REVIEW

Adenosine-to-inosine RNA editing in the immune system: friend or foe?

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Abstract

Our body expresses sensors to detect pathogens through the recognition of expressed molecules, including nucleic acids, lipids, and proteins, while immune tolerance prevents an overreaction with self and the development of autoimmune disease. Adenosine (A)-to-inosine (I) RNA editing, catalyzed by adenosine deaminases acting on RNA (ADARs), is a post-transcriptional modification that can potentially occur at over 100 million sites in the human genome, mainly in *Alu* repetitive elements that preferentially form a double-stranded RNA (dsRNA) structure. A-to-I conversion within dsRNA, which may induce a structural change, is required to escape from the host immune system, given that endogenous dsRNAs transcribed from *Alu* repetitive elements are potentially recognized by melanoma differentiation-associated protein 5 (MDA5) as non-self. Of note, loss-of-function mutations in the *ADAR1* gene cause Aicardi–Goutières syndrome, a congenital autoimmune disease characterized by encephalopathy and a type I interferon (IFN) signature. However, the loss of ADAR1 in cancer cells with an IFN signature induces lethality via the activation of protein kinase R in addition to MDA5. This makes cells more sensitive to immunotherapy, highlighting the opposing immune status of autoimmune diseases (overreaction) and cancer (tolerance). In this review, we provide an overview of insights into two opposing aspects of RNA editing that functions as a modulator of the immune system in autoimmune diseases and cancer.

Keywords Innate immunity · Adaptive immunity · PD-1 · RIG-I · RNase L · SINE

Abbreviations

A	Adenosine
ADAR	Adenosine deaminase acting on RNA
AGS	Aicardi-Goutières syndrome
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APC	Antigen-presenting cell
AZIN1	Antizyme inhibitor 1
COPA	Coatomer protein complex, subunit alpha
dsRNA	Double-stranded RNA
DC	Dendritic cell
DNMT	DNA methyltransferase
DSH	Dyschromatosis symmetrica hereditaria
eIF2α	Eukaryotic initiation factor 2 alpha
EIF2AK2	Eukaryotic translation initiation factor 2 alpha kinase 2
ERV	Endogenous retroviruse
G	Glycine
$GABA_A$	Type A gamma-aminobutyric acid
GABRA3	$GABA_A$ receptor subunit α-3
I	Inosine
IFN	Interferon
ISG	IFN-stimulated gene
KI	Knock-in
KO	Knockout
LINE	Long interspersed element
LTR	Long terminal repeat
MAVS	Mitochondrial anti-viral-signaling protein
MDA5	Melanoma differentiation-associated protein 5
MHC	Major histocompatibility complex
miRNA	MicroRNA
mTEC	Medullary thymic epithelial cell
m^7G	5′Triphosphate-linked methylguanosine
N	Asparagine
N1	5′-Terminal nucleotide
OAS	Oligoadenylate synthetase
ORF	Open-reading frame
PAS	Periodic acid-Schiff

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PBMC	Peripheral blood mononuclear cell
PD-L1	Programmed cell-death ligand-1
PD-1	Programmed cell death 1
PKR	Protein kinase R
Pol	Polymerase
Q	Glutamine
R	Arginine
RA	Rheumatoid arthritis
RHOQ	Ras Homolog Family Member Q
RIG-I	Retinoic acid-inducible gene I
RLR	RIG-I-like receptor
PRR	Pattern recognition receptor
S	Serine
SINE	Short interspersed element
SLE	Systemic lupus erythematosus
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
UTR	Untranslated region
U	Uridine
2′OMe	2′-O-Methylation

Introduction

The immune system, composed of innate and adaptive immunity, is essential for host defense and protection against foreign agents such as viruses. As the first line of host defense during viral infections, pattern recognition receptors (PRRs), abundantly expressed in innate immune cells such as dendritic cells (DCs) and macrophages, detect viral components and induce anti-viral cytokines, particularly type I interferons (IFNs) [1]. In the second line of defense, adaptive immune cells, such as CD4$^+$ and CD8$^+$ T cells, are activated by viral antigens loaded on major histocompatibility complexes (MHCs) expressed in antigen-presenting cells (APCs), especially DCs, and infected cells [2]. Subsequently, CD8$^+$ T cells directly attack infected cells, whereas CD4$^+$ T cells help antibody production by B cells and activate not only macrophages, but also CD8$^+$ T cells [3].

The immune system simultaneously possesses tolerance to prevent an overreaction to self-antigens. T and B cells mature in the thymus and bone marrow, respectively. Autoreactive cells are eliminated in these organs during their maturation steps, in a process termed central tolerance, while autoreactive cells escaping into peripheral tissues are subjected to peripheral tolerance [4, 5]. Intriguingly, foreign proteins sometimes utilize this tolerance to escape from the host immune system. For instance, programmed cell-death ligand-1 (PD-L1), which is highly expressed in various human cancers, induces tolerance by binding to its receptor, programmed cell death 1 (PD-1), expressed on the surface of T cells [6]. Therefore, blockade of the PD-L1/PD1 pathway with antibodies, an immune checkpoint therapy,

induces anticancer immune responses and a marked effect in the treatment of human cancers [7].

Endogenous retrotransposons, considered remnants of past retrovirus integration into the host genome, constitute 43% of the human genome [8]. Their unique retrovirus characteristics can be recognized by the host immune system [9]. Endogenous retrotransposons can be divided into two groups: those with long terminal repeats (LTRs), including endogenous retroviruses (ERVs), make up 8% of the genome, whereas those without LTRs, including long interspersed elements (LINEs) and short interspersed elements (SINEs), account for more than 30% of the human genome [10, 11]. The most common type of SINE in humans is an *Alu* repetitive element, which can be divided into polymerase (pol) II-transcribed retrotransposition-incompetent elements embedded in mRNAs and pol III-transcribed retrotransposition-competent elements [12, 13]. LINEs are autonomous, because they have two open-reading frames (ORFs) that encode RNA-binding protein, nuclease, and reverse transcriptase, and are required for transposition, whereas SINEs are non-autonomous and utilize LINE transposition machinery [14]. All these retrotransposons can be detected as non-self by nucleic acid sensors under certain conditions.

Retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) belong to the RIG-I–like receptor (RLR) family, which is a type of PRR (Fig. 1). Such RLRs are cytosolic sensors for viral dsRNA, the detection of which leads to the recruitment of mitochondrial anti-viral-signaling protein (MAVS) to activate TANK-binding kinase 1 and downstream interferon regulatory factor 3, in turn leading to type I IFN production [15-18]. However, accumulating evidence has shown that endogenous dsRNAs formed by retrotransposon-derived repetitive elements potentially activate these cytosolic dsRNA sensors [19-22]. Therefore, to prevent activation of such sensors, endogenous dsRNAs are simultaneously subjected to chemical modifications such as adenosine (A)-to-inosine (I) RNA editing [23-29].

ADAR1-mediated RNA editing prevents MDA5 sensing endogenous dsRNAs

A-to-I RNA editing is a post-transcriptional modification occurring within dsRNA [30, 31]. In mammals, such deamination is catalyzed by adenosine deaminases acting on the RNA (ADAR) protein family [32], composed of ADAR1 [33-36], ADAR2 [37-39], and ADAR3 [40, 41], which all contain dsRNA-binding domains (Figs. 1, 2). ADAR1 is expressed as two isoforms driven by different promoters: interferon (IFN)-inducible full-length ADAR1 p150 that contains a nuclear export signal and is mainly localized in the cytoplasm, and constitutively expressed truncated
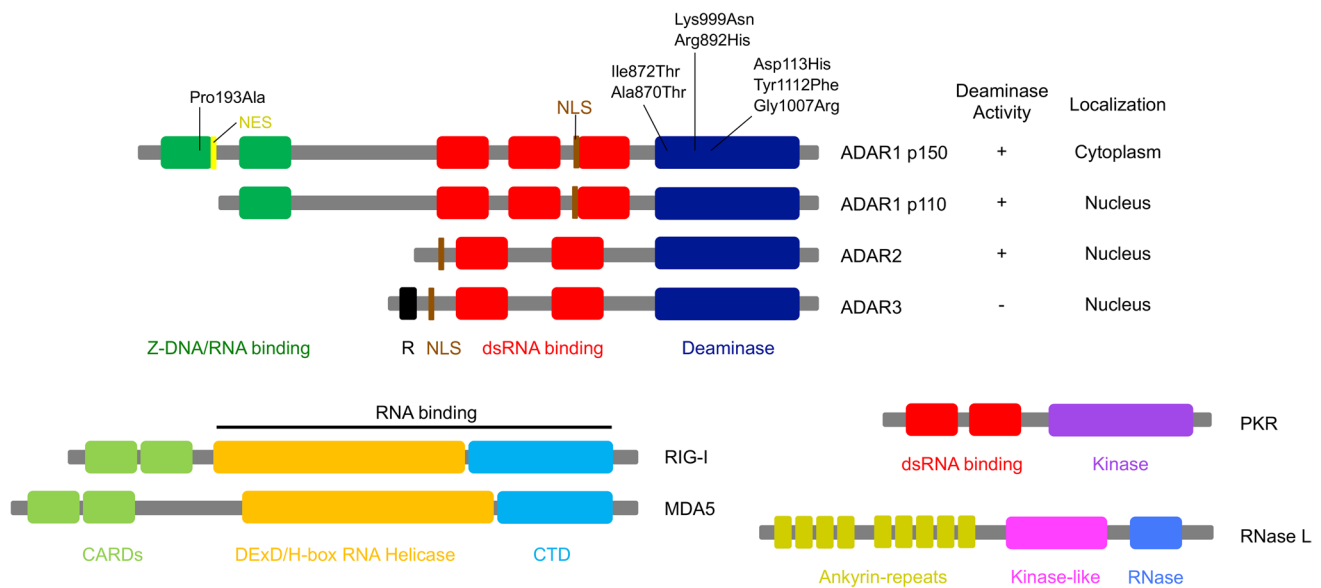
Fig. 1 Structural representation of ADARs and RNA-binding proteins involved in dsRNA-sensing pathways. Cytoplasmic adenosine deaminase acting on RNA 1 (ADAR1) p150 comprises two Z-DNA/RNA binding domains (green), three double-stranded (ds)RNA-binding domains (red), and a deaminase domain (dark blue), while nuclear ADAR1 p110 is a truncated isoform that lacks a Z-DNA/RNA-binding domain. A nuclear localization signal (NLS; shown in brown) is present in both p150 and p110 isoforms, whereas a nuclear export signal (NES; shown in yellow) is present in the p150 isoform only. Both ADAR2 and ADAR3 are composed of two dsRNA-binding domains and a deaminase domain, and are located in the nucleus. ADAR3, which contains arginine-rich domain (R; shown in black), has not been shown to have editing activity. Amino acid substitutions resulting from point mutations in the *ADAR1* gene, identified in patients with Aicardi–Goutières syndrome (AGS), are also shown. Retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) are members of RIG-I-like receptors and comprise two caspase activation and recruitment domains (CARDs; shown in light green), which mediate signal transduction through interaction with the mitochondrial anti-viral-signaling protein (MAVS) with a DExD/H-box RNA helicase domain (orange) and a C-terminal domain (CTD; shown in light blue), both of which are required for RNA binding. Protein kinase R (PKR) is composed of two dsRNA-binding domains (red) and a kinase domain (purple). RNase L comprises nine ankyrin-repeats domain (dark yellow), a kinase-like domain (pink) and an RNase domain (blue). An ankyrin-repeats domain contains the site for binding to 2′,5′-oligoadenylates, which is produced by oligoadenylate synthetase (OAS) proteins
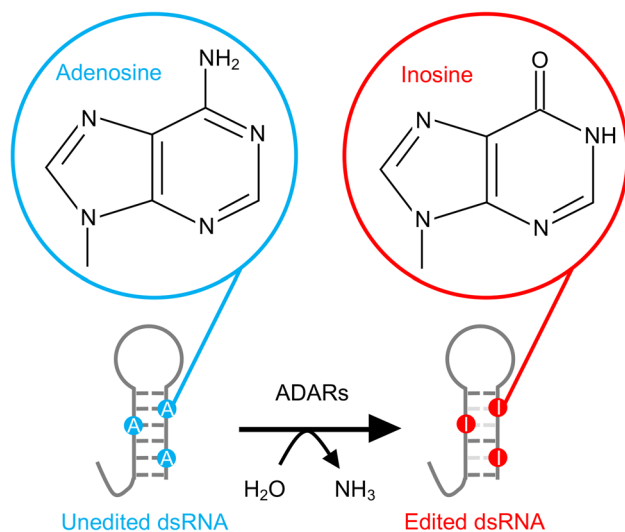

Fig. 2 Conversion of adenosine into inosine by ADARs. Adenosine deaminases acting on RNA (ADARs) recognize double-stranded (ds)RNA structures as targets and catalyze the deamination of adenosines in dsRNA into inosine

ADAR1 p110, which is localized in the nucleus [42-45] (Fig. 1). Although both ADAR2 and ADAR3 are located in the nucleus [46, 47], ADAR3 is expressed to a much more limited extent in the brain. Because it is catalytically inactive in vitro, ADAR3 is considered to act as a dominant negative regulator of RNA editing [40, 48, 49]. However, a recent study demonstrated that ADAR3 deficiency in mice does not substantially modulate RNA-editing activity [50]. Therefore, the function of ADAR3 remains undetermined. In contrast, ADAR1 p110 and ADAR2 are active RNA-editing enzymes that are highly expressed in the brain, whereas ADAR1 p150 is especially enriched in the thymus and spleen [51].

Because the structure of inosine is very similar to guanosine, the cellular machinery recognizes the inosine within dsRNA as if it were guanosine [52-54]. Therefore, any outcome depends on sites where RNA editing occurs. Although RNA editing in protein coding sequences rarely takes place [55], it can potentially change amino acid sequences, called recoding, and their protein functions [56-62]. It is worth noting that the biological significance of individual recoding events has been demonstrated by

introducing edited or unedited versions of the gene of interest in vivo [63-66]. In contrast, of over 100 million sites, approximately 85% of pre-mRNAs are estimated to be edited in humans [67, 68]. This preferentially occurs in the non-coding region of mRNA, especially in the 3′untranslated region (UTR) and introns [69-71]. This is because inverted retrotransposon-derived repetitive elements, which are frequently found in the non-coding region, form intramolecular dsRNA structures targeted by ADARs [67, 72]. Therefore, more than 90% of all RNA-editing events occur within *Alu* repetitive elements in humans, especially within retrotransposition-incompetent *Alu* elements embedded in mRNAs but not retrotransposition-competent elements [12]. Although the majority of RNA-editing sites are also found within SINEs in mice, the total number of sites is smaller due to the higher divergence of repeats as compared to humans [73]. It has been reported that RNA editing in the non-coding region of mRNA as well as non-coding RNA modulates splicing patterns [74-78], micro(mi)RNA target specificity [79-81], mRNA stability [82, 83], and circular RNA biogenesis [84-86], although these events are applicable to limited sites only. This indicates that RNA editing in the non-coding region has distinct functions that affect cellular homeostasis in a global manner.

Growing evidence suggests that ADAR1-mediated RNA editing in repetitive elements plays a pivotal role in preventing activation of the host immune system. Given that ADAR1 and ADAR2 have the same preference of $U > A > C > G$ at the nearest 5′ neighbor and a different preference of $G > C \sim A > U$ and $G > C > U \sim A$ at the nearest 3′ neighbor, respectively [87], a rigid motif for RNA editing does not exist. However, a comprehensive study has described how ADAR1 preferentially edits non-coding regions, whereas ADAR2 mainly edits coding regions [49]. Accordingly, *Adar1* and *Adar2* knockout (KO) mice show different phenotypes: *Adar1* KO mice die by embryonic day E12.5, with widespread apoptosis and the overproduction of type I IFN [88-90], whereas *Adar2* KO mice show postnatal lethality with progressive seizures [64], which can be rescued by the expression of an edited *GRIA2* encoding glutamate receptor subunit GluA2 [59, 64]. Although critical substrates of ADAR1 are unknown, unlike ADAR2, recent studies have reported that several *Adar1* mutant mice, such as *Adar1* p150-specific KO and *Adar1* knock-in (KI) mice that harbor the editing-inactive E861A point mutation (*Adar1* E861A KI mice), also show phenotypes similar to those found in *Adar1* KO mice; the concurrent deletion of either MDA5 or MAVS rescues embryonic lethality and type I IFN production in these three mutant lines [91-94]. Therefore, it is thought that ADAR1 p150-mediated RNA editing prevents MDA5 sensing endogenous dsRNAs transcribed from repetitive elements as non-self [91-93, 95, 96].

Possible mechanisms underlying the prevention of MDA5-sensing endogenous dsRNAs by RNA editing

Given that RLRs, including RIG-I and MDA5, detect unique structures of viral dsRNA, self-RNAs also possess host-specific molecular markers to prevent recognition by these cytosolic sensors [24] (Fig. 1). Because RIG-I detects short dsRNA with 5′triphosphate blunt ends [97-99], the 5′triphosphate-linked methylguanosine (m^7G) cap, only present in eukaryotic organisms, is considered to prevent RIG-I activation. Interestingly, Schuberth–Wagner et al. showed that 2′-*O*-methylation (2′*O*Me) at the 5′-terminal nucleotide (N1) completely prevented RIG-I activation, whereas an m^7G cap only partially suppressed it [27]. Furthermore, the same group showed that knockdown of the endogenous methyltransferase, MTr1, which is responsible for 2′*O*Me at N1, caused a loss of RIG-I tolerance to self-RNAs.

In contrast, MDA5 recognizes internal long dsRNA but without characteristic features, unlike RIG-I [100, 101]. Importantly, gain-of-function mutations in *IFIH1* that encode MDA5 cause several autoimmune diseases, such as systemic lupus erythematosus (SLE), Singleton–Merten syndrome, and Aicardi–Goutières syndrome (AGS), which is characterized by a childhood-onset autoimmune encephalopathy that shows an excessive expression of type I IFN [102-105]. Although the mechanism underlying mutation-induced MDA5 activation remains controversial, two suggestions have been proposed, which include being constitutively activated in a ligand-independent manner [103, 105], or being activated by self-RNAs due to misrecognition in a ligand-dependent manner [102]. Recently, Ahmad et al. showed that a lack of RNA-binding domain caused by a premature termination single-nucleotide polymorphism failed to activate MDA5 with gain-of-function mutations, supporting the mechanism in a ligand-dependent manner [19]. They further demonstrated that MDA5 activation induced by gain-of-function mutations is caused by the misrecognition of endogenous repetitive elements.

Under physiological conditions, ADAR1-mediated RNA editing prevents MDA5 sensing endogenous dsRNAs transcribed from repetitive elements as non-self [91-93, 95, 96]. However, the mechanisms that underlie escaping MDA5 recognition by A-to-I conversion in dsRNAs remain elusive. Considering the RNA-editing level of each site differs dramatically between developmental stages, organs, and cells [49], one possibility is that edited substrates competitively inhibit MDA5 binding to unedited dsRNAs [91, 106]. It is noteworthy that dsRNAs formed by wobble I–U pairs bind to MDA5, leading to the inhibition of binding of perfect RNA duplexes containing I–C base pairs and the suppression of induced IFN-stimulated genes (ISGs) [106].

In contrast, another possibility is that RNA editing destabilizes A–uridine (U) base pairs by generating multiple I–U mismatches, leading to the prevention of MDA5 recognition [91]. However, when RNA editing occurs at A–C mismatches, which are preferred by ADARs [107], it results in stabilizing a dsRNA structure. Indeed, RNA secondary structure modeling and free energy calculations revealed that a large subset of imperfect RNA duplexes would be stabilized as a consequence of RNA editing [91, 96]. In contrast, a dsRNA structure destabilized by RNA editing can be found in inverted *Alu* repetitive elements within the 3′UTR of genes involved in vital biological processes in humans. These targets may contain the critical RNA-editing sites required for escaping MDA5 sensing (which needs further study) given that *Alu* repeats are specific to primates and the inserted position of these repetitive elements is mostly not conserved.

Other dsRNA-sensing pathways regulated by ADAR1

Although concurrent deletion of MDA5 or MAVS extends the survival of *Adar1* KO mice until the day of birth, *Adar1* E861A KI mice do not show postnatal lethality and survive until adulthood, highlighting the contribution of ADAR1 in alternative signaling pathways [91-93]. Recently, Chung et al. demonstrated that protein kinase R (PKR), a dsRNA sensor, is activated in an ADAR1-deficient human cell line during an IFN response [12]. PKR, encoded by the eukaryotic translation initiation factor 2 alpha kinase 2 (*EIF2AK2*) gene, is a ubiquitously expressed anti-viral protein that is induced by type I IFN [108] (Fig. 1). Once activated by dsRNA, PKR phosphorylates eukaryotic initiation factor 2 alpha (eIF2α), leading to the inhibition of translational initiation [109]. Although it was observed that ADAR1-deficient 293 T cells did not show upregulated expression of type I IFN or ISGs, global translational efficiency and cell proliferation with IFN treatment were impaired in response to PKR activation [12]. It was further demonstrated that the suppression of PKR activation by ADAR1 required dsRNA-binding and catalytic activities. These lines of evidence suggest that upon activation by dsRNAs, PKR has distinct functions that differ from those of MDA5. In addition, the embryonic lethality of *Adar1* KO mice could not be rescued by concurrent deletion of PKR [90], which suggests that as-yet-undetermined critical RNA editing targets required for suppressing PKR activation, such as certain *Alu* elements, may be specific to humans.

In contrast, the lethal phenotype induced by ADAR1 depletion in a human lung adenocarcinoma A549 cell line could be rescued by the concurrent deletion of RNase L, which is involved in another dsRNA-activated anti-viral pathway [110] (Fig. 1). RNase L is a ubiquitously expressed single-stranded RNA–specific ribonuclease that cleaves viral and host RNAs, leading to translational inhibition [111-115]. The molecule, 2′,5′-oligoadenylate, which is produced by oligoadenylate synthetase (OAS) proteins upon dsRNA recognition, binds to monomeric inactive RNase L, leading to catalytically active dimers. Of note, depletion of RNase L restored the lethality of ADAR1-deficient A549 cells in the presence of MDA5, indicating that the OAS–RNase L system is likely the primary pathway activated by ADAR1 depletion, at least in this cell line [110].

A-to-I RNA editing in innate immune cells

Although how RNA editing induces MDA5 tolerance to self-dsRNAs has been clearly demonstrated [91], its role in innate immune cells has not been fully investigated. Recently, Baal et al. reported a role for ADAR1 in the development of DCs using the *CD11c-cre* transgene, which deletes floxed genes in DCs and alveolar macrophages [116]. *CD11c-cre*–driven conditional ADAR1 deletion inhibits differentiation and expansion of CD103$^+$ cells among DC subsets, whereas apoptosis, which is generally observed in multiple tissues of *Adar1* KO mice, is not induced (Fig. 3). CD103$^+$ DCs mainly contribute to CD8$^+$ T-cell priming via antigen cross-presentation during host defense [117, 118]. In accordance with this, ADAR1-deficient DCs failed to expand CD8$^+$ T cells [116]. Furthermore, *CD11c-cre*–driven conditional *Adar1* KO mice showed the presence of Periodic acid–Schiff (PAS)-positive giant alveolar macrophages; this was also observed when ADAR1 was specifically depleted in macrophages by the *LysM-cre* transgene, resembling symptoms of pulmonary alveolar proteinosis [119] (Fig. 3). In addition, although the contribution of the MDA5-sensing pathway was not examined, ADAR1-deficient alveolar macrophages showed upregulated ISG expression. Consistently, in humans, knockdown of ADAR1 induces type I IFN responses in primary macrophages differentiated from peripheral blood mononuclear cells (PBMCs) [120]. Given that DCs and macrophages are major type I IFN-producing cells, it is worth investigating how ADAR1 deficiency in these innate immune cells contributes to the pathogenesis of autoimmune diseases such as AGS, caused by loss-of-function mutations in the *ADAR1* gene [121].

A-to-I RNA editing in adaptive immune cells

Although MDA5 as a specialized molecule for innate immunity has been well studied, given that ADAR1 p150 is especially abundant in lymphoid organs such as the thymus and spleen, the RNA editing/MDA5 axis also has a potential role
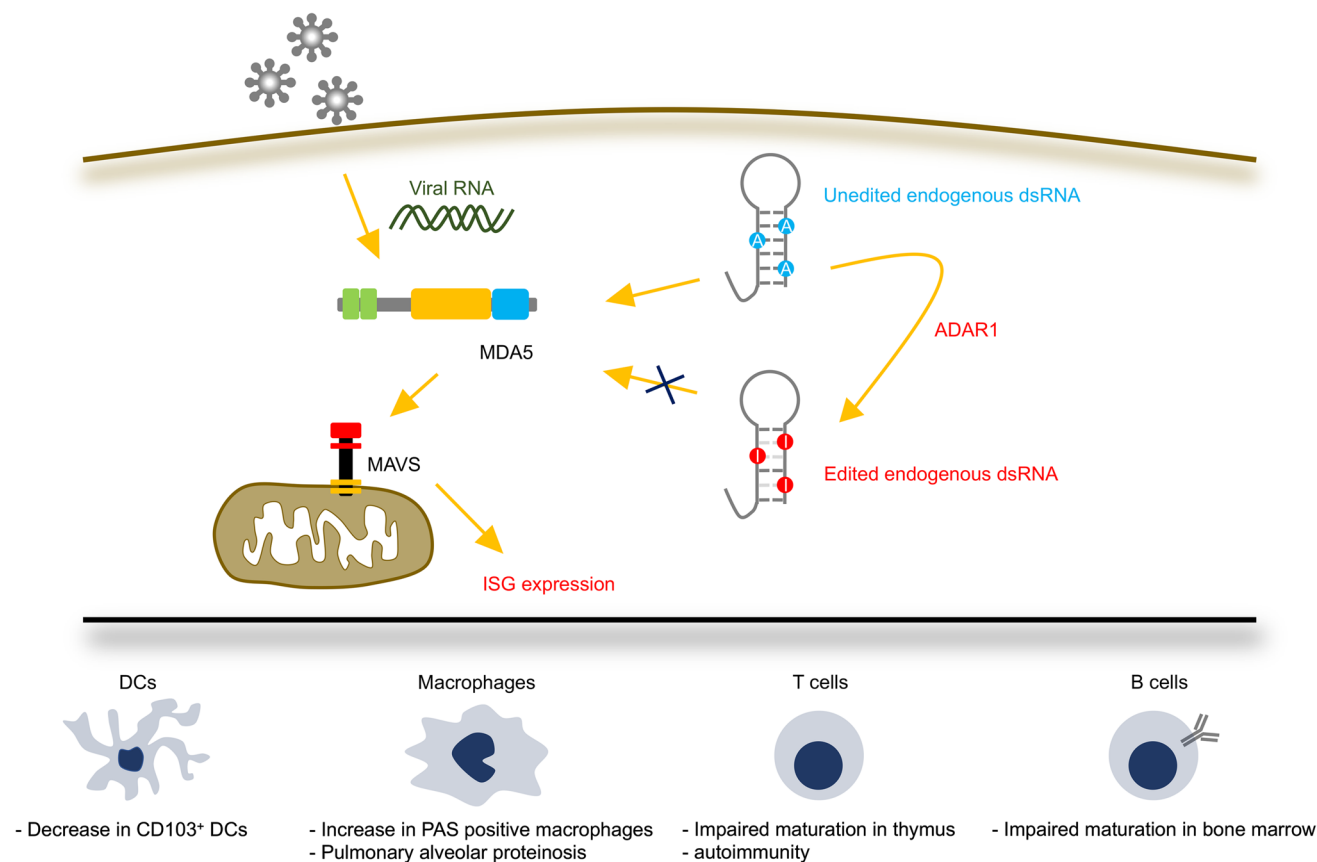
Fig. 3 ADAR1-mediated MDA5 tolerance to self-dsRNAs in innate and adaptive immune cells. Melanoma differentiation-associated protein 5 (MDA5) senses viral RNAs upon infection, promoting polymerization of mitochondrial anti-viral-signaling protein (MAVS), and leading to the expression of interferon-stimulated genes (ISGs). To avoid the recognition of self-double-stranded (ds)RNAs by MDA5, adenosine deaminase acting on RNA 1 (ADAR1)-mediated RNA editing is required. Loss of ADAR1 results in activation of the MDA5–MAVS signaling pathway, which impairs homeostasis of innate immune cells, such as dendritic cells (DCs) and macrophages, as well as adaptive immune cells, such as T and B cells

in lymphocytes. We recently reported a role for RNA editing during T-cell maturation in the thymus [51, 122]. T-cell-specific ADAR1 deficiency reduces mature CD4^{+} and CD8^{+} thymocytes due to an impairment of T-cell receptor (TCR) signal transduction (Fig. 3). This comes from the excessive expression of ISGs, given that type I IFN inhibits TCR signal transduction and has an anti-proliferative effect on T cells. Moreover, ADAR1-deficient thymocytes are resistant to negative selection, a process that establishes central tolerance by eliminating autoreactive T cells [123], leading to autoimmunity including intestinal inflammation [51] (Fig. 3). Importantly, this symptom is sometimes observed in patients with AGS [124]. It is worth noting that the concurrent deletion of MDA5 rescues these abnormalities. However, it remains unknown whether the RNA editing/MDA5 axis regulates T-cell functions in peripheral tissues, and this, therefore, requires further study. Another group reported a proviral function of ADAR1 using primary CD4^{+} T cells isolated from patients with AGS [125]. In accordance with our observation in the mouse, AGS patient-derived primary CD4^{+} T cells showed the upregulated expression of ISGs, providing a resistant phenotype to infection by HIV-1 [51, 125].

In contrast, Marcu–Malina et al. reported an essential role for ADAR1 in B cells [126]. B-cell-specific ADAR1 deficiency induced by the *CD19-cre* transgene in mice severely inhibits immature and mature recirculating B cells in the bone marrow (Fig. 3). In agreement with this, peripheral blood and splenic B cells were also reduced in the mutant mice. Importantly, ADAR1-deficient B cells isolated from bone marrow showed upregulated ISG expression and enhanced apoptosis. Of note, Pestal et al. reported that *Adar1* p150–MAVS double KO (dKO) mice showed a dramatic reduction in mature B cells, indicating that ADAR1 p150 regulates B-cell homeostasis in a MAVS-independent manner [93]. In contrast, another group reported that both *Adar1* KO and *Adar1* E861A KI mice on an *Ifih1* (encoding MDA5) KO background at the day of birth exhibited a

normal proportion of splenic B cells [127], suggesting that aberrantly activated MDA5-dependent signaling, which is caused by ADAR1 deficiency, results in immature B-cell differentiation at this stage. Given that nearly half of *Adar1* p150–MAVS dKO mice die around 15–21 days postnatally and that 21-day-old surviving mutant mice affected with several developmental defects were used, the observed reduction in splenic B cells may be derived from an adaptation for survival [93].

Another aspect of RNA editing in adaptive immunity has been reported by Danan–Gotthold et al. [128]. They found abundant RNA-editing events, including recoding in medullary thymic epithelial cells (mTECs), comparable to those of the brain, an organ considered to undergo higher RNA-editing events in the body [129]. During negative selection in the thymus, mTECs present a broad spectrum of self-antigens; autoreactive thymocytes expressing TCRs that strongly react with these cells are eliminated by apoptosis [123]. Therefore, such recoding events are probably important for the elimination of autoreactive thymocytes by the recognition of edited self-antigens, which may be required to prevent their recognition in peripheral tissues. In fact, the same group reported that RNA-editing events, including recoding, were elevated in patients with SLE [130]. Such observations suggest that recoded proteins through RNA editing are processed and loaded on MHCs as recoded self-peptides, which may then be recognized as neo–self-antigens to trigger subsequent autoimmune responses.

A-to-I RNA editing in autoimmune diseases

ADAR1 mutations cause AGS [121] (Fig. 1), a rare autosomal recessive encephalopathy that is characterized by basal ganglia calcification and white matter abnormalities [124]. Intriguingly, other genes found in patients with AGS, such as *TREX1* [131], *RNASEH2A*, *RNASEH2B*, *RNASEH2C* [132], *SMAHD1* [133], and *IFIH1* [102], are all involved in nucleic acid metabolism and signaling [134]. Because patients with AGS show upregulated type I IFN activity and an increased expression of ISGs in the absence of infections, this suggests that a type I IFN signature is likely triggered by impaired metabolism or the sensing of host nucleic acids [9, 135]. *ADAR1* mutations in patients with AGS are frequently located in the catalytic domain and decrease the RNA-editing activity of ADAR1 p150, more so than that of ADAR1 p110 [92]. This indicates that the reduced RNA-editing activity of ADAR1 p150 is probably a cause of AGS pathogenesis. In this regard, *Adar1* p150-specific KO and *Adar1* E861A KI mice show embryonic lethality with a type I IFN signature resembling AGS symptoms [91, 94]. Of note, this lethality was rescued by concurrent deletion of MDA5 [91, 93]. Furthermore, considering that mutations in

IFIH1 also cause AGS via the aberrant activation of MDA5 [19, 102, 103, 105], the pathogenesis of AGS caused by *ADAR1* mutations is most likely mediated by an activated MDA5-sensing pathway.

In addition, it is worth noting that a P193A mutation, located in the N-terminal Z-DNA/RNA-binding domain of *ADAR1* p150, was sometimes observed in patients with AGS [121] (Fig. 1). Z-DNA/RNA form a left-handed double helix in contrast to general right-handed B-DNA/RNA; proline at position 193 is required to interact with Z-DNA and Z-RNA [136]. Intriguingly, dsRNA with Z-RNA is more efficiently edited by ADAR1 p150 than dsRNA without Z-RNA [137]. Therefore, it is worth investigating how Z-RNA modulates RNA-editing activity. Another problem is that AGS pathogenesis has not been fully investigated because of the embryonic lethality of *Adar1* KO and *Adar1* E861A KI mice that completely lack editing activity [87, 88, 91]. Given that AGS mutations reduce but still retain some ADAR1 editing activity [92] and AGS symptoms appear after birth, KI mice harboring the same *Adar1* mutation that is found in patients with AGS may be viable and reflect AGS symptoms more precisely.

In comparison, mutations in the *ADAR1* gene are also found in patients with dyschromatosis symmetrica hereditaria (DSH), a pigmentary genodermatosis characterized by hyper- and hypo-pigmented skin lesions [138]. Because several mutations found in patients with DSH are located upstream of the start codon of ADAR1 p110, it is thought that ADAR1 p150 is responsible for pathogenesis [139]. In contrast to AGS mutations, which are generally biallelic except for a G1007R substitution [121], patients with DSH have heterozygous mutations with symptoms obvious only in the skin and that are not fatal, unlike AGS [138]. Importantly, the monoallelic G1007R mutation was identified in DSH patients with neurological symptoms [140], indicating that a mechanism of DSH pathogenesis is at least partially shared with AGS. However, it remains unknown why heterozygotes of *Adar1* KO or E861A KI mice do not exhibit skin abnormalities resembling those of DSH, suggesting that further investigation is required.

Dysregulation of RNA editing has also been reported in other autoimmune diseases. ADAR1 p150, but not the p110 isoform, was upregulated in synovium and PBMCs isolated from patients with rheumatoid arthritis (RA) [141]. Accordingly, RNA editing of the 3′UTR of cathepsin S transcripts is increased, and is ameliorated together with decreased ADAR1 p150 expression by anti-rheumatic treatment depending on the clinical response. Stellos et al. previously showed that ADAR1-mediated RNA-editing stabilized cathepsin S transcripts through the recruitment of HuR, an RNA-binding protein [83]. Cathepsin S, a lysosomal cysteine protease, was indispensable for antigen presentation by MHCs [142],

autoantibody production [143], and the development of collagen-induced arthritis in a mouse model of RA [144]. Therefore, the stabilization of cathepsin S transcripts by increased ADAR1 p150 expression may contribute to RA pathogenesis.

The upregulation of ADAR1 p150 expression has also been shown in T cells isolated from patients with SLE, which resulted in the increased RNA editing of an α regulatory subunit of type 1 protein kinase A [145]. This may have led to impaired activity of this protein as found in most patients with SLE [146]. The same group further observed changes in RNA-editing efficiency in known and novel RNA-editing sites of ADAR2 transcripts [147]. Consistently, a comprehensive analysis by Rhoth et al. revealed an increase of recoding events in patients with SLE [130], suggesting that recoded self-peptides presented by MHCs potentially behave as neo–self-antigens and contribute to SLE pathogenesis.

A-to-I RNA editing in cancer

Large RNA sequencing data sets obtained from The Cancer Genome Atlas (TCGA) revealed that RNA-editing events and ADAR1 expression were upregulated in most cancers and inversely correlated with patient survival [148, 149]. This upregulation of ADAR1 expression is in response to the increased copy number of chromosome 1q, which contains the *ADAR1* gene locus, and a response to type I IFN produced from the chronic inflammatory environment of cancers [150]. However, when we focus on specific RNA-editing sites, the editing efficiency is perturbed, sometimes being upregulated in some sites but downregulated in others (Table 1). These alterations are especially important for RNA recoding events, given that each recoding event alters, in a positive or negative manner, the function of a protein thus regulating cancer progression. For instance, nearly 100% of the RNA editing of GRIA2 transcripts, which leads to changing glutamine (Q) at position 607 of GluA2 to arginine (R), occurs in

Table 1 RNA-editing-mediated functional alterations found in various cancers

Gene	Protein	Alteration of amino acid residue[a]	Function of RNA editing in cancer	RNA-editing level and cancer types	Responsible ADARs	References
AZIN1	AZIN1	S367G	Promoting tumor initiation and development	Increase in hepatocellular carcinoma, esophageal squamous cell carcinoma and colorectal cancer	ADAR1	[57, 159, 160]
COPA	COPA	I164V	Not determined	Decrease in hepatocellular carcinoma	ADAR2	[161]
FLNB	Filamin B	M2269V	Not determined	Increase in hepatocellular carcinoma	ADAR1 and ADAR2	[161]
GABRA3	GABA$_A$ receptor subunit α-3	I342M	Inhibiting cancer metastasis by suppressing AKT pathways	Increase in non-invasive breast cancer	ADAR1	[162]
GRIA2	AMPA receptor GluA2 subunit	Q607R	Inhibiting migration and proliferation by blocking Ca^{2+}-permeability	Decrease in glioblastoma	ADAR2	[48, 156, 157]
RHOQ	RHOQ	N136S	Promoting an invasive potential by increasing RHOQ protein activity	Increase in colorectal cancer	Not determined	[58]
miR-21 and miR-222/221	-	-	Inhibiting migration and proliferation by preventing microRNA maturation	Increase in glioma cells	ADAR2	[166]
miR-367a*	-	-	Inhibiting invasive properties by altering target transcript	Decrease in glioblastoma multiforme	ADAR2	[79]

[a]An amino acid substitution due to RNA editing and the position of the residue are shown

the brain to regulate Ca^{2+} permeability of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor [59, 151]. The impairment of such RNA editing was not only found in neurodegenerative diseases such as amyotrophic lateral sclerosis, Huntington's disease, and Alzheimer's disease [152-155], but also in glioblastoma multiforme [156]. Overexpression of unedited GluA2 (Q) promotes migration and proliferation of glioblastoma cells [157]. Dysregulated RNA editing of GRIA2 transcripts may be partially attributed to the increased expression of inactive ADAR3, which inhibits the catalytic activity of ADAR2 [48]. In contrast, RNA editing–mediated asparagine (N) to serine (S) substitution at position 136 of Ras Homolog Family Member Q (RHOQ), a member of the Rho family of small GTP-binding proteins that regulates actin-based structures, is increased in patients with colorectal cancer [58, 158]. Such RNA-editing changes the activity of RHOQ and reorganization of the actin cytoskeleton, and promotes an invasive potential. In addition, an amino acid substitution from S to glycine (G) at the position 367 residue of antizyme inhibitor 1 (AZIN1) was increased in hepatocellular carcinoma [57]. This recoding changes the conformation of AZIN1 and its localization from the cytoplasm to the nucleus, and yields gain-of-function phenotypes. Although it is believed that ADAR2 preferentially targets editing sites in coding regions, it is notable that the RNA-editing level of AZIN1 is highly correlated with ADAR1 expression, but not that of ADAR2 [57]. An increase in AZIN1 S/G substitution is also observed in patients with esophageal squamous cell carcinoma and colorectal cancer [159, 160].

The overexpression of ADAR1 and downregulation of ADAR2 can predict a poor clinical outcome for patients with hepatocellular carcinoma [161]. This imbalanced gene expression reflects changes in gene-specific recoding events: an increase in M2269V of FLNB transcripts that encodes filamin B, and a decrease in I164V of coatomer protein complex, subunit α (COPA) transcripts [161]. The other recoding site involved in cancer pathogenesis is type A gamma-aminobutyric acid (GABA$_A$) receptor subunit α-3 (GABRA3), which is edited at a I342M site with nearly 100% efficiency in the adult brain [62]. Intriguingly, such RNA editing of GABRA3 transcripts is detected in non-invasive, but not invasive breast cancers [162]. In this regard, the unedited GABA$_A$ receptor shows increased expression on the cell surface and activates AKT pathways, contributing to breast cancer metastasis. Finally, another aspect of recoding function has been reported by Zhang et al. [163]. Using mass spectrometry, they identified several edited peptides as epitopes loaded on the human leukocyte antigen that potentially activate CD8^{+} T cells. They also showed that edited, but not unedited,

cyclin I peptide triggers a cytotoxic response in melanoma cells by CD8^{+} T cells specific for the edited epitope.

In comparison, RNA-editing events in micro(mi)RNAs were found to be globally downregulated in human cancers and correlated with a poor prognosis in general, given that RNA editing affects miRNA expression and target recognition [80, 164, 165]. For instance, RNA editing of miR-367a* was significantly reduced in human gliomas [79]. Intriguingly, unedited miR-367a* plays a role in glioma cells, which acquire invasive properties, by targeting the tumor suppressor gene, *PAP2A*, whereas the oncogene, *AMFR*, a target of edited miR-367a*, failed to be silenced. In contrast, ADAR2-mediated RNA editing inhibits glioma cell proliferation and migration by preventing the maturation of oncogenic miR-21 and miR-222/221 during cleavage steps mediated by DROSHA and DICER [166].

In contrast to the role of ADAR1- and ADAR2-mediated RNA editing at specific sites affecting recoding and miRNA biogenesis, in cancer pathogenesis, the upregulated expression of ADAR1 in most cancers increases RNA-editing frequency in retrotransposon-derived repetitive elements in non-coding regions. This may enhance immune tolerance by preventing activation of dsRNA-sensing pathways associated with MDA5, PKR, and RNase L. Indeed, DNA methyltransferase (DNMT) inhibitors ameliorate hematological and epithelial tumor cells [167]. This clinical effect may be explained by the molecular mechanism in which the hypermethylated promoters of tumor suppressor genes are re-activated by their DNA demethylating function [168, 169]. However, the presence of hypomethylated promoters of tumor suppressor genes observed in patients after DNMT inhibitor treatment is not consistent with the clinical response [170], thus suggesting the involvement of an unknown mechanism in anti-tumor function. Intriguingly, it has been demonstrated that treatment with DNMT inhibitors leads to hypomethylation and subsequent production of self-dsRNAs from ERVs, SINEs, and other repetitive elements [20, 22, 171]. This triggers activation of MDA5, RNase L, and other dsRNA-sensing pathways, thereby contributing to immunotherapy against cancer. Based on these studies, it was expected that ADAR1 depletion may also decrease immune tolerance in cancer cells by activating dsRNA-sensing pathways.

Liu et al. recently reported the existence of ISG signature–positive tumors even without the infiltration of type I IFN-producing immune cells, indicating that they acquire the ability to produce type I IFN [172]. Intriguingly, ISG signature-positive cancer cells are sensitive to ADAR1 depletion. This is in accordance with findings from another group that type I IFN production and lethality induced by ADAR1 depletion in cancer cells could be predicted by the abundance of ISG products, such as MDA5 and PKR [173]. They showed that an increase in type I IFN production

was ameliorated by the concurrent deletion of MDA5 or MAVS, whereas the viability of cancer cells was not restored (Fig. 4). In contrast, concurrent deletion of PKR rescued the lethality of cancer cells induced by ADAR1 depletion [173], indicating the different role of MDA5 and PKR in cancer cells. Intriguingly, the overexpression of ADAR1 E861A p150, but not wild-type p110, partially prevented this lethality [173], which is in accordance with a previous finding that the suppression of PKR activation by ADAR1 required its dsRNA-binding and catalytic activities [12]. Of note, Liu et al. showed that an ISG signature was established by the activation of STING, a cytosolic sensor for DNA, and was followed by IFN production, providing a novel cross-talk between DNA- and RNA-sensing pathways [172]. Li et al. further reported that RNase L was activated by ADAR1 deficiency, and induced the death of the human lung adenocarcinoma A549 cell line even in the presence of MDA5 (Fig. 4), suggesting that the OAS–RNase L system is likely the primary pathway activated by ADAR1 depletion [110]. Accordingly, ADAR1 depletion increased DNMT inhibitor-induced cytotoxicity in A549 cells via an OAS–RNase L signaling pathway [171]. Further investigation is required whether ADAR1 depletion exerts the same effect on other cancer cells via activation of RNase L.

Ishizuka et al. recently reported that the loss of ADAR1 in cancer cells sensitized these to immunotherapy, overcoming resistance to immune checkpoint blockade [174] (Fig. 4). They showed that tumor sizes of implanted ADAR1-deficient B16 melanoma cells were smaller and more sensitive to anti–PD-1 antibodies. Single-cell RNA sequencing analysis revealed an increase in CD8$^+$ T cells and a decrease in M2 macrophages and myeloid-derived suppressor cells,
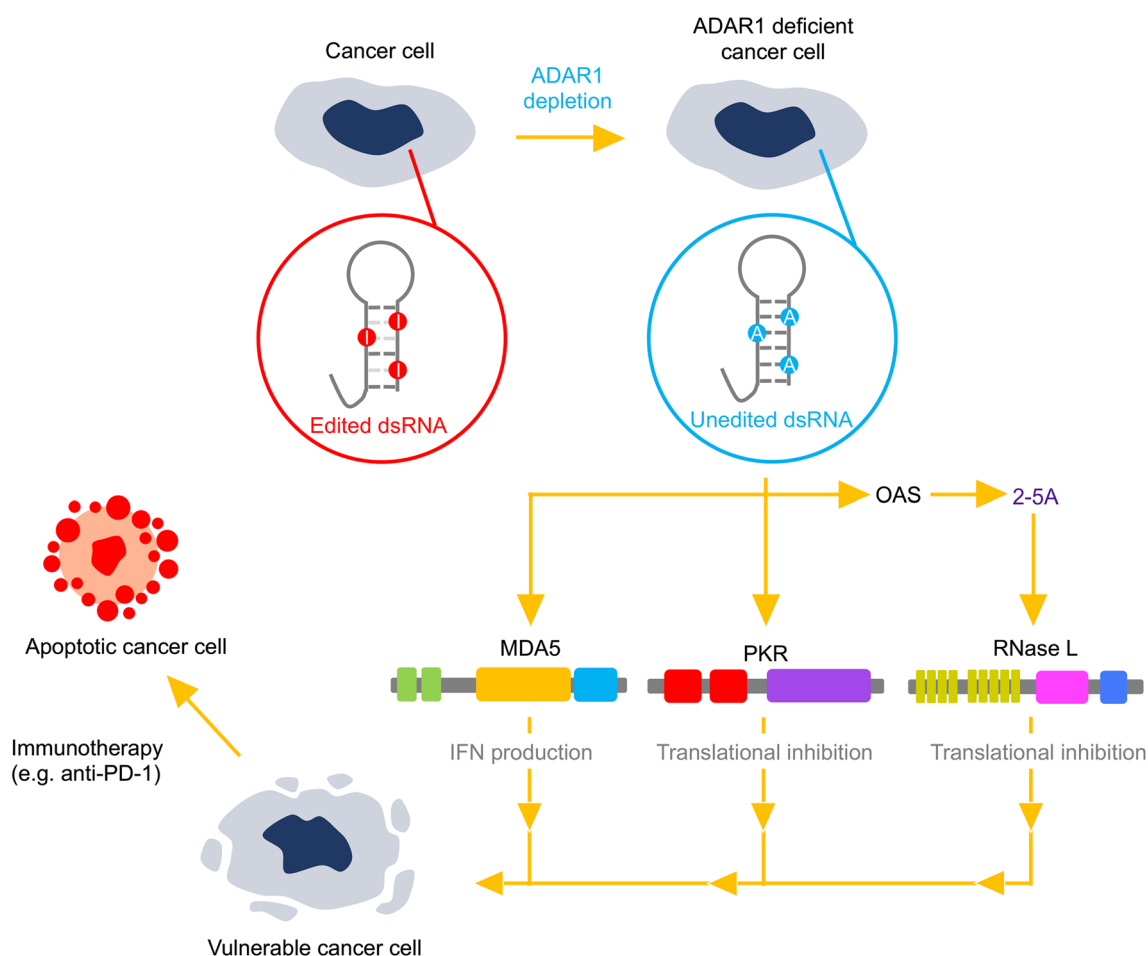

Fig. 4 Depletion of ADAR1 induces vulnerability in cancer cells. RNA-editing efficiency and the expression of adenosine deaminase acting on RNA 1 (ADAR1) are generally upregulated in most cancers. Loss of RNA editing followed by ADAR1 depletion activates multiple double-stranded (ds)RNA-sensing pathways mediated by melanoma differentiation-associated protein 5 (MDA5), protein kinase R (PKR), and oligoadenylate synthetase (OAS), which produces 2′,5′-oligoadenylate (2-5A) resulting in activation of RNase L. The activation of these pathways leads to type I interferon (IFN) production and translational arrest, which make cancer cells vulnerable. In addition, ADAR1 depletion causes cancer cells to be more sensitive to cancer immunotherapy involving, for instance, anti–programmed cell death 1 (PD-1) antibodies

which have a pro-tumor phenotype, in an ADAR1-deficient tumor microenvironment. Moreover, the vulnerability of ADAR1-deficient B16 melanoma cells was canceled by the concurrent deletion of both MDA5 and PKR, but not either alone, suggesting that either PKR or MDA5 is sufficient to sensitize ADAR1-deficient tumor cells to immunotherapy. Importantly, it was shown that the sensitive phenotype of ADAR1-deficient tumor cells to immunotherapy was still observed with the concurrent deletion of beta 2-microglobin, which disrupted MHC-I expression and thus prevented CD8^{+} T-cell attack. This overcoming of tumor resistance is accompanied by a significant increase in non-MHC-I restricted cytotoxic cells. Taken together, ADAR1 depletion decreases immune tolerance in cancer cells, which is beneficial for cancer therapy.

Concluding remarks

In this review, we summarized RNA-editing function in the immune system and its implication for autoimmune diseases and cancer. The classical functions of RNA editing, which can modulate amino acid sequences, splicing patterns, miRNA target specificity, mRNA stability, and circular RNA biogenesis, have been well investigated. However, recent studies have uncovered the novel role of RNA editing in the immune system in inhibiting the activation of MDA5 and PKR, in addition to the OAS–RNase L system, by preventing their recognition of endogenous dsRNAs formed by retrotransposon-derived repetitive elements. Although the mechanisms underlying the prevention of MDA5-sensing endogenous dsRNAs by RNA editing remain unresolved, the RNA editing/MDA5 axis is not only indispensable for innate immune cells, but is also required for the development and homeostasis of adaptive immune cells. Furthermore, impairment of the RNA-editing/MDA5 axis is most likely a cause of autoimmune disease, given that *Adar1* E861A KI mice show a type I IFN signature resembling AGS symptoms and can be rescued by the concurrent deletion of MDA5. Collectively, we expect to determine the critical editing substrates essential for suppressing MDA5 activation as the next step to establishing a strategy for AGS treatment. In contrast, ADAR1 also inhibits the activation of another dsRNA sensor, PKR, through its RNA editing and binding functions. Although several studies reported that PKR activation by a loss of ADAR1 sensitized cancer cells to immunotherapy, this appears to be limited in humans in which dependence may come from a different proportion of SINE repetitive elements between the human and mouse genome [175]. The mechanism of how ADAR1 prevents PKR activation and the critical editing substrates required for preventing PKR activation also requires further investigation. In addition, although recent studies showed that the ADAR1/PKR axis is

critical for tumor vulnerability [172-174], it is worth investigating its role in AGS pathogenesis.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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