# RNA EDITING IN PATHOGENESIS OF CANCER

**Bora E. Baysal[1*], Shraddha Sharma[1], Seyedsasan Hashemikhabir[2], Sarath Chandra Janga[2,3,4]**

[1]Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY 14263 and
[2]School of Informatics and Computing, Indiana University Purdue University, 719 Indiana Ave Ste 319, Walker Plaza Building, Indianapolis, Indiana 46202
[3]Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, 5021 Health Information and Translational Sciences (HITS), 410 West 10th Street, Indianapolis, Indiana, 46202
[4]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Medical Research and Library Building, 975 West Walnut Street, Indianapolis, Indiana, 46202

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*To whom correspondence should be addressed: Dr. Bora E. Baysal
Department of Pathology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, New York 14261, USA. Phone: +1-716-845-3204 Fax: +1-716-845-3427 E-mail: bora.baysal@roswellpark.org

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**ABSTRACT**

Several adenosine or cytidine deaminase enzymes deaminate transcript sequences in a cell type or environment-dependent manner by a programmed process called RNA editing. RNA editing enzymes catalyze A>I or C>U transcript alterations and have the potential to change protein coding sequences. In this brief review, we highlight some recent work which shows aberrant patterns of RNA editing in cancer. Transcriptome sequencing studies reveal increased or decreased global RNA editing levels depending on the tumor type. Altered RNA editing in cancer cells may provide a selective advantage for tumor growth and resistance to apoptosis. RNA editing may promote cancer by dynamically recoding oncogenic genes, regulating oncogenic gene expression by noncoding RNA and miRNA editing, or by transcriptome scale changes in RNA editing levels which may affect innate immune signaling. Although RNA editing markedly increases complexity of the cancer cell transcriptomes, cancer-specific recoding RNA editing events have yet to be discovered. Epitranscriptomic changes by RNA editing in cancer represent a novel mechanism contributing to sequence diversity independently of DNA mutations. Therefore, RNA editing studies should complement genome sequence data to understand the full impact of nucleic acid sequence alterations in cancer.

## Introduction

The central dogma of biology refers to the faithful transmission of genetic information from DNA to RNA and from RNA to protein. This dogma underlies the rationale to examine the genome to understand pathogenesis of human diseases especially cancer. Abundant data now show that DNA mutations are fundamental to cancer initiation and progression (1). Whereas genetic linkage based approaches in rare cancer-prone families have identified many classical tumor suppressor genes, recent high throughput sequence analyses of cancer genomes showed somatic mutations driving the neoplastic process (2). Recent studies also show that enzymatic alterations in RNA sequences, without any corresponding mutation at the DNA level, can also contribute to pathogenesis of cancer (3-7).

RNA editing refers to programmed alterations in transcripts catalyzed by adenosine or cytidine deaminating enzymes, and benefits the organism by allowing cell-type specific, developmentally-regulated or environmentally-induced expression of protein isoforms (8, 9). RNA editing alters adenine to inosine (A>I) and cytosine to uracil (C>U) by adenosine and cytidine deaminases, respectively. These base transitions at the transcript level can lead to missense (by A>I and C>U editing) or nonsense (by C>U editing) protein alterations. Recent sequencing studies highlight that cancer cell transcriptomes are more complex than their genomes in part due to widespread RNA editing (4-7). Since levels of RNA editing may dynamically change by micro-environmental factors or during tumor progression, and that edited transcripts have a limited life span, the functional impact of RNA editing on cancer cells will be different than those of permanent DNA mutations. Here, we provide a brief overview of the known RNA editing enzymes and highlight some recent studies on the role of RNA editing in cancer.

## RNA editing by ADARs

A>I RNA editing is catalyzed by the ubiquitously expressed ADAR (ADAR1) and ADARB1 (ADAR2) adenosine deaminase enzymes (Table 1) (8). ADARB2 (ADAR3) enzyme is considered catalytically inactive. Full length ADAR1p150 and amino terminal

truncated ADAR1p110 isoforms of ADAR are transcribed by alternative promoter usage. Except for ADARp150, an interferon-inducible isoform which can accumulate in the cytoplasm, all other ADARs are localized to the nucleus. ADARs catalyze site-specific RNA editing in short imperfect RNA duplexes, whereas hyperediting that involves many adenosines occurs in long perfect RNA duplexes. Majority of ADAR-mediated RNA editing events in long duplex RNAs occurs in the 3'-UTR and 5'-UTR of mRNAs and in introns, especially in the context of Alu sequences. Noncoding edited sites may play roles in the regulation of splicing, gene expression and miRNA binding (10). In addition, RNA editing by ADAR recodes mRNAs of several genes including *NEIL1* (11), *BLCAP*, *FLNA* (12) and *NARF* (13).

Site-specific A>I RNA editing events that alter the amino acid code by missense substitutions occurs only in a handful of genes, which are often involved in neurotransmission in brain. For example, ADARB1 edits *GluR-B* mRNA leading to near 100% change from the germ line encoded glutamine at amino acid 607 to arginine at the mRNA level. This change significantly alters the AMPA receptor neurotransmitter function. Loss of this editing in *Adarb1*-/- mice leads to lethal seizures shortly after birth (14). In contrast, loss of *Adar* gene leads to early embryonic lethality via defective hematopoietic stem cells, increased activation of interferon signaling and apoptosis (15), although the identity of the edited RNAs involved is unknown.

Recently germ line mutations in *ADAR* were identified in the autoimmune disorder Aicardi-Goutières syndrome (AGS) (16). *ADAR* mutations in AGS and *Adar*-/- mice upregulate interferon type I (IFN1) regulated genes. AGS is a genetically heterogeneous Mendelian disease caused by mutations in several genes involved in nucleic acid metabolism and is characterized by early onset progressive brain disease, certain skin lesions, glaucoma and, in some cases, features resembling systemic lupus erythematosus (17). Upregulation of IFN1 signaling pathway by *ADAR* mutations suggests that the editing activity of ADAR is required to block activation of innate immune signaling. It is thought that the lack of ADAR-mediated RNA editing in double stranded RNAs

stimulates cytosolic RNA sensing by MDA5-MAVS pathways, which are normally blocked by mismatched I-U base pairs (18, 19).

**RNA editing by APOBECs**

C>U RNA editing catalyzed by the APOBEC cytidine deaminases is significantly less common than A>I editing in baseline transcriptome sequencing studies. The prototype of cytidine deaminases that edit RNA is the APOBEC1 enzyme. APOBEC1 site-specifically edits mRNA of the *APOB* gene to introduce a premature stop codon enabling intestinal cells to produce a short protein isoform of Apo B (20). Recent transcriptome sequencing studies identified additional RNA editing sites of APOBEC1, mostly in the 3'-UTRs (21, 22). APOBEC1 was the only C>U RNA editing enzyme known until the discovery of APOBEC3A (A3A) (23). A3A differs from other RNA editing enzymes in that its editing function is observed only after induction by certain stimulations in monocytes and macrophages or by exogenous overexpression in 293T cells (24). Hypoxia (1% $O_2$) or IFN1 in primary peripheral blood monocytes or IFN1 in monocyte-derived macrophages induce widespread site-specific RNA editing by A3A. In monocytes, hypoxia and IFN1 additively increases RNA editing levels which leads to recoding of over 80% of transcripts of certain genes. In contrast to ADARs, most RNA editing by A3A is highly site-specific and targets the coding regions of genes, often resulting in missense/nonsense alterations.

Whether other APOBECs, including APOBEC2, A3B, A3C, A3DE, A3F, A3G, A3H and APOBEC4, also edit cellular RNAs under certain physiological circumstances is unknown. Although deamination of viral genetic materials or cancer genome by some APOBEC3s was observed (25), cytidine deaminase activity of these enzymes under non-infectious, non-neoplastic physiological conditions has not yet been demonstrated. We recently described that transient overexpression of A3G in HEK293T cells also induces C>U RNA editing of distinct cellular transcripts (26). Although physiological function of RNA editing by A3A and A3G is unknown, the targeting of hundreds of cellular RNAs raises the possibility that aberrant activation of APOBECs, by overexpression, hypoxia or inhibition of mitochondrial respiration (27), may contribute to transcriptome-level

mutations in cancer cells. Since certain hypermutations in cancer genome have been attributed to A3A (28, 29), it is conceivable that A3A may also mediate RNA editing of cancer related genes. We have shown that overexpression of A3A in 293T cells causes missense mRNA alterations in tumor associated genes *ATM, BARD1, BRCA1, BRCA2, BRIP1, MDM2, KMT2A, MSH2, PTEN, SF3B1* and *TSC2* (24). The mechanism by which A3A is expressed in cancer cells to cause genome mutations is uncertain, since A3A expression is largely confined to myeloid cells. Perhaps, epigenetic alterations in cancer lead to aberrant expression of A3A. Alternatively, A3A RNA or protein may be physically transferred from myeloid cells to cancer cells through exosomes or by cell fusion (30). A3A-mediated RNA editing may also be induced in myeloid cells of tumor microenvironment (e.g. macrophages, myeloid derived suppressor cells) in hypoxic or inflammatory conditions, and affect tumor progression by altering the immunologic milieu (31).

**Altered RNA editing in cancer**

*Recoding RNA editing in cancer*

RNA editing has been linked to tumorigenesis by either site-specific editing of tumor promoting genes or by transcriptome-scale changes in RNA editing levels.

A>I RNA editing of *AZIN1*, which encodes an antizyme inhibitor, causes S367G amino acid substitution. RNA editing level of *AZIN1* increases by at least 10% in hepatocellular carcinoma compared to normal unaffected liver (3). This editing generates an isoform with increased affinity to antizyme, promoting cell proliferation by reducing antizyme-mediated degradation of ornithine decarboxylase and cyclin D1. Site-specific A>I RNA editing of transcription factor PROX1 causes several missense alterations including E328G, R334G and H536R in a small number of esophageal, pancreatic and colon cancer samples, but no such editing is seen in a number of cDNA libraries of many normal tissues (32). By comparing the genome/transcriptome sequences, recoding A>I RNA editing, causing N136S amino acid change in *RHOQ* is found in colorectal cancer (33). This editing increases RhoQ GTPase enzyme activity, cancer invasion potential and recurrence of colorectal cancer when present in the tumor. Increased recoding (M2269V)

RNA editing of filamin B gene (*FLNB*) is noted in hepatocellular (34) and esophageal squamous cell carcinomas (35). Increased recoding RNA editing of DNA repair enzyme NEIL1 (K242R) is identified in non-small-cell lung cancer samples as a result of *ADAR* gene amplification (36). A rare example of C>U RNA editing in cancer involves the neurofibromatosis type I gene (*NF1*) mRNA editing that introduces a nonsense mutation in subset of peripheral nerve–sheath tumors (37-39).

Reduced recoding RNA editing has also been observed in several tumors. For instance, RNA editing of *GluR-B* also causes R701G substitution in normal cerebellum and skin but it is markedly reduced in medulloblastoma cell lines and basal cell carcinoma samples (40). *GluR-B* Q607R editing is substantially lower in malignant gliomas which have reduced expression of the ADARB1 enzyme (41). In gastric cancer, oncogenic activity is promoted by the loss of *ADARB1* which normally mediates recoding RNA editing H241R in *PODXL* to eliminate tumor promoting function of the wild type gene (42). Chen et al (43) suggested that RNA editing enables proapoptotic function of IGFBP7, the loss of which may promote tumorigenesis in esophageal squamous cell carcinoma. The chloride receptor *Gabra3* transcripts undergo recoding editing in the brain (44). Reduced RNA editing of *GABRA3* in breast cancer is suggested to promote tumor progression, invasion and metastatic potential (45).

*Noncoding RNA editing in cancer*

Noncoding RNA editing is also suggested to promote tumorigenesis. In CD34+/CD117+ myeloblasts of acute myeloid leukemia, transcripts of *PTPN6,* which encodes SH2 domain-containing tyrosine phosphatase, were found to retain an intron as a result of multiple A>I RNA editing events mainly at the intronic putative branch site (46). Such editing occurred at lower levels in remission blasts suggesting a link between editing and leukomogenesis. MicroRNAs are small noncoding RNAs that play an important role in post-transcriptional gene regulation by silencing gene expression. RNA editing of miRNAs can alter these regulatory functions of miRNAs. Several studies have suggested that altered RNA editing of miRNAs or miRNA binding sites promote tumorigenesis. Increased ADAR-mediated RNA editing of stem cell regulatory let-7 micro-RNAs may

enhance leukemic self-renewal and contribute to blast crisis in CML (47). In contrast, decreased RNA editing of miR-455-5p in melanoma enables downregulation of tumor suppressor CPEB1 and promotes tumor progression (48). Increased RNA editing of miR-381, which is involved in stemness and chemoresistance is observed in non-small-cell lung cancer (36). Zhang et al (7) suggested that RNA editing at miRNA binding sites at 3'-UTR of gene transcripts may play an important role in suppressing the expression of tumor suppressor genes or increasing the expression of oncogenes. This study showed that increased RNA editing at miRNA binding sites at 3'-UTR of *MDM2* increases the protein levels of MDM2 which is a negative regulator of p53 protein and is known to be elevated in many cancer types.

*Transcriptome scale analysis of RNA editing events in cancer*

Development of high throughput sequencing and analysis techniques has enabled researchers to analyze transcriptome-scale RNA editing events in cancer. These studies reveal unanticipated heterogeneity of the cancer transcriptome, conferred largely due to A>I RNA editing. The first genome scale analysis of RNA editing in cancer examined sequences of expressed sequence tags in normal and neoplastic tissues, and found hypoediting of Alu repetitive elements in brain, prostate, lung, kidney, and testis tumors (49). More recently, several groups examined the high throughput cancer RNA sequencing data, mostly from The Cancer Genome Atlas (TCGA) database, to determine the frequency of RNA editing in various neoplasms. Han et al (4) analyzed 17 cancer types and found abundant A>I editing, mostly in intronic, intergenic regions and in 3'-UTR. They found increased global editing levels in breast tumors, as well as in head/neck squamous cell, thyroid, lung adenocarcinoma, bladder, kidney renal cell carcinomas. Decreased global editing levels were seen in kidney chromophobe, and renal papillary carcinoma. No difference in editing levels was seen in prostate, lung squamous, liver, stomach adenocarcinoma compared to the normal tissues. Interestingly, they found a positive correlation between global RNA editing levels with ADAR, but not with ADARB1/ADARB2 expression. In all tumors, editing levels in most sites were similar between normal control tissues and their cancer counterpart. For example, only 16.7% of all edited sites showed increased editing levels in BRCA and 19.3% of all edited sites

showed decreased levels in kidney chromophobe cell cancer. Only several dozen nonsynonymous editing sites were identified. Correlations with one or more clinical outcomes (tumor subtype, stage and survival) were detected for S367G in *AZIN1*, I164V in *COPA*, I635V in *COG3*, R764G in *GRIA2*, T262A in *ACBD4*, S59G in *PPIL3*, Q5R in *BLCAP* and H241R in *PODXL*. Edited gene variants in *AZIN1*, *GRIA2* and *COG3* increased cell viability in MCF10A (normal human breast epithelium cell line) and Ba/F3 (a murine leukemia cell line) cells.

Paz-Yaacov (5) showed increased A>I RNA editing levels (>5%) in most cancer types, largely at Alu sites, but also at 60 recoding sites. Lower editing levels correlated with a better survival in hepatocellular and head/neck carcinoma cases. Authors suggested that mutation load contributed by RNA editing may be more than those contributed by DNA mutations. Fumagalli et al (6) showed that the same sites are edited in primary breast cancer, normal breast tissue and breast cancer cell lines. However, higher frequency of editing is observed in tumor tissues as compared to normal and correlates positively with higher ADAR expression. Editing was mostly confined to Alu sites.

Zhang et al (7) showed widespread A>I RNA editing events in cancer but they were not specific to a certain cancer type and were present in all tissues including normal controls. They identified 166 differentially edited genes between normal and tumor tissues. Smallest number (n=11) of differentially edited genes occurred in esophageal carcinoma, largest (n=62) in breast adenocarcinoma. They confirmed increased editing levels of *AZIN1* and decreased levels in *IGFBP7* in most tumor types. The authors did not find a strong correlation between editing levels and ADAR expression levels, and suggested that RNA editing of 3'-UTR miRNA binding sites may strongly influence expression levels of tumor promoting or suppressor genes.

Transcriptome sequencing studies in different cancer types are summarized in Supplementary Table 1. Although ADAR is the primary mediator of the A-to-I RNA editing events, there is no strong consensus on how to explain the editing efficacy of the events by correlation analysis against ADAR expression profiles. RNA editing efficacy

is generally defined by the frequency of editing events or the extent of editing. Several studies reported that frequency of editing events is correlated with ADAR expression levels (4), however, others also show that editing levels might not be directly associated with the ADAR expression profiles (7). This might suggest an alternative editing mediator (e.g. ADARB1) is activated to regulate the editing mechanism. In general, majority of the events have low editing levels and consequently it is often difficult to make a confident estimation when the sequencing depth is low. Increasing the sequencing depth might contribute to identifying the true positive hits and could improve the correlation of editing levels and ADAR expression profiles or better able to address the inconsistencies reported in the literature. We obtained reported gene expression profiles based on RNA-sequencing for the cancer types with at least five normal samples, from The Cancer Genome Atlas (TCGA) project (https://portal.gdc.cancer.gov/). Comparing the distribution of expression levels for ADAR and ADARB1 between the tumor and normal samples for the selected cancers, fold change in their median expression levels and corresponding significance was calculated using Mann-Whitney U test (See Supplementary Table 1, Figure 1). Figure 1 organizes the cancer types based on reported editing levels in the literature (4-7, 42, 49, 50) for an easy comparison with the observed expression alterations for ADAR genes. Our analysis suggests that the increase in ADAR expression levels is correlated with the reported increases in editing levels in majority of the TCGA cancers. Extent of editing and ADAR expression levels are consistently increased in majority of the tumor types compared to the tissue matched normal samples, however, kidney cancers (i.e. Kidney Renal Clear Cell Carcinoma (KIRC), Kidney Renal Papillary Cell Carcinoma (KIRP) and Kidney Chromophobe (KICH)) exhibited low ADAR expression in agreement with the reported reduced editing levels (4, 5, 7). On the other hand, the change in ADARB1 expression did not appear to be associated with the corresponding reported changes in editing levels across cancers (See Figure 1).

**Summary and outlook**

Initial studies of RNA editing in cancer suggests that both genome and transcriptome sequencing studies are required to capture all sources of protein mutations in cancer.

Several patterns emerge from these initial studies. (a) Although RNA editing levels are altered in cancer, RNA editing does not appear to create new cancer-specific alterations since all sites edited in cancer are also edited in normal control tissues to some degree. Thus, cancer related changes in RNA editing appear to be in quantity rather than quality. (b) Most editing events detected to date occur in introns and 3'-UTRs. RNA editing in coding regions of genes are rare. (c) Tumor types show consistent patterns of increased or decreased RNA editing levels at the transcriptome scale. Despite these global patterns, editing levels change in the opposite direction at some edited sites in a given tumor type. For example, editing levels decrease in less than 10% of the edited sites in breast cancer, which overall show increased RNA editing levels. (d) Increase in editing levels in cancer often correlates with increased expression of the ADAR enzyme.

In summary, recent studies have revealed abundant A>I RNA editing events in cancer which have been linked to tumor development through altered protein function caused by missense mutations, disrupted regulation by intronic or noncoding RNAs such as miRNAs and global or dynamic changes in RNA editing levels (Figure 2). Despite these promising data, how critical protein recoding RNA editing events are for the initiation and progression of cancer as well as the significance of vast number of non-coding RNA editing events in cancer remains uncertain. Recent studies linking ADAR-mediated RNA editing to suppression of IFN1 signaling raise the possibility that increased global A>I RNA editing observed in several cancers may serve to antagonize activation of IFN1 responses which is known to be pro-apoptotic, anti-proliferative and anti-tumorigenic (51). The lack of cancer specific RNA editing events starkly contrasts with numerous somatic DNA mutations in hundreds of genes identified in cancer, and raises the question as to why recoding RNA editing variants implicated in cancer (e.g. *AZIN1*) do not occur at the DNA level. Perhaps, mutations advantageous for cancer cell in most microenvironments are hardwired in the DNA, whereas those advantageous only in certain stage or changing environments may be regulated by RNA editing. Therefore the advantage of RNA editing for cancer cell may be in its dynamic nature. Consequently, RNA sequencing of cancer cells in different stages, histologic grades or micro-environments may be required to identify the full compendium of fluctuating targets of

RNA editing. Such dynamic alterations may especially apply for C>U RNA editing by APOBEC3 enzymes since A3A-mediated RNA editing occurs only after hypoxia and/or IFN exposure. RNA editing represents an exciting new frontier in cancer research with the potential to discover a rich source of epitranscriptomic mutations elusive to DNA sequencing.

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**Table 1**

**RNA editing enzymes in humans**

| Enzyme (editing activity) | Function of RNA editing | Cell type where RNA editing occurs | Subcellular localization | Recoding RNA editing targets |
|---|---|---|---|---|
| ADAR (A>I) | Suppression of innate immunity and protein diversification | Many | Nuclear* | Several (e.g. *NEIL1*) |
| ADARB1 (A>I) | Protein diversification for normal neuronal signaling | Many, but mostly CNS cells | Nuclear | Several dozens (e.g. *GluR-B*) |
| ADARB2 (A>I) | Inactive (expressed in brain) | None | Nuclear | Unknown |
| APOBEC1 (C>U) | Apo B isoform (Apo B-48) production for absorption of dietary fat | Intestine, liver | Nuclear | *APOB* |
| APOBEC3A (C>U) | Protein diversification for unknown function | Monocytes and macrophages | Nuclear/cytoplasm | Hundreds to thousands |
| APOBEC3G (C>U) | Protein diversification for unknown function | Unknown | cytoplasm | Hundreds |

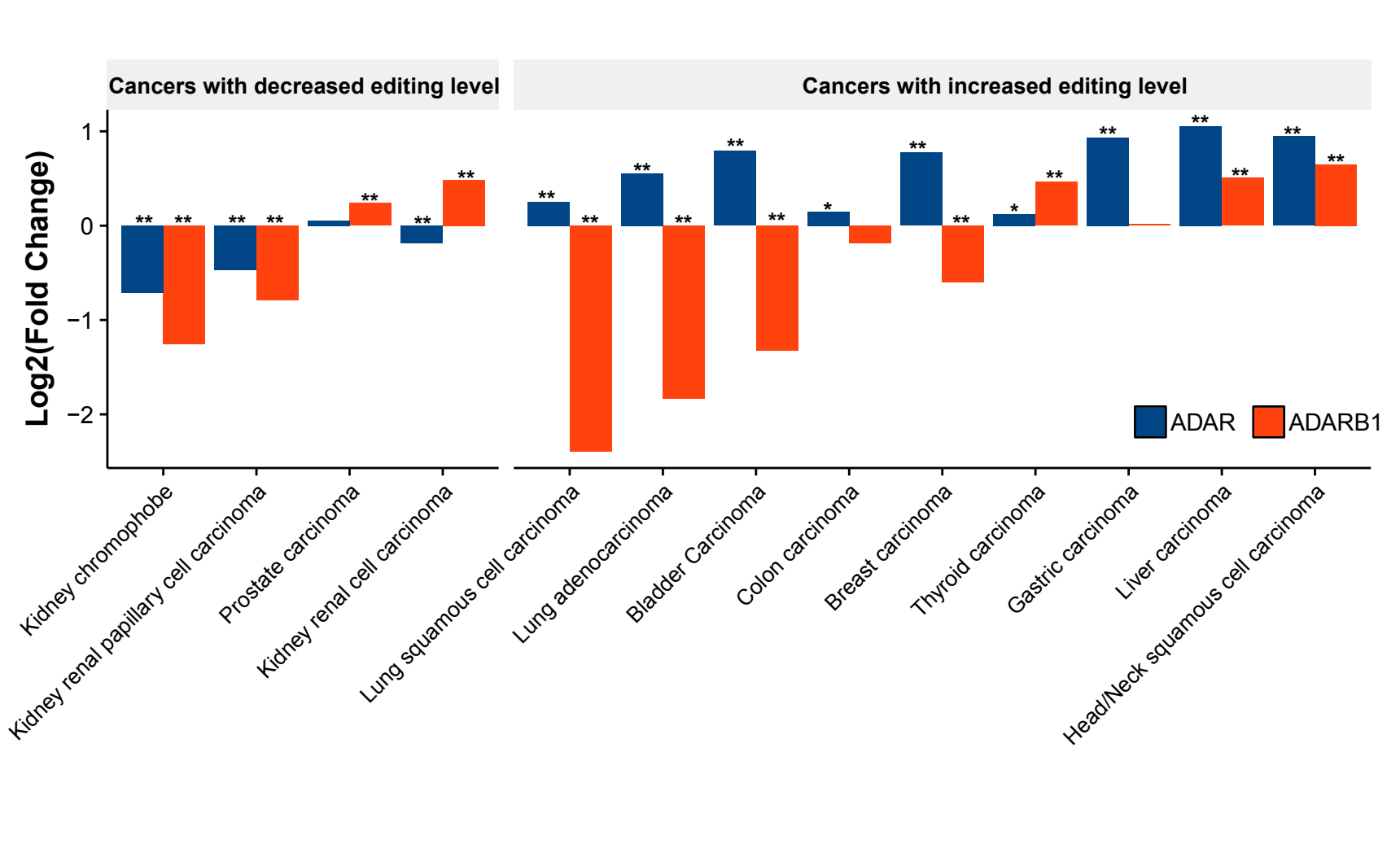
*ADARp150 isoform is localized to cytoplasm.

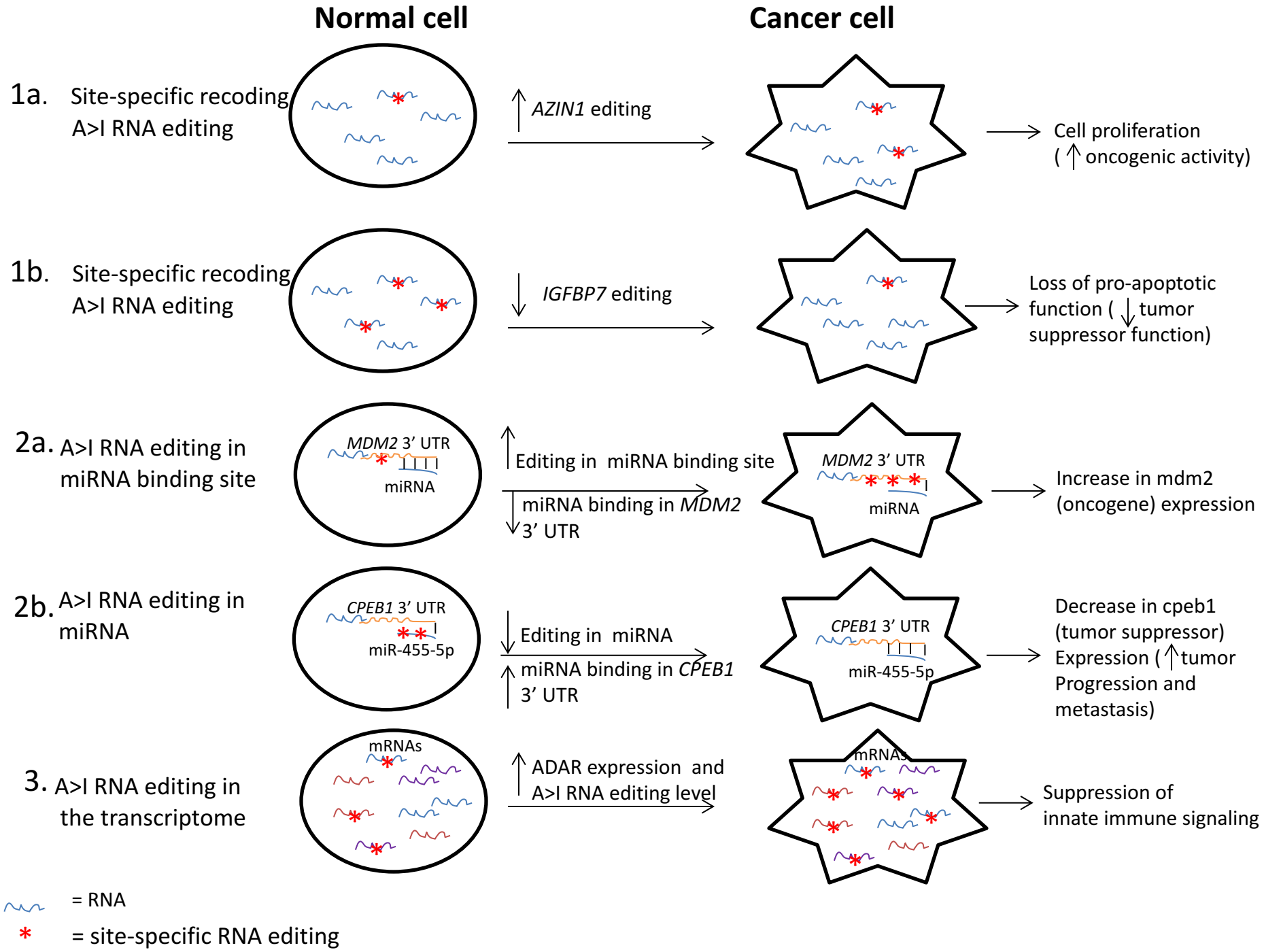
**Legend for Figure 1**

Histograms showing the fold change in median expression of ADAR and ADARB1 in a cancer type compared to normal samples. RNA-sequencing based gene expression profiles for ADARs were obtained for cancer types, with at least five normal samples from the same tissue, from the TCGA project (https://portal.gdc.cancer.gov/). Statistical significance was calculated using Mann-Whitney U-test comparing ADAR expression in normal and tumor samples (P-value; * <0.05, ** <0.01). Cancer types are organized based on reported editing levels in literature. Majority of the cancer types with increased extent of editing exhibited elevated ADAR1 expression in cancer compared to normal samples. Overedited sites outnumber underedited sites in kidney renal cell carcinoma (4,7), although global RNA editing levels are decreased (5).

**Legend for Figure 2**

Summary of various mechanisms through which RNA editing plays a role in the pathogenesis of cancer. (1) Increased or decreased recoding RNA editing can occur site-specifically in oncogenes or tumor suppressor genes (3,32-29). (2) Increased or decreased RNA editing occurs in miRNA binding sites or miRNAs, resulting in increased or decreased expression of oncogenes or tumor suppressor genes, respectively (7,36, 46-48). (3) Increased global RNA editing occurs in the transcriptome resulting in suppression of the innate immune signaling (4-6). (4) APOBEC3 mediated RNA editing occurs dynamically (23) which might result in increased mutational load in cancer cells.


Cancers with decreased editing level
Cancers with increased editing level
Log2(Fold Change)
1
0
−1
−2
ADAR
ADARB1
Kidney chromophobe
Kidney renal papillary cell carcinoma
Prostate carcinoma
Kidney renal cell carcinoma
Lung squamous cell carcinoma
Lung adenocarcinoma
Bladder Carcinoma
Colon carcinoma
Breast carcinoma
Thyroid carcinoma
Gastric carcinoma
Liver carcinoma
Head/Neck squamous cell carcinoma


Normal cell
Cancer cell
1a. Site-specific recoding A>I RNA editing
AZIN1 editing
Cell proliferation ( ↑ oncogenic activity)
1b. Site-specific recoding A>I RNA editing
IGFBP7 editing
Loss of pro-apoptotic function ( ↓ tumor suppressor function)
2a. A>I RNA editing in miRNA binding site
MDM2 3' UTR
miRNA
Editing in miRNA binding site
miRNA binding in MDM2 3' UTR
MDM2 3' UTR
miRNA
Increase in mdm2 (oncogene) expression
2b. A>I RNA editing in miRNA
CPEB1 3' UTR
miR-455-5p
Editing in miRNA
miRNA binding in CPEB1 3' UTR
CPEB1 3' UTR
miR-455-5p
Decrease in cpeb1 (tumor suppressor) Expression ( ↑ tumor Progression and metastasis)
3. A>I RNA editing in the transcriptome
mRNAs
ADAR expression and A>I RNA editing level
mRNAs
Suppression of innate immune signaling
= RNA
= site-specific RNA editing