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Utilizing partial information decomposition to evaluate the complex interplay between microRNA and RNA-binding protein in regulating the shared target mRNA

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MicroRNAs (miRNAs) bind to the 3′ untranslated region of mRNA transcripts, exerting inhibitory activity over gene expression. RNA-binding proteins (RBPs) involved in post-transcriptional regulation also play a pivotal role in modulating mRNA, exhibiting similar binding and regulatory effects to mRNA as miRNAs. This convergence raises the intriguing possibility of coordinated or competitive regulation between miRNAs and RBPs when targeting the common mRNA. However, accurately quantifying the complex regulatory relationship between miRNAs and RBPs remains a challenge. To address this challenge, we here propose a novel multivariate information-based approach to quantitatively capture the nonlinear regulatory relationships between miRNAs and RBPs in the context of shared mRNA targets. Our method integrates the sequence information with gene expression data, unveiling a comprehensive perspective on such an intricate regulatory network. Our findings reveal a prevalent synergistic relationship between miRNAs and RBPs, surpassing instances of competitive relationship. This innovative approach enhances our understanding of the complex interplay between miRNAs and RBPs, shedding light on the cooperative mechanisms that drive post-transcriptional regulation.

Keywords microRNAs, RNA-binding proteins, Cooperative and competitive regulatory relationship, Partial information decomposition

Abbreviations

miRNA	MicroRNA
RBP	RNA-binding protein
mRNA	Messenger RNA
PID	Partial information decomposition
UTR	Untranslated region
RPM	Reads per million
FPKM	Fragments per kilobase of transcript per million mapped reads
BRCA	Breast invasive carcinoma
PRAD	Prostate adenocarcinoma
LIHC	Liver hepatocellular carcinoma
TCGA	The cancer genome atlas
UCSC	University of California, Santa Cruz

MicroRNA (miRNA), a short non-coding RNA molecule, plays a crucial role in orchestrating post-transcriptional regulation of mRNA[1,2]. MiRNAs align with the 3′ untranslated region (3′ UTR) of the target mRNA by sequence complementarity principle[3]. Once interacted, miRNAs impede the translation of the target

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mRNA and subsequently reduce its protein synthesis. This selective regulatory mechanism is instrumental in maintaining the equilibrium of intracellular gene expression. RNA-binding protein (RBP) is a type of protein that engages in interactions with RNA molecules[4–7]. Specifically, these proteins exhibit the capability to bind to the 3′ UTR of mRNA transcripts[4,8] and either enhance[9] or inhibit[10] the expression of target genes. RBPs also serve as key regulators of gene expression at the post-transcriptional level. Mounting evidence indicated that miRNAs and RBPs, as key post-transcriptional regulators, play critical roles in cancer biology[4,11]. Dysregulation of their interactions is closely associated with tumor cell proliferation, invasion, and metastasis[12–14]. Therefore, elucidating the mechanisms underlying miRNA–RBP–mRNA interactions is essential for advancing our understanding of post-transcriptional regulation in cancer.

This convergence of miRNAs and RBPs in post-transcriptional regulation suggests a fascinating potential for their interaction. Recent findings indicated that miRNAs and RBPs typically work together via binding to sequences or structures on shared mRNA targets. Specifically, this interaction results in a dynamic interplay of cooperation and competition between miRNAs and RBPs in mRNA binding[15], influencing key post-transcriptional processes such as mRNA stability, localization and translation. For example, previous studies have demonstrated that the regulatory effects of ELAVL1, a prominent mammalian RBP, on its target transcripts often depend on its interaction with miRNAs that bind to the same mRNAs. As shown by Seo et al.[16] and Goswami et al.[17], ELAVL1 can either cooperate with or compete against miRNAs. Cooperative interactions between ELAVL1 and miRNAs typically lead to reduced expression of shared target genes[18]. In contrast, competitive interactions generally result in increased gene expression when ELAVL1 binding predominates, or decreased expression when miRNA binding is dominant[19].

Nonetheless, the task of accurately mapping out these complex regulatory connections between miRNAs and RBPs poses a significant computational hurdle. Currently developed computational methods fall into two main groups. Firstly, sequence-based methods depend on sequence complementarity and conservation such as miRbiom[20] and doRiNA[21] often leading to many false positives due to their lack of consideration for cellular context. For instance, doRiNA integrated RBP and miRNA binding sites by including only RBP high-throughput detection-derived RBP datasets and a set of predictions for miRNA. It utilizes the UCSC database genome viewer annotated with binding sites, providing a variety of possibilities. Secondly, network-based approaches involve the construction of regulatory networks that include miRNAs, RBPs and mRNAs to study their interactions. For instance, a tool known as SimiRa[22] was used to assess the Go term pathway enrichment in target sets involving miRNA and RBP to predict the correlations between them. Although this approach can provide a snapshot of potential interactions, it struggles to fully capture the dynamic nature of these interactions under different biological conditions. The limitations of these current methods highlight the continuous need for ongoing development and integration of computational approaches to more accurately model and understand these intricate regulatory networks.

In this paper, we utilize the partial information decomposition (PID), a multivariate information measure, to quantify the nonlinear contribution of both miRNA and RBP as they converge on a shared target mRNA. Our method integrates sequence and expression data[23,24] to deliver a comprehensive understanding of the mechanisms governing these interactions, particularly in the context of multiple cancer types.

Methods

Data collection and preprocessing

For sequence data, we referred to the TargetScan database[25] (http://www.targetscan.org/) to determine the binding sites between miRNA and the 3′ UTR of target mRNA. In total, we obtained 203,789 interactions between 321 miRNAs and 11,646 mRNAs (see Supplementary Material 1).We chose to employ TargetScan because it is regularly updated, actively maintained, and supported by prior studies, ensuring both accuracy and relevance[26]. For RBP binding sites, we utilized the dataset provided by Liu et al.[27], derived from the POSTAR2 database[28] (http://lulab.life.tsinghua.edu.cn/postar/) resulting in 3,016,002 binding sites between 171 RBPs and 14,499 mRNAs (see Supplementary Material 2). Besides, we utilized the LiftOver tool (https://genome.ucsc.edu/cgi-bin/hgLiftOver) to map the coordinates of miRNA and RBP binding sites from hg19 to hg38 to ensure the comparability of sites.

For expression profile data, we downloaded RNA-seq datasets for three cancer types from the TCGA data reposi-tory[29] (https://cancergenome.nih.gov/), including breast invasive carcinoma (BRCA)[30], prostate adenocarcinoma (PRAD)[19] and liver hepatocellular carcinoma (LIHC)[31]. Specifically, for miRNA expression profiles, we selected reads per million (RPM) values corresponding to mature miRNAs. For mRNA expression profiles, we extracted fragments per kilobase of transcript per million mapped reads (FPKM) values corresponding to mRNA transcripts. Regarding RBP expression profiles, we used the corresponding mRNA transcript expression profiles as substitutes, as TCGA does not provide protein expression data for RBPs. We further filtered molecules (i.e., miRNA, mRNA and RBP) with missing values that do not exceed 50% of the sample size and imputed these missing values with 0. Additionally, we applied a log2 transformation to the expression profile data.

Classification of interaction between miRNA and RBP

As illustrated in Fig. 1A, we categorize the interaction patterns between miRNA and RBP into three distinct types based on their binding sites on the target mRNA. The first category is adjacent that describes instances where miRNA and RBP bind to contiguous but non-overlapping sites on the same target mRNA, suggesting a spatial closeness that might influence the mRNA's fate through synergistic interactions. The second category is overlapping that occurs when miRNA and RBP share common sequences on the mRNA, potentially leading to direct competition for binding sites and thus affecting the mRNA's stability or its translational efficiency via antagonistic interactions. The third and most complex category is hybrid that encompasses scenarios where

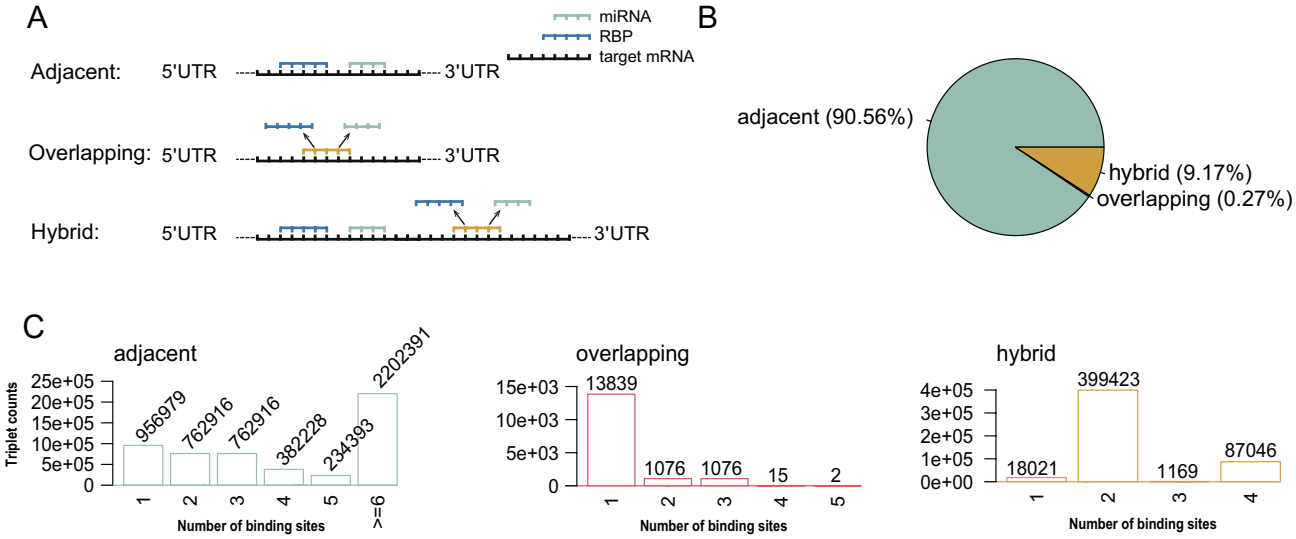

Fig. 1. Overview of sequence-level interactions between miRNA and RBP when targeting the common mRNA. (**A**) A schematic diagram illustrates three types of miRNA–mRNA–RBP triplets at binding sites. (**B**) The percentage of three interaction types. (**C**) Different numbers of binding sites were observed in cases of adjacent, overlapping and hybrid.

miRNA and RBP binding sites exhibit characteristics of both adjacent and overlapping, indicating a highly nuanced regulatory interaction that could significantly impact mRNA processing and function.

Using PID to evaluate the intricate relationship between miRNA and RBP

PID, a multivariate information measurement introduced by Williams and Beer in 2010[32], is used to decompose the total information that a set of source variables provides about a target variable into multiple distinct components. PID offers a granular perspective on how information flows from sources to the target, enabling researchers to capture complex and nonlinear relationships among multiple variables.

In our case, relationships between miRNA and RBP are inherently complex, with multiple components interacting in a non-linear way. PID allows for the dissection of these interactions, helping to determine how miRNA and RBP individually and collectively contribute to a shared target mRNA. Let X, Y, and Z be the two source variables miRNA and RBP, and the target variable mRNA, respectively. For each triplet of miRNA-mRNA-RBP, PID decomposes the information provided by the source variable set (i.e., miRNA and RBP) about a given target variable (i.e., mRNA) into four components: cooperative information, two unique information components, and redundant information[33,34]. The formula is as follows:

$$\mathrm{PID}(Z;X,Y) = \mathrm{synergy}(Z;X,Y) + \mathrm{unique}X(Z;Y) + \mathrm{unique}Y(Z;X) + \mathrm{redundancy}(Z;X,Y)$$

where *synergy*(*Z*; *X*,*Y*) denotes the additional information about the mRNA that is provided jointly by the miRNA and the RBP. $unique_X$ (*Z*;*Y*) and $unique_Y$ (*Z*; *X*) represent the information uniquely contributed by the miRNA and the RBP, respectively, regarding the mRNA. *redundancy*(*Z*; *X*,*Y*) refers to the overlapping information about the mRNA that is provided by either the miRNA or the RBP. As both $unique_X$ (*Z*;*Y*) and $unique_Y$ (*Z*; *X*) are typically low compared to synergy and redundancy, we utilized the difference between synergy and redundancy to quantitatively capture the nature of regulatory interaction between miRNA and RBP when targeting the same mRNA. A positive score indicates that synergistic regulation predominates, indicating cooperation between the miRNA and RBP. Conversely, a negative score indicates that redundant regulation dominates, suggesting a competitive interaction.

Here this formula delineates the information roles of miRNA and RBP in their joint and separate influences on mRNA, clarifying the synergy as the information arising from the collaboration of miRNA and RBP, and redundancy as the overlap in their informational contribution to mRNA. The unique information points to the exclusive contribution each source variable makes towards understanding mRNA. Therefore, the output of PID offers a quantitative score to assess the contribution of miRNA and RBP towards explaining the behavior of mRNA.

Results

Three interaction types between miRNA and RBP at the sequence level

In our study, we divided miRNA–mRNA–RBP triplets into three categories according to the specific binding locations of miRNA and RBP on the target mRNA (see Supplementary Material 3). Our analysis unveiled an interesting distribution of interaction types. The vast majority, numbering 4,993,023 miRNA–mRNA–RBP triplets which were 90.56% of the total, exhibited adjacent binding sites. The smaller group, consisting of 505,659 miRNA–mRNA–RBP triplets (9.17%), showed hybrid interactions of both adjacent and overlapping

characteristics. The smallest portion of 15,001 miRNA–mRNA–RBP triplets (0.27%) demonstrated overlapping binding sites(Fig. 1B).

In the adjacent interaction category, we identified 956,979 interaction units, each involving a pair of binding sites on the same target mRNA. Additionally, a larger subset comprising 4,036,044 interaction units was identified, where two or more independent binding site pairs are involved, indicating that the same miRNA–RBP pair affects multiple distinct regions of the 3′ UTR of the same mRNA.In the overlapping interaction category, 13,839 interaction units were found to share a single overlapping binding site, while a smaller subset of 1162 interaction units contained two or more overlapping binding sites. This suggests that the same miRNA–RBP pair can exert regulatory effects in multiple overlapping regions within the 3′ UTR of a single mRNA. The hybrid interaction category combines the features of both adjacent and overlapping interactions. In this category, we identified 18,021 interaction units, each containing one overlapping binding site and one adjacent binding site, both mediated by the same miRNA–RBP pair on the same target mRNA. Furthermore, a smaller group of 487,638 interaction units was identified, each containing two or more such binding site pairs(Fig. 1C). This suggests that the same miRNA–RBP pair can participate in multiple adjacent and overlapping binding events on the same mRNA. It is important to note that, unless otherwise specified, all "binding sites" mentioned above refer to the sites of action of the same miRNA–RBP pair on the same target mRNA.

Diverse regulatory patterns between miRNA and RBP at the expression level

To deepen our understanding of the regulatory mechanisms governing miRNA–mRNA–RBP triplets, our study further analyzed the expression dynamics of these entities. To this end, we systematically apply PID to each miRNA–mRNA–RBP triplet. This analysis encompassed three different cancer types, allowing us to explore the potential universality as well as specificity in regulatory interactions across different cancer contexts. As illustrated in Fig. 2, we observed that in three cancer types, the overall median values of synergy and redundancy are far exceed the corresponding median value of unique values. This observation indicated that the contribution of miRNAs and RBPs co-regulating target mRNAs is greater than their individual regulation of target genes. Therefore, we used "synergy-redundancy" score to evaluate the contribution of miRNA and RBP towards the shared target mRNA. A positive "synergy-redundancy" score suggests synergy between miRNA and RBP, while a negative score implies potential competition.

As shown in Fig. 2B, most miRNA–mRNA–RBP triplets showed positive "synergy-redundancy" scores across three cancer types. In the BRCA dataset, we identified 3,586,295 miRNA–mRNA–RBP triplets with positive scores, while 79 miRNA-mRNA-RBP triplets showed negative scores (see Supplementary Material 4). In the LIHC dataset, 3,629,231 miRNA–mRNA–RBP triplets displayed positive scores, while 501 miRNA–mRNA–RBP triplets showed negative scores (see Supplementary Material 5). The PRAD dataset contained 3,651,711 miRNA–mRNA–RBP triplets with positive scores and 94 miRNA–mRNA–RBP triplets with negative scores (see Supplementary Material 6). Notably, 3,515,081 miRNA–mRNA–RBP triplets with positive scores were common between BRCA and LIHC, 3,544,931 between BRCA and PRAD, and 3,543,221 miRNA–mRNA–RBP triplets between LIHC and PRAD. There is no overlap in the miRNA–mRNA–RBP triplets with negative "synergy-redundancy" scores between any two cancer types. Upon examining the binding patterns at the sequence level, we found that, in the BRCA dataset, among the miRNA–mRNA–RBP triplets classified as the positive "synergy-redundancy" case, there were 2,944,167 pairs of miRNAs and RBPs that have multiple adjacent binding sites on their commonly targeted mRNAs. Similarly, there were 2,981,220 such miRNA–mRNA–RBP triplets in LIHC, and 2,992,459 miRNA–mRNA–RBP triplets in PRAD.

Among miRNA–mRNA–RBP triplets with positive synergy-redundancy scores, we further filtered the triplets in three cancer types using two criteria. First, the binding sites of miRNA and RBP on the target mRNA must not overlap. Second, the Pearson correlation coefficient between miRNA and RBP must exceed 0.3, while the coefficients between miRNA and mRNA, as well as RBP and mRNA, must be less than − 0.3. As shown in Fig. 3A, most miRNA–mRNA–RBP triplets were cancer type-specific, with only a small number of overlaps across the three cancer types. Notably, three miRNA–mRNA–RBP triplets were shared among all three cancer types. We visualized the top 50 miRNA–mRNA–RBP triplets ranked by decreasing 'synergy-redundancy' scores using Cytoscape software (version 3.7.2, https://cytoscape.org) (Fig. 3B). Interestingly, ELAVL1 emerged as one of the most common RBPs in the miRNA–mRNA–RBP triplet network. Consequently, we further examined the information variables and corresponding correlations for two miRNA–mRNA–RBP triplets shared across all three cancer types.

As illustrated in Fig. 4A, the miRNA–mRNA–RBP triplet of hsa-miR-19a-3p-RHOB-ELAVL1 presented particularly high positive "synergy-redundancy" scores across all three cancer types. At the sequence level, we found that hsa-miR-19a-3p and ELAVL1 have 59 adjacent binding sites and 3 overlapping binding sites on their shared target mRNA RHOB. Additionally, the Pearson correlation coefficient indicated a positive correlation between hsa-miR-19a-3p and ELAVL1. In contrast, both hsa-miR-19a-3p and ELAVL1 were negatively correlated with the target mRNA RHOB. This suggested that hsa-miR-19a-3p and ELAVL1 may work cooperatively to regulate RHOB. Similarly, as shown in Fig. 4B, the miRNA-mRNA-RBP triplet of hsa-miR-93-5p-CALD1-NOP58 also exhibited positive "synergy-redundancy" scores across three cancer types. At the sequence level, hsa-miR-93-5p and NOP58 have one adjacent binding site on their shared target mRNA CALD1. The hsa-miR-93-5p and NOP58 exhibit a positive Pearson correlation coefficient and both show negative correlations with their target mRNA CALD1.

These findings suggested that miRNAs and RBPs typically exhibit synergistic regulatory effects, collaboratively inhibiting the expression of target mRNA. Consequently, the magnitude of the synergy-redundancy score serves as a determinant for identifying the dominant force in the dynamic between synergy and redundancy.

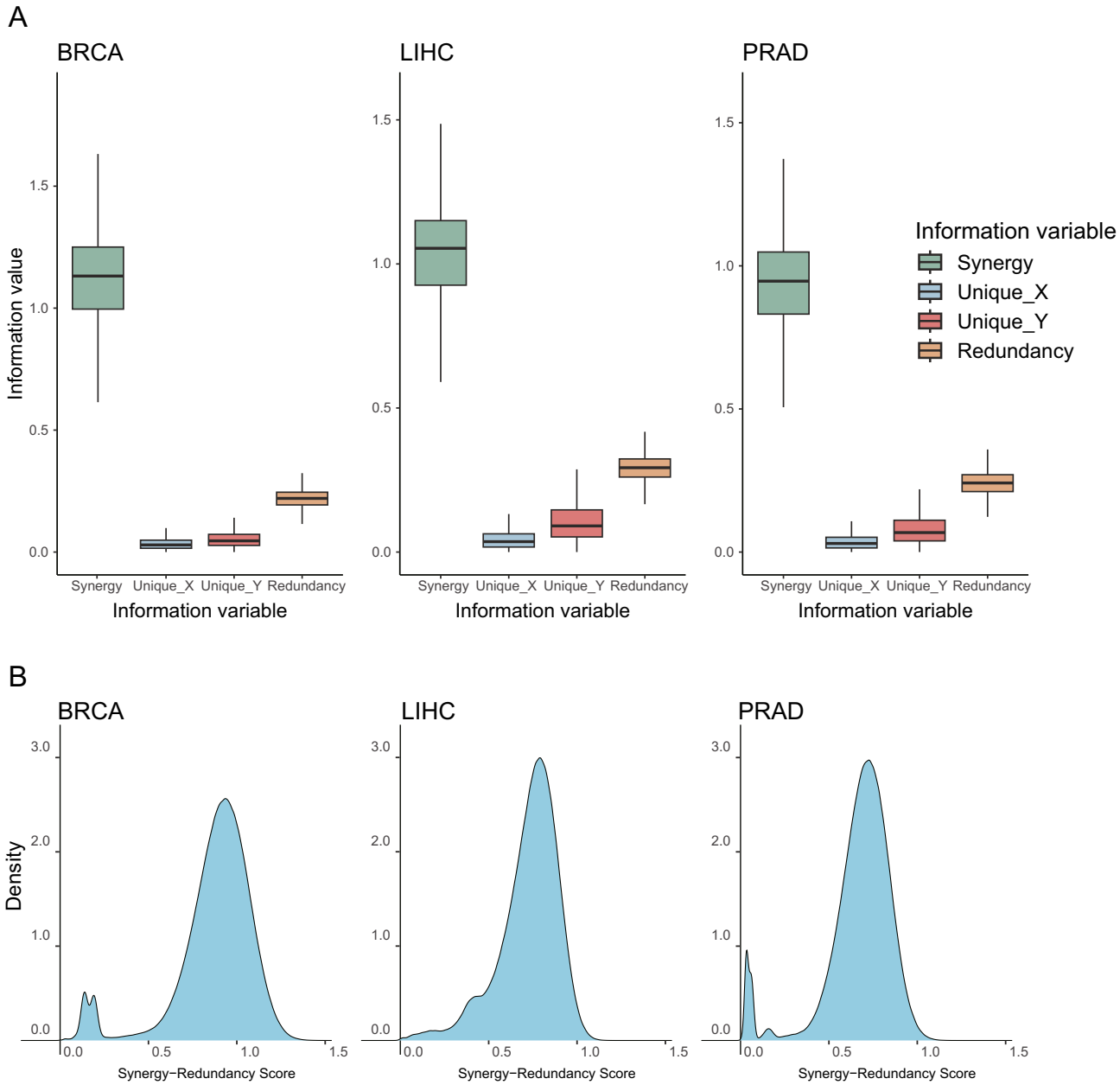

Fig. 2. Analysis of information dynamics in miRNA–mRNA–RBP triplets across three different cancer types. (**A**) Box plots depict the distribution of information variables for BRCA, LIHC and PRAD (**B**) Density plots display the distribution of "synergy-redundancy" scores in BRCA, LIHC and PRAD.

Discussion and conclusion

In this paper, we presented an innovative information-based computational approach designed to evaluate complex interactions between miRNAs and RBPs when they concurrently target a shared mRNA. These interactions are important for understanding how gene expression is regulated at post-transcriptional level. We first checked the sequence data of miRNA and RBP binding to common target mRNA. We observed a wide array of adjacencies and overlaps between miRNA and RBP, indicating potential synergistic or competitive interactions between these two regulators. We then applied the PID algorithm to gene expression data corresponding to miRNA–mRNA–RBP to assess regulatory patterns of each miRNA–mRNA–RBP triplet.

We found that miRNAs and RBPs typically demonstrate synergistic regulatory effects, working together to inhibit the expression of target mRNA. This finding is in agreement with several prior functional studies[35–37], which similarly emphasize the biological significance of the miRNAs–RBPs synergistic regulatory mechanism identified in our research. The reason could be attributed to two aspects. Firstly, even in cases where a pair of miRNAs and RBPs bind to the same mRNA with a conflicting binding site, alternative non-overlapping sites on the mRNA transcript provide additional binding options for two regulators. Analysis of binding sites showed that 9.17% of miRNA–mRNA–RBP triplets possess both neighbor sites and overlapping sites on binding the

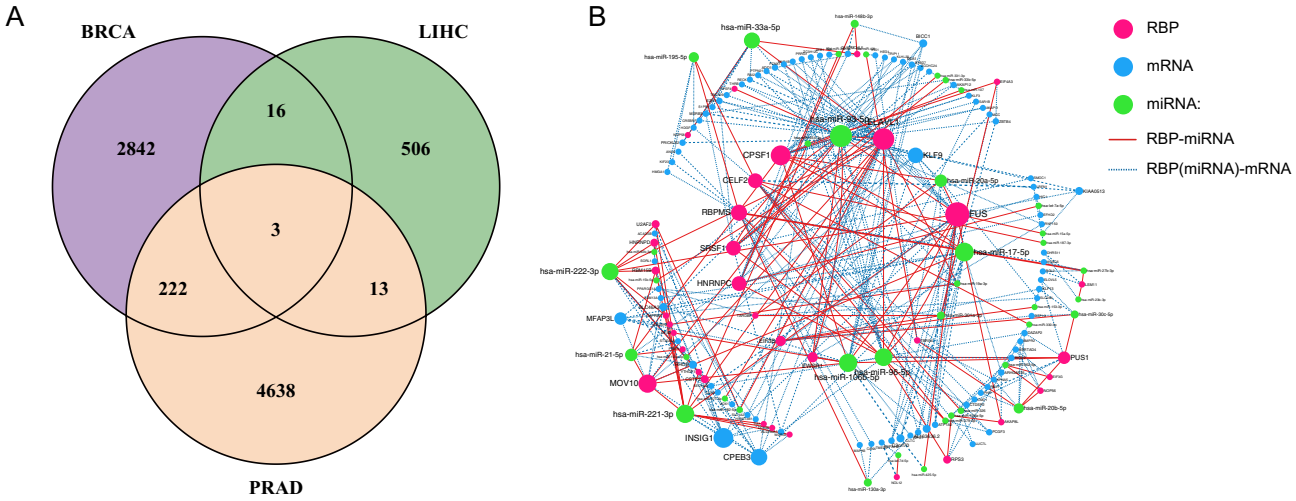

Fig. 3. Comparative analysis of miRNA–mRNA–RBP triplets across three cancer types. (**A**) Venn diagram shows the distribution of miRNA–mRNA–RBP triplets among BRCA, LIHC and PRAD. (**B**) miRNA–mRNA–RBP triplet network represents the interaction among miRNAs, mRNAs and RBPs.

same mRNA transcript. Secondly, while a small percentage of the miRNA–mRNA–RBP triplets show negative "synergy-redundancy" scores in three cancer types, the low Pearson correlation coefficient between miRNA and RBP, with an average value of 0.2, indicates a lack of substantial functional similarity, preventing the formation of a competitive regulatory pattern. This divergence in functional similarity explains the limited redundancy information shared by miRNAs and RBPs concerning the common target mRNA. These findings emphasize the critical role of targeting miRNAs-RBPs regulatory nodes in the post-transcriptional regulation of mRNAs, offering a new perspective on the mechanisms underlying gene expression imbalance in cancer initiation and progression. In-depth analysis of cancer-related data revealed that the synergistic interaction between specific miRNAs and RBPs results in the suppression of shared target gene expression during cancer development. This suppression likely contributes to the malignant transformation of cells and the overexpression of abnormal proteins, which in turn promotes hallmark cancer traits such as sustained cell proliferation and enhanced invasiveness. This synergistic effect may act as a catalyst in cancer progression, accelerating tumor growth. Therefore, targeting this regulatory network, particularly by knocking out key factors within miRNAs or RBPs to disrupt their cooperative mechanism, could be effective in suppressing the malignant phenotype of cancer cells and inhibiting tumor progression and metastasis. A thorough understanding of the intricate interactions among miRNAs, RBPs, and mRNAs will not only provide insights into the molecular basis of the synergistic regulation in cancer, but also lay a strong theoretical foundation for the development of combined blockade strategies.

In conclusion, we introduced a novel computational approach that is dedicated to investigating the intricate interplay between miRNAs and RBPs when they jointly target the common mRNA. Our findings illustrated a pervasive coordinated molecular mechanism in gene regulation where miRNAs and RBPs collaborate to regulate mRNA expression, thereby shedding light on the multifaceted nature of RNA-level gene regulation. In this study, a nonlinear computational model was employed to predict and preliminarily uncover the synergistic regulatory patterns between miRNAs and RBPs. However, the predicted results may include false positives, which require further experimental validation. This research lays the groundwork for experimental investigations into cancer-specific mechanisms. Future targeted experimental validations across various malignant tumors can identify key intervention targets, further elucidate their functional mechanisms, and provide novel directions for the development of targeted therapeutic strategies. This research significantly contributes to our understanding of the intricate regulatory networks governing gene expression, highlighting the collaborative efforts of miRNAs and RBPs.

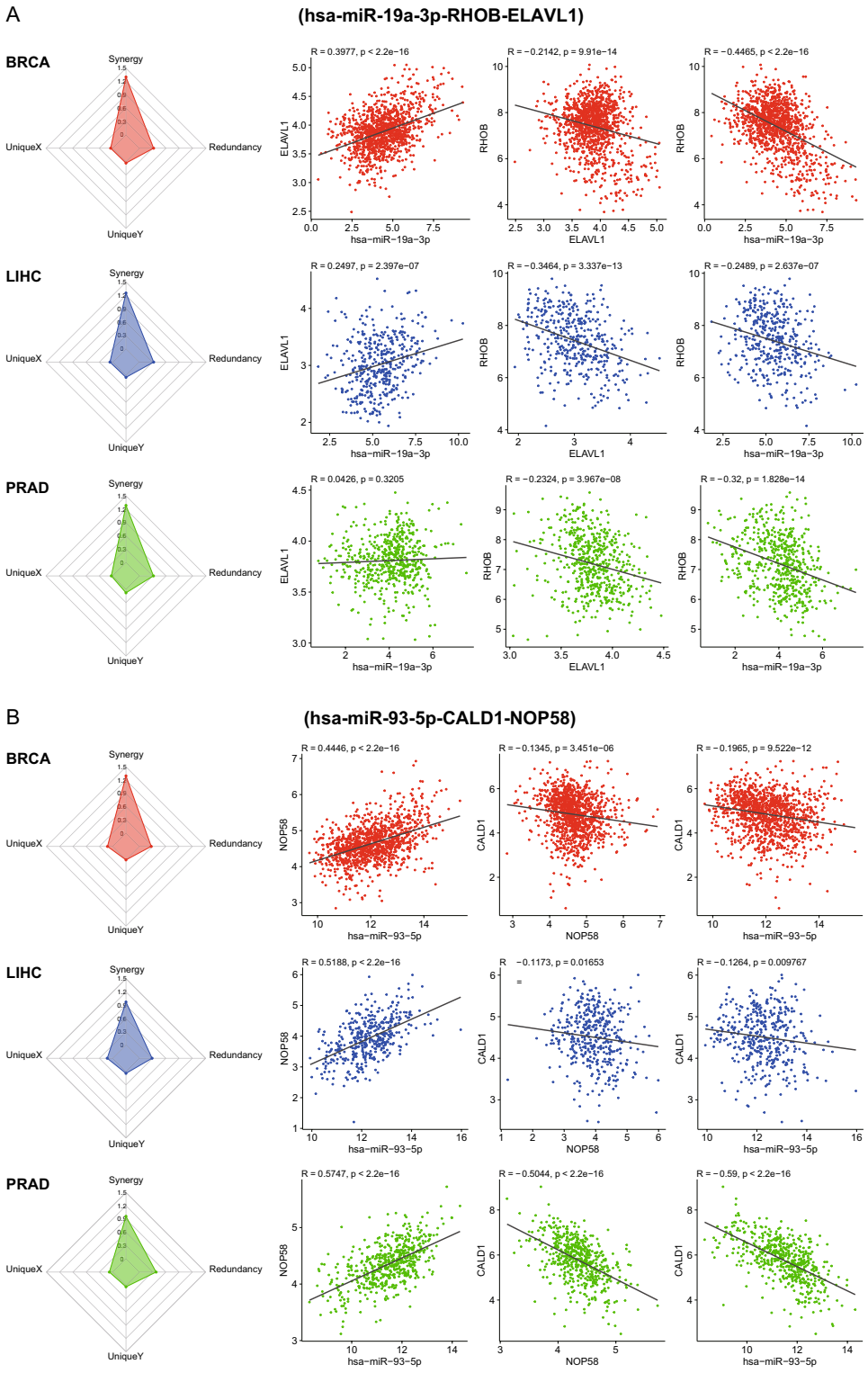

Fig. 4. Information variables and correlation analysis for miRNA–mRNA–RBP triplets in three cancer types. (**A**) Radar plots and scatter plots represent the information variables and correlation coefficients for the miRNA–mRNA–RBP triplet hsa-miR-19a-3p-RHOB-ELAVL1 across BRAC, LIHC and PRAD. (**B**) Radar plots and scatter plots represent the information variables and correlation coefficients for the miRNA-mRNA-RBP triplet hsa-miR-93-5p-CALD1-NOP58.

Data availability

The RNA-seq datasets for three cancer types are publicly available from the TCGA data repository at https://cancergenome.nih.gov/. Additional datasets supporting the conclusions of this article are included within the article and its supplementary information files.

Code availability

The PID was implemented in our previously developed R package, Informeasure[38]. The source code supporting the conclusions of this study is available at the GitHub repository https://github.com/sl74910/miRNA_RBP_Interaction_Analysis.

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Author contributions

T.Z. conceptualization, algorithm development, results analysis, writing-original draft and funding acquisition. Y.C. algorithm development, results analysis, writing-original draft. W.W. data integration, writing-original draft. C.P. conceptualization, supervision, algorithm development, writing-review and editing, and funding acquisition.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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