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Critical Reviews and Perspectives

ADARs: pleiotropy in function, versatility in application

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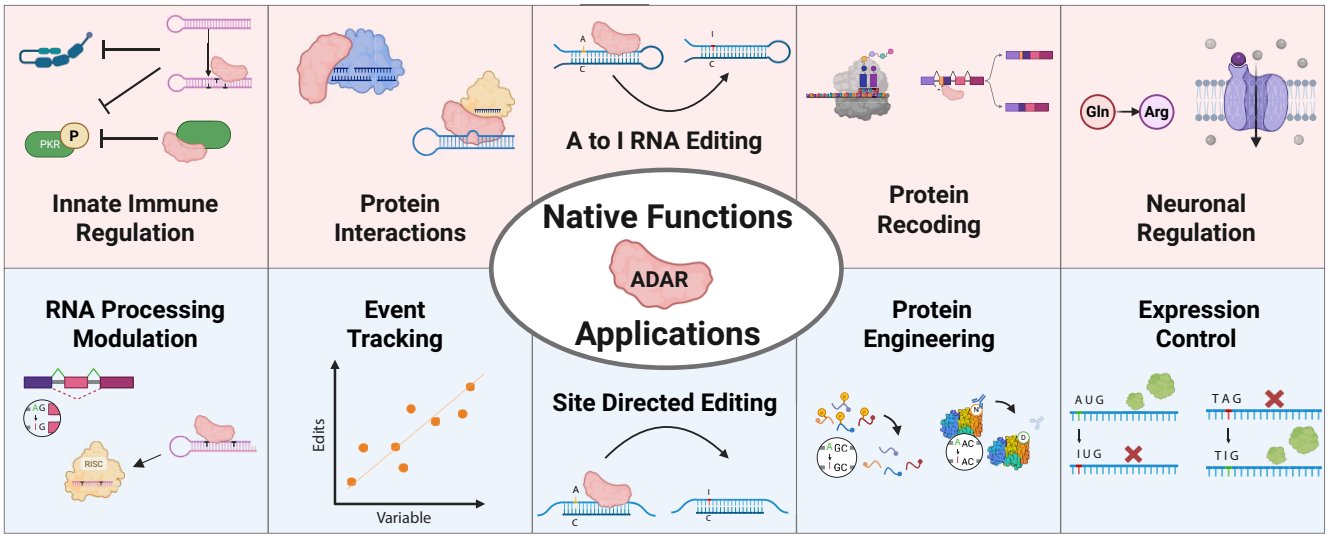
Abstract

RNA processing is essential for proper cellular function, contributing to protein and cell state diversity, and is often dysregulated in diseased states. A key subset of RNA regulators is the double-stranded RNA-specific adenosine deaminase (ADAR) protein family, which hydrolytically deaminates double-stranded RNA, causing an adenosine-to-inosine edit (A-to-I). Active ubiquitously throughout the body, this pleiotropic protein family plays critical roles in embryonic patterning, neurological function, and immune regulation. Their aberrant activity has in turn been implicated in a spectrum of disorders, including cancer, metabolic diseases, and autoimmune conditions. By instead purposefully modulating their activity, ADARs have been leveraged to create a versatile toolset for transcriptome engineering. This includes enabling programmable RNA editing, controlled RNA splicing, reversibly modulating protein interactions, and altering cellular inflammation. Here, we review the pleiotropic functions and versatile applications of ADARs, as well as outline areas for growth and potential new avenues in both therapeutics and research.

Graphical abstract



Introduction

Since its identification in the late 1980s [1], the adenosine deaminase acting on RNA (ADAR) protein family has emerged as a pivotal regulator of RNA processing and protein diversity. In humans, ADAR activity accounts for more than 18 million RNA edits spanning thousands of genes, and influences diverse biological processes from neural function to innate immunity [2–7]. Although ADAR enzymes act broadly, they demonstrate higher efficiency on certain motifs and secondary structures, indicating that editing can be precisely targeted [8]. Harnessing this specificity holds significant promise for site-directed RNA editing, and has shown progressive improvement with the growing insights into ADAR specificity, recruitment, and function in both normal physiology and disease [3, 9–11]. This review explores the four mammalian ADAR isoforms, examining strategies to engineer site-directed genome editing and highlighting the broader significance of ADAR activity beyond canonical A-to-I editing function, in particular their impact on innate immune regulation.

ADAR proteins bind double-stranded RNA (dsRNA) and hydrolytically deaminate adenosines to inosines (A-to-I), which are interpreted as guanosines by cellular machinery [12]. The resultant inosine modification alters RNA folding, degradation, and RNA-protein interactions [13]. Inverted Alu

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repeats act as powerful ADAR recruiters as they can pair with each other to create hyper-edited, long, stable, double-stranded regions. While Alu regions only account for 10% of the human genome, 99% of ADAR-mediated editing occurs in them [14–16]. Additionally, ADAR proteins can interact with other RNA-binding proteins (RBPs), and ADAR isoforms with nonfunctional deaminases may outcompete other RBPs for dsRNA substrates [17, 18].

ADARs are highly conserved throughout the metazoan clade, playing a critical role in physiological processes in the brain, immune system, and embryonic development [19–22]. For instance, ADARs act as an essential editor of neuroreceptors, help endogenous dsRNA avoid triggering an innate immune response, and critically regulate RNA processing during embryonic development. As ADARs are linked to these essential processes, their aberrant activity has detrimental effects. ADAR mutations resulting in hypo-editing are linked to metabolic and neurodegenerative diseases, while hyper-editing is associated with aggressive cancers [23]. While we will present what is known of ADAR activity and regulation, more work is required to fully characterize ADAR proteins and all their native roles.

Recent work has shown ADAR's selective deamination can be utilized for novel, site-directed RNA editing platforms, further motivating the need to better understand and engineer ADAR's innate activity. At the core of these programmable RNA editing methods is a sequence-specific "guide" that creates a stabilized, ADAR-editable, dsRNA region by pairing with endogenous RNA. With appropriate guide design, endogenous ADARs may be directly recruited, or exogenously delivered ADARs may be used instead [24, 25].

The ubiquitous and systemic relevance of ADAR-driven effects offers a unique opportunity for therapeutic development, despite many remaining hurdles. Utmost is ADAR recruitment and sensitivity in tissues with little ADAR expression or dampened RNA editing activity. Operating in an already complex biological environment requires careful consideration of off-target effects, endogenous interference, and variable activity across guides and effectors. We first review how these systems have been engineered and then discuss both current and envisioned applications of RNA-editing platforms, in addition to highlighting necessary improvements. With careful understanding of ADAR biology and improved RNA engineering principles, researchers will be able to advance programmable ADAR-driven RNA editing systems for a broad range of targeting and sensing applications.

Protein structure

The known mammalian ADAR protein family includes four major isoforms that differ in biological functions and expression patterns produced by three genes: the constitutive ADAR1 p110 and interferon-inducible ADAR1 p150 by ADAR, ADAR2 by ADARB1, and ADAR3 by ADARB2 (Fig. 1A) [26]. ADAR1 p150 is the only major isoform to include a nuclear export signal that enables it to translocate between the cytoplasm and nucleus, though it primarily localizes to the cytoplasm [27]. ADAR1 p110, ADAR2, and ADAR3 lack a nuclear export signal and are almost exclusively found in the nucleus [28–32]. All isoforms contain N-terminal dsRNA binding domains (dsRBDs), a nuclear import signal, and a conserved C-terminal deamination domain, which is inactive in ADAR3 [33]. The nuclear localization signal of the two ADAR1 isoforms is atypical and overlaps with the third dsRNA binding domain [34]. The dsRBDs recognize nonspecific double-stranded regions longer than 15 bp in addition to specific motifs; upon recognition, they form homodimers, which are crucial for efficient editing [35–39]. Both ADAR1 isoforms include Z-domains, which facilitate binding to immunogenic left-handed RNA or DNA (Z-RNA, Z-DNA) [40]. However, while both isoforms include a Zβ domain, only ADAR1 p150 includes a Zα domain, which binds to Z-RNA or Z-DNA at a much higher rate than Zβ does [41]. Additionally, ADAR3 includes an arginine-rich R domain, allowing it to also bind to single-stranded RNA [42, 43]. These structural differences lead to subtle variations in substrate preferences.

Native functions

ADAR1 and innate immunity

ADAR1 is ubiquitously expressed in virtually all tissues, with the highest relative expression levels and activity among ADAR proteins (Fig. 1B) [26, 44]. It is suggested that ADAR1 primarily edits non-specifically within long double-stranded regions [45]. Due to this ubiquitous expression and nonspecific substrate targeting, ADAR1 labels a wide variety of endogenously occurring dsRNA as "self" through editing [46]. This masking prevents an antiviral-immune response by other cytosolic dsRNA sensors and is critical for modulating innate immune function. The innate immune system recognizes conserved motifs in pathogens' dsRNA, which is characteristic of viral infection, eventually triggering an interferon (IFN) response [47, 48].

In the absence of ADAR1 editing, dsRNA is bound by RIG-I-like receptors and melanoma-differentiation-associated gene 5 (MDA-5), which recruit the mitochondrial antiviral signaling protein (MAVS) and trigger IFN responses [6, 20, 46, 49–51]. Both type I and type II IFN-stimulated genes become highly expressed, hindering cellular function and initiating a stress response [52, 53]. It is hypothesized that this stress response causes the lethal defects in hematopoiesis and widespread apoptosis in ADAR null zebrafish and mice embryos [54–56]. In humans, Aicardi–Goutières syndrome (AGS), an inflammatory autoimmune and neurological disease, can be caused by mutations in ADAR1, which leads to a persistent type I IFN response and clinically presents with microcephaly, developmental delays, and seizures [57].

ADAR1 also regulates innate immunity through interactions with the protein kinase R (PKR) pathway. PKR is a dsRNA-binding protein that helps phosphorylate IκBα through the IKK complex, thus activating nuclear factor kappa-B (NF-κB), which induces cytokine and chemokine production, signaling an infection to immune cells [58–62]. Activated PKR also phosphorylates eukaryotic initiation factor 2a (eIF2α) to inhibit protein synthesis, consequently leading to cellular growth arrest [63]. It is also known to phosphorylate p38 and JNK, triggering the MAPK proinflammatory signaling pathway [64]. ADAR-mediated dsRNA editing and destabilization render dsRNA unrecognizable by PKR, preventing autophosphorylation and complex downstream pathways from activating [64–67].

Beyond substrate editing, it is thought that the primary mechanism of ADAR-based PKR inhibition is editing-independent, direct interaction with PKR [68]. ADAR1 and PKR co-immunoprecipitate in a variety of cell types and

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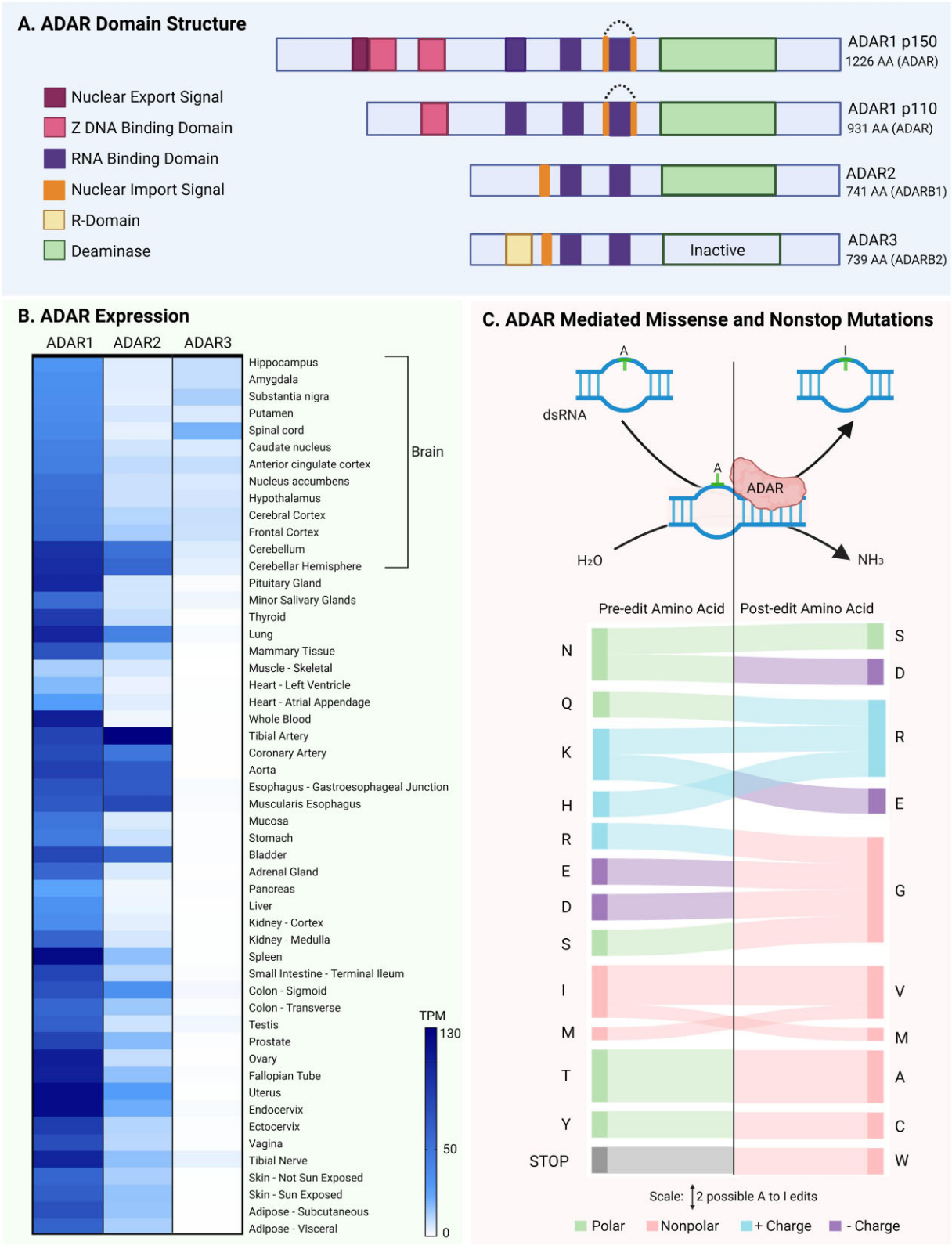

Figure 1. ADAR structure, biology, and function. (**A**) Domain structure of four ADAR isoforms, ADAR1 p150, ADAR1 p110, ADAR2, and ADAR3, highlighting each of their catalytic and functional domains. (**B**) Heatmap of ADAR expression across human tissues in transcripts per million (TPM), data provided by GTEXportal.org. (**C**) Schematic of ADAR-mediated editing of dsRNA and the possible, novel, amino acid mutations that may occur. Of all possible ADAR-mediated edits, 31 will create missense mutations, and 2 will create nonstop mutations. Twelve amino acids and two stop codons can be edited to create a different amino acid, and 10 amino acids can be created. Amino acids are color-coded based on their polarity or charge. The Sankey diagram was created using sankeymatic.com. Created in BioRender. Zhang, Y. (2025) https://BioRender.com/ihoud9l.

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ADAR overexpression reduces endogenous PKR levels [67–69]. In particular, the dsRBD3 of ADAR has been shown to cause this effect, reducing activation by competitively binding dsRNA and interacting with PKR [65, 68]. ADAR/MAVS knockout mice pups die upon birth due to a PKR-induced integrated stress response, while ADAR/MAVS/PKR knockout pups survive until adulthood, further highlighting this important connection [68]. PACT has been shown to work cooperatively with ADAR1 to reduce this abhorrent response [70]. While this mechanism is theorized to be entirely editing independent, the ADAR1 R790E mutant found unable to interact with and inhibit PKR is also unable to edit dsRNA despite intact dsRBDs [68].

PKR activity is also essential for AGS disease phenotype in *AdarP195A/ADARp150−* mice [53]. While exact structures are still needed, this work proposes that inhibition occurs when an ADAR dimer is anchored to the dsRNA by a single dsRBDIII, leaving the second dsRBDIII free to bind the kinase domain of a dimerized PKR that is attached to the same dsRNA. ADAR1 p150 inhibits activation of MDA-5 and MAVS by editing dsRNA substrates that would otherwise interact with these two proteins [71, 72]. As these proteins induce ADAR1 p150 via IFN responses, the p150 isoform can act as a negative regulator of itself. This is indicative of some of the regulatory mechanisms over ADAR activity that must be elucidated to better understand and engineer ADAR therapeutics.

Targeted editing by ADAR2

ADAR2 (ADARB1) is most highly expressed in the brain and peripheral nervous system, though it is also expressed at a lower rate throughout the heart, digestive tract, and reproductive organs (Fig. 1B) [73, 74]. ADAR2 is considered to have higher specificity than ADAR1, typically editing specific sites on short dsRNA sequences with mismatches, while ADAR1 prefers long repeat regions [73, 75]. It is responsible for many ADAR-mediated protein recoding events enabled by the 33 possible ADAR-mediated codon switches (Fig. 1C) [76]. Variations in substrate preferences result from differences in binding domain composition, though binding strength does not necessarily correlate to editing activity [75].

It is most notable for its essential activity of editing glutamine (Q) to arginine (R) in the GluA2 subunit of the glutamate-gated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor found in 99% of healthy adult humans [77]. Without the Q/R edit, this glutamate-gated ion channel found throughout the CNS will be calcium ion permeable and cause excitotoxicity, abnormal physiology, behavior, and function [78, 79]. Other essential membrane proteins recoded by ADAR2 include the 5-HT2C serotonin receptor, KV1.1 voltage-gated potassium channel, and GABAA receptor subunit α3 [80–83]. RNA editing throughout the brain serves to increase protein diversity and add another dimension to the atlas of potential cell states [10]. Dysregulation of editing in the brain has pathological effects and is associated with neurological conditions such as epilepsy, Alzheimer's, and amyotrophic lateral sclerosis (ALS) [84–86].

Competitive inhibition by ADAR3

ADAR3 (ADARB2) is almost exclusively expressed in the brain and at a much lower level than any of the other ADAR isoforms [19, 74]. While ADAR3 has a nonfunctional deaminase, its binding to RNA transcripts is inversely correlated with ADAR1 editing and therefore may act as an inhibitor of A-to-I deamination in the brain [42]. It is capable of competing with ADAR1 and ADAR2 for double-stranded substrates, which may be how it inhibits editing activity [32, 87]. As ADAR3 has distinct substrate preferences, its expression can dramatically alter the RNA editing profile of certain brain transcripts rather than agnostically reducing transcriptome-wide editing [19].

Despite low global ADAR3 expression, it displays highest expression in the CNS regions of the hippocampus, substantia nigra, amygdala, and spinal cord (Fig. 1B). In mice, ADAR3 knockout results in long- and short-term memory deficits as well as development of anxious behaviors [88]. It is suggested that this knockout impacts the gene expression networks of synaptic function and neurogenesis, though more work is required to confirm [88]. Alternately, ADAR3 is significantly overexpressed in the hippocampal transcriptome of late-onset Alzheimer's disease patients [89]. As insufficient GRIA2 Q/R editing is also characteristic for these patients, it has been proposed that overexpressed ADAR3 binding outcompetes ADAR2 at the Q/R editing site [89, 90]. Dysregulation of ADAR3 in either direction is deleterious to the hippocampus and memory health.

ADAR protein interactions

Beyond editing RNA, there are numerous instances of ADAR interacting directly with other proteins, which impacts the function of both species. As mentioned previously, ADAR1 interacts extensively with PKR to regulate innate immunity [65, 68]. ADAR1 cooperates with HuR, another RNA-binding protein, to stabilize AU-rich regions in the 3′ UTR [44]. As many as 98% of ADAR-bound transcripts in AU-rich regions also have HuR binding sites, and these two RNA-binding proteins co-immunoprecipitate [44]. It has additionally been shown that ADAR targeting small interfering RNA (siRNA) will reduce HuR binding to RNA transcripts, despite unaffected HuR protein levels [44]. ADAR1 additionally regulates microRNA (miRNA) by editing pri-miRNA to disrupt their structure and processing by the RNase, DROSHA, reducing the rate of conversion to fully functional miRNA [91]. By preferentially stabilizing and degrading specific transcripts, ADAR1 helps control the overall protein expression pattern in cells. While these interactions occur upon RNA binding, ADAR1 can occasionally interact with other proteins prior to, and independently of, RNA binding. ADAR1 heterodimerizes with the RNase, Dicer, to promote miRNA processing and influence RNA silencing, increasing degradation rates of target transcripts [92]. ADAR1 mutants with defective dsRBD still co-immunoprecipitate with Dicer, suggesting this dimerization occurs prior to a dsRNA binding event [92]. While Dicer can act independently of ADAR1, once they bind, Dicer pre-siRNA cleavage efficiency improves 2–6-fold [92]. When the deaminase dead ADAR1 E912A mutant is used, Dicer editing was still 3–6-fold more efficient, indicating that this mechanism is independent of dsRNA ADAR editing [92].

In addition, protein–protein interactions can modulate ADAR function and impact RNA editing. The editing of ADAR1 and ADAR2 is negatively regulated by direct interaction with several proteins, including ILF3, FMRP, SFRS9, and AIMP2, the last of which reduces ADAR expression

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[4, 19, 93, 94]. In contrast, N4BP2L1 interacts with both catalytically active ADARs to increase editing rates [4]. ADAR has a wide variety of protein interactions impacting both its function and the function of countless other proteins.

ADAR and disease

ADAR1 interacts with viral infections in a number of ways that range from inhibiting the infection to promoting it [95]. While the exact mechanisms of ADAR-mediated antiviral activity are poorly understood, they seem to revolve around hyper-editing of specific sites, likely leading to reduction of viral protein function or alteration of 3D RNA–protein complex formation [29, 46, 96–98]. On the other end of the spectrum, many viruses, such as the measles virus, hepatitis delta virus (HDV), human immunodeficiency virus (HIV), and Kaposi's sarcoma-associated herpesvirus, have each evolved mechanisms to benefit from ADAR editing [40, 99–102]. HIV avoids other dsRNA sensors by ADAR-mediated editing of its transcripts, while ADAR editing of HDV triggers viral RNA packaging [100, 101]. Direct RNA editing of viral transcripts can lead to gain or loss of function depending on the target. RNA viruses may utilize this mechanism to increase genetic diversity and accelerate evolution [103].

Beyond exogenous infection, ADAR1 plays a critical role in many cancers and is typically upregulated, contributing to growth, colony formation, and self-renewal, often by evading the immune response [17, 23, 27, 104, 105]. Typical targets for increased editing leading to more aggressive forms of cancer include transcription factors, cyclin-dependent kinases, miRNA, and enzymes such as AZIN1 [17, 106–110]. ADAR1 knockout in tumor cells has been shown to increase the efficacy of checkpoint blockade immunotherapies by a pro-inflammatory effect resulting from reduced dsRNA editing [111]. However, in some oncology contexts, notably melanoma and breast cancer, ADAR editing is associated with suppressing growth and invasion [112, 113].

As ADAR is an essential component of innate immunity, it is unsurprising that dysregulated ADAR is implicated in a number of autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [114–116]. RA is characterized by systemic inflammation; previous work has shown ADAR editing destabilizes and partially linearizes messenger RNA (mRNA) of inflammatory genes, which makes the HuR target motifs accessible for HuR binding and stabilization, leading to an increase of pro-inflammatory proteins, including ADAR1 p150 [115]. ADAR's role in SLE is less clear as SLE patients have overexpressed ADAR1, yet underexpressed ADAR2 [116]. It is suggested that editing from ADAR1 produces autoantigens, causing a chronic immune response [116].

Evidently, ADAR dysregulation can be a key component of disease pathology both when it is under- and overexpressed. While ADAR activity has yet to be fully elucidated, this highlights the versatile and context-dependent roles of ADAR proteins in mammalian biology.

ADAR in non-mammalian organisms

Other organisms in the metazoan clade have ADAR orthologs that perform site-specific RNA editing but there are key differences in protein isoforms and native function. *Drosophila* only have a single ADAR gene, most closely resembling ADAR2, that is critical for both immune and brain function, thus serving similar purposes to both mammalian ADAR1 and ADAR2 [117, 118]. *Caenorhabditis elegans* possesses two ADAR genes, Adr-1 and Adr-2, though the former is catalytically inactive and serves to regulate RNA editing by the latter [119]. Combined, they serve critical roles in maintaining *C. elegans* behavior and health as ADAR knockout mutants exhibit reduced chemotaxis and shortened lives, likely due to ADAR-mediated changes in gene expression patterns [119–121]. Zebrafish have four ADAR genes, ADAR1, ADAR2a, ADAR2b, and ADAR3, which are orthologous to mammalian ADAR1, ADAR2, and ADAR3 proteins, respectively [122]. ADAR editing patterns in zebrafish are temperature dependent indicating thermoregulation as a potential function in addition to key roles in embryonic patterning and innate immune regulation similar to mammalian systems [56, 122, 123].

Coleoid cephalopods have a particularly robust A-to-I editing landscape with upwards of 60% of transcripts containing a recoding site, in contrast to the human rate of ∼3% [124–126]. A high number of editing sites are conserved across cephalopods, indicating an evolutionary advantage, whereas in other organisms editing is assumed to be neutral or detrimental [124]. This editing is driven by ADAR orthologs sqADAR1, sqADAR2, and sqADAR/D-like corresponding to ADAR1, ADAR2, and ADAR3, respectively, and performing similar functions [126]. Unlike human ADAR1, sqADAR1 contains a serine-rich region and numerous RNA editing sites, alluding to self-regulation [126]. sqADAR2 differs from human ADAR2 in that it also localizes to the cytoplasm [126]. This ability of sqADAR1 to self-regulate could be transferred to ADAR-engineering applications where the effector protein limits its own activity to reduce off targets if overexpressed.

Current framework suggests that RNA editing in cephalopods serves to increase transcriptome plasticity at the cost of evolutionary speed [124]. This theory is highlighted by the adjustment of RNA editing patterns in response to temperature fluctuations indicating a homeostatic control mechanism [126, 127]. Overall, understanding how ADAR orthologs function in non-mammalian systems gives insight to the evolutionary biology behind RNA editing and hints at new potential utility of ADAR-based systems.

ADAR functionality

ADAR has a pleiotropy of native function through three core interactions as it can edit RNA to cause sequence changes, bind to RNA modulating its availability, and interact with other proteins altering their activity (Fig. 2A). These three core interactions cause downstream effects through a variety of intermediate mechanisms, most notably codon changes, splicing modulation, and dsRNA labeling (Fig. 2B). The diversity of substrates ADAR is capable of interacting with and the multitude of ways it can affect them leads to its vast aforementioned biological effects and many potential novel utilities (Fig. 2C).

As ADAR technologies may include programmable editing, it is notable that ADAR-mediated A-to-I changes in codons can edit 12 amino acids, as well as 2 stop codons, into 10 different amino acids through 33 unique codon edits (Fig. 1C). Additional edits will result in silent mutations, which are unlikely to be helpful for therapeutics, but may still hold value for tracking ADAR editing activity over time. One of the most desirable ADAR functions for both therapeutic and synthetic biology is the ability to create nonstop mutations on the UAG stop codon [128, 129]. It can correct nonsense mutations to

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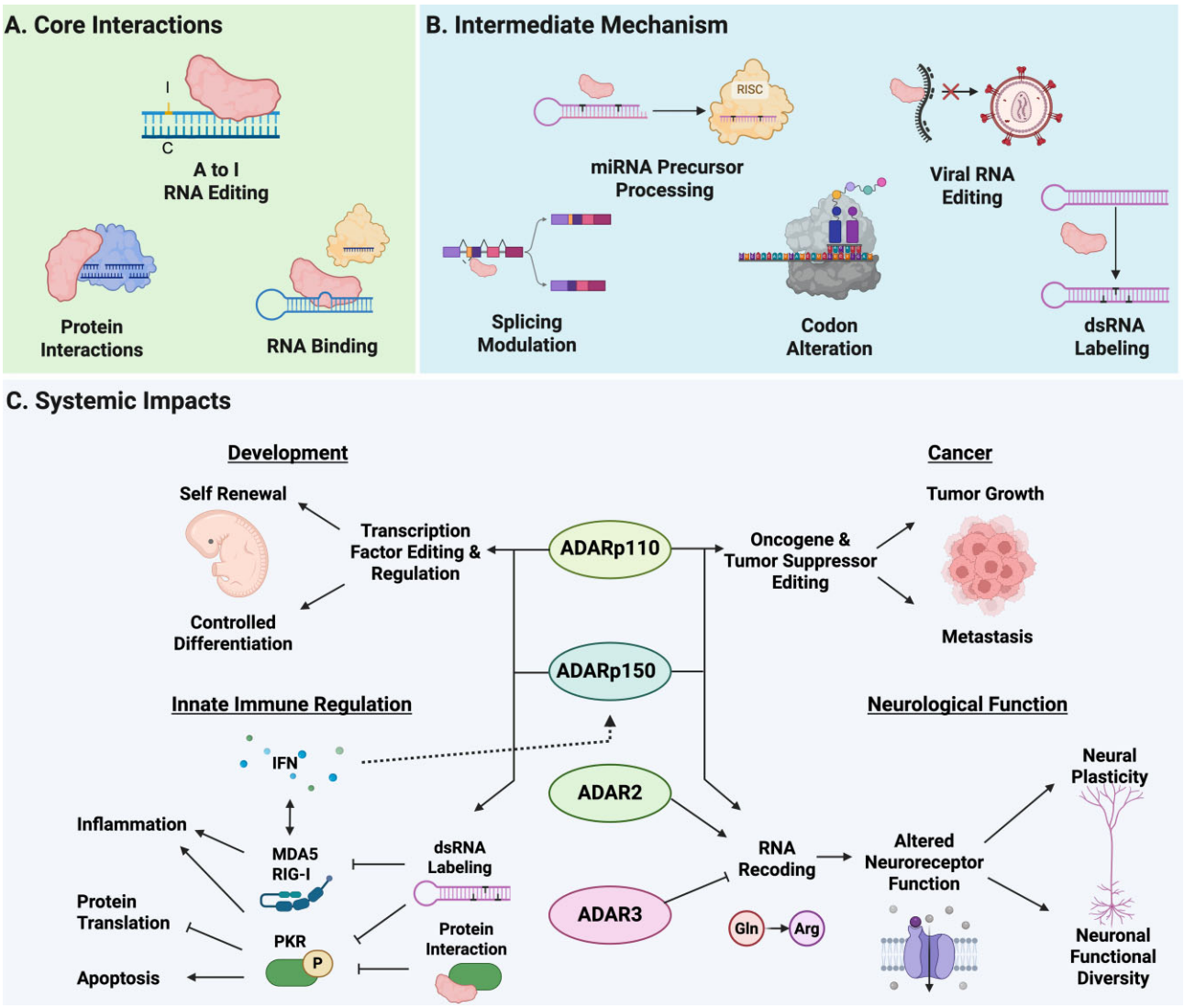

Figure 2. ADAR protein family functions: (**A**) Core interactions: A to I editing of dsRNA, dsRNA binding, and protein–protein interactions, (**B**) Intermediate mechanism: altered coding sequences, alternatively spliced transcripts, and labeled endogenous dsRNA, (**C**) Systemic impact: development, cancer, neurological function, and innate immune regulation. Created in BioRender. Zhang, Y. (2025) https://BioRender.com/ihoud9l.

allow translation of a complete downstream protein, which is one focus of current ADAR editing technologies.

ADAR binding and editing is mostly dependent on structure. They preferentially bind to A-form dsRNA with a few "bulges" caused by base pair mismatches [24, 75]. This conformation best facilitates ADAR editing at adenosine-cytidine mismatched bases [8, 130, 131]. Beyond changing single amino acids, A to I editing can also impact splicing by modifying splice donor and acceptor sites, causing the machinery to utilize specific splice sites and helping determine the final isoform of a protein (Fig. 2B) [14, 104, 132]. While this effect can be due to direct editing of splice sites, it is more commonly the result of RNA editing of *trans*-acting factors, which allows for a broader influence [132]. For example, RNA processing genes and splicing related genes, such as *HNRNPR*, are themselves significantly enriched in genes that are differentially spliced upon ADAR knockout [132]. Even without editing, ADARs have the potential to modulate expression patterns and protein function by sequestering RNA regions and competitively inhibiting spliceosome proteins (Fig. 2A and B). This effect has notably been shown with regard to splicing modulation as ADAR binding can preclude U2AF65 access to 3′ splice sites [104]. The reverse can also be true as SRSF9 is known to inhibit ADAR2 dimerization and activity by competitively binding near editing sites [133, 134].

Although ADAR's protein–protein interactions are less well characterized, it tends to interact with other RBPs such as ILF3, HuR, and Dicer, as previously mentioned [4, 44, 92]. Understanding how ADAR interacts directly with other proteins, particularly in the context of dsRNA, is critical to elucidating the full spectrum of its functions, especially if it is to be used therapeutically, whether delivered exogenously or recruited endogenously. Any mechanism in which ADAR abundance or activity is increased, whether locally or ubiquitously, may have compounding biological impacts that must be thoroughly explored. Expanding ADAR technology to utilize all of its native functionality (Fig. 2A and B) opens the door to innumerable possibilities.

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RNA editing technology using ADARs

Current technology platforms that utilize ADARs for site-directed RNA editing typically consist of two common components: a programmable, sequence-specific "guide" and a catalytic "ADAR effector" (Fig. 3A). The guide RNA base pairs with the endogenous RNA of interest, creating a stabilized, ADAR-editable dsRNA region, where successful ADAR recruitment will result in the desired RNA editing event [24]. Selection and design of these components offer critical choices and determine the on-target effectiveness as well as potential off-target effects. Guides may include RNA aptamers that recruit exogenously delivered ADARs or have deaminase domains fused to corresponding aptamer binding proteins or RNA-targeting CRISPR–Cas systems [135]. The guide sequence selection is critical as the target must be able to specifically and stably pair with an accessible region of mRNA.

Guide design and optimization

Guides are programmable molecules that direct ADAR effectors to the target RNA substrate. The majority of reported guides are RNAs or RNA-loaded ribonucleoproteins (RNPs) such as Cas13b and CasRx [24, 136–143]. By reprogramming its sequence, the guide RNA is directed to bind a specific RNA substrate via base pairing. The guide-target hybridization forms the dsRNA product required for ADAR activity. Multivalent binding and RNP loading have been implemented to enhance the search kinetics of guide-target binding (Fig. 3B) [136–138, 144]. Specifically, RNP loading has been hypothesized to protect guide RNAs and facilitate their diffusion process in search of the targets, similar to the behaviors of Ago2 and Cas9 [145, 146]. Circularization and chemical modifications significantly improve the stability of guide RNAs and hence editing yields [25, 142, 147–150]. While not as common, protein-based guides have also been attempted, leveraging the motif-to-base pairing between Pumilio and FBF homology (PUF) proteins and RNAs [151].

With a guide bound to the intended RNA substrate, ADAR effectors are needed to perform base conversion. Strategies differ for exogenous and endogenous ADAR effectors since the former can be extensively modified. Engineered exogenous ADAR effectors can be directly coupled to the guide component via genetic fusion, covalent conjugation, or hairpin-based *trans* tethering (Fig. 3D) [24, 135–138, 152–155]. Endogenous ADAR effectors, on the other hand, rely on dsRNA formation for recruitment. The dsRNA product formed between long (>70 nt) guide and target RNA is sufficient for endogenous ADAR recruitment [24], while shorter (<20 nt) guide oligonucleotides require a natural, highly active ADAR substrate motif, such as the GluR2 hairpin, to enable efficient ADAR enlistment (Fig. 3B) [25].

Directing ADAR effectors to the target RNA molecule is insufficient for precise editing. Without base-level specificity, off-target "bystander" editing can happen in the vicinity of the desired site, especially within the dsRNA structure formed by guide and target RNAs. Conveniently, the editing activity of ADARs is largely dictated by the identity of the counter-base (on the guide) opposite the target adenosine: a cytidine or N-3-uridine counter-base triggers editing, while a counter-base that is unmodified guanosine, that is 2′-*O*-methylated, or that is deleted suppresses editing [130, 143, 147–149, 154, 156, 157]. Utilizing this preference, we can achieve single-base precision by positioning editing-favoring counter-bases at desired editing sites and editing-suppressing bulges or counter-bases at potential bystander sites (Fig. 3B) [142, 143, 147]. Previous work with a cytidine counter base has shown low (∼1%), yet statistically significant bystander editing [158]. However, off-target suppression with guanosine or depleted counter-bases often drastically decreases on-target editing by reducing substrate favorability as a whole [147, 148]. Additionally, interspersed loops along the dsRNA can reduce off-target events while preserving on-target efficiency [147, 159]. Alternatively, a recent report showed that strategically positioned G·U wobble bases in the guide could suppress bystander editing more effectively than complete counter-base mismatches without sacrificing on-target efficiency [148].

ADAR effector engineering and engagement

All active ADAR isoforms can catalyze editing with comparable efficiencies when overexpressed [142]. For exogenous ADAR effectors that are directly tethered to the guide, deaminase domains from both ADAR1 and ADAR2 have been used [136, 154]. The hyperactive E > Q mutants (ADAR1^{E1008Q} or ADAR2^{E488Q}) increase the base-flipping capabilities of ADARs and are usually incorporated to enhance editing efficiency [160, 161]. Other modifications can be introduced to improve or alter effector activity. For example, the additional T375G mutation in ADAR2^{E488Q} can significantly reduce both local and transcriptome-wide off-targets while preserving efficient—albeit reduced—on-target activity [136]. Alternatively, reconstituting halves of a split ADAR effector at the target site can reduce transcriptome-wide off-targets by >1000-fold [152]. ADAR2 has also been rationally evolved into a cytosine deaminase capable of both A-to-I and C-to-U conversions (Fig. 3C) [137]. Further attempts to reduce off-target editing include development of a photoactivatable system and fusion of an ADAR inhibitor [162, 163].

Despite the remarkable editing efficiency from ectopic overexpression of ADAR, the utility of exogenous ADAR effectors is critically hampered by its delivery burden *in vivo*, prominent off-target effects, and potential immunogenicity associated with its delivery and targeting mechanisms, such as viral capsids and MS2 coat proteins [136, 164]. Thus, recruiting endogenous ADAR effectors that are ubiquitous in human tissues is the preferred therapeutic alternative to reduce unintended effects. A handful of platforms have achieved meaningful editing outcomes by recruiting native ADAR effectors with highly engineered guides [25, 142–144, 147, 148, 150, 165]. Endogenous ADAR1, particularly the weakly expressed p150 isoform, appears predominantly responsible for guide-directed editing in most cells [25, 150]. A few strategies have been proposed to enhance the editing outcome by endogenous ADARs. IFN-α treatment induces robust p150 expression and significantly improves editing; however, can lead to side effects of its own [25]. Alternatively, "AIMer" oligonucleotides with chemically optimized stereopure backbones can elicit robust endogenous p110-mediated editing largely independent of p150, circumventing the need for immune stimulation [150]. In terms of *trans* regulators, genome-wide screens have identified DSS1/SHFM1, hnRNP A2/B1, and one 3′ UTR as enhancers of editing and helicase DDX39B as a suppressor [166, 167]. These factors may be leveraged to fine-tune the activity of endogenous ADARs.

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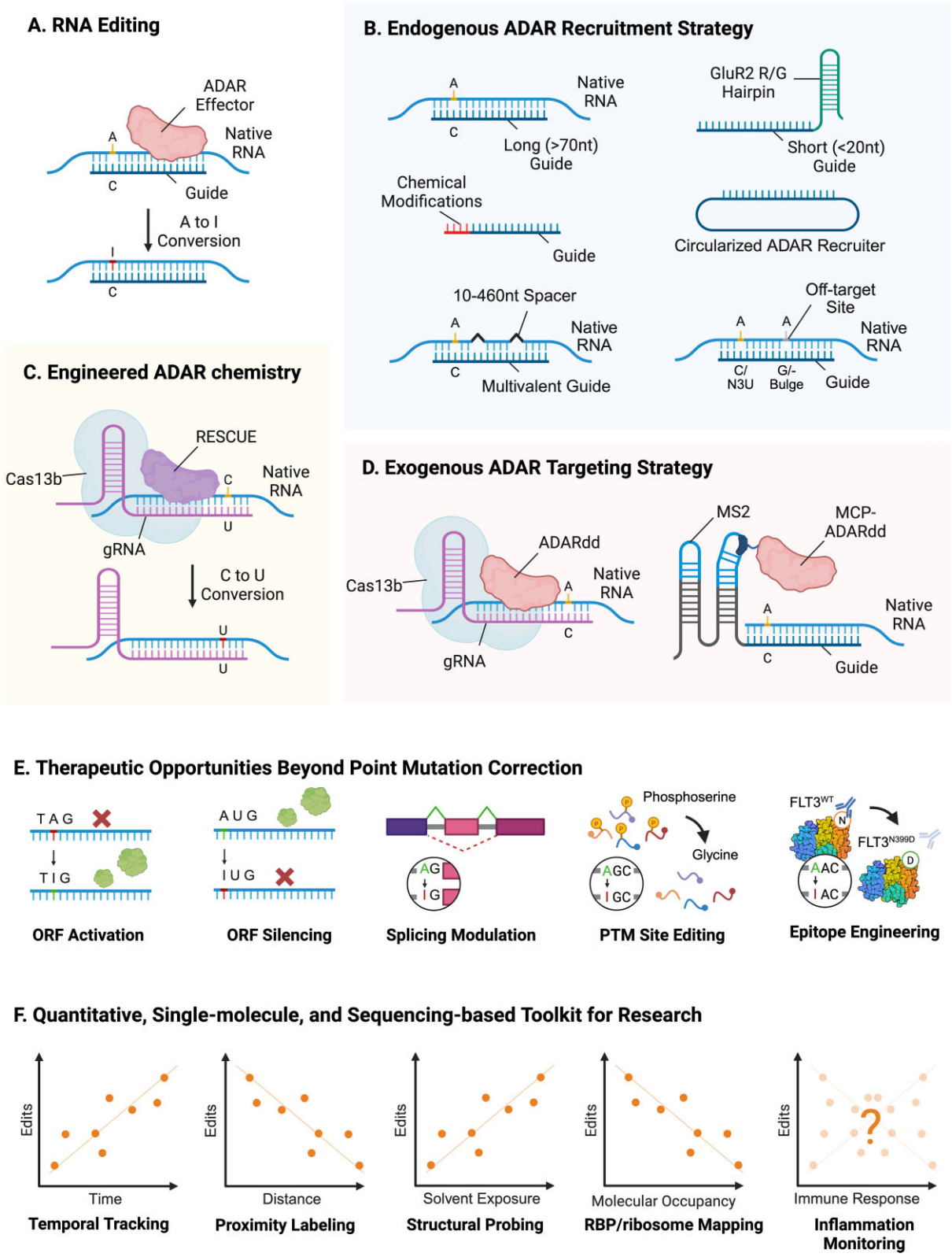

Figure 3. ADAR-based technologies. (**A**) Basic design of ADAR-based site-directed RNA editing typically consists of two standard components: a programmable, sequence-specific "guide" and a catalytic "ADAR effector." (**B**) Strategies for recruiting endogenous ADAR effectors. (**C**) Exogenously supplemented ADAR effectors can be evolved or intelligently engineered. (**D**) Methods for directing exogenous effectors to the target site. (**E**) Vast therapeutic space exists beyond point mutation correction. (**F**) ADARs and RNAs are ideal agents for writing and storing biological information in quantitative, single-molecule formats retrievable by next-generation sequencing (NGS). Created in BioRender. Zhang, Y. (2025) https://BioRender.com/ihoud9l.

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Therapeutic opportunities

Point mutation correction

The most intuitive application for site-directed RNA editing is to correct pathogenic G > A point mutations. To date, more than 23,000 pathogenic G > A mutations have been reported in ClinVar, accounting for 24.4% of all reported pathogenic point mutations [168]. In light of safety concerns around DNA editing, RNA editing platforms, particularly those utilizing endogenous ADARs, offer an appealing alternative owing to their high precision, low immunogenicity, temporal reversibility, and tunable dose dependency [169–172, 33, 173]. They have been employed to correct nonsense and missense G > A mutations in several preclinical animal models for Hurler syndrome, Rett syndrome, Duchenne muscular dystrophy, α1-antitrypsin deficiency, and cholestatic diseases [24, 142, 147, 150, 174–176]. Excitingly, the first-ever clinical trial of RNA editing in humans, adopting the chemically modified AIMer platform, has reported positive outcomes in treating α1-antitrypsin deficiency [177–179]. Several other ADAR-based editors anticipated to enter the clinical pipeline are lining up to treat both rare and common diseases [180].

While ADARs have been leveraged to restore protein expression by repairing pathogenic nonsense and splicing-altering mutations, we can repurpose ADAR editing to disrupt the translation of pathological proteins as well (Fig. 3E) [24, 142, 147]. ADAR-catalyzed A-to-I conversion is sufficient to induce mis-splicing, remove start codons, or install upstream start codons, all of which can disrupt the original open reading frame. Although stop codon installation is not directly accessible with ADAR chemistry, it is possible with engineered ADAR effectors or as a byproduct of frame disruption [137]. Premature stop codons may decrease transcript abundance via nonsense-mediated decay, potentially beneficial for conditions involving both protein and RNA toxicities [181–184].

Conditional expression

Vast therapeutic opportunity also exists beyond point mutation correction (Fig. 3E). Several groups have designed mRNAs whose translation is conditional upon endogenous transcript sensing [131, 158, 164, 185, 186]. In most of these systems, native transcripts serve as the guide RNA to hybridize to the programmable region of the sensor and enable the ADAR editing of a premature stop codon placed upstream of the cargo into a sense codon, thereby licensing payload expression. When customized to sense cell-type-specific transcripts, such designs offer a universal strategy for restricting therapeutic protein expression to defined cell populations, both spatially and temporally. Beyond transcript sensing, a recent aptamer-containing hairpin design enables protein and small molecule sensing via a toehold-like conformation switch upon molecular binding. The editing site is initially in a single-stranded region but enters an extended, stable double-stranded region upon the conformational shift [131]. While incredibly sensitive and highly inducible, the editing rates in these systems tend to be low, requiring exogenous engineered ADAR to function and currently limiting therapeutic relevance.

A major advantage of RNA-based systems for controlled expression is their transient manner, which can express a desired protein without integrating into the genome. While techniques can be employed to extend the RNA half-life, it will eventually be degraded. Most genes are highly regulated as they will cause disease if overexpressed or underexpressed, so this technology offers the opportunity to express a protein of interest in specific cellular contexts without risking permanent, pathological overexpression [187]. This offers the potential to deploy powerful but non-native proteins like Cas9 and reprogramming factors *in vivo*, limiting expression to specific tissues or cell states. Additionally, RNA-based systems for expressional control circumvent the issue of constant, potentially immunogenic foreign protein expression utilized by systems such as Tet-ON [188, 189].

Modifying protein function

ADARs can perform non-synonymous codon transitions that mutate amino acid identities, many representing significant changes in chemical properties. This allows us to modulate protein activities by introducing certain gain- or loss-of-function amino acid variants. For example, many amino acid residues available for post-translational modifications, including heavily modified lysine and all common phosphorylation sites (tyrosine, threonine, and serine), can be mutated by ADARs into unmodifiable residues (Fig. 1C) [155]. Intermolecular, protein–protein interactions could also potentially be modulated with ADAR-enabled residue substitution. For instance, ADARs can mutate asparagines into aspartic acids, which is the single mutation needed in FMS-like tyrosine kinase 3 (FLT3) to abolish binding by its cognate monoclonal antibody and confer hematopoietic lineages with resistance to chimeric antigen receptor (CAR) T cells [190]. Besides non-synonymous conversions, exploring synonymous mutations that alter codon usage might be another avenue for fine-tuning protein activity and expression [191–193].

Another potential therapeutic path is the use of ADAR editing or binding to alter how mRNA is processed by other proteins. Utilizing guides to recruit ADAR and change splicing patterns of a target protein, preferentially producing one native isoform or introducing an artificial form, offers vast therapeutic potential [132]. Furthermore, ADAR's effects on transcript stability through HuR binding and RNA sequestration could be utilized to extend the life of target transcripts and increase downstream protein expression [44, 194].

Delivery challenges and opportunities

As with any gene therapy, *in vivo* delivery presents unique challenges and opportunities for improvement. The guide and effector components of programmable editing systems can be delivered as RNA or DNA. The effector may also be delivered as a protein, but a mixed modality adds complications [33]. The optimal delivery for ADAR based therapeutics is tissue-specific, robustly expressed, persistent, and reversible, the sum of which is yet to be achieved.

The current gold standard for RNA delivery is lipid nanoparticles, which have been proven safe and effective, but ongoing work on formulation and protein coating is improving efficiency and expanding targeting potential beyond the liver [195–197]. Polymer nanoparticles present another promising vehicle for RNA delivery due to increased stability and reproducibility; however, they can trigger an immune response and are less well characterized for this specific application [197, 198]. Lipid-polymer hybrids are being explored to combine the best of both systems and have shown improved stability and delivery [197]. As the majority of native editing occurs in the nucleus, nuclear delivery of the guide RNA in

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endogenous ADAR recruiting systems is usually desired. The IFN-induced cytosolic ADAR1 p150 isoform can be recruited but reliance on an immune response adds complexity [33].

Viral delivery vectors, namely adeno-associated viruses (AAVs), currently offer the most robust DNA-based delivery systems with widespread targeting and efficient transduction of many different cell types [199]. Work is ongoing to modify tropism beyond liver-dominant native serotypes as well as reducing immunogenicity from repeat dosing, and modified capsids have been found to efficiently target tissues of interest and cross the blood-brain barrier [200–203]. Delivery by AAV offers the benefit of long-term expression; however, this comes at the cost of tunability. There are many genetic switches in development to effectively control transgene expression but all are limited by adjustable range or systemic complexity [189, 204–206]. Many systems have already used circularized guide RNAs to increase editing efficiency and emerging circular RNA strategies for transgene expression offer the potential to express ADAR effectors transiently without requiring as frequent re-dosing [142, 147, 207]. Additional strategies to combine the delivery efficiency of viral systems with the low immunogenicity of non-viral delivery vectors are emerging in the form of virus-like particles, extracellular vesicles such as exosomes and microvesicles, and bacteriophages [208–211]. The viability and efficacy of *in vivo* applications of ADAR-mediated genetic therapies will improve in tandem with these delivery techniques.

Emerging toolkit for research

Beyond therapeutic use, ADAR editing possesses many attractive traits that make it a powerful and versatile toolkit in the laboratory. For genetic perturbations, RNA editing with endogenous ADAR can generate efficient editing comparable to state-of-the-art adenine base editors, yet with simpler and faster experimental schemes and significantly reduced off-targets [142, 147, 148, 212]. We anticipate ADAR editing will be particularly valuable for targeted mutagenesis and massively parallel screens in models where the toxicity, delivery burden, and off-target effects of DNA editors are of concern and where genomic mutations are undesired or impossible, potentially exploring homogeneously lethal mutations.

Circumventing laborious genomic engineering, ADAR-based molecular sensors allow facile, minimally perturbative tracking of dynamic events in living cells, animals, and plants [131, 158, 164, 185, 186]. They also enable targeted genetic manipulation in cell populations with defined molecular signatures when alternative targeting strategies, such as tissue-specific enhancers and viral tropism, are unavailable [185]. For example, an ADAR sensor has been developed to target *Ctip2*-positive neurons, while the tropism of natural AAVs is often too broad for such a molecularly fine-grained population and an enhancer element that can be used to target the same population is yet to be identified and validated [185]. These programmable platforms harbor the potential to greatly expand the arsenal for research pursuits where temporal dynamics and cell-type specificity are crucial. Additionally, these low-cost, low-effort platforms can empower research communities with limited resources, particularly those studying non-model organisms. The development of cell-type-specific enhancers and viruses is risky, costly, and laborious, even for global consortia studying major model organisms [213]. With the programmability of ADAR-based sensors and the wide availability of transcriptomic atlases at single-cell resolution, the sequence of a unique marker transcript is sufficient for specific expression. While NGS is often utilized to quantify off-target deamination, on-target editing can often be approximated with Sanger sequencing. Moreover, the availability of open-source algorithms, such as RADAR: RNA sensing using ADAR helps with the design of programmable components. We anticipate that the relatively low cost and ease of use will allow for a broad variety of research groups to use genome engineering and site-directed ADAR editing in their organism of choice.

The measurement of ADAR activity has evolved from its early days of radiolabeling and chromatography into its current state, where massively parallel, single-molecule sequencing is commonplace [214–219]. ADARs and RNAs are ideal agents for writing and storing biological information. Active and ubiquitous, ADARs leave behind lasting, easily retrievable footprints from each substrate encounter. There are tremendous opportunities in developing ADAR-based methods that provide quantitative, single-molecule, sequencing-based readouts for cellular history and molecular interactions (Fig. 3F). For example, by accumulating edits in the untranslated region of a transcript via site-directed editing, the age of single RNA molecules can be inferred retrospectively [220]. Recently, it has been shown that naturally occurring transcriptome-wide A-to-I editing is sufficient for recapitulating transcriptional history in single cells [221]. On the other hand, as its distance from the substrate increases, ADARs presumably would be less effective at installing edits. ADAR can be used as an RNA proximity-labeling enzyme similar to the protein-labeling TurboID [222]. By tethering hyperactive ADAR to a protein bait or localizing ADAR to an organelle, RNA species interacting with the protein bait or enriched in the organelle would be labeled with elevated A-to-I edits, as demonstrated in TRIBE and HyperTRIBE technologies [223–225]. Analogous to the protein-tracking TransitID [226], ADARs can potentially record ontological information in RNAs to investigate their spatial trafficking. Recently, a technology engineered ligand-induced proximity between ADAR and its RNA substrate to record and report ligand activities [227], highlighting how the spatial dependency of ADAR-substrate interaction can be harnessed. Additionally, as solvent accessibility and molecular occupancy of the edit site are reasonable determinants of ADAR editing efficiency, editing could reasonably be used to map the solvent-accessible surface of large RNA molecules and sites unoccupied by ribosomes and RBPs along mRNAs. Finally, ADAR activity is deeply involved in the regulation of innate immunity, which itself is modulated by a variety of factors [115, 228–230]. The dysregulation of ADAR editing has the promise to serve as a sensitive, quantitative proxy for global inflammation at the single-cell level over time and space [215].

Points of improvement

Despite tremendous progress in repurposing ADAR for therapeutic use, many challenges remain. Endogenous ADARs are only known to catalyze A-to-I conversions, and their efficiency depends highly on the sequence context [143, 148]. Additionally, many current technologies require exogenous ADAR or even the hyperactive ADAR1^{E1008Q} or ADAR2^{E488Q} forms to achieve meaningful editing. As previously delineated, overexpressed ADAR increases off-target editing and can even risk

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creating tumorigenic phenotypes by circumventing the natural immune response. Engineered ADAR-like effectors that enable novel chemical modifications, like RESCUE [137], and improved strategies to remove the contextual constraints would greatly expand the substitution space accessible by ADARs. In addition, our limited ability to deliver ADAR-based systems to the desired tissue [200, 231–234], compounded by the tissue [148] and cell type [143] variabilities of endogenous ADAR activities, restricts their therapeutic use. If these platforms are delivered systemically, but only intended to effect change in cells where their target is highly expressed, there needs to be a thorough characterization of what concentrations of target transcripts or small molecules are required to trigger the system. Simultaneously, any leakiness or background expression must be characterized and minimized. Accordingly, ADAR-based platforms currently need to carve out their niche in the clinic but will certainly benefit from improved delivery modalities. Finally, we need to define and monitor the long-term, *in vivo* efficacy and safety profile of ADAR therapeutics, especially those involving exogenous effectors.

Conclusions and outlook

Since the discovery of ADAR in the 1980s [1], we have made considerable progress in learning its functions and mechanisms, elucidating its involvement in pathology, and leveraging it for both therapy and research. Simple, precise, efficient, and reversible, ADAR-based platforms occupy a unique niche and hold tremendous promise in the era of precision medicine, as evidenced by its recent clinical trial [177–179]. We are just beginning to envision enabling creative repurposing of ADARs beyond point mutation correction. At the same time, room for improvement exists regarding efficiency, specificity, targeting scope, and delivery modalities. We also see great potential of ADAR-based methods for programmable manipulation and quantitative measurement in the laboratory, for which ingenuity and significant development efforts are still needed. Exciting discoveries and technological advances await as our understanding of ADAR biology and the rules that govern RNA editing grows.

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Conflict of interest

P.M. is a scientific co-founder of Shape Therapeutics, Boundless Biosciences, Navega Therapeutics, Pi Bio, and Engine Biosciences. The terms of these arrangements have been reviewed and approved by the University of California San Diego in accordance with its conflict of interest policies.

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Data availability

No new data were generated or analysed in support of this research.

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