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Research article

REMR: Identification of RNA Editing-mediated MiRNA Regulation in Cancers

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ABSTRACT

Dysregulation of adenosine-to-inosine (A-to-I) RNA editing has been implicated in cancer progression. However, a comprehensive understanding of how A-to-I RNA editing is incorporated into miRNA regulation to modulate gene expression in cancer remains unclear, given the lack of effective identification methods. To this end, we introduced an information theory-based algorithm named REMR to systematically identify 12,006 A-to-I RNA editing-mediated miRNA regulatory triplets (RNA editing sites, miRNAs, and genes) across ten major cancer types based on multi-omics profiling data from The Cancer Genome Atlas (TCGA). Through analyses of functional enrichment, transcriptional regulatory networks, and protein-protein interaction (PPI) networks, we showed that RNA editing-mediated miRNA regulation potentially affects critical cancer-related functions, such as apoptosis, cell cycle, drug resistance, and immunity. Furthermore, triplets can serve as biomarkers for classifying cancer subtypes with distinct prognoses or drug responses, highlighting the clinical relevance of such regulation. In addition, an online resource (http://www.jianglab.cn/REMR/) was constructed to support the convenient retrieval of our findings. In summary, our study systematically dissected the RNA editing-mediated miRNA regulations, thereby providing a valuable resource for understanding the mechanism of RNA editing as an epi-transcriptomic regulator in cancer.

1. Introduction

RNA editing is a widespread and essential modification process that alters RNA sequences without affecting the DNA sequences [1]. The most common type of RNA editing is the conversion of adenosine to inosine (A-to-I), which is catalysed by the adenosine deaminase acting on the RNA (ADAR) family of enzymes [2]. Inosine is recognized as guanosine by the cellular machinery, thus altering the sequence and function of RNA molecules [3]. Previous studies demonstrated that RNA editing plays a crucial role in complex diseases, including cancer [4–7]. With the development of high-throughput sequencing technologies and RNA editing detection methodologies, millions of known editing sites have been identified in the human transcriptome [8]. In cancers, most informative editing sites are located at genomic regions with unknown functions, such as 3′-untranslated regions (UTRs) and intronic regions [9,10]. Previous studies have indicated that dysregulation of RNA editing in 3′-UTRs can affect post-transcriptional regulation, subsequently influencing the cancer hallmark-associated processes, such as cell proliferation, differentiation, and drug resistance [11–13]. However, the landscape of the editing sites that mediate post-transcriptional regulatory perturbations has not been systematically studied. Furthermore, the comprehensive identification of post-transcriptional regulation mediated by editing sites in the transcriptome offers a new perspective and resource for epitranscriptome-based gene regulation strategies.

MicroRNA (miRNA) is a class of non-coding RNAs typically

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consisting of approximately 22 nucleotides, which post-transcriptionally regulates gene expression by binding to the 3′-UTR of target messenger RNA (mRNA) molecules [14,15]. The dysregulation of miRNAs has been implicated in various diseases, particularly cancer [16]. The miRNA regulatory network, composed of regulatory circuits from miRNAs to their target genes, provides detailed maps of gene expression regulation in specific cellular contexts [17]. Understanding the intricate mechanisms of dysregulation of miRNA-gene associations is expected to assist in developing therapeutic strategies for complex diseases. Extensive studies have indicated the critical role of miRNA regulatory networks in tumor progression and treatment [18–20]. Previous studies have demonstrated that RNA editing can alter miRNA binding sites, thereby influencing miRNA regulation and driving crucial cancer-related functions [21–24]. For example, ADAR1-mediated RNA editing in the 3′-UTR of *MDM2* disrupts miR-155 binding, stabilizing *MDM2* mRNA and inhibiting p53 activation, which in turn enhances the self-renewal and quiescence of chronic myeloid leukemia progenitor cells [21]. Similarly, RNA editing in the 3′-UTR of *DHFR* prevents the binding of miR-25–3p and miR-125a-3p, leading to *DHFR* upregulation in breast cancer, enhanced cell proliferation, and methotrexate resistance [22]. Notably, most RNA editing events in cancer occur in 3′-UTR, highlighting its critical role in mediating miRNA regulation. Consequently, RNA editing in the 3′-UTR has the potential to significantly reshape miRNA-gene regulatory networks. However, most previous studies have little attention to RNA editing for de novo reconstruction of miRNA regulatory networks in cancers. With the continuous emergence of RNA editing data and improvements in detection accuracy, there is an urgent need for the systematic identification of RNA editing-mediated miRNA regulatory perturbations.

In this study, we used conditional mutual information (cMI) measurements [25,26] to identify RNA editing-mediated miRNA regulation triplets in ten cancer types. Through analyses of miRNA regulatory network, protein-protein interaction (PPI) network modules, and functional enrichment, we discovered that RNA editing-mediated miRNAs and genes predominantly participate in crucial pathways related to cancer, including apoptosis, the cell cycle, platinum drug resistance, and immune-related pathways. Furthermore, we identified RNA editing site-miRNA-gene triplets associated with drug response and patient prognosis. Finally, we constructed an omnibus repository that provided a user-friendly interface for the convenient retrieval of our findings (freely available at http://www.jianglab.cn/REMR/). Overall, this study provides new resources and insights for deciphering potential post-transcriptional regulatory mechanisms from the perspective of RNA editing mediation in cancer.

2. Materials and methods

2.1. Data collection and preprocessing

The RNA editing profiles of various cancer types were downloaded from Synapse (syn2374375, https://www.synapse.org/). The Annovar tool [27] was used to re-annotate the genomic information of the RNA editing sites. The miRNA expression data (reads per million mapped reads [RPM]), gene expression data (transcripts per million mapped reads [TPM]), and clinical data of the patient samples were obtained from the GDC Data Portal (https://portal.gdc.cancer.gov/). In the present study, we used log-transformed miRNA and gene expression values.

2.2. REMR algorithm

2.2.1. Prediction of miRNA targets using TargetScan

For the editing sites in 3′-UTRs, sequences of ± 50 base pairs (bp) relative to each editing site were extracted by using the bedtools (v2.29.2). Based on the 101 bp edited and unedited sequences, the TargetScan tool (v7.0) was used to predict potential miRNA binding to the sequences [28]. We retained the miRNA-gene associations where the editing sites were located in the seed regions.

2.2.2. Calculation of conditional mutual information

For each RNA editing site-miRNA-gene triplet filtered as mentioned above, the cMI was computed based on the editing level of the site and the expression data of the miRNA and gene, that is, *cMI* (*miRNA*, *gene* | *site*). cMI evaluates the dependence of miRNA regulation on the editing levels of sites in the 3′-UTR. To ensure statistical power, triplets were required to have simultaneous RNA editing, miRNA expression, and gene expression levels in at least 200 samples. As a result, only ten cancer types were available for downstream analysis. Here, we used equal-width discretization with 10 bins. The R (v4.2.0) package infotheo (v1.2.0.1) was used to calculate the cMI of each triplet in each cancer type. Moreover, for each triplet, a null distribution of *cMI* (*miRNA*, *gene* | *shuffle* (*site*)) was constructed by shuffling the sample labels of the editing profiles for 1000 randomized permutations. Thereafter, the *p*-value was calculated by counting the number of times the random cMI values exceeded the observed cMI value, and then dividing by the total number of permutations (1000). A one-tailed test was used to identify RNA editing-mediated miRNA regulatory triplets with $p < 0.05$.

2.3. Validation of RNA editing-mediated miRNA regulations

For each triplet, the samples were sorted in ascending order, based on the editing level of the site. All samples were then categorised into a high editing group (top 25 %) and a low editing group (bottom 25 %). Pearson correlation coefficients of miRNA and gene expression were calculated for the two groups. Differential miRNA and gene expression analyses between two groups were performed separately using a t-test.

2.4. Functional annotation and enrichment

Functional annotation and enrichment of the gene sets were conducted using the R (v4.2.0) package clusterProfiler (v4.6.2) [29]. The clusterProfiler package provides two functions, enrichGO and enrichKEGG, to perform functional enrichment analyses of Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genome (KEGG) pathways through a hypergeometric test. Functional annotation and enrichment of the miRNA sets were conducted using miRNA Enrichment Analysis and Annotation Tool (miEAA) [30]. Significantly enriched GO terms and KEGG pathways with $p < 0.05$ were used for the downstream analyses.

2.5. Construction and analyses of PPI network

High-quality PPIs were assembled in a previous study that included 217,160 PPIs connecting 15,970 unique proteins [31]. RNA editing-mediated miRNA regulation may affect translation. Therefore, we extracted genes in the triplets and their interacting neighbours in the PPI network as a neighbour network. The MCODE tool[32] with default parameters in Cytoscape was used to identify densely connected modules in the neighbouring network.

2.6. Collections of functional gene sets

Genes in the Cancer Gene Census (CGC), which included mutations that had been causally implicated in cancers, were downloaded from COSMIC (https://cancer.sanger.ac.uk/census). The KEGG-cancer, KEGG-immunity, and KEGG-resistance gene sets were downloaded from the KEGG pathway database (https://www.genome.jp/kegg/pathway.html). Experimentally validated drug resistance-related genes were downloaded from DRESIS [33].

2.7. Identification of prognosis-associated triplets

To identify prognosis-associated RNA editing site-miRNA-gene trip-

lets, patients were randomly divided into training and test sets for each cancer type. Next, univariate Cox regression analysis was used to evaluate the association between patient survival time and editing levels of a site, as well as the expression levels of miRNAs and genes separately. A negative regression coefficient suggests that an increase in the value of this element is associated with increased survival, indicating that it is a protective factor. Conversely, a positive coefficient suggests that an increase in the value of this element is associated with decreased survival, indicating that it is a risk factor. Subsequently, a mathematical formula for survival prediction was created, considering both the strength and direction of each factor in the triplet for survival. Based on the same principle used in previous studies [34], the risk score for each patient was calculated as follows:

$$RiskScore = \sum_{i=1}^{k} a_i X_i,$$

where k is the number of molecules in a triplet (site, miRNA, or gene). a_i is the regression coefficient of the i-th molecule (site, miRNA, and gene) obtained from the univariate Cox regression analysis, X_i is the expression level or editing level of the i-th molecule. We used a five-fold cross-validation repeated 100 times with random groupings to evaluate the performance of each triplet model. We calculated the risk scores for the samples in the training set and used the median score in training as the cut off to categorise the patients into high-risk and low-risk groups. The coefficients and risk score cut offs obtained in the training set were then applied to the test set. Similarly, we divided the patients in the test set into high and low-risk groups. The Kaplan-Meier (KM) curve and log-rank test were used to evaluate whether there was a significant difference in survival time between the high and low-risk groups. The time-dependent Receiver Operating Characteristic (timeROC) curve is used to evaluate the performance of a survival model at specific time points. Finally, we selected the triplets with a log-rank test $p < 0.05$ in at least 80 out of 100 repeated 5-fold CV.

2.8. Identification of drug response-associated triplets

Drug response data of tumor samples from The Cancer Genome Atlas (TCGA) were downloaded from the GDC Data Portal. Only samples labelled “progressive disease” and “complete response” were referred to as resistant and sensitive samples, respectively. We then defined the drug and treated cancer type as a condition, and assigned patient samples to each condition. Here, we selected conditions that included at least ten samples from both the resistant and sensitive groups for further analyses. Thereafter, a five-fold cross-validation repeated 100 times with random groupings was used to evaluate the performance of each triplet model. Under each condition, samples were randomly divided into five equal groups, ensuring that the number of resistant and sensitive samples was balanced across all groups. Univariate logistic regression was used to train the model parameters for sites, miRNAs, and genes in each triplet, respectively. The model parameters were integrated according to the following formula to calculate the probability values of drug resistance for the samples:

$$prob = \sum_{k=1}^{m} \frac{1}{1 + e^{-(\alpha_k + \beta_k X_k)}},$$

where m represents the number of molecules in a triplet (site, miRNA, gene), α_k and β_k are parameters of the k-th molecules (site, miRNA, and gene) obtained from the univariate logistic regression analysis, X_k is the expression level or editing level of the k-th molecules. The predicted probability values (*prob*) of > 0.5 indicated drug resistance, whereas values of < 0.5 suggested drug sensitivity. We applied the parameters in the training sets to the test sets and predicted the drug responses of the patient samples in the test sets. The area under the receiver operating characteristic curve (AUROC) was used to measure the predictive performance of triplet-based models. Triplets with an average AUROC of > 0.8 were considered reliable drug response-associated triplets.

3. Results

3.1. Landscape of the RNA editing-mediated miRNA regulatory triplets in cancers

To comprehensively analyse of the effect of A-to-I RNA editing on miRNA regulation in cancer, we introduced an information theory-based method termed REMR to systematically identify RNA editing-mediated miRNA regulatory triplets by integrating RNA editing, miRNA expression, and gene expression data from various cancer types in TCGA (refer to the Methods section for details). Fig. 1 illustrates the integrative framework used in this study. First, we identified miRNA-gene associations with potential A-to-I editing sites in their seed regions. The combination of sites, miRNAs and genes was referred to as the potential triplet for further screening. Subsequently, the cMI value for each potential triplet, which assessed the dependence of miRNA regulation on the editing levels of a site, was calculated based on the editing levels (site) and the expression levels of molecules (miRNA and gene) in each cancer type. The number of samples with available data from the cancer types is shown in Fig. 2a, and the number of editing sites before and after filtering is shown in Fig. 2b. A total of 2964–23,988 sites were involved in the cMI calculation across the cancer types. Statistical significance was determined by comparing the actual cMI with that of the null distributions (refer to the Methods section for details). Finally, we identified 12,006 significant RNA editing-mediated miRNA regulation triplets in all ten cancer types.

The number of identified triplets varied across the cancer types, ranging 216–2743 (Fig. 2c, Supplementary Table S1). In addition, the number of miRNA-gene associations affected by the editing sites in each cancer type ranged 214–2691 (Fig. 2d). A significant correlation was observed between the number of triplets and number of editing sites (Supplementary Fig. S1a and Fig. 2e) across different cancer types. Similarly, the number of miRNA-gene associations in triplets was also significantly correlated with the number of editing sites (Supplementary Fig. S1b and Fig. 2f). A previous study showed that large variations in the number of informative editing sites among cancer types were primarily attributed to differences in the number of tumor samples per cancer type and in the number of mappable reads per sample [9]. These results indicate that RNA editing-mediated miRNA regulatory triplets showed no significant bias toward one or a few cancer types. Furthermore, the triplets included 132–559 miRNAs, regulating 104–657 target genes modulated by 199–2458 editing sites in various cancer types (Fig. 2g). We observed that only 7.7 % of the triplets were recognized in at least two cancer types, with most triplets exhibiting cancer-type specificity (Fig. 2h). Similarly, only 13.1 % of the miRNA-gene associations were identified in at least two cancer types (Fig. 2i). This may be due to the tissue-specific expression of miRNAs in different cancer types. In contrast, we observed that 28.9 % of the sites, 74.1 % of the miRNAs, and 68.3 % of the genes appeared in at least two cancer types (Supplementary Fig. S1c–e), respectively. These findings suggest that RNA editing influences various miRNA regulation in different cancer types.

3.2. Validation and case study of RNA editing-mediated miRNA regulations

To validate the reliability of the identified triplets, we initially examined the correlation between editing levels of single site in the 3′-UTRs and expression levels of *ADAR*1, *ADAR*2, and *ADAR*3, respectively. Compared to *ADAR*2 and *ADAR*3, *ADAR*1 expression exhibited the strongest correlation with the editing levels of the sites (Supplementary Fig. S2a and Fig. 3a), consistent with a previous study [2], suggesting that the data were qualitatively reliable for downstream

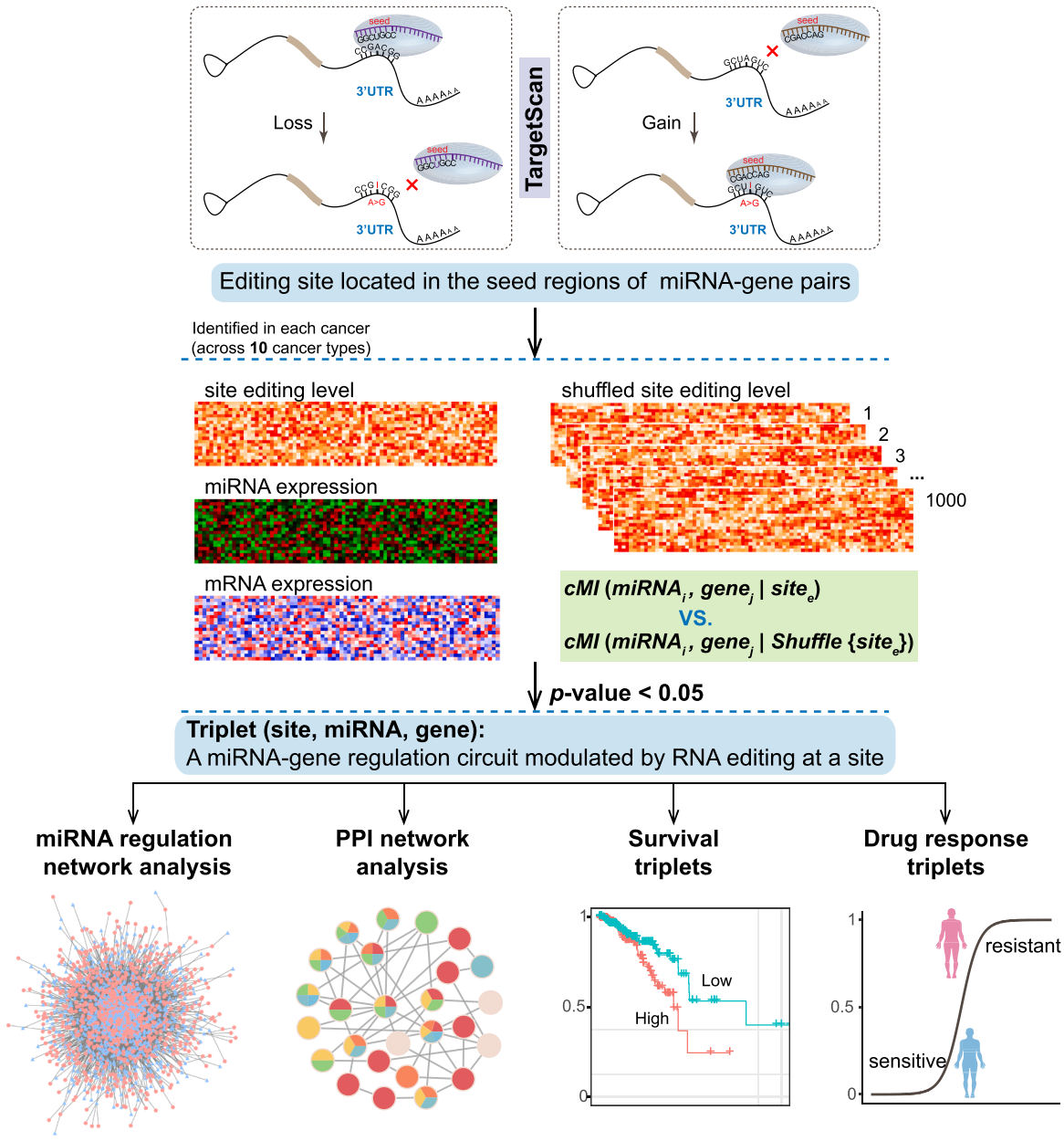

Fig. 1. Workflow of dissection of RNA editing-mediated miRNA regulations. Using a miRNA *i* (*miRNA*$_i$), a potential target gene *j* (*Gene*$_j$), and an A-to-I RNA editing site *e* (*site*$_e$) within the seed region of miRNA binding as examples, the diagram illustrates the utilization of multi-omics data in identifying RNA editing-mediated miRNA regulatory triplets. The identified triplets were analyzed for different functional characteristics, including cancer hallmarks and underlying mechanisms, as well as their association with drug response and prognosis.

analyses. In this study, the computational approach for identifying triplets follows a two-step filtering process. We observed that the editing levels of the sites in the triplets identified at each step exhibited a higher correlation with the expression levels of *ADAR*1 than those not selected (Fig. 3b), which has been validated in most cancer types (Supplementary Fig. S2b). In addition, ADAR enzymes must bind to mRNA to perform their editing functions [35,36]. Thus, a correlation analysis between the expression levels of ADARs and genes harboring editing sites in the 3′-UTRs was further conducted. *ADAR*1 expression levels exhibited the strongest correlation with gene expression levels compared to *ADAR*2 and *ADAR*3 (Supplementary Fig. S2c and Fig. 3c). Similar to the analysis of the editing site, we observed that the expression levels of genes in the triplets identified at each step exhibited a stronger correlation with the expression levels of *ADAR*1 than those not selected (Fig. 3d), which was also observed in most cancer types (Supplementary Fig. S2d). This result confirms the effectiveness of our two-step filtering process. Collectively, these results suggested that *ADAR*1 played more important roles for the editing of sites in the triplets, affecting the expression of genes harboring the editing sites in the 3′-UTRs.

On the other hand, we also validated the reliability of the miRNA-gene associations in the triplets. Specifically, experimentally validated miRNA-gene associations in human tissues or cell lines were obtained from miRTarBase [37] and TarBase [38]. We determined that miRNA-gene associations in triplets were significantly enriched in the experimentally validated associations (Fig. 3e, hypergeometric test, $p = 2.56 \times 10^{-130}$). In addition, we showed two examples to illustrate our hypothesis (refer to the Methods section for details): (1) The editing of chr2:216808755 in the 3′-UTR of *MREG* may lead to the loss of miR-130–3p and *MREG* association (Fig. 3f): the expression levels of miR-130–3p were not correlated with *MREG* expression levels in the

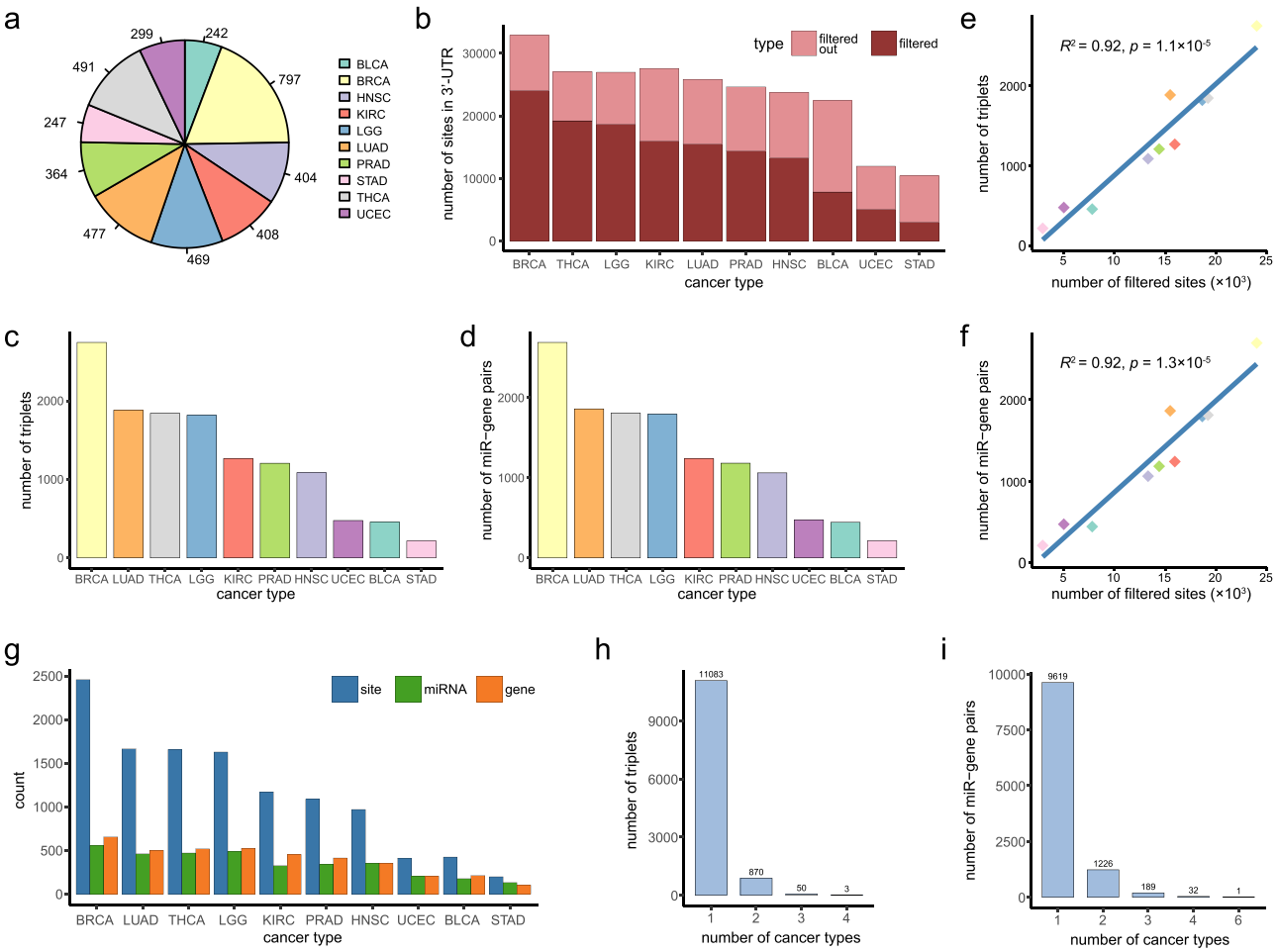

Fig. 2. Overview of A-to-I RNA editing-mediated miRNA regulatory triplets in ten cancer types. a) Number of samples used for each cancer type. b) Number of sites before and after filtering in each cancer type. c) Number of triplets identified in each cancer type. d) Number of miRNA-gene associations in triplets in each cancer type. e) Associations between the number of filtered sites and the number of identified triplets across ten cancer types. f) Associations between the number of filtered sites and the number of miRNA-gene associations across ten cancer types. R^2 values were calculated using linear regressions in e and f. g) Number of sites, miRNAs, and genes in triplets in each cancer type. h) Number of triplets that were identified in a different number of cancer types. i) Number of miRNA-gene associations that were identified in a different number of cancer types.

high editing group, but showed a significant negative correlation with *MREG* expression levels in the low editing group. The edited site may have disrupted the association between miR-130–3p and *MREG*, leading to increased *MREG* expression in the high editing group; (2) The editing of chrX:48436349 in the 3′-UTR of *RBM3* may lead to the gain of miR-139–5p and *RBM3* association (Fig. 3g): In our results, the high editing group showed a significant negative correlation between the expression levels of miR-139–5p and *RBM3*, whereas no correlation was observed in the low editing group. It is possible that A-to-I editing led to the gain of miR-139–5p and *RBM3* association, resulting in a decrease in *RBM3* expression in the high editing group. Collectively, the RNA editing-mediated miRNA regulation identified in this study may serve as a post-transcriptional regulatory resource for gene expression in cancer.

3.3. Overview of RNA editing-mediated miRNA regulatory networks

We identified miRNA regulation that depend on RNA editing levels of specific site in the 3′-UTR for each cancer type. This miRNA regulation forms an interconnected miRNA regulatory network, which is defined as an editing-mediated miRNA regulatory network (edMRN), for each cancer type. Furthermore, the edMRNs were constructed separately for each cancer type. Subsequently, we combined all the edMRNs as pan-cancer edMRN (Supplementary Fig. S3a). We observed a power-law distribution in the degrees of nodes within these edMRNs (Fig. 4a and Supplementary Fig. S3b), suggesting that these networks adhered to a scale-free structure. In such networks, a few nodes, referred to as hubs, exhibited a substantial number of connections.

Hubs play a crucial role in scale-free networks. Hence, the top ten genes with the highest degrees were selected as hub genes in the edMRN for each cancer type (Fig. 4b). We observed that 81.4 % of these genes have been experimentally validated for their involvement in cancer progression and drug resistance, including *XIAP* [39], *PSMB2* [40], *CTSS* [41], and *CTSB* [42]. We conducted functional annotation and enrichment analysis of the hub genes to identify critical functions and pathways associated with cancer (Supplementary Table S2), such as apoptosis, the PPAR signalling pathway, fatty acid metabolism, and immune-related functions. For instance, *XIAP*, a crucial member of the apoptosis inhibitory gene family, is closely linked to tumor progression [43,44], and has been validated as a potential therapeutic target in cancer [39]. In this study, we identified several editing sites in the 3′-UTR of the *XIAP* that may influence miRNA regulations. Furthermore, we showed the miRNA-gene associations involving *XIAP*, identified in at least two cancer types (Fig. 4c). These triplets contained 24 miRNAs and 40 editing sites. Notably, 11 of these miRNAs had been experimentally confirmed to regulate *XIAP*, including miR-129–5p [45] and miR-10a-5p [46]. In addition, we predicted several potential miRNAs that regulate *XIAP*, including miR-769–3p and miR-214–5p.

Similarly, we screened the hub miRNAs in the edMRN of each cancer

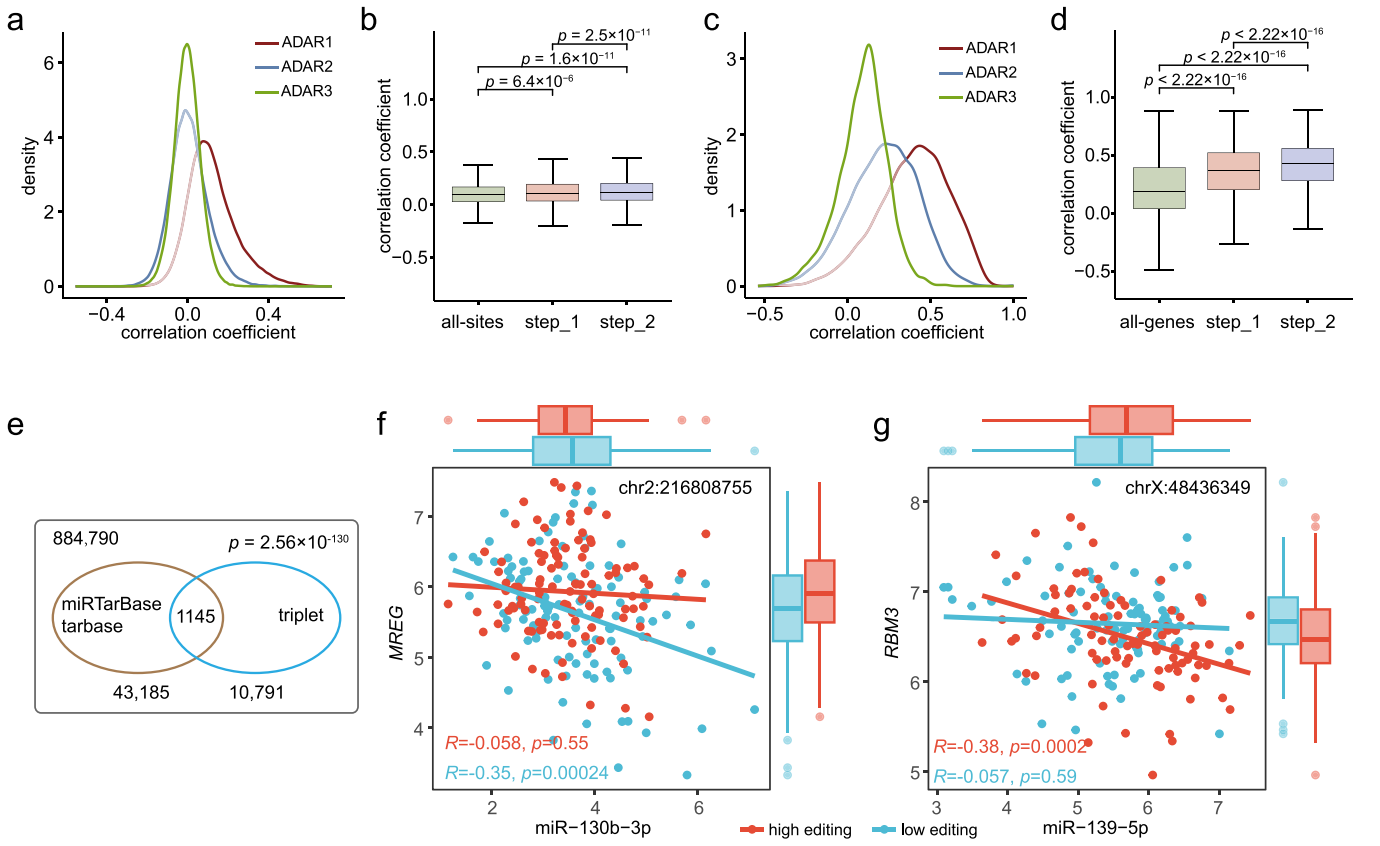

Fig. 3. Potential regulatory mechanisms of RNA editing. a) Distribution of Spearman correlation coefficients between the RNA editing levels of each site in the 3′-UTR of genes within triplets and the expression levels of *ADAR*1, *ADAR*2, and *ADAR*3. b) Comparison of Spearman correlation coefficients between *ADAR*1 expression and RNA editing levels across the all-sites, step 1 and step 2 groups. Step 1 represents the first screening, where the editing site occurs within the miRNA-gene binding region. Step 2 represents the second screening, where conditional mutual information (cMI) was applied to further refine the candidate triplets. Sites that did not pass either filtering step are classified as the all-sites group. c) Distribution of Spearman's correlation coefficients between the expression of gene harboring editing sites in the 3′-UTR and the expression of *ADAR*1, *ADAR*2, and *ADAR*3. d) Comparison of Spearman correlation coefficients between *ADAR*1 and other gene expression across the all-genes, step 1 and step 2 groups. e) Overlap of miRNA-gene associations in the triplets and the experimentally validated pairs in miRTarBase and TarBase databases. Significance of the overlap was assessed using a hypergeometric test. f, g) Case studies of RNA editing-mediated miRNA regulations. Boxplots show miRNA and gene expression in the high and low editing level group. Lines show the correlation between miRNA and gene expression in two subgroups. Blue, low editing level group; red, high editing level group. In these analyses, the significance of the difference between two groups was assessed using a Wilcoxon test.

type (Supplementary Fig. S3c). All 31 hub miRNAs identified in ten cancer types were confirmed to be associated with cancer occurrence, progression, metastasis, or drug resistance. We used the miEAA tool [47] to conduct functional annotation and enrichment analysis of hub miRNAs, revealing their involvement in crucial cancer-related functions and pathways (Supplementary Table S3). These pathways include apoptosis, epithelial-mesenchymal transition, and B-cell receptor signalling pathway. A previous study has reported that miR-24–3p is associated with innate immunity and cancer malignancy [48]. Furthermore, we identified miRNA-gene associations involving miR-24–3p in at least two cancer types (Supplementary Fig. S3d). Triplets of miR-24–3p involved 17 genes and 30 editing sites, with 64.7 % (11/17) of the genes experimentally confirmed as targets of miR-24–3p, such as *KPNA*6 [49]. We also predicted the potential target genes regulated by miR-24–3p, including *APOL*6, *GATD*1, and *PTGR*2. Collectively, these results suggest that RNA editing-mediated miRNA regulation is a crucial biological process in human cancers.

3.4. Biological insights of RNA editing mediated miRNA regulation

We observed that the intersection of genes within triplets was larger than that of triplets between any two cancer types (Supplementary Fig. S4a), indicating the presence of similar functional consequences of RNA editing across different cancer types. To further elucidate the biological functions governed by RNA editing-mediated miRNA regulation, we conducted a functional enrichment analysis for genes involved in triplets in each cancer type. Cancer-related GO terms were significantly enriched across various cancer types, including RNA modification, ribosome biogenesis, and ncRNA processing (Supplementary Fig. S4b). Moreover, cancer-related pathways, including RNA polymerase, platinum drug resistance, and apoptosis, were significantly enriched in various cancer types (Supplementary Fig. S4c). Abnormalities in miRNA regulation could affect the translation of target genes [50]. Therefore, we investigated the interactions between genes within the triplets in the PPI network. A highly reliable PPI network has been obtained from a previous study [31]. Genes in the CGC and cancer-related pathways from KEGG were obtained as cancer-related genes. Drug resistance-related genes were extracted from the KEGG and DRESIS databases [33], and immune-related genes were downloaded from the KEGG database. We observed that genes in the triplet were more likely to interact with genes related to cancer, immunity, and drug resistance in the PPI network (Supplementary Table S4, chi-square test, CGC $p < 2.2 \times 10^{-16}$, KEGG-cancer $p < 2.2 \times 10^{-16}$, KEGG-immunity $p = 1.3 \times 10^{-14}$, DRESIS $p < 2.2 \times 10^{-16}$, KEGG-resistance $p = 9.7 \times 10^{-16}$). These results suggest that miRNA regulation influenced by RNA editing may mediate

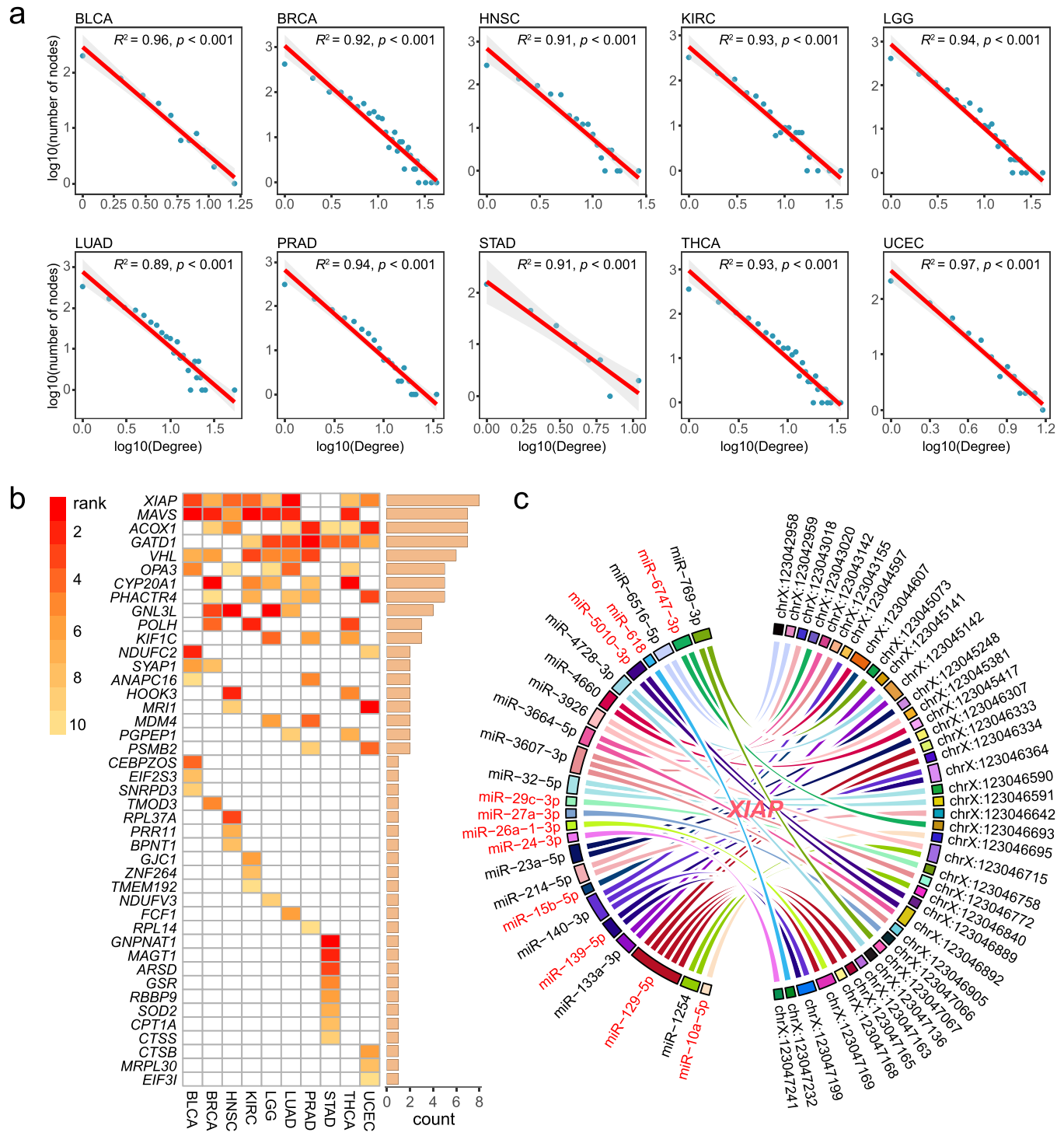

Fig. 4. Overview of RNA editing-mediated miRNA regulation networks (edMRNs). a) Node degrees in the edMRNs exhibit a power-law distribution for each cancer type. b) Hub genes in each cancer type. The darker the color, the higher the degree. c) 24 miRNAs were identified to target *XIAP* in at least two cancer types, and the triplets including these miRNA-gene associations are shown. Red miRNA names indicate that these miRNAs have been experimentally confirmed to target *XIAP*.

important biological functions related to cancer, immunity, and drug resistance.

In addition, we explored the biological functional modules mediated by RNA editing. Briefly, we extracted genes in triplets and their directly interacting neighbours from the PPI network to construct a neighbour network. Subsequently, we utilized the MCODE tool to identify densely connected modules in the neighbouring network [32]. Eighteen modules were identified (Supplementary Table S5), and the top five modules with the highest scores were presented in Fig. 5a. Functional enrichment analysis of each module revealed that densely connected modules governed distinct biological functions (Fig. 5b). Specifically, Module 1 was primarily involved in ribosome biogenesis and assembly, Module 2 played a key role in tumor stem cell differentiation and immune-related functions, Module 3 was primarily associated with functions related to DNA replication, cell cycle, and immune response, Module 4 was primarily involved in functions related to DNA transcription and RNA polymerase, and Module 5 was primarily involved in cell apoptosis. These results suggest that RNA editing may mediate different miRNA

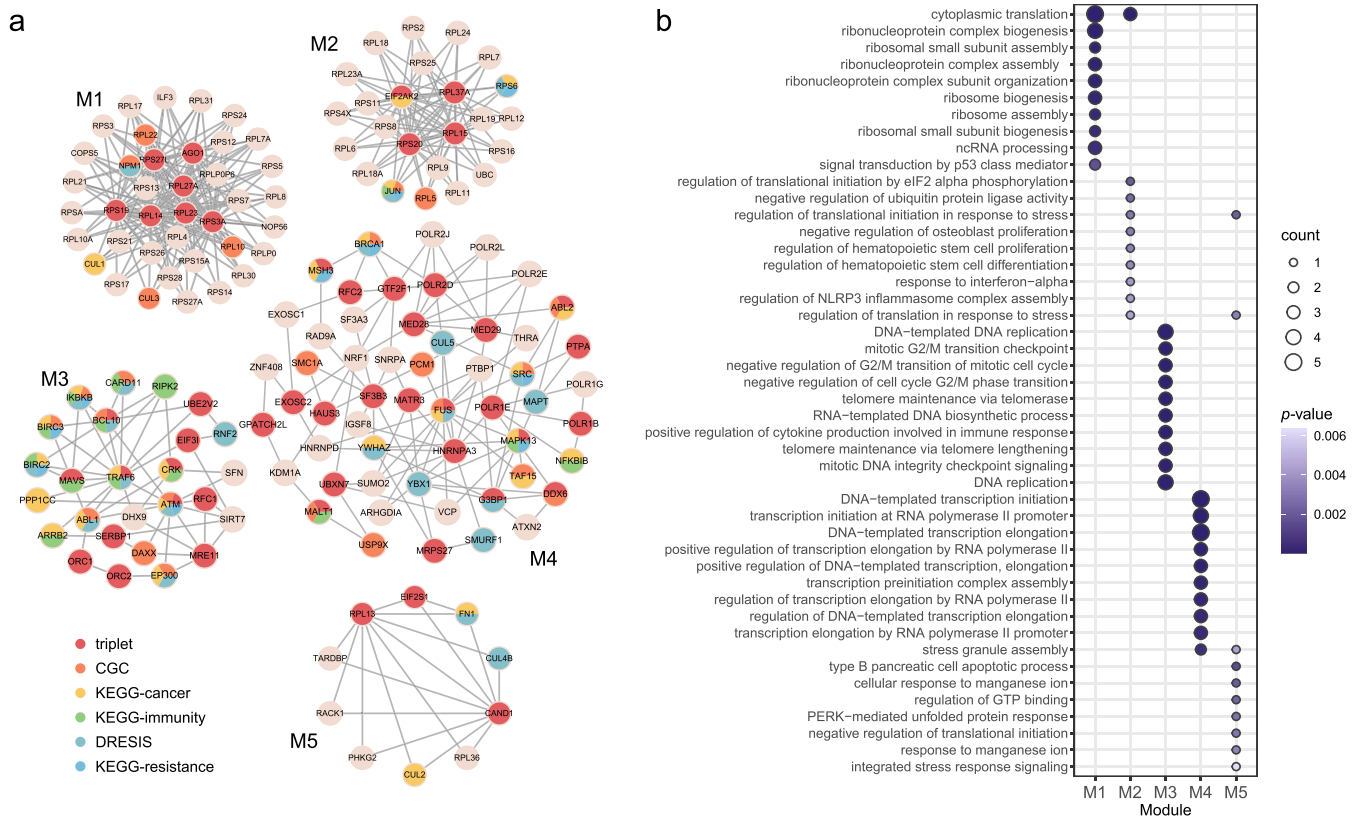

Fig. 5. Biological functional modules mediated by RNA editing in protein-protein interaction (PPI) network. a) Top five modules identified by MCODE in the neighbouring network of genes in the triplets. The colors of nodes represent a known function. b) Top ten significantly enriched GO terms ($p < 0.05$) in each module.

regulations that affect distinct cellular functional mechanisms.

3.5. Clinical relevance of identified triplets

Recent studies have indicated that RNA editing signatures can be used to stratify patients with different prognoses, suggesting their potential as effective prognostic markers [51,52]. Thus, we identified prognosis-associated RNA editing site-miRNA-gene triplets by integrating the clinical data of patients (refer to the Methods section for details). Specifically, for all ten cancer types, we identified a total of 15.6 % triplets associated with prognosis (Fig. 6a, Supplementary Table S6). To verify the key roles of triplets in predicting patient prognosis, we first compared the predictive performance of models based on triplets and those based on single molecules (site, miRNA, and gene) in the triplets. Compared to models based on single molecules, the triplet-based models showed better predictive performance (Fig. 6b). This indicates that prognostic-associated triplets could serve as markers for prognostic subtypes. We showed the top ten prognostic-associated triplets with the highest significance based on their *p*-values in the full sets (Fig. 6c).

As an illustrative example, we highlight a triplet involving chr1:204521711, miR-9–5p, and *MDM4*. Our analysis predicts that, RNA editing at chr1:204521711 in the 3′-UTR of *MDM4* may disrupt the binding of miR-9–5p, potentially leading to altered mRNA stability. Previous studies have demonstrated that inhibiting *MDM4* can activate the p53 tumor suppressor pathway, which in turn inhibits tumor growth [53]. Additionally, the prognostic risk model based on this triplet effectively predicted survival outcomes for lower-grade glioma (LGG) patients, with a highly significant log-rank test result ($p < 0.0001$, Fig. 6d). The time-dependent receiver operating characteristic (time-ROC) analysis further demonstrated the robust predictive performance of the prognostic risk model, with area under the curve (AUC) values of 0.87 at 1 year, 0.80 at 2 years, and 0.78 at 3 years (Fig. 6e). These findings underscore the relevance and efficacy of the identified triplet in prognosis prediction.

Another example of a prognostic-associated triplet identified in our study involves chr17:4929934, *KIF1C*, and miR-15b-5p. The RNA editing at chr17:4929934 within the 3′-UTR of *KIF1C* may lead to gain of binding site of miR-15b-5p, which could alter the regulation of *KIF1C* expression. *KIF1C*, a member of the kinesin-3 family, is recognized as a crucial factor in cancer cell invasion [54]. The prognostic model developed based on this triplet exhibited strong predictive power, with a log-rank test $p < 0.0001$ and AUC values of 0.82 at 1 year, 0.85 at 2 years, and 0.82 at 3 years (Fig. S5a). These results suggest that the regulatory impact of the editing event on *KIF1C* via miR-15b-5p may contribute to cancer progression, making this triplet a robust marker for prognostic assessment. Other triplets among the top candidates that were significantly associated with patient prognosis are shown in Supplementary Fig. S5b–i. Collectively, our study successfully identified RNA editing site-miRNA-gene triplets associated with prognosis, providing valuable support and reference for the development of tumor prognostic markers.

3.6. Drug resistance mechanism revealed through the identified triplets

The dysregulation of RNA editing is associated with anticancer drug resistance [55]. In this study, we discovered that RNA editing-mediated miRNA regulation can affect crucial genes in drug resistance-related pathways, including platinum drug resistance pathways, the cell cycle, and apoptosis (Supplementary Fig. S4b and c, and Supplementary Table S2, 3). Therefore, we integrated data on RNA editing levels, along with miRNA and gene expression data, and identified 41 triplets associated with drug response. This analysis, which was performed under five conditions across four distinct cancer types (Fig. 7a, Supplementary

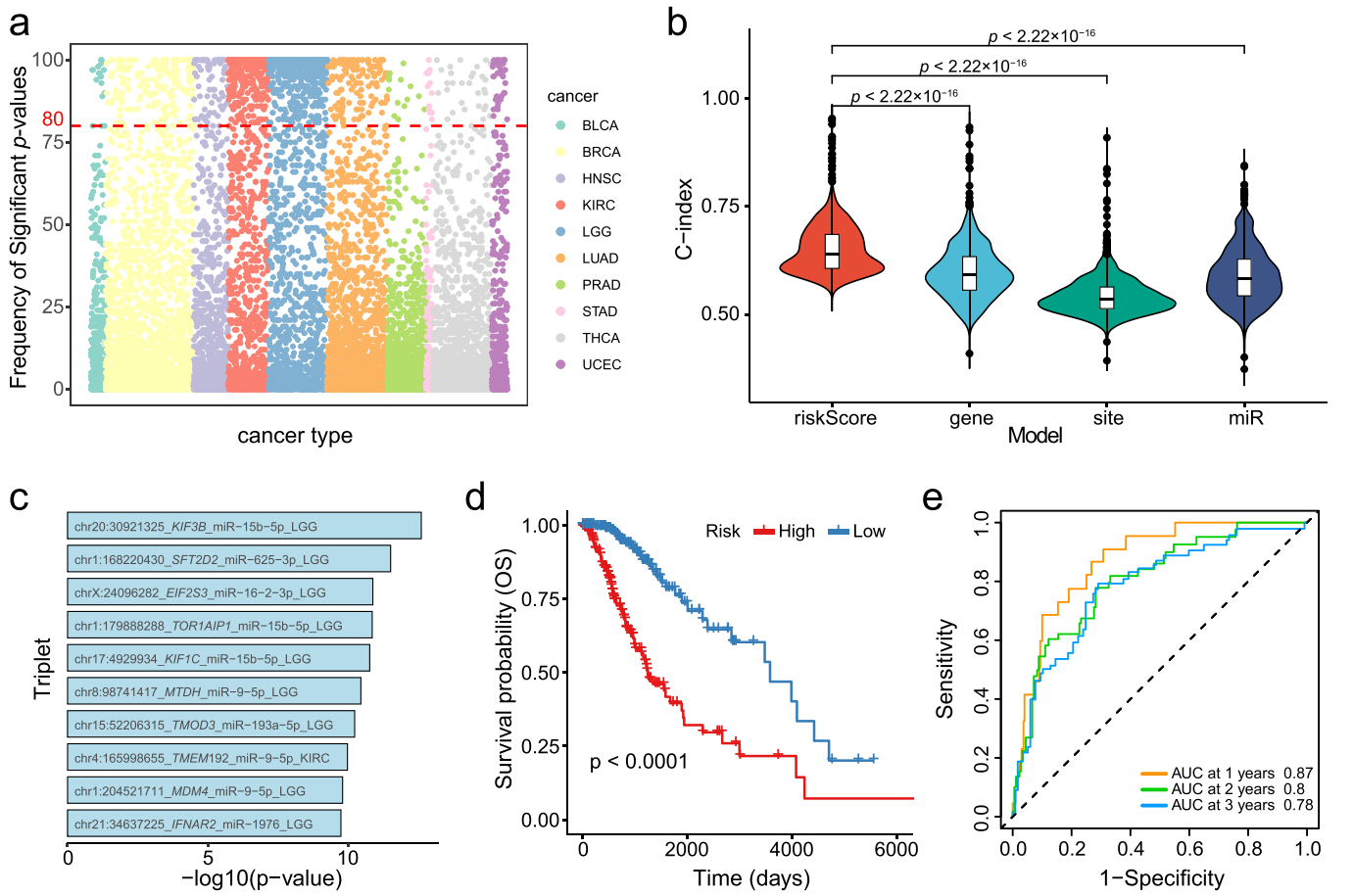

Fig. 6. Prognosis-associated triplets in various cancer types. a) Survival landscape of site-miRNA-gene triplets. The X-axis indicates cancer type, and the Y-axis indicates the number of 5-fold cross-validation iterations with a log-rank test $p < 0.05$. Each dot represents a triplet identified in each cancer type. Dots are marked by the same color as the corresponding cancer type. b) Comparison of the concordance index (C-index) of single-molecule-based (site editing level, miRNA expression, or gene expression) and triplet-based risk models. The difference among groups was calculated using a Wilcoxon test. c) Top 10 candidate prognosis-associated triplets. d) For the triplet, chr1:204521711_*MDM*4_miR-9–5p, KM plot of survival for Lower Grade Glioma (LGG) patient with different risk scores. The survival difference among groups was calculated using a log-rank test. Red, high-risk group; blue, low-risk group. e) Time-dependent ROC curves illustrate the model's ability to predict outcomes at different time points.

Table S7), was based on the implementation of a logistic regression algorithm (refer to the Methods section for details). Furthermore, the triplet-based models exhibited better predictive performance than the single-molecule-based models (Fig. 7b). This result indicated that the drug response-associated triplets identified in this study could serve as biomarkers for precision medicine.

In our study, we identified that the RNA editing at chr1:179325742 in the 3′-UTR of *SOAT*1 may lead to the loss of miR-485–5p binding. Previous research has reported that dysregulation of *SOAT*1 is strongly linked to the proliferation of glioma[56]. Furthermore, miR-485–5p has been shown to be significantly related to drug resistance in glioma [57]. Therefore, this RNA editing site has a potential impact on drug resistance in glioma. Our analysis further demonstrated that a model based on this triplet effectively predicts the response of LGG patients to temozolomide. This triplet-based model shows significantly superior predictive performance compared to models based on single molecules (Fig. 7c). These findings suggest that incorporating the impact of RNA editing sites on miRNA binding sites into predictive models can more accurately assess drug response of LGG patients.

In addition, we also examined the RNA editing at chr11:125526139 in the 3′-UTR of *CHEK*1. This RNA editing event may lead to the gain of miR-150–5p binding. Previous studies have shown that *CHEK*1 dysregulation impacts DNA repair and apoptosis [58]. Moreover, miR-150–5p has been implicated in drug resistance across various types of cancer [59,60]. Our research found that this triplet effectively predicts the drug response of bladder cancer (BLCA) patients to cisplatin. This triplet-based model outperforms single-molecule-based models in predictive performance (Fig. 7d). Fig. S6 presented the model performance based on several triplets associated with cancer progression and drug resistance. In summary, the miRNA regulations modulated by RNA editing could serve as biomarkers for predicting drug response and exploring the mechanisms of anticancer drug resistance.

4. Discussion

RNA editing in 3′-UTR of transcripts has been recognized as modulators of gene expression by affecting binding of miRNAs [22,61]. The dysregulation of RNA editing is closely associated with the progression of numerous complex diseases, including cancer. Studies have reported that RNA editing events are abundant in the non-coding regions in cancer. Most previous studies have focused on specific sites or coding regions. However, a comprehensive investigation of the potential functions of RNA editing in cancer is lacking.

Perturbations in miRNA regulation have been reported and studied in several cancer types [62,63]. Unraveling the potential factors underlying cancer disruption has emerged as an important and challenging topic in the field of tumor biology. In this study, we used cMI to systematically delineate the mechanisms of A-to-I RNA editing-mediated miRNA regulation by leveraging multi-omics data from TCGA. Our study encompassed the entire transcriptome and explored each RNA

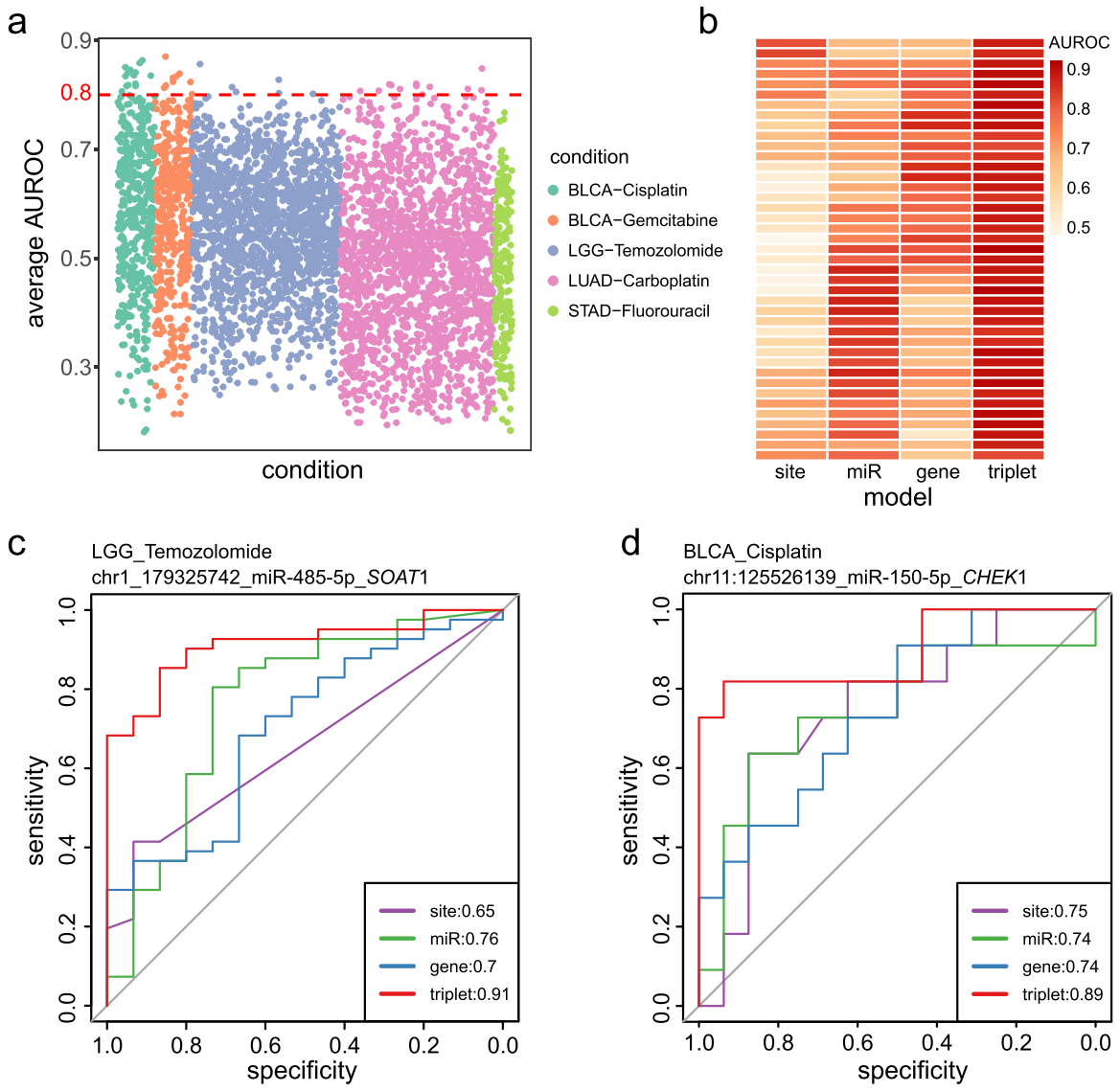

Fig. 7. Drug response-associated triplets across different conditions. a) Drug response landscape of site-miRNA-gene triplets. The X-axis indicates condition, and the Y-axis indicates average AUROC in repeat 5-fold cross-validation (CV) 100 times. Each dot represents a triplet in each condition, and the color of dots represents conditions. b) Comparison of performance (AUROC) between models based on single molecule (site, miRNA, or gene) and triplets. Each Row represents a drug response-associated triplet. c, d) For two candidate triplets, chr1:179325742_*SOAT*1_miR-485–5p in LGG_Temozolomide and chr11:125526139_*CHEK*1_miR-150–5p in BLCA_Cisplatin, the comparison of performance of triplet-based and single-molecule-based models.

editing site across multiple cancer types. Firstly, we predicted that editing events in 3′-UTRs of genes could lead to the gain or loss of miRNA binding, specifically focusing on the seed regions. This not only ensured the reliability of the identified miRNA-gene associations but also reduced the computational time for subsequent analyses. Next, by integrating the RNA editing, miRNA, and gene expression profiles of patients with tumors from TCGA, we used cMI measurements to identify miRNA regulation mediated by RNA editing in each cancer type. In particular, cMI has been used to effectively assess the dependence of transcriptional regulation on methylation levels of CpG sites in cancers [25]. We observed that the miRNA-gene associations in our results were significantly enriched in experimentally validated miRNA-gene associations. This underscores the reliability of the triplets identified in this study. In this study, we constructed an edMRN for each of the ten major cancer types by linking miRNAs and genes in triplets. The edMRN represents a novel reconstruction of the miRNA regulatory network mediated by RNA editing. Moreover, we systematically explored the functional implications of RNA editing-mediated miRNA regulation in both miRNA regulation and PPI networks. The genes in the triplets exhibited a preference for interacting with cancer, immune, and drug resistance-related genes, highlighting their potential involvement in crucial biological processes and functions. In addition, we explored the clinical relevance of these triplets and uncovered their potential as biomarkers for predicting patient prognosis and drug response. These findings further underscores the importance of the triplets identified in our study for understanding the regulatory effect of RNA editing abnormalities on cancer progression.

However, this study has some inherent limitations associated with computational predictions, underscoring the need for comprehensive experimental validation to augment the robustness of our findings in the future. Due to sample size constraints, our study currently covers ten major cancer types from the TCGA. As more extensive and diverse datasets become available, we plan to extend our algorithm to additional cancer types. This will enhance our understanding of RNA editing's role across a broader range of cancers. Furthermore, integrating a broader spectrum of omics data, such as DNA mutations, copy number variations, and epigenetics, has the potential to boost the accuracy of identifying and quantifying the effect of RNA editing. Additionally, the

choice of discretization methods and bin number can influence results. In the future, emerging gold-standard datasets will help optimize discretization methods and bin number, improving accuracy and minimizing biases. Moreover, cMI is a valuable measurement for capturing both linear and non-linear regulatory interactions, making it particularly effective for revealing complex miRNA-gene dependencies. Our two-step filtering framework, which first identifies RNA editing sites that affect miRNA binding and then uses cMI to assess the strength of dependencies, aims to minimize false positives. Future work will focus on expanding and validating this framework using more extensive data and experimental studies. RNA editing can affect miRNA regulation, leading to changes in mRNA levels. Thus, the emerging proteomic data from patient with tumors will provide valuable support for comprehending RNA editing-mediated miRNA regulation. Our study focused primarily on regulatory effects of RNA editing on miRNA-mediated gene expression. However, notably, additional post-transcriptional regulatory factors, such as long non-coding RNAs or RNA-binding proteins, should be included in future studies. Despite these limitations, our work provides valuable insights into the intricate landscape of RNA editing-mediated miRNA regulation in cancer, paving the way for further investigation in this field.

5. Conclusions

In conclusion, an information theory-based method REMR was used to systematically identify RNA-mediated miRNA regulation across various cancer types using TCGA multi-omics data. These results provide a comprehensive functional evaluation of RNA editing-dependent miRNA regulation in cancers. This study provides a computational algorithm and serves as a resource for exploring the regulation of gene expression and the mechanisms related to cancer progression.

CRediT authorship contribution statement

Xu Zhou: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Haizhou Liu**: Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Fei Hou**: Writing – review & editing, Validation, Investigation. **Zong-Qing Zheng**: Writing – review & editing, Validation, Investigation. **Xinyu Cao**: Writing – review & editing, Validation, Investigation. **Quan Wang**: Writing – review & editing, Supervision, Project administration, Conceptualization. **Wei Jiang**: Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of Competing Interest

The authors have declared no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.csbj.2024.09.011.

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