Clinical Relevance of Noncoding Adenosine-to-Inosine RNA Editing in Multiple Human Cancers

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PURPOSE RNA editing is a post-transcriptional process that alters the nucleotide sequences of certain transcripts, in vertebrate most often converting adenosines to inosines. Multiple studies have recently implicated RNA editing in cancer development; however, most studies have focused on recoding RNA editing events. The function and clinical relevance of noncoding RNA (ncRNA) editing events in cancers have not been systematically examined.

PATIENTS AND METHODS We improved our previously published pipeline to identify ncRNA editing sites from four human cancers: liver hepatocellular carcinoma, lung adenocarcinoma, kidney renal clear-cell carcinoma, and thyroid carcinoma. We then developed multiple advanced statistical models to identify significantly differential edited (DE) sites between tumor and normal samples and clinical relevance ncRNA editing sites, as well as to investigate the association between gene expression, ncRNA editing, and microRNAs. Finally, we validated computational results with experiments.

RESULTS We identified 3,788 ncRNA editing sites of high confidence from the four cancers. We found thousands of DE sites which had distinct profiles across the four cancers. In kidney cancer, which had the largest uncensored survival data among the four cancers, 80 DE sites were significantly associated with patient survival. We identified 3' untranslated region (UTR) RNA editing sites that can affect gene expression, either independent of or by working with microRNAs. We validated that the 3'UTR RNA editing sites in *CWF19L1* and *F11R* genes resulted in increased protein levels and that alterations of the expression of the two genes affected the proliferation of human embryonic kidney cells.

CONCLUSION On the basis of our computational and experimental results, we hypothesize that 3'UTR editing sites may affect their host gene expression, thereby affecting cell proliferation.

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RNA editing is a post-transcriptional mechanism that can diversify the transcriptome by changing the sequences of RNA.¹ Adenosine to inosine (A-to-I) is the most common type of RNA editing in humans. The RNA editing process affects multiple biologic processes, including splicing,² RNA interference,³ and immune function.⁴ As a result of these diverse and important roles, defects in the RNA editing process can induce disease, including tumor progression.⁵

However, most studies of RNA editing have focused on a few recoding cases, which change the amino acid sequence, despite the fact that 99% of the human genome is noncoding and that noncoding (ie, not coding for amino acids) portions of transcripts have been demonstrated to be involved in many fundamental cellular processes.^{6,7} Although some studies have investigated editing sites in 3' untranslated region (UTR), a noncoding region of genes,^{8,9} no study has explored the RNA editing sites in all noncoding regions

of genes and revealed the possible mechanisms of the noncoding RNA (ncRNA) editing effect on cancer progression. To investigate the function of ncRNA editing and its association with cancers, we analyzed 1,866 RNA sequencing samples across four cancer types in The Cancer Genome Atlas—liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), kidney renal clear-cell carcinoma (KIRC), and thyroid carcinoma (THCA)—by identifying and quantifying noncoding A-to-I RNA editing events that may be associated with cancer development and patient survival.

IDENTIFICATION OF HIGH-CONFIDENCE RNA EDITING SITES FROM FOUR CANCER TYPES

We used the RNA sequencing data sets from paired tumor and normal samples and matched exome data to identify RNA editing sites, then quantified the RNA editing level for each site using all tumor samples. We

ASSOCIATED CONTENT

Data Supplement

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CONTEXT

Key Objective

The function and clinical relevance of noncoding RNA editing sites and the potential mechanisms of the noncoding RNA editing effect in cancer development are not well studied.

Knowledge Generated

By using a mixed-effect logistic regression model, we identified thousands of significantly differential edited noncoding RNA editing sites from multiple human cancers. Furthermore, we found a set of clinical associated sites using a Cox proportional hazards regression model from kidney cancer. To identify the mechanisms that underlie how RNA editing sites affect cancer development, we developed a sparse regression model to study the association between gene expression, RNA editing, and microRNAs. We found that 3' untranslated region editing sites may work independently or through microRNAs to alter the expression of their host gene and thus affect cancer progression.

Relevance

Our study identifies a set of editing sites and edited genes that can be potential biomarkers for diagnosis as well as potential targets for developing treatments, and a possible mechanism to explain the effect of RNA editing in cancer development.

analyzed a total of 1,866 RNA sequencing data sets from The Cancer Genome Atlas for the four cancer types: LIHC, LUAD, KIRC, and THCA. Sample size for each cancer type is listed in the Data Supplement.

The identification procedure for RNA editing sites was similar to that indicated in our previously published pipeline,¹⁰ but here we used more stringent thresholds and additional filters on the basis of RNA sequencing data (Data Supplement). With the availability of exome data, we additionally removed potential DNA variants if the sites seemed to be in the corresponding exome. C→U editing sites were used as a false positive control and analyzed in parallel to A→I sites. The enzyme known to catalyze C→U editing, APOBEC1, showed no detectable expression in the four cancer types; therefore, the identified C→U editing sites were likely artifacts. The proportion of C→U editing sites of all candidate editing sites was less than 0.4% (13 C→U substitutions; Data Supplement), which suggests that a majority of the A→I RNA editing sites we observed are likely true positives. To further validate our results, we compared the observed 3,800 A-to-I editing sites with the human RNA editing sites in the RADAR database (version 2; 2,576,460 in total; <http://rnaedit.com>)¹¹ and found that the majority of sites also exist in the database (approximately 96.5%; 3,666 sites; Data Supplement). The remaining 134 novel RNA editing sites may be a combination of newly discovered sites and false positives (Data Supplement). Of the 3,800 A-to-I editing sites, 12 sites were located in the coding region. As our study focused on noncoding sites, we removed the coding sites from additional analysis and retained a total of 3,788 noncoding A-to-I editing sites. The majority (> 95%) of these A-to-I editing sites were detectable in both tumor and normal samples across all four tumor types, indicating that RNA editing sites were conserved across cancers (Data Supplement). Most of these sites were in Alu repeats (3,417; approximately 90%; Data Supplement) and 3'UTRs (2,357; approximately

62%; Data Supplement). These sites were significantly enriched at target sites of known microRNAs (miRNAs; Data Supplement), similar to observations documented in previous reports.^{10,12} The seed region is the key sequence for an miRNA to recognize its targets¹³; therefore, regions that complement the seed region are considered miRNA target sites (2nd to 8th nucleotides of miRNAs). We observed that RNA editing sites can either create new miRNA target sites or interrupt the target sites of known miRNAs, similar to findings in our previous report in mouse¹⁰ (Data Supplement). The majority of the 134 novel RNA editing sites were also located in Alu repeats and 3'UTR regions (Data Supplement). The consistent features of A-to-I editing we observed with previous studies demonstrate again that the 3,788 RNA editing sites are high-confidence ncRNA editing sites.

NONCODING DIFFERENTIAL RNA EDITING SITES SHOWED DISTINCT PROFILES ACROSS THE FOUR CANCER TYPES

We then assessed whether RNA editing sites demonstrated differential editing efficiency between tumor and normal samples. We measured RNA editing efficiency using an RNA editing ratio, defined as $r_{ij} = \frac{e_{ij}}{t_{ij}}$, where r_{ij} is the editing ratio, e_{ij} is the number of edited reads, and t_{ij} is the total number of reads; i represents the i th site and j represents the j th sample. We first examined the mean editing ratio for each editing site in each cancer, which was defined as $\bar{r}_i = \frac{1}{J} \sum J \cdot r_{ij}$, where $\bar{r}_i$ is the mean editing ratio for the editing site i , J is the total number of samples in a cancer, r_{ij} is the editing ratio from the j th sample. We found that the mean RNA editing ratio was higher in tumor samples than in normal samples in KIRC, LUAD, and THCA, but lower in tumor samples than in normal samples in LIHC. To accurately estimate the difference in RNA editing between tumor samples and normal samples as well as identify individual noncoding differential RNA editing (ncDE) sites, we developed a mixed-effect logistic regression model that included a random effect term to account for variability in

the tumor and normal samples from the same individual (Data Supplement). We found thousands of ncDE sites (false discovery rate: 5%) after removing the confounding effects from sample size and sequencing depth (Data Supplement). The number of ncDE sites was distributed unevenly across the four tumor samples, with THCA having the highest number and proportion (2,266; 62.4%); LUAD (1,065; 30%) and KIRC (1,445; 38.9%) in between; and LIHC the lowest (361; 10.5%; Data Supplement and Figs 1A and 1B). Similar to the distribution of all editing sites, most ncDE sites were within 3'UTR and enriched at the target sites of miRNAs (Data Supplement).

Although editing efficiency was generally elevated in KIRC, LUAD, and THCA tumor samples and reduced in LIHC tumors, efficiency may be elevated or reduced at specific editing sites in each cancer type. For example, the *AJUBA* editing site (chr14: 23,442,114) showed a higher degree of editing in tumor samples than in normal samples in LIHC, but the opposite in KIRC. The *AGMAT* site (chr1:

15,898,554) had a higher degree of editing in kidney and liver normal samples than in tumor samples, but showed the opposite pattern in LUAD. The *SAMD5* editing site (chr6: 147,890,224) was more highly edited in tumor samples than in normal samples in LIHC, LUAD, and THCA (Fig 1C). These observations indicate that specific RNA editing sites may act as biomarkers for different types of cancer.

EIGHTY ncDE SITES WERE SIGNIFICANTLY ASSOCIATED WITH SURVIVAL OF PATIENTS WITH KIRC

We next investigated ncDE sites that were associated with patient survival in KIRC samples, because KIRC had the largest number of uncensored ($n = 161$) and also many censored ($n = 346$) samples (Data Supplement). We first filtered out editing sites that were not supported by at least two edited reads in more than 20 samples and retained 3,567 sites. We then compared these sites with the 1,445 ncDE sites in KIRC from the previous section and removed

FIG 1. Profile of noncoding RNA editing sites in the four cancer types. (A) An overview of the noncoding editing sites in the four cancer types. Each column represents an editing site and each row a cancer type. NormalHigh indicates significantly higher editing in normal samples than in tumor samples. TumorHigh indicates significantly higher editing in tumor samples. SameLevel indicates no significant difference between tumor and normal samples. (B) Breakdown of noncoding differentially edited (DE) sites with differential editing in tumor and normal samples in kidney renal clear-cell carcinoma (KIRC), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), and thyroid carcinoma (THCA). (C) Distinct profiles of RNA editing ratio at three noncoding DE sites across the four cancer types. The genomic locations of the three RNA editing sites in *AJUBA*, *AGMAT*, and *SAMD5* are as follows: chr14: 23,442,114; chr1: 15,898,554; and chr6: 147,890,224, respectively.

the sites for which the average editing ratios between tumor and normal samples differed by less than 0.04—similar to the threshold used in Han et al.¹⁴ We applied a Cox proportional hazards¹⁵ regression model to each of these sites with RNA editing and gene expression as covariates and identified 80 sites at a false discovery ratio of 10%. We used the Cox model here instead of the Kaplan-Meier method, another popular method in survival analysis, because the Cox model allows for additional covariates—for example, RNA editing ratio, gene expression, etc—to be incorporated into regression such that the effects from these covariates on survival may be accounted for, whereas the Kaplan-Meier method only constructs survival curves for two or more groups and cannot quantify potential association between survival and continuous covariates, such as RNA editing ratio or gene expression (Data Supplement).

Most of the 80 sites were in 3'UTRs ($n = 52$; approximately 65%) or downstream of genes ($n = 16$; approximately 20%; Fig 2A and Data Supplement). Four editing sites selected from the 3'UTRs of *CWF19L1* and *F11R* are shown as examples in Figures 2B and 2C, whose clinical relevance was successfully validated experimentally—described in Clinically Associated ncRNA Editing Sites at 3'UTRs Can Affect the Expression of Their Host Gene and Thus Affect Cell Proliferation. In addition, 28 of these 80 sites were also reported in Han et al¹⁴ (Data Supplement).

It is common for a 3'UTR to harbor multiple RNA editing sites. In general, sites in the same 3'UTR tend to have the same direction of effect between tumor and normal samples—that is, they were either all upregulated or all downregulated in tumor samples—indicating that these sites may contribute to the association with clinical outcome (Data Supplement); however, there are exceptions. For example, at the 3'UTR of *GGCX*, 16 of 19 RNA editing sites had a higher mean editing ratio of tumor than in normal samples, whereas the remaining three sites were the opposite, indicating that RNA editing has site-specific functional effects as well as shared effects across a group of editing sites.

3'UTR RNA EDITING SITES MAY WORK INDEPENDENTLY OF OR PAIR WITH miRNAs TO ALTER THE EXPRESSION OF THEIR HOST GENES

3'UTRs are involved in mRNA stability, translation, and localization.^{16,17} RNA editing sites in 3'UTRs have been reported to be capable of affecting the stability of mRNA and of potentially altering gene expression.^{18,19} A recent report has demonstrated that 3'UTR editing can affect gene expression by perturbing the efficiency of miRNA binding.⁸ We aimed to explore the possibility that RNA editing alters gene expression by altering the efficiency of miRNA binding. For this purpose, we searched for genes that are associated with editing sites and miRNAs. To ensure high-confidence results, genes with a small sample size (< 50 samples) and many covariates (the number of covariates chosen by lasso regression is higher than one sixth of the sample size) were filtered out (Data

Supplement). For each of the 241 genes that had an acceptable sample size, we performed two types of regression—standard linear regression and lasso regression—to select the important variables, using RNA editing sites and miRNAs as covariates and gene expression as the response variable (Data Supplement). We next retained 194 genes that were associated with at least one RNA editing site. This procedure allowed us to find a small set of genes with a conservative number of covariates (miRNAs or RNA editing sites). We further performed bootstrap of 2,000 iterations to obtain the CI for each regression coefficient. If all regression coefficients of one gene were outside the 95% bootstrap CI, then this gene was removed from results. In the end, we identified a total of 193 genes. Eighty of these genes were associated with at least one pair of RNA editing site and miRNA, which indicates the joint impact of RNA editing and miRNA on gene expression. We defined this group of genes with associated editing sites and miRNAs as group 1 (Data Supplement) and the remaining 113 genes with associated RNA editing as group 2 (Data Supplement).

Effects of 3'UTR RNA editing sites on gene expression can be complex. Editing sites in group 2 and the majority of editing sites in group 1 had no paired miRNAs that significantly affected gene expression, which indicates that most RNA editing sites may not work with miRNAs to alter gene expression at the RNA level (Data Supplement). Nonetheless, 96 paired editing sites and miRNAs were predicted to significantly affect gene expression together either multiplicatively ($n = 81$) or additively ($n = 15$; Data Supplement). We also found that RNA editing sites may create novel target sites for miRNAs ($n = 42$) or interrupt known target sites ($n = 29$; Data Supplement). They also can alter the target site of one miRNA such that the altered target site became recognizable to another miRNA ($n = 27$; Data Supplement). Of interest, there were more RNA editing sites which created target sites for known miRNAs than those that interrupted target sites (Data Supplement; proportion test $P = .022$). These results support the notion that if RNA editing affects gene expression jointly with miRNAs, it is more likely to enhance, rather than weaken, the function of miRNAs.

With our conservative approach described above, 44 of the 80 clinically associated editing sites were tested here. Sixteen of these sites were found to significantly influence gene expression, among which seven were found to be in group 2 (without paired miRNAs), which is consistent with the earlier observation for all tested editing sites, further indicating that RNA editing can either function independently of miRNAs or alter the binding efficiency of miRNAs (Data Supplement).

CLINICALLY ASSOCIATED ncRNA EDITING SITES AT 3'UTRS CAN AFFECT THE EXPRESSION OF THEIR HOST GENE AND THUS AFFECT CELL PROLIFERATION

Many of the differentially edited and clinically associated editing sites identified were in the 3'UTRs of genes, which suggests the functional importance of 3'UTR sites. Our

FIG 2. Distribution of clinically associated noncoding RNA (nsRNA) editing sites. (A) Distribution of clinically associated sites across different regions of genes. (B) Editing ratio of two adjacent 3' untranslated region (UTR) sites in *CWF19L1* and *F11R* were significantly higher in kidney renal clear-cell carcinoma than in normal samples. *CWF19L1* site1: chr10:101992898; *CWF19L1* site2: chr10:101992899; *F11R* site1: chr1:160966351; and *F11R* site2: chr1:160966352. (C) Survival probability distribution for the *CWF19L1* site1 (right) and *F11R* site1 (left). Risk tables for the two editing sites are shown beneath of the respective survival probability plot. HighEdit represents the group of patients with higher editing ratio and LowEdit represents the group of patients with lower editing ratio. The two groups were classified using hierarchical cluster method. A higher editing ratio was associated with a reduced probability of patient survival. Similar distributions were also observed for *CWF19L1* site2 and *F11R* site2.

sparse regression analysis further demonstrated that the 3'UTR RNA editing sites were able to affect their host gene expression with or without cooperation with miRNA. We therefore hypothesized that the clinically associated 3'UTR sites may affect their host protein expression. To test this hypothesis, we used human embryonic kidney cells (HEK293T) and selected two genes, namely *CWF19L1* and *F11R*, that had clinically associated RNA editing sites in

their respective 3'UTRs (Fig 2C and Data Supplement). *CWF19L1* has not been well studied but was reported to be associated with Spinocerebellar ataxia,²⁰ a genetic disease. *F11R*, also known as *JAM-A* (junctional adhesion molecule-A), is important in multiple cellular adhesive processes and its expression has been demonstrated to be positively correlated with the progression of breast cancer²¹ and can be altered by 3'UTR RNA editing sites upon hypoxia.¹⁹

FIG 3. The 3' untranslated region (UTR) noncoding RNA editing sites can significantly alter the expression of their host gene and further promote HEK293T cell proliferation in experimental validation. (A) The luciferase assay demonstrated that the *CWF19L1* editing site (left) and *F11R* editing site (right) increase the expression of *CWF19L1* and *F11R*, respectively. (B) Gene expression level after knocking down and overexpressing of *CWF19L1* (top), *F11R* (middle), and *ADAR1* (bottom). (C) Absorbance level in the MTT assay after knocking down *CWF19L1* and *F11R* (top), and after overexpressing *CWF19L1* and *F11R* (bottom). (D) A possible model to explain the function of *CWF19L1* and *F11R* editing sites: the 3'UTR editing sites in *CWF19L1* and *F11R* increased the expression of *CWF19L1* and *F11R* in tumor samples and resulted in the promotion of tumor progress. In panels A-C, three replicates were used for each group and the standard deviation was calculated for each comparison and indicated by error bars. An unpaired two-tailed *t* test, assuming unequal variance, was used for hypothesis testing. (*) Significant *P* value. MUT, mutant; OE GeneName, overexpressing the gene; siCon, control for knocking down experiment; siGeneName, knocking down the gene; OE GFP, the control for overexpressing gene; WT, wild type.

We constructed a luciferase vector for each 3'UTR with mutations at the several RNA editing sites—five sites in *CWF19L1* and six sites in *F11R*—that showed the same direction of effect on clinical outcome (Data Supplement and Figs 2B and 2C). Luciferase can be used as reporter genes to measure the target protein expression levels. Details on setting up a luciferase reporter assay to detect the protein expression of *CWF19L1* and *F11R* are provided in the Data Supplement. We referred to these two vectors as *CWF19L1* MUT and *F11R* MUT. Compared with wild-type 3'UTR of *CWF19L1* and *F11R* (*CWF19L1* WT and *F11R* WT), the two mutant vectors significantly increased the level of the luciferase, which indicated that both mutations led to an increase in gene expression (Fig 3A), confirming that the 3'UTR editing sites can affect the expression of their host gene.

We next assessed whether the altered gene expression could lead to tumor proliferation by knocking down or overexpressing *CWF19L1* and *F11R* in HEK293T cells (Fig 3B). We observed that after knocking down *CWF19L1* and *F11R*, the absorbance value from the MTT assay, which measures the number of viable cells, significantly decreased (Fig 3C), indicating that these two genes potentially promoted tumor progression via proliferation. Our results were consistent with a previous study on the role of *F11R* in advancing tumor progression,²¹ although the authors studied the function of *F11R* in breast cancer. We also observed significantly elevated values after overexpressing *CWF19L1* (Fig 3C), which strongly supported the role of *CWF19L1* in promoting tumor cell proliferation. Although overexpressing *F11R* did not lead to notable changes in the absorbance value in our experiments (Fig 3C), this might be a result of *F11R* having already reached its maximum abundance level. In summary, our results indicate that ncRNA editing sites that are associated with clinical outcome play a functionally significant role in the regulation of host gene expression (Fig 3D).

DISCUSSION

A notable result was the identification of RNA editing sites that can change their host gene expression. To identify the mechanisms that underlie how the RNA editing sites alter their host gene expression, we performed multiple analyses. We first found that RNA editing sites were enriched at miRNA target sites and then hypothesized that RNA editing sites may affect their host gene expression via the miRNA pathway. Using a sparse regression model, we successfully identified a set of pairs of RNA editing sites and miRNAs that may work jointly to alter host gene expression, as well as a set of RNA editing sites that seemed to act independently of miRNAs. Apparently, our analysis results supported our hypothesis that the miRNA pathway was one of the mechanisms, and the interaction between RNA editing sites and miRNAs was also reported recently by Zhang et al.⁸ In their study, Zhang et al demonstrated that the increasing expression of the *MDM2* gene may be via the interruption of miRNA binding, which is consistent with our systematic data analysis results. For the RNA editing sites that seemed to be independent of miRNA, we demonstrated using a reporter gene assay that they were able to change the host gene expression at the protein level. To find possible explanations for why these sites can change their host gene expression, we analyzed the RNA secondary structure of the edited and unedited 3'UTR regions of the two validated genes *CWF19L1* and *F11R*. We found that these RNA editing sites may have the potential to alter the secondary structure of the RNAs (Data Supplement), especially the two adjacent RNA editing sites that altered the structure from a bulge into base pairs after editing. The change of the secondary structure could facilitate or block the binding of other factors, which might affect the expression of genes. As it is widely accepted that the secondary structure of RNA is a key player in the RNA editing process, the many ncRNA editing sites that we identified as acting independently of miRNAs may regulate their host gene expression via this alternative mechanism.

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