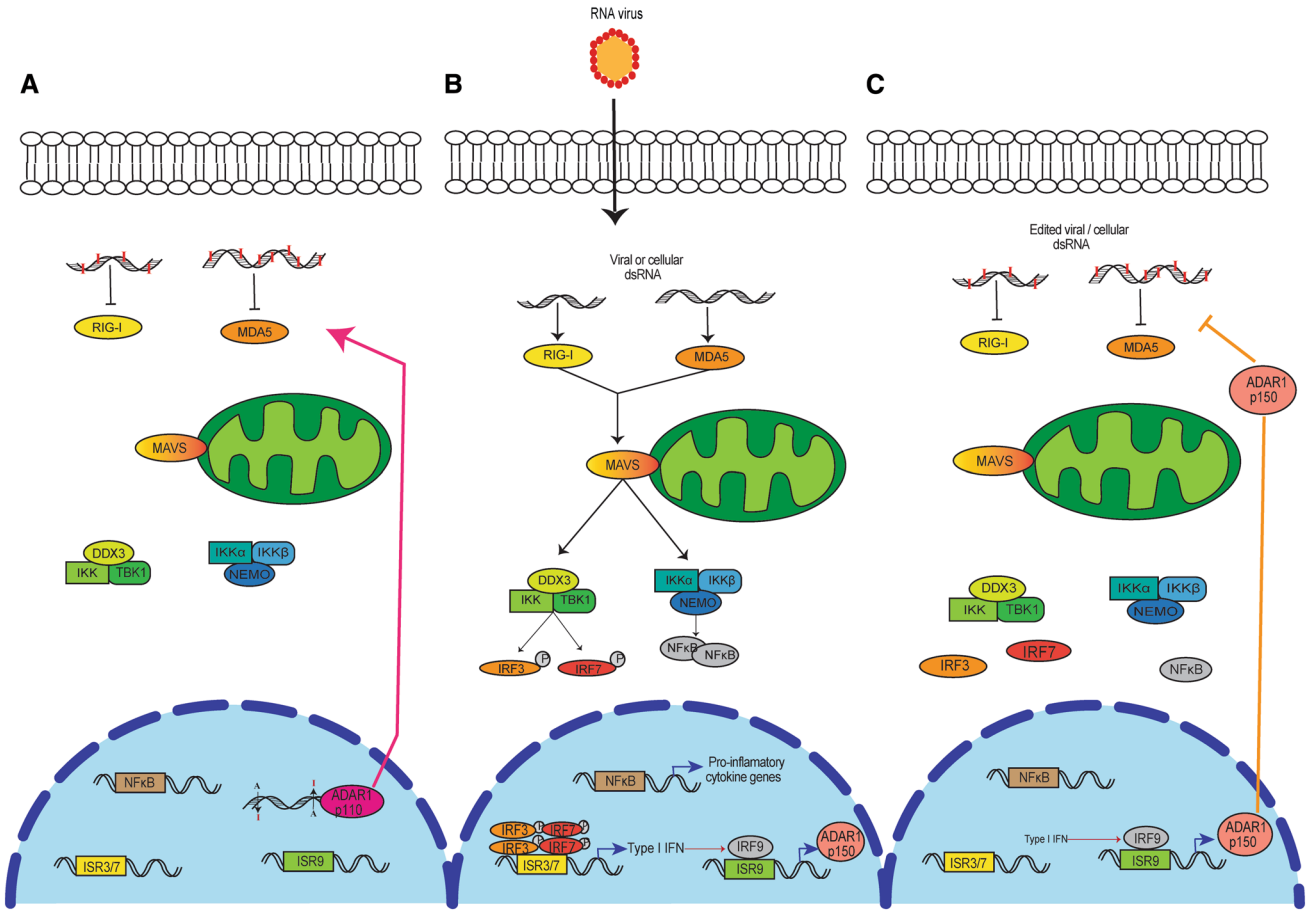

Fig. 2 Intracellular detection of dsRNA and role of ADAR1. **a** Constitutively expressed isoform ADAR1p110 converts A to I in dsRNA produced during transcription. Edited dsRNAs are unable to activate the main cytoplasmic RIG I-like receptors (RLRs), MDA5 and RIG-I. **b** Viral dsRNA or cellular dsRNA that is unedited due to absence or inactivation of ADAR1 is detected in the cytoplasm by MDA-5 or RIG-I. Upon activation, these receptors interact with the MAVS adaptor protein located on the mitochondrial membrane and activate NFκB. Activation of NFκB lead to transcription of proinflammatory cytokines. IRF3 and IRF7 phosphorylation lead to their translocation into the nucleus and induction of type I IFN. **c** One of the proteins induced by type I IFN is ADAR1 p150. This protein, mainly localized in the cytoplasm, edits all dsRNA. Such edited dsRNA is not detected by MDA-5 and RIG-I, and this leads to a termination of further IFN signaling

response thresholds in different individuals that affect resistance to infectious diseases.

ADAR2

ADAR 2 protein–RNA interactions

Until recently ADAR2 proteins received more experimental attention than ADAR1 proteins. ADAR2 has been preferred for studies on site-specific ADAR–RNA interactions in vitro; it has a simpler domain structure than ADAR1 and it can be expressed to higher levels in, and purified from, heterologous cells. Therefore, studies on ADAR2 have contributed more to understanding how ADAR proteins recognize editing sites and how the editing reaction is catalysed. The RNA editing substrate at the *Gria2* R/G site has been minimized to a 72 base RNA hairpin that has been the mainstay of in vitro studies to understand site-specific RNA editing by ADARs (Ohman et al. 2000; Schoft et al. 2007).

The ADAR 2 protein consists of the C-terminal deaminase domain and two dsRNA-binding domains (dsRBDs) (Fig. 1). All three domains contribute to dsRNA binding. The dsRBD domains are 65–75 amino acids long (St Johnston et al. 1992) and found in eukaryotic, prokaryotic and viral proteins (Masliah et al. 2013). The dsRBD structure is a mixed α/β fold with conserved αββββα topology (Bycroft et al. 1995). The structures of the individual human ADAR2 dsRBDs I and II alone and in complexes with portions of the *mouse Gria2 R/G* RNA hairpin were determined by NMR studies (Stefl et al. 2010). The mode of recognition is the interaction of helix α1 and the β1–β2 loop with successive

minor grooves in a partially sequence-specific manner. Conserved positively charged residues at the N-terminus of helix α2 also interact across the major groove with the phosphodiester backbone. The RNA recognition is achieved mainly through direct interactions with 2′-hydroxyl groups of RNA by dsRBDs and also through a small number of interactions with bases (Gan et al. 2006; Matthews et al. 2016; Ramos et al. 2000; Ryter and Schultz 1998; Stefl et al. 2010).

The structure of the 45 kD deaminase domain of hADAR2 has been solved by X-ray crystallography (Macbeth et al. 2005); it forms a globular structure and is composed of two α-helices, 4 β-strands and numerous loops. The active site contains a zinc (Zn^{2+}) ion coordinated by two cysteines and a histidine; mutation of these residues or the highly conserved active site glutamate (E396), involved in proton transfer during adenosine deamination, abolish catalytic activity. Matthews, Beal and coworkers recently used X-ray crystallography to describe the interaction of human ADAR2 deaminase domain with different dsRNAs and elucidated the unique base-flipping mechanism of the deaminase domain of ADAR2. A flipping loop approaches the target adenosine residue from the minor groove side, altering the dsRNA helical conformation by widening the major groove and shifting the bases immediately 5′ to the editing site toward the helical axis (Matthews et al. 2016). The adenosine is flipped out through the minor groove and enters the catalytic site while the glutamate of the flipping loop provides compensatory interactions with the unpaired base on the unedited strand. The ADAR proteins edit in a sequence-specific manner. Both ADAR1 and ADAR2 prefer target adenosines with 5′neighbor A or U and 3′neighbor G, i.e., a U/AAG site, where the edited base is underlined (Eggington et al. 2011; Lehmann and Bass 2000). The importance of the 5′ neighbor was proved by replacing 5′ A-U by 5′ C-G or 5′ G-C, both of which result in 80% decreases in editing of the yeast-derived *Bdf2* dsRNA by ADAR2. The decrease of editing activity is a result of a steric clash between the 2-amino group of the 5′ guanosine and the glycine 489 residue in the flipping loop. The structure of a *Gria2 R/G* site complex with full length ADAR2 or ADAR2 dsRBD II plus deaminase domain will be necessary to define a canonical interaction pattern. This RNA is not in the complexes solved so far; also details of the RNA interactions with full length ADAR2 and with different RNA substrates may differ from those observed with deaminase domains alone. The Beal group has also shown that ADARs are able to edit the DNA strand in a DNA–RNA hybrid in vitro, as the hybrid retains the A-form helix of dsRNA (Zheng et al. 2017). The efficiency is about 15-fold lower than with dsRNA and ancillary factors may be required to edit DNA/RNA hybrids in vivo.

ADAR2 is primarily nuclear and nucleolar, similar to ADAR1p110 (Desterro et al. 2003; Sansam et al. 2003). When plasmids encoding editable transcripts are transfected into cells both ADAR1p110 and ADAR2 re-localize from the nucleolus to the nucleoplasm where they can edit the target transcripts (Desterro et al. 2003). Recently the NLS for ADAR2 was located (Behm et al. 2017); two NLS elements are close together in the amino terminus adjacent to the first dsRBD. Importin-α4 interacts with ADAR2 and is required for the nuclear localization.

ADAR2 is posttranslationally modified; it can be phosphorylated at the N-terminus by an unknown kinase and then becomes a substrate for Pin1 (peptidylprolyl cis/trans isomerase, NIMA-interacting 1) (Marcucci et al. 2011); the isomerization of proline of ADAR2 is necessary for nuclear retention of ADAR2. However even in the absence of Pin1, a large cytoplasmic accumulation of ADAR2 is not observed, due to the E3 ligase WWP2 in the cytoplasm that ubiquinates ADAR2, resulting in its degradation by the proteasome. Therefore, in the absence of both Pin1 and WWP2, ADAR2 can accumulate in the cytoplasm. Recently, it has been reported that nuclear localization is less complete and lower levels of ADAR2 are seen in the nucleus in immature neurons (Behm et al. 2017), in agreement with the observation of an increase in nuclear editing of transcripts in neurons (Veno et al. 2012). An increase in the editing level of several sites was found in vivo during mouse brain development (Wahlstedt et al. 2009) and in vitro during rat neuron maturation (Orlandi et al. 2011), but a parallel increase in the expression level of ADAR was not always found (Paupard et al. 2000; Wahlstedt et al. 2009).

Roles of ADAR2 site-specific RNA editing in CNS transcripts

ADAR2 site-specifically edits codons of CNS transcripts, leading to substitution of a different amino acid because inosine decodes as guanosine during translation (Basilio et al. 1962). ADAR2 edits specific adenosine residues within RNA hairpins that typically are formed between a portion of an exon flanking the edited adenosine and sequences in a nearby intron (Higuchi et al. 1993). ADAR2 and RNA editing events that change specific codons in edited transcripts have important roles in the central nervous system (CNS). The glutamine to arginine (Q/R), editing sites in the mouse *Gria2* and human *GRIA2* transcripts encoding the ionotropic glutamate receptor A2 subunit (GluA2), are edited with over 99% efficiency (Sommer et al. 1991). *GRIA2* Q/R site editing changes a key residue in the ion channel pore of this dominant α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit, making AMPA receptors containing the GluA2 R subunit impermeable to calcium. Q/R sites are edited also in transcripts encoding kainate receptor subunits and have a similar effect on calcium permeability of the kainate class of glutamate receptors (Evans et al. 2017). The nomenclature for glutamate receptor

subunits has changed over time (Collingridge et al. 2009); the mouse gene and the encoded protein were previously named *GluR B* and Glu R B, respectively.

Mice homozygous for a targeted *Adar2 (*named *Adarb1* in the MGI database) deletion of exon 6, which encodes the C-terminal deaminase domain, developed progressive seizures as pups and died around weaning (by 21 days) (Higuchi et al. 2000). Mutations in *Gria2* transcripts that prevent formation of the dsRNA structure required for editing similarly led to death of mice, with increased calcium permeability in and death of hippocampal neurons (Higuchi et al. 1993). The death of *Adar2* mutant pups is prevented by combining the *Adar2* mutation with a *Gria2* mutant in which the arginine residue at the Q/R editing site is introduced in the genomic sequence (Higuchi et al. 2000), demonstrating that the Q/R site is the key physiological target of ADAR2 editing. Another specific editing event in GluA2 at the R/G site, has less dramatic effects on AMPA receptor function (Lomeli et al. 1994).

Glutamate excitotoxic neuron death is an important factor in certain neurodegenerations, such as the spreading spinal neurodegeneration in ALS (King et al. 2016). *ADAR2* expression is proposed to decrease in ALS motor neurons and downregulation of editing at the *GRIA2* Q/R site is observed in motor neurons of patients with ALS (Aizawa et al. 2016; Hideyama et al. 2012). The *Adar2* mutant mice die too quickly to show more extensive neurodegeneration; however, targeted deletion of *Adar2* in motor neurons in young mice leads to slow motor-neuron degeneration (Hideyama et al. 2010). When vertebrate neuronal cells are treated with excess glutamate to induce neurotoxicity, ADAR2 protein is cleaved by a calcium-activated protease, indicating that glutamate excitotoxicity is mediated in part by suppression of GluA2 Q/R site editing (Mahajan et al. 2011). Intriguingly, not all excitatory neurotransmitters but only glutamate is capable of killing vertebrate neurons by excitotoxicity. Glutamate is not excitotoxic to invertebrate neurons, which do not have editing of glutamate receptor transcripts.

Why vertebrate neurons have evolved to incur the risk of excitotoxic neuron death by glutamate if ADAR2 RNA editing fails was an unanswered question (Buckingham et al. 2008), that may now have an answer. Recent findings indicate that the purpose may be to allow regulated ADAR2 RNA editing of glutamate receptor transcripts in response to neuronal excitation. RNA editing in GluA2 changes residues at subunit interfaces and affects assembly of receptor tetramers (Greger and Esteban 2007). Glutamate receptors with Q/R site-unedited subunits more efficiently undergo intracellular membrane transport to the cell surface near synapses (Greger et al. 2002, 2017). Q/R site-edited subunits accumulate in ER and may be destroyed before reaching the cell surface, i.e., ADAR2 editing evolved to restrain glutamate signaling by synaptic scaling in response to general neuronal excitation (Penn et al. 2013). This occurs in both AMPA and kainite receptors and is important for neuronal synaptic plasticity responses (Evans et al. 2017); it remains to be determined whether editing effects on membrane trafficking apply to other classes of receptors or other edited proteins also. Loss of edited isoforms of many proteins (Graveley et al. 2011) is nonlethal in *Drosophila* and editing may preferentially alter surface residues of independently folding domains in many edited proteins, but this remains to be established by mapping editing events on protein structures (Solomon et al. 2016). ADAR2 is also expressed in pancreatic beta cells, where it is required for efficient secretion of insulin in response to high blood sugar (Gan et al. 2006). No trans-acting human disease mutations in *ADAR2* have been described; loss of function mutations in human *ADAR2* might contribute to seizures, epilepsy or neurodegenerations (Higuchi et al. 2000), based on the calcium permeability effects. ADAR2 mutations might also contribute to human diseases such as autism (Filippini et al. 2017) that may involve defects in synaptic scaling or to psychiatric illnesses because of effects on glutamate receptor transport. Lower expression of ADAR2 and lower levels of R/G site editing were also observed in patients with mood disorders (Kubota-Sakashita et al. 2014).

A recent publication shows a strong effect of ADAR2 RNA editing on circadian cycling of transcripts in liver (Terajima et al. 2017), indicating another entirely new way in which ADAR 2 variants may contribute to human disease. The authors suggest that previous efforts to detect consistent circadian effects on editing in whole *Drosophila* brain, even though the *period* mutant significantly affects editing of some sites (Hughes et al. 2012), might have been due to different clock behaviors in different brain regions. Another hint about roles of vertebrate ADARs comes from a *Drosophila* study showing that mutating the homolog of ADAR2 dramatically affects sleep (Robinson et al. 2016). It is possible that circadian effects on editing have complicated studies on vertebrate CNS editing. For instance, transcripts encoding a G protein-coupled serotonergic receptor, the 5-hydroxytryptamine Receptor 2C (*HTR2C*), are edited by both ADAR1 and ADAR2 (Burns et al. 1997). The extensively edited isoforms (5-$HT_{2C\text{-}VGV}$R, 5-$HT_{2C\text{-}VSV}$R) show decreased serotonin responses because of less effective coupling with the phospholipase C signaling cascade (Fitzgerald et al. 1999; Niswender et al. 1999). Many studies showed higher editing of the A site in brains of patients who committed suicide (Dracheva et al. 2008; Iwamoto and Kato 2003; Lyddon et al. 2013; Niswender et al. 2001), although other studies failed to replicate the findings. Difficulties may reflect limited numbers of brain samples or imperfect matching of samples. It also remains to be determined whether RNA editing events reported to be affected in mood

disorders show circadian cycling in CNS or in other simpler tissues. It is probably advisable to record the time of day to which RNA editing data applies and to beware of circadian mismatches between samples from now on.

Other proteins that interact with the same RNAs as ADAR2 may affect the ability of ADAR2 to edit these transcripts. The ADAR3 protein is very similar to ADAR2 (the *Adar3* gene is named *Adarb2* in the MGI database), but no enzymatic activity has been reported for ADAR3, which is mainly expressed in the amygdala and hypothalamus region in the brain (Chen et al. 2000). ADAR3 is a dsRNA binding protein, thought to modulate the activities of ADAR1 and ADAR2, through binding and sequestering shared target transcripts (Donnelly et al. 2013; Oakes et al. 2017); other proteins inhibiting ADAR2 editing have also been identified (Filippini et al. 2017). Overexpression of *Adar2* gave rise to obese mice due to overeating caused by a hypothalamic effect (Singh et al. 2007). Human variants of either ADAR2 or the hypothalamus-enriched ADAR3 could contribute to mood disorders or eating disorders.

ADARs in cancer

Elevated ADAR1 and promiscuous RNA editing in cancers

Until recently, cancer research focused mainly on the identification and dissection of the roles played by DNA mutations as important drivers for tumorigenesis and tumor progression. Recently, however, a growing body of evidence shows that both C-to-U and A-to-I RNA editing are also important contributors to cancer. The importance of integrating RNA-Seq data and genomic deep-sequencing has been revealed by recent studies (Han et al. 2015; Paz-Yaacov et al. 2015).

ADAR1 is upregulated and gives elevated, widespread RNA editing in many cancers; different tumors have distinct and characteristic RNA editing patterns compared to their normal tissue counterparts (Fumagalli et al. 2015; Han et al. 2015; Paz-Yaacov et al. 2015). Paired exome and transcriptome sequencing of normal and cancerous breast tissues (triple-negative, HER2-positive, luminal A and luminal B tumors) was carried out by Fumagalli and co-workers. The authors in this study called RNA versus DNA single nucleotide A to G differences (RDDs), with most of them located in regions encoding *Alu* elements. Analyzing these editing sites they reported a significant increase of editing frequency in tumor cells. ADAR1 overexpression was observed in cancer samples and was due to both DNA copy number amplification and inflammatory pathway activation in cancer cells. Although no correlation between ADAR1 and HER2 status or tumor size was found, *ADAR1* silencing in breast cancer cells led to less cell proliferation and increased apoptosis. Of note, ADAR1 expression does not correlate with any specific breast cancer subtype (Fumagalli et al. 2015). ADAR1 is one of the top 5% of upregulated genes in relapsed lobular breast cancer (Shah et al. 2009). The authors demonstrated that lobular metastatic cancer accumulated not only genomic mutations but also a high frequency of non-synonymous hypothetical editing events, resulting in variant protein sequences (Shah et al. 2009).

Consistent with the above study another group found that elevated RNA editing activity is a major contributor to transcriptomic diversity in several tumors (Paz-Yaacov et al. 2015). This study also focused on *Alu* hyper editing sites, demonstrated that editing is significantly elevated in many different cancer types with only few tumors showing lower editing frequency compared to normal controls (Paz-Yaacov et al. 2015); increased editing also reflects ADAR1 overexpression in these tumors.

The Cancer Genome Atlas (TCGA) has enabled researchers to address important questions about RNA editing on a large scale. TCGA RNA-seq data was analyzed and RNA editing signals in 17 different cancer types detected and related to normal tissues (Han et al. 2015). While this study focused on RNA-Seq data, both *Alu* and non-*Alu* RNA editing events were taken into consideration. Most of the informative RNA editing sites were in 3′ UTRs and intronic regions, as observed previously in mouse tissues (Gu et al. 2012). The study revealed specific altered RNA editing patterns in tumor samples relative to normal tissues, which correlate best with global *ADAR1* expression levels. The authors went further by focusing on a few nonsynonymous RNA editing sites that may be "master" driver events in different tumors. By correlating RNA editing, tumor subtype, stage and survival, the authors detected a number of recoding RNA editing sites with potential clinical relevance. These editing sites show marked editing differences between distinct patient groups within a cancer type, and they may represent promising biomarker candidates for further assessment (Han et al. 2015).

ADAR1 RNA site-specific editing in cancers

While recent studies provide a global picture of editing alteration in cancer, parallel investigations on how specific editing events may affect cancer are also necessary. One of the first cancers to be associated with altered A-to-I RNA editing was acute myeloid leukemia (AML) (Beghini et al. 2000), an acute, fast growing form of leukemia affecting the myeloid line of blood cells. In AML, blast cells do not develop and patients are unable to defend against infections. The *PTPN6* transcript is hyper-edited in low-differentiated CD34(+)/CD117(+) blasts isolated from AML patients (Beghini et al. 2000). PTPN6 (tyrosine-protein phosphatase non-receptor type 6) is an important protein

for hematopoietic development recognises and dephosphorylates tyrosine residues of several target proteins such as growth-promoting receptors, including c-Kit tyrosine kinase. In CD34(+)/CD117(+) blasts an aberrant *PTPN6* transcript encoding a protein with an altered SH2 domain was observed; the PTPN6 SH2 (Src Homology 2)-domain mediates target protein recognition. The aberrant *PTPN6* transcript has multiple editing events, among them an editing event at a splicing branch-point that leads to a non-functional transcript retaining intron 3. It is important to underline that PTPN6 exerts a tumor-suppressor role by down-regulating a broad spectrum of growth-promoting receptors and cytokine receptors. Expression of the non-functional PTPN6 from aberrantly edited transcripts may be a key step for hematopoietic transformation. It remains unclear which ADAR is involved.

CML (chronic myeloid leukemia), another leukemia affecting myeloid cells is slow growing and associated with the abnormal Philadelphia chromosome (Ph chromosome) carrying a *Bcr-Abl* fusion gene. CML has three stages: the chronic phase, the accelerated phase and blast crisis. A role for A-to-I editing in CML has been established recently (Jiang et al. 2013); whole-transcriptome sequencing of normal, chronic phase and blast crisis cells from CML patients revealed increased IFN-γ pathway gene expression, in concert with *Bcr-Abl* amplification. Interestingly, along with disease progression from chronic phase to blast crisis, the authors observed enhanced expression of the IFN-induced ADAR1 p150 isoform. Increased ADAR1 p150 was associated with a substantial enrichment of A-to-G changes at target sites and with RNA editing-dependent transcriptional gene modulation. For example, increased ADAR1 p150 was associated with upregulation of myeloid transcription factor PU.1 and downregulation of the erythroid transcription factor GATA1, thereby contributing to myeloid lineage skewing. Moreover, shRNA knockdown of ADAR1 in leukemia cells induced a significant reduction in leukemia stem cells in serial transplantation studies. The authors hypothesize that *Bcr-Abl*–mediated up-regulation of inflammatory pathway receptors could sensitize hematopoietic progenitors to inflammatory stimuli that drive ADAR1 overexpression (Jiang et al. 2013). These data suggest that ADAR1 plays a pivotal role in malignant progenitor self-renewal and is an important driver of malignant progenitor reprogramming into self-renewing leukemia stem cells. In addition ADAR1 has been shown to be important for maintenance of hematopoietic stem cells in mice (Hartner et al. 2009).

More recently, another study also underlines the urgent need for data collection on both DNA damage and post-transcriptional events such as RNA editing in cancers (Steinman et al. 2013). By transplanting *Bcr-Abl* marrow cells in which *ADAR1* could subsequently be conditionally knocked-out, it was possible to monitor the effect of *ADAR1* deletion after leukemia had been established. It was observed that *ADAR1* is indeed required for leukemia cell survival in vivo and that knocking down *ADAR1* results in rapid leukemic cell loss, suggesting ADAR1 as a molecular target for CML-directed therapeutics (Steinman et al. 2013). However, contrary to the earlier study, these authors reported that *ADAR1* expression is independent of *Bcr-Abl*. Recently, it has been shown that ADAR1 drives leukemia (CML) stem cell self-renewal by impairing pri-let-7 biogenesis (Zipeto et al. 2016). Despite a long list of studies pointing at ADAR1 as a master gene in several leukemias recently another RNA-seq study has shown that both ADAR enzymes also have roles in myeloid leukemia cell differentiation (Rossetti et al. 2017).

Reduced levels of A-to-I RNA editing have been observed in metastatic melanoma. ADAR1 downregulation is mediated by cAMP response element-binding protein (CREB) in metastatic melanoma (Shoshan et al. 2015). In this cellular context, reduced levels of ADAR1 promoted tumor growth and cell proliferation, accompanied by a metastatic phenotype. Changes in melanoma gene expression profiles and miRNA expression levels were observed and can be attributed to reduced ADAR1 activity in a cell type- and context-specific manner. A decrease in editing by ADAR1 within miR-455-5p promotes melanoma growth and metastasis (Shoshan et al. 2015). RNA editing-independent changes in miRNA expression may also occur as a result of direct binding of ADAR1 to pri-miRNA or regulation of the miRNA processing machinery by ADAR1 (Nemlich et al. 2013).

In hepatocellular carcinoma, editing of the transcript encoding the antizyme inhibitor-1 (*AZIN1*) to give a high-frequency S/G amino acid substitution, has been reported as causative during the multistep progression from healthy hepatic progenitors (Chen et al. 2013). Notably, increased editing in *AZIN1* was associated with upregulation of both ADAR1 p150 and p110 levels. Increased editing of *AZIN1* transcripts promoted tumor initiation by increasing both invasiveness and tumorigenic potential. These enhanced tumorigenic properties occur as a result of amino acid substitutions that increase binding of AZIN1 to antizyme1, thereby neutralizing antizyme-mediated degradation of downstream oncoproteins such as OCD and cyclin D1. Screening for A-to-I editing in a broad spectrum of cancers identified increased *AZIN1* recoding also in esophageal squamous cell carcinoma samples (ESCC) and identified ADAR1 as an oncogene and negative predictor of overall survival during ESCC progression (Qin et al. 2014).

Alteration of another A-to-I editing recoding event has been identified within a RAS homolog family member Q (RHOQ) in colorectal cancer (CRC) (Han et al. 2014). Notably, altered editing at this site was reported to be common in many tumors, including gastric and lung cancer, as well as in HCC. A-to-I editing in *RHOQ* transcripts resulted in an amino acid substitution from asparagine to serine that

enhanced protein activity and mediated dynamic actin cytoskeletal reorganization, thereby increasing the invasive potential of the cells. Similar to this observation, edited RHOQ was associated with increased recurrence rates that were even higher when combined with mutant KRAS (G12D). Although editing of RHOQ was functionally relevant for invasiveness and recurrence in CRC, the amino acid substitution did not appear to alter either protein stability or structural folding, and further investigation is required (Han et al. 2014).

ADAR2 in cancers

A-to-I editing at the *GRIA2 Q/R* site has been reported to be altered in glioblastoma (also known as grade IV astrocytoma), a deadly brain cancer (Maas et al. 2001). Progressive decrease of ADAR2-mediated editing correlates with the grade of malignancy in paediatric astrocytomas (from low to high grade of malignancy) (Cenci et al. 2008). Forced expression of ADAR2 in glioblastoma cells indeed inhibited both cell proliferation and migration (Cenci et al. 2008; Galeano et al. 2013). Hypo-editing in glioblastoma, was also found in microRNAs (Alon et al. 2011). Decreased ADAR2-mediated editing within the *miR-376* cluster increased glioblastoma invasiveness in vivo (Choudhury et al. 2012). Additionally, loss of ADAR2 editing in several key microRNA precursors (pri-miR221/222 and pri-miR-21) was also reported to lead to glioblastoma cell proliferation and increased migration (Tomaselli et al. 2015). The findings that ADAR2 suppresses growth and metastatic features of brain cancer cells suggest that human *ADAR2* genetic variants with reduced *ADAR2* expression might not only have increased excitability, seizure susceptibility and increased risk of neurodegeneration but also they may lead to greater risk for developing brain tumours. In oesophageal squamous cell carcinoma (ESCC), it was also reported that ADAR2 acts as a tumor suppressor gene as it inhibits tumor growth in vitro and in vivo by editing the IGFBP7 transcript (Chen et al. 2017). In summary, while ADAR1 acts as an oncogene, ADAR2 acts as a tumor suppressor gene in brain tumors (such as astrocytomas) and ESCC.

Conclusions

For ADAR1 we now have a better sense of the main biological role, associated with discrimination between self and non-self RNA as well as with some site-specific RNA editing events. *ADAR1* mutations causing AGS are by far the most interesting human genetic finding in the ADAR RNA editing field. It is not yet clear if AGS mutations mainly affect ADAR1 RNA-binding and editing or if interactions with other proteins are affected by AGS mutations. Interactions of ADAR1 with DICER proteins, RLRs and other RNA helicases require further study. It is often difficult to predict which genetic defects will associate with particular proteins. In the case of ADAR2, this is partly because we do not know whether there is an overall biological principle that has governed the evolution of the site-specific editing performed by ADAR2. We do know, for instance, that ADAR2 itself is regulated by levels of neurotransmitters, by excitatory states of neurons/glia and by circadian clocks—we should expect to be further surprised.

Upregulation of ADAR1 in cancers may be linked to inflammation in tumors and the inflammatory status of these tumors may allow them to be targeted for immune checkpoint therapies combined with ADAR inhibitors. It remains to be established in vivo that ADARs mutates DNA, either in somatic hypermutation, class switching, aberrantly in cancers or in genomes over evolutionary time. So, despite the ADAR activity having been first identified over 30 years ago, many question still remain unanswered.

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