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Identifying and characterizing drug sensitivity-related lncRNA-TF-gene regulatory triplets

Congxue Hu[†], Yingqi Xu[†], Feng Li[†], Wanqi Mi, He Yu, Xinran Wang, Xin Wen, Shuaijun Chen, Xia Li [iD], Yanjun Xu and Yunpeng Zhang [iD]

Corresponding authors: Yunpeng Zhang, College of Bioinformatics Science and Technology, Harbin Medical University, Harbin 150081, China. Tel.: +86-451-86615922; Fax: +86-451-86615922; E-mail: zhangyp@hrbmu.edu.cn; Yanjun Xu, College of Bioinformatics Science and Technology, Harbin Medical University, Harbin 150081, China. Tel.: +86-451-86615922; Fax: +86-451-86615922; E-mail: xuyanjun@hrbmu.edu.cn; Xia Li, College of Bioinformatics Science and Technology, Harbin Medical University, Harbin 150081, China. Tel.: +86-451-86615922; Fax: +86-451-86615922; E-mail: lixia@hrbmu.edu.cn
[†]These authors have contributed equally to this work.

Abstract

Recently, many studies have shown that lncRNA can mediate the regulation of TF-gene in drug sensitivity. However, there is still a lack of systematic identification of lncRNA-TF-gene regulatory triplets for drug sensitivity. In this study, we propose a novel analytic approach to systematically identify the lncRNA-TF-gene regulatory triplets related to the drug sensitivity by integrating transcriptome data and drug sensitivity data. Totally, 1570 drug sensitivity-related lncRNA-TF-gene triplets were identified, and 16 307 relationships were formed between drugs and triplets. Then, a comprehensive characterization was performed. Drug sensitivity-related triplets affect a variety of biological functions including drug response-related pathways. Phenotypic similarity analysis showed that the drugs with many shared triplets had high similarity in their two-dimensional structures and indications. In addition, Network analysis revealed the diverse regulation mechanism of lncRNAs in different drugs. Also, survival analysis indicated that lncRNA-TF-gene triplets related to the drug sensitivity could be candidate prognostic biomarkers for clinical applications. Next, using the random walk algorithm, the results of which we screen therapeutic drugs for patients across three cancer types showed high accuracy in the drug-cell line heterogeneity network based on the identified triplets. Besides, we developed a user-friendly web interface-DrugSETs (http://bio-bigdata.hrbmu.edu.cn/DrugSETs/) available to explore 1570 lncRNA-TF-gene triplets relevant with 282 drugs. It can also submit a patient's expression profile to predict therapeutic drugs conveniently. In summary, our research may promote the study of lncRNAs in the drug resistance mechanism and improve the effectiveness of treatment.

Keywords: lncRNA-TF-gene triplets, drug sensitivity

Introduction

Despite the great advances in cancer research over the past decades, the treatment of cancer is still confronted with serious challenges. Among them, drug resistance is still a major limiting factor for the realization of curing cancer patients [1, 2]. Many factors contribute to drug resistance in cancer treatment, including tumor burden and growth dynamics, and correlations between tumor burden and curability were almost universal [3, 4]. In particular, heterogeneity of tumors can also lead to the development of drug resistance [2, 5, 6], and the tumor microenvironment may mediate drug resistance through various mechanisms, including block tumor cell immune clearance and hinder the drug absorption to promote the growth of tumor cells [7, 8]. Although the mechanisms of drug resistance in some tumors are well understood, most of them remain unknown. Therefore, it is meaningful to study the mechanism of cancer drug resistance and to predict individualized drug screening.

LncRNA is a new type of non-coding RNA with a length of over 200 nt and no protein coding ability [9, 10]. Furthermore, lncRNAs are abnormally expressed in a variety of human diseases and play an important role in promoting or maintaining disease progression. Previous studies have shown that lncRNA is involved in the regulation of drug resistance in various cancers [11–14]. LncRNA can mediate drug resistance by regulating the expression of genes related to drug sensitivity [15–17]. For instance, overexpression of lncRNA H19 was correlated with acquired resistance to cisplatin, and lncRNA NBR2 can regulate the sensitivity of cancer cells to biguanide by regulating GLUT1 [18]. Moreover, downregulated expression of lncRNA HOTAIR inhibited the expression of MRP, leading to increased sensitivity of cells to imatinib [19]. In addition to regulating genes related to drug sensitivity, lncRNAs can also affect drug sensitivity by affecting the upstream and downstream regulatory mechanisms of drug sensitivity-related genes. Experiments have confirmed that lncRNA can regulate the expression of transcription factors and then regulate the expression of transcription factor target genes to cause the body to develop drug resistance. For example, Zhang *et al.* [20] demonstrated that the lncRNA FOXC2-AS1 may promote doxorubicin resistance in OS by increasing the expression of transcription factor FOXC2, further facilitating ABCB1 expression. Özeş *et al.* [21] presented the opinion that HOTAIR regulates the activation of NF-κB and establish that by inducing prolonged NF-κB activation

and expression of transcription factor NF-κB target genes during DNA damage, HOTAIR plays a critical role in platinum sensitivity. Wu *et al.* [22] proved that LINC00160 mediated paclitaxel-and doxorubicin-resistance in breast cancer cells by regulating TFF3 via transcription factor C/EBPβ. Therefore, it is meaningful to study the role of lncRNA in mediating TF-gene regulation for understanding the mechanism of cancer drug resistance. These studies are only studies on the regulatory mechanism of a lncRNA for a pair of TF-target genes in a certain drug response. Therefore, there is an urgent need to develop a method to systematically identify lncRNAs that can mediate the regulation of TF-target genes in drug sensitivity.

Predicting the patient's drug response based on various genetic information is a basic problem in current precision medicine research. Most of the current approaches use genes or pathways to build predictive models to predict drug responses [23–25]. For example, Garnett *et al.* [26] systematically identified drug sensitive genomic markers in cancer cells. And Zhang *et al.* [27] proposed a method to identify significantly associated biomarkers and develop genomic classifier using hierarchical ordinal logistic regression to predict multi-level drug response using hierarchical ordinal regression. In addition, Wang *et al.* [25] developed a method to predict drug sensitivity of cancer cells with pathway activity inference. Ammad-Ud-Din *et al.* [28] presented a method to predict drug response by inferring pathway-response associations with kernelized Bayesian matrix factorization. These methods provide help for predicting drug response, but new research is still needed.

Here, we first developed a method to systematically construct lncRNA-TF-gene regulatory triplets and totally identified regulatory triplets associated with 282 drugs. Based on these identified triplets, we constructed a drug-cell line heterogeneity network. Finally, we apply the method to individualized applications, screen therapeutic drugs for The Cancer Genome Atlas (TCGA) patients and verify their accuracy. In addition, our method was also more accurate than other methods in predicting cancer cell lines associated with drug sensitivity. We have identified a total of 1570 triplets related to drug sensitivity. Drug similarity analysis showed that drugs with a high number of shared triplets also had higher phenotypic similarities, including the structure and indications of the drugs. We investigated in depth the role of LncRNA in drug resistance mechanisms. Our analysis revealed the differential regulatory mechanism of lncRNA in different drugs. In addition, lncRNA-TF-gene that are survival related were identified as potential oncogenic drivers. Through our proposed method, we can commendably find appropriate therapeutic drugs for patients. As a consequence, our method has guiding significance for individual drug screening and drug response prediction. Finally, we have developed a data resource that not only captures the triplets associated with the drug sensitivities but also screens the appropriate treatment agents for individuals.

Materials and methods
Drug IC50 and gene expression profile of cancer cell lines

We downloaded the half maximal inhibitory concentration (IC50) value of drugs in cell lines from The Genomics of Drug Sensitivity in Cancer (GDSC) database (https://www.cancerrxgene.org/) [29]. IC50 is the concentration of a drug or inhibitor required to inhibit half of a specified biological process (or a component in the process, such as enzymes, receptor cells, etc.). The dataset comprises 304 drugs and 988 cell lines. And we downloaded gene expression data from The Cancer Cell Line Encyclopedia (CCLE)

(www.broadinstitute.org/ccle) [30]. The dataset consisted of expression values of 57 820 genes in 1019 cell lines. We extracted 297 cell lines common to GDSC database and CCLE database. Next, we filtered out genes whose expression value was 0 in more than half of the cell lines. After the previous step, we obtained a gene expression profile consisting of 25 655 genes and 297 cell lines.

Collection of the TF and its target genes data from TRANSFAC

The data of TF and its target genes are obtained from the TRANSFAC (http: //transfac. Gbf. De/TRANSFAC/) / (http://gene-regulation.com/) database [31]. It contains 708 transcription factors and 1991 target genes, and a total of 5825 regulatory relationships are formed between transcription factors and target genes.

Gene expression data and drug response data of tumor individuals

We downloaded the gene expression data and drug response information of the samples from TCGA (https://portal.gdc.cancer.gov/) database. We define Complete Response and Partial Response samples for drug treatment as samples that respond to treatment, and define Clinical Progressive Disease and Stable Disease samples as samples that do not respond to treatment. Thus, the data set contains 1576 non-response samples and 2296 response samples.

Identification of the lncRNA-TF-gene regulatory triplets associated with drug sensitivities
Construction of candidate lncRNA-TF-gene regulatory triplet

Here, we proposed a concept of lncRNA-TF-gene triplet based on that LncRNA can mediate the regulation between TF and target genes. We constructed the lncRNA-TF-gene triplets through the following three steps: (i) We divided the cell lines into two groups according to the level of lncRNA expression. (ii) We calculated the correlation between TF and target gene in the two groups of cell lines by Pearson correlation coefficient according to the expression value. Through this step, we can obtain the expression correlation r1 between TF and target gene in cell lines with high lncRNA expression and r2 between TF and target gene expression in cell lines with low lncRNA expression. (iii) The difference between the two correlations was used as a criterion to determine whether lncRNA could mediate regulation of TF and its target genes. That is, $\Delta r = | r_1 - r_2 |$. If $\Delta r > 0.7$, it is believed that lncRNA can mediate the regulation of TF and target genes, so lncRNA, TF, gene can be used as a candidate triplet (Figure 1A).

Evaluating the associations of triplets with drug sensitivity

Based on the candidate triplets, we further screened the triplets related to drug sensitivity. The Spearman correlation coefficient was used to calculate the correlation between the IC50 value of the drug and the expression value of lncRNA. Similarly, the correlation between the expression value of target gene of TF and the IC50 value of the drug was calculated. LncRNA and target genes with *P*-value <0.05 were selected as drug sensitivity-related lncRNA and target genes. For a triplet, if both lncRNA and target gene are associated with drug sensitivity, this triplet is considered to be sensitivity-related triplet of the drug. In the end, for each drug, we screened its sensitivity-related triplets (Figure 1B).
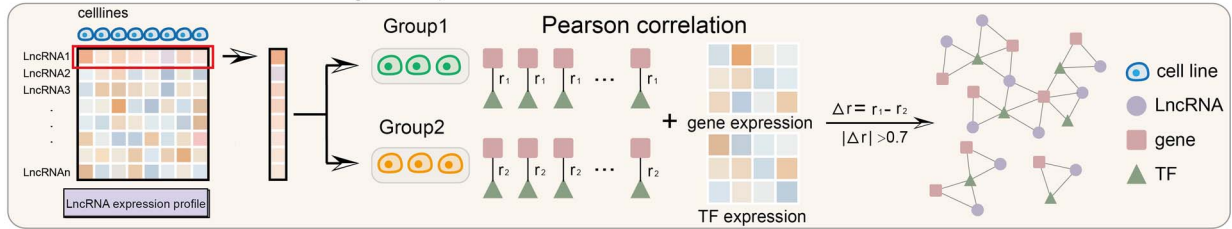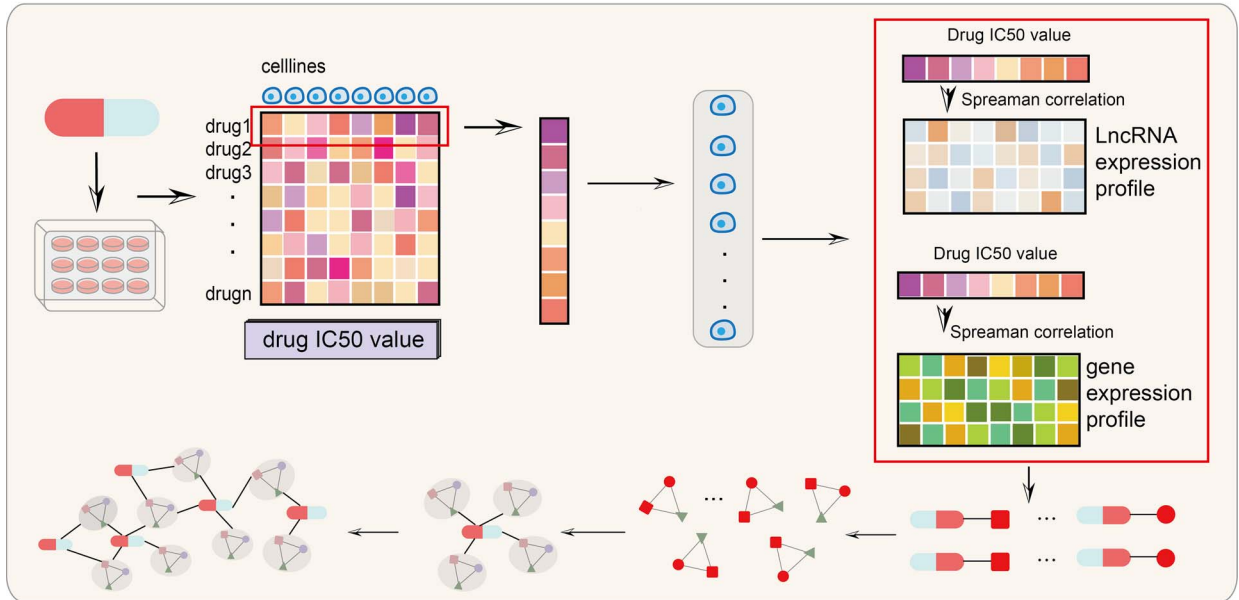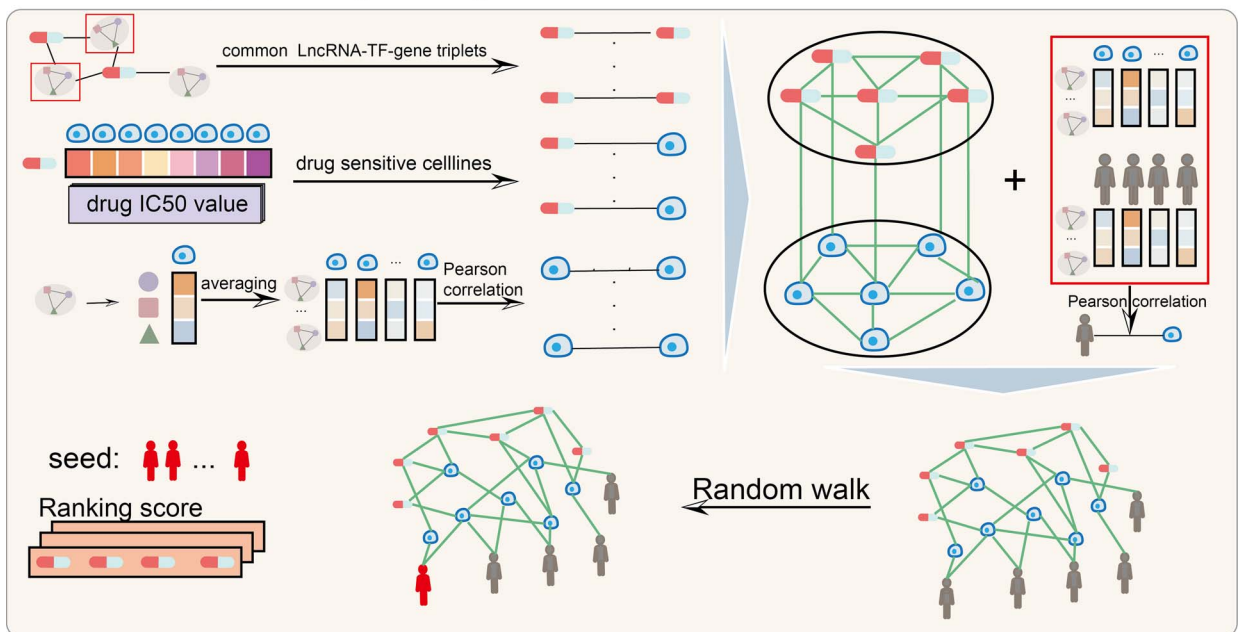
A.Construction of lncRNA-TF-gene triplet.

B.Identifying for triplets related to drug sensitivity.

C.Personalized precision drug screening.

Figure 1. Schematic overview of method for identifying drug sensitivity-related lncRNA-TF-gene regulatory triplets and individualized application.

Individualized drug screening based on drug sensitivity-related triplets
Construction of drug-cell line heterogeneity network

Based on the assumption that individuals with similar molecular characteristics have more similar targeted drugs, we further constructed a drug-cell line heterogeneous network through the following three steps: (i) Based on the screened triplets related to drug sensitivity, we constructed a drug–drug similarity network. An edge between two drugs means that there are shared triplets between them. (ii) In this step, we constructed a cell line similarity

network. We calculated the mean expression values of lncRNA, TF and gene of each triplet in the cell line as the activity values of the triplet in the cell line. The edge between the cell lines in the network represents a significant correlation between the triplet activity values of the two cell lines ($P < 0.05$ and $r > 0.8$ for Pearson correlation coefficient). (iii) Construction of drug-cell line sensitivity correlation based on drug sensitivity data. We sorted the cell lines from low to high according to the IC50 value of each drug in the cell line. We use the top 12.5% of cell lines as drug-sensitive cell lines to construct drug-cell line sensitivity associations. Through the above three steps, we can obtain a drug-cell line heterogeneity network (Figure 1C).

Individualized drug screening using random walk algorithm

Random walk is a globally optimal method. Random walk algorithms have been developed and used in the analysis of various disease mechanisms, and have shown greater advantages in identifying risk or prognostic genes based on global networks [32–34]. It has been demonstrated in the literature that random walks capture global relationships within interaction networks, substantially outperforming local distance measures within interaction networks, as well as other previously published methods. Therefore, we use random walk algorithm for individual drug screening and drug response prediction. Based on the drug-cell line heterogeneity network constructed by the above steps, personalized drug selection was realized through the following three steps: (i) For a disease sample, we calculated the activity values of triples associated with drug sensitivity in the sample. (ii) Pearson correlation coefficient is used to calculate the correlation between the sample and the cell line based on the activity value of the triplets. Similarly, we screened for cell lines and samples with the P-value of <0.05 and the correlation coefficient greater than 0.8, and add them to the network. (iii) We use the sample as a seed node and use random walk algorithm [32] (Equation (1)) to score the nodes in the network.

$$P^{t+1} = (1 - r) WP^t + rP^0, \qquad (1)$$

where W is the adjacency matrix of the global network, which consisted of 0 and 1. P^t was a vector, in which a node in the global network has the probability of finding itself in this process until the step t. The initial probability vector P^0 is constructed in this way, the seed node is 1 and the remaining nodes are 0. In addition, the walker is restarted at each step with a probability r ($r = 0.7$). When the difference between P^t and P^{t+1} is less than 10^{-6}, the probability reaches a steady state. Finally, each node in the global network is scored according to the value in the steady-state probability vector. The scores of all drugs in the network are extracted. A higher score indicates that the sample is more similar to a drug-adapted sample. The more likely the drug was to be a candidate for that patient's treatment (Figure 1C).

Calculating the similarity score of structure and indication between drugs

We use the R package RxnSim [35] based on the two-dimensional structure of drugs, which provides a method to calculate the chemical similarity between two or more reactions and molecules. Molecular similarity is calculated according to the structural characteristics of drugs. The package can calculate the structural similarity between drugs according to the structural information of SMILES format, using the Tanimoto coefficient.

And the similarity of indications between drugs was calculated using Jaccard coefficient (Equation (2)).

$$\text{Indication similarity}_{(a,b)} = \frac{A \cap B}{A \cup B}, \qquad (2)$$

where A and B represent indications for drug A and drug B, respectively.

Results
Characterizing the lncRNA-TF-gene triplets related to 282 drugs sensitivity

In order to better understand the role of lncRNAs regulating TF-gene pairs in drug sensitivity, we systematically identified and analyzed the lncRNA-TF-gene regulatory triplets associated with drug sensitivity. First, we totally constructed 3118 lncRNA-TF-gene triplets. Then, we screened out drug sensitivity-related 2482 lncRNAs and 1382 TF target genes. In total, we identified 1570 lncRNA-TF-gene triplets of 282 drugs, and 16 307 relationships were formed between drugs and triplets. Next, we divided 282 drugs into 15 classes, which are Antineoplastic Agents, Enzyme Inhibitors, Antimitotic Agents, Anti-Infective Agents and so on according to the Drug Information Portal [36] (Supplementary Figure S1, see Supplementary Data available online at https://academic.oup.com/bib). In addition, a total of 1059 lncRNAs were involved in the drug sensitivity-related triplets, most of which were related to the antineoplastic agents sensitivity (Figure 2B). For example, through our method, lncRNA FLNB-AS1 was identified as a lncRNA associated with Tamoxifen sensitivity, and literature has confirmed that FLNB-AS1 may be a potential diagnostic or prognostic marker of Tamoxifen resistance [37]. Moreover, many lncRNAs related to drug sensitivity have been confirmed in literature, including FOXD2-AS1 [38], LINC00641 [39], LBX2-AS1 [40] and so on. Next, we systematically characterized these lncRNAs. They mainly belonged to long intergenic non-coding RNA (lincRNA) and antisense classes (Figure 2C). We constructed a circular chromosome map to provide a global view of genomic location annotation of each lncRNA across 15 drug classes, and the types of lncRNAs in each drug class were also shown (Figure 2A). We observed that most of these lncRNAs distributed in chr1, chr2, chr6, chr12, chr17 and chr19.

To understand the function of these target genes that involved in drug sensitivity-related triplets, we performed functional enrichment analysis for target genes in the drug sensitivity-related triplets which were related to the sensitivity of more than 50 drugs. As a result, we found that the genes were significantly enriched on the response to corticosteroid and response to antineoplastic agent in the biological process part of GO, and they were enriched on vesicle lumen and growth factor binding in the cellular component and molecular function, respectively. Furthermore, the genes were also enriched on HIF-1 signaling pathway and Apoptosis in KEGG (Figure 2D). Hallmark gene set better represents a wider range of biological processes and cancers. Therefore, we enrich the target genes in the triplets related to anticancer drug sensitivity with Hallmark gene set. The result suggests that multiple pathways, including evading immune detection, insensitivity to antigrowth signals and self-sufficiency in growth signals, as well as sustained angiogenesis and tissue invasion and metastasis, were targeted by genes in some antineoplastic agents (Figure 2E). Drug sensitivity-related triplets whose genes were enriched in eight pathways across drug
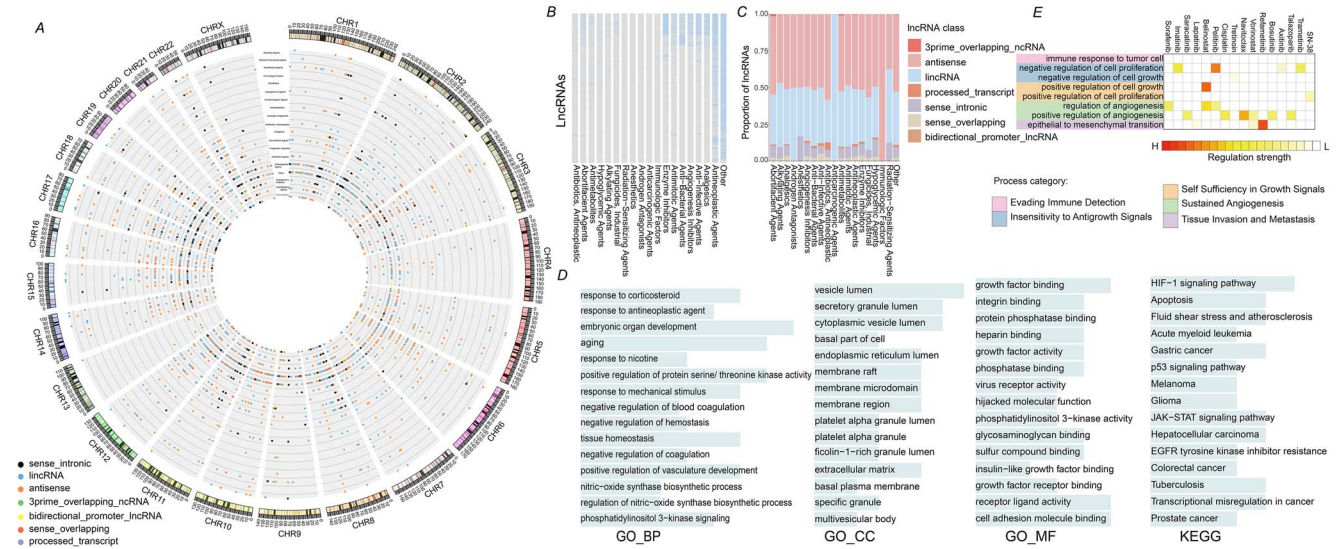
Figure 2. (**A**) A global map of LncRNAs in sensitivity-related triplets of different drug types. (**B**) Categories of lncRNAs in different types of drugs. (**C**) Genomic locations of lncRNAs. Each dot refers to a lncRNA. The colors of the dots represent different types of lncRNAs. The dot tracks correspond to different drug types. (**D**) GO function enrichment and KEGG pathway enrichment of genes in the triplets related to drug sensitivity. (**E**) Hallmark gene sets of genes in the triplets related to drug sensitivity. The regulation strength represents the *P*-value in the hypergeometric test, and the smaller the *P*-value, the higher the regulation strength.

types, including immune response to tumor cell and negative regulation of cell proliferation and so on. This indicates that these genes can affect multiple biological functions.

Drug-related triplets reveal the similarity of drug structures and indications

In order to better understand the relationship between drugs with a large number of shared triplets, we integrated the two-dimensional structure information of drugs from PubChem [41] and used the R package RxnSim [35] to calculate the structural similarity between them (Figure 3E). Interestingly, we found that drugs with a high number of shared triplets had higher structural similarity than drugs with a low number of shared triplets (*P* = 0.014) (Figure 3A, B and F). In addition, we also download the drug-disease associations from the Comparative Toxicogenomics Database [42]. By calculating the Jacquard coefficient, we found that drugs with more shared triplets related to drug sensitivity had higher similarity in their indications. In other words, if there are more triplets shared between drugs, the diseases they treat will be more similar (*P* = 0.00054) (Figure 3C, D and G). In summary, drugs with a large number of shared triplets showed higher similarity in both the two-dimensional structure and the indication compared with those with a small number of shared triplets. This indicates that the triplets related to drug sensitivity that we have identified have potential clinical applications.

In order to make results more reliable, we compared the results with those of the random case. We randomly selected from the shared with large and small quantity of triplets' drugs of the same number of drug combinations, and calculate two-dimensional structure similarity and similarity of indications between each pair of drug combination. Next, the two-dimensional structure similarity score and indication similarity score of all drug pairs are averaged as the structure similarity score and indications similarity score between drugs under random conditions. By comparing with the real results, we found that the similarity score of drug indications with more shared triplets was significantly higher than that of random cases, while the similarity scores of drug indications with few shared triplets were significantly lower than

those of random cases. (Supplementary Figure S2A, see Supplementary Data available online at https://academic.oup.com/bib). Similarly, the same results were observed for the comparison of structural similarity scores of drugs (Supplementary Figure S2B, see Supplementary Data available online at https://academic.oup.com/bib). This shows that our results have good stability.

Depicting high-frequency drug sensitivity related triplets and the diverse regulation of lncRNAs across drugs

Based on the above analysis results, we first separately counted the number of lncRNA and TF-gene pairs regulated drugs in the triplets related to drug sensitivity. Next, we counted the number of shared drugs in the top 40 lncRNAs and TF-gene pairs, and we found that there are common drugs between triplets (Figure 4A). Next, we construct the network of lncRNA-TF-gene triplets with the number of sensitivity-related drugs greater than 50 (Figure 4C). It is composed of some high-frequency triplets, including 64 lncRNAs, 36 TFs and 35 target genes. Among them, EGFR can affect the drug sensitivity of anti-dimerization agents (e.g. cetuximab) in non-small cell lung cancer (NSCLC) [43–45]. Besides, serum retinol binding protein 4 (RBP4) contributes to insulin resistance in obesity and type 2 diabetes [46–48]. And, luminal B tumors had the highest rates of ESR1 mutations and had increased sensitivity *in vitro* to bicalutamide and tamoxifen [49]. It shows that triplets can affect drug sensitivity in therapy of disease.

After that, we calculated the number of lncRNA-regulated TF-gene pairs in the triplets related to drug sensitivity. Next, we calculated the number of TF and target gene pairs regulated by the top 49 lncRNAs in antineoplastic agents (Figure 4B). We observed that the maximum number of TF and target gene pairs regulated by the lncRNA was 4. Next, we dissected lncRNA mediated TF-gene pairs and found that lncRNA not only regulated the same TF-gene pairs in different drugs but also regulated different TF-gene pairs. For example, lncRNA RP3-508I15.19 regulates RARA-EGFR pair in both Belinostat and Trametinib, but it also regulated CEBPA-CES1 pair and CEBPA-CPB2 pair in
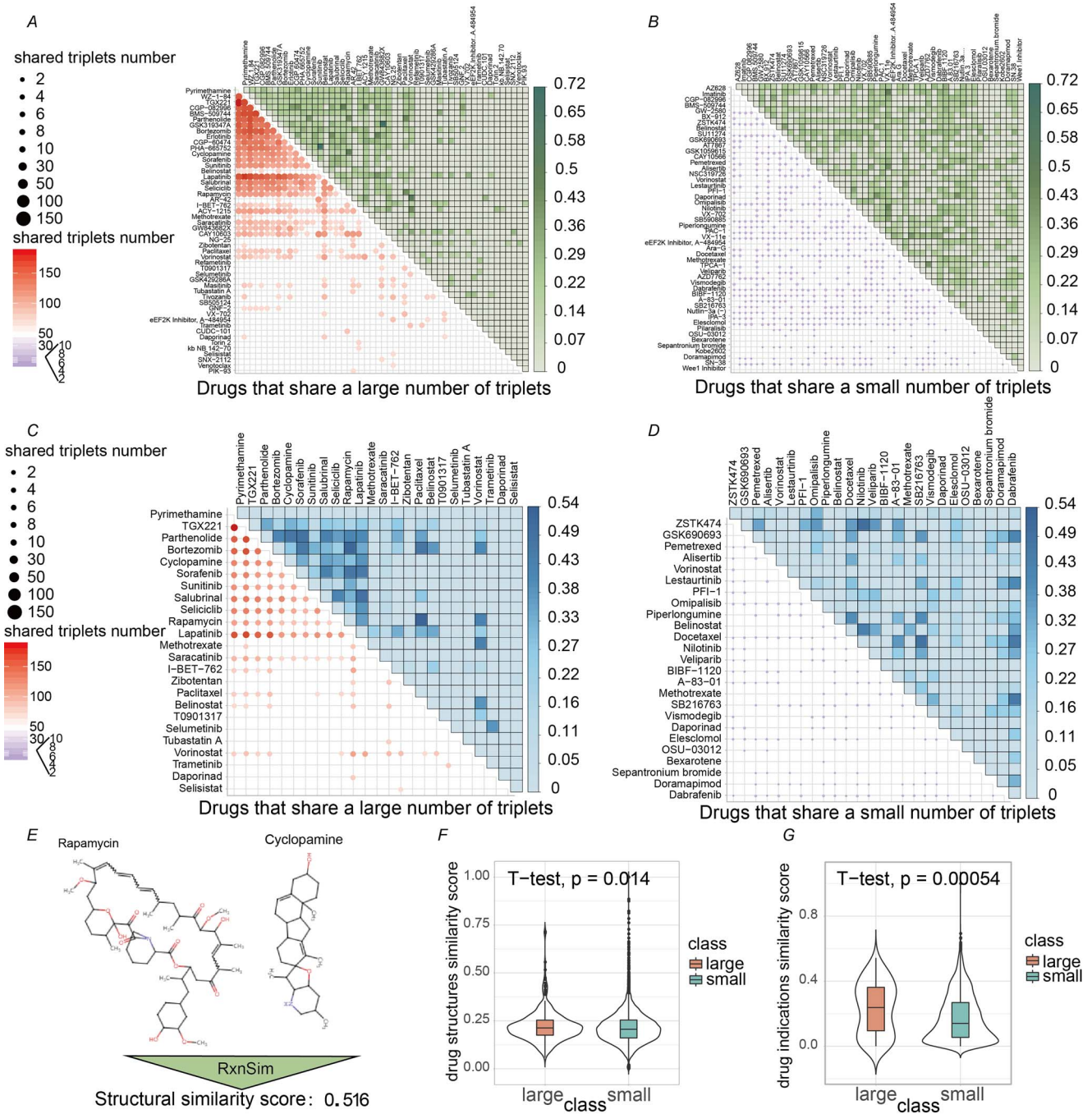
Figure 3. (A) The heat map shows the similarity score of two-dimensional structures between drugs sharing more than 70 triplets (upper triangle). The dot plot shows the number of triplets shared between drugs sharing more than 70 triplets (lower triangle). The size and color of the dots represent the number of triplets. **(B)** The heat map shows the similarity score of two-dimensional structures between drugs sharing less than 10 triplets (upper triangle). The dot plot shows the number of triplets shared between drugs sharing less than 10 triplets (lower triangle). The size and color of the dots represent the number of triplets. **(C)** The heat map shows the similarity score of disease phenotype between drugs sharing more than 70 triplets (upper triangle). The dot plot shows the number of triplets shared between drugs sharing more than 70 triplets (lower triangle). The size and color of the dots represent the number of triplets. **(D)** The heat map shows the similarity score of disease phenotype between drugs sharing less than 10 triplets (upper triangle). The dot plot shows the number of triplets shared between drugs sharing less than 10 triplets (lower triangle). The size and color of the dots represent the number of triplets. **(E)** A map of calculating two-dimensional structural similarity between drugs. **(F)** The violin chart shows differences in structural similarity scores between the two groups of drugs. Large represents drugs with more shared triplets, and small represents drugs with fewer shared triplets. **(G)** The violin chart shows differences in disease phenotype similarity scores between the two groups of drugs. Large represents drugs with more shared triplets, and small represents drugs with fewer shared triplets.

the Belinostat and regulated IKZF1-CD8A pair and TCF7-CD8A pair in the Trametinib, respectively. Furthermore, Belinostat markedly decrease the expression of EGFR in the NSCLC cell [50]. Besides, in case of wild-type KRAS and high EGFR expression, MEK inhibitor-induced Akt phosphorylation leads to trametinib resistance [51–53]. In addition, similar results were also found in LINC01589 (Figure 4D). The above analysis further revealed that drug-related triplets can affect drug sensitivity. Although
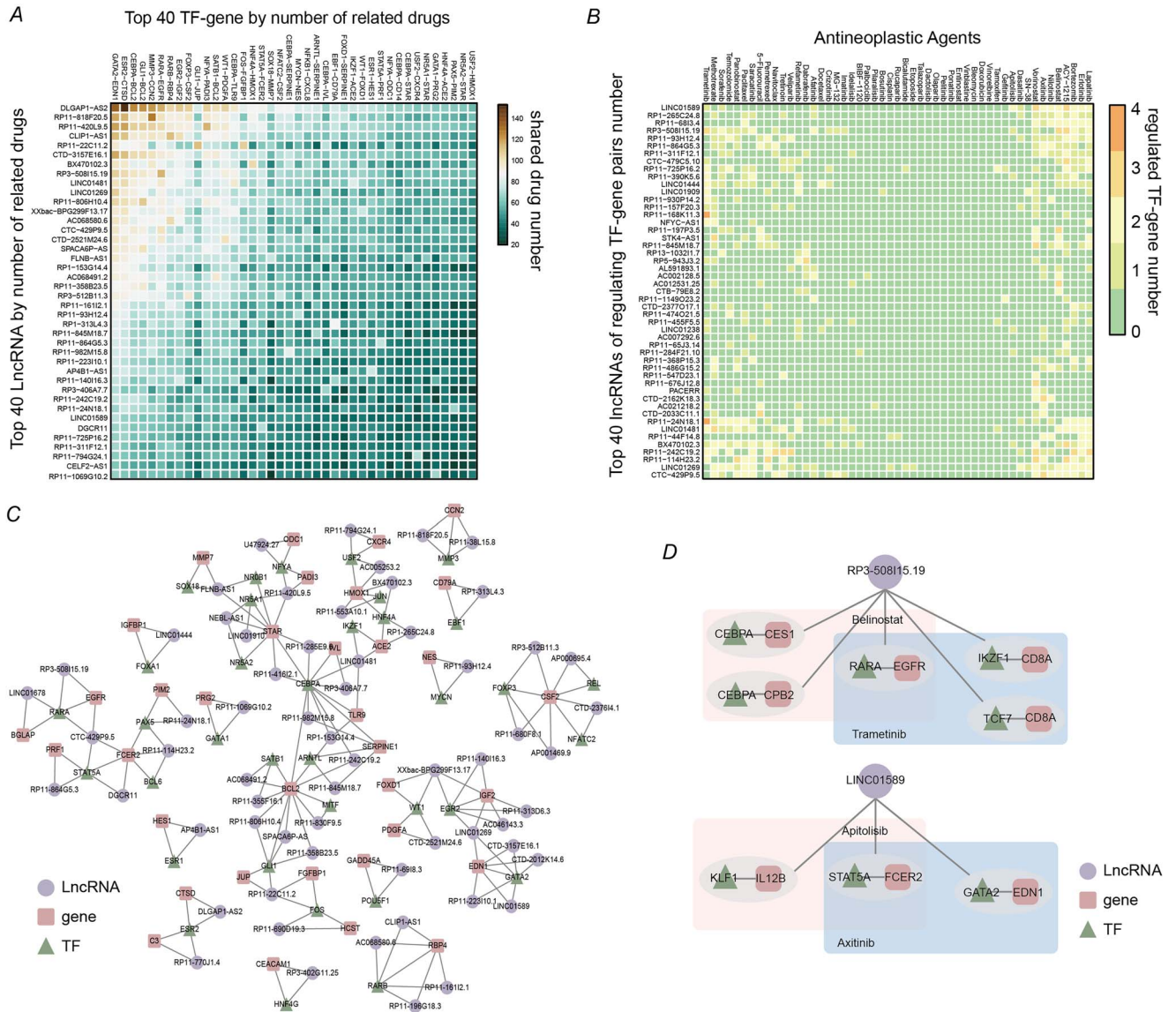
Figure 4. (**A**) The heat map shows the number of shared drugs between lncRNAs and TF- gene regulation pairs with the number of related drugs ranked in top 40. (**B**) The heat map shows the number of TF and target gene pairs regulated by lncRNAs in antineoplastic agents. Simultaneously, the number of TF-gene regulation pairs regulated by these lncRNAs were ranked in top 40. (**C**) A regulatory network of triplets which associated with more than 50 drugs. The circles represent lncRNAs, the triangles represent TFs and the rectangles represent genes. (**D**) LncRNA RP3-508I15.19 and LINC01589 regulates TF-gene pairs in different drugs.

lncRNA regulated many identical TF and target gene pairs in different drugs, lncRNA also regulates TF and target gene pairs differently in different drugs. This indicates the differential regulation mechanism of lncRNA in different drugs. It can also help us better understand the mechanism of drug resistance and provide new ideas for subsequent research.

Drug-related triplets could be potential biomarkers for cancer prognosis

The above analyses revealed that drug-related triplets play an important role in mechanism of drug resistance. This highlighted that they may serve as promising biomarkers to affect the survival of cancer patients. To assess the clinical relevance of these triplets, we integrated the clinical data and then perform the survival analysis for CESC, BLCA and HNSC. As a result, we totally identified 497 (32%) survival-related triplets in three cancer types, and the proportions of survival-related triplets in three cancer

types were shown in Figure 5A. Among them, HNSC has most survival related triplets, about 55% (Figure 5A). This indicated that lncRNA-TF-gene triplets could affect prognosis of cancer patients.

Further exploration of these survival-associated triplets found that some experimentally validated cancer prognostic markers were included. For example, AP001469.9- FOXP3- CSF2 was identified as a survival-related triplet in the BLCA (Figure 5B) and has been demonstrated that CSF2 overexpression is associated with STAT5 phosphorylation and poor prognosis in patients with urothelial carcinoma [54]. In addition, RP11-152P23.2-RARA-EGFR was also identified as a survival-related triplet in the CESC (Figure 5C), and the EGFR was found to act as a strong prognostic indicator in cervical cancer [55–58]. Moreover, another tripletRP11-547D23.1-IKZF1-FGFR4 was significantly prognostic-related with HNSC (Figure 4D), and it is demonstrated that STAT5A was found to be associated with a poor prognosis for head and neck squamous cell carcinoma [59–61]. The
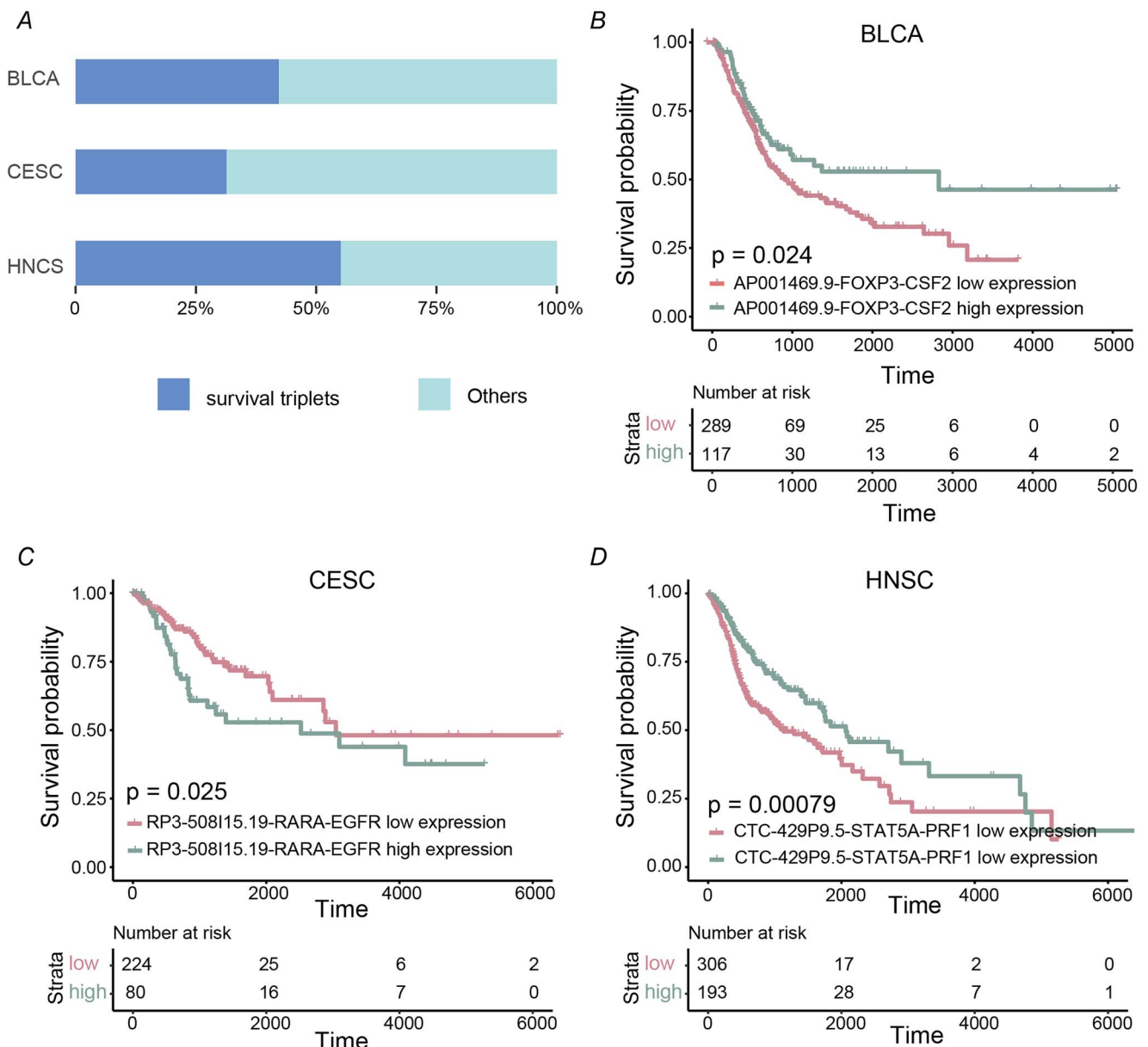
Figure 5. (**A**) The percentages of survival-related triplets in the 3 cancer types. (**B–D**) K-M plots of samples from the low expression group and samples from the high expression group for PAXIP1-AS1-POU2F2-BLC2, RP11-152P23.2-RARA-EGFR and RP11-547D23.1-IKZF1-FGFR4 in 3 cancer types, respectively.

above observation provided further evidence for conclusion that lncRNA-TF-gene triplets play a via role in promoting the development of cancer. In summary, our analysis indicated the driving roles of triplets and their potential clinical usages as prognosis biomarkers in cancer.

Application for screening individual medication and drug sensitive cell lines

The above studies found that the drug sensitivity-related lncRNA-TF-gene regulatory triplets we identified could reflect the similarity of therapeutic phenotypes between drugs. Therefore, we attempted to personalize the application by identifying the lncRNA-TF-gene triplets associated with drug sensitivity.

Case Study I: Individual drug screening.

First, we built a network of drugs and cell lines, in which there are edges between drugs and drugs, cell lines and cell lines, and

drugs and cell lines. Next, we connected the sample to the cell line by the Pearson correlation coefficient between the activity values of the triplets in the sample and in the cell line. Finally, we use the sample as a seed node to perform a random walk to score drugs in this network (Materials and Methods). For purpose of evaluating the accuracy of the method, we applied the method to the bladder urothelial carcinoma (BLCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) and head and neck squamous cell carcinoma (HNSC) data in TCGA. The ROC curve was drawn based on the drug response data of the sample in TCGA and the drug scores calculated by random walk for three cancer types. The AUCs of ROC curves of the BLCA, CESC and HNSC were 0.721, 0.824 and 0.713, respectively (Figure 6A). These results confirm the reliability of using our proposed method to screen therapeutic agents for individuals.

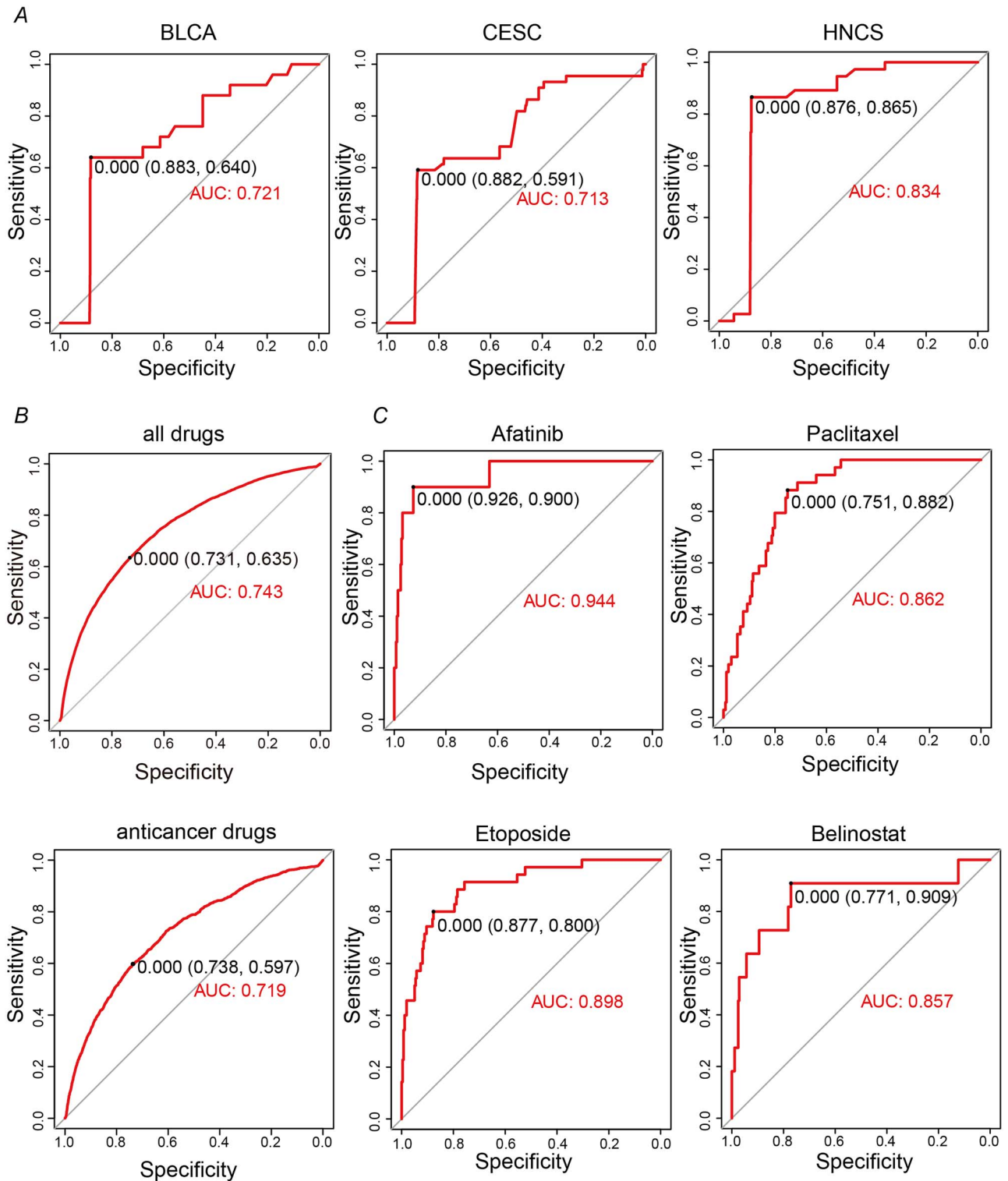Case Study II: Prediction of drug-sensitive cell lines.

Figure 6. (**A**) Predictive power of our method across three cancer-drug response datasets from TCGA, including BLCA, CESC and HNSC. (**B**) Predictive power of our method for drug-sensitive cell lines datasets, including all drugs, anticancer drugs. (**C**) Predictive power of our method for drug-sensitive cell lines datasets, including partial anticancer drugs Afatinib, Paclitaxel, Etoposide and Belinostat.

Through the above analysis, we found that the drug sensitivity-related triplets had good accuracy in predicting individual drug screening. Next, we further evaluated the predictive ability of the drug sensitivity-related triplets in terms of drug-sensitive cell line. Likewise, we use the drug as a seed node to execute random walk to score the cell lines (Materials and Methods). We drew ROC curves based on the random-walk calculated cell line scores and the gold standard of cell lines associated with drug sensitivity. As a result, the AUCs of the ROC curves of all drugs and antineoplastic agents were 0.743 and 0.719 (Figure 6B). Among them, the AUCs of the ROC curves of afatinib, paclitaxel and etoposide were 0.944, 0.862 and 0.898, respectively (Figure 6C). Furthermore, the BT-549

cell line was identified as a paclitaxel sensitivity-related cell line by our method, and through the drug sensitivity data in the GRAY database, we found that the IC50 value of paclitaxel in the BT-549 cell line was very low, indicating that the BT-549 cell line is a paclitaxel sensitivity-related cell line. This verifies the accuracy of our method at the experimental level. This shows that our method can accurately identify drug sensitive cell lines. This also provided guidance to the experimenters to subsequent the analysis.

To evaluate the accuracy of our method on independent data, we downloaded drug sensitivity data from the CellMiner database, in which 89 drugs overlapped with drugs in our previously constructed drug-cell line heterogeneity network, and 15 cell lines overlapped with cell lines in the network. Similarly, we use drugs as seed nodes to score cell lines on the network, and the results show that drug response prediction also has high accuracy. AUC value for all drugs is 0.711 (Supplementary Figure S3A, see Supplementary Data available online at https://academic.oup.com/bib). In particular, AUC values for 5-Fluorouracil, Cytarabine and Belinostat exceeded 0.9 (Supplementary Figure S3B–D, see Supplementary Data available online at https://academic.oup.com/bib). These results show that our method also has high accuracy on independent datasets.

To comprehensively evaluate the efficiency of our method in predicting drug response and compare our method with existing state-of-the-art methods, Zhang Fei *et al.* [62] propose a novel heterogeneous network-based method for drug response prediction in cancer cell lines—HNMDRP. We compare the method proposed in this paper with the HNMDRP method proposed by Zhang Fei *et al.* By comparing, we find that the accuracy of the prediction of both all drugs and anticancer drugs as a whole is higher than that of HNMDRP (Figure 6B and Supplementary Figure S4A and B, see Supplementary Data available online at https://academic.oup.com/bib). Furthermore, our individual drugs method also shows better prediction performance. For example, when using our method to predict afatinib sensitivity-related cell lines, the AUC value of the ROC curve was 0.944, while the AUC value using the HNMDRP method was 0.850 (Supplementary Figure S4C, see Supplementary Data available online at https://academic.oup.com/bib). In addition, our method is also much lower than HNMDRP in time complexity. From these results, we know that our method can predict drug response more accurately and efficiently than other state-of-the-art methods.

DrugSETs: An online database exploring sensitivity-related lncRNA-TF-gene triplets across 282 drugs

In order to promote the research of lncRNA-TF-gene Triplets in drug response prediction, we have developed DrugSETs (Drug SEnsitive related lncRNA-TF-gene Triplets), an online database of 282 drugs and their sensitivity-related lncRNA-TF-gene triplets. In total, DrugSETs documents 1631 entries of associations between 1570lncRNAs-TF-gene triplets and 282drugs. In addition to the name of the drug and the sensitivity-related triplet, each entry also includes the names and the Ensembl ID of lncRNAs, TF and genes as well as triplets score. The DrugSETs database is available at http://bio-bigdata.hrbmu.edu.cn/DrugSETs/.

DrugSETs provide a user-friendly interface mainly consisting of three modules: Search, Browse and Download. The quick search enables users to filter entries with one keyword of interest, such as a lncRNA (name or ensembl ID), or drug name. Also, an advanced search is provided in 'Search' page for more specific requirements. The users can input interested lncRNA and drug at the same time to obtain desired associations. In 'Browse' page, all lncRNAs

and drugs in DrugSETs are listed, respectively, for users to query. The search and browse results can be freely downloaded. In 'Prediction' page, Users can upload patients' expression profiles, and DrugSETs will screen them for appropriate treatment drugs. Furthermore, 'Help' page contains detailed guidance for users.

Discussion

In recent years, more and more attention has been paid to the role of lncRNA in drug resistance mechanism, and it has been reported that lncRNA can affect drug sensitivity. However, it remains a challenge to study the regulatory role of lncRNA in drug resistance mechanisms. In this study, the regulatory triplets of lncRNA-TF-gene related to drug sensitivity were systematically identified and individually applied, providing guiding significance for the screening of therapeutic drugs for patients and screening cell lines related to drug sensitivity.

In this study, we integrated human cancer transcriptome data and drug sensitivity data and developed a method to identify drug sensitivity-related lncRNA-TF-gene regulatory triplets. First, constructing the lncRNA-TF-gene regulatory triplets based on the transcriptome data. And we systematically characterized the identified lncRNA-TF-gene regulatory triplets. Dissecting the global properties of the regulatory triplets found that they widely affect a variety of biological functions including drug response. This indicated that the lncRNA-TF-gene regulatory triplets played an important role in drug response, which highlights the importance of its function prediction and analysis. And then identifying the drug sensitivity-related lncRNA-TF-gene regulatory triplets based on the drug sensitivity data. In addition, network analysis of lncRNA-TF-gene found that lncRNA affects drug sensitivity by regulating different TF-genes in different drugs. Furthermore, the survival analysis of the lncRNA-TF-gene regulatory triplets highlights its clinical application potential as a prognostic biomarker and suggests its driving role in cancer. Moreover, drugs that share more triplets also have higher similarities in the indications of the drugs, which also indicates that triplets related to drug sensitivity have potential clinical application value. Therefore, based on the identified triplets, a drug-cell line heterogeneity network was further constructed. We used random walk algorithm based on network to screen drugs for patients in the TCGA database and predicted drug-sensitive cell lines. The results show that our method is highly accurate in both individual drug screening and drug-sensitive cell line prediction. These analyses revealed the ability of the lncRNA-TF-gene regulatory triplets to predict drug response. In recent years, several methods have been proposed to help researchers for studying the functions of lncRNAs in the drug sensitivity. For example, Hu *et al.* [63] discovered a novel mechanism by which LncRNA CCAT1 promotes cell proliferation and enhances drug resistance by regulating the miR-143/PLK1/BUBR1 signaling axis. Wang *et al.* [64] proposed that LncRNA MEG3 enhances cisplatin sensitivity in NSCLC by regulating miR-21-5p/SOX7 axis. Zhang *et al.* confirmed that LncRNA KCNQ1OT1 promoted cisplatin resistance and cell proliferation by regulating miR-211-5p-mediated Ezrin/Fak/Src signaling [65]. There is still a lack of systematic identification of lncRNA-mediated regulation of TF and gene in drug sensitivity. To fill this gap, we conducted a study, which mainly focused on lncRNA-TF-gene.

Our method has great advantages over other methods, including Zhang Fei's method [62], Stanfield's method [66] and Zhang Naiqian's method [67] (Supplementary Table S1, see Supplementary Data available online at https://academic.oup.com/bib). Only

our method provides a user-friendly data resource from which users can download our provided data, and we also identified 1570 triplets associated with drug sensitivity, while other methods did not identify the markers related to the drug sensitivity. Furthermore, our method also outperforms other methods in the number of drugs. And our method considers the regulation between the upstream and downstream of the gene, while other methods only consider the gene. More importantly, our method can not only predict cell lines related to drug susceptibility but also can screen individuals for medication and provide personalized medication guidance. By comparison, it is found that our method outperforms the existing methods in both function and coverage.

Our research has some unique aspects. First, we constructed the lncRNA-TF-gene regulatory triplets, considering the upstream and downstream regulatory relationship between them. Second, we focus on the triplets related to drug sensitivity, which can help us better understand the mechanisms of drug resistance. Finally, we applied the method to screen individual drugs and predict drug-sensitive cell lines. The results show that our method has good predictive ability. To sum up, we not only proposed an effective method but also performed a systematic analysis, revealing the role of LncRNA-TF-gene regulatory triplets in drug sensitivity, and deepening our understanding of its role in drug response.

Key Point

- This study provided a strategy to identify lncRNA-TF-gene regulatory triplets related to drug sensitivity based on transcriptome data and drug sensitivity data and constructed drug-triplet association landscape.
- The comprehensive characterization and analysis of these lncRNA-TF-gene regulatory triplets revealed the differential regulatory mechanisms of LncRNA across different drugs and highlighted the potential of these triplets as prognostic biomarkers in clinical applications.
- The ability of drug sensitivity-related triplets to reflect similarities in drug indications underscores the potential of triplets to predict individual drug screening.
- A user-friendly web resource was constructed to explore drug sensitivities associated with lncRNA-TF-gene regulatory triplets and predict individual precision medication.

Authors' Contributions

Y.P.Z., Y.J.X. and X.L. conceived and designed the overall study. C.X.H. and Y.Q.X. participated in data processing and program implementation. F.L., W.Q.M., H.Y. and X.R.W. participated in study design. C.X.H. and Y.Q.X. wrote the manuscript. X.W. and S.J.C. revised the manuscript. C.X.H. and F.L. organized the figures and tables. All authors read and approved the final manuscript.

Supplementary Data

Supplementary data are available online at https://academic.oup.com/bib.

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Disclaimer

This study has neither been presented nor submitted or accepted anywhere.

Data Availability

The expression profiles and anticancer drug response data of these three cancer types are available at TCGA data portal (https://tcga-data.nci.nih.gov/tcga). The drug sensitivity data of cell lines are available at GDSC database (https://www.cancerrxgene.org/). RNAseq gene expression data of cancer lines are available at Cancer Cell Line Encyclopedia (https://sites.broadinstitute.org/ccle/).

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